A Well-Defined Ni Pincer Catalyst for Cross Coupling of Non-Activated Alkyl Halides and Direct C-H Alkylation

THÈSE N^{O} 5058 (2011)

PRÉSENTÉE LE 23 JUIN 2011

À LA FACULTÉ SCIENCES DE BASE
LABORATOIRE DE SYNTHÈSE ET DE CATALYSE INORGANIQUE
PROGRAMME DOCTORAL EN CHIMIE ET GÉNIE CHIMIQUE

ÉCOLE POLYTECHNIQUE FÉDÉRALE DE LAUSANNE

POUR L'OBTENTION DU GRADE DE DOCTEUR ÈS SCIENCES

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Suisse
2011

ACKNOWLEDGEMENTS

It was a big pleasure for me to do my Ph.D. thesis at EPFL. This is an amazing place with very good equipment and nice research atmosphere.

First, I would like to thank my advisor Prof. Xile Hu for his continuous guidance, advice and support. His energy and inspiration always made any problem seem simple and with his very optimistic attitude, you would believe that all goals could be reached. I will be always thankful for the experiences obtained under his guidance.

I would like to thank my thesis jury: Prof. Vassily Hatzimanikatis, Prof. Kay Severin, Prof. Karl Gademann and Dr. Michael Greaney for accepting to examine this thesis.

I would like to thank a lot to two wonderful apprentices Valérie and Nathalie for the amazing quantity of work, which they did for me. It was a big luck for me to work in a small team with these people. Thank you also for the improvement of my French, without you it would be much more difficult to do progress in this language.

Very many thanks to Zsolt for his help and advices during my first experiments in the lab and for the friendly atmosphere in our small group during my first year at EPFL.

I would also like to thank the past and present members of our group for their support and friendship over the years. Especially I want to thank Heron for the helping to solve a lot of technical problems and for the fabrication of the special equipment and instruments. The glassware, made by Heron, was very useful for lots of my synthesis. Thanks to Dafa for the final proof of this thesis.

Many thanks to all bachelor and master students who worked with me during these years. Julie, Baihua, Mattia, Rima and Matthias, thank you for your good job. Big thanks to Delphine for her wonderful work on Sonogashira coupling. Thanks to Kim, for his persistence in ligands syntheses. Special thanks to Aswin, who helped me a lot during my first weeks in Lausanne. Without his help it would be much more difficult to start my life here.

I am thankful to Prof. Jérôme Waser for the practical advices and remarks for the organic syntheses. I thank him a lot for the utilization of his GC-MS, without this equipment it would be not possible to get these results. Many thanks to all members of his group, who always helped me with my work and borrowed me a lot of chemicals.

I would like to thank Dr. Rosario Scopelliti and Dr. Euro Solari for performing the X-ray and elemental analyses; Gladys Pache, AnneLise Carrupt, and Giovani Petrucci, for the plenty of chemicals, which they ordered for me and for the nice small talks during my visits to magasin; Francisco Sepulveda and Dr. Laure Menin for the hundreds of mass-spectra they did for me; Dr. Martial Rey for the help with the NMR machines, and Anne-Lene Odegaard and Christina Zamanos-Epremian for the administrative work.

And of course I would like to thank my family for the constant support and encouragement during all these years.

ABSTRACT

Carbon-carbon bond forming reactions are among the most important and useful methods for organic synthesis. During the last years, significant progress has been made in this field. Whereas many catalysts were developed for the coupling of aryl, alkenyl, and alkynyl halides, non-activated alkyl halides remain challenging substrates, mainly due to unproductive β-hydride elimination and difficulty in oxidative addition of alkyl halides. This dissertation is devoted to the development of a well-defined nickel catalyst for cross coupling of non-activated alkyl halides and direct alkylation of C–H bonds.

Chapter 2 describes the synthesis of a new pincer $^{Me}N_2N$ ligand and its Ni complexes. This ligand can be obtained by Pd-catalyzed C–N coupling of 2-amino-N,N-dimethylaniline and 2-bromo-N,N-dimethylaniline. Reaction of its Li salt with $Ni(dme)Cl_2$ gives [($^{Me}N_2N$)Ni-Cl] (**1**). Complex **1** can be akylated with Grignard reagents to give [($^{Me}N_2N$)Ni-Alkyl] species. Stability of the alkyl complexes against β-hydride elimination inspired us to use the [($^{Me}N_2N$)Ni-Cl] complex as a catalyst for cross coupling of carbon nucleophiles with alkyl halides.

After investigating different experimental conditions, we found that complex **1** is an active catalyst for cross coupling of non-activated alkyl polyhalides (Chapter 3) and alkyl monohalides (Chapter 4) with alkyl Grignard reagents. The reaction with alkyl monohalides can be done at -35^0C in DMA and only 30min is required to accomplish the formation of the desired products. The high activity of the catalyst resulted in a high group tolerance. Ester, ketone, amide, nitrile, heterocyclic, and acetal groups didn't pose problems.

In Chapter 5, the catalysis was extended to include aryl and heteroaryl Grignard reagents as nucleophiles. The best results were obtained with primary alkyl bromides and iodides and cyclic secondary alkyl iodides in THF and at room temperature. Addition of an additive such as TMEDA or bis[2-(N,N-dimethylaminoethyl)]ether (O-TMEDA) was necessary to prevent the formation of undesired homocoupling products. Functionalized Grignard reagents could be readily coupled.

The [($^{Me}N_2N$)Ni-Cl] catalyst was then used for the Sonogashira coupling of alkyl halides with alkynes (Chapter 6). A wide range of functionalized alkyl halides could be used for this reaction. Not only alkyl iodides and bromides but also alkyl chlorides can be used. Moreover, by changing reaction conditions (additive and temperature), selective coupling of C–Br bond

in the presence of C–Cl bond, and of C–I bond in the presence of both C–Br and C–Cl bonds can be achieved. This feature allowed us to carry out multiple and selective Sonogashira coupling of the substrates containing different alkyl halide bonds. We could combine Sonogashira coupling with Kumada-Corriu-Tamao coupling. Utilization of these two methods leads to a simple and rapid synthesis of organic molecules.

Similar conditions were then applied for the direct alkylation of aromatic heterocycles in Chapter 7. Aromatic heterocyclic compounds are widely used as bio-active molecules, pharmaceuticals, and organic materials. Direct C–H functionalization represents the most straightforward way for the derivatization of these compounds. Despite of the developments during the last years, direct alkylation of C–H bond with alkyl halides is still challenging. Utilization of our [($^{Me}N_2N$)Ni-Cl] catalyst gives the desired products in high yields and a wide range of aromatic heterocyclic compounds can be used for the reaction.

The well-defined nature and a high stability of [($^{Me}N_2N$)Ni-Cl] complex and its derivatives enabled us to perform detailed mechanistic investigations of the catalytic transformations. Presumed intermediates of catalytic cycles were determined and some of them were synthesized or separated from the reaction mixture. The resting states of the catalysts were also defined in most of the cases, giving important information for the mechanistic elucidation.

In the last part (Chapter 8) we developed a direct C–H carboxylation chemistry for aromatic heterocycles. The carboxylation can be done under catalyst-free conditions and with a mild base Cs_2CO_3. The unstable carboxylic acids were converted to the more stable esters by a one-pot reaction with MeI. A wide substrate scope was achieved.

Keywords

pincer complex, catalysis, cross coupling, C–H activation, alkyl halides

RÉSUMÉ

Les réactions de formation de la liaison carbone-carbone sont parmi les méthodes les plus importantes et les plus utilisées en synthèse organique. Un progrès important a été fait dans ce domaine au cours des dernières années. Tandis que de nombreux catalyseurs ont été développés pour le couplage des halogénures d'aryle, d'alcènyle et d'alcynyle, les halogénures d'alkyle non-activés restent des substrats épineux, principalement en raison de l'élimination improductive de β-hydrure et de la difficulté d'addition oxydante des halogénures d'alkyle. Cette thèse est consacrée au développement d'un catalyseur au nickel caractérisé pour le couplage croisé des halogénures d'alkyle non-activés et l'alkylation directe des liaisons C–H.

Le chapitre 2 décrit la synthèse d'un nouveau ligand pincer $^{Me}N_2N$ et de ses complexes de nickel. Ce ligand peut être obtenu par le couplage C–N entre le 2-amino-N,N,-diméthylaniline et le 2-bromo-N,N-diméthylaniline catalysé par Pd. La réaction de son sel de lithium avec le $Ni(dme)Cl_2$ forme [($^{Me}N_2N$)Ni-Cl] (**1**). L'alkylation du complexe **1** par les réactifs de Grignard produit des complexes de type [($^{Me}N_2N$)Ni-Alkyle]. La stabilité des complexes [($^{Me}N_2N$)Ni-Alkyle] face à l'élimination de β-hydrure nous a dirigé pour l'utilisation du complexe [($^{Me}N_2N$)Ni-Cl] comme catalyseur pour le couplage croisé de nucléophiles carbonés avec des halogénures d'alkyle.

Après l'étude des différentes conditions expérimentales, nous avons constaté que le complexe **1** est un catalyseur actif pour le couplage croisé des polyhalogénures d'alkyle (Chapitre 3) et des monohalogénures d'alkyle (Chapitre 4) non-activés avec les réactifs alkyles de Grignard. La réaction correspondante aux monohalogénures d'alkyle peut être effectuée à -35^0C dans la DMA et seulement 30 minutes sont nécessaires pour aboutir à la formation des produits. L'activité élevée du catalyseur résulte en une bonne tolérance à plusieurs groupes fonctionnels, tels qu'ester, cétone, amide, nitrile, hétérocycle et acétal.

Dans le chapitre 5, la catalyse a été élargie pour inclure les réactifs de Grignard aryle et hétéroaryle comme nucléophiles. Les meilleurs résultats ont été obtenus avec des bromures et iodures d'alkyle primaire et avec des iodures d'alkyle secondaire cyclique dans le THF à température ambiante. L'addition d'un additif tel que la TMEDA ou le bis[2-(N,N-diméthylaminoéthyl)]éther (O-TMEDA) a été nécessaire pour empêcher la formation de

produits indésirables d'homocouplage. Les réactifs de Grignard fonctionnalisés peuvent ainsi être facilement couplés.

Le catalyseur [($^{Me}N_2N$)Ni-Cl] a ensuite été utilisé pour le couplage de Sonogashira entre des halogénures d'alkyle et des alcynes (Chapitre 6). Une grande variété d'halogénures d'alkyle fonctionnalisés peut être utilisée pour cette réaction. Non seulement les iodures et bromures d'alkyle peuvent être couplés mais aussi les chlorures d'alkyle. En outre, en changeant les conditions de réaction (additif et température), le couplage sélectif d'une liaison C–Br en présence d'une liaison C–Cl, et d'une liaison C–I en présence de liaisons C–Br et C–Cl peut être réalisé. Cette particularité nous a permis d'effectuer des couplages de Sonogashira multiples et sélectifs de substrats contenant différentes liaisons d'halogénures d'alkyle. Le couplage de Sonogashira peut aussi être combiné avec un couplage de Kumada-Corriu-Tamao. L'utilisation de ces deux méthodes permet la synthèse rapide et facile des molécules organiques.

Des conditions similaires ont ensuite été utilisées pour l'alkylation directe des hétérocycles aromatiques dans le Chapitre 7. Les composés hétérocycliques sont souvent utilisés en tant que molécules bioactives, produits pharmaceutiques, et substrats organiques. La fonctionnalisation directe de la liaison C–H représente la méthode la plus simple pour la dérivatisation de ces composés. Malgré le progrès au cours de ces dernières années, l'alkylation directe de la liaison C–H avec les halogénures d'alkyle reste toujours difficile. L'utilisation de notre complexe [($^{Me}N_2N$)Ni-Cl] permet la formation de composés avec un très bon rendement et un grand éventail de composés hétérocycliques pouvant être utilisés pour cette réaction.

La structure bien définie et la grande stabilité du complexe [($^{Me}N_2N$)Ni-Cl] et de ses dérivés nous a permis d'effectuer des recherches détaillées sur les mécanismes des transformations catalytiques. Les intermédiaires présumés du cycle catalytique ont été déterminés et certains d'entre eux ont même été synthétisés ou séparés du mélange réactionnel. Les états finaux du catalyseur après les réactions ont également été définis dans la plupart des cas, donnant des informations importantes pour l'élucidation des mécanismes réactionnels.

Dans la dernière partie (Chapitre 8) nous avons développé une méthode de carboxylation C–H directe des hétérocycles aromatiques. La carboxylation peut être effectuée sans catalyseur et avec une base douce Cs_2CO_3. Les acides carboxyliques instables ont été convertis en esters

plus stables par une réaction “one-pot” avec MeI. Une grande gamme de substrats peut être utilisée pour ce type de réaction.

Mots Clefs

complexe pincer, catalyse, couplage croisé, C–H activation, halogénures d'alkyle

LIST OF SYMBOLS AND ABBREVIATIONS

Å	angstrom
δ	chemical shift
^{0}	degree
λ	wavelength
acac	acetylacetonate
aq.	aqueous
atm	atmosphere
BBN	9-borobicyclo[3.3.1]-nonane
Boc	tert-butyloxycarbonyl
br	broad
Bu	butyl
Bz	benzyl
calcd	calculated
cat	catalyst
cod	1,5-cyclooctadiene
Cy	cyclohexyl
d	doublet
dba	dibenzylideneacetone
DBU	1,8-diazabicycloundec-7-ene
dd	doublet of doublets
DFT	density functional theory
DMA	N,N-dimethylacetamide
dme	1,2-dimethoxyethane
dmeda	N,N'-dimethylethane-1,2-diamine
DMF	N,N-dimethylformamide
DMSO	dimethyl sulfoxide
dppf	1,1'-bis(diphenylphosphino)ferrocene
dppp	1,3-bis(diphenylphosphino)propane
equiv.	equivalent
ESR	electron spin resonance
Et	ethyl
Et_3N	triethylamine

FID	flame ionization detector
g	gram
GC-MS	gas chromatography mass spectrometry
HMTA	hexamethylenetetramine
hr	hour
HR-MS	high resolution mass spectrometry
^{i}Bu	iso-butyl
^{i}Pr	iso-propyl
K	Kelvin
KCT	Kumada-Corriu-Tamao
Me	methyl
Me_2NH	dimethylamine
Me_2SO_4	dimethyl sulfate
$^{Me}N_2N$	bis[(2-dimethylamino)phenyl]amine
mer	meridional
mg	mili-gram
MHZ	mega-hertz
mL	mili-liter
mmol	mili-mole
mol	mole
NaOMe	sodium methoxide
^{n}Bu	normal-butyl
^{n}Bu-Li	n-butyllithium
NMR	nuclear magnetic resonance
OAc	acetate
OTf	triflate
O-TMEDA	bis[2-(N,N-dimethylaminoethyl)]ether
$Pd_2(dba)_3$	tris(dibenzylideneacetone)dipalladium(0)
Ph	phenyl
ppm	part per million
pybox	2,6-bis[(4R)-4-phenyl-2-oxazolinyl]pyridine
r.t.	room temperature
s	second
s	singlet

salen	N,N'-ethylenebis(salicylimine)
t	triplet
T	temperature
^{t}BuOLi	lithium tert-butoxide
^{t}BuONa	sodium tert-butoxide
td	triplet of doublets
THF	tetrahydrofuran
TMEDA	tetramethylethylenediamine
TMS	trimethylsilyl
TOF-MS	time-of-flight mass spectrometry
TON	turnover number
xantphos	9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene

TABLE OF CONTENTS

Chapter 1

Introduction

1.1. Transition metal catalyzed C-C cross-coupling reactions

Transition metal catalyzed cross-coupling is one of the most important methods for the construction of new carbon-carbon bonds.[1] This simple and straightforward technique can be applied for the synthesis of complex organic molecules and important pharmaceuticals. A lot of progress and discovery have been made in this field over the last forty years. The high impact of cross-coupling reactions is marked by the attribution of the Nobel Prize 2010 to the pioneer researches in this field, Suzuki, Negishi and Heck, "for palladium-catalyzed cross couplings in organic synthesis".[2]

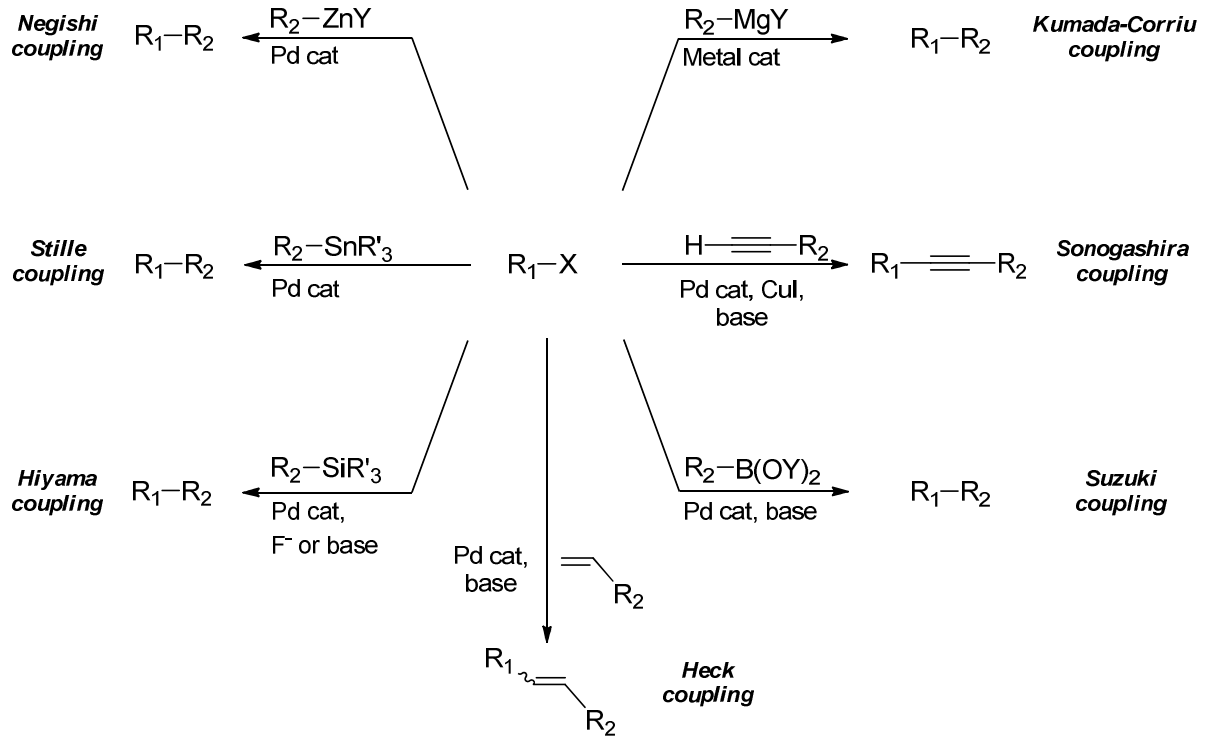

Figure 1. Common cross-coupling reactions.

A wide range of organometallic reagents can be used in cross-coupling reactions, starting from very reactive and highly inflammable organo-magnesium or organo-lithium reagents to moisture and oxygen tolerant organoboron compounds. The most important examples of metal-catalyzed cross-coupling reactions are represented in Figure 1. A wide range of different electrophiles can be used in cross-coupling reactions. Among them, aryl, alkenyl and alkyl halides, triflates and tosylates are the most popular substrates. Most of the work on cross-coupling reactions deals with Pd- or Ni-catalyzed processes. Recent work shows that many other transition metals can be used as catalysts. Nonetheless, Pd- and Ni-catalysts remain most efficient.

Much work has been done to elucidate the mechanism of coupling reactions. Many hypotheses and speculations have been made concerning the details of the transformations in the catalytic cycle. The mechanism can vary greatly depending on the catalyst, substrates, additives, solvent, temperature, etc. Nonetheless, the most general mechanism of the Pd-catalyzed cross-coupling reactions can be described by the catalytic cycle in Figure 2. A Pd^{II} precatalyst is reduced by ligands or substrates to form Pd^0. An oxidative addition of R-X occurs on the Pd^0 center, giving $Pd^{II}(R)(X)$. Transmetalation with an organometallic reagent happens on the next step. Finally, reductive elimination of the desired product closes the catalytic cycle and regenerates Pd^0, which can be further used in catalytic process.

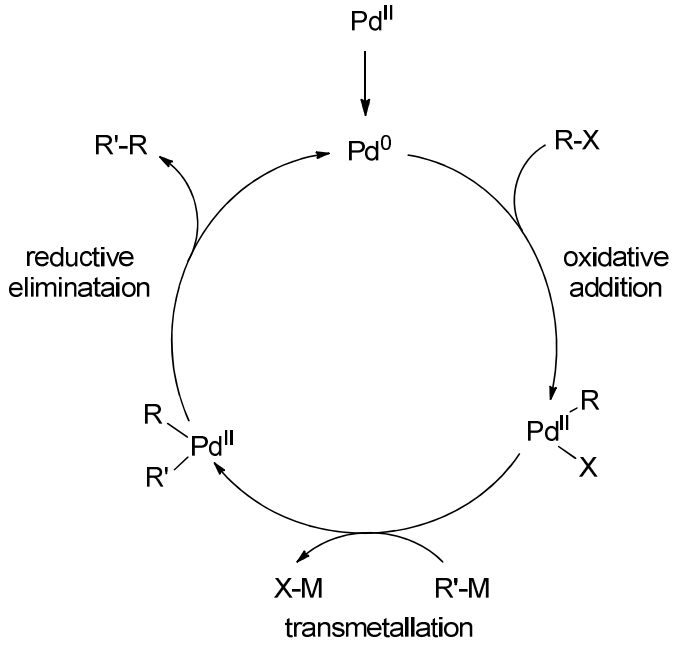

Figure 2. General mechanism for Pd-catalyzed cross-coupling reactions.

An appropriate ligand should be used for the stabilization of Pd^0 to avoid its destruction to Pd metal particles. Oxidative addition can be a problem for substrates with a very strong C-X bond, such as aryl chlorides or alkyl halides. Formation of the homocoupling products is another challenge which can be solved sometimes by the addition of stabilizing additives or by particular precautions during the mixing process. Another significant problem is unproductive β-hydride elimination, which is often met when alkyl nucleophiles and especially electrophiles are used as substrates. This problem is very difficult to overcome in case of Pd-catalysts.

Despite of these difficulties, much progress has been made in the field, and C-C cross-coupling reactions are now widely used in organic syntheses and industrial processes. This chapter summarizes some of the most important developments.

1.1.1. Kumada–Corriu–Tamao coupling

One of the first and the most important cross-coupling reactions was discovered independently by Kumada[3] and colleagues, and Corriu[4] and Masse in 1972. They showed that catalytic amounts of Ni salts can catalyze the coupling between Grignard reagents and aryl or vinyl halides (Figure 3). This method was developed further over the last decades. Many Ni,[5,6] Pd,[7,8] Fe,[9,10,11,12] Co,[13,14,15] and Cu[16] salts and complexes were found to be active and selective catalysts. The availability of a wide range of the catalysts, based on cheap and abundant elements such as iron or nickel, makes this cross-coupling method an attractive way for the sustainable synthesis of the organic molecules.

Figure 3. Kumada–Corriu–Tamao coupling.

The high reactivity of Grignard reagents can be an advantage, because relatively inert substrates can be used. However, it can also pose a problem in terms of functional group tolerance. The latter problem was a big hurdle for the utilization of Kumada–Corriu–Tamao coupling in the organic synthesis. Another challenge is the synthesis of Grignard reagents containing functional groups. This problem was partially solved by the work of Knochel.[17] The new methods for the synthesis of functionalized Grignard reagents were developed, thus improving the scope of application of the Kumada–Corriu–Tamao coupling. However, this method is still not general and cannot be used for all range of the Grignard reagents.[18]

Alkyl halides are difficult substrates for the Kumada–Corriu–Tamao coupling. In contrast to aryl, alkenyl, and alkynyl halides, there are only few efficient catalysts for the reaction with alkyl halides.[19,20] β-hydride elimination and difficulty in oxidative addition of alkyl halides are the main problems.[19,21]

The use of inflammable Grignard reagents is a disadvantage of Kumada coupling. The utilization of micro reactor technologies can be one of the possible solutions.[22] A better control of the reaction conditions and the use of reduced quantities of Grignard reagents in this technique can be beneficial for the industrial application of Kumada–Corriu–Tamao

coupling. Utilization of stabilizing additives is another possible solution, which requires further scientific investigations.[23]

1.1.2. Negishi coupling

Negishi coupling can be considered as an alternative to the Kumada–Corriu–Tamao coupling, which suffers from poor functional group tolerance and limitations in large scale applications. Negishi coupling is the cross-coupling of organozinc reagents with alkyl, aryl and alkenyl electrophiles (Figure 4).[24] The main advantage of this coupling process is the use of more stable and less reactive organozinc reagents. This results in a high functional group tolerance. Functionalized organozinc compounds can be synthesized and many of them are commercially available.

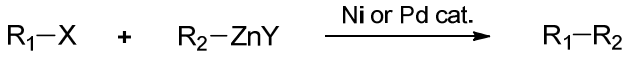

Figure 4. Negishi coupling.

A wide range of metal catalysts are available for the Negishi coupling. Ni- and Pd-based complexes are the most efficient and most used catalysts.[25,26]

One of the main problems of the Negishi coupling is the synthesis of organozinc reagents. Most zinc reagents were synthesized by transmetalation of Grignard reagents or organolithium compounds with Zn salts. Highly inflammable Grignard or organolithium reagents are still used. Some organozinc compounds can be prepared by the direct insertion of Zn into a carbon-halide bond.[27] But this direct zincation method is not universal and it can be used only for alkyl iodides. The utilization of a highly active form of zinc (Rieke zinc)[28] considerably improves the scope of the zincation method, but the increased cost and the difficulty in the generation of Rieke zinc are still obstacles.

Despite of these drawbacks, Negishi coupling is one of the best developed cross-coupling reactions. Great improvements during the last years lead to the utilization of Negishi coupling for a wide range of substrates, including alkyl halides. Reaction can be done at very mild conditions, resulting in excellent yields and high group tolerance.

1.1.3. Suzuki-Miyaura coupling

Cross-coupling between organoboron compounds and aryl halides can be smoothly done in a presence of Pd catalyst and a base (Figure 5). This reaction was discovered by Suzuki and coworkers[29] and is widely used now in organic laboratories and industrial syntheses.

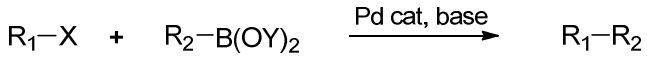

Figure 5. Suzuki coupling.

While there are examples of Suzuki coupling catalyzed by other metals, Pd is the most used metal.[30] The chemistry of Suzuki coupling is highly developed and a library of Pd catalysts is available, even for difficult substrates. In some cases, other metals can be advantageous compared to Pd. Ni based catalysts are particularly good for the reactions with aryl chlorides and mesylates.[31] The most common inorganic bases, such as Na_2CO_3 or K_3PO_4, are efficient for this reaction. Traces of water accelerate the reaction.[32] An addition of water to anhydrous bases is recommended for a faster formation of the desired products.

Oxygen and moisture stability of organoboron compounds is a big advantage of Suzuki coupling. However, organoboron compounds are not easy to make and their prices are often much higher than those of other organometallic nucleophiles. This can be explained by the fact that the most common way to an organoboron compound is the transmetalation of an organo-magnesium or -lithium reagent with a boron ester.[33] This process often requires a low temperature and again the use of organomagnesium or -lithium reagents. Cross-coupling with pinacolborane or bis(pinacolato)diboron is another possible way to synthesize organoboron compounds.[34] But this Pd-catalyzed process suffers from a high price of the boron starting materials.

Even though organoboron compounds are more expensive than many other nucleophiles, they are widely used in organic synthesis due to the high group tolerance, and the stability of the starting materials.

1.1.4. Heck coupling

Heck coupling is one of the best developed methods of cross-coupling reactions. Research work in this area was started over 30 years ago and the quantity of scientific publications

reported every year in this field is still remarkable. The reaction is Pd-catalyzed coupling of alkenes with aryl and alkenyl halides, triflates and similar compounds (Figure 6).[35]

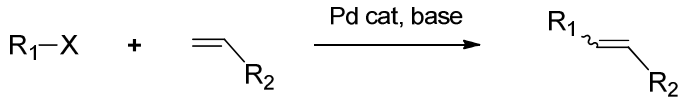

Figure 6. Heck coupling.

A wide range of Pd-based catalysts are used in this reaction, from cheap and air stable $PdCl_2$ and $Pd(OAc)_2$, to Pd complexes with special phosphine ligands.[36] A range of bases and solvents can be used for this reaction.

All kinds of alkenes can be used for the Heck reaction. Even simple ethylene can be successfully coupled.[37] But the most common substrates are mono-substituted or 1,1-disubstituted ethylenes, which are more reactive and have better selectivity. Tri- and even tetra-substituted alkenes can be also used, although more rarely.[38]

Coupling of alkenes can be done with different kind of aryl, alkenyl, allyl, benzyl and some alkyl halides and triflates.[39] Iodides are usually the best substrates among the halides, but recent developments in this area allow the utilization of chlorides.[40] Moreover, intramolecular and enantioselective Heck reactions can be done, and this method was used in several syntheses of natural products and pharmaceuticals.[41] Heck reaction can be combined with other cross-coupling reactions, leading to the formation of new carbon–carbon bonds with alkylpalladium intermediates.[42]

A very wide scope of substrate, mild reaction conditions, and the possibility of combination with other reactions make Heck coupling one of the most popular cross-coupling processes in organic synthesis.

1.1.5. Sonogashira coupling

The discovery of the cross-coupling reaction between alkynes and alkyl or aryl electrophiles was a big contribution to the development of the alkyne chemistry. Sonogashira and coworkers showed in 1975 that Pd-catalyzed formation of substituted alkynes can be done with a base and a CuI co-catalyst (Figure 7).[43]

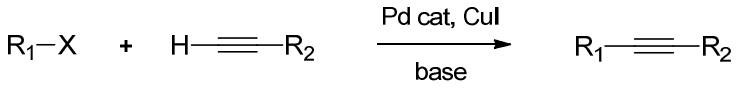

Figure 7. Sonogashira coupling.

Since then, a lot of developments have been performed in this field. Big advance was made towards the utilization of cheaper and more abundant metals for the Sonogashira coupling.[44] But Pd-based catalysts in conjunction with Cu co-catalysts are still the most used.[45] Pd^0 was shown to be the active catalyst, thus the utilization of Pd^{II} sources always provokes the formation of some homocoupling side-products. Different phosphine ligands can be used. Addition of a mild base, such as triethylamine or diisopropylethylamine, is necessary for the neutralization of the formed acid.

Stability of the starting materials and simple operation procedures can be considered as the biggest advantages of the Sonogashira coupling. Mild reaction conditions result in a high group tolerance.

Sonogashira coupling of alkyl halides is still challenging. Alkyl halides are prone to β-hydride elimination and are not stable in the presence of the base on heating, resulting in the formation of elimination products. Only several examples are known.[46,47]

1.2. Transition metal catalyzed cross-coupling reactions of alkyl electrophiles

1.2.1. Palladium catalyzed cross-coupling reactions of alkyl electrophiles

The application of Pd-based catalysts in cross-coupling reactions with alkyl electrophiles is challenging mainly due to the formation of side-products, caused by unproductive β-hydride elimination. This is the reason why many catalysts work well for coupling of aryl or alkenyl halides but give unsatisfied results for coupling of alkyl electrophiles. Some progress however has been made. The first example of a successful Pd-catalyzed cross-coupling of β-hydrogen-containing alkyl iodides was shown by Suzuki in 1992.[48] He explored $Pd(PPh_3)_4$-catalyzed reaction between alkyl iodides and alkyl-, aryl-, and vinyl-9-BBN compounds (Figure 8). The products were obtained in good yields.

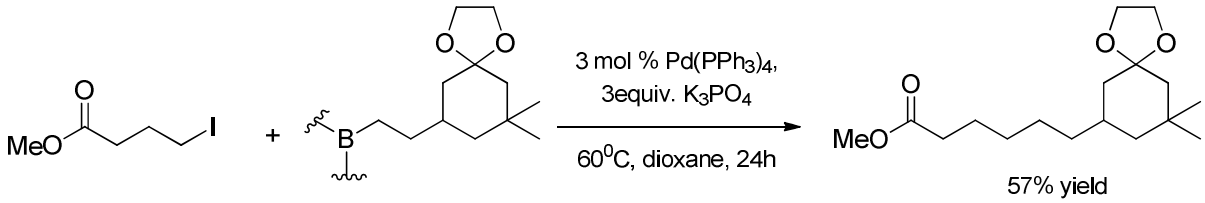

Figure 8. The first example of Suzuki coupling of alkyl electrophiles, containing β-hydrogen atoms.

1.2.1.1. Pd-catalyzed Suzuki coupling

The early work of Suzuki showed that Pd-catalyzed coupling of alkyl halides is possible; however the yields and scope of the reactions were still modest. This domain of chemistry stayed underexplored during almost 10 years after the initial report of Suzuki.

Fu and coworkers showed the first examples of Suzuki coupling of alkyl bromides in 2001.[49] The effectiveness of the bulky phosphine ligands, like PCy_3, for the Pd-catalyzed cross-coupling reactions was demonstrated in this work (Figure 9). The reaction was carried out at room temperature in a presence of a mile base $K_3PO_4*H_2O$. As in many other Suzuki coupling reactions, a small amount of water in the base was favorable for the fast formation of the desired products. A good functional group tolerance was observed. Unfortunately only 9-BBN derivatives were active in this coupling process and no products were obtained with other organoboron compounds.

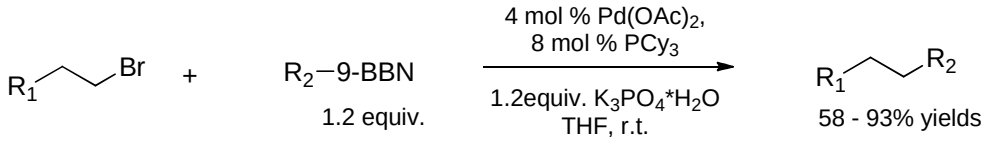

Figure 9. Pd-catalyzed Suzuki coupling of alkyl bromides in a presence of bulky phosphine ligand.

Alkyl chlorides are the least active substrates among alkyl halides, and cross-coupling of alkyl chlorides represents a challenge. The coupling conditions for alkyl bromides in the above work were not efficient for the coupling of alkyl chlorides. However, Fu reported that alkyl chlorides can be coupled when the conditions in Figure 10 were employed.[50] The products were separated in good yields and a good functional group tolerance was observed.

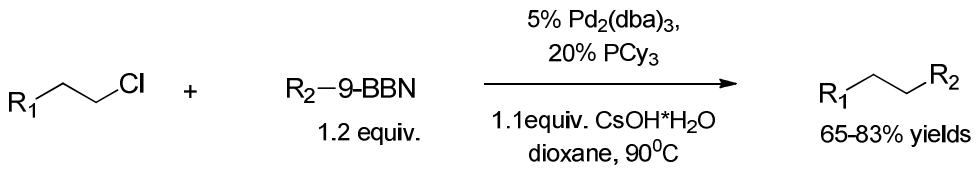

Figure 10. The best conditions, developed by Fu, for the Suzuki coupling of alkyl chlorides.

All previous examples employed organo-9-BBN derivatives as the boron reagents. The utilization of commercially available and air-stable derivatives of boronic acids would be an improvement. In 2002, Fu showed that the use of P^tBu_2Me and KO^tBu can lead to successful coupling of alkyl bromides with aryl, vinyl-, and alkyl-boronic acids (Figure 11).[51] A good functional group tolerance was demonstrated; however the yields in the reactions with alkyl-boronic acids were lower than with aryl and alkenyl boron reagents.

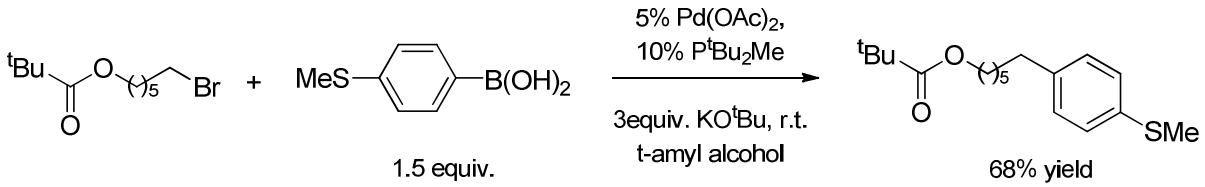

Figure 11. Utilization of the boronic acids for the Suzuki coupling of alkyl electrophiles.

1.2.1.2. Pd-catalyzed Negishi coupling

In 2003, Fu described a first and very efficient Pd-catalyzed Negishi coupling of alkyl halides and tosylates with alkyl-, aryl-, and vinylzinc halides (Figure 12).[26] The efficiency of this catalytic system was checked on a wide scope of substrates. Even alkyl chlorides can be coupled with good yields. A very good functional group tolerance was observed.

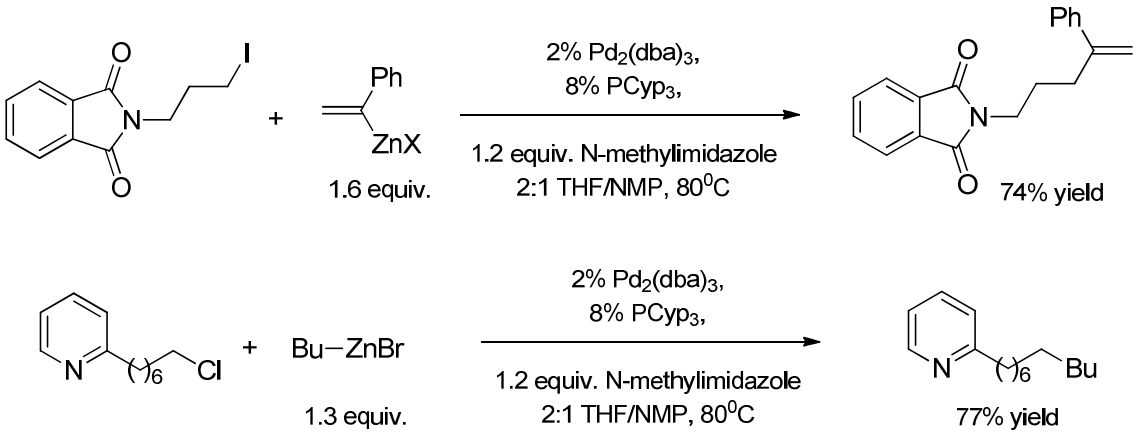

Figure 12. Pd-catalyzed Negishi coupling of alkyl halides.

1.2.1.3. Pd-catalyzed Sonogashira coupling

Sonogashira coupling is the most versatile method for the synthesis of substituted alkynes. β-hydrogen containing alkyl halides are difficult substrates. The presence of a base at elevated temperatures in Sonogashira coupling poses a problem for alkyl halides, because they might decompose under these conditions to give elimination products. In 2003, Fu and coworkers showed that this coupling can be achieved using a Pd-catalyst with a N-heterocyclic carbene ligand (Figure 13).[46] The commonly used organic base for Sonogashira coupling, Et_3N, was not efficient and the inorganic base Cs_2CO_3 was necessary. A wide substrate scope and a very good functional group tolerance were observed.

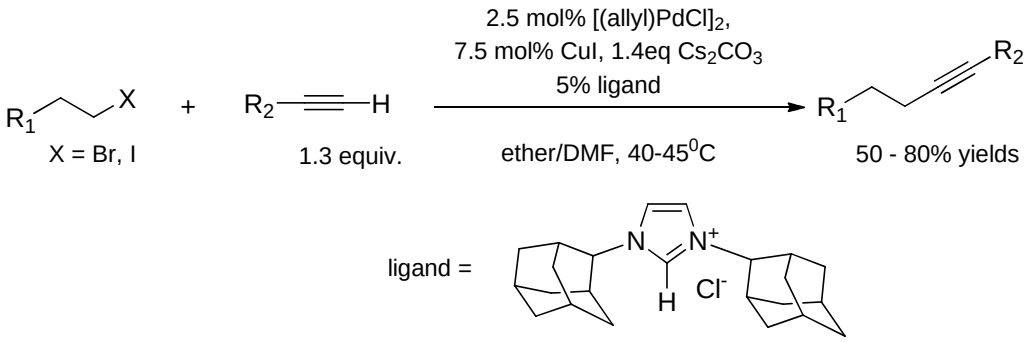

Figure 13. Pd-catalyzed Sonogashira coupling of primary alkyl halides.

Later, a similar catalytic system was developed by Glorius and coworkers for the Sonogashira coupling of secondary alkyl bromides (Figure 14).[47] A temperature of 60^0C was needed and the preformed Pd-complex $[IBiox7PdCl_2]_2$ was used as the catalyst. A series of cyclic and non-cyclic secondary alkyl bromides were converted to the desired products. The corresponding iodides can be also used but the obtained yields were significantly lower. A good functional group tolerance was observed. However, only simple unfunctionalized alkynes, like hexyne or octyne, can be used for this reaction.

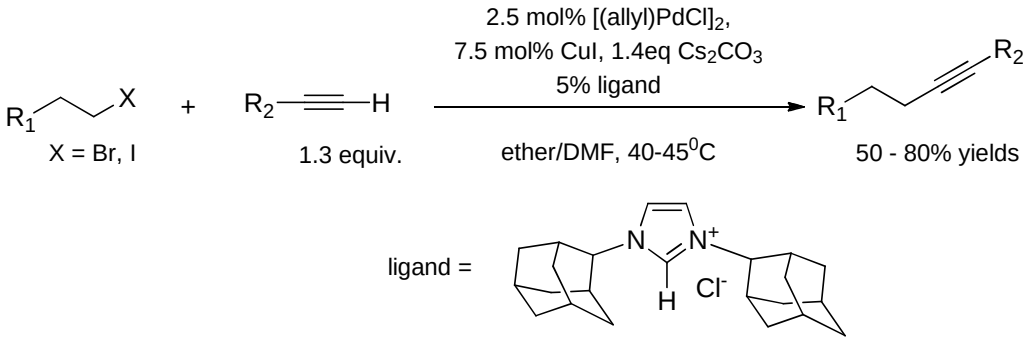

Figure 14. Pd-catalyzed Sonogashira coupling of secondary alkyl bromides.

1.2.1.4. Pd-catalyzed Kumada-Corriu-Tamao coupling

The first examples of Pd- catalyzed Kumada-Corriu-Tamao coupling of unactivated alkyl chlorides were shown by Beller and coworkers in 2002 (Figure 15).[7] Alkyl chlorides can be successfully coupled in a presence of catalytic amount of $Pd(OAc)_2$ and PCy_3. A variety of alkyl halides containing various functional groups can be used. The reactions were done at room temperature, even though the cross-coupling of alkyl chlorides often requires a high temperature.

Figure 15. Pd-catalyzed Kumada-Corriu-Tamao coupling of unactivated alkyl chlorides.

Another development of Pd-catalyzed Kumada-Corriu-Tamao coupling of unactivated alkyl bromides and tosylates was made by Kambe and coworkers (Figure 16).[52] A catalytic system based on $Pd(OAc)_2$ in a presence of excess of 1,3-butadiene can be applied for the cross-coupling of alkyl bromides and tosylates with alkyl and aryl Grignard reagents. Only 6 entries were tested by Kambe, and thus the scope of the reactions remains to be verified.

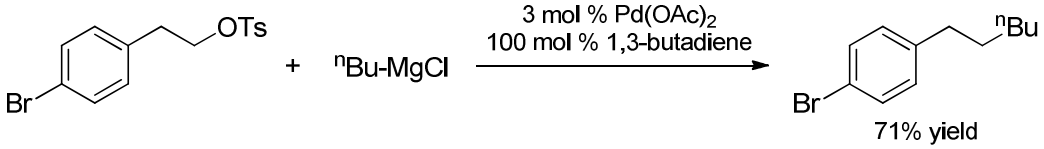

Figure 16. Pd-catalyzed Kumada-Corriu-Tamao coupling of unactivated alkyl chlorides.

1.2.2. Nickel catalyzed cross-coupling of alkyl electrophiles

1.2.2.1. Ni-catalyzed Negishi coupling of alkyl electrophiles

The first Ni-catalyzed Negishi coupling of alkyl halides with alkyl zinc reagents was discovered by Knochel and coworkers.[53] It was found that a mixture of $Ni(acac)_2$/LiI can serve as an efficient catalyst for the carbon-carbon bond formation between two sp^3 carbon atoms (Figure 17). The interesting fact was that a double bond in a substrate was essential for the successful formation of the products. The undesired zinc exchange reaction took place in the absence of the double bond (Figure 17).

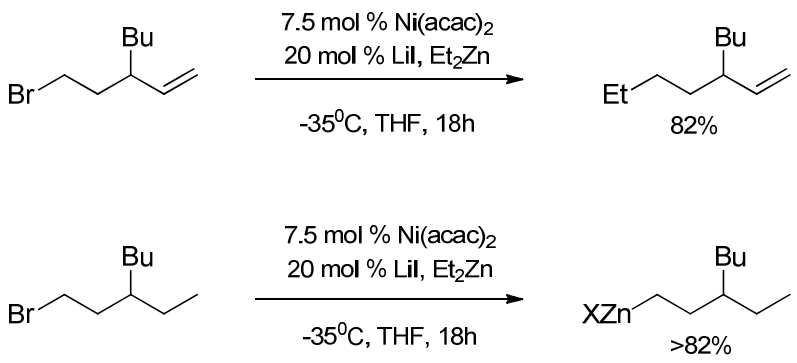

Figure 17. Structure-dependence of the chemical reactivity of alkyl halides in Negishi coupling.

It was assumed that a double bond in the substrate had an important role as it coordinates to the Ni center. It was demonstrated on a series of substrates that this catalytic system can catalyze the formation of a carbon-carbon bond between alkyl halides and alkyl zinc reagents. A good group tolerance was observed, for example, ester and nitrile groups didn't pose problems. The requirement of an internal double bond in the substrate limits the scope of the substrates. The addition of an external additive with a double bond was proposed as a solution of this problem. Indeed, 3-(triflouromethyl)styrene or acetophenone can be used as additive, allowing the synthesis of a wide range of molecules (Figure 18).[54]

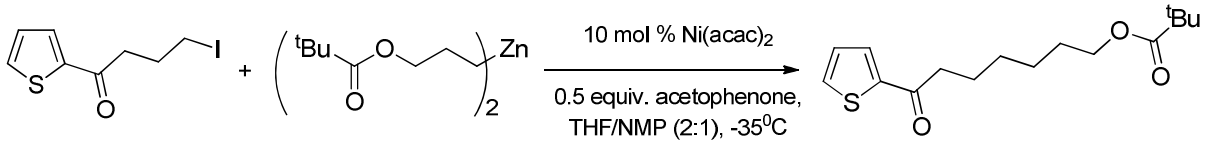

Figure 18. Ni-catalyzed Negishi coupling of alkyl halides in a presence of acetophenone additive.

Later, this method was also improved to include aryl zinc[55] and benzyl zinc[56] nucleophiles. The cheap $Ni(acac)_2$ was used as catalyst. The scope was wide, and group tolerance was high.

1.2.2.2. Ni-catalyzed Kumada-Corriu-Tamao coupling

Ni-catalyzed cross-coupling reaction of Grignard reagents with alkyl, aryl and alkenyl halides and pseudo-halides was one of the first well-developed methods of the cross-coupling reactions. In 1972 Kumada[3] and Corriu[4] discovered independently that Ni salts can serve as active catalyst for the cross-coupling of Grignard reagents with aryl and alkenyl halides. Good yields of the reactions were obtained.

In 1976, a full paper of Kumada and coworkers was published.[57] The focus was the mechanism of the cross-coupling between various Grignard reagents and aryl and alkenyl halides (Figure 19). Even β-hydrogen containing alkyl Grignard reagents were good substrates and a wide variety of products were obtained in good yields.

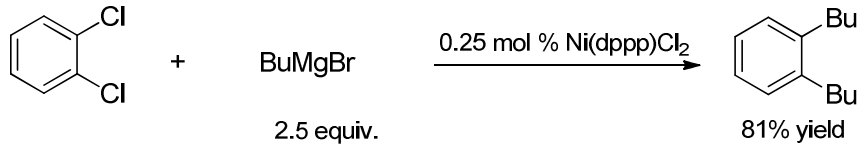

Figure 19. The work of Kumada and coworkers on Ni-catalyzed cross-coupling reactions of Grignard reagents.

Several further improvements were done in this field after the work of Kumada. The Ni-complex with a pincer (PNP) ligand was used by Liang and coworkers (Figure 20).[58] Good results were obtained for the reaction between aryl Grignard reagents and aryl electrophiles, however only poor yields were obtained when β-hydrogen containing alkyl Grignard reagents were used for the reaction.

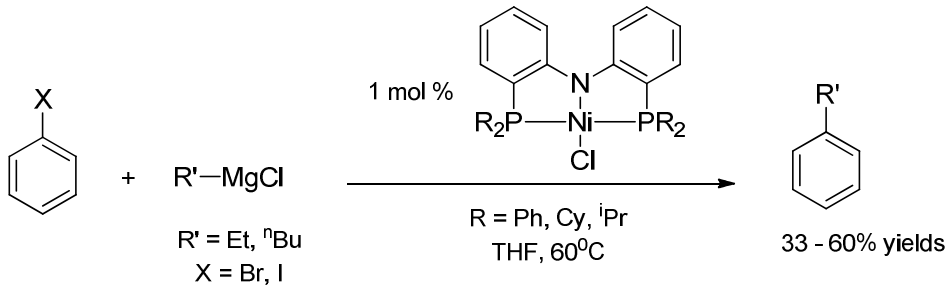

Figure 20. Reactivity of the Liang pincer complex in the Kumada-Corriu-Tamao coupling.

Kumada-Corriu-Tamao coupling of alkyl Grignard reagents with alkyl halides was much less developed. 30 years after the pioneer work of Kumada and Corriu, the first successful protocol for the coupling between two sp^3 carbon atoms was reported by Kambe in 2002.[5] $NiCl_2$ in conjunction with an excess of 1,3-butadiene is active for this reaction (Figure 21). Alkyl bromides, tosylates and chlorides can be coupled with alkyl and aryl Grignard reagents, with good to excellent yields. 1,3-butadiene is essential, as reduction or elimination was severe in the absence of this additive.

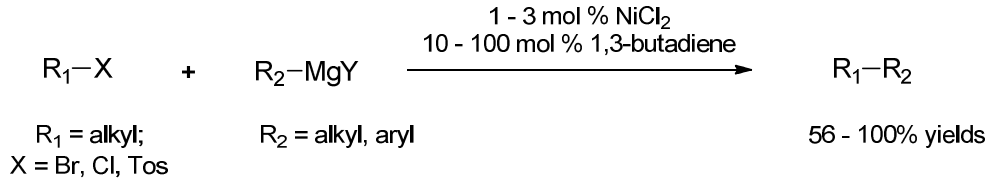

Figure 21. Kambe work on cross-coupling of Grignard reagents with alkyl electrophiles.

Surprisingly, even alkyl fluorides with very strong carbon-fluorine bond can be used for coupling with alkyl Grignard reagents under the same conditions. However, these reactions were done with simple substrates without functional groups, representing a limitation for application in synthesis. In later 2009, the Kambe group published new results with improved functional group tolerance.[59] Similar reaction conditions were used in this method (Figure 22).

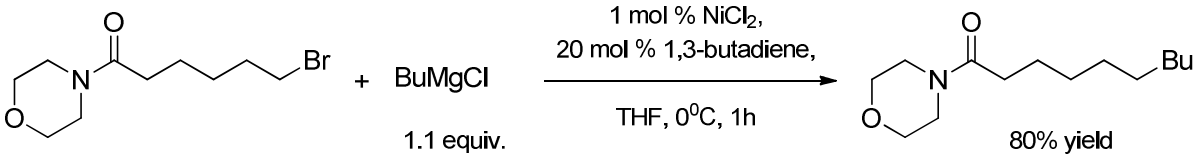

Figure 22. Improved functional group tolerance in Kambe method.

1.2.2.3. Ni-catalyzed Suzuki coupling of alkyl electrophiles

Ni-based catalysts can be used for Suzuki coupling. Alkyl halides can be coupled with boronic acids in the catalytic system developed by Fu and coworkers (Figure 23).[60] This reaction can be done with catalytic amounts of $Ni(cod)_2$ and bathophenantroline. The coupling can be done with primary alkyl iodides and secondary alkyl bromides, but the coupling of primary alkyl bromides was not efficient. The yields are lower for functionalized substrates. It is worth to note that $Ni(cod)_2$ is highly sensitive and requires special precautions during handling and storage. The cost of $Ni(cod)_2$ is even higher than that of common Pd-salts.[61]

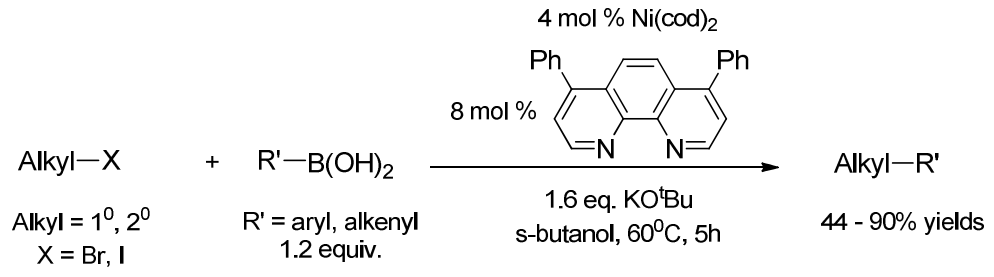

Figure 23. Ni-catalyzed Suzuki coupling of non-activated alkyl halides.

1.2.3. Iron catalyzed cross-coupling reaction of alkyl electrophiles

Iron is one of the most abundant elements in the Earth's crust. Iron is not toxic, and thus is more environmentally friendly.[62] Iron is also cheap. These factors make iron-based catalysts desirable for chemical processes. An early example of work on iron catalyzed organic reaction was done by Kharasch and Fields in 1941, on the homocoupling of Grignard reagents.[63] The real start of the chemistry of Fe-catalyzed cross-coupling reactions was marked by the work of Kochi in 1970s.[64] The catalytic reactions between alkenyl halides and Grignard reagents were explored. Attention was made to the mechanistic investigations of the catalytic process. But the real advance in the iron-catalyzed cross-coupling reactions was made in 2000s starting with the work of Fürstner and Leither.[65] Their work on the Fe-catalyzed cross-coupling reactions of aryl halides with alkyl Grignard reagents was a starting point for the modern interest of the chemists in iron catalyzed cross-coupling reactions. Iron-catalysts are mostly employed in Kumada–Corriu–Tamao coupling, but less in other cross-coupling reactions.

1.2.3.1. Fe-catalyzed Kumada–Corriu–Tamao coupling

Whereas the chemistry of iron catalyzed Kumada–Corriu–Tamao coupling is well developed for a wide range of substrates, Alkyl-Aryl, Aryl-Alkyl and Alkyl-Alkyl coupling reactions are the most interesting and are discussed in details.

Cross-coupling of alkyl Grignard reagents with aryl electrophiles

Iron catalyst for cross-coupling of aryl electrophiles with alkyl Grignard reagents was shown by Pridgen and coworkers in 1989.[66] $Fe(acac)_3$ was shown to be an effective catalyst for the reaction between alkyl Grignard reagents and ortho-halobenzaldimines (Figure 24). The reaction didn't work without a catalyst; Pd- and Ni-catalysts were found not to be efficient.

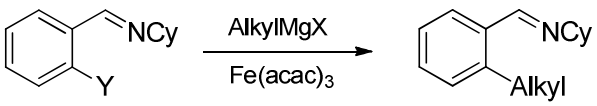

Figure 24. The first example of Fe-catalyzed cross-coupling of alkyl Grignard reagents with aryl halides.

A more general procedure was developed by Fürstner and Leither, using $Fe(acac)_3$ or [Fe(salen)Cl] as catalysts (Figure 25).[67] A wide range of aryl halides, triflates and tosylates

were used. Interestingly, aryl chlorides were the best substrates. Other halides suffer from the reduction of carbon halide bonds. A very good functional group tolerance was demonstrated, allowing the coupling of substrates containing esters, nitriles, ethers and heterocyclic groups.

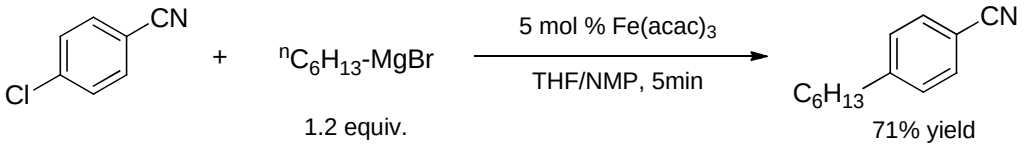

Figure 25. Cross-coupling of alkyl Grignard reagents with aryl electrophiles, catalyzed by $Fe(acac)_3$.

The efficiency of the developed method was confirmed by several total syntheses of natural products.[68]

Cross-coupling of aryl Grignard reagents with alkyl electrophiles

Nakamura and coworkers discovered the first efficient method for Fe-catalyzed cross-coupling between aryl Grignard reagents and alkyl halides (Figure 26).[9] The crucial factor was a slow addition of Grignard reagents to the solution of alkyl halides, catalyst and additive at -78^{0}C. Addition of an additive such as TMEDA is required for the high efficiency. Alkyl iodides, bromides, and even chlorides can be coupled. Some functional group tolerance was demonstrated.

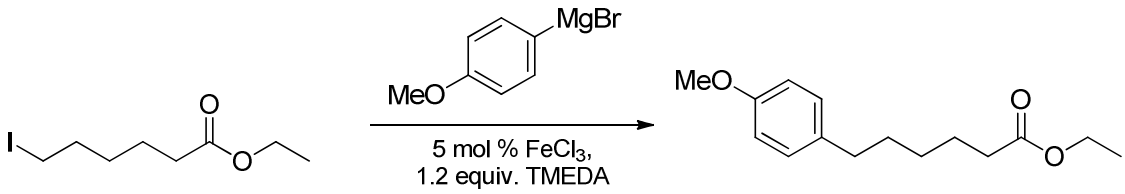

Figure 26. $FeCl_3$ catalyzed cross-coupling of alkyl halides with aryl Grignard regents.

Sometime later, one of the most important work on Fe-catalyzed cross-coupling of alkyl halides with aryl Grignard reagents was published by Fürstner and coworkers.[12] $[Li(tmeda)]_2[Fe(C_2H_4)_4]$ with a formal Fe^{-II} center was used as a catalyst. A large number of primary and secondary alkyl iodides, bromides and even some chlorides could be coupled (Figure 27). An excellent group tolerance was observed and products were separated with good to excellent yields.

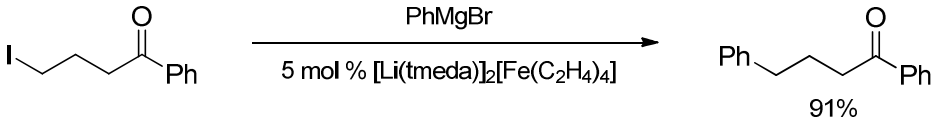

Figure 27. Fe-catalyzed cross-coupling of aryl Grignard reagents with alkyl halides.

Several further investigations have been done on Fe-catalyzed alkyl-aryl coupling.[10,69] One outstanding problem is the mechanism of these reactions.

Cross-coupling of alkyl Grignard reagents with alkyl electrophiles

A number of investigations were made towards Fe-catalyzed cross-coupling of alkyl Grignard reagents with alkyl electrophiles. Yet, the alkyl-alkyl Kumada coupling is still challenging. It was found that only substrates without β-hydrogen atoms, such as methyl-, neopentyl- or benzyl-derivatives can form the desired products. In all other cases the β-hydride elimination compounds are always the major products.

In the recent work of Chai and coworkers it, was shown that iron catalyzed sp^3-sp^3 cross-coupling reaction can be done in a presence of $Fe(OAc)_2$ and Xantphos ligand (Figure 28).[70] However the yields were generally low (<65%) and no functional group tolerance was achieved.

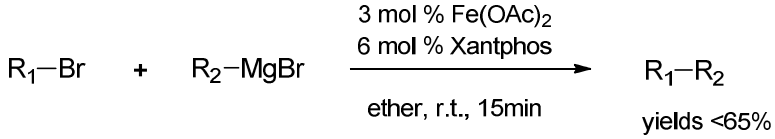

Figure 28. Fe-catalyzed cross-coupling of alkyl Grignard reagents with alkyl bromides.

1.2.3.2. Fe-catalyzed other cross-coupling reactions

Despite of the advances in the iron catalyzed Kumada–Corriu–Tamao coupling reactions, there were only a few reports on Fe-catalyzed coupling reaction using other nucleophiles. Recent reports on Fe-catalyzed Sonogashira, Negishi and Suzuki coupling show the potential of Fe catalysis.

Fe-catalyzed Sonogashira coupling

An example of Sonogashira coupling, catalyzed by Fe catalyst, was reported by the group of Bolm and coworkers in 2008 (Figure 29).[71] The reaction between aryl iodides and different alkynes can be catalyzed by $FeCl_3$ in conjunction with 2 equiv. of dmeda ligand. The

functional group tolerance and efficiency of this reaction were high. No alkyl halides were tested in this catalytic system. However, it was shown later that these reactions were most likely catalyzed by the Cu impurities.[72]

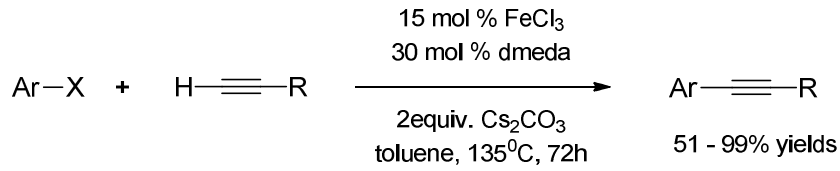

Figure 29. Fe-catalyzed Sonogashira coupling of aryl iodides.

Fe-catalyzed Negishi coupling

Nakamura and co-workers expanded their research work to iron catalyzed cross-coupling of diarylzinc reagents with alkyl halides (Figure 30).[73] The presence of magnesium salts (left in the solution of organozinc compound after transmetalation of Grignard reagents with zinc salts) was essential for the successful coupling. As organozinc compounds are less reactive than Grignard reagents, the group tolerance was good.

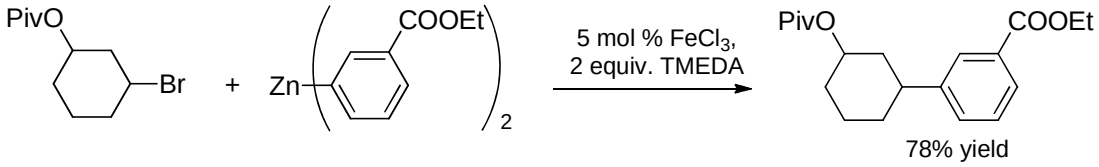

Figure 30. Fe-catalyzed Negishi coupling.

Fe-catalyzed Suzuki coupling

Another interesting application of iron catalysts is for cross-coupling of organoboron compounds. Pd-based complexes are the common catalysts for Suzuki coupling. Their reactivity is remarkable and very small percentage of Pd salts is enough to catalyze this cross-coupling reaction. It was shown that even small impurities of Pd in the glassware, stirrer bars and even in the iron salts can be an active catalyst.[74] Thus, a lot of precautions should be done in order to avoid the contamination of the reaction mixture with the source of palladium salts. Some of the reported Fe-catalyzed Suzuki couplings are found afterwards to be catalyzed by Pd impurities.

A Fe-catalyzed Suzuki coupling was presented by Nakamura in 2010 (Figure 31).[75] With catalytic amounts of an iron(II) chloride diphosphine complex and magnesium bromide, the

coupling between lithium arylborates and alkyl halides could be done with high yields and a good functional group tolerance.

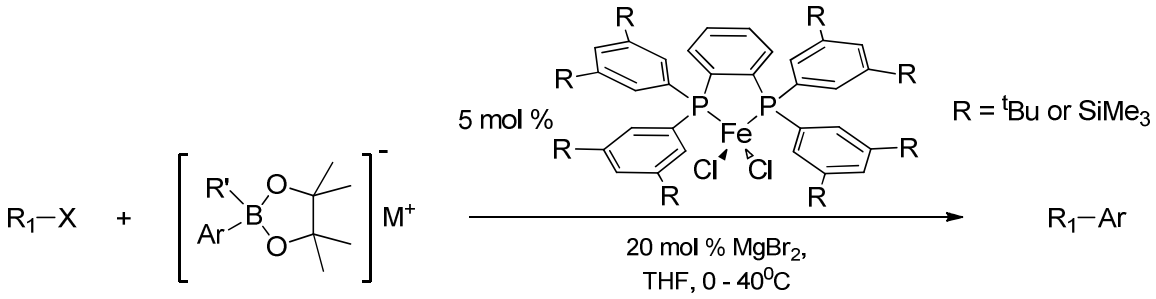

Figure 31. Fe-catalyzed Suzuki coupling reported by Nakamura.

1.2.4. Cobalt catalyzed cross-coupling reaction of alkyl electrophiles

Another popular transition metal for cross-coupling reactions is cobalt. The chemistry of cobalt-catalyzed cross-coupling reactions is not as well developed as palladium- or nickel-catalysis. During the last years, several interesting and important publications describing Co-catalyzed cross-coupling reactions were reported.

Co-catalyzed Kumada–Corriu–Tamao coupling

The chemistry of cobalt-catalyzed cross-coupling reactions started with the utilization of cobalt salts as catalysts for the reactions between Grignard reagents and aryl, alkenyl and alkyl halides. One of the first examples was described by Cahiez and Avedissian.[76] $Co(acac)_2$ was used as a catalyst for the reaction between vinyl halides and Grignard reagents in 1 :1 mixture of NMP : THF (Figure 32).

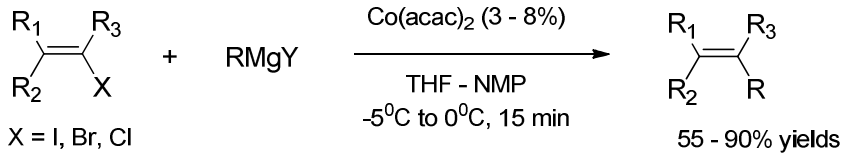

Figure 32. Co-catalyzed cross-coupling of vinyl halides with Grignard reagents.

The coupling of alkyl halides is also possible with Co-based catalysts. It was demonstrated in the work of Oshima and coworkers that $CoCl_2$(dppp) can catalyze the cross-coupling reaction between primary, secondary and tertiary alkyl halides with allyl Grignard reagents.[13] Even a very bulky alkyl halide represented in the Figure 33 can be successfully coupled with allyl Grignard reagent in a 73% yield.

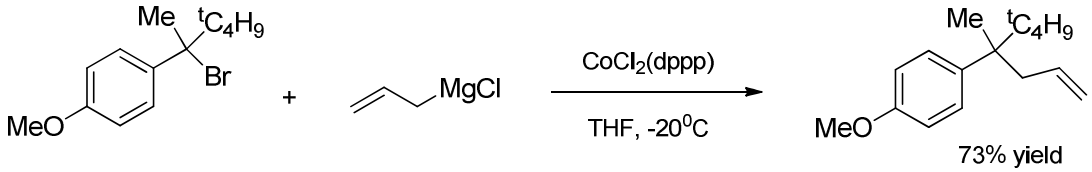

Figure 33. Co-catalyzed cross-coupling of alkyl halides with allyl Grignard reagents.

It was showed later that other types of Grignard reagents, such as benzyl, aryl, heteroaryl and vinyl Grignard reagents, could also be coupled to with alkyl halides, using a Co salt and a diamine ligand. Oshima and coworkers showed that this reaction could be performed in the presence of 5 mol% of $CoCl_2$ and 6 mol% of (R,R)-diamine (Figure 34).[15] A good functional group tolerance was shown.

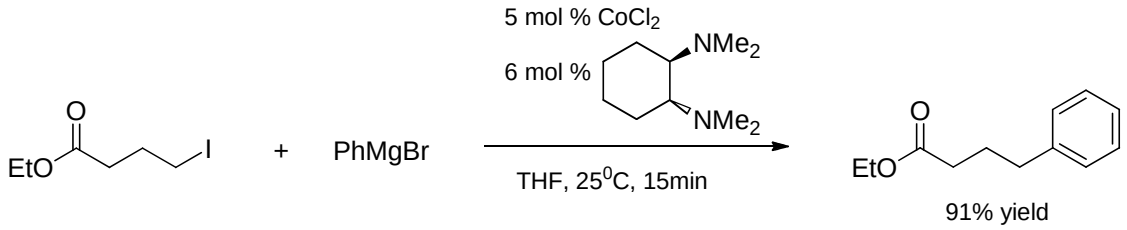

Figure 34. Co-catalyzed cross-coupling of alkyl halides with aryl Grignard reagents.

Co-catalyzed Negishi coupling

Knochel and coworkers showed in 1998 that Co-catalyzed Negishi coupling of alkyl Zn reagents with vinyl halides could be done with a $Co(acac)_2$ catalyst (Figure 35).[77] Retention of the double bond configuration was obtained.

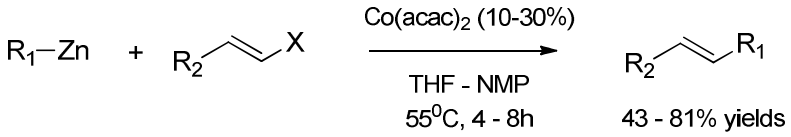

Figure 35. Co-catalyzed Negishi coupling of vinyl halides.

1.2.5. Copper catalyzed cross-coupling reaction of alkyl electrophiles

The first Cu-catalyzed cross-coupling reaction was discovered by Ullman in 1901.[78] He reported the synthesis of biaryls by heating of the aryl bromides and iodides in a presence of a stochiometric amount of copper (Figure 36). The harsh conditions in Ullman coupling result in modest to good yields of the reaction, but poor functional group tolerance. Certain

improvements, done from that time, permitted the use of Ullman coupling for the preparation of some substrates even in the industrial scale.[79]

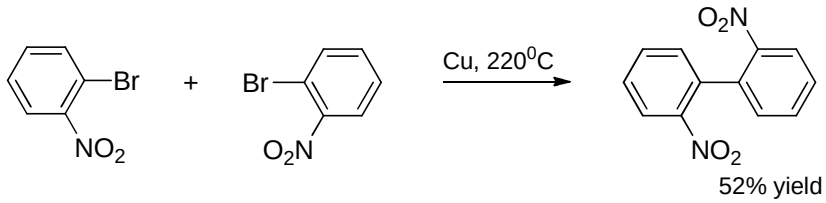

Figure 36. Cu-catalyzed Ullman coupling.

The first report of Kochi and coworkers about copper-catalyzed cross-coupling reactions between alkyl halides and Grignard reagents was done in 1972.[80] Their experiments showed that $CuCl_2$ and $CuBr_2$ are efficient catalysts for the reaction between EtMgBr and Et-Br. The main disadvantage of this research work was that most of the experiments were done between EtMgBr and Et-Br. In this case, homo-coupling of both starting materials as well as hetero-coupling between them give the same product n-butane. The yields, represented in this paper for the n-butane formation, can be confusing because it was not possible to prove if homo- or hetero-coupling was responsible for the product formation.

A comprehensive exploration of Cu-catalyzed cross-coupling reaction was done by Kambe and his coworkers.[81] One of the most interesting results, is the coupling between Grignard reagents and alkyl fluorides. Alkyl-fluoride bond is very strong and often very inert. It was shown in this work that $CuCl_2$ in conjunction with an excess of 1,3-butadiene was very efficient for the reaction between alkyl fluorides and alkyl or aryl Grignard reagents (Figure 37). Reactions were done at room temperature and 3 mol% of $CuCl_2$ was sufficient. Interestingly, these conditions can be employed for the coupling of alkyl bromides but not alkyl chlorides. The yields of only 3% were obtained for alkyl chlorides.

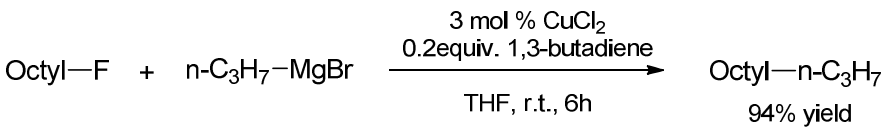

Figure 37. Cu-catalyzed cross-coupling of alkyl fluorides.

An improvement of this method was done by Kambe in 2007. It was found that a similar catalytic system could be used for cross-coupling of alkyl chlorides with alkyl or aryl Grignard reagents by a different additive.[82] The best results were obtained when 2 mol% of

$CuCl_2$ and 10 mol% of 1-phenyl-1-propyne (Figure 38). These conditions could be used for alkyl chlorides and alkyl fluorides and mesylates. Even the bulky ^{t}Bu-MgCl Grignard reagent could be successfully coupled. However, in both reports of Kambe, only a limited number of substrates were tested. And only simple and unfunctionalized substrates were used.

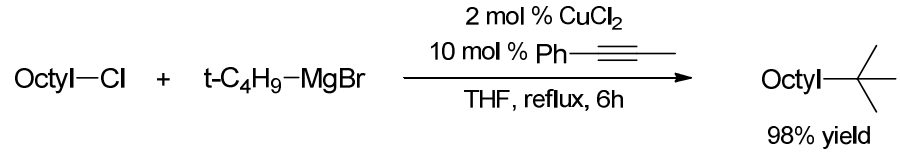

Figure 38. Cu-catalyzed cross-coupling of alkyl chlorides.

1.3. Metal-catalyzed C—H activation and functionalization

Selective transformation of unfunctionalized C—H bonds represents an attractive method of synthesis.[83] The selectivity between different C—H bonds is still a major problem. Most organic molecules contain a wide range of different C—H bonds. The strength and chemical activity of these bonds can be similar. The field of metal-catalyzed C—H functionalization is developing very rapidly and a lot of progress has been achieved.[84] However, the reactions are still not general and there is much room for improvement.

1.3.1. First progress in the metal-catalyzed C—H activation

Early work on metal-catalyzed C—H activation was concentrated on intramolecular C—H activation reactions. Special substrates and metallacycle formation were required. However, this approach has limitation for applications in synthesis. It was found that intermolecular C—H activation was possible and it occurred in several systems. However, the products were not stable and hard to detect.[85] This was the reason why attention was made to carefully choose the substrates, so that stable products from C—H activation could be isolated.

One of the seminar examples of metal mediated C—H activation was reported by Bergman in 1982.[86] Irradiation of an Ir-based complex in cyclohexane resulted in C—H activation and H_2 elimination (Figure 39). Similar results were obtained in benzene and neopentane solutions. The products were separated, purified and analyzed by NMR spectroscopy.

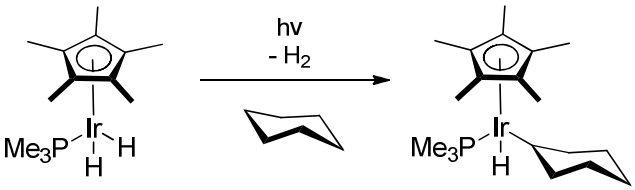

Figure 39. Bergman work on C—H activation of hydrocarbons.

This work made a big impulse for further investigations in the field of C—H activation reactions and the reports of many other groups followed this publication.

1.3.2. Selective functionalization of alkanes by transition-metal boryl complexes

Another very important work, is the work of Hartwig and coworkers, reported in 1997.[87] The most difficult substrates for the C—H activation – alkanes, were selectively borylated in high yields by transition-metal boryl complexes. Steric effects were used in this work for the desired selectivity. Only primary C—H bonds of the substrates were activated and converted to boron derivatives. The selectivity was remarkable in the presence of a large number of secondary and tertiary C—H bonds. The best results were obtained with tungsten complex under irradiation conditions (Figure 40).

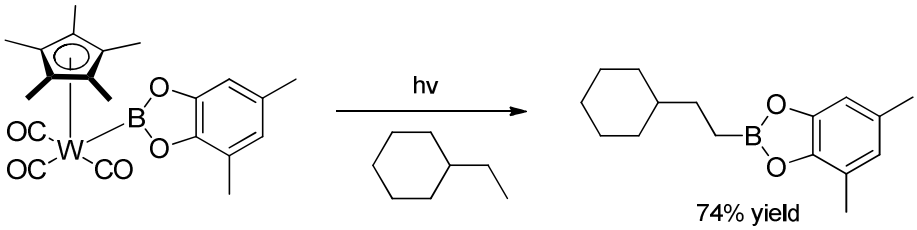

Figure 40. Selective borylation of alkanes, developed by Hartwig.

It was shown later by the same group that even catalytic reactions were possible.[88] A Re-complex with a similar ligand was used. 3 – 5 mol% of catalyst was enough to ensure good yields and a high selectivity on primary C—H bonds. A dimeric boron compound B_2pin_2 was used for the reaction (Figure 41).

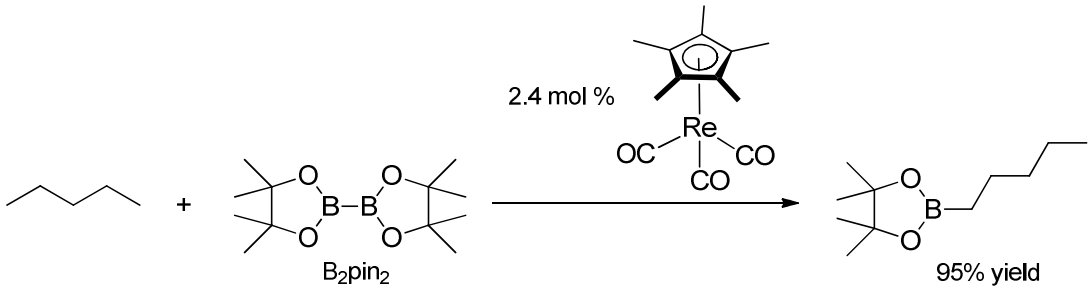

Figure 41. Catalytic borylation of alkanes.

1.3.3. Directing group assisted C—H activation

The work of Sanford is an interesting development in C—H functionalization.[89] As one of the main problems in this chemistry is selectivity, the use of directing groups was showed to be a powerful tool for the differentiation between various C—H bonds. The general idea of this method is represented in Figure 42. A palladium catalyst coordinates to the directing groups in the substrates. As formation of five- or six-member rings is favorable, an activation of C—H bond leading to a five- or six-member palladacycle occurs. After ligand exchange or functional group transfer from the oxidizing agent, reductive elimination leads to the formation of the desired product and the regeneration of the palladium complex.

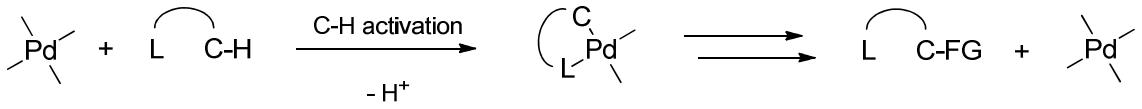

Figure 42. General scheme for the directing group C—H activation.

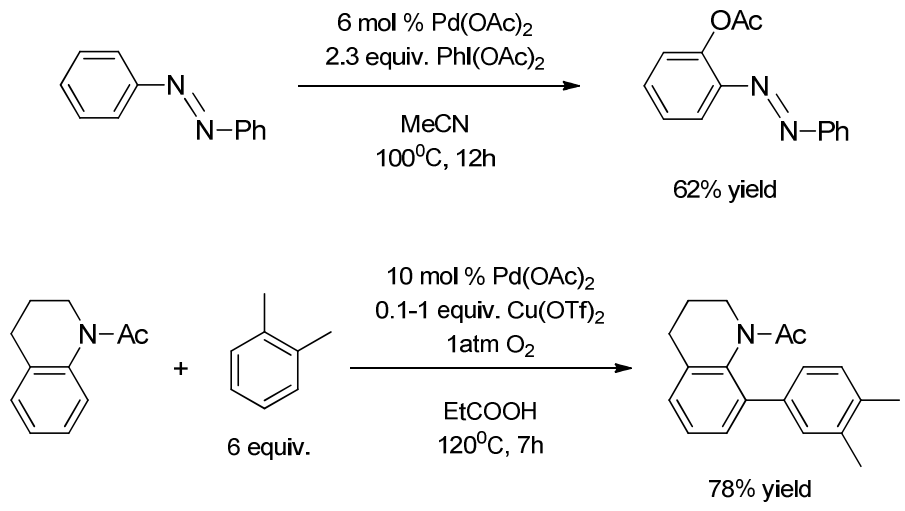

Figure 43. Directing group assisted C—H activation.

A range of functional groups can coordinate to palladium center and serve as directing groups. The transformation of the carbon-hydrogen bond to carbon-acetate bond was widely studied.[90] Oxidants, such as $PhI(OAc)_2$ and IOAc or even AcOH in a presence of oxygen, were successfully employed. Similar methods could be used for the formation of carbon-halide,[91] carbon tosylate,[92] and carbon-nitrogen bonds.[93] This method was also used for the formation of carbon-carbon bonds.[94] Some examples are represented in Figure 43.

1.3.4. Direct C—H functionalization of aromatic heterocycles

Daugulis and coworkers reported Cu-catalyzed direct C-H functionalization of aromatic heterocyclic compounds (Figure 44).[95] The method was based on the difference in the acidity of different C—H bonds. When a mild base is used, only relatively acidic C—H protons were deprotonated. Daugulis showed that with a catalytic amount of CuI and phenanthroline, a wide range of heterocyclic compounds can be selectively arylated. Despite of the elevated temperature used (120^0C for 12-24 hours), a good functional group tolerance was observed.

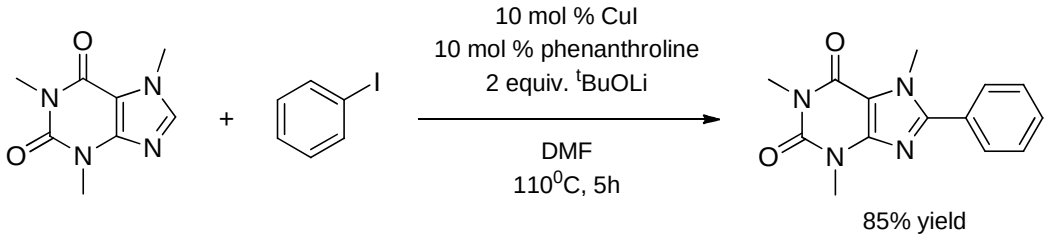

Figure 44. Direct C—H activation of aromatic heterocycles.

These selected examples highlighted the progress made in the field of C—H activation and functionalization reactions. However, most methods have limited scopes. Thus, further work is required for the generalization of the catalytic methods.

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Chapter 2

*Synthesis of a New Pincer Type $^{Me}N_2N$ Ligand and Formation of its Ni Complexes**

*The results presented in this chapter were published in:

Csok, Z.; Vechorkin, O.; Harkins, S. B.; Scopelliti, R.; Hu, X. L. *J. Am. Chem. Soc.* **2008**, *130*, 8156-8157.

Vechorkin, O.; Csok, Z.; Scopelliti, R.; Hu, X. L. *Chem.-Eur. J.* **2009**, *15*, 3889-3899.

2.1. Introduction to the chemistry of pincer ligands

2.1.1. Pincer ligands

The chemistry of metal-catalyzed cross-coupling reactions and C-H activation became a very powerful tool for organic synthesis.[1] The demand in efficient and selective catalysts grew constantly, provoking intensive research towards the development of new catalysts with improved properties. The ligand of the catalyst is one of the most important constituents, responsible for the stability and reactivity of the designed catalytic system.[2] Thus, the design and elaboration of ligands represents an important objective in catalysis development.

Among a wide range of ligand types available for complexation with transition metals, pincer-type ligands are one of the most popular and most used in organometallic chemistry.[3] The general structure of the complexes with pincer ligands is represented in Figure 1. The molecule of these complexes consists of two fused metalocycles. The structure of a pincer complex is described by the (EYE) architecture. In most of the cases the groups, like NR_2, PR_2, SR, and SeR are used as E groups. Most pincer ligands have two same E groups, but unsymmetrical structures with different E groups are also known.[4] There is a less variety for the Y groups; carbon or nitrogen atoms are used in most cases.

Figure 1. General structure of pincer complexes.

The tridentate nature of pincer ligand assumes the stability of the corresponding metal complexes. A high stability of the complexes results in relatively easy synthetic procedures and facile purification and separation. The stability of the pincer complexes is also an important advantage in catalysis, because pincer complexes can be heated, exposed to aggressive reagents such as acids, bases and oxidants without decomposition. High turnover numbers might be obtained. Another important feature of pincer ligands is the facile possibility of fine tuning on the ligand properties. Different substituent on the atoms and on the backbone of the ligand can change considerably the reactivity of the complexes. The use of well-defined pincer complexes enables the investigation of the details of reaction mechanism and the detection and isolation of catalytic intermediates.

2.1.2. The pioneer works in the area of pincer ligands

The first examples of transition metal complexes with pincer ligands were reported by the group of Shaw in the middle of 1970s.[5] The complexes of (PCP) pincer ligand with Ni-, Pd-, Pt- and other metals were synthesized and characterized. These complexes (Figure 2) were easily synthesized from free ligand and the corresponding metal salts.

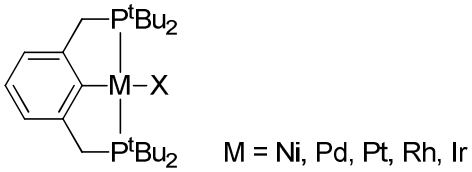


Figure 2. Complexes with pincer ligands, synthesized by Shaw and coworkers.

Several years later van Koten and coworkers reported the synthesis of another (NCN) pincer ligand and its palladium and platinum complexes.[6] The lithium salt of the ligand was used as the precursor for the synthesis of Pd- and Pt-complexes (Figure 3). The structure of the complexes was confirmed by X-ray analysis.

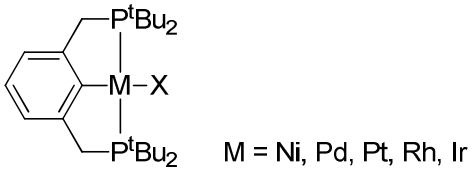


Figure 3. Van Koten synthesis of Pd- and Pt-complexes with (NCN) pincer ligand.

2.1.3. Ni pincer complexes with (PNP) pincer ligands

A lot of other pincer type ligands were developed since the first reports of Shaw and van Koten. The syntheses of pincer complexes with almost all transition metals were reported. The pincer complexes of Pd, Pt, Ni and other metals are widely used in catalytic processes.[3]

Several examples of nickel complexes with pincer ligands are described below.

Liang and coworkers synthesized a (PNP) pincer ligand and its Ni complex.[7] This complex reacted cleanly with aryl and alkyl Grignard reagents to give corresponding alkyl or aryl derivatives (Figure 4). This complex was tested for the cross coupling reactions between alkyl or aryl Grignard reagents and aryl halides. Even though good yields were observed in the reactions with aryl Grignard reagents, low yields were obtained for the alkyl Grignard reagents.

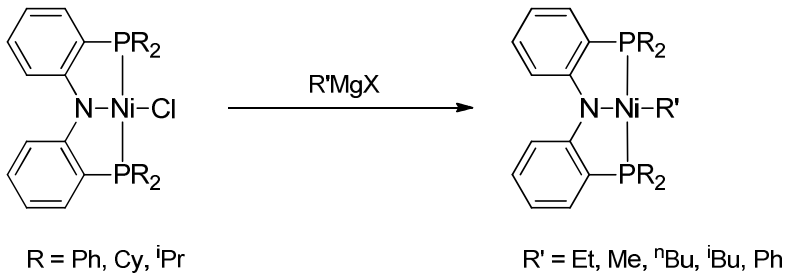


Figure 4. Ni-complex of (PNP) pincer ligand, reported by Liang.

Another synthesis of the Ni PNP complex was reported by Ozerov and coworkers (Figure 5).[8] Et_3N was able to deprotonate amide hydrogen, and it was used to synthesize the Ni complex. Reduction with $NaBH_4$ allowed the synthesis of hydride complex which can be transformed back to the chloride complex by the reaction with $CHCl_3$.

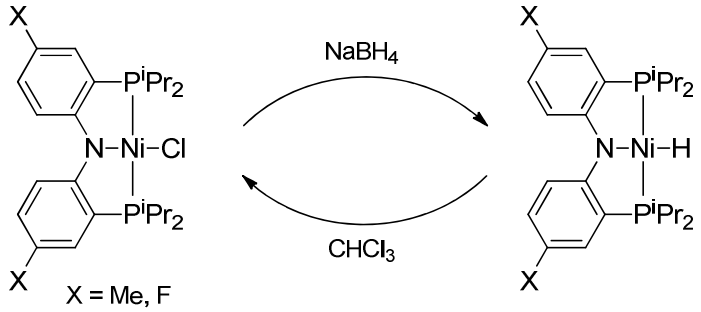


Figure 5. Ni-complex of (PNP) pincer ligand, reported by Ozerov.

2.1.4. A new (N_2N) pincer ligand

We set out to develop the coordination chemistry of a new pincer-type amido bis(amine) ligand $^{Me}N_2N$ (Figure 6). This is inspired by the fascinating chemistry that has been unfolded lately on metal complexes of analogous amido or pyridyl bis(phosphine) ligands (NP_2). The NP_2 ligands combine structural rigidity and electronic flexibility, and stabilize nucleophilic and electron-rich late metal centers. This leads to a broad range of applications in N_2,[9] C-H,[10] and N-H[11] activation, hydrogenation, and C-C bond forming reactions.[7,12] Replacing two phosphine donors with amine donors in N_2N significantly increases the "hardness" of the ligand and should stabilize metals in higher oxidation states. A few related cyclometallated bis(amine) and amido bis(quinoline) ligands are known and show interesting reactivities.[13,14] However, the chemistry of late transition metal complexes of pincer amide/amine ligands remains to be explored. This chapter describes the synthesis of a new pincer type $^{Me}N_2N$ ligand and its Ni complexes.

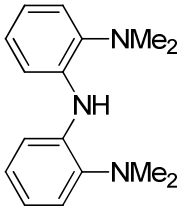


Figure 6. A new (N_2N) pincer ligand.

2.2. The synthesis of (N_2N) pincer ligand and its Ni complexes

2.2.1. Ligand synthesis

The protonated form of ligand $^{Me}N_2N$ is accessible through a Pd-catalyzed C-N coupling[15] of 2-amino-N,N-dimethylaniline with 2-bromo-N,N-dimethylaniline. These two compounds can be synthesized from the commercially available starting materials according to Figure 7.

1-fluoro-2-nitrobenzene reacted with a 40% aqueous solution of $HNMe_2$ in DMSO in the presence of potassium carbonate. This reaction resulted in the formation of 2-nitro-N,N-dimethylaniline in a quantitative yield. The product could be used for the next step without purification. The hydrogenation of the nitro-group with hydrogen gas in the presence of a Pd/C catalyst proceeded at room temperature, resulting in the formation of 2-amino-N,N-dimethylaniline. This colorless liquid is air-sensitive and becomes immediately black on contact with oxygen. Vacuum distillation is an efficient method for the purification of 2-amino-N,N-dimethylaniline. The resulting product should be stored and handled under inert atmosphere.

2-bromo-N,N-dimethylaniline could be obtained by a one step synthesis from the commercially available 2-bromoaniline. The methylation of the amino-group could be done with dimethyl sulfate. After 3 cycles of addition of 1.2 equiv. of Me_2SO_4, the desired product was obtained in a high yield. Purification by vacuum distillation gave a colorless liquid, which could be used for the next step of the synthesis.

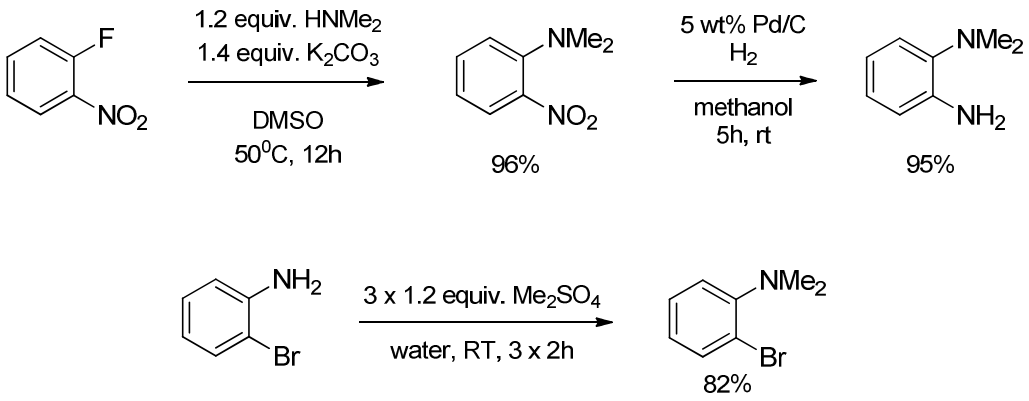


Figure 7. The synthesis of 2-amino-N,N-dimethylaniline and 2-bromo-N,N-dimethylaniline.

The C-N coupling between 2-amino-N,N-dimethylaniline and 2-bromo-N,N-dimethylaniline could be done with a Pd^0 catalyst and dppf. This reaction required heating at 100^0C and NaO^{t}Bu. After separation of the resulting NaBr and palladium salts, the product was obtained as a black solid. A vacuum distillation resulted in the formation of a slightly yellow solid (Figure 8).

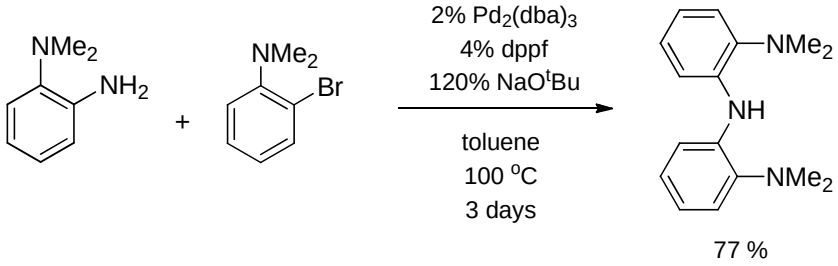


Figure 8. Synthesis of bis[(2-dimethylamino)phenyl]amine by Pd-catalyzed C-N coupling.

2.2.2. Synthesis of the Ni complex

Lithiation of $^{Me}N_2NH$ with n-Bu-Li produced [($^{Me}N_2N$)Li]$_2$ (**2**) as a white solid (Figure 9). The dimeric structure of **2** was first inferred by the presence of two methyl singlets corresponding to the diastereotopic methyl groups of $^{Me}N_2N$ in its ^{1}H-NMR spectrum. The structure was confirmed by an X-ray crystallographic analysis. Similar structure was found previously for the bis(quinolinyl)amide complex [(BQA)Li]$_2$.[13]

The Ni(II) complex [($^{Me}N_2N$)Ni-Cl] (**1**) could be obtained by the reaction of **2** with Ni(dme)Cl$_2$ in THF solution overnight. After the reaction was finished, the solvent was switched to toluene and LiCl was removed by filtration through celite. An addition of pentane to a concentrated toluene solution of [($^{Me}N_2N$)Ni-Cl] resulted in the formation of brown crystals. The complex is moisture sensitive and it changes color to green after exposure to air.

The monomeric structure of **1** was indicated by the presence of only one singlet in the ^{1}H-NMR spectrum for the methyl groups of $^{Me}N_2N$, and was confirmed by an X-ray single-crystal diffraction study.

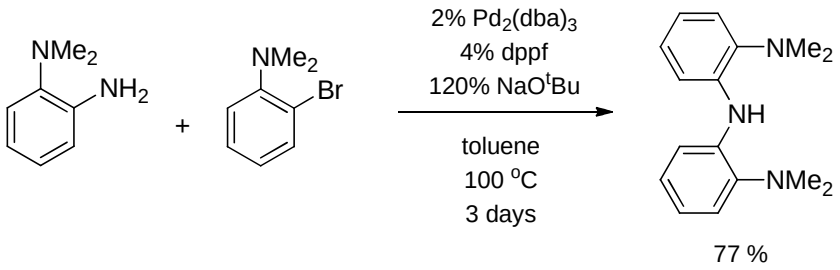


Figure 9. Lithiation of the ligand and the synthesis of the [($^{Me}N_2N$)NiCl] complex.

2.2.3. Synthesis of the alkyl and aryl derivatives

Reactions of **1** with alkyl and aryl Grignard reagents yielded the corresponding [($^{Me}N_2N$)Ni-R] complexes (R = Me (**3**), Et (**4**), and Ph (**5**)) (Figure 10). Alkyl and aryl Grignard reagents are very reactive compounds and cooling to -60^{0}C was required for the reaction of these reagents with **1**. After warming up to room temperature, and subsequent purification, the [($^{Me}N_2N$)Ni-R] species were isolated as orange or red solids. In some cases the formation of up to 10% of [($^{Me}N_2N$)Mg(THF)-Cl] was observed during the reactions.

These [($^{Me}N_2N$)Ni-R] complexes are stable compounds under an inert atmosphere, even for **4** which contains β-hydrogens.

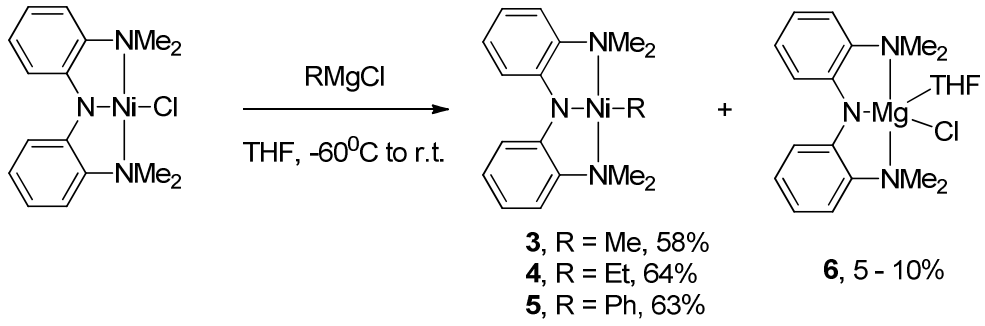


Figure 10. Reaction of the [($^{Me}N_2N$)NiCl] complex with alkyl and aryl Grignard reagents.

An examination of the thermal stability of nickel alkyl complexes **3** and **4** was done. Under an inert atmosphere and when dissolved in benzene, **3** didn't undergo decomposition even when heated at 120^{0}C for days. Similarly, **4** was stable up to 80^{0}C; when heated at 100^{0}C in benzene, it decomposed to form insoluble solids. The stability of **4** against β-H elimination at

80^0C is noteworthy. Similar stability of Ni^{II} alkyl species was reported by Liang et al. on isoelectronic Ni-PNP complexes.[7]

2.2.4. Salt metathesis reactions of [($^{Me}N_2N$)NiCl]

Salt metathesis reaction of **1** with AgOTf produced the corresponding Ni^{II} triflate (**7**) complex (Figure 11). The reaction proceeded smoothly at room temperature and only filtration of AgCl was necessary for the separation of the product. [($^{Me}N_2N$)Ni-OAc] (**10**) could be obtained in a similar way. However, 10 equiv. of NaOAc was necessary to ensure a 100% conversion. Reaction of **1** with 1 equiv. of NaOMe in THF led to the formation of the violet Ni^{II} methoxide complex **9**.

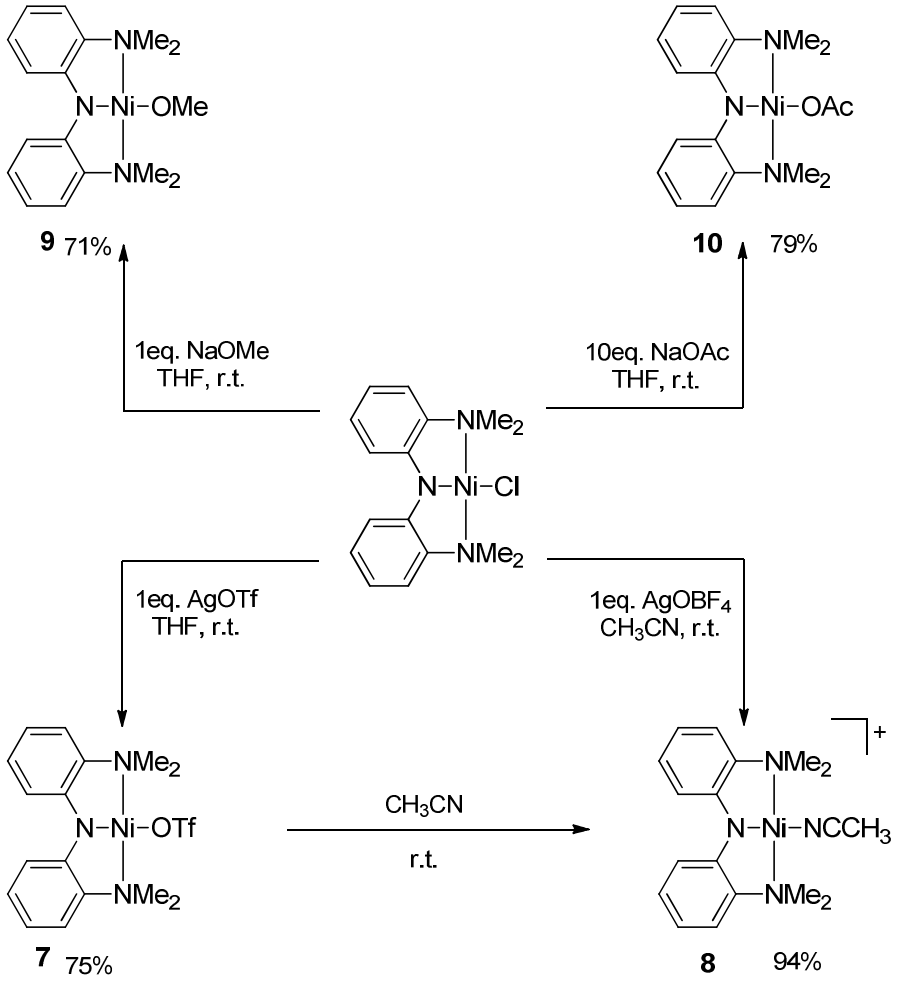


Figure 11. Salt metathesis reactions of [($^{Me}N_2N$)NiCl].

Abstraction of the chloride ligand in **1** by $AgBF_4$ in CH_3CN gave the cationic CH_3CN complex with BF_4 as the counter anion (**8•BF$_4$**); alternatively, dissolution of **7** in CH_3CN

gave the same cation with triflate as the counter anion (Figure 11). The latter reaction suggests that the triflate ligand in **7** is labile.

The NMR spectra of **7** - **10** are consistent with the structures determined by X-ray analysis. An effective C_{2v} symmetry was observed for the protons of the $^{Me}N_2N$ ligand, suggesting a fast rotation of the Ni-O bond in **7**, **9**, and **10**. The Lewis acidity of a metal center can be measured by how tightly it binds to a Lewis base, e.g., crotonaldehyde or CH_3CN.[16,17] Previous studies employed CH_3CN to probe the Lewis acidity of group 10 metal pincer complexes. To better compare the Lewis acidity of [($^{Me}N_2N$)Ni^{II}] with them, we chose CH_3CN as well. The magnitude of the downfield shift for the methyl protons of the coordinated CH_3CN is proportional to the Lewis acidity of the complex. The ^1H signal for CH_3CN in **8** was observed at 2.60 ppm in $CDCl_3$, 0.50 ppm higher than free CH_3CN. The [($^{Me}N_2N$)Ni^{II}] cation thus has a similar Lewis acidity as the [(PNP)Ni^{II}] cation (δ (H) = 2.69 ppm for CH_3CN),[18] but is more Lewis acidic than 2,6-bis(2-oxazolinyl)phenyl Ni^{II} and [(POCOP)Ni^{II}] complexes (δ (H) = 2.4 and 2.2 ppm for CH_3CN, respectively).[17,19]

2.3. Structures of the complexes in the solid state

The solid-state structures of the complexes were determined by X-ray crystallography (Figures 12-18). The key structural parameters for these complexes are summarized in Tables 1 and 2.

The coordination geometry of Ni^{II} is approximately square-planar in all Ni complexes. The pincer N_2N ligand binds to Ni in the expected *mer*-fashion, and the fourth coordination site is occupied by an additional donor. The two phenyl rings are slightly deviated from co-planar, with an angle of 19.04 (**1**), 21.06 (**4**), 0.35 (**5**), 7.51 (**7**), 16.95 (**8**), 25.67 (**10**), respectively. The amide nitrogen is sp^2 hybridized, as the sums of the three bond angles around it is close to 360^0. The Ni-N(amide) distance is about 1.83 Å in **1**, **7**, **8**, and **10** but increases to 1.89 Å in **4** and **5**. This is consistent with a high trans-influence of alkyl and aryl ligands.[2] The Ni-N(amide) bonds are always ca. 0.1 Å shorter than the corresponding Ni-N(amine) bonds, suggesting some degree of π-donation from the amide lone pair.

Table 1. Selected bond distances for [($^{Me}N_2N$)Ni^{II}] complexes.[a]

Complex	Ni-N(amide)	Ni-N(amine)$_{av.}$	Ni-X[b]
[($^{Me}N_2N$)Ni-Cl][c]	1.835(2)	1.956(2)	2.2029(7)
[($^{Me}N_2N$)Ni-Et]	1.8907(18)	1.976(2)	1.959(2)
[($^{Me}N_2N$)Ni-Ph]	1.888(11)	1.969(15)	1.886(15)
[($^{Me}N_2N$)Ni-OC(O)CH_3][c]	1.831(3)	1.957(3)	1.890(3)
[($^{Me}N_2N$)Ni-OTf]	1.830(2)	1.9357(17)	1.946(2)
[($^{Me}N_2N$)Ni-NCCH_3](BF_4)[c]	1.825(5)	1.944(5)	1.875(6)

[a] Bond distances are in Å. [b]X is the fourth ligand on Ni besides the tridentate N_2N chelate; [c]Average of two independent molecules in the asymmetric unit.

Table 2. Selected bond angles for [($^{Me}N_2N$)Ni^{II}] complexes.[a]

Complex	N(amine)-Ni-N(amide)$_{av.}$	N(amine)-Ni-X$_{av.}$[b]	C-N(amide)-C	Ni-N(amide)-C$_{av.}$
[($^{Me}N_2N$)Ni-Cl][c]	86.26(8)	94.04(6)	127.2(2)	116.12(16)
[($^{Me}N_2N$)Ni-Et]	84.47(8)	95.51(10)	127.93(19)	113.93(17)
[($^{Me}N_2N$)Ni-Ph]	86.56(6)	93.60(6)	129.66(5)	115.17(8)
[($^{Me}N_2N$)Ni-OAc][c]	85.63(13)	93.27(18)	127.6(3)	116.1(2)
[($^{Me}N_2N$)Ni-OTf]	87.33(5)	92.65(5)	128.8(3)	115.22(13)
[($^{Me}N_2N$)Ni(AN)](BF_4)[c]	86.8(2)	93.3(2)	128.8(5)	115.5(4)

[a] Bond angles are in degree. [b] X is the fourth ligand on Ni besides the tridentate N_2N chelate; [c]Average of two independent molecules in the asymmetric unit.

Replacement of an anionic fourth ligand by a neutral donor (e.g., from **7** to **8**) causes no appreciable structural change in the [($^{Me}N_2N$)Ni^{II}] fragment. The acetate ligand in **10** is

coordinated in an η^1 fashion, a common coordination mode for mononuclear Ni^{II} acetate complexes.[20] The Ni-O distance is slightly shorter in **10** (1.890(3) Å) than in **7** (1.946(2) Å).

The overall structure of these [($^{Me}N_2N$)Ni^{II}] complexes is similar to that of their counterparts supported by anionic NCN and PNP ligands. For the Ni^{II}-Cl complexes, the Ni-Cl distances are comparable in **1**, [(N($SiMe_2CH_2PPh_2$)$_2$)Ni-Cl] (**11**, 2.1703(6) Å),[21] [(N(o-$C_6H_4PPh_2$)$_2$)Ni-Cl] (**12**, 2.1636(11) Å),[7] and {2,6-bis[(dimethylamino)methyl)]phenyl}Ni-Cl (**13**, 2.2388(5) Å).[22] The Ni-N(amine) distances in **1** and **13** are also close (1.9909(13) Å in the latter); however, the Ni-N(amide) bond in **1** is slightly shorter than in **11** and **12** (1.924(2) and 1.895(3) Å, respectively). For the Ni^{II}-alkyl complexes, the Ni-C distance in **4** is nearly identical to that in [(N(o-$C_6H_4PPh_2$)$_2$)Ni-Me] (**14**, 1.967(11) Å) and [(N(o-$C_6H_4PPh_2$)$_2$)Ni-*n*Bu] (**15**, 1.971(3) Å), while the Ni-N(amide) distance is again shorter in **4** than in **14** and **15** (1.967(8) and 1.966(2) Å, respectively).[7]

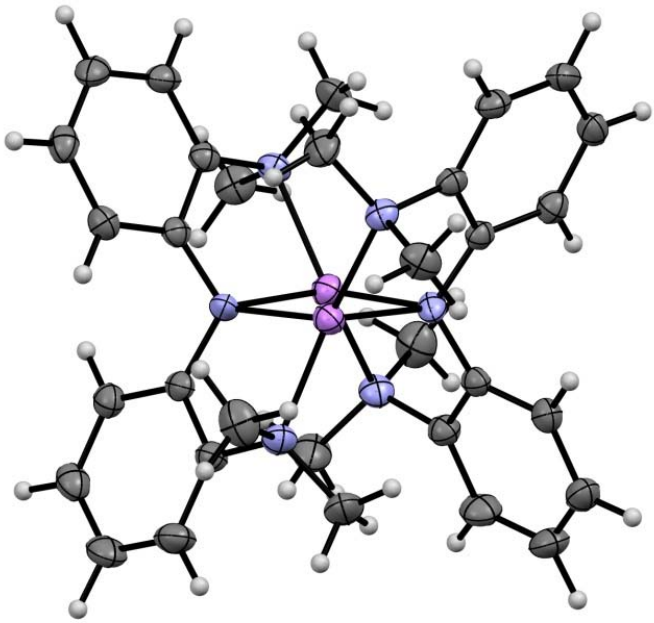


Figure 12. Crystal structure of *[($^{Me}N_2N$)Li]$_2$* (**2**).

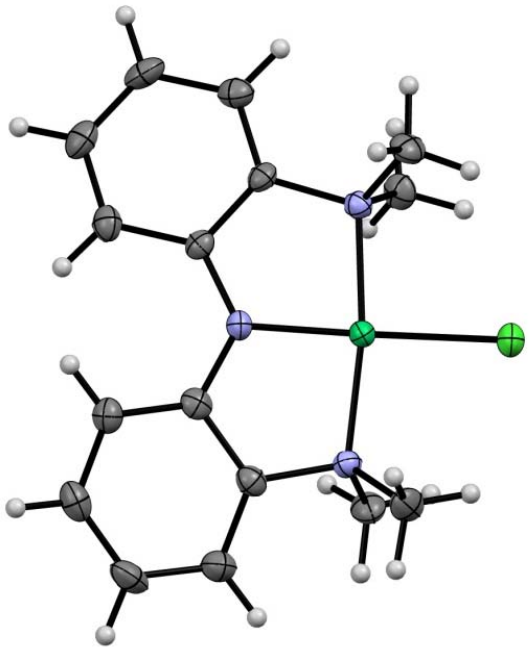


Figure 13. Crystal structure of *[($^{Me}N_2N$)NiCl]* (**1**).

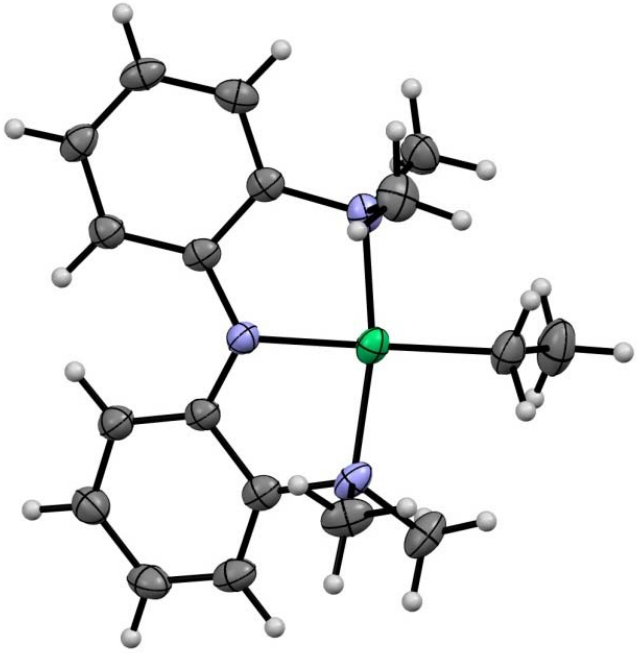


Figure 14. Crystal structure of *[($^{Me}N_2N$)NiEt]* (**4**).

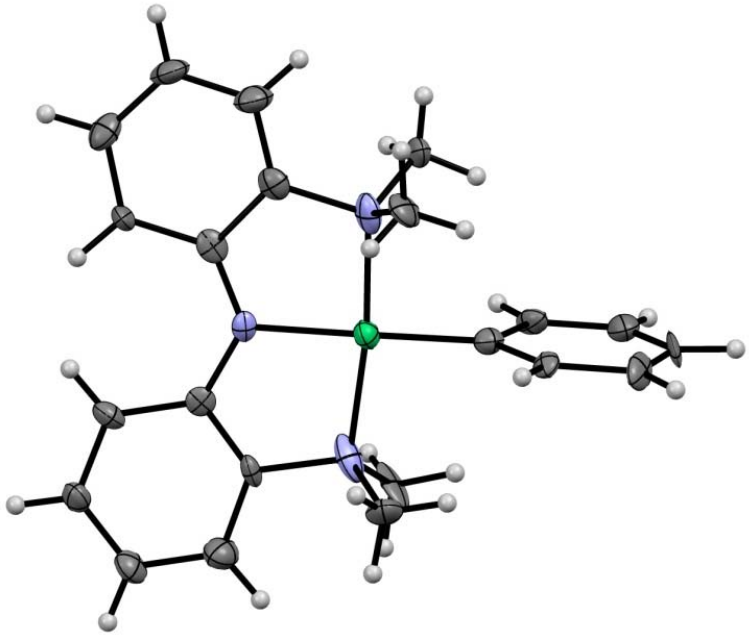


Figure 15. Crystal structure of *[($^{Me}N_2N$)NiPh]* (**5**).

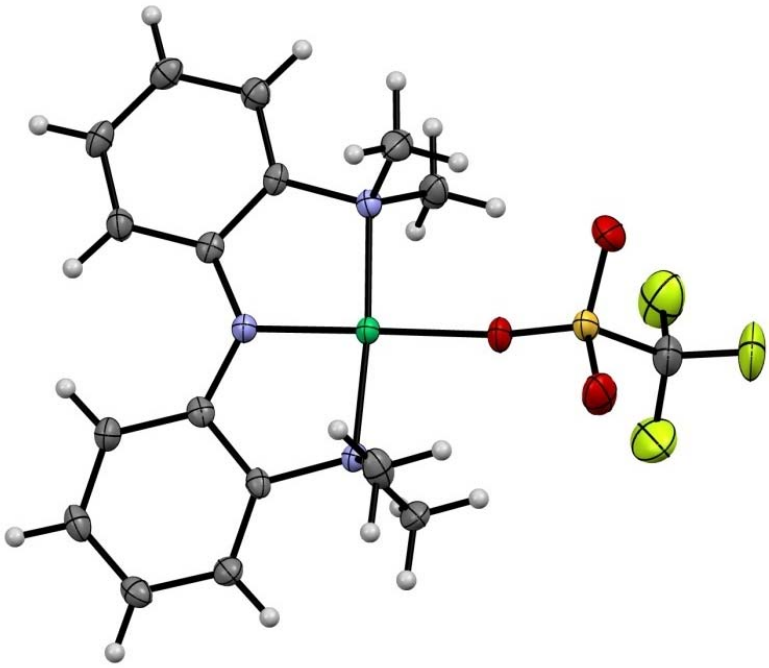


Figure 16. Crystal structure of *[($^{Me}N_2N$)NiOTf]* (**7**).

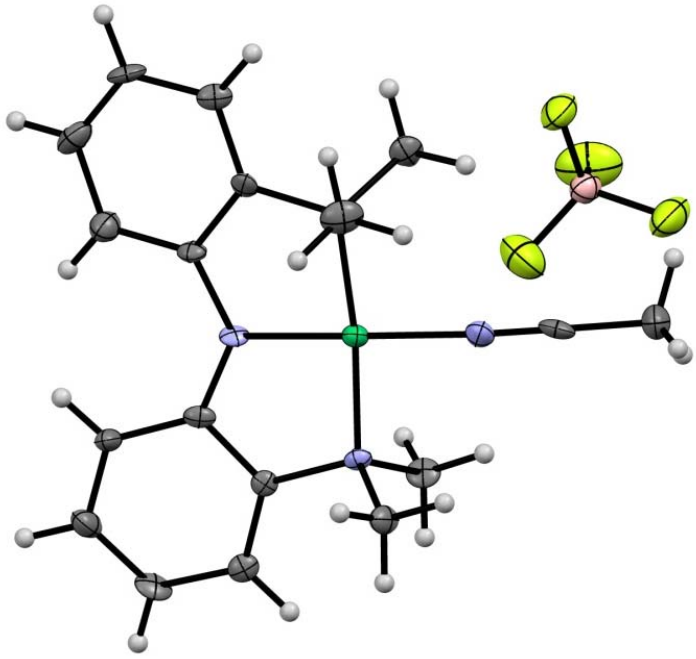


Figure 17. Crystal structure of *for [($^{Me}N_2N$)Ni-NCCH$_3$](BF$_4$)* (***8•BF$_4$***).

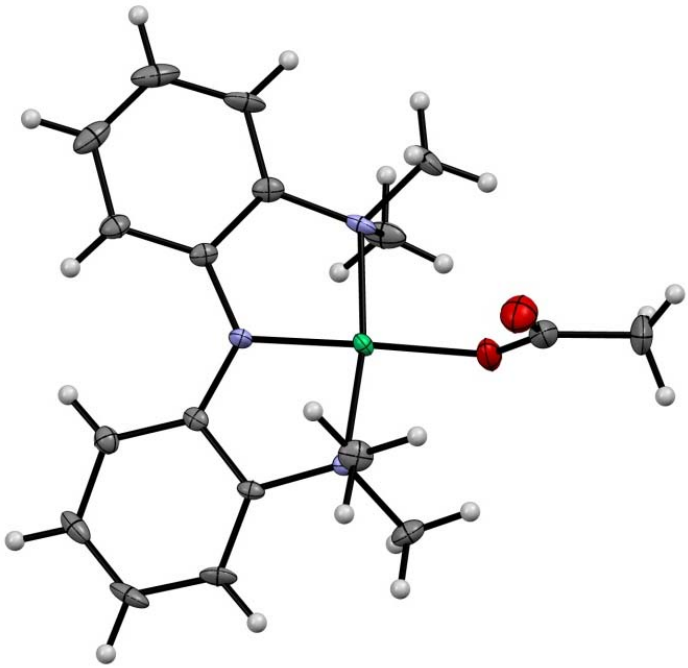


Figure 18. Crystal structure of *[($^{Me}N_2N$)NiOAc]* (**10**).

2.4. Conclusions

The synthesis of the pincer $^{Me}N_2N$ ligand and its Ni complexes was presented in this chapter. It was shown that the ligand could be prepared in a fast and simple way. All intermediate products were obtained with high yields and in pure form. Vacuum distillation was an ideal purification method for the organic precursors. The $^{Me}N_2N$ ligand was used to prepare the [($^{Me}N_2N$)Ni-Cl] complex, which was a starting material for the synthesis of a wide range of [($^{Me}N_2N$)Ni-X] derivatives. Single crystals were obtained for most of the compounds and their structures were confirmed by X-ray analysis. The synthesis of [($^{Me}N_2N$)Ni-Cl] complex could be done in multi gram scales and batches of 20 grams were prepared, highlighting the efficiency of the synthetic method.

2.5. Experimental part

Chemicals and Reagents

All manipulations with [($^{Me}N_2N$)Ni-X] complexes and [($^{Me}N_2N$)Li]$_2$ salt were carried out under an inert N_2(g) atmosphere using standard Schlenk or glovebox techniques. Solvents were purified using a two-column solid-state purification system (Innovative Technology, NJ, USA) and transferred to the glove box without exposure to air. Deuterated solvents were purchased from Cambridge Isotope Laboratories, Inc., and were degassed and stored over activated 3 Å molecular sieves. All other reagents were purchased from commercial sources and were degassed by standard freeze-pump-thaw procedures prior to use.

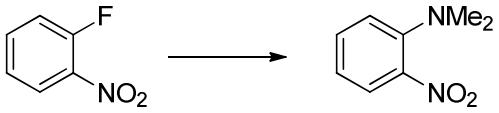
Physical methods

The ^{1}H and ^{13}C NMR spectra were recorded at 293 K on a Bruker Avance 400 spectrometer. ^{1}H NMR chemical shifts were referenced to residual solvent as determined relative to Me_4Si (δ = 0 ppm). The $^{13}C\{^1H\}$ chemical shifts were reported in ppm relative to the carbon resonance of $CDCl_3$ (77.00 ppm) or C_6D_6 (128.02 ppm). Mass spectrometic data were obtained on a Shimadzu Axima CFRplus MALDI-TOF spectrometer at the EPFL MS Facility, using 2,5-dihydroxybenzoic acid as matrix. Elemental analyses were performed on a Carlo Erba EA 1110 CHN instrument at EPFL. GC measurement was conducted on a Perkin-Elmer Clarus 400 GC with a FID detector. X-ray diffraction studies were carried out in the EPFL Crystallographic Facility. Data collections were performed at 140(2) K on a four-circle

kappa goniometer equipped with an Oxford Diffraction KM4 Sapphire CCD. Data were reduced by CrysAlis PRO.[23] The absorption correction was applied using a semiempirical method.[24] The SHELXTL program was used for structure solution, refinement, and geometrical calculation.[25]

Synthesis of substrates

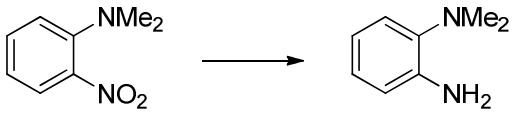
2-nitro-N,N-dimethylaniline



1-fluoro-2-nitrobenzene (2 g, 14 mmol) was dissolved in 20 mL of DMSO and K_2CO_3 (2.2 g, 16 mmol) was added. 2 mL of the solution of Me_2NH (40% in water) was added slowly under stirring to the resulted mixture. After the addition was finished, the reaction was heated at 50^0C overnight. Then the reaction was cooled to r.t. and 50 mL of water was added. The product was extracted with ethyl acetate (3 times, 30 mL each) and the organic phase was washed with brine (2 times, 30 mL each). The organic phase was then dried over Na_2SO_4, filtered and the solvent was evaporated under vacuum to give the product. Yield: 2.23 g (96 %).

^{1}H NMR (400.13 MHz, $CDCl_3$): 7.74 (dd, J = 8.2, 1.6 Hz, 1H), 7.38 (td, J = 7.7, 1.6 Hz, 1H), 7.01 (d, J = 8.2 Hz, 1H), 6.80 (t, 7.7 Hz, 1H), 2.87 (s, 6H).

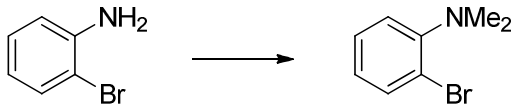
2-amino-N,N-dimethylaniline



2-nitro-N,N-dimethylaniline (2 g, 12 mmol) was dissolved in methanol and 100 mg of Pd/C (5% of Pd) was added. The reaction flask was degassed and flushed with hydrogen twice and stirred under hydrogen at r.t. After the orange color of the starting material disappeared, the reaction was stirred 30 minutes further. The Pd catalyst was filtered off, and the solvent was removed under a reduced pressure. The product was purified by vacuum distillation and was transferred to a glove box without exposure to oxygen. In case of contact to oxygen, the product becomes immediately black, but it can be purified again by distillation. Yield: 1.55 g (95 %).

^{1}H NMR (400.13 MHz, $CDCl_3$): 7.05 (d, J = 7.8 Hz, 1H), 6.95 (t, J = 7.6 Hz, 1H), 6.77 (m, 2H), 4.03 (br, 2H), 2.70 (s, 6H).

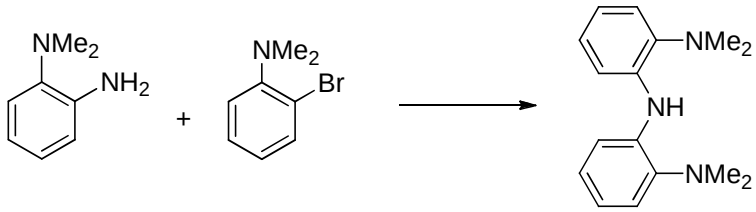
2-bromo-N,N-dimethylaniline



A procedure described in *"Journal of the Chemical Society, Dalton Transactions: Inorganic Chemistry* **1979** (11), 1718-24" was used without any modification. In the end the product was purified by vacuum distillation and was transferred to glove box without exposure to oxygen. Yield: 82 %.[26]

^{1}H NMR (400.13 MHz, $CDCl_3$): 7.56 (dd, J = 7.9, 1.5 Hz, 1H), 7.26 (td, J = 7.6, 1.5 Hz, 1H), 7.09 (dd, J = 7.9, 1.5 Hz, 1H), 6.89 (td, 7.6, 1.5 Hz, 1H), 2.81 (s, 6H).

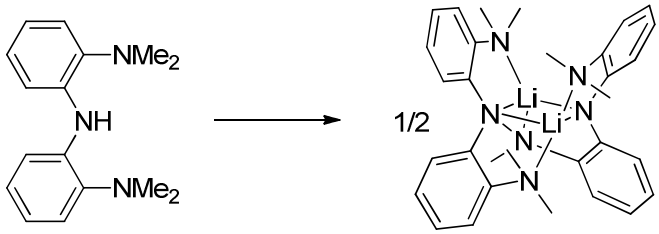
Bis[(2-dimethylamino)phenyl]amine



A 250 mL reaction vessel was charged with $Pd_2(dba)_3$ (1.36 g, 1.49 mmol), bis(diphenylphosphino)-ferrocene (DPPF) (1.65 g, 2.97 mmol), NaO^tBu (9.84 g, 0.098 mol) and toluene (100 mL) under a dinitrogen atmosphere. 2-bromo-N,N-dimethylaniline (14.6 g, 0.073 mol) and 2-amino-N,N-dimethylaniline (9.95g, 0.073 mol) were added to the reaction mixture. The resulting brown solution was vigorously stirred for 3 days at 100^0C. The solution was then cooled to room temperature and was filtered through Celite. Removal of the solvent yielded a black liquid which was then taken up in dichloromethane and was "flashed" through a silica plug. Removal of the volatiles gave a brown solid which was purified by vacuum distillation, resulting slightly yellow solid. Yield: 13 g (70 %).

^{1}H NMR (400.13 MHz, C_6D_6): 7.54 (d, J = 7.8 Hz, 2H), 7.45 (s, 1H), 6.99 (m, 4H), 6.87 (t, J = 7.6 Hz, 2H), 2.43 (s, 12H). ^{1}H NMR (400.13 MHz, $CDCl_3$): 7.40 (dd, J = 8.0, 1.4 Hz, 2H), 7.16 (br, 1H), 7.11 (dd, J = 7.8, 1.4 Hz, 2H), 7.0 (td, J = 7.7, 1.5 Hz, 2H), 6.87 (td, 7.6, 1.5 Hz, 2H), 2.69 (s, 12H). ^{13}C NMR (100.62 MHz, $CDCl_3$): 143.3, 137.5, 123.6, 119.9, 119.3, 115.4, 43.9. MS: 256.38 $[M+H]^+$.

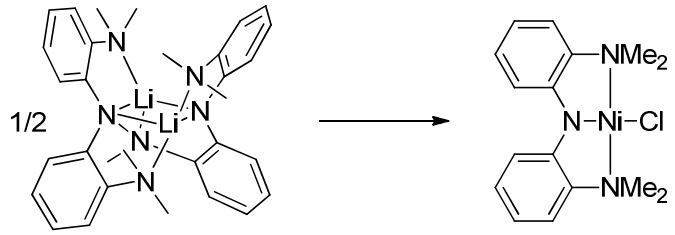
Bis[(2-dimethylamino)phenyl]amine lithium dimer



^{n}BuLi (22.3 mmol, 1.6 M in hexane) was slowly added to a toluene solution (60 mL) of the $H^{Me}N_2N$ ligand (5.43 g, 21.3 mmol) at room temperature. The reaction mixture was stirred for 1 h, and then the solvent was removed under vacuum. Addition of pentane afforded a white precipitate, which was filtered, washed with additional pentane, and dried *in vacuo*. Li salt of $H^{Me}N_2N$ ligand is sensitive to moisture and should be handled under an inert atmosphere. Yield: 4.73 g (85 %).

^{1}H NMR (400.13 MHz, C_6D_6): 6.98-7.11 (m, 4H), 6.93 (dd, J = 7.8, 1.3 Hz, 2H), 6.64 (m, 2H), 2.20 (s, 6H), 1.95 (s, 6H). ^{13}C NMR (100.62 MHz, C_6D_6): 157.4, 146.3, 127.6, 122.9, 120.8, 116.1, 48.9, 43.5.

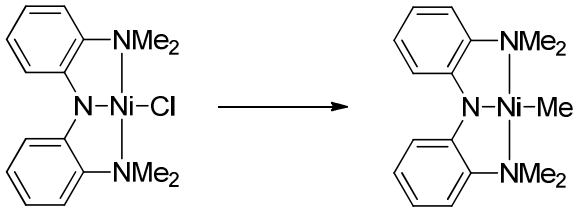
Bis[(2-dimethylamino)phenyl]amine nickel(II) chloride



A THF solution (50 mL) of $Li^{Me}N_2N$ (2 g, 7.65 mmol) was added to a THF suspension (25 mL) of $NiCl_2$(dme) (1.68 g, 7.65 mmol, dme=dimethoxyethane) under a nitrogen atmosphere. The reaction mixture was stirred overnight at room temperature. After removal of the solvent, the black residue was taken up in toluene and filtered through Celite and then was concentrated to *ca.* 2 mL. Addition of pentane resulted in formation of a brownish solid, which was filtered, washed with pentane and dried under vacuum. Yield: 2.19 g (82 %).

^{1}H NMR (400.13 MHz, C_6D_6): 7.47 (dd, J = 8.3, 1.0 Hz, 2H), 6.93 (m, 2H), 6.42 (dd, J = 8.0, 1.6 Hz, 2H), 6.36 (td, J = 7.0, 1.0 Hz, 2H), 2.57 (s, 12H). ^{1}H NMR (400.13 MHz, $CDCl_3$): 7.43 (d, J = 7.6 Hz, 2H), 6.99 (m, 4H), 6.48 (t, 7.1 Hz, 2H), 2.91 (s, 12H). ^{13}C NMR (100.62 MHz, C_6D_6): 147.9, 147.2, 128.5, 120.5, 116.1, 114.6, 51.1. TOF-MS: 348.09 $[M+H]^+$.

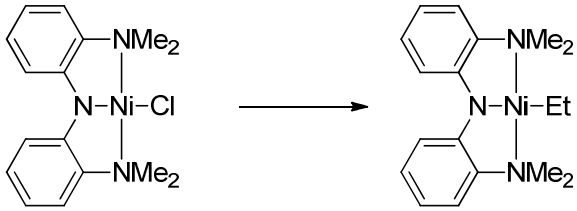
Bis[(2-dimethylamino)phenyl]amine nickel(II) methyl



MeMgCl (0.67 mL, 3 M solution in THF, 2.01 mmol) was added dropwise to a THF (5 mL) solution of **1** (600 mg, 1.83 mmol) at -60 °C. Upon addition, the brown solution became deep red. The reaction mixture was warmed up to room temperature and was stirred overnight. After evaporation of the solvent, the solid residue was extracted with pentane (3x20 mL) and filtered through Celite. Removal of the solvent afforded the product as a red solid. Yield: 350 mg (58 %).

^{1}H NMR (400.13 MHz, C_6D_6): 7.65 (dd, J = 8.5, 1.5 Hz, 2H), 7.07 (m, 2H), 6.61 (dd, J = 7.9, 1.5 Hz, 2H), 6.45 (m, 2H), 2.38 (s, 12H), -0.93 (s, 3H). ^{13}C NMR (100.62 MHz, C_6D_6): 149.05, 147.80, 128.31, 120.08, 114.25, 114.09, 50.22, -6.33. Calcd for $C_{17}H_{23}N_3Ni$: C, 62.24; H, 7.07; N, 12.81. Found: C, 62.29; H, 6.69, N, 11.59.

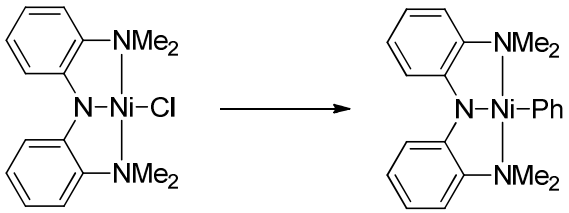
Bis[(2-dimethylamino)phenyl]amine nickel(II) ethyl



EtMgCl (0.46 mL, 2 M solution in THF, 0.91 mmol) was added dropwise to a THF (5 mL) solution of **1** (300 mg, 0.91 mmol) at -60 °C. Upon addition, the brown solution turned red. The reaction mixture was warmed up to room temperature and was stirred overnight. After evaporation of the solvent, the solid residue was extracted with pentane (3x20 mL) and filtered through Celite. Removal of the solvent afforded the product as an orange solid. Yield: 200 mg (64 %). Red needle crystals suitable for X-ray diffraction analysis were obtained by slow evaporation of a concentrated pentane solution.

^{1}H NMR (400.13 MHz, C_6D_6): 7.61 (dd, J = 8.2, 1.2 Hz, 2H), 7.06 (m, 2H), 6.63 (dd, J=7.9, 1.5 Hz, 2H), 6.44 (m, 2H), 2.38 (s, 12H), 0.91 (t, J=7.9 Hz, 3H), -0.46 (q, J=7.6 Hz, 2H). ^{13}C NMR (100.62 MHz, C_6D_6): 149.21, 147.59, 128.22, 119.46, 114.04, 113.88, 49.62, 13.55, 1.36. Calcd for $C_{18}H_{25}N_3Ni$: C, 63.19; H, 7.37; N, 12.28. Found: C, 62.72; H, 7.39, N, 11.57.

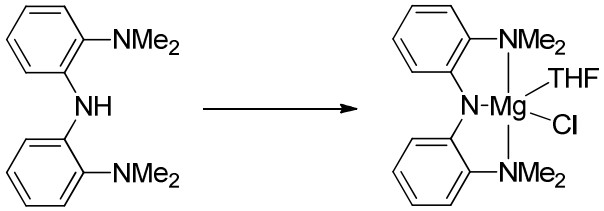
Bis[(2-dimethylamino)phenyl]amine nickel(II) phenyl



PhMgCl (0.92 mL, 2 M solution in THF, 1.83 mmol) was added dropwise to a THF (5 mL) solution of **1** (600 mg, 1.83 mmol) at -60 °C. Upon addition, the brown solution became red. The reaction solution was warmed up to room temperature and was stirred overnight. An orange precipitate was formed, which was filtered and washed with pentane. The solid was taken up in toluene and filtered through Celite. Removal of the solvent afforded the product as a yellow solid. Yield: 450 mg (63 %).

^{1}H NMR (400.13 MHz, C_6D_6): 7.90 (dd, J = 7.9, 1.5 Hz, 2H), 7.62 (dd, J = 8.2, 0.9 Hz, 2H), 7.14 (m, 2H), 7.04 (m, 3H), 6.52 (dd, J = 8.2, 1.5 Hz, 2H), 6.42 (td, J = 7.3, 1.2 Hz, 2H), 2.25 (s, 12H). ^{1}H NMR (400.13 MHz, CD_2Cl_2): 7.95 (dd, J = 7.5, 1.0 Hz, 2H), 7.37 (dd, J = 8.2, 1.4 Hz, 2H), 6.97 (m, 6H), 6.84 (m, 1H), 6.41 (dd, J = 7.5, 1.0 Hz, 2H), 2.60 (s, 12H). ^{13}C NMR (100.62 MHz, C_6D_6): 165.23, 148.68, 147.77, 138.77, 128.33, 125.96, 122.80, 119.94, 114.46, 114.04, 50.80. Calcd for $C_{22}H_{25}N_3Ni$: C, 67.73; H, 6.46; N, 10.77. Found: C, 67.32; H, 6.45, N, 9.67.

Bis[(2-dimethylamino)phenyl]amine magnesium chloride

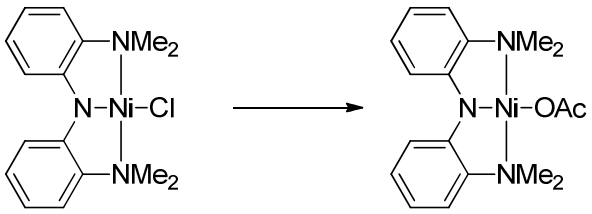


A 3.0M solution of CH_3MgCl in THF (0.26 mL, 0.78 mmol) was added to a solution of $H^{Me}N_2N$ (200 mg, 0.78 mmol) in THF (5 mL) under stirring. After 1h, the solvent was evaporated and the solid residue was dissolved in a minimum quantity of benzene and was filtered. Pentane was added to the filtrate and a precipitate was formed. The precipitate was collected, washed with pentane, and dried under vacuum (204 mg, 83%).

^{1}H NMR (400.13 MHz, C_6D_6): δ = 7.84 (dd, J = 8.2, 1.0 Hz, 2 H), 7.12 (td, J = 7.2, 1.7 Hz, 2 H), 7.00 (dd, J = 7.9, 1.4 Hz, 2 H), 6.64 (td, J = 7.9, 1.4 Hz, 2 H), 3.54 (b, 4H, THF), 2.55

(s, 12 H), 1.31 ppm (b, 4H, THF). ^{13}C NMR (100.62 MHz, C_6D_6): δ = 147.1, 142.2, 127.1, 119.9, 114.9, 113.9, 68.3 ($CH_2CH_2O^{THF}$), 45.8, 25.2 ($CH_2CH_2O^{THF}$).

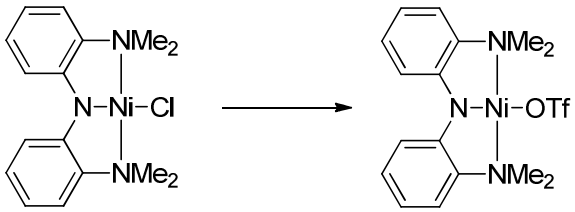
Bis[(2-dimethylamino)phenyl]amine nickel(II) acetate



[($^{Me}N_2N$)Ni-Cl] (**1**) (50 mg, 0.14 mmol) was dissolved in THF (5 mL) and 10 mol excess of NaOAc (118 mg, 1.40 mmol) was added. This mixture was vigorously stirred for 6 hours and the resulting precipitate was filtered off. 10 mol excess of NaOAc (118 mg, 1.40 mmol) was added again and mixture was stirred for another 6 hours. The precipitate was filtered off and the filtrate was evaporated. The green solid residue was washed with a mixture of pentane and benzene (5:1, 3*2 mL), and was dried under vacuum (42 mg, 79%). Single crystals suitable for X-ray crystallography were obtained by cooling a toluene/pentane solution (1:4) of **10** at -35^{o}C.

^{1}H NMR (400.13 MHz, C_6D_6): δ = 7.30 (d, J = 8.4 Hz, 2 H), 6.95 (t, J = 8.1 Hz, 2 H), 6.48 (dd, J = 7.7, 1.0 Hz, 2 H), 6.32 (t, J = 7.7 Hz, 2 H), 2.64 (s, 12 H), 2.04 ppm (s, 3 H). ^{13}C NMR (100.62 MHz, C_6D_6): δ = 175.3, 146.6, 145.8, 127.7, 119.6, 116.0, 115.3, 49.3, 24.6. Anal. Calcd (%) for $C_{18}H_{23}N_3NiO_2$: C, 58.10; H, 6.23; N, 11.29. Found: C, 57.44; H, 6.22, N, 11.37.

Bis[(2-dimethylamino)phenyl]amine nickel(II) triflate

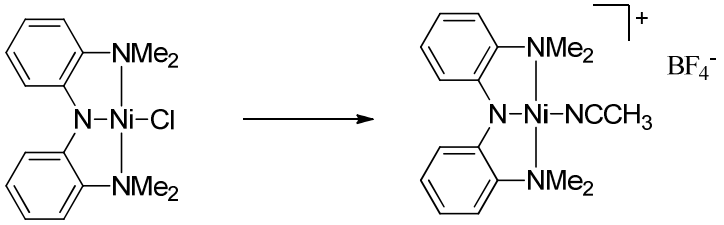


A solution of AgOTf (73 mg, 0.39 mmol) in THF (2 mL) was added to a solution of [($^{Me}N_2N$)Ni-Cl] (**1**) (100 mg, 0.39 mmol) in THF (3 mL). The resulting solution was stirred for 30 min and then the white precipitate of AgCl was filtered off. The filtrate was evaporated and the green solid residue was washed with pentane (3 mL) and dried under vacuum (99 mg,

75%). Single crystals suitable for X-ray crystallography were obtained by diffusion of pentane into a benzene solution of **7**.

^{1}H NMR (400.13 MHz, [D_6]DMSO): δ = 7.27 (dd, J = 8.2, 1.4 Hz, 2H), 7.13 (dd, J = 8.2, 1.7 Hz, 2H), 6.98 (td, J = 7.5, 1.4 Hz, 2H), 6.84 (m, 2H), 2.60 ppm (s, 12H). ^{13}C NMR (100.62 MHz, [D_6]DMSO): δ = 143.4, 137.3, 128.8, 124.1, 120.5, 120.0, 115.4, 44.1. Anal. Calcd (%) for $C_{17}H_{20}N_3NiSO_3F_3$: C, 44.18; H, 4.36; N, 9.09. Found: C, 44.76; H, 4.44, N, 9.14.

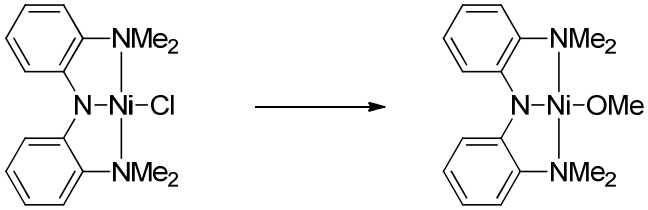
Bis[(2-dimethylamino)phenyl]amine nickel(II) tetrafluoroborate



A solution of $AgBF_4$ (56 mg, 0.39 mmol) in CH_3CN (2 mL) was added to a solution of [($^{Me}N_2N$)Ni-Cl] (**1**) (100 mg, 0.39 mmol) in CH_3CN (3 mL). The resulting green solution was stirred for 30 min and then the white precipitate of AgCl was filtered off. The filtrate was evaporated and the green solid was washed with benzene (2 mL) and pentane (3 mL), and dried under vacuum (119 mg, 94%). Single crystals suitable for X-ray crystallography were obtained by cooling a CH_3CN/ether (1:4) solution of **8** at -35^{o}C.

^{1}H NMR (400.13 MHz, CD_3CN): δ = 7.32 (dd, J = 7.8, 1.0 Hz, 2 H), 7.24 (m, 4 H), 6.49 (m, 2 H), 3.54 ppm (s, 12 H). ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 7.40 (dd, J = 8.2, 1.0 Hz, 2H), 7.05 (m, 4H), 6.59 (td, J = 8.2, 1.0 Hz, 2H), 2.98 (s, 12H), 2.60 ppm (br, 3H, CH_3CN). ^{13}C NMR (100.62 MHz, CD_3CN): δ = 145.7, 142.6, 129.5, 121.4, 119.3, 118.8, 50.4. Anal. Calcd (%) for $C_{18}H_{23}N_4NiBF_4$: C, 49.03; H, 5.26; N, 12.71. Found: C, 48.97; H, 5.34, N, 12.26.

Bis[(2-dimethylamino)phenyl]amine nickel(II) methoxide



[($^{Me}N_2N$)Ni-Cl] (**1**) (150mg, 0.43mmol) was dissolved in THF (2 mL) and a solution of NaOMe (23mg, 0.43mmol) in THF (1 mL) was added. The mixture was stirred for 1 h and

the solvent was evaporated. The solid residue was dissolved in benzene and the resulting solution was filtered to remove NaCl. The filtrate was evaporated to give **9** as the crude product. It was recrystallized from a mixture of toluene-pentane (3:1, 2 mL) at -35^{0}C (105 mg, 71%).

^{1}H NMR (400.13 MHz, C_6D_6): δ = 7.39 (dd, J = 8.5, 1.4 Hz, 2 H), 6.95 (td, J = 7.2, 1.4 Hz, 2H), 6.59 (dd, J = 7.9, 1.4 Hz, 2 H), 6.40 (td, J = 7.2, 1.4 Hz, 2H), 3.35 (s, 3H, OCH_3), 2.53 ppm (s, 12H, N(CH_3)$_2$). ^{13}C NMR (100.62 MHz, C_6D_6): δ = 147.9, 147.5, 128.0, 119.8, 114.9, 114.1, 53.8, 49.0. Anal. Calcd (%) for $C_{17}H_{23}N_3NiO$: C, 59.34; H, 6.74; N, 12.21. Found: C, 59.26; H, 6.62, N, 11.82.

Crystallographic details

Crystallographic Details for [(^{Me}N$_2$N)Li]$_2$ (2)

A total of 21646 reflections (-10 ≤ *h* ≤ 11, -20 ≤ *k* ≤ 19, - 23 ≤ *l* ≤ 24) were collected at *T* = 140(2) K in the range of 2.72 to 26.37^o of which 3081 were unique (R_{int} = 0.0513); $Mo_{K\alpha}$ radiation (λ= 0.71073 Å). The structure was solved by the Direct method. All non-hydrogen atoms were refined anisotropically, and hydrogen atoms were placed in calculated idealized positions. The residual peak and hole electron densities were 0.278 and –0.185 eA^{-3}, respectively. The absorption coefficient was 0.068 mm^{-1}. The least squares refinement converged normally with residuals of $R(F)$ = 0.0476, $wR(F^2, all\ data)$ = 0.1251 and a GOF = 1.128 (I>2σ(I)). C_{32} $H_{40}Li_2N_6$, Mw = 522.58, space group Pccn, Orthorhombic, *a* = 9.3505(3), *b* = 16.1767(6), *c* = 19.9603(7), α = 90.00 $^\circ$, β = 90.00°, γ = 90.00 $^\circ$, *V* = 3019.20(18) A^3, *Z* = 4, ρ_{calcd} = 1.150 Mg/m^3.

Crystallographic details for [(^{Me}N$_2$N)NiCl] (1)

A total of 11508 reflections (-37 ≤ *h* ≤ 38, -11 ≤ *k* ≤ 11, - 12 ≤ *l* ≤ 13) were collected at *T* = 140(2) K in the range of 2.66 to 26.37^o of which 5542 were unique (R_{int} = 0.0169); $Mo_{K\alpha}$ radiation (λ = 0.71073 Å). The structure was solved by the Direct method. All non-hydrogen atoms were refined anisotropically and hydrogen atoms were placed in calculated idealized positions. The residual peak and hole electron densities were 0.411 and –0.245 eA^{-3}, respectively. The absorption coefficient was 1.406 mm^{-1}. The least squares refinement converged normally with residuals of $R(F)$ = 0.0223, $wR(F^2, all\ data)$ = 0.0578 and a GOF = 1.065 (I>2σ(I)). $C_{16}H_{20}ClN_3Ni$, Mw = 348.51, space group Cc, Monoclinic, *a* = 31.1523(6), *b*

= 9.2463(2), c = 11.0586(2), α = 90 °, β = 100.598(2)°, γ = 90°, V = 3131.02(11) A^3, Z = 8, ρ_{calcd} = 1.479 Mg/m^3.

Crystallographic details for [($^{Me}N_2N$)NiEt] (4)

A total of 13988 reflections (-10 ≤ h ≤ 10, -18 ≤ k ≤ 17, - 17 ≤ l ≤ 17) were collected at T = 140(2) K in the range of 2.82 to 26.37° of which 3384 were unique (R_{int} = 0.0384); $Mo_{K\alpha}$ radiation (λ = 0.71073 Å). The structure was solved by the Direct method. All non-hydrogen atoms were refined anisotropically and hydrogen atoms were placed in calculated idealized positions. The residual peak and hole electron densities were 0.375 and –0.251 eA^{-3}, respectively. The absorption coefficient was 1.164 mm^{-1}. The least squares refinement converged normally with residuals of $R(F)$ = 0.0357, $wR(F^2, all\ data)$ = 0.0843 and a GOF = 1.053 (I>2σ(I)). $C_{18}H_{25}N_3Ni$, Mw = 342.12, space group P2(1)/c, Monoclinic, a = 8.6148(3), b = 14.4586(5), c = 13.8551(4), α = 90 °, β = 104.9288(4)°, γ = 90°, V = 1667.51(9) A^3, Z = 4, ρ_{calcd} = 1.363 Mg/m^3.

Crystallographic details for [($^{Me}N_2N$)NiPh] (5)

The crystals were severely twined and thus the data were treated with twin refinement. The residual R value remains high and therefore the structure is used mainly to prove the connectivity of the molecule. A total of 3882 reflections (-10 ≤ h ≤ 10, -18 ≤ k ≤ 17, - 17 ≤ l ≤ 17) were collected at T = 100(2) K in the range of 3.49 to 26.37° of which 3882 were unique (R_{int} = 0.000); $Mo_{K\alpha}$ radiation (λ = 0.71073 Å). The structure was solved by the Direct method. All non-hydrogen atoms were refined anisotropically and hydrogen atoms were placed in calculated idealized positions. The residual peak and hole electron densities were 3.051 and -1.783 eA^{-3}, respectively. The absorption coefficient was 1.022 mm^{-1}. The least squares refinement converged with residuals of $R(F)$ = 0.1586, $wR(F^2, all\ date)$ = 0.4088 and a GOF = 1.201 (I>2σ(I)). $C_{22}H_{25}N_3Ni$, Mw = 390.16, space group P2(1)/n, Monoclinic, a = 13.520(13), b = 7.298(3), c = 20.276(13), α = 90 °, β = 106.74(6)°, γ = 90°, V = 1916(2) A^3, Z = 4, ρ_{calcd} = 1.353 Mg/m^3.

Crystallographic details for [($^{Me}N_2N$)NiOTf] (7)

A total of 16903 reflections (-8 ≤ h ≤ 8, -17 ≤ k ≤ 17, - 24 ≤ l ≤ 23) were collected at T = 140(2) K in the range of 2.80 to 26.37° of which 2107 were unique (R_{int} = 0.0529); $Mo_{K\alpha}$ radiation (λ = 0.71073 Å). The structure was solved by the Direct method. All non-hydrogen atoms were refined anisotropically and hydrogen atoms were placed in calculated idealized

positions. The residual peak and hole electron densities were 0.340 and –0.388 eA^{-3}, respectively. The absorption coefficient was 1.129 mm^{-1}. The least squares refinement converged normally with residuals of $R(F)$ = 0.0344, $wR(F^2)$ = 0.0597 and a GOF = 1.076 ($I>2\sigma(I)$). $C_{17}H_{20}F_3N_3O_3SNi$, Mw = 462.13, space group *P*nma, Orthorhombic, a = 7.0081(3), b = 14.5619(6), c = 19.5131(9) Å, V = 1991.34(15) $Å^3$, Z = 4, ρ_{calcd} = 1.541 Mg/m^3.

Crystallographic details for [($^{Me}N_2N$)Ni-NCCH$_3$](BF$_4$) (8•BF$_4$)

A total of 31050 reflections (-22 ≤ h ≤ 21, -7 ≤ k ≤ 7, - 47 ≤ l ≤ 47) were collected at T = 140(2) K in the range of 2.80 to 26.37° of which 7783 were unique (R_{int} = 0.0467); $Mo_{K\alpha}$ radiation (λ = 0.71073 Å). The structure was solved by the Direct method. All non-hydrogen atoms were refined anisotropically and hydrogen atoms were placed in calculated idealized positions. The residual peak and hole electron densities were 1.353 and –1.632 eA^{-3}, respectively. The absorption coefficient was 1.041 mm^{-1}. The least squares refinement converged normally with residuals of $R(F)$ = 0.0613, $wR(F^2)$ = 0.1108 and a GOF = 1.268 ($I>2\sigma(I)$). $C_{18}H_{23}BF_4N_4Ni$, Mw = 440.92, space group *P*ca2$_1$, Orthorhombic, a = 17.8380(7), b = 5.7806(2), c = 37.8747(12) Å, V = 3905.4(2) $Å^3$, Z = 8, ρ_{calcd} = 1.500 Mg/m^3.

Crystallographic Details for [($^{Me}N_2N$)NiOAc] (10)

A total of 30213 reflections (-10 ≤ h ≤ 10, -15 ≤ k ≤ 15, - 39 ≤ l ≤ 39) were collected at T = 140(2) K in the range of 2.76 to 26.37° of which 6862 were unique (R_{int} = 0.0349); $Mo_{K\alpha}$ radiation (λ = 0.71073 Å). The structure was solved by the Direct method. All non-hydrogen atoms were refined anisotropically, and hydrogen atoms were placed in calculated idealized positions. The residual peak and hole electron densities were 1.615 and –0.487 eA^{-3}, respectively. The absorption coefficient was 1.166 mm^{-1}. The least squares refinement converged normally with residuals of $R(F)$ = 0.0441, $wR(F^2)$ = 0.1046 and a GOF = 1.049 ($I>2\sigma(I)$). $C_{18}H_{23}N_3NiO_2$, Mw = 522.58, space group $P2_12_12_1$, Orthorhombic, a = 8.3469(2), b = 12.7857(4), c = 31.5964(9) Å, V = 3372.00(16) $Å^3$, Z = 8, ρ_{calcd} = 1.466 Mg/m^3.

2.6. References

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Chapter 3

*Catalytic Coupling of Grignard Reagents with Alkyl Polychlorides**

*The results presented in this chapter were published in:

Csok, Z.; Vechorkin, O.; Harkins, S. B.; Scopelliti, R.; Hu, X. L. *J. Am. Chem. Soc.* **2008**, *130*, 8156-8157.

Vechorkin, O.; Csok, Z.; Scopelliti, R.; Hu, X. L. *Chem.-Eur. J.* **2009**, *15*, 3889-3899.

3.1. Introduction

Our exploration of a new pincer amidobis(amine) ligand ($^{Me}N_2N$) and its Ni^{II} complexes (**A**, Figure 1) in coordination chemistry and catalysis was inspired by wonderful results obtained in the field of pincer complexes by other research groups during the last years.[1,2b,3,5,6] We noticed particularly the broad applications of pincer phosphine ligands (**B** and **C**, Figure 1) in late transition metal mediated small molecule activation and homogeneous catalysis.[2-6] Pincer amine ligands are less exploited for similar applications. One might expect a mismatch between a soft late transition metal and the hard amine donors, yet the work by van Koten and others demonstrated that stable pincer NCN complexes (**D**, Figure 1) of late transition metals could be made and showed promising activity in C–H activation, transfer hydrogenation, and C–C bond forming reactions.[3,7,8] Our entry to Ni-mediated C–C coupling is provided by Ni^{II} alkyl complexes of the $^{Me}N_2N$ ligand. These compounds are thermally stable and the [($^{Me}N_2N$)Ni-Et] complex resists β-H elimination. The reactions between [($^{Me}N_2N$)Ni-Alkyl] species and organic polychloride compounds, and catalytic coupling of alkyl polychlorides are described in this chapter.

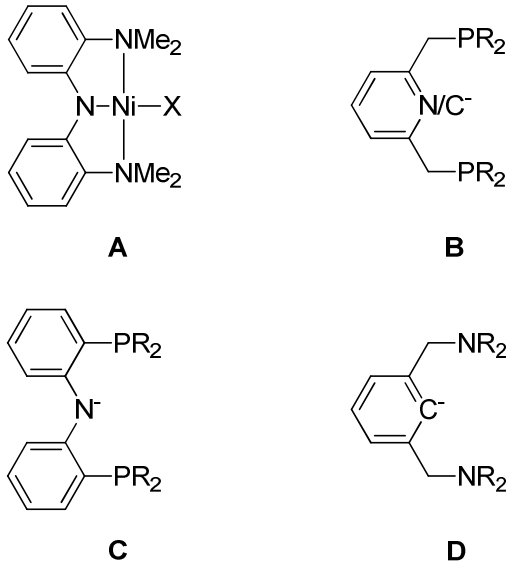


Figure 1. [($^{Me}NN_2$)Ni-X] complexes (**A**) and selected pincer ligands (**B – D**).

3.2. Reaction of [($^{Me}N_2N$)Ni-Alkyl] species with organic polychlorides

3.2.1. Reaction with CH_2Cl_2 and $CHCl_3$

As described in Chapter 2, [($^{Me}N_2N$)Ni-Cl] complex can be alkylated with alkyl Grignard reagents to give [($^{Me}N_2N$)Ni-Alkyl] species. When a [($^{Me}N_2N$)Ni-Alkyl] complex was dissolved in deuterated chloroform for NMR measurements, a rapid chemical transformation of [($^{Me}N_2N$)Ni-Alkyl] to [($^{Me}N_2N$)Ni-Cl] was observed (Figure 2). The fact that the only source of chlorine atoms in the solution is dueterated chloroform indicates that there is a chemical reaction between chloroform and [($^{Me}N_2N$)Ni-Alkyl] complexes. It was found later that similar transformations occurred also in CD_2Cl_2, indicating the possibility of the general reactions between [($^{Me}N_2N$)Ni-Alkyl] species and organic polychlorides. This interesting transformation was then studied in detail.

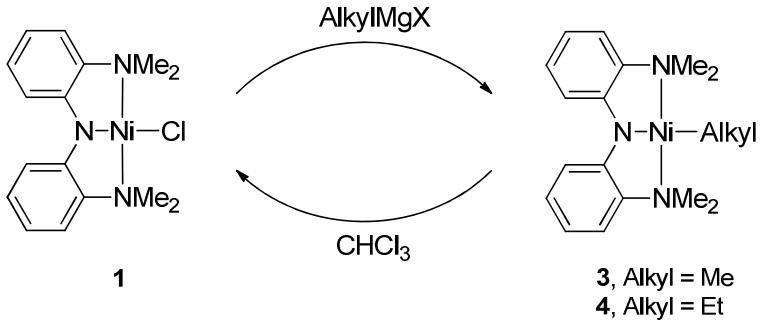


Figure 2. The transformations between [($^{Me}N_2N$)Ni-Cl] and [($^{Me}N_2N$)Ni-Alkyl] complexes.

The reactions of [($^{Me}N_2N$)Ni-Me] with organic polychloride compounds were performed in deuterated benzene and the products were analyzed by ^{1}H-NMR spectroscopy. The only detectable organic compounds after the reactions are the fully C–C coupled products. Thus, in the reactions with CH_2Cl_2 and $CHCl_3$, propane and isobutane are formed exclusively and respectively (R = Me, Figure 3). While it was difficult to quantify the yields for gases, the observed yields for the products that remained in the solution mixture were ca. 50% for propane and 55% for isobutane, underscoring the high selectivity for the multiple C–C bond forming reactions. Partially methylated products such as CH_3CH_2Cl, CH_3CHCl_2, or $(CH_3)_2CHCl$ were not observed, even when an excess of CH_2Cl_2 or $CHCl_3$ was used. Similar reactivity patterns were found for the ethyl complex [($^{Me}N_2N$)Ni-Et] (**4**). The phenyl complex [($^{Me}N_2N$)Ni-Ph] is however inert under the same conditions.

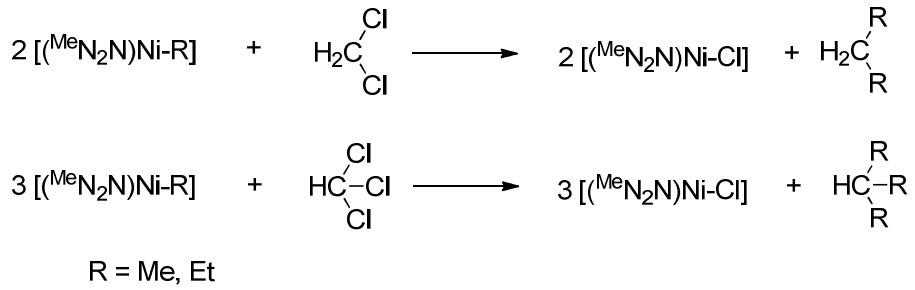


Figure 3. Reaction between [($^{Me}N_2N$)Ni-R] and CH_2Cl_2 or $CHCl_3$.

These reactions are unusual in several ways. They take place under very mild conditions and are the first examples of late-transition metal alkyl compounds that react with CH_2Cl_2 and $CHCl_3$ to give fully alkylated organic products in high yields.[5,9] The selectivity is impressive as the overall process involves the cleavage of up to three C–Cl bonds to form three new C–C bonds at the same carbon center.

3.2.2. Reaction with other organic polychlorides

Several other organic polychlorides were tested for reactions with [($^{Me}N_2N$)Ni-Alkyl]. However, no methylation products were observed in the reactions with [($^{Me}N_2N$)Ni-Me]. The reaction between [($^{Me}N_2N$)Ni-Me] and (trichloromethyl)benzene proceeded at room temperature (entry 1, Table 1). However a mixture of cis/trans isomers of 1,2-dichloro-1,2-diphenylethene was found as major products of the reaction. The same products were obtained by other research groups with this substrate under similar reaction conditions.[10] A similar result was obtained when (dichloromethyl)benzene was used as the substrate (entry 2, Table 1). A mixture of cis/trans isomers of 1,2-diphenylethene was the only identified product of the reaction. Other polychloride compounds were also reacted with [($^{Me}N_2N$)Ni-Me] (entries 4-6, Table 1). Decomposition or formation of unidentified products was observed by the ^{1}H-NMR spectroscopy.

Table 1. Organic products identified in reactions of [($^{Me}N_2N$)Ni-Me] (**3**) with di- and poly-chloroalkanes.[a]

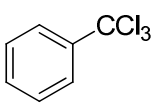
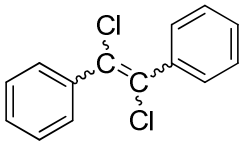
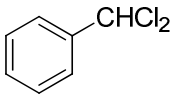
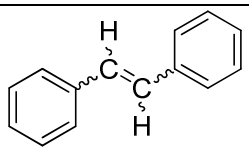
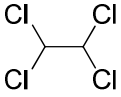
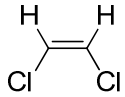
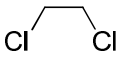
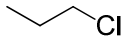
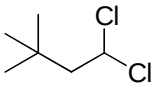
Entry	Substrate	Condition	Product	Yield (%)
1		r.t. 5 min		55

Table 1. (Continued)

Entry	Substrate	Condition	Product	Yield (%)
2		r.t. 24 h		30
3		r.t. 24 h		4
4		100^0C 24 h	 $H_2C=CH_2$	5 6
5		60^0C 24 h	-	-
6		RT 24 h	-	-

[a] See experimental part for the conditions.

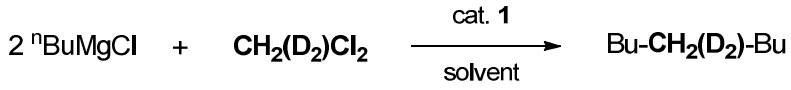
3.3. Catalytic reactions with polychlorides

3.3.1. Optimization of the reaction conditions

The multiple C–C coupling reactions described above for CH_2Cl_2 and $CHCl_3$ are applicable in organic synthesis if they can be rendered catalytically. Indeed, our experiments demonstrated that CH_2Cl_2 can be doubly coupled to an alkyl Grignard reagent (^{n}BuMgCl) using **1** as the catalyst (Table 2). Higher yields were obtained when CH_2Cl_2 was in excess and the optimal CH_2Cl_2:^{n}BuMgCl ratio is 25:1 (entries 1-3, Table 2). The optimal temperature is -20^0C and the catalysis completes within 30 minutes (entries 4-10, Table 2). Higher loadings of catalyst increase both the reaction rates and yields, but decrease the turnover numbers (entries 8-10, Table 2). A conversion of 82% was achieved in 5 minutes at -20^0C using 12 mol% of catalyst (entry 9, Table 2) and a TON of 47 was obtained in 30 minutes at -20^0C

using 1 mol% of catalyst (entry 10, Table 2). Control experiment showed that without [(^{Me}N$_2$N)Ni-Cl] catalyst, the yield is negligible (entry 11, Table 2). The deuterated analogue CD_2Cl_2 can be also used and gives $BuCD_2Bu$ in 84% yield (entry 12, Table 2), showing the possibility of the utilization of this method for the synthesis of deuterium- or ^{13}C-labeled organic compounds.

Table 2. Optimization of the reaction conditions for the reaction between alkyl Grignard reagents and CH_2Cl_2.[a]



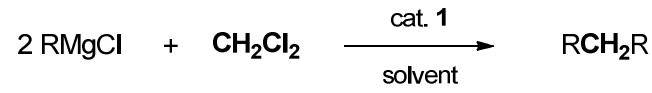
Entry	Eq. of halide	R	Mol% cat.	Temp. (^{o}C)	Time (hour)	Yield (%)[b]
1	0.5[c]	CH_2	3	20	24	5
2	25[d]	CH_2	3	20	24	15
3	100[d]	CH_2	3	20	24	11
4	25[d]	CH_2	3	20	0.5	17
5	25[d]	CH_2	3	0	0.5	25
6	25[d]	CH_2	3	-20	0.1	44
7	25[d]	CH_2	3	-40	0.5	16
8	25[d]	CH_2	6	-20	0.1	59
9	**25[d]**	**CH_2**	**12**	**-20**	**0.1**	**82**
10	25[d]	CH_2	1	-20	0.5	47
11	25[d]	CH_2	0	-20	0.5	0.4
12	**25[d]**	**CD_2**	**12**	**-20**	**0.1**	**84**

[a] 0.95 mmol of [n]BuMgCl (2.0 M solution in THF) as the limiting reagent. [b] GC yields relative to [n]BuMgCl. [c] THF as the solvent. [d]nBuMgCl was added dropwise to a 1.5 mL of CH_2Cl_2 (CD_2Cl_2) solution of catalyst.

3.3.2. Catalytic C–C coupling of CH_2Cl_2

Gratifyingly, other primary alkyl Grignard reagents can be used for this reaction. For example, coupling of CH_2Cl_2 with $^nC_5H_{11}MgCl$ using 3 mol% of catalyst gave 68% of $^nC_5H_{11}$-CH_2-$^nC_5H_{11}$ (entry 2, Table 3). The yield could be increased to 81% if 6 mol% of catalyst was used (entry 3, Table 3). $^nC_5H_{11}MgCl$ in THF gave the best results; changing to $^nC_5H_{11}MgBr$ in THF or in ether lowered the yields (entries 4 and 5, Table 3). Coupling of CH_2Cl_2 with $^nC_8H_{17}MgCl$ gave 69% of $^nC_8H_{17}$-CH_2-$^nC_8H_{17}$ (entry 6, Table 3). Bulkier alkyl Grignard reagents could be used but gave lower yields. For instance, ^{i}BuMgCl coupled with CH_2Cl_2 to give ^{i}Bu-CH_2-^{i}Bu in 30% yields using 4.5 mol% of catalyst (entry 7, Table 3). Increasing the catalyst loading to 12% improved the yield to 49% (entry 8, Table 3). BenzylMgCl did not work, as it gave mainly the homo-coupling product $C_6H_5CH_2CH_2C_6H_5$ (60% yield, entry 9, Table 3). Coupling was not efficient with secondary or tertiary Grignard reagents (entries 10 – 12, Table 3). When another soluble Ni^{II} complex, e.g., $Ni(dme)Cl_2$ was used as the catalyst for the reaction, only a trace amount of the doubly coupled product was formed (entry 13, Table 3), confirming the unique activity of **1** for this reaction.

Table 3. Double C–C coupling of CH_2Cl_2 with Grignard reagents.[a]



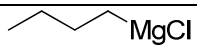
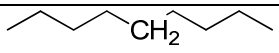
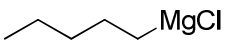
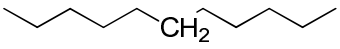
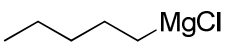
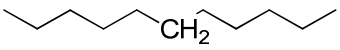
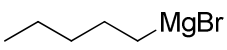
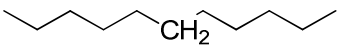
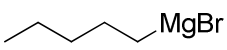
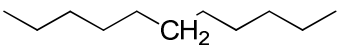
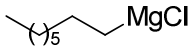
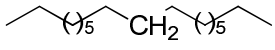
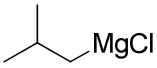
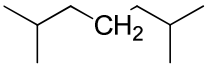
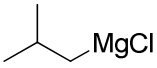
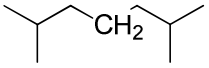
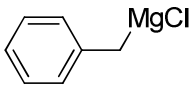
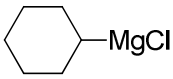
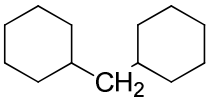
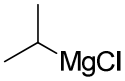
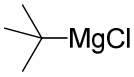
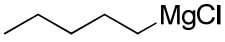
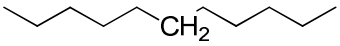
Entry	RMgCl	Mol% of cat.	Time (hour)	Product	Yield (%)[b]
1		6	0.1		59
2		3	0.3		68
3		6	0.3		81
4[c]		3	0.3		51
5[d]		3	0.3		23

Table 3. (Continued)

Entry	RMgCl	Mol% of cat.	Time (hour)	Product	Yield (%)[b]
6		3	0.3		69
7		4.5	0.3		30
8		12	0.3		49
9		3	0.3	-	0
10		9	0.5		6
11		3	0.3	-	0
12		3	0.3	-	0
13		0[e]	0.5		4

[a] 0.8 mmol of RMgCl (1-2 M solution in THF) as the limiting reagent; RMgCl was added dropwise to a CH_2Cl_2 (1.5 mL, 25 eq.) solution of **1**. [b] GC yields relative to the Grignards. [c] $C_5H_{11}MgBr$ in THF was used. [d] $C_5H_{11}MgBr$ in ether was used. [e] 3 mol% (dme)$NiCl_2$ was used as the precatalyst.

3.3.3. Catalytic C-C coupling of other polychloride compounds

The experiments on catalytic coupling were also carried out with other polychloride compounds using 3 mol% of **1** as the catalyst. No doubly C–C coupled products were formed, even with CH_3CHCl_2. This is consistent with the results from stoichiometric reactions of **3** and dichloroalkanes (Table 3). One of the possible problems is a different solvent of the reaction. Catalytic experiments with CH_2Cl_2 were done with an excess of this

compound, which was also used as a solvent. Utilization of other polychloride compounds in large excess or as solvent would change the polarity and other properties of the reaction mixture, causing problems for the alkylation reaction. The steric and electronic properties of CH_2Cl_2 are also unique and are much different from other polychloride substrates.

The identification of the main products of the catalytic reactions with the other polychloride compounds was performed for a better understanding of these transformations. For instance, coupling of (trichloromethyl)benzene with CH_3MgCl gave 1,2-dichloro-1,2-diphenylethylene in 25% yield (entry 1, Table 3), and coupling of (dichloromethyl)benzene with CH_3MgCl gave stilbene, styrene, and $(Ph(CH_3)CH)_2$ in 8%, 16%, and 22% yields, respectively (entry 2, Table 3). Coupling of 1,1-dichloro-3,3-dimethylbutane with ^nBuMgCl (R^1Cl_2) gave BuR^1R^1Bu in 42% yield (entry 3, Table 3), and coupling of Ph_2CCl_2 with CH_3MgCl gave $Ph_2C{=}CPh_2$ in 70% yield (entry 4, Table 3). A radical dimerization process is likely operational in these reactions.

Table 4. Catalytic coupling of alkyl polyhalides.[a]

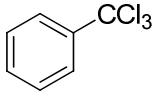
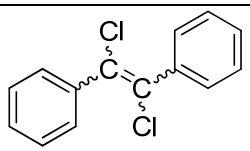
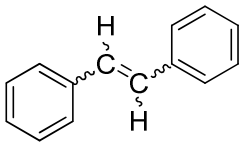
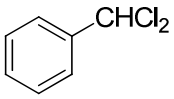
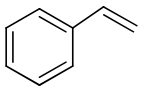
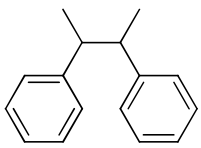
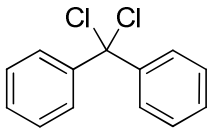
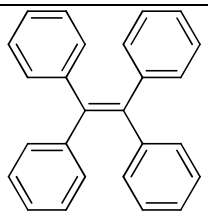
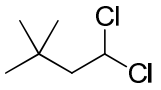
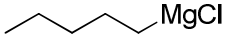
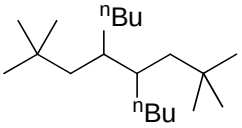
Entry	RCl_x	R'MgCl	Product	Yield (%)[b]
1		CH_3MgX		25%
				8%
2		CH_3MgX		16%
				22%

Table 4. (Continued)

Entry	RCl_x	R'MgCl	Product	Yield (%)[b]
3		CH_3MgX		70%
4				40%

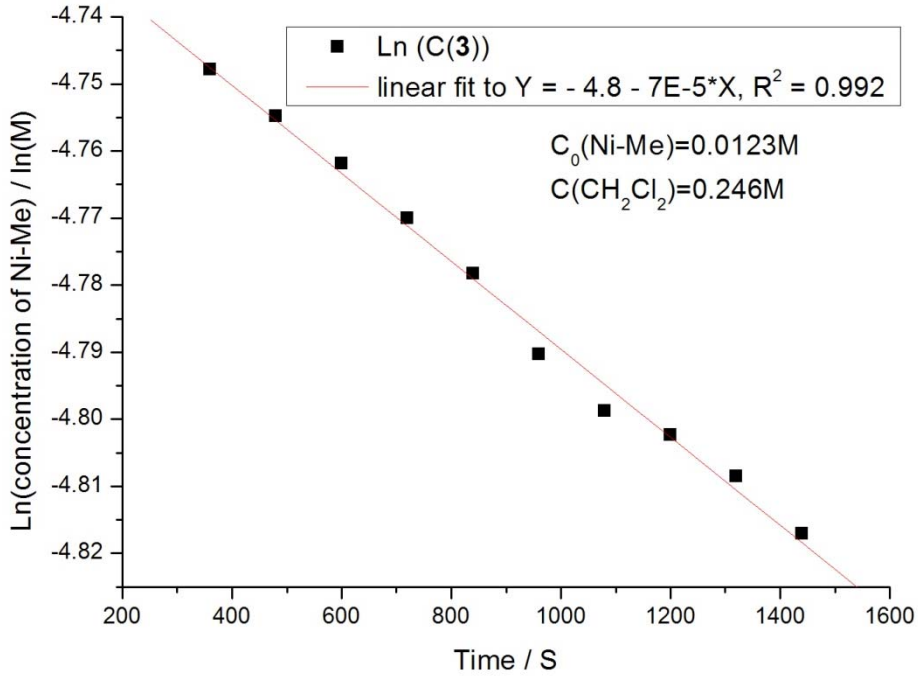
[a] 0.4 mmol of RMgCl (1-2 M solution in THF) was added dropwise to a THF (1.5 mL) solution of polyhalides (1 eq. with respect to the number of C-Cl bonds) and **1**(3 mol%). [b] GC and/or NMR yields relative to the organic polyhalides.

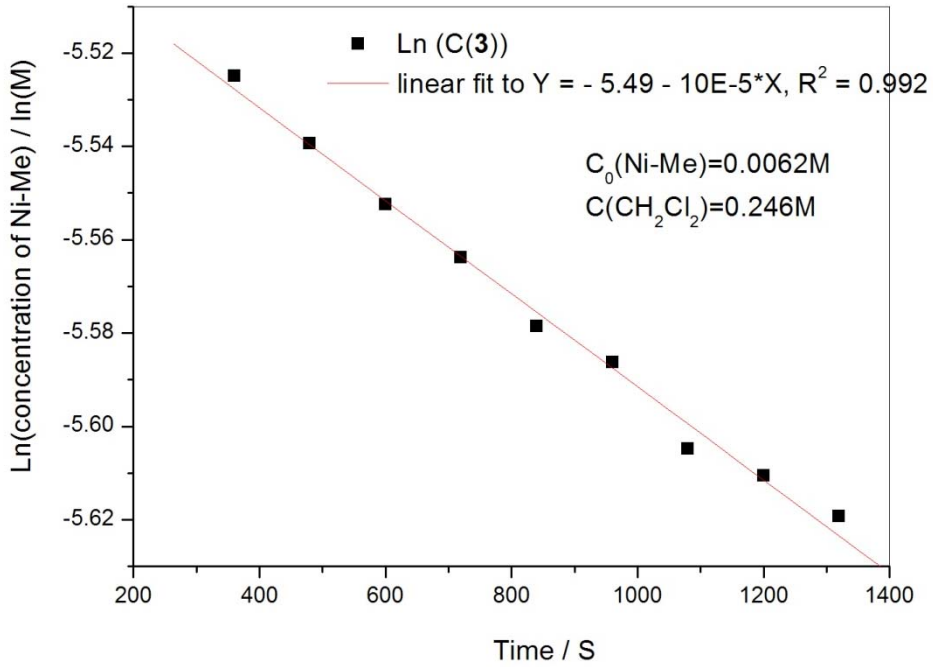
3.4. Mechanistic investigations

Based on stoichiometric reactions, the double coupling catalysis is proposed to proceed through similar sequences as in the Kumada-Corriu-Tamao coupling: transmetallation of **1** by a Grignard reagent gives a Ni^{II} alkyl species, which reacts with CH_2Cl_2 to give the coupling product and regenerate **1**. A radical pathway of the reaction is proposed based on the following observations:

- CH_2Cl_2 and $CHCl_3$ react with **3** faster than octyl-Cl
- Reaction of **3** with CH_2Cl_2 was retarded in the presence of radical trap TEMPO and TEMPO-CH_3 was formed during the reaction
- 1-pentene was formed in the reaction of **3** with bromomethylcyclopropane

Monitoring by ^1H NMR, the reactions of **3** with CH_2Cl_2 was found to be approximately first order in the concentration of **3** (Figure 4). The reaction was fit to the first order in the concentration of **3** because: (1) the rate constants obtained assuming a first-order in **3** are nearly equal under different initial concentrations of **3**; (2) the initial rate has a first order dependence on the initial concentration of **3**.


Ln (C(3))
linear fit to Y = - 4.8 - 7E-5*X, R2 = 0.992
C0(Ni-Me)=0.0123M
C(CH2Cl2)=0.246M
Ln(concentration of Ni-Me) / ln(M)
Time / S
-4.74
-4.75
-4.76
-4.77
-4.78
-4.79
-4.80
-4.81
-4.82
200
400
600
800
1000
1200
1400
1600


Ln (C(3))
linear fit to Y = - 5.49 - 10E-5*X, R2 = 0.992
C0(Ni-Me)=0.0062M
C(CH2Cl2)=0.246M
Ln(concentration of Ni-Me) / ln(M)
Time / S
-5.52
-5.54
-5.56
-5.58
-5.60
-5.62
200
400
600
800
1000
1200
1400

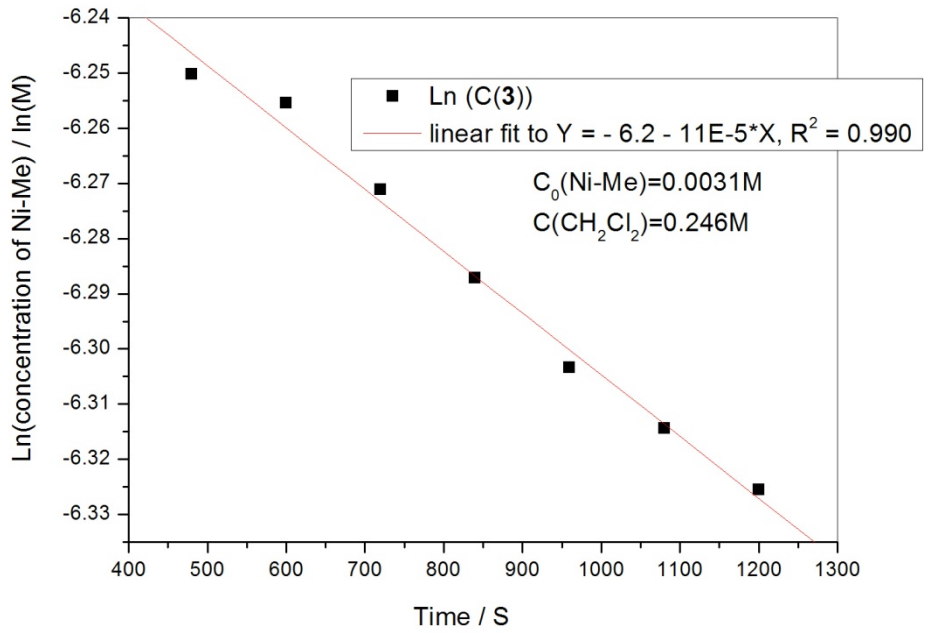
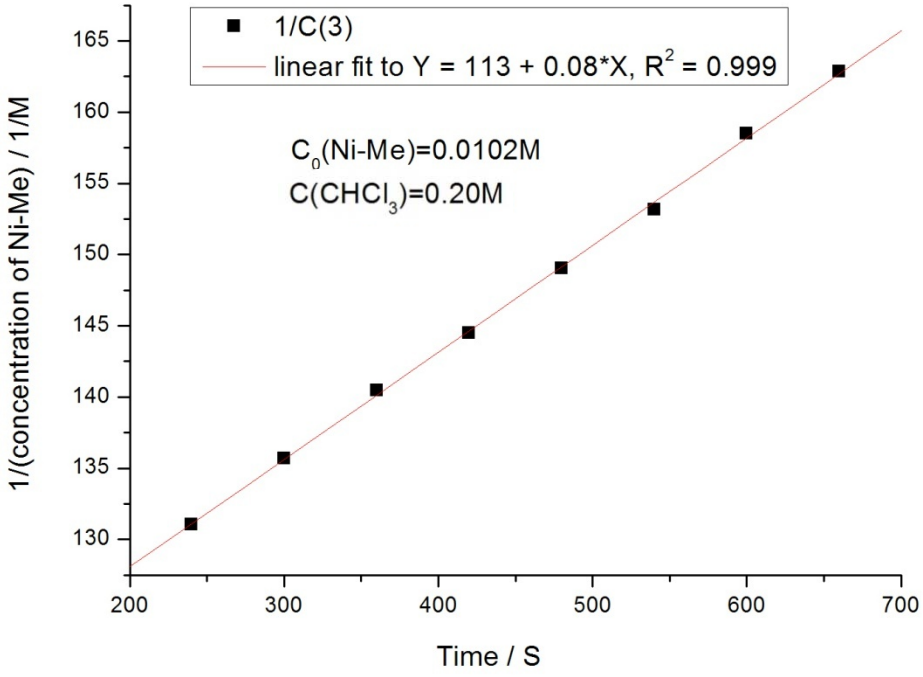
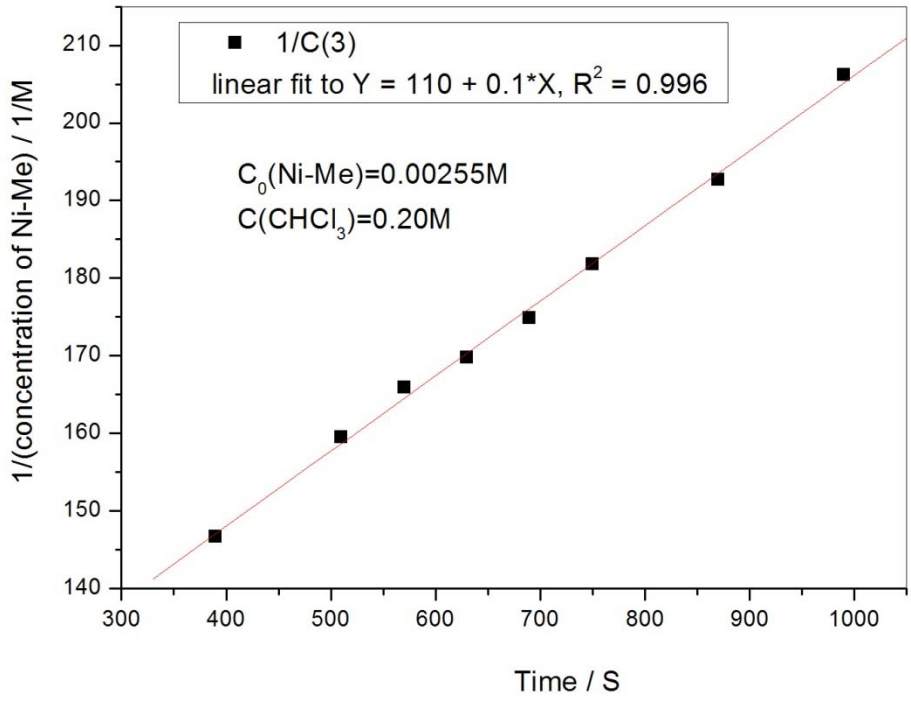


Figure 4. Kinetic plots of the reaction between **3** and CH_2Cl_2

Monitoring by ^1H NMR, the reactions of **3** with $CHCl_3$ was found to be approximately second order in the concentration of **3** (Figure 5). The reaction was fit to the second order in the concentration of **3** because: (1) the rate constants obtained assuming a second-order in **3** are nearly equal under different initial concentrations of **3**; (2) the initial rate has a second order dependence on the initial concentration of **3**.





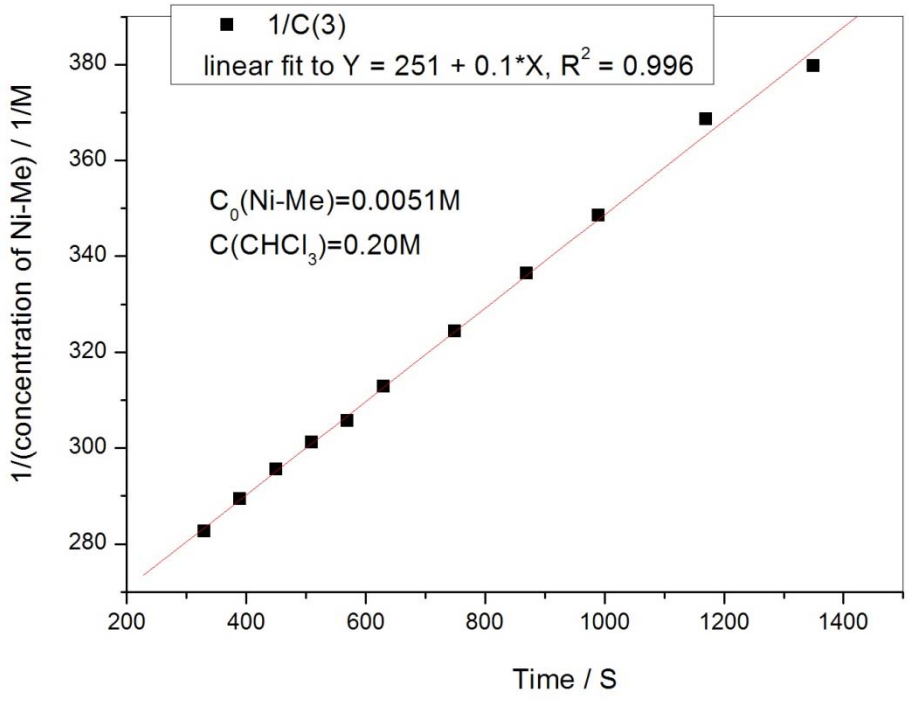


Figure 5. Kinetic plots of the reaction between **3** and $CHCl_3$.

3.5. Conclusions

In summary, using [($^{Me}N_2N$)Ni-alkyl] complexes, we have discovered a new type of multiple C–Cl activation reactions with CH_2Cl_2 and $CHCl_3$. The reactions lead to selective C–C bond formations which enable the first catalytic couplings of CH_2Cl_2 with Grignard reagents. The overall results suggest that the double C–C coupling between CH_2Cl_2 and a primary alkyl Grignard is general and rapid. The yields are remarkably high considering the fact that these alkyl Grignard reagents contain β-hydrogen atoms. The ability of ($^{Me}N_2N$)Ni alkyl species to resist β-hydrogen elimination is likely a key factor for this high efficiency. The catalysis does not tolerate well the steric bulkiness of the Grignard compounds, as bulkier primary Grignard reagents give lower yields, and secondary and tertiary Grignard reagents cannot be coupled. Coupling of other di- and poly-chloroalkanes with Grignard reagents was attempted, and in several cases, radical dimerization products were produced.

3.6. Experimental part

Chemicals and Reagents

All manipulations were carried out under an inert N_2(g) atmosphere using standard Schlenk or glovebox techniques. Solvents were purified using a two-column solid-state purification system (Innovative Technology, NJ, USA) and transferred to the glove box without exposure to air. Deuterated solvents were purchased from Cambridge Isotope Laboratories, Inc., and were degassed and stored over activated 3 Å molecular sieves. All other reagents were purchased from commercial sources and were degassed by standard freeze-pump-thaw procedures prior to use.

Physical methods

The ^1H and ^{13}C NMR spectra were recorded at 293 K on a Bruker Avance 400 spectrometer. ^1H NMR chemical shifts were referenced to residual solvent as determined relative to Me_4Si (δ = 0 ppm). The $^{13}C\{^1H\}$ chemical shifts were reported in ppm relative to the carbon resonance of DMSO-D6 (δ = 39.52 ppm), CD_3CN (δ = 118.26 ppm) or C_6D_6 (δ = 128.02 ppm). GC-MS measurements were conducted on a Perkin-Elmer Clarus 600 GC equipped with Clarus 600T MS. GC measurement was conducted on a Perkin-Elmer Clarus 400 GC with a FID detector.

Typical Procedure for the Synthesis of RCH_2R from CH_2Cl_2 and RMgCl

A vial was charged with a certain amount of [($^{Me}N_2N$)Ni-Cl] (**1**) and CH_2Cl_2 (1.5 mL). After the solution reached the desired temperature, a solution of RMgCl was added dropwise under vigorous stirring. The reaction was kept for a certain period of time, and then warmed to room temperature. A mixture of distilled water (15 mL), hydrochloric acid (25%, 1 mL) and dodecane (internal standard, 60 µL, 0.265 mmol) were added to the reaction mixture. The resulting solution was extracted with diethyl ether (10 mL x 3) and the organic phase was separated, dried over $MgSO_4$, and filtered. The identification of the organic products was made by GC-MS. The yield of RCH_2R was determined by gas chromatography, using decane or dodecane as the internal standard.

Reaction of [($^{Me}N_2N$)Ni-Me] with Alkyl Polyhalides

In a typical experiment, 0.015 mmol of [($^{Me}N_2N$)Ni-Me] (**3**) was loaded into an NMR tube along with 0.6 ml of C_6D_6. 0.15 mmol of alkyl polychloride (10 equiv.) or 0.015 mmol (1 equiv.) was added to this solution and the reaction was periodically monitored by ^{1}H-NMR. If the reaction did not occur at room temperature, the solution would be heated at 60^0C or 100^0C. The identification and quantification of products were determined by ^{1}H NMR. The results are summarized in Table 1. Yields are referred to the formation of Ni^{II} chlorides.

3.7. References

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Chapter 4

*Ni-Catalyzed Cross Coupling of Non-Activated and Functionalized Alkyl Halides with Alkyl Grignard reagents**

*The results presented in this chapter were published in:

Vechorkin, O.; Hu, X. L. *Angew. Chem., Int. Ed.* **2009**, *48*, 2937-2940.

4.1. Introduction

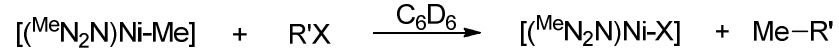
Non-activated alkyl halides are among the most difficult substrates for metal-catalyzed C-C coupling reactions because of their reluctance to undergo oxidative addition and because metal alkyl intermediates are prone to unproductive β-H elimination.[1,2] Despite of these challenges, recent progress in Ni and Pd catalysis has resulted in a number of efficient protocols for catalytic C-C coupling of non-activated primary and secondary alkyl halides.[1-8] With the use of zinc, boron, and silicon nucleophiles, even functionalized alkyl halides can be coupled.[2-4,8] Grignard nucleophiles are seldom used for the coupling of functionalized organic halides due to their high reactivity.[9] The use of Grignard reagents is however desirable as they are economic, easy to synthesize, and many of them are commercially available.[9,10] The emergence of Fe catalysis has expanded the scopes of coupling reactions between alkyl halides and Grignard reagents.[11] Thanks to the high activities of Fe-based catalysts, the coupling can be carried out at low temperatures where Grignard reagents do not react with the functional groups of the alkyl halides.[12] This improvement is however limited to alkyl-aryl/alkenyl coupling,[12,13] as Fe catalyzed sp^3-sp^3 coupling is more difficult.[14] There are only a few reports of metal-catalyzed cross coupling of functionalized alkyl halides with alkyl Grignards.[15,16] Several keto and ester derivatives were successfully alkylated using a Mn/Cu[16] or Cu[15] catalyst, but the scopes of these transformations were not fully developed. A Ni-catalyzed Kumada-Corriu-Tamao coupling[17] of non-activated and functionalized alkyl bromides and iodides with alkyl Grignard reagents is represented in this chapter. The (pre)catalyst is an isolated and well-defined Ni^{II} coordination compound. The catalysis is general, highly efficient, and tolerates a wide range of important functional groups.

4.2. Reactions of [($^{Me}N_2N$)Ni^{II}-Me] with alkyl halides

During earlier studies as described in Chapter 3, it was found that [($^{Me}N_2N$)Ni-Me] (**3**) reacted cleanly with alkyl polyhalides to give the C-C coupled products. However, the scope of the successful substrates was limited to chloroform and dichloromethane. Further experiments showed that similar reactions occurred when alkyl monohalides were added to a benzene solution of [($^{Me}N_2N$)Ni-Me]. A wide range of primary and secondary alkyl halides was tested in this reaction and the results are represented in Table 1.

In general, the reaction rates follow the order of RI > RBr > RCl, and benzyl > octyl > cyclohexyl. Although Ni based catalysts have been used for C-C coupling reactions,[1,7,8] well-defined Ni alkyl compounds that react with alkyl halides,[7,18] especially alkyl chlorides, to give the alkyl-alkyl coupled products[7] are rare. These reactions suggest that similar Ni(II) alkyl compounds can be the active species in Kumada coupling of alkyl halides with Grignard reagents. Interestingly, reactions of **3** with aryl halides are slower than with alkyl halides. **3** reacts with 10 eq. of PhI at room temperature for 3 hours to give a 50% conversion. The metal containing products were [($^{Me}N_2N$)Ni-Ph] (**5**) (25%) and [($^{Me}N_2N$)Ni-I] **6** (15%). No toluene was formed. The phenyl complex **5** did not react with either alkyl or aryl halides.

Table 1. C-C coupling of **3** with alkyl halides (10 equiv.).



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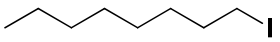
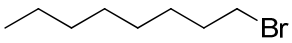
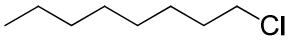
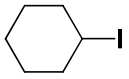
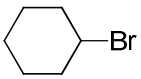
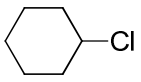
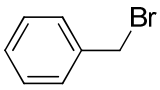
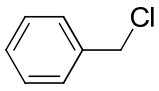
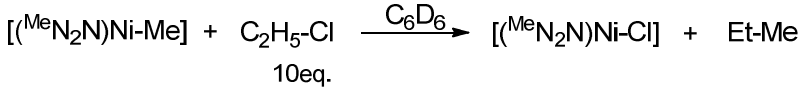
2		r.t.	12	100
3		60	2	100
4		100	3	100
5		60	4	>95
6		60	6	>95
7		100	12	>95
8		60	2	>95
9		60	12	>95

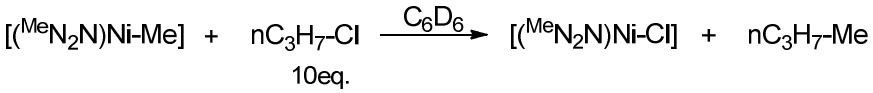
A large difference in the reaction rates was found among different primary alkyl halides. For instance, reaction with C_2H_5-Cl takes place at room temperature (Table 2), but the reaction with $^nC_3H_7$-Cl requires heating for the complete conversion of **3** to **1** (Table 3).

Table 2. Profiles for the reactions of Ni-Me with C_2H_5-Cl.



[($^{Me}N_2N$)Ni-Me] consumption	Time	Temperature
45%	30min	r.t.
60%	1.5h	r.t.
75%	4h	r.t.
100%	18h	r.t.

Table 3. Profiles for the reactions of Ni-Me with C_3H_7-Cl.



[($^{Me}N_2N$)Ni-Me] consumption	Time	Temperature
10%	1h	60^0C
14%	2h	60^0C
33%	18h	60^0C
80%	2h	100^0C
100%	4h	100^0C

4.3. Kumada-Corriu-Tamao coupling of non-functionalized alkyl halides

As described in Chapter 2, reactions between [($^{Me}N_2N$)Ni-Cl] complex and alkyl Grignard reagents produce [($^{Me}N_2N$)Ni-Alkyl] compounds in high yields. Furthermore, [($^{Me}N_2N$)Ni-Alkyl] species react smoothly with alkyl halides to regenerate [($^{Me}N_2N$)Ni-X] (X = Br, I, Cl) complex and to form alkyl-alkyl coupling products (Figure 1). These two processes can be combined together to form a catalytic cycle for cross-coupling reactions between alkyl Grignard reagents and alkyl halides. The activity of complex **1** in Kumada-Corriu-Tamao coupling was investigated.

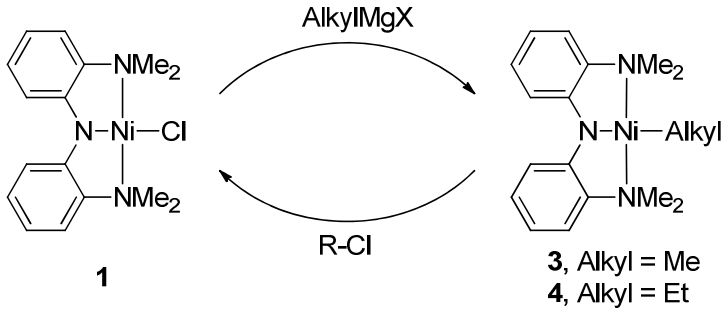
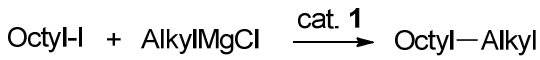


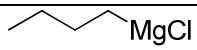
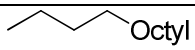
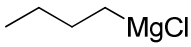
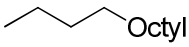
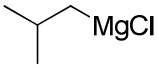
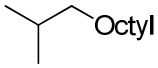
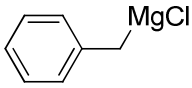
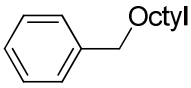
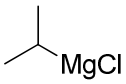
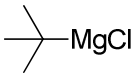
Figure 1. Inter-transformations between [($^{Me}N_2N$)Ni-Cl] and [($^{Me}N_2N$)Ni-Me] complexes.

Because the reaction of **1** with CH_3MgCl to give **3** has a higher yield when carried out at low temperature and because previous experiments showed that coupling of CH_2Cl_2 with ^{n}BuMgCl had the best yield at -20^{0}C, we decided to conduct the catalysis at the same temperature. Octyl iodide was chosen as the test substrate because it could react with **3** at room temperature and it contains β-hydrogens.

A yield of 69% was obtained for the reaction between octyl-I and CH_3MgCl in a presence of 9 mol% **1** in THF (entry 2, Table 4). However, the yield of only 30% was obtained for ^{n}BuMgCl at the same conditions (entry 1, Table 4). The yields for both Grignard reagents were improved by changing the solvent to DMA. Whereas an improvement for CH_3MgCl (74% yield, entry 4, Table 4) was not significant, a drastic increase of yield was observed for the β-H containing ^{n}BuMgCl (65% yield, entry 3, Table 4). Therefore DMA was chosen as the solvent for other substrates. A series of Grignard reagents were. ^{i}BuMgCl could be coupled in a good yield (entry 5, Table 4). A benzyl Grignard reagent gave a lower yield, due to the formation of a homo-coupling side-product (entry 6, Table 4). Coupling was ineffective for secondary and tertiary Grignard reagents (entries 7 and 8, Table 4).

Table 4. Catalytic Coupling of Octyl-I with Alkyl Grignard reagents.[a]



Entry	RMgCl	Product	Solvent	Yield (%)[b]
1			THF	30
2	CH_3–MgCl	CH_3–Octyl	THF	69
3			DMA	65
4	CH_3–MgCl	CH_3–Octyl	DMA	74
5			DMA	77
6			DMA	54
7		-	DMA	0
8		-	DMA	0

[a] 0.6 mmol (1.2 eq.) of RMgCl in THF (1-3 M) was added dropwise to a DMA (0.75 mL) solution of **1** (9 mol%) and octyl-I (0.5 mmol) at -20°C. The reaction time was 30 minutes. [b] GC yields relative to the organic halides.

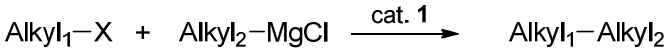
The same protocol was then used for the coupling of other substrates. Primary and secondary alkyl iodides could be coupled to primary alkyl Grignard reagents in 70% - 80% yields (entries 1-3, 5, and 6, Table 5). An exception is the coupling of cyclohexyl-I with CH_3MgCl which gave only 39% yield (entry 7, Table 5). Benzyl Grignard reagent again gave lower coupling yields (entries 4 and 8, Table 5). Tertiary alkyl iodide could not be coupled (entry 9, Table 5).

Primary alkyl bromide could also be used to give comparable yields (entries 10 -16, Table 5). Coupling of benzyl bromide was sluggish due to the formation of the $PhCH_2CH_2Ph$ dimer (entry 17, Table 5). The yield also dropped when a secondary alkyl bromide was used (entry 18, Table 5). Coupling of alkyl chlorides was ineffective (entries 19 – 21, Table 5).

Only a small decrease of yields was observed when the catalyst loading was lowered to 3 mol%. For instance, coupling of $PhCH_2CH_2Br$ with CH_3MgCl gave $PhCH_2CH_2CH_3$ in a 65% yield, and coupling of octyl-Br with *n*BuMgCl gave dodecane in a 70% yield (entries 10 and 15, Table 5, footnote).

Coupling of aryl Grignard reagents under the same conditions was not efficient. The homo-coupling of Grignard reagents was found to be the main product of these reactions.

Table 5. Catalytic Coupling of Alkyl Halides with Alkyl Grignards.[a]



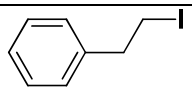
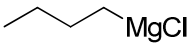
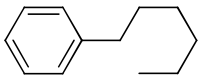
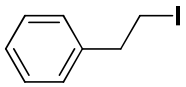
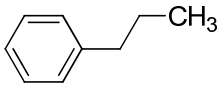
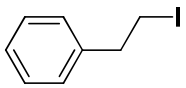
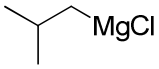
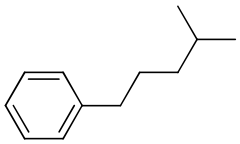
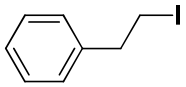
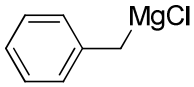
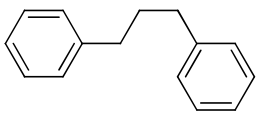
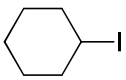
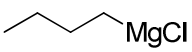
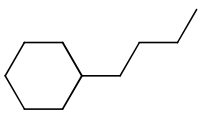
Entry	R^1-X	R^2MgCl	Product	Yield (%)[b]
1				70
2		$CH_3–MgCl$		80
3				75
4				47
5				76

Table 5. (Continued)

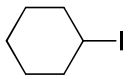
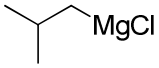
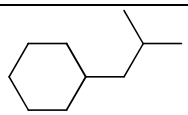
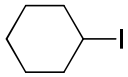
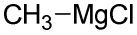
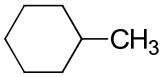
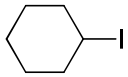
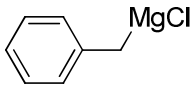
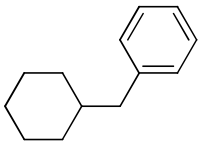
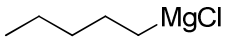
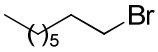
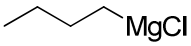
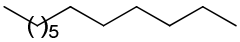
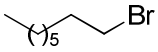
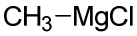
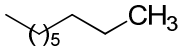
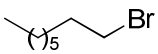
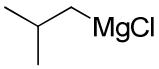
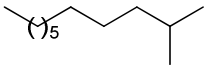
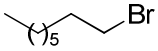
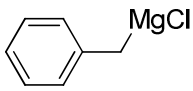
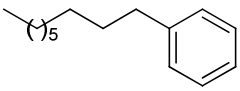
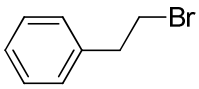
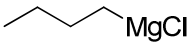
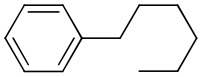
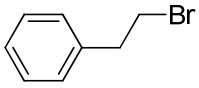
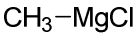
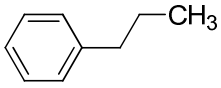
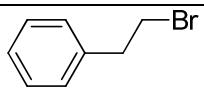
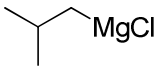
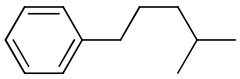
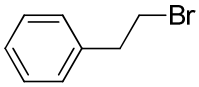
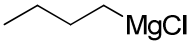
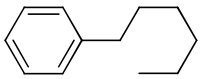
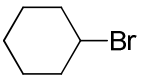
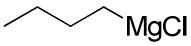
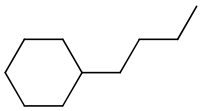
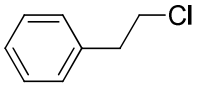
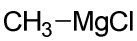
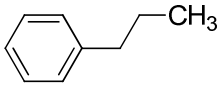
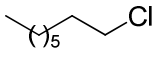
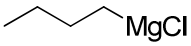
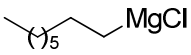
Entry	R^1-X	R^2MgCl	Product	Yield (%)[b]
6				78
7				39
8				10
9			-	0
10				75[c]
11				80
12				58
13				23
14				88
15				87[d]

Table 5. (Continued)

Entry	R^1-X	R^2MgCl	Product	Yield (%)[b]
16				78
17				32[e]
18				45
19				4/25[f]
20			-	0
21			-	0

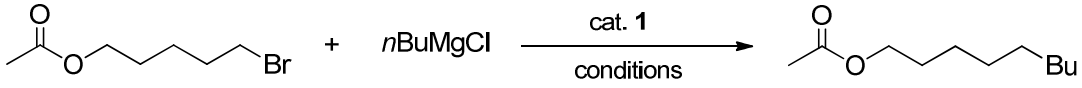
[a] 0.6 mmol (1.2 eq.) of RMgCl in THF (1-3 M) was added dropwise to a DMA (0.75 mL) solution of **1** (9 mol%) and organic halides (0.5 mmol) at -20°C. The reaction time was 30 minutes. [b] GC yields relative to the organic halides. [c] 70% yield when 3 mol% of **1** was used. [d] 65% yield when 3 mol% of **1** was used. [e] $PhCH_2CH_2Ph$ was formed in 62% yield. [f] 4% yield at -20°C, and 25% yield at 60°C.

4.4. Optimization of reaction conditions for coupling of functionalized alkyl halides

The [($^{Me}N_2N$)Ni-Cl]-catalyzed sp^3-sp^3 coupling of non-activated and unfunctionalized alkyl halides with alkyl Grignard reagents take place under very mild conditions (-20^{0}C). Since Grignard reagents are known to tolerate a wide range of functional groups at such a low temperature, a similar protocol might be efficient for the coupling of functionalized alkyl halides with alkyl Grignard reagents. Initial tests were carried out on the coupling of 5-bromopentyl acetate with ^{n}BuMgCl (Table 6).

To our delight, the coupling succeeded in a 60% yield under the conditions previously used for the coupling of unfunctionalized alkyl halides (entry 1, Table 6). The yield was further improved when the reaction was carried out at -35^{0}C, just above the melting point of the reaction mixture (entries 2 and 3, Table 6).[19] 3 mol% of catalyst was adequate to ensure a good yield (78% isolated yield, entry 3, Table 6). Increasing the amount of Grignard reagent led to a lower yield, probably due to the reaction of extra Grignard reagent with the acetate group of the substrate (entry 4, Table 6). Higher temperatures decreased the yields (entries 5-6, Table 6). Other solvents were less efficient, even for N-methylpyrrolidone (NMP), a solvent widely used to promote C-C coupling reactions (entries 7 and 8, Table 6).[1, 15]

Table 6. Catalytic coupling of 5-bromopentyl acetate with *n*BuMgCl.[a]



Entry	Temp. (^{o}C)	Eq. of BuMgCl	Cat. (mol%)	Time (hour)	Yield[b] (%)
1	-20	1	9	0.5	62
2	-35	1	9	1	75
3	**-35**	**1**	**3**	**0.5**	**73/78[c]**
4	-20	1.8	9	0.75	32
5	0	1	9	1	47
6	20	1	9	1	38
7	-35	1	9	0.5	30[d]
8	-35	1	9	0.5	67[e]

[a] General conditions: *n*BuMgCl in THF (2 M) was added dropwise to a DMA (0.75 mL) solution of **1** and octyl-I (0.5 mmol) according to the conditions specified in Table 1. [b] GC yields relative to the organic halides. [c] Isolated yield. [d] THF was used as the solvent. [e] NMP was used as the solvent.

4.5. Scope of Kumada-Coriu-Tamao coupling of functionalized alkyl halides with alkyl Grignard reagents.

Encouraged by these findings, we explored the scope of this catalysis. As shown in Table 7, an array of non-activated and functionalized alkyl bromides and iodides could be coupled under similar conditions.[20] 3 mol% of catalyst was enough to afford high coupling yields for most of the substrates, whereas several substrates demanded a catalyst loading of 9 mol%. Ester, amide, ether, acetal, nitrile, and thioether groups did not interfere with the cross coupling (entries 1-10, Table 7). Substrates containing reactive keto groups were successfully coupled (entries 11-14, Table 7). This is rather unusual since addition of Grignard reagents to ketones is a popular method for the generation of tertiary alcohols. It underscores the high activity of the cross-coupling reactions, which surpass the other reactivity of the Grignard reagents. An alcohol-containing substrate worked when 2 equiv. of Grignard reagent was used (entry 15, Table 7). Alkyl-Cl bond was inert and did not interfere the coupling of alkyl-Br unit (entry 16, Table 7). The coupling of activated alkyl halides (allyl, benzyl, and β-halocarbonyl) is inefficient (data not shown). The current system thus is complementary to the Ni(pybox) system, which is highly active for the coupling of activated alkyl halides.[21] Gratifyingly, alkyl halides containing heterocyclic groups could be coupled to give, for instance, indole, pyrrole, and furan derivatives in high isolated yields (entries 17-20, Table 7).

Importantly, the scope for the electrophile was expanded to include cyclic secondary alkyl iodides (entries 21, 22, 24 Table 7). Alkylation of secondary alkyl iodide is selective in the presence of aryl-bromide bond (entry 24, Table 7). Thus the Ni catalysis improves significantly upon the Cu-catalyzed alkylation protocol,[15] which was ineffective for secondary alkyl halides. This echoes the previous finding that Ni complexes were uniquely situated to the cross-coupling catalysis of secondary alkyl halides, whereas Pd-catalysis is limited to primary alkyl halide substrates.[3] Unfortunately the coupling of a non-cyclic secondary alkyl halide was less efficient (35% yield).

Furthermore, the nucleophiles for this coupling catalysis are not limited to non-branched alkyl Grignard reagents. Sterics at the β-position of the Grignard partner was tolerated (entries 23 and 24, Table 7). Phenyl ethyl Grignard reagents were effective (entries 25 and 26, Table 7). Even acetal functionalized Grignard reagents could be used (entry 27, Table 7). Interestingly, di-alkylation using an alkyl di-Grignard reagent was also successful (entry 28, Table 7).

Table 7. Catalytic coupling of functionalized alkyl bromides and iodides with alkyl Grignard reagents.[a]

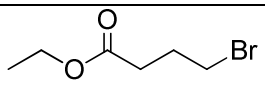
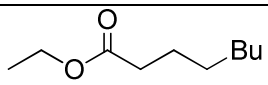
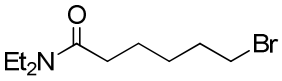
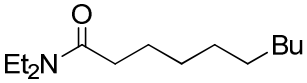
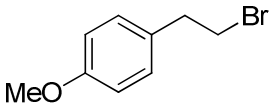
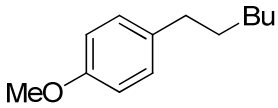
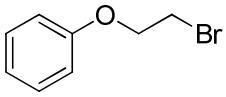
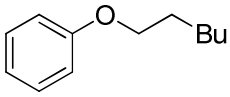
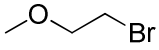
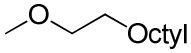
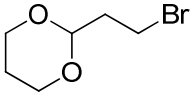
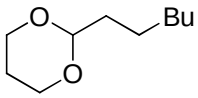
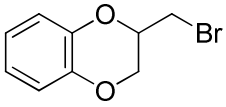
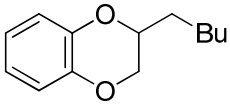
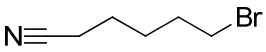
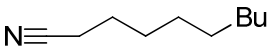
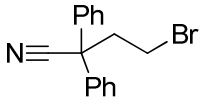
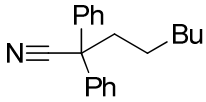
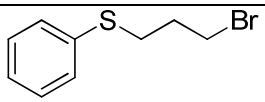
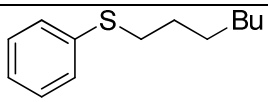
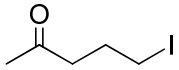
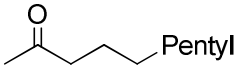
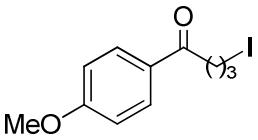
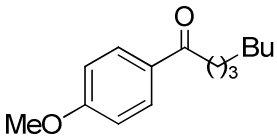
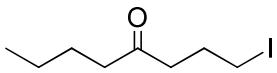
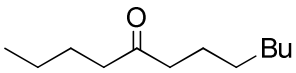
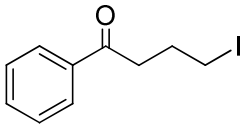
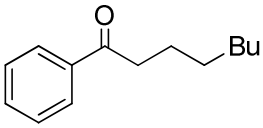
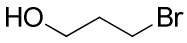
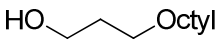
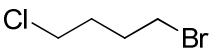
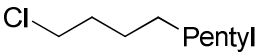
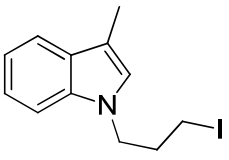
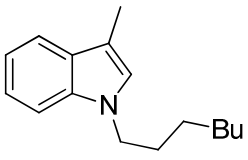
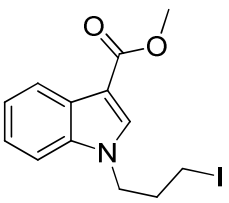
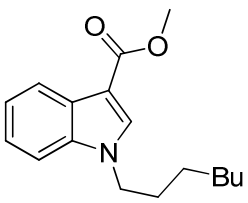
Entry	R^1X	R^2	Product	Yield (%)[b]
1		*n*Bu		85
2		*n*Bu		78
3		*n*Bu		80
4		*n*Bu		97
5		*n*Oct		98
6		*n*Bu		99
7		*n*Bu		71[c]
8		*n*Bu		77[c]
9		*n*Bu		99

Table 7. (Continued)

Entry	R^1X	R^2	Product	Yield (%)[b]
10		*n*Bu		56[c]
11		*n*Pent		60
12		*n*Bu		68[c]
13		*n*Bu		75
14		*n*Bu		74
15		*n*Oct		79[c,d]
16		*n*Pent		91[e]
17		*n*Bu		95
18		*n*Bu		91

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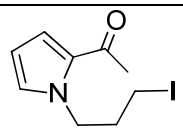
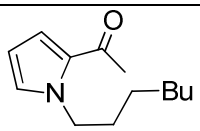
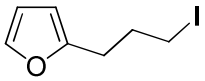
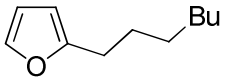
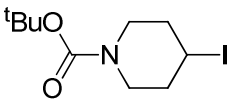
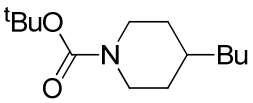
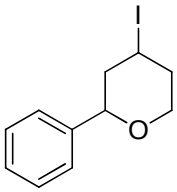
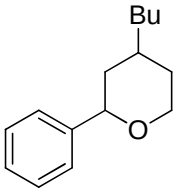
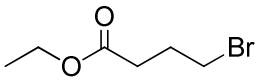
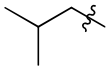
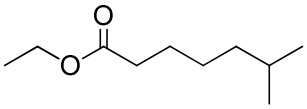
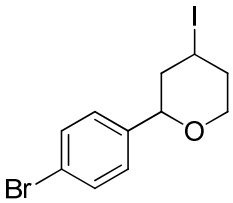
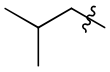
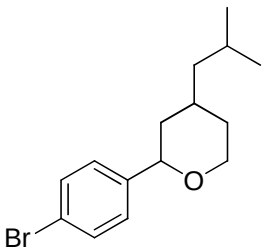
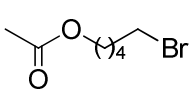
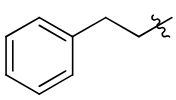
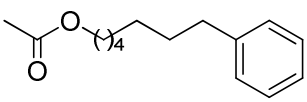
19		*n*Bu		93
20		*n*Bu		99
21		*n*Bu		86
22		*n*Bu		79
23				71
24				89[f]
25				65

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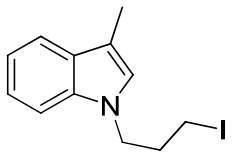
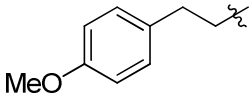
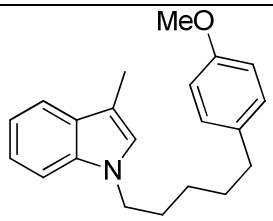
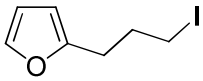
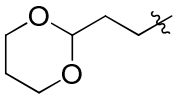
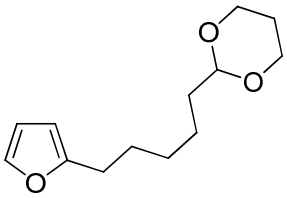
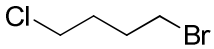
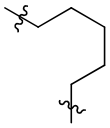
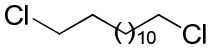
26				87
27				60[g]
28				66[e,g]

[a] General conditions unless specified: 1 eq. of R^2MgCl in THF (1-3 M) was added dropwise to a DMA (0.75 mL) solution of **1** (3 mol%) and R^1X (0.5 mmol) at -35°C. The reaction mixture was then removed from the cold bath while allowing for further reaction for 30 minutes. [b] Isolated yields. [c] 9 mol% catalyst. [d] 2 eq. of Grignard. [e] Only the alkyl-Br bond was coupled. [f] Only the alkyl-I bond was coupled. [g] R^2MgBr instead of R^2MgCl was used.

4.6. Mechanistic investigations

The well-defined nature of the Ni catalyst in the current catalytic system gives an opportunity for a detailed investigation of the reaction mechanism. A series of experiments were done to detect possible intermediates and to isolate the final catalysts after the catalysis.

4.6.1. ^{1}H-NMR experiments

All [($^{Me}NN_2$)Ni^{II}] complexes have distinctive colors and their electronic absorption spectra are shown in Figure 2. There is a significant difference between the hydrocarbyl complexes (**3**-**5**) and the other derivatives (**1**, **7**, **8**, **10**) in the visible spectra: the hydrocarbyl complexes

do not absorb between 600 nm to 800 nm, whereas the spectra of the other compounds exhibit an absorption maximum with a molar absorption coefficient of 100-200 L cm^{-1} mol^{-1}.

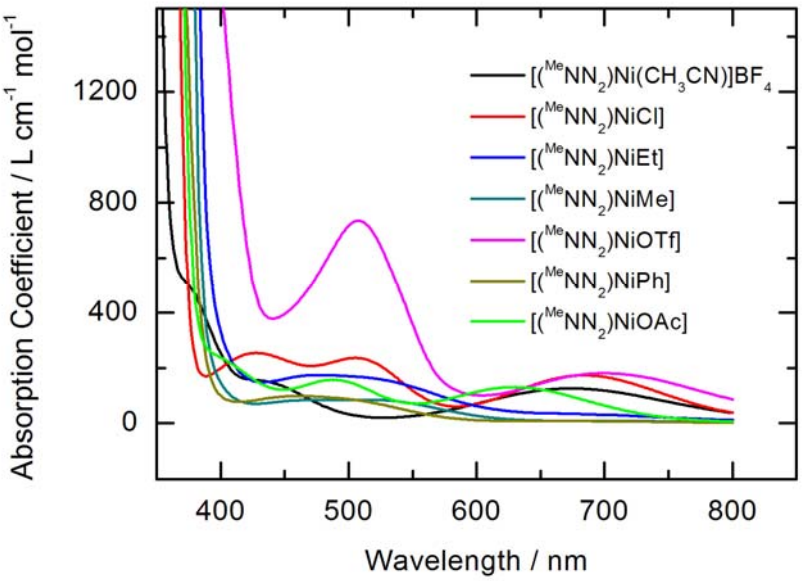


Figure 2. Electronic absorption spectra of nickel complexes. The spectra were recorded in CH_3CN of [($^{Me}NN_2$)Ni-Cl], of [($^{Me}NN_2$)Ni(CH_3CN)]BF_4 (**8•BF$_4$**), of [($^{Me}NN_2$)Ni-Ph] (**5**); in CH_2Cl_2 of [($^{Me}NN_2$)Ni-OTf] (**7**); and in pentane of [($^{Me}NN_2$)Ni-Me] (**3**) and of [($^{Me}NN_2$)Ni-Et] (**4**).

When a Grignard reagent is added to the reaction mixture in the coupling catalysis, the solution turns red, which is also the color of **3** and **4**. When an excess of Grignard reagent is used, the color of the reaction stays red even after addition is completed. This suggests that the resting state of the catalyst is a [($^{Me}N_2N$)Ni-Alkyl] species. In order to confirm this hypothesis, the catalysis was investigated *in-situ* with ^{1}H-NMR spectroscopy.

The reaction between Bu-I (0.5 equiv.) and MeMgCl (1 equiv.) was carried out with 18 mol% (in comparison to BuI) of [($^{Me}N_2N$)Ni-Cl] catalyst. The substrates were chosen for a better quality of ^{1}H-NMR spectrum. When the reaction was finished, the solvent and all products of the reaction were evaporated under vacuum and the spectrum of the solid residue was recorded in C_6D_6. The spectrum is represented in Figure 3 and it corresponds to a very pure [($^{Me}N_2N$)Ni-Me] complex.

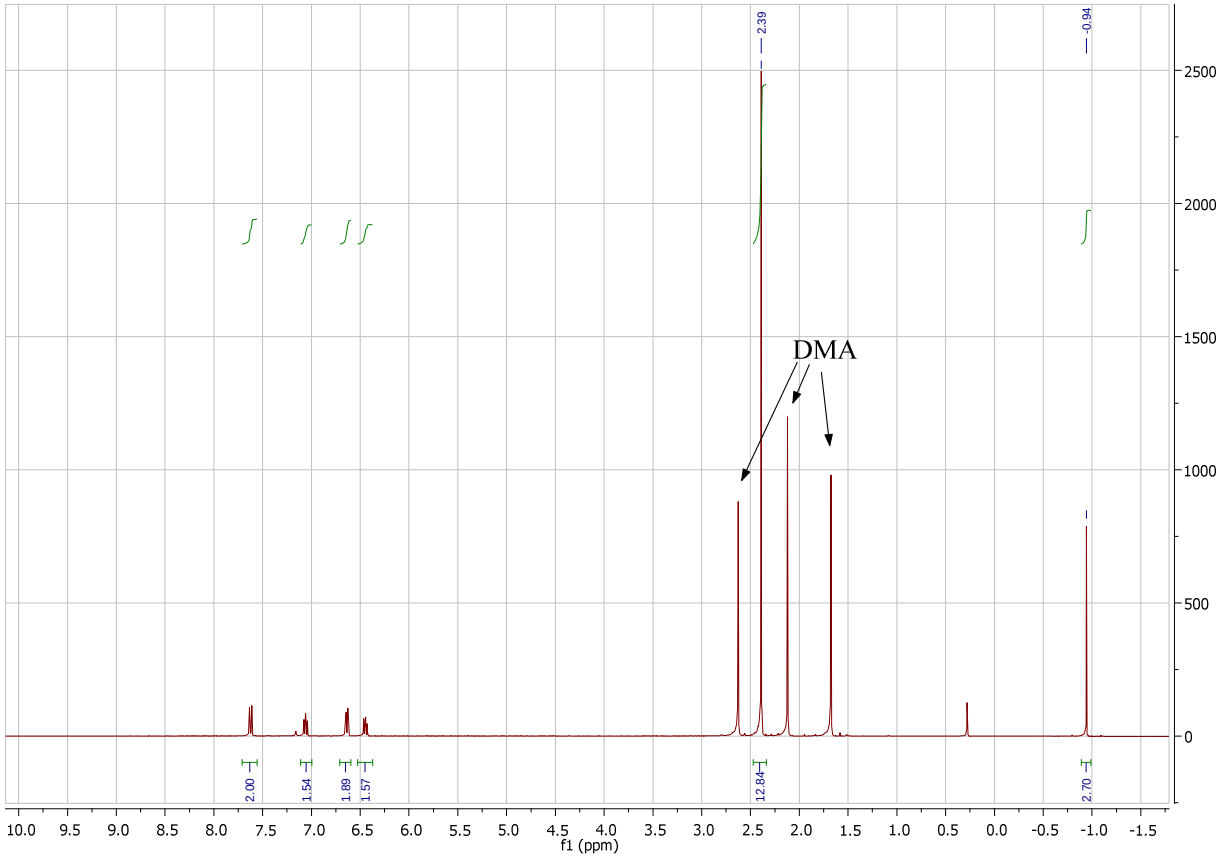


Figure 3. The ^{1}H-NMR spectrum of solid residue in catalytic reaction with Bu-I (0.5equiv.) and MeMgCl (1equiv.).

Similar experiment was done with the inverse ratio of starting materials: Bu-I (1 equiv.) and CH_3MgCl (0.5 equiv.). The ^{1}H-NMR spectrum of the solid residue of the reaction was recorded and it is represented in Figure 4. This spectrum corresponds to the [($^{Me}N_2N$)Ni-Cl] complex and not to the expected [($^{Me}N_2N$)Ni-I] complex. The observed fact can be explained by the transformation of the obtained [($^{Me}N_2N$)Ni-I] complex to [($^{Me}N_2N$)Ni-Cl] compound by I/Cl exchange in DMA. The CH_3MgCl Grignard reagent was a source of chloride anions in the reaction mixture. In a similar reaction, the [($^{Me}N_2N$)Ni-Br] complex was obtained when CH_3MgBr was used for the same experiment.

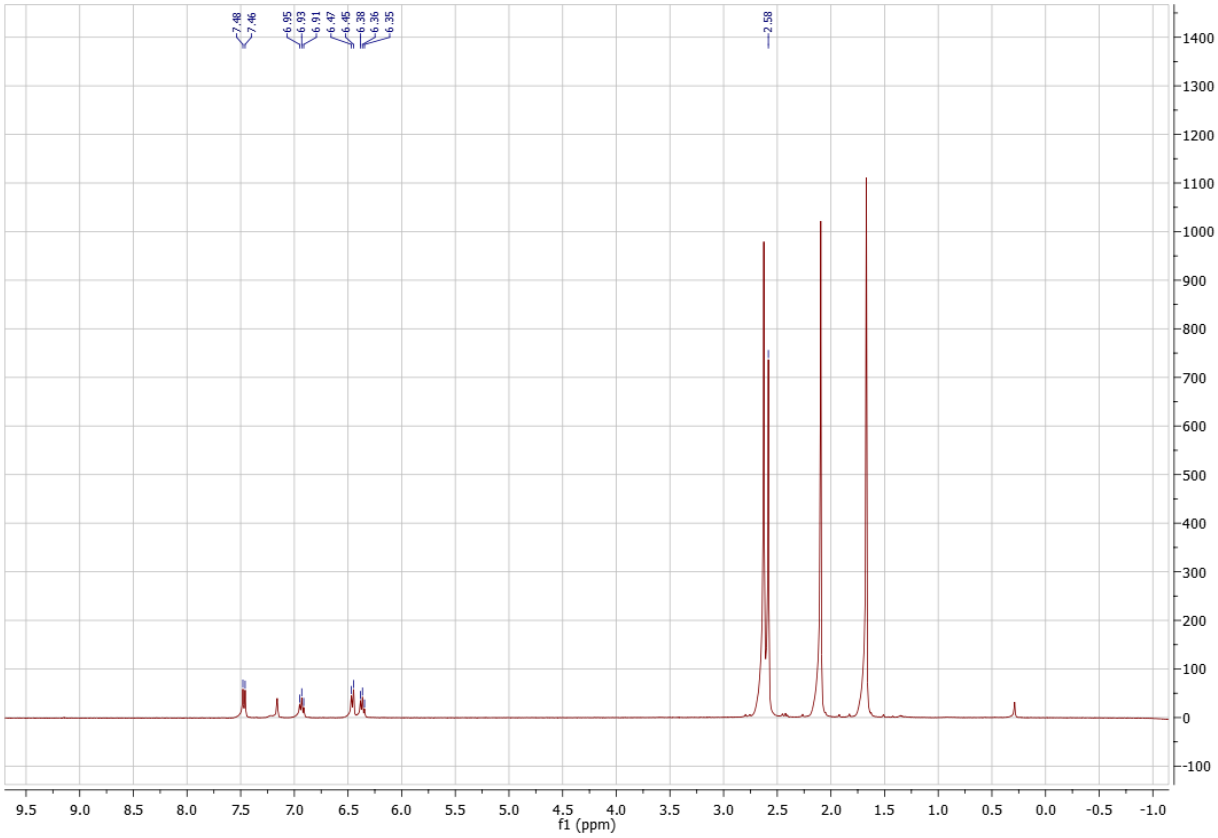


Figure 4. The ^{1}H-NMR spectrum of solid residue in catalytic reaction with Bu-I (1eq) and MeMgCl (0.5eq).

A separate experiment was done to confirm the possibility of I/Cl exchange in DMA. Thus, [(^{Me}N$_2$N)Ni-I] compound was stirred with 5 equiv. of $MgCl_2$ in DMA during 1h at room temperature. Then the solvent was evaporated and the solid mixture was analyzed by NMR spectroscopy. The only Ni-complex, found in the reaction mixture, was [(^{Me}N$_2$N)Ni-Cl] (Figure 5).

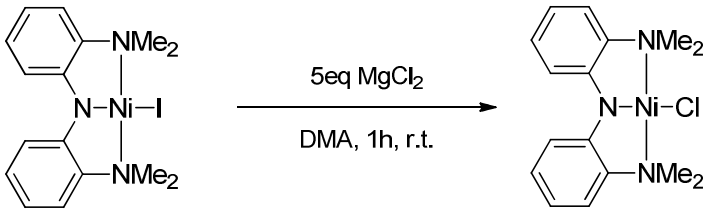


Figure 5. I/Cl exchange in DMA solvent.

4.6.2. Competition reactions

When an equal mixture of octyl-I and $C_6H_5CH_2CH_2Br$ was coupled with ^{n}BuMgCl, the yields for $C_{12}H_{26}$ and C_6H_5-C_6H_{13} were 66% and 44%, respectively (Figure 6). When an

equal mixture of octyl-I and cyclohexyl-I was coupled with ^{n}BuMgCl, the yields for $C_{12}H_{26}$ and C_6H_5-C_6H_{13} were 58% and 25%, respectively (Figure 6). Thus, alkyl iodides react faster than alkyl bromides but the difference between them is not enormous. Primary iodides react faster than secondary iodides during the catalysis. Both these results would be consistent with the turnover determining step of the catalysis being the C-X activation of alkyl halides by the nickel alkyl intermediates.

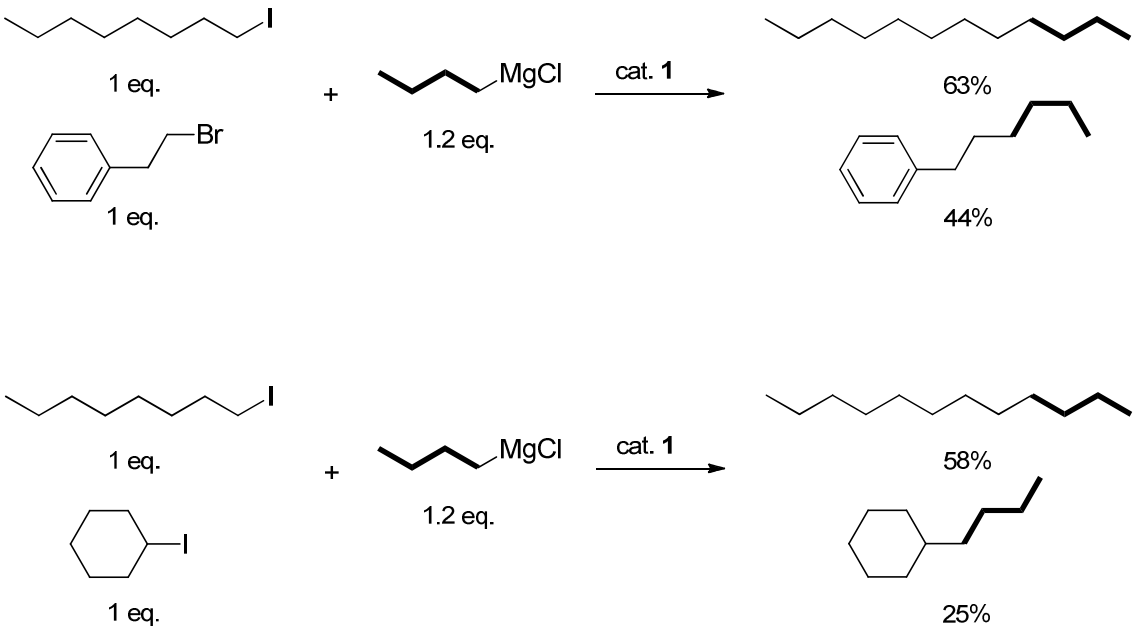


Figure 6. Experiment with competing reactions.

4.6.3. Radical probe experiments

When bromomethylcyclopropane was coupled to nC$_5$H$_{11}$MgCl, 1-nonene was formed as the major product, giving further evidence to the intermediacy of an alkyl radical in the C-X activation step (Figure 7). Coupling of certain alkene-containing substrates gave mostly non-cyclized products (Figure 7). This was probably due to a much slower rate of cyclization for alkyl radicals derivatized from these substrates ($k \sim 1\ s^{-1}$) than the ring-opening of cyclopropanyl methyl radical ($k \sim 10^7\ s^{-1}$), which competed with the cross-coupling reaction.[14] Similar observations were reported earlier by Cárdenas.[14]

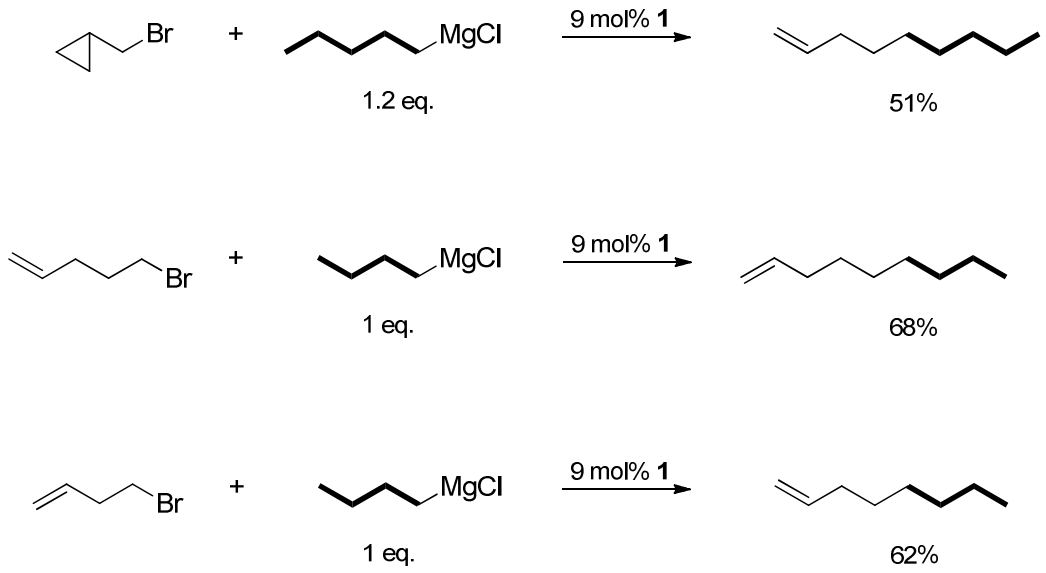


Figure 7. Opening/closing of cycle during catalytic transformations.

Nucleophilic substitution mechanism can be also discarded by the fact that no reaction was observed between [($^{Me}N_2N$)Ni-Alkyl] complexes and TMS-OTf or Alkyl-OTs in C_6D_6.

4.6.4. Proposed mechanism

Concerning the mechanism of the catalysis, stoichiometric reactions of **1** and **3** suggest that the first step is the transmetallation of **1** by a Grignard reagent to form a Ni^{II} alkyl intermediate, which then reacts with an alkyl halide to form the C-C coupled product and **1** again, thereby reentering the catalyst cycle (Figure 8). Further support for this proposal comes from the fact that when 9 mol% of **3** was used as the precatalyst for the coupling of octyl iodide with CH_3MgCl, nonane was formed in 79% yield, comparable to the result obtained using **1**. While Ni has been widely used for Kumada-Corriu-Tamao coupling, this is the first time an isolable Ni^{II} alkyl intermediate has been shown to be a competent intermediate in the catalytic cycle. This is in contrast to the Ni terpyridyl system, where a Ni^{II} alkyl was catalytically incompetent for the Negishi type alkyl-alkyl coupling, but its one-electron reduced species was effective.[12] The mechanism is also different from the classical C-C coupling mechanism by Pd^0, where the activation of organic halides proceeds prior to transmetallation, rather than the reverse in the current system.

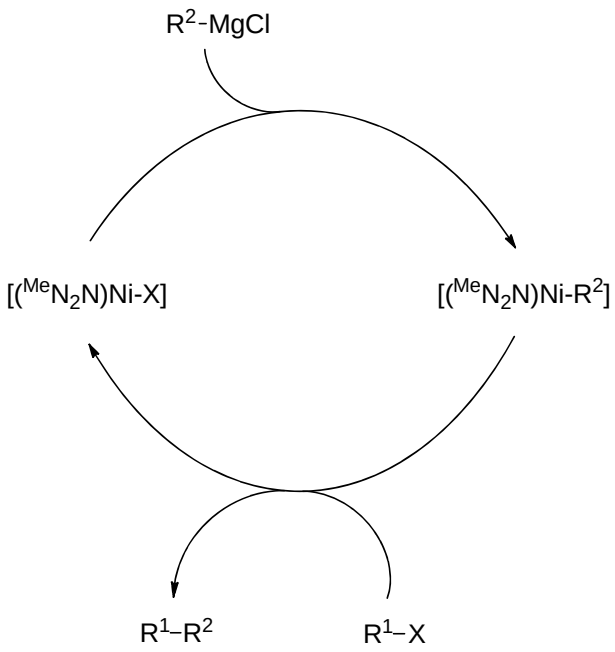


Figure 8. Proposed mechanism for the alkyl-alkyl coupling catalyzed by **1**.

The scopes and limitations of the catalysis are in line with the proposed mechanism. Low temperature (e.g., -20^{0}C) assures the efficiency of transmetallation and the stability of Ni-alkyl intermediates, yet under such conditions only weaker alkyl-Br and alkyl-I bonds, but not alkyl-chloride bonds can be activated. Therefore no satisfactory cross coupling of alkyl chlorides could be obtained. The tridentate ligand $^{Me}N_2N$ remains on the metal center throughout the catalytic cycle, including at the Ni^{II} alkyl stage. Such 4-coordinate square-planar Ni^{II} species is coordinatively rather saturated, and its subsequent reaction with alkyl halides would be sensitive to steric demands. This may lead to the inefficiency for the cross coupling of bulky Grignards and/or alkyl halides. The activation of organic halides goes through a single-electron transfer step, which can explain why aryl halides were not active.

The mechanism in Figure 8 is quite similar to that proposed for the Ni catalyzed cross coupling of unactivated alkyl halides with alkyl Grignards in the presence of 1,3-butadiene. Kambe et al. suggested that in the latter catalysis, the $NiCl_2$ precatalyst was first reduced to Ni^0 by a Grignard reagent, then reacted with 2 eq. of 1,3-butadiene to give a bis-π-allyl Ni^{II} complex.

The allkyl species then reacted again with the Grignard to form a nucleophilic Ni^{II} alkyl anion, which activated alkyl halides by oxidative addition to form a Ni^{IV} bis(alkyl) intermediate. Subsequent reductive elimination afforded the coupling product and completed the catalytic cycle.[7] Both systems involve first transmetallation by Grignards to give a

nucleophilic Ni^{II} alkyl intermediate, then activation of alkyl halides to give a formal Ni^{IV} bis(alkyl) species, and finally productive C-C reductive elimination. Whether this general reaction scheme operates for other Ni-catalyzed Kumada-Corriu-Tamao coupling remains to be seen. There is however one major difference between the two systems: the activation of alkyl halide involves radical intermediates here but not in the Kambe system.[7]

4.7. Conclusions

In summary, an efficient Kumada-Corriu-Tamao coupling of alkyl halides with alkyl Grignard reagents was possible using the [($^{Me}N_2N$)Ni^{II}-Cl] catalyst. A wide range of substrates could be used, and a very good functional group tolerance was achieved. The products can be separated and characterized with spectroscopic methods. The work extends significantly the scope of cross-coupling reactions using Grignard nucleophiles, making these readily available reagents useful for the synthesis of organic molecules containing reactive functional groups. The mechanism of the process was probed.

4.8. Experimental part

The coupling products are fully characterized, and their characterization data can be found in the Chapter 9 and in the supporting information (available free online) of the paper.[22]

Chemicals and Reagents

All manipulations were carried out under an inert N_2(g) atmosphere using glovebox techniques. Solvents were purified using a two-column solid-state purification system (Innovative Technology, NJ, USA) and transferred to the glove box without exposure to air. Deuterated solvents were purchased from Cambridge Isotope Laboratories, Inc., and were degassed and stored over activated 3 Å molecular sieves. Unless noted, all other reagents were purchased from commercial sources and used without further purification. Liquid compounds were degassed by standard freeze-pump-thaw procedures prior to use in the glovebox. The following starting materials in Table 7 were prepared according to literature procedures: 6-bromo-N,N-diethylhexanamide (entry 2),[6] [(3-bromopropyl)sulfanyl]benzene (entry 10),[23] 5-iodopentan-2-one (entry 11), 4-iodo-1-(4-methoxyphenyl)butan-1-one (entry 12) and 4-iodo-1-phenylbutan-1-one (entry 14),[24] 1-iodooctan-4-one (entry 13),[25] 1-(3-

iodopropyl)-3-methyl-1H-indole (entry 17 and 26), methyl 1-(3-iodopropyl)-1H-indole-3-carboxylate (entry 18) and 1-[1-(3-iodopropyl)-1H-pyrrol-2-yl]ethanone (entry 19),[26] 2-(3-iodopropyl)furan (entry 20 and 27),[27] tert-butyl 4-iodopiperidine-1-carboxylate (entry 21),[28] 4-iodo-2-phenyltetrahydro-2H-pyran (entry 22) and 2-(4-bromophenyl)-4-iodotetrahydro-2H-pyran (entry 24),[29] ethyl 4-iodopentanoate (trial with non-cyclic secondary alkyl iodide).[30]

Physical methods

The ^{1}H and ^{13}C NMR spectra were recorded at 293 K on a Bruker Avance 400 spectrometer. ^{1}H NMR chemical shifts were referenced to residual solvent as determined relative to Me_4Si ($\delta = 0$ ppm). The $^{13}C\{^{1}H\}$ chemical shifts were reported in ppm relative to the carbon resonance of $CDCl_3$ (77.16 ppm). GC-MS measurements were conducted on a Perkin-Elmer Clarus 600 GC equipped with Clarus 600T MS. GC measurement was conducted on a Perkin-Elmer Clarus 400 GC with a FID detector. UV-Vis measurements were carried out using a Varian Cary 50 Bio Spectrophotometer controlled by Cary WinUV software. HRCI-MS measurements were conducted at the EPFL ISIC Mass Spectrometry Service at Micro Mass QTOF Ultima. Elemental analyses were performed on a Carlo Erba EA 1110 CHN instrument at EPFL. The temperature of reactions below room temperature was regulated by a Julabo FT-902 chiller.

Reaction of [($^{Me}N_2N$)Ni-Me] with Alkyl Monohalides

In a typical experiment, 0.015 mmol of [($^{Me}N_2N$)Ni-Me] (**3**) was loaded into an NMR tube along with 0.6 ml of C_6D_6. 0.15 mmol of alkyl halides (10 eq.) or 0.015 mmol (1 eq.) was added to this solution and the reaction was periodically monitored by ^{1}H NMR. If the reaction did not occur at room temperature, the solution would be heated at 60 °C or 100 °C. The identification and quantification of products were determined by ^{1}H NMR.

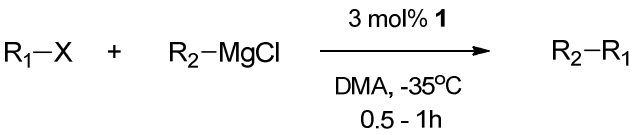
General Procedure for the Synthesis of R-R' from non-functionalized R'-X and RMgCl

$$R_1{-}X \;+\; R_2{-}MgCl \xrightarrow[\text{DMA}]{\text{cat. 1}}{}^{0.5\text{ - }1h} R_2{-}R_1$$

A vial was charged with a certain amount of [($^{Me}N_2N$)Ni-Cl] (**1**), R'-X and DMA (0.75 mL). After the solution reached the desired temperature, a solution of RMgCl in THF was added dropwise under vigorous stirring. The reaction was kept for a certain period of time, and then warmed or cooled to room temperature. A mixture of distilled water (15 mL),

hydrochloric acid (25%, 1 mL) and dodecane (internal standard, 60 µL, 0.265mmol) or decane (internal standard, 60 µL, 0.422mmol) were added to the reaction mixture. The resulting solution was extracted with diethyl ether (10 mL x 3) and the organic phase was separated, dried over $MgSO_4$, and filtered. The identification of the organic products was made by GC-MS, and the yields were determined by gas chromatography, using decane or dodecane as the internal standard.

General Procedure for the Synthesis of R_1-R_2 from functionalized R1-X and R_2MgCl.



Representative coupling procedure: methyl 1-(3-iodopropyl)-1*H*-indole-3-carboxylate (substrate in entry 18, Table 2, 425 mg, 1.24 mmol) and 3 mol% of [($^{Me}N_2N$)Ni-Cl] (**1**) (13 mg, 0.037 mmol) were dissolved in DMA (3 mL). The solution was cooled to -35^{0}C and 2.0 M solution of ^{n}BuMgCl in THF (632 mL, 1.26 mmol) was added dropwise under vigorous stirring. After the addition was completed, the reaction mixture was removed from the cold bath to allow for warming up to room temperature. After 30 minutes, the reaction was quenched with a saturated solution of NH_4Cl (15 mL). The resulting solution mixture was then extracted with ether (3 times, 15 mL each), dried over Na_2SO_4, filtered, and finally evaporated under a reduced pressure. The residue was purified by flash chromatography (silica-gel, hexane/ether 10:1 to 8:2) to afford the product as a colorless oil (308 mg, 91%).

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Chapter 5

*Functional Group Tolerant Kumada-Corriu-Tamao Coupling of Non-Activated Alkyl Halides with Aryl and Heteroaryl Nucleophiles**

*The results presented in this chapter were published in:

Vechorkin, O.; Proust, V.; Hu, X. L. *J. Am. Chem. Soc.* **2009**, *131*, 9756–9766.

5.1. Introduction

The Kumada-Corriu-Tamao coupling, in which an organic electrophile is coupled to a Grignard nucleophile, was discovered at the very early stage of modern cross coupling chemistry.[1] The high reactivity of Grignard reagents, however, results in poor compatibility with functional groups. Subsequently, alternative coupling protocols employing less reactive organometallic reagents such as Zn, B, Sn, and Si nucleophiles were developed.[2,3] Even so, Grignard reagents remain desirable coupling partners because they are economical, easy to synthesize, and many of them are commercially available. Furthermore, many other organometallic coupling partners are prepared from the corresponding Grignard reagents. Thus, the Kumada-Corriu-Tamao coupling provides a more direct access to the same desired products.[4-8] Improvements of functional group tolerance in the Kumada-Corriu-Tamao coupling will encourage the application of this atom-economic[9] coupling reaction in synthesis.

Several recent developments demonstrate that good functional group compatibility can be achieved in the Kumada-Corriu-Tamao coupling. A few catalytic systems based on Mn/Cu,[10] Cu,[11] Pd,[4,12] Ni,[13,14] Co,[15-18] and particularly Fe[19-22] are active enough that the coupling can be carried out at mild conditions (e.g., room temperature and below). Consequently, a large number of alkyl halides containing reactive functional groups such as keto, ester, amide, nitrile, alcohol, heterocycles, etc. were selectively coupled to simple sp^3 or sp^2 Grignard reagents. In terms of the electrophilic coupling partner, the scope of these reactions is comparable to that of Negishi coupling,[23] and in some cases approaches that of Suzuki-Miyaura coupling.[24,25] Nonetheless, the nucleophiles are limited to conventional Grignard reagents.

Parallel to this, the pioneer work of Knochel and coworkers on the preparation of functionalized Grignard reagents make these nucleophiles readily available for further reactions.[5,26] Unfortunately, under most circumstances, these compounds cannot be directly used for cross coupling reactions because they are unstable under the conditions required for such reactions (e.g., elevated temperature). Only a few exceptions are known so far. Knochel et al. showed that aryl Grignard reagents containing ester and nitrile groups and pyridyl Grignard reagents could be coupled to alkenyl halides, halopyridones, and lately aryl bromides.[8,27,28] Buchwald et al. developed a Pd-catalyzed sp^2-sp^2 Kumada-Corriu-Tamao

coupling process that tolerates a wide range of functional groups in either coupling partners using Knochel-type Grignard reagents.[7] Coupling of these reagents to alkyl halides, however, has been scarce prior to the current study.

Because aryl and heteroaryl groups are ubiquitous in natural products, biologically active small molecules, and organic materials, we are interested in developing a method for the coupling of sp^2 Grignard nucleophiles with alkyl halides. We show in this chapter that by judicious choices of reactions conditions and additives, the Kumada-Corriu-Tamao coupling of non-activated alkyl halides with aryl and heteroaryl Grignard reagents can be achieved using the [($^{Me}N_2N$)NiCl] (**1**) pre-catalyst. The catalysis tolerates a wide variety of functional groups in both coupling partners, and allows the use of Knochel-type functionalized Grignard reagents in sp^3-sp^2 coupling.

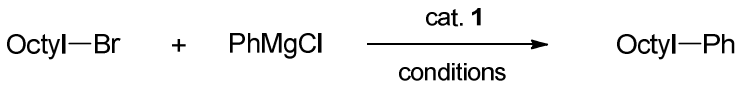
5.2. Optimization of reaction conditions for coupling of alkyl halides with aryl Grignard reagents

Under the same conditions previously employed for alkyl-alkyl Kumada-Corriu-Tamao coupling, the reactions of alkyl halides with aryl Grignard reagents gave low yields of coupling products, mainly due to homo-coupling of aryl Grignard reagent. For instance, in the presence of 9 mol% [($^{Me}N_2N$)NiCl] (**1**), coupling of octyl-Br with PhMgCl produced octyl-Ph only in 36% yield (entry 1, Table 1).

However, the yields of cross coupling reactions can be significantly improved by judicious choice of solvent, temperature, and additives. Amine ligands[18] and additives such as TMEDA[19,20,29] were widely used to promote alkyl-aryl Kumada-Corriu-Tamao coupling, especially in Fe-catalyzed systems. The synergy of THF and TMEDA is well documented in Fe catalysis,[19,20,29] but is less reported in Ni case. We thus investigated the influence of TMEDA in our catalytic system. The addition of TMEDA significantly improved the yields of coupling in THF. In the presence of 1 equivalent of TMEDA in THF at room temperature, 86% of coupling product could be obtained using 5 mol% of **1** (entry 2, Table 1). In the absence of TMEDA, the coupling only had a 20% yield (entry 3, Table 1). The main side products in this case are Ph-Ph (55%) and octyl-octyl (50%). Other amine additives, such as NEt_3, NEt^iPr_2, HMTA, had only modest effects (entries 10-12, Table 1).

Slow addition of PhMgCl (during 1h) was slightly beneficial (compare entries 2 and 4). In the absence of **1**, no coupling product was observed (entry 5, Table 1). The use of 5 mol% of another soluble Ni^{II} compound, $Ni(dme)Cl_2$ or $Ni(PPh_3)_2Cl_2$, as the pre-catalyst resulted in ~ 20% coupling products (entries 6 and 7, Table 1). This underscores the unique activity of complex **1** for this catalysis.

Table 1. Kumada-Corriu-Tamao coupling of octyl bromide with PhMgCl.[a]



Entry	Solvent	Cat., (mol%)	T, (^oC)	Additive	Yield (%)[b]
1	DMA	9	-35	-	36
2	THF	5	20	1 equiv. TMEDA	84
3	THF	9	20	-	20
4	THF	5	20	1 equiv. TMEDA	63[c]
5	THF	0	20	1 equiv. TMEDA	0
6	THF	5 mol% $NiCl_2(dme)$	20	1 equiv. TMEDA	23
7	THF	5 mol% $NiCl_2(PPh_3)_2$	20	1 equiv. TMEDA	15
8	THF	3	20	0.03 equiv. TMEDA	85
9	**THF**	**3**	**20**	**0.3 equiv. TMEDA**	**81[d]**
10	THF	5	20	1 equiv. NEt_3	34
11	THF	5	20	1 equiv. NEt^iPr_2	31
12	THF	5	20	1 equiv. HMTA	59

[a] 0.6 mmol (1.2 equivalent) of PhMgCl in THF (3 mL, 2 M) was added dropwise via a syringe pump (1h) to a solution (1 mL) of **1** and octyl-Br (0.5 mmol) according to the conditions specified in Table 1. The reaction time was 30 minutes to 1 hour. [b] GC yields relative to the organic halides. [c] PhMgCl was added at once. [d] 1 equivalent of PhMgCl was used.

The catalyst loading could be reduced to 3 mol% of catalyst and the amounts of TMEDA could be decreased without sacrificing the yields (entries 8, Table 1). 0.03 equivalent of TMEDA relative to the alkyl halide, or 1 equivalent relative to the catalyst was enough to ensure a high yield. For further reactions, 0.3 equivalent of TMEDA was used for convenience in sample handling.[30] The yield of reaction remained satisfactory with 1 equivalent of PhMgCl (entry 9, Table 1).

5.3. Scope of Kumada-Coriu-Tamao coupling of alkyl halides with aryl and heteroaryl Grignard reagents

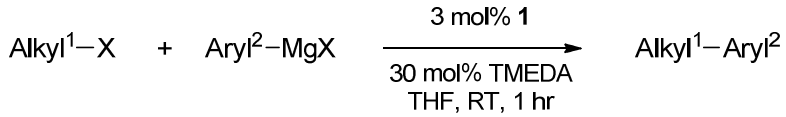
5.3.1. Alkyl-Aryl coupling using common Grignard reagents

We explored the scope of this new coupling protocol for a wide range of alkyl halides and aryl Grignard reagents. Primary alkyl bromides and iodides could be coupled in high yields (Table 2). Thus, Grignard reagents containing fluorine, methoxy and amino groups could be used (entries 1-26, Table 2). Aniline derivatives could be prepared starting from bis(trimethylsilyl)amino-substituted Grignard reagents (entries 3, 13, 17, 25, Table 2). Branching at the β-position of the alkyl halides was tolerated (entries 15-19, Table 2). Coupling of alkyl chloride was inefficient (entry 30, Table 2), likely due to the high C—Cl bond energy.

Cyclohexyl iodide and bromide could also be coupled in modest to high yields (entries 23-26, Table 2). Non-cyclic secondary alkyl halides could only be coupled in low yields (entries 27 and 28, Table 2). This could be attributed to the less steric hindrance in cyclic alkyl halides for C—X activation, and the higher stability of the corresponding metal cycloalkyl intermediates against β-H elimination.[17]

Both 4- and 3-substituted Grignard reagents could be coupled; the coupling of 2-substituted Grignard reagents did not occur (entry 31, Table 2). Tertiary iodide could not be coupled (entry 29, Table 2). This should be a consequence of having a tridentate chelating ligand (N_2N) on the Ni center, which leaves limited space for interaction with the coupling partners. The GC yields were close to the isolated yields (e.g., entries 1 and 11, Table 2).

Table 2. Kumada-Corriu-Tamao coupling of alkyl halides with aryl Grignard reagents.[a]



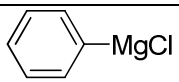
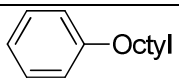
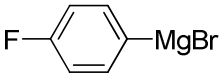
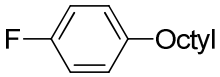
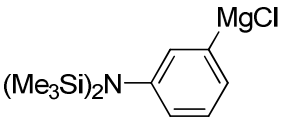
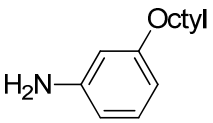
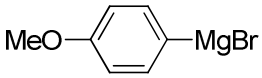
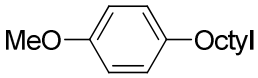
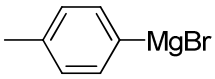
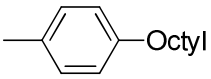
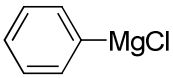
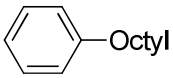
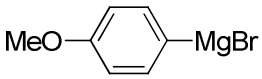
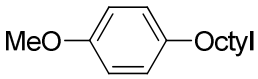
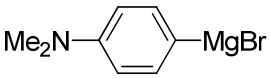
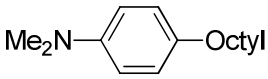
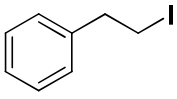
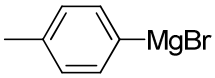
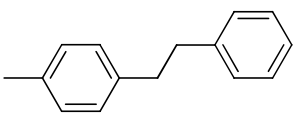
Entry	Alkyl[1]-X	Aryl[2]-MgX	Product	Yield (%)[b]
1	Octyl—I			88/92[c]
2	Octyl—I			98
3	Octyl—I			99[d]
4	Octyl—I			80
5	Octyl—Br			87
6	Octyl—Br			86
7	Octyl—Br			82
8	Octyl—Br			67
9				74

Table 2. (Continued)

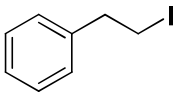
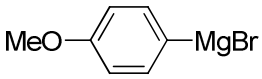
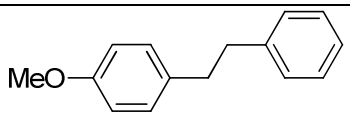
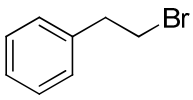
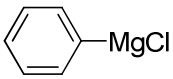
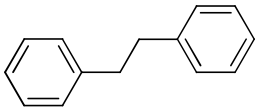
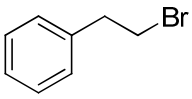
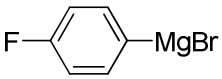
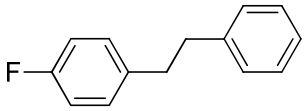
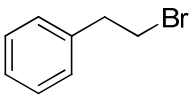
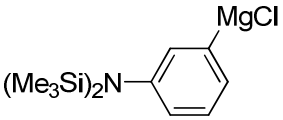
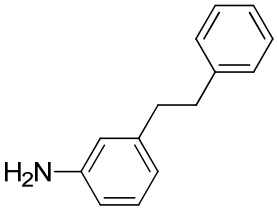
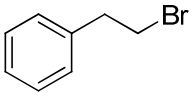
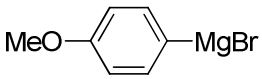
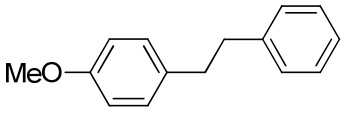
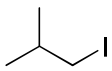
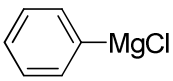
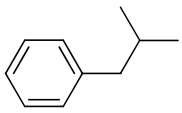
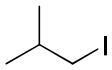
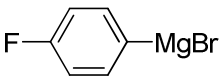
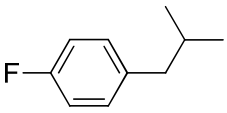
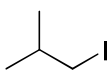
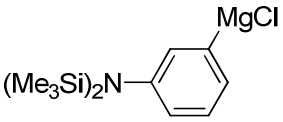
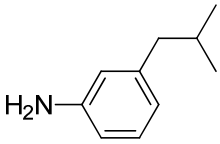
Entry	Alkyl[1]-X	Aryl[2]-MgX	Product	Yield (%)[b]
10				72
11				91/90[c]
12				78
13				99[d]
14				85
15				86
16				86
17				99[d]

Table 2. (Continued)

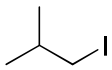
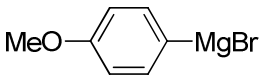
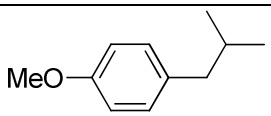
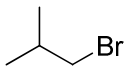
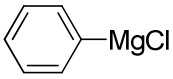
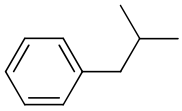
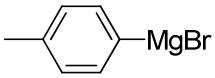
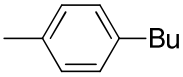
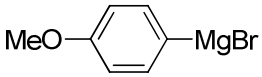
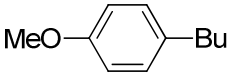
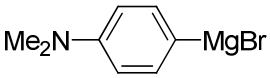
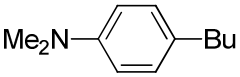
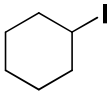
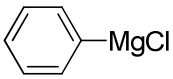
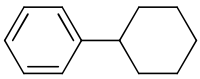
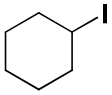
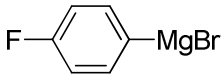
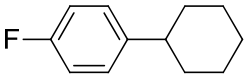
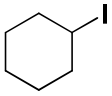
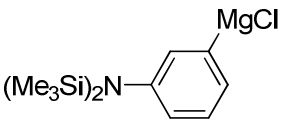
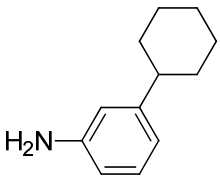
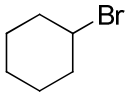
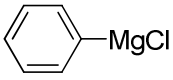
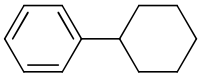
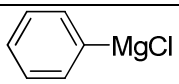
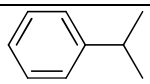
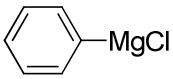
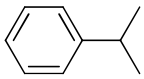
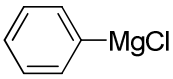
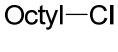
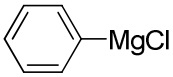
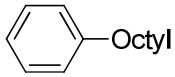
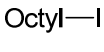
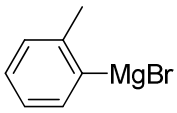
Entry	Alkyl[1]-X	Aryl[2]-MgX	Product	Yield (%)[b]
18				72
19				77
20				99
21				85
22				85
23				62
24				51
25				92
26				65

Table 2. (Continued)

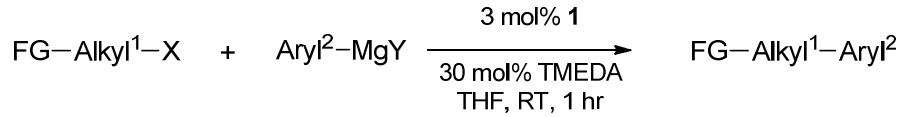
Entry	Alkyl[1]-X	Aryl[2]-MgX	Product	Yield (%)[b]
27				18
28				11
29			-	-
30				22[e]
31			-	-

[a] Reaction procedure unless otherwise specified: 0.6 mmol (1.2 equivalents) of ArMgX and 0.17 mmol of TMEDA in THF (3 mL) was added dropwise via a syringe pump (1 h) to a solution (1 mL) of **1** (5.2 mg, 0.015 mmol) and alkyl-X (0.5 mmol) at room temperature. The reaction time was 1 hour. [b] Unless otherwise specified, GC yields relative to the organic halides. [c] Isolated yields relative to the organic halides. [d] Amine was formed after work up. [e] at 40°C and with 9 mol% catalyst.

We next applied the same conditions to the coupling of functionalized alkyl halides. To our delight, a wide range of functional groups were tolerated. The desired cross coupling products could be easily separated from the reaction mixture in high isolated yields. Nitrile, ether, thioether, acetal, and amide groups did not interfere with the C—C coupling (entries 1-8, Table 3). Coupling of alkyl-Br was selective in the presence of alkyl-Cl, aryl-Cl, and aryl-Br groups (entries 9-11, Table 3), giving rise to products containing the latter groups, which could be subject to further functionalization. An alcohol-containing substrate could be used without protecting groups (entry 12, Table 3). Alkyl halides containing heterocyclic groups could be coupled to give furan, indole, and pyrrole derivatives (entries 13-16, Table 3). Coupling of an aromatic conjugate enone containing substrate was also effective (entry 16,

Table 3). The coupling of ester containing substrates was successful, but required the use of bis[2-(N,N-dimethylaminoethyl)]ether (O-TMEDA) rather than TMEDA as the additive (entries 15-19, Table 3). Functionalized secondary cyclic iodides were coupled similarly (entries 19-20, Table 3). More reactive keto groups however could not be tolerated (entry 21, Table 3). It was found that coupling of alkyl iodides containing ester, amide, and nitrile groups is more efficient that of the respective alkyl bromides. In terms of functional group compatibility on the alkyl halides, the current Ni-system is in line with the most tolerant Pd,[4,12] Fe,[20] and Co[15,17,18] systems.

Table 3. Kumada-Corriu-Tamao coupling of functionalized alkyl halides with aryl Grignard reagents.[a]



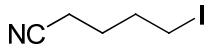
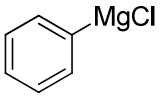
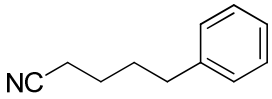
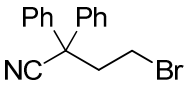
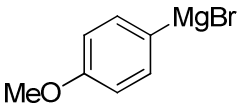
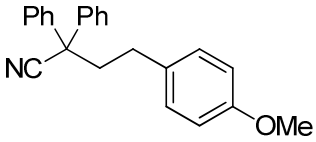
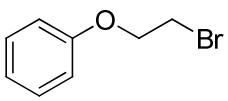
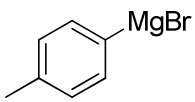
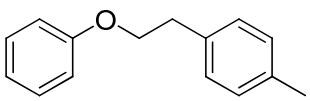
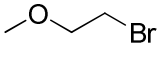
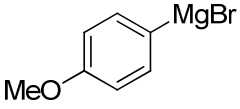
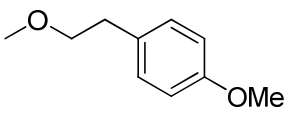
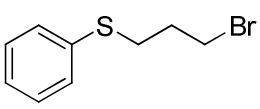
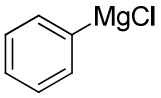
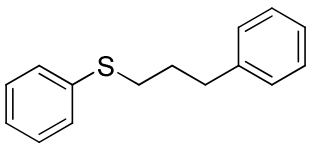
Entry	FG-Alkyl^1-X	Aryl^2-MgX	Product	Yield (%)[b]
1				80
2				89
3				99
4				89
5				66

Table 3. (Continued)

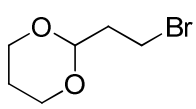
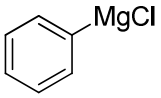
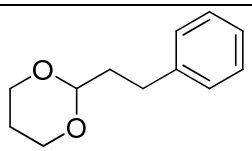
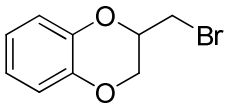
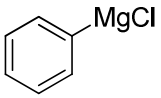
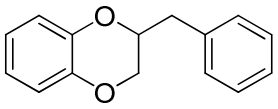
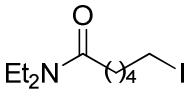
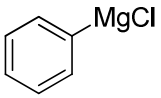
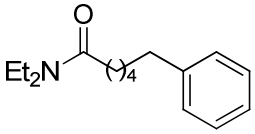
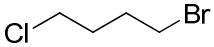
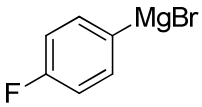
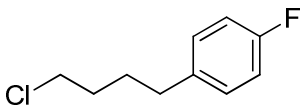
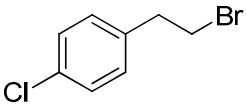
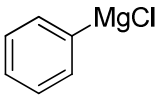
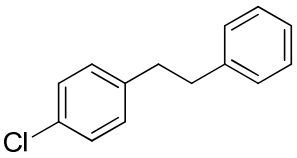
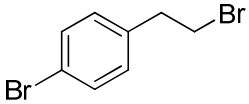
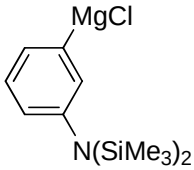
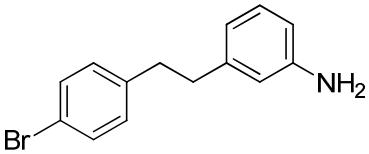
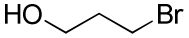
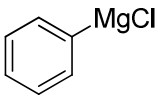
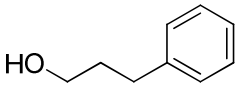
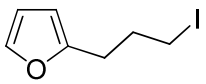
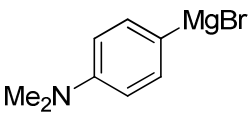
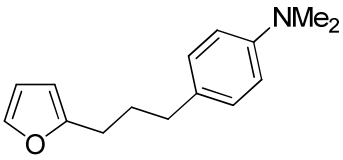
Entry	FG-Alkyl[1]-X	Aryl[2]-MgX	Product	Yield (%)[b]
6				96
7				85
8				84
9				76
10				98
11				98
12				74[c]
13				83

Table 3. (Continued)

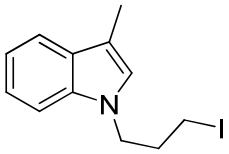
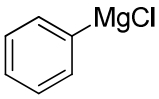
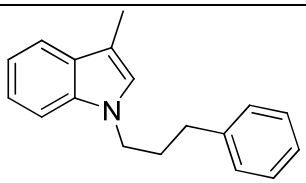
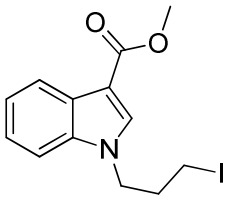
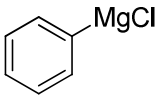
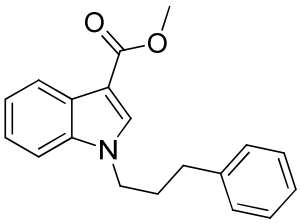
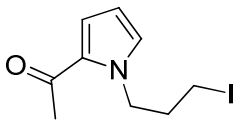
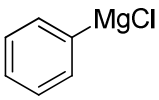
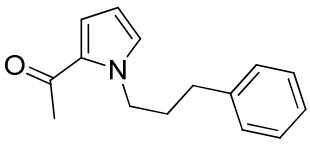
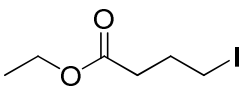
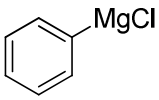
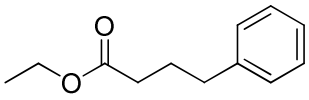
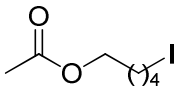
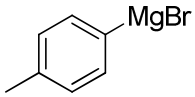
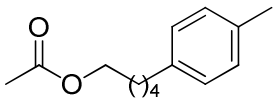
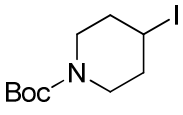
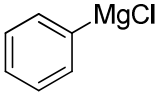
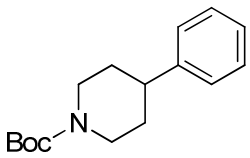
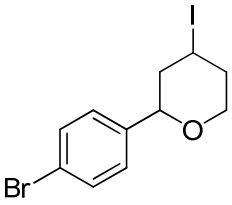
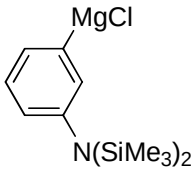
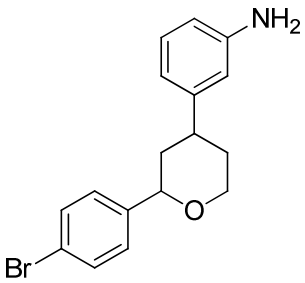
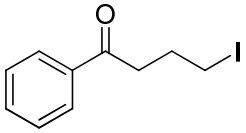
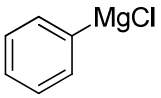
Entry	FG-Alkyl[1]-X	Aryl[2]-MgX	Product	Yield (%)[b]
14				81
15				81[d]
16				62[d]
17				75[d]
18				63[d]
19				65[d]
20				73

Table 3. (Continued)

Entry	FG-Alkyl[1]-X	Aryl[2]-MgX	Product	Yield (%)[b]
21			-	-

[a] Reaction procedure unless otherwise specified: 1.2 mmol (1.2 equivalent) of ArMgX and 0.34 mmol of TMEDA in THF (6 mL) was added dropwise via a syringe pump (1h) to a solution (2 mL) of **1** (10.4 mg, 0.03 mmol) and alkyl-X (1 mmol) at room temperature. The reaction time was 1 hour. [b] Isolated yields relative to the organic halides. [c] 2.4 equiv. of **3a** used. [d] 60 mol% O-TMEDA was used in place of TMEDA.

5.3.2. Alkyl-Aryl coupling using Knochel-type Grignard reagents

The mild conditions and the good functional group compatibility of this coupling method encouraged us to explore the coupling of alkyl halides with functionalized Grignard reagents. The extension to include the functionalized aryl Grignard reagents as coupling partners posed several challenges. These nucleophiles have limited stability at room temperature and above, and thus they should be used at lower temperatures. However, they contain electron withdrawing groups (CN, RCO, CF_3) which in turn make them less nucleophilic. A highly active catalyst is thus required, which might explain why there are only very few reports succeeding in the coupling of these Grignard reagents.[7,8,27] All prior examples concern sp^2-sp^2 C—C coupling. The coupling of alkyl halides could be more difficult due to the possibility of unproductive β-H elimination. Gratifyingly, complex **1** is able to catalyze the sp^3-sp^2 Kumada-Corriu-Tamao coupling of alkyl iodides with these Grignard reagents.

Knochel et al. developed two different general procedures for the preparation of Grignard nucleophiles containing nitrile, ester, and CF_3 groups. In method A, a functionalized aryl halide underwent a halide/Mg exchange with an isopropyl Grignard reagent to yield a functionalized Grignard reagent and an isopropyl halide; in method B, with the aid of LiCl, Mg inserted into the same aryl halide precursor to form the desired Grignard reagent (Figure 1).

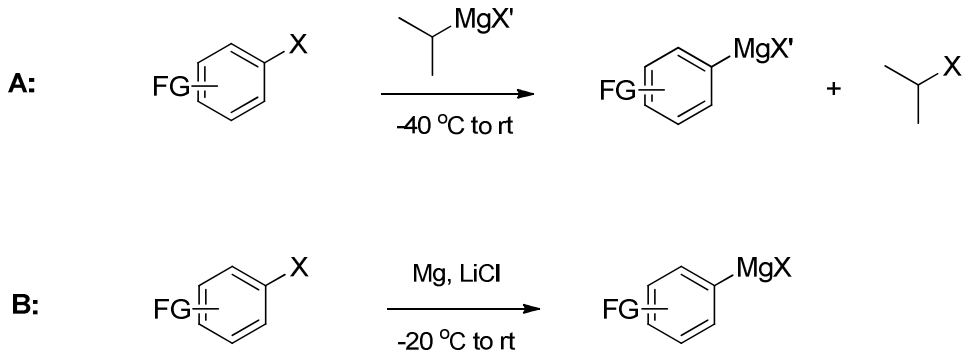


Figure 1. The Knochel procedures for the synthesis of functionalized Grignard reagents.

We prepared the Knochel-type Grignard reagents in a slightly modified procedure (see experimental part) and used them in-situ for alkyl-aryl coupling reactions employing the newly developed protocol. We initially chose octyl-I as the test substrate. When method A was used to make the Grignard reagents, isopropyl bromide or iodide was presented as a side-product in the reaction mixture. This complicated the cross coupling of such Grignard reagents with other alkyl halide because under the same conditions, reactions with the isopropyl halide dominated (entry 1, Table 4). No isopropyl-aryl cross coupling product was found. We suspect that the main side reaction was HX elimination from the isopropyl halide.

This problem was remediated using an excess of the coupling partners, and a 5:1 ratio of alkyl halide versus Grignard reagent was enough to ensure an efficient coupling. In cases where the electrophilic coupling partner was cheap and readily available (such as octyl-I), this method was sufficient. If the alkyl halides were expensive and required several steps to prepare, then an improvement was warranted. It was thus satisfying to find that about 2.5-3.7 equivalents of the unreacted alkyl halides could be recycled from the product mixtures in high purity.

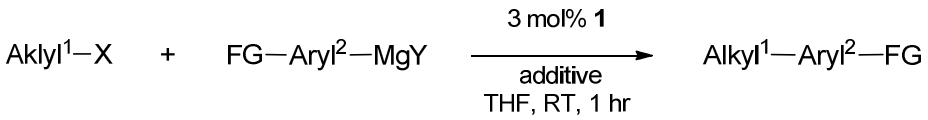
As reported by Wang et al., O-TMEDA increased the stability of the functionalized Grignard reagents.[31] Thus, octyl-I could be coupled to ester, nitrile, and amide containing Grignard nucleophiles in high isolated yields (entries 2-6, Table 4).

The preparation of Grignard reagents via Method B was more attractive because it did not require a pre-made Grignard reagent, but just Mg. However, among Grignard reagents prepared by this method, only those contain CF_3 and nitrile groups could be further used in the coupling reactions. And a 1:2 ratio of alkyl halide versus Grignard reagent was necessary for high yields (entries 7 and 8, Table 4).

The modified procedure was efficient for the coupling of other alkyl halides, including functionalized alkyl halides, with the Knochel-type Grignard reagents. Homobenzylic iodide, primary iodides containing heterocyclic, nitrile, enone, ester, and amide groups could be readily coupled (entries 9-14, Table 4). Alkyl-I was selectively arylated in the presence of alkyl-Cl and aryl-Cl groups (entries 15-17, Table 4). Grignard reagents containing ester, amide, tertiary amine, and CF_3 groups could be readily coupled. Although 5 equivalents of alkyl halides were needed when employing method A, these coupling partners could be recycled from the final product mixtures in high purity. Gratifyingly, secondary cyclic iodides could also be used (entries 18-20, Table 4).

Whereas the coupling of alkyl bromides with simple aryl Grignard reagents was efficient, the coupling of them with the Knochel-type Grignard reagents was less efficient (entries 21 and 22, Table 4). This is probably due to the higher barrier in C—Br bond activation, which makes the C—C coupling slower than the competing side reactions such as reaction with isopropyl halides (for method A), HX elimination, and/or decomposition of the Grignard reagents.

Table 4. Kumada-Corriu-Tamao coupling of alkyl halides with the Knochel-type aryl Grignard reagents.[a]



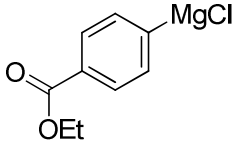
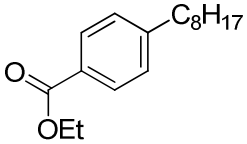
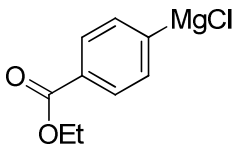
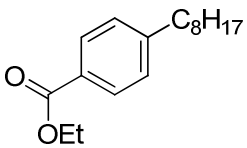
Entry	Alkyl[1]-X	FG-Aryl[2]MgX	Product	Yield (%)
1	Octyl—I			27(A)[d]
2	Octyl—I			83(A)[d]

Table 4. (Continued)

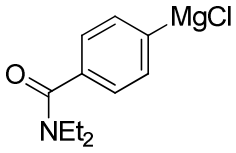
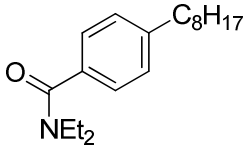
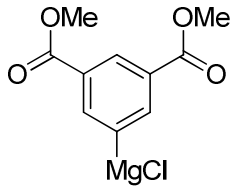
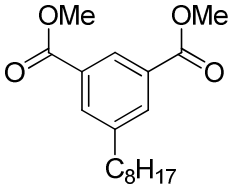
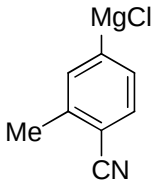
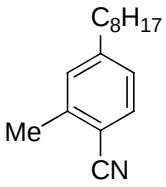
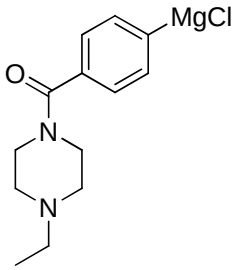
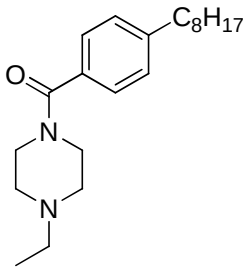
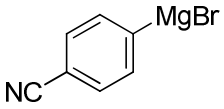
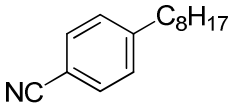
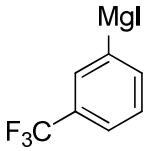
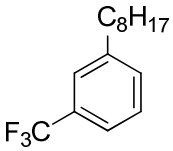
Entry	Alkyl[1]-X	FG-Aryl[2]MgX	Product	Yield (%)
3	Octyl—I			75(A)[d]
4	Octyl—I			70(A)[d]
5	Octyl—I			58(A)[d]
6	Octyl—I			86(A)[d]
7	Octyl—I			62(B)[e]
8	Octyl—I			70(B)[e]

Table 4. (Continued)

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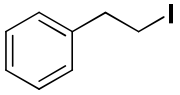
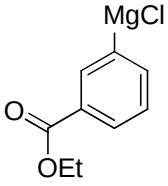
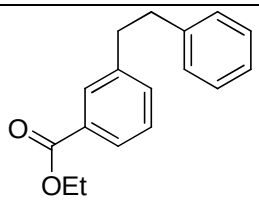
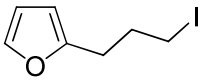
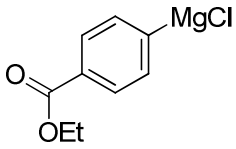
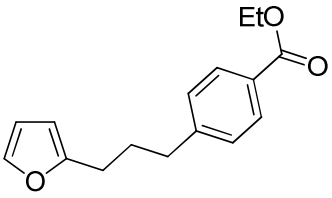
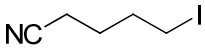
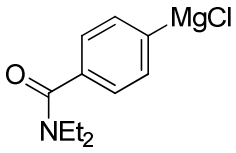
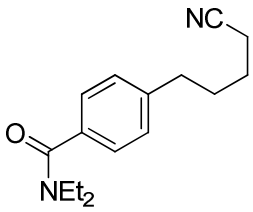
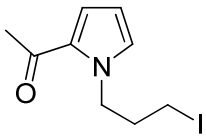
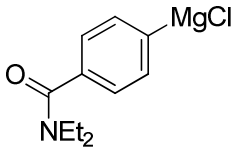
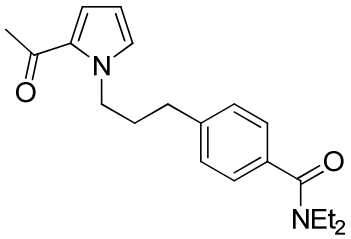
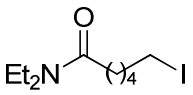
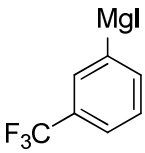
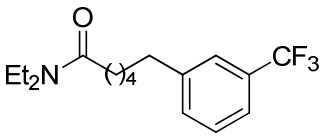
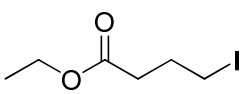
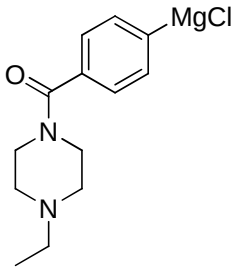
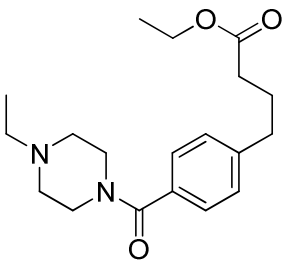
9				88(A)[d]
10				74(A)[d]
11				70(A)[d]
12				72(A)[d]
13				69(B)[e]
14				86(A)[d]

Table 4. (Continued)

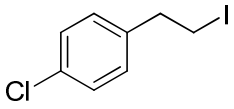
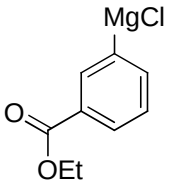
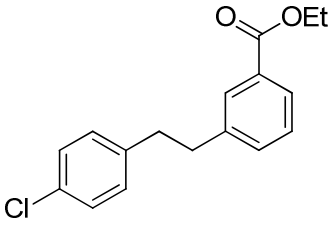
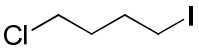
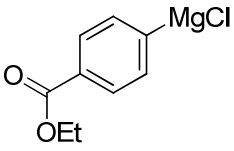
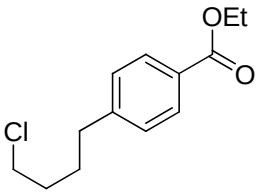
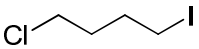
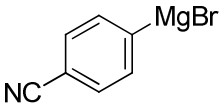
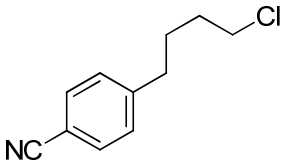
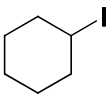
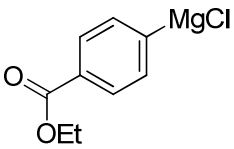
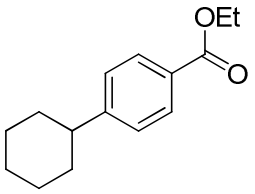
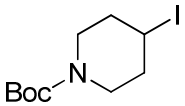
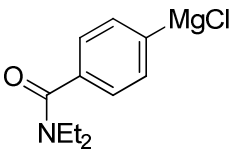
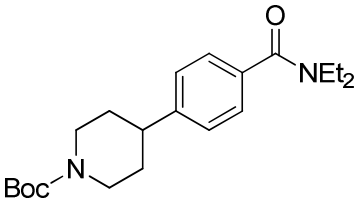
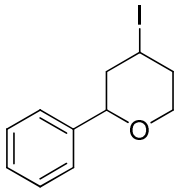
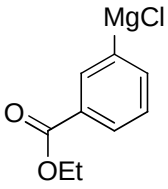
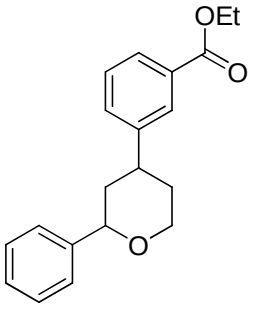
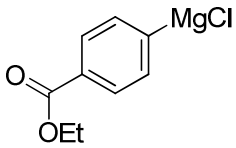
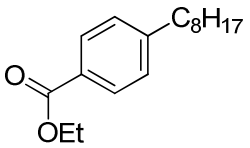
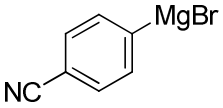
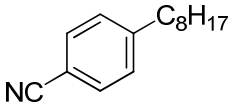
Entry	Alkyl[1]-X	FG-Aryl[2]MgX	Product	Yield (%)
15				76(A)[d]
16				86(A)[d]
17				72(B)[e]
18				61(A)[d]
19				60(A)[d]

Table 4. (Continued)

Entry	Alkyl[1]-X	FG-Aryl[2]MgX	Product	Yield (%)
20				58(A)[d]
21	Octyl—Br			31(A)[d]
22	Octyl—Br			32(B)[e]

[a] Reaction procedure unless otherwise specified: ArMgX (prepared by method A or B) and TMEDA or O-TMEDA in THF (8 mL) was added dropwise via a syringe pump (1h) to a solution (2 mL) of **1** (10.4 mg, 0.03 mmol) and alkyl-X (1 mmol) at room temperature (see experimental section for details). The reaction time was 1 hour. [b] Method A: The Grignard reagent was prepared by X/Mg exchange; ArMgX : Alkyl-X = 1 : 5 except in entry 1, where ArMgX : Alkyl-X = 1 : 1. [c] Method B; The Grignard reagent was prepared by Mg insertion; ArMgX : Alkyl-X = 2 : 1. [d] Isolated yields relative to the Grignard reagents. [e] Isolated yields relative to the organic halides.

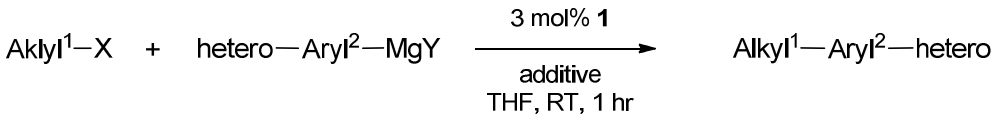
5.3.3. Alkyl-heteroaryl Kumada-Corriu-Tamao coupling

We next explored the coupling of alkyl halides with heteroaryl Grignard reagents. Whereas a number of reports on cross coupling of alkyl halides with aryl nucleophiles have been published in recent years,[24,32] coupling of alkyl halide with heteroaryl nucleophiles is rare.[29,33,34]

The reactions took place smoothly and gave the coupling products in high yields. Thiophen-2-yl-MgBr was coupled in the same fashion as simple aryl Grignard reagents, except that the

coupling with alkyl bromide was not successful (entries 1-4, Table 5). The Knochel-type heteroaryl Grignard reagents could also be coupled. Again, either method A or method B was employed for the preparation of these reagents in situ. The coupling with pyridine- and thiophene-containing Grignard reagents was possible with method B (entries 5-8, Table 5), whereas the coupling with the other functionalized heteroaryl Grignard reagents required method A (entries 9-11, Table 5). The coupling tolerated functional groups in both coupling partners, and primary and cyclic secondary alkyl iodides were selectively coupled. The potentially coordinating pyridine and pyrazole groups did not inhibit the catalysis, likely because they were unable to displace the chelating N_2N ligand even when in large excess.

Table 5. Kumada-Corriu-Tamao coupling of alkyl halides with the hetero-aryl Grignard reagents.[a]



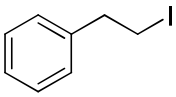
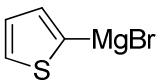
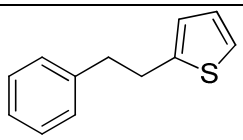
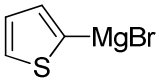
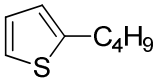
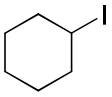
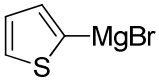
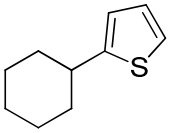
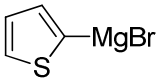
Entry	Alkyl[1]-X	heteroAryl[2]MgX	Product	Yield (%)
1				99[d]
2	Bu—I			93[d]
3				54[d]
4	Octyl—Br		-	0

Table 5. (Continued)

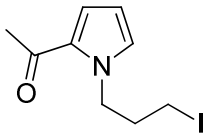
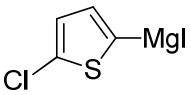
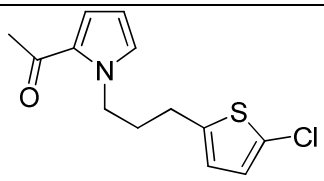
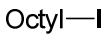
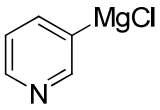
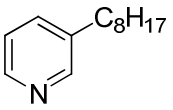
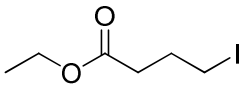
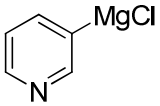
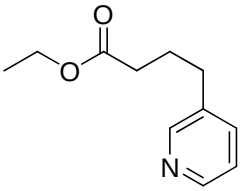
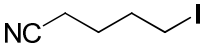
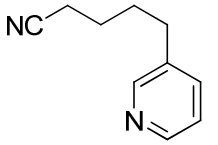
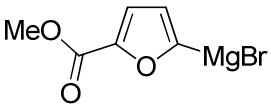
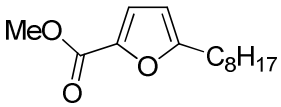
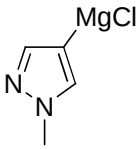
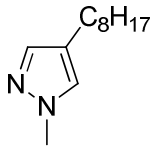
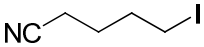
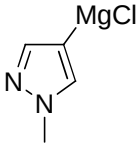
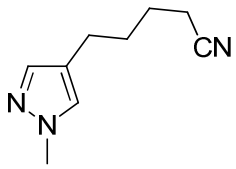
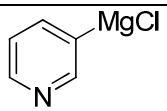
Entry	Alkyl[1]-X	heteroAryl[2]MgX	Product	Yield (%)
5				62(B)[e]
6				76(B)[e]
7				69(B)[e]
8				78(B)[e]
9				65(A)[f]
10				91(A)[f]
11				74(A)[f]

Table 5. (Continued)

Entry	Alkyl[1]-X	heteroAryl[2]MgX	Product	Yield (%)
12	Octyl—Br		-	0(B)

[a] Reaction procedures are the same as the coupling of alkyl halides with simple aryl Griganrd reagents (Table 2) or with the Knochel-type Grignard reagents (Table 4) (see experimental section for more details). [b] Method A: The Grignard reagent was prepared by X/Mg exchange; ArMgX : Alkyl-X = 1 : 5. [c] Method B; The Grignard reagent was prepared by Mg insersion; ArMgX : Alkyl-X = 2 : 1. [d] GC yields relative to the organic halides. [e] Isolated yields relative to the organic halides. [f] Isolated yields relative to the Grignard reagents.

5.4. Mechanistic investigations

5.4.1. Radical probe experiments

A few experiments were conducted to probe the mechanism for this sp^3-sp^2 cross coupling. When bromomethylcyclopropane was coupled to PhMgCl, the ring-opening product 4-phenyl-1-butene was isolated as the main product in 78% yield. When 5-bromo-1-pentene was coupled to PhMgBr, 5-phenyl-1-pentene was isolated in 87% yield (Figure 2).

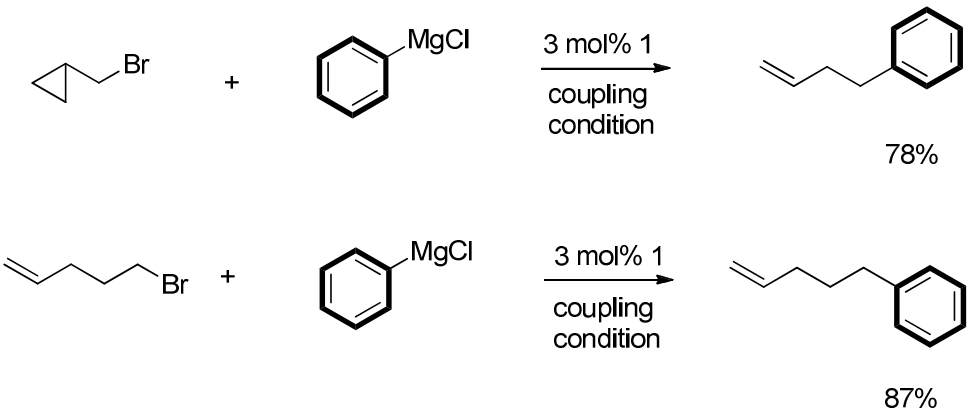


Figure 2. Radical probe experiments.

5.4.2. Competition reactions

The following experiments were done in order to check the relative activity of alkyl iodides versus alkyl bromides. A mixture of 50% of octyl bromide with 50% of butyl iodide was used for the reaction. The GC analysis showed a significant difference in the yield of the coupling

of two halides. 79% of PhMgCl was reacted with Bu-I, whereas only 9% reacted with octyl-Br (Figure 3). This result explains the difference between alkyl iodides and bromides, observed during catalytic reactions.

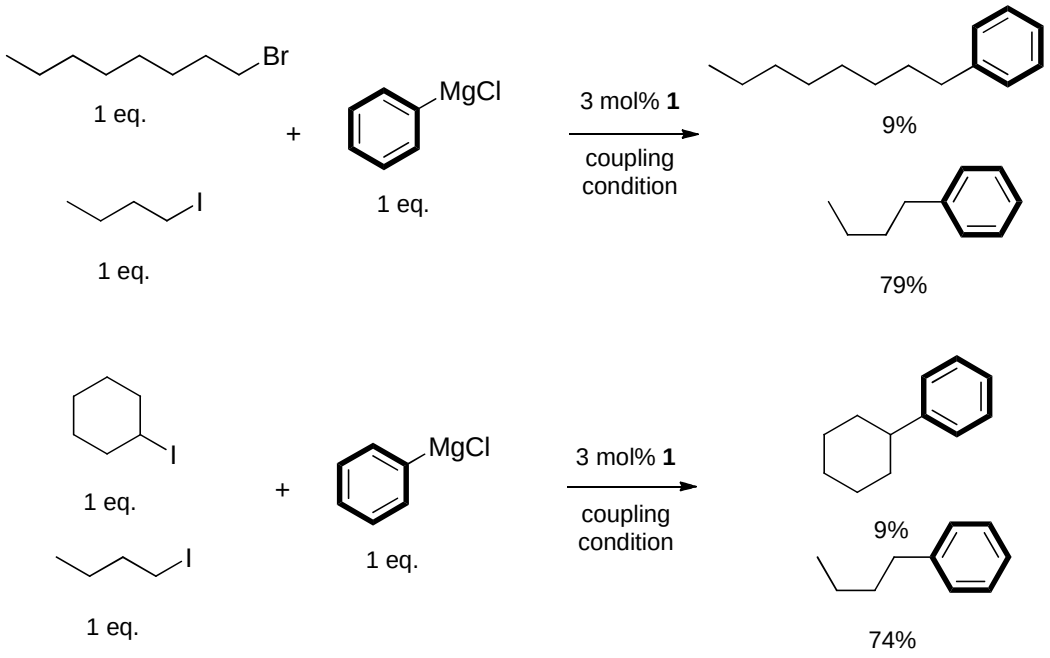


Figure 3. Competition reactions between different alkyl halides.

A similar difference was observed between primary and secondary alkyl halides. When a mixture of 50% of butyl iodide with 50% of cyclohexyl iodide was used for the reaction with PhMgCl, the main coupling product butylbenzene was obtained in 74% yield. Only 9% of PhMgCl reacted with cyclohexyl iodide, again confirming results, obtained for the catalytic reactions (Figure 3).

5.4.3. The active catalyst

When the coupling of octyl-I with PhMgCl was conducted in the presence of 100 equivalents of Hg (relative to the catalyst), octyl-Ph was produced in a 84% yield, nearly identical to the coupling in the absence of Hg (Figure 4). This suggests that heterogeneous metal particles are not responsible for the catalysis.[35]

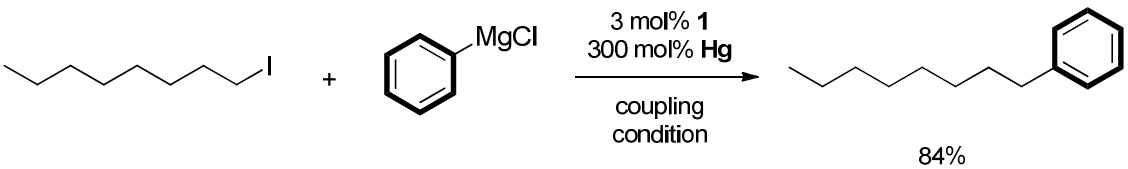


Figure 4. Catalytic coupling in the presence of 100 equiv. of Hg.

We attempted to identify the metal-containing species after the catalysis. In the coupling of octyl-I with PhMgBr, when 3 mol% of [($^{Me}N_2N$)NiCl] (**1**) was used as the precatalyst, we isolated [($^{Me}N_2N$)Ni-Ph] (**5**) in 72% yield (relative to **1**) from the catalysis mixture after acidic workup in air. Complex **5** was synthesized by reaction of **1** with PhMgBr,[36] and it is apparently stable under air and in protic solutions. We then tested a pre-made sample of **5** for the coupling of octyl-I and octyl-Br with PhMgBr following our optimized protocol. Using 3 mol% of **5** as the precatalyst, the reactions produced octyl-Ph in 92% and 72% yields, respectively. These results are comparable to those obtained using 3 mol% of **1** as the precatalyst.

As described in Chapter 2, [($^{Me}N_2N$)Ni-Ph] (**5**) failed to react with alkyl halides in C_6D_6 to give C—C coupled products.[36] We reinvestigated the reaction of **5** with 20 equivalents of octyl-I under catalytically relevant conditions (in THF in the presence of TMEDA) by NMR, but again no reaction was observed over 24 hours (Figure 5).

Figure 5. Reaction between [($^{Me}N_2N$)Ni-Ph] and 20 equiv. of octyl-I.

Complex **5** did react slowly with PhMgBr under the same conditions to give the previously reported Mg complex [($^{Me}N_2N$)(THF)Mg-Cl] (**6**), with 25% conversion after 2 hours (Figure 6). No other Ni-complexes were detected in the reaction mixture. The rate of this reaction is roughly 2 times slower in the presence than in the absence of TMEDA. The reaction seems too slow to be relevant to the catalysis, which finishes within 1 hour with more than 30 turnovers. Additionally, when **6** was used as the precatalyst for the coupling of octyl-I with PhMgCl, only 2% of octyl-Ph was formed under the same conditions, suggesting that **6** is not a competent catalyst for this catalysis.

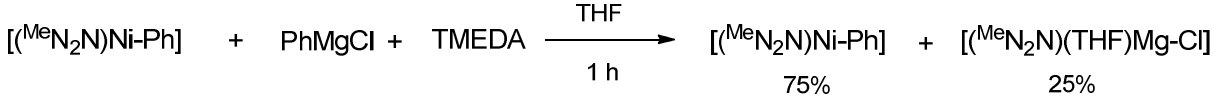


Figure 6. Reaction between [($^{Me}N_2N$)Ni-Ph] and PhMgCl.

Interestingly, when **5** was mixed with an equal mixture of PhMgCl, octyl-I, and TMEDA (all 1 equivalent relative to **5**) in THF, a rapid reaction occurred, which gave the C—C

coupled product octyl-Ph (Figure 7). When the addition of PhMgCl was slow (20 minutes), only trace of **6** was formed. When the addition was fast (in one portion), 25% of **6** was formed. Thus the benefit of slow addition of Grignard reagents for some coupling reactions (vide supra) might be due to the suppression of the reaction indicated in Figure 6, which leads to the decomposition of the active catalyst.

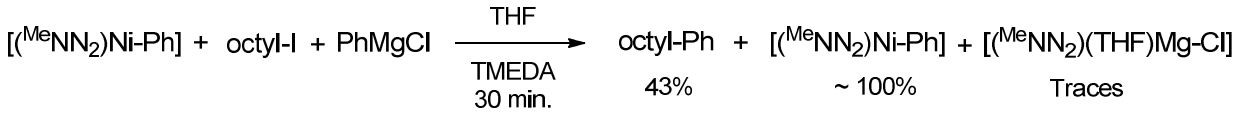


Figure 7. The reaction in the mixture of PhMgCl, octyl-I, and TMEDA.

5.4.4. Proposed mechanism

Taking into consideration that [(^{Me}N$_2$N)Ni-Ph] (**5**) is an active catalyst and is also the resting state of the catalyst in the coupling reactions of alkyl halides with PhMgCl, we propose that analogous Ni^{II}-(hetero)aryl species [(^{Me}N$_2$N)Ni-R^2] (**A,** R$_2$ is an aryl or heteroaryl group) is an intermediate in the Ni-catalyzed sp^3-sp^2 coupling reactions (Figure 8).

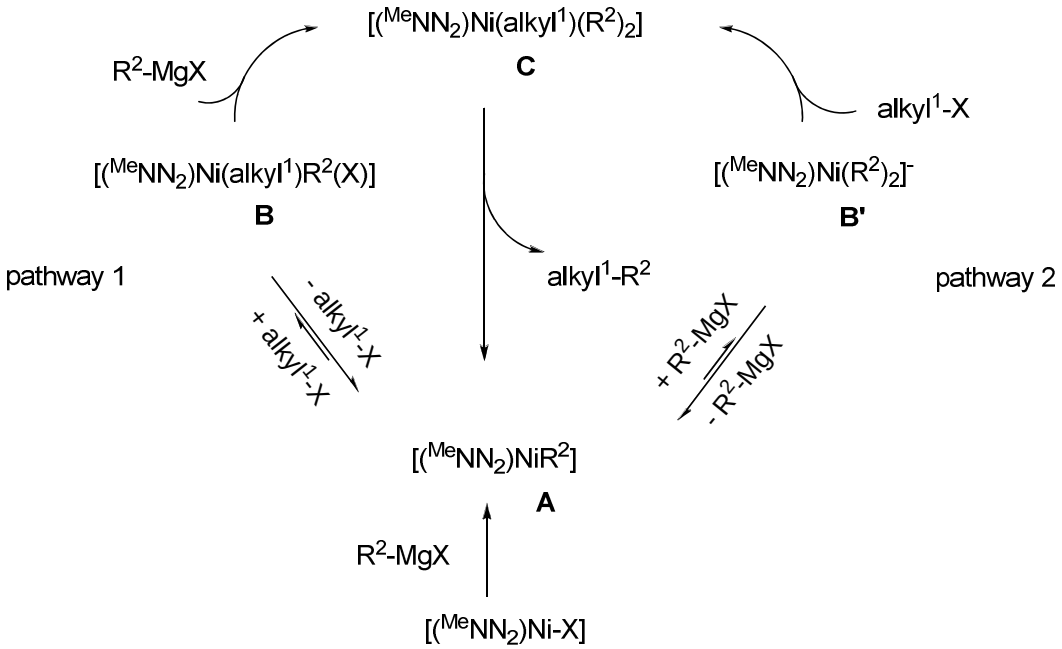


Figure 8. Proposed catalytic cycles for sp^3-sp^2 coupling; R^2 represents an aryl or heteroaryl group.

This intermediate is formed by transmetallation of the [($^{Me}N_2N$)Ni-Cl] precatalyst with a Grignard reagent. It reacts with a mixture of alkyl halide and Grignard reagent to give a six-coordinate complex [($^{Me}N_2N$)Ni(alkyl)(R^2)$_2$] (**C**). Reductive elimination then gives the alkyl-aryl coupling product and regenerates **A**. The high yield of alkyl-aryl coupling suggests that alkyl-aryl reductive elimination is faster than aryl-aryl reductive elimination. Whereas a DFT study found that sp^2-sp^2 reductive elimination is faster than its sp^3-sp^3 counterparts,[37] it was recently shown that the two reactions can become competitive in pincer complexes.[38] Thus the observed higher selectivity for alkyl-aryl coupling does not necessarily contradict the proposed mechanism.

From **A** to **C**, there are two conceivable pathways. **A** could react with alkyl halide to form [($^{Me}N_2N$)Ni(alkyl)(R^2)X] (**B**), which could then be transmetallated by the Grignard reagent to give **C** (pathway 1). Alternatively, **A** could react with a Grignard reagent to give an anionic species [($^{Me}N_2N$)Ni(R^2)$_2$]$^-$ (**B'**), which then reacts with alkyl halide to form **C** (pathway 2). Model reactions between **5** and octyl-I or PhMgCl did not produce **B** or **B'** in a detectable amount (Figures 5 and 6). This however does not exclude either pathway, as the transformation from **A** to **B** or **B'** can be fast and reversible, but thermodynamically uphill. Thus **B** or **B'** exists in a very small percentage, but upon treatment with a second coupling partner, quickly forms **C** and then the coupling product. This is supported by the fact that **5** reacted rapidly with a mixture of octyl-I and PhMgCl to give octyl-Ph (Figure 7).

We prefer pathway 1 because the analogous Ni^{II} alkyl complexes [($^{Me}N_2N$)Ni-alkyl] reacted with alkyl halides to give alkyl-alkyl coupled products in the absence of a Grignard reagent.[36,39] The Ni^{II} (hetero)aryl complexes are less electron-rich and the same reactions with alkyl halides may become thermodynamically un-favored, as is suggested by the catalytic cycle shown in Figure 8. The fact that reductive elimination occurs from **C** but not from **B** is unusual and suggests that the axial ligand (phenyl versus Cl^-) has a big impact in the compound's reactivity.

The oxidation state of Ni in intermediates **B** and **C** warrants a few further notes. If the ligand is redox-innocent, then the Ni center is formally Ni^{IV}. However, it has been shown that pincer amido ligands can be redox active. For example, the [(PNP)NiCl](OTf) complex (PNP = N[2-P($CHMe_2$)$_2$-4-methylphenyl]$_2$ is best formulated as a Ni^{II} center coordinated to a ligand cation.[40] Therefore, **B** and **C** are perhaps better described as Ni^{III} ligand cation

complexes. If this is the case, the Ni center would have 19 electrons, which is less common but not unprecedented for organometallic complexes.[41] On the other hand, the Ni center has a stable 18-electron configuration in the Ni^{IV} formulation, and thus such possibility cannot be excluded. Several stable Ni^{IV} alkyl complexes have been recently reported.[42]

The oxidative addition of alkyl halide to **A** or **B'** likely takes place via single-electron transfer. Thus, **A** or **B'** reacts with the alkyl halide to form an alkyl radical, which quickly recombine to form [($^{Me}N_2N$)Ni(alkyl)(R^2)X] (**B**) [($^{Me}N_2N$)Ni(alkyl)(R^2)$_2$] (**C**). This radical-rebound mechanism is supported by the result of the coupling of PhMgCl with the radical clock, bromomethylcyclopropane, which yielded 4-phenyl-1-butene (Figure 2, vide supra). The radical recombination process hence is slower than the ring opening of cyclopropanylmethyl radical ($k \approx 10^7\ S^{-1}$).[43] It is however faster than the cyclization of 4-pentenyl radical ($k \approx 1\ S^{-1}$), as the coupling of 5-bromo-1-pentene with PhMgCl yielded 5-phenyl-1-pentene (Figure 2). The radical mechanism may also explain why aryl halides could not be coupled under the same conditions.

Competition experiments show that under the same catalytic conditions, activation of alkyl iodides is faster than bromides, consistence with the relative strength of alkyl-X bonds. Activation of primary alkyl halides is faster than secondary alkyl halides. This probably has a steric origin, since secondary alkyl radicals tend to be more stable than their primary counterparts.

In a number of reactions, the coupling is efficient for alkyl iodides but less so for the alkyl bromides. This would be consistent, although does not prove, that the turn-over determining step is the activation of alkyl halides. Since the activation of the more inert alkyl bromides is slower, side reactions compete favorably and the coupling yields diminish.

The addition of TMEDA and O-TMEDA suppresses the homo-coupling of both coupling partners (vide supra). As in other reported systems,[19,20,29] how these additives involve in the catalysis are not clear at this moment. A recent study suggested that in Fe-catalysis, TMEDA can serve as the ligand for the Fe center.[44] Since the Ni center is coordinated by a strong pincer chelate, it is not likely that the additives serve as ligands for Ni ion. They can however bind to Mg, and make the Grignard reagents more nucleophilic. It was reported that in the presence of amine ligands like PMDTA (N,N,N',N'',N''-pentamethyldiethylenetriamine), the Schlenk equilibrium of Grignard reagents is shifted to the side of dismutation (RMgX).[45]

Similar effects might be induced by TMEDA and O-TMEDA in the current system. Furthermore, O-TMEDA is known to stabilize functionalized Grignard reagents.[31] The beneficial effects of TMEDA and O-TMEDA likely have multiple origins.

It is possible that the amido nitrogen in complex **1** is involved in the catalytic cycle. Like TMEDA and O-TMEDA, it could complex the Mg ion of Grignard reagents and enhances their reactivity. It may also act as a nucleophile towards alkyl halides. Since the activation of alkyl halides involves radical intermediates, the latter possibility is however not very likely.

5.5. Conclusions

Applying a newly developed and straightforward protocol, we show here that a preformedand easy to handle Ni^{II} complex [($^{Me}N_2N$)Ni-Cl] (**1**) catalyzes efficiently the sp^3-sp^2 Kumada-Corriu-Tamao coupling of non-activated and β-H containing alkyl halides with aryl and heteroaryl Grignard reagents. The catalysis demands only a relatively low loading of catalyst (3 mol%) and is completed within a short period of time (1h). Primary iodides and bromides and certain secondary iodides can be coupled in high yields. Thanks to the mild conditions employed, the reactions tolerate a wide range of sensitive functional groups. Alkyl halides containing ester, amide, nitrile, ether, thioether, acetal, alcohol, indole, pyrrole, furan, pyrazole, NBoc groups are selectively coupled. Furthermore, functionalized aryl and heteroaryl Grignard reagents, including those of the Knochel-type, could be coupled to non-activated alkyl halides for the first time. In terms of functional group compatibility in both coupling partners, the scope of this Kumada-Corriu-Tamao catalysis is in line with those of the very few reported examples of Negishi[23] and Suzuki-Miyaura[5] sp^3-sp^2 coupling of alkyl halides.[33,46] The advantages of using Grignard reagents as coupling partners include their low cost, ease and atom-economy in preparation, and high reactivity resulting in short reaction time. With the demonstration of efficient coupling between functionalized alkyl halides and functionalized Grignard reagents, the work expands significantly the scope of Kumada-Corriu-Tamao coupling, making this atom-economic and cost-effective cross coupling technology attractive for the construction of more complex molecules and materials.

5.6. Experimental part

The coupling products are fully characterized, and their characterization data can be found in the Chapter 9 and in the supporting information (available free online) of the paper. [47]

Chemicals and Reagents

The following starting materials in **Tables 3-5** were prepared according to literature procedures: 5-iodopentanenitrile (entry 1, Table 3),[48] [(3-bromopropyl)sulfanyl]benzene (entry 5, Table 3),[49] 2-(3-iodopropyl)furan (entry 13, Table 3),[50] 1-(3-iodopropyl)-3-methyl-1*H*-indole (entry 14, Table 3), methyl 1-(3-iodopropyl)-1*H*-indole-3-carboxylate (entry 15, Table 3) and 1-[1-(3-iodopropyl)-1*H*-pyrrol-2-yl]ethanone (entry 16, Table 3),[51] ethyl 4-iodobutanoate (entry 17, Table 3),[52] *tert*-butyl 4-iodopiperidine-1-carboxylate (entry 19, Table 3),[53] 4-iodo-2-phenyltetrahydro-2*H*-pyran (entry 20, Table 4) and 2-(4-bromophenyl)-4-iodotetrahydro-2*H*-pyran (entry 20, Table 3),[54] 4-iodo-1-phenylbutan-1-one (entry 21, Table 3).[55] The following starting materials for Grignard formation were prepared according to literature procedures: N,N-diethyl-4-iodobenzamide (entry 3, Table 4) and (4-ethylpiperazin-1-yl)(4-iodophenyl)methanone (entry 6, Table 4),[56] dimethyl 5-iodoisophthalate (entry 4, Table 4),[57] 2-chloro-5-iodothiophene (entry 10, Table 5),[58] 4-iodo-1-methyl-1H-pyrazole (entry 10, Table 5).[59]

Physical methods

The ^{1}H and ^{13}C NMR spectra were recorded at 293 K on a Bruker Avance 400 spectrometer. ^{1}H NMR chemical shifts were referenced to residual solvent as determined relative to Me_4Si ($\delta = 0$ ppm). The $^{13}C\{^{1}H\}$ chemical shifts were reported in ppm relative to the carbon resonance of $CDCl_3$ (77.00 ppm). GC-MS measurements were conducted on a Perkin-Elmer Clarus 600 GC equipped with Clarus 600T MS. GC measurement was conducted on a Perkin-Elmer Clarus 400 GC with a FID detector. HRCI-MS measurements were conducted at the EPFL ISIC Mass Spectrometry Service at Micro Mass QTOF Ultima. Elemental analyses were performed on a Carlo Erba EA 1110 CHN instrument at EPFL. The temperature of reactions below room temperature was regulated by a Julabo FT-902 chiller. Room temperature ESR measurements were performed using a cw X-band ESR spectrometer (Model ESP300E), from Bruker BioSpin GmbH, equipped with a standard rectangular TE102 cavity. Low temperature ESR measurements were performed using a cw X-band ESR

spectrometer, Model EleXsys 500, from Bruker BioSpin GmbH, equipped with: a Gunn diode–based microwave bridge (Model SuperX), super high-Q cylindrical cavity (Model ER4122SHQE), and Helium gas-flow cryostat (Model ESR900), from Oxfords Instruments (Grand Britain).

Typical procedures for reactions shown in Table 2

A mixture of an alkyl halide (0.5 mmol), [($^{Me}N_2N$)Ni-Cl] (5.2 mg, 0.015 mmol), and TMEDA (25 µL, 0.17 mmol) were dissolved in 1 mL of THF. A solution of an aryl Grignard reagent (0.6 mmol) in THF (3 mL) was added dropwise with a syringe pump (1 h) to this solution. After the addition was completed, the reaction mixture was stirred for 1 h. The reaction was quenched with a saturated aqueous solution of NH_4Cl (15 mL). The resulting solution mixture was then extracted with ether (3 times, 10 mL each), dried over Na_2SO_4, filtered, and subject to GC analysis. 60 µL of dodecane was used as an internal standard.

Typical procedure for reactions shown in Table 3

A mixture of an alkyl halide (1 mmol), [($^{Me}N_2N$)Ni-Cl] (10.4 mg, 0.03 mmol) and TMEDA (50 µL, 0.34 mmol) or O-TMEDA (114 µL, 0.6 mmol) were dissolved in 2 mL of THF (O-TMEDA was used for substrates containing ester or ketone functional group). A solution of an aryl Grignard reagent (1.2 mmol) in 6 mL of THF was added dropwise with a syringe pump (1h) to the above solution. After the addition was completed, the reaction mixture was stirred for 1h. The reaction was then quenched with a saturated solution of NH_4Cl (30 mL). The resulting solution mixture was then extracted with ether (3 times, 20 mL each), dried over Na_2SO_4, filtered, and finally evaporated under a reduced pressure. The residue was purified by flash chromatography on silica-gel.

Typical procedure for reactions shown in Tables 4 and 5, including the preparation of functionalized Grignard reagents in situ

Method A

To a solution of O-TMEDA (228 µL, 1.2 mmol) in 6 mL of THF was added a 2.0 M solution of $^{iso}PrMgCl$ (600 µL, 1.2 mmol) at 0^0C. The mixture was stirred for 20min and a solution of an aryl iodide or aryl bromide (1 mmol) in 2 mL of THF was added by one portion. The resulting mixture was stirred at room temperature for 10 min and then is added

by syringe pump (1h) to a solution containing an alkyl halide (5 mmol) and [($^{Me}N_2N$)Ni-Cl] (10.4 mg, 0.03 mmol) in THF (2 mL). After the addition was completed, the reaction mixture was stirred for 1h. The reaction was then quenched with a saturated solution of NH_4Cl (30 mL). The resulting solution mixture was extracted with ether (3 times, 20 mL each), dried over Na_2SO_4, filtered, and finally evaporated under a reduced pressure. The residue was purified by flash chromatography on silica-gel.

Method B

Magnesium (122 mg, 5 mmol) were placed in a vial to which a 0.5M solution of LiCl (5.0 mL, 2.5 mmol) was added. The magnesium was activated by adding a small amount of diisobutylaluminum hydride (20µL, 1M in THF, 0.02mmol). The resulting mixture was stirred for 5min and a solution of an aryl iodide or aryl bromide (2 mmol) in 2 mL of THF was added at room temperature. The reaction mixture was stirred for 30min (or 2h in case of 4-bromobenzonitrile) and added by syringe pump (1h) to a solution of an alkyl halide (1 mmol), and [($^{Me}N_2N$)Ni-Cl] (10.4 mg, 0.03 mmol) and TMEDA (50 µL, 0.34 mmol) or O-TMEDA (114 µL, 0.6 mmol) in 2 mL of THF (O-TMEDA was used for substrates containing ester or ketone functional group). After the addition was completed, the reaction mixture was stirred for 1h. The reaction was quenched with a saturated solution of NH_4Cl (30 mL). The resulting solution mixture was then extracted with ether (3 times, 20 mL each), dried over Na_2SO_4, filtered, and finally evaporated under a reduced pressure. The residue was purified by flash chromatography on silica-gel.

Stoichiometric reactions of 5 with PhMgCl and octyl-I under catalytically relevant conditions:

For Figure 5:

[($^{Me}N_2N$)Ni-Ph] (complex **6**, 20 mg, 0.05 mmol) was dissolved in THF-D8 (1 mL) and TMEDA (7.5 µL, 0.05 mmol) and 20 equivalents of octyl-I (180 µL, 1 mmol) were added to this solution. The reaction mixture was transferred to an NMR tube and analyzed by NMR.

For Figure 6:

[($^{Me}N_2N$)Ni-Ph] (20 mg, 0.05 mmol) was dissolved in THF-D8 (1 mL) and TMEDA (7.5 µL, 0.05 mmol) was added to this solution. A 2.0M solution of PhMgCl (25 µL, 0.05 mmol)

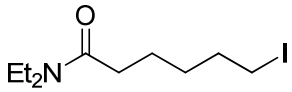
was added by one portion. After the addition was finished, the reaction mixture was transferred to an NMR tube and analyzed by NMR.

For Figure 7:

[($^{Me}N_2N$)Ni-Ph] (20 mg, 0.05 mmol) was dissolved in THF-D8 (1 mL) and TMEDA (7.5 μL, 0.05 mmol) and octyl-I (9 μL, 0.05 mmol) were added to this solution. 2.0M solution of PhMgCl (25 μL, 0.05 mmol) was then added to the resulting mixture (by one portion for fast addition or was dissolved in 1 mL of THF-D8 and was added with a syringe pump during 20min for slow addition). After the addition was finished, the reaction mixture was stirred for 15 minutes, filtered, and transferred to an NMR tube and checked by NMR. After the NMR analysis was finished, the composition of the organic products was checked by GC using 10 μL of dodecane as an internal standard.

Synthesis of substrates

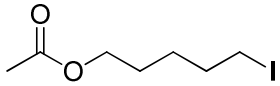
N,N-diethyl-6-iodohexanamide



N,N-diethyl-6-iodohexanamide was synthesized from N,N-diethyl-6-bromohexanamide by the same method as for 4-iodo-1-phenylbutan-1-one (entry 21, Table 3).

^{1}H NMR (400MHz, $CDCl_3$): 3.30 (q, *J* = 7.3 Hz, 2H), 3.24 (q, *J* = 7.0 Hz, 2H), 3.14 (t, *J* = 7.0 Hz, 2H), 2.24 (t, *J* = 7.3 Hz, 2H), 1.79 (m, 2H), 1.61 (m, 2H), 1.38 (m, 2H), 1.11 (t, *J* = 7.3 Hz, 3H), 1.04 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 171.5, 41.7, 39.9, 33.1, 32.6, 30.1, 24.1, 14.2, 12.9, 6.7. HRCI-MS: calculated for ($C_{10}H_{20}NOI$, M+H), 298.0668; found, 298.0669.

5-iodopentyl acetate



5-iodopentyl acetate was synthesized from 5-bromopentyl acetate by the same method as for 4-iodo-1-phenylbutan-1-one (entry 21, Table 3).

^{1}H NMR (400MHz, $CDCl_3$): 4.01 (t, *J* = 6.7 Hz, 2H), 3.14 (t, *J* = 6.7 Hz, 2H), 2.00 (s, 3H), 1.80 (m, 2H), 1.60 (m, 2H), 1.44 (m, 2H).^{13}C NMR (100 MHz, $CDCl_3$): 170.8, 63.9, 32.8, 27.3, 26.7, 20.8, 6.4. HRCI-MS: calculated for ($C_7H_{13}O_2I$, M+H), 257.0038; found, 257.0036.

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Chapter 6

*Ni-Catalyzed Sonogashira Coupling of Non-Activated Alkyl Halides**

*The results presented in this chapter were published in:

Vechorkin, O.; Barmaz, D.; Proust, V.; Hu, X. L. *J. Am. Chem. Soc.* **2009**, *131*, 12078-12079.

6.1. Introduction

Substituted alkynes are recurring units in numerous natural products, bioactive molecules, and organic materials.[1] They are also versatile synthetic intermediates.[2] During the last decades, the Sonogashira coupling has become one of the most widely used methods for the incorporation of alkynyl functionality into organic compounds.[3] It enables the efficient coupling of an organic halide or pseudo-halide with a terminal alkyne, normally with of a Pd catalyst and a Cu co-catalyst. The electrophilic coupling partners for Sonogashira reactions, however, are generally limited to aryl and vinyl halides and triflates. Coupling of non-activated and β-H containing alkyl halides has been challenging due to their reluctance for oxidative addition and the tendency of metal-alkyl intermediates to undergo unproductive β-H elimination. Moreover, in Sonogashira coupling, the organometallic reagents available for transmetallation are the in-situ generated Cu-alkynyl species. They are in sub-stoichiometric amounts (a few mol%) with respect to the substrates, which further disfavors the competition between C—C coupling and β-H elimination.[4] Consequently, in contrast to the recent progress of other cross-coupling reactions of non-activated alkyl halides,[5] there are only two prior reports of successful Sonogashira coupling of such substrates. In their important pioneering studies, Fu et al.[4] and later Glorius et al.,[6] demonstrated the coupling of alkyl iodides and bromides, but not chlorides, using Pd(N-heterocyclic carbene) catalysts. A Ni-catalyzed Sonogashira coupling of non-activated alkyl halides including chlorides is described in this chapter. The different reactivity of alkyl—X (X = I, Br, Cl) bonds allows us to develop coupling protocols selective for a specific C—X bond, leading to orthogonal functionalization of alkyl halides.

6.2. Sonogashira coupling of alkyl iodides and bromides

6.2.1. Optimization of the reaction conditions

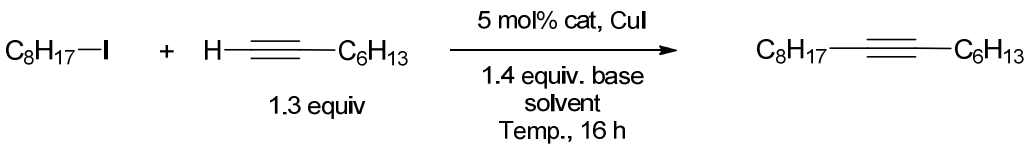
Inspired by our earlier results on the catalytic coupling between alkyl halides and alkyl or aryl Grignard reagents using [($^{Me}N_2N$)NiCl] (**1**) as the catalyst, we decided to use it for Sonogashira coupling. The in-situ generated Cu-alkynyl species in the Sonogashira coupling

are much less reactive compared to Grignard reagents, so a higher reaction temperature should be necessary.

Octyne was used as the test substrate as it is commercially available and it is big enough for the GC-analysis of possible decomposition products. Alkyl iodides are usually the best substrates among alkyl halides in cross-coupling reactions. Octyl iodide was chosen as the other coupling partner.

After exploring a wide range of conditions, we found that 7-hexadecyne could be produced in 75% yield in dioxane with 5 mol% of [(^{Me}N$_2$N)NiCl] as catalyst,[7,8] 3 mol% of CuI as co-catalyst, and 1.4 equivalent of Cs_2CO_3 as base (entry 11, Table 1). The best results were obtained at 100^{o}C. Lower yields were obtained in other solvents (entries 1-3, Table 1). Some side reactions, such as reaction with a solvent or a base, were observed for octyl iodide in more polar solvents, such as NMP and DMA. Other bases were less efficient (entries 5-6, Table 1), possibly due to the lower solubility of these bases in organic solvents. Replacing **1** by H^{Me}N$_2$N, [(^{Me}N$_2$N)$_2$Li$_2$], or Ni(dme)Cl$_2$ completely shut down the catalysis, confirming the role of complex **1** as catalyst (entries 12-14, Table 1). The reaction did not occur under metal-free conditions (entry 16, Table 1).

Table 1. Optimization of the reaction conditions for Alkyl-I and control experiments.[a]



Entry	CuI	Base	Solvent	Cat.	Temp.	Time	Yield
1	7.5mol%	Cs_2CO_3	NMP	[(^{Me}N$_2$N)Ni-Cl]	80	16h	21
2	7.5mol%	Cs_2CO_3	DMA	[(^{Me}N$_2$N)Ni-Cl]	80	16h	36
3	7.5mol%	Cs_2CO_3	Toluene	[(^{Me}N$_2$N)Ni-Cl]	80	16h	46
4	7.5mol%	Cs_2CO_3	Dioxane	[(^{Me}N$_2$N)Ni-Cl]	80	16h	79
5	7.5mol%	K_2CO_3	Dioxane	[(^{Me}N$_2$N)Ni-Cl]	120	16h	23
6	7.5mol%	Na_2CO_3	Dioxane	[(^{Me}N$_2$N)Ni-Cl]	120	16h	10

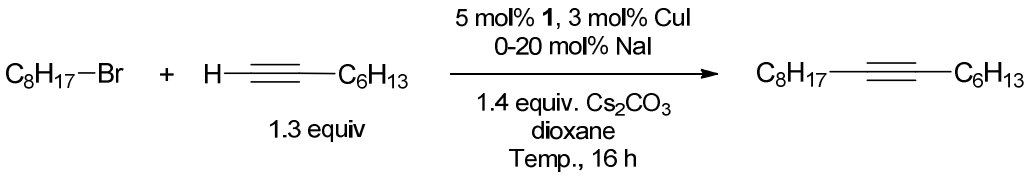
Table 1. (Continued)

Entry	CuI	Base	Solvent	Cat.	Temp.	Time	Yield
7	7.5mol%	Cs_2CO_3	Dioxane	[($^{Me}N_2N$)Ni-Cl]	120	16h	83
8	7.5mol%	Cs_2CO_3	Dioxane	[($^{Me}N_2N$)Ni-Cl]	60	16h	67
9	7.5mol%	Cs_2CO_3	Dioxane	[($^{Me}N_2N$)Ni-Cl]	120	2h	34
10	7.5mol%	Cs_2CO_3	Dioxane	[($^{Me}N_2N$)Ni-Cl]	120	8h	59
11	**3mol%**	**Cs_2CO_3**	**Dioxane**	**[($^{Me}N_2N$)Ni-Cl]**	**100**	**16h**	**75**
12	3mol%	Cs_2CO_3	Dioxane	[($^{Me}N_2N$)$_2Li_2$]	100	16h	0
13	3mol%	Cs_2CO_3	Dioxane	H$^{Me}N_2N$	100	16h	0
14	3mol%	Cs_2CO_3	Dioxane	Ni(dme)Cl_2	100	16h	0
15	3 mol%	Cs_2CO_3	Dioxane	-	100	16h	4.1
16	-	Cs_2CO_3	Dioxane	-	100	16h	0

[a] Reactions were performed with 0.5 mmol of octyl-I, 1.3eq. of octyne, 5mol% of cat. in absence of oxygen.

Fortunately, similar conditions can be also applied for the coupling of alkyl bromides. The best conditions for the alkyl bromides were quickly found using octyl bromide as a test substrate. The only modification needed is an addition of iodide containing additive. In the presence of 20 mol% of NaI, and under the same conditions as were previously employed for the alkyl iodides, the coupling of alkyl bromides can be achieved with high yields (entries 2-3, Table 2). The coupling presumably occurs after the alkyl bromides are converted into their corresponding iodides *in situ* via a Br/I exchange. This fact can be also confirmed by the presence of octyl iodide in the reaction mixture when the reaction is quenched before the full conversion is achieved. No product was obtained in the absence of additive (entry 1, Table 2). No other iodide salts were tested, as NaI is one of the cheapest and the most available source of iodine.

Table 2. Optimization of the reaction conditions for Alkyl-Br.[a]



Entry	Additive	Solvent	Temp.	Yield
1	-	Dioxane	120	0
2	20% NaI	Dioxane	120	79
3	**20% NaI**	**Dioxane**	**100**	**78**

[a] Reactions were performed with 0.5 mmol of octyl-Br, 1.3 equiv. of octyne, 5 mol% of cat [($^{Me}N_2N$)Ni-Cl], 1.4 equiv. of Cs_2CO_3, 3 mol% of CuI in absence of oxygen.

6.2.2. Sonogashira coupling of functionalized alkyl iodides and bromides

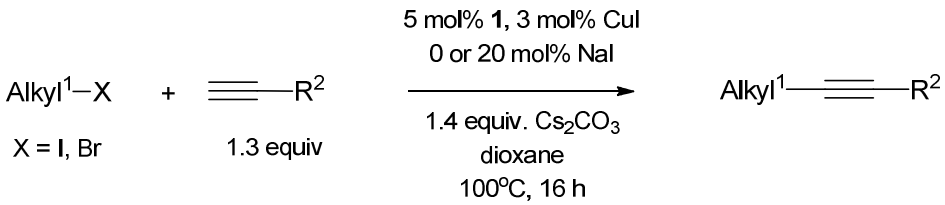
The Sonogashira coupling of other alkyl iodides and bromides was performed using the optimized conditions (Table 3).

Branching at the β-position of the iodide was tolerated (entry 3, Table 3). Substrates containing reactive functional groups such as ester, amide, aromatic enone, and heterocycle were successfully coupled (entries 4-7, Table 3). Moreover, an array of terminal alkynes with alkyl, aryl, TMS and OTMS substituents could be used (entries 1-7, Table 3). Even alkyl-Cl bond in alkynes was tolerated, leaving possibility for the further functionalizations of the obtained products (entry 3, Table 3). Coupling of cyclic and non-cyclic secondary alkyl iodides was unfortunately not successful.

A series of functionalized alkyl bromides were used for the reaction. Alkyl bromides containing ester and ether groups were readily converted into substituted alkynes (entries 9-12, Table 3). The presence of a double bond doesn't pose problem and the products containing double and triple bond in specific positions can be synthesized (entry 13, Table 3). Coupling of alkyl-Br is selective in the presence of Ar-Br bonds (entry 14, Table 3). The good selectivity was also observed for the coupling of alkyl-Br bond in a presence of a very similar alkyl-Cl bond (entries 10-11, Table 3). As the reaction goes through Br/I exchange, no

attempts were made for the coupling of secondary alkyl bromides given the negative results with secondary alkyl iodides.

Table 3. Sonogashira coupling of alkyl iodides and bromides.[a]



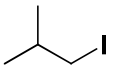
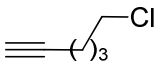
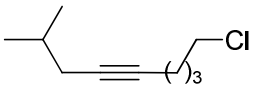
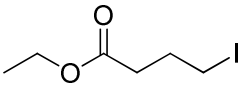
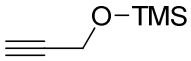
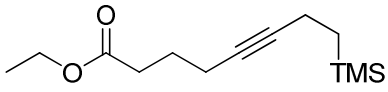
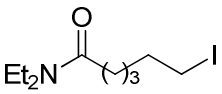
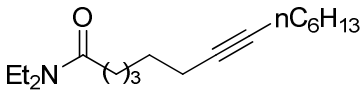
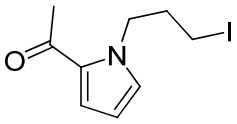
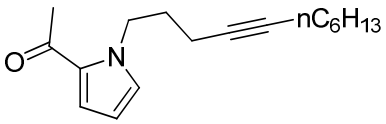
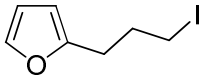
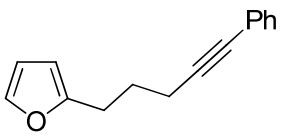
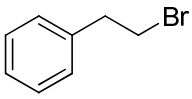
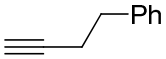
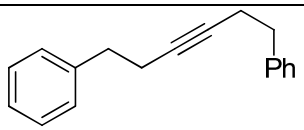
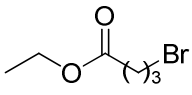
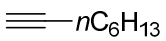
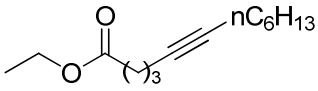
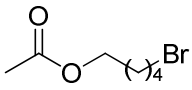
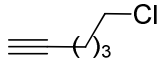
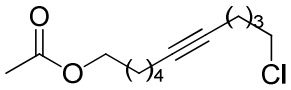
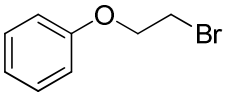
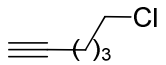
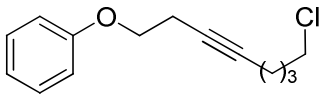
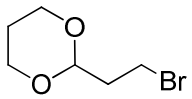
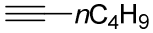
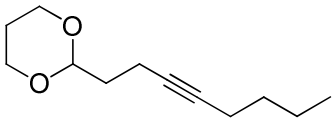
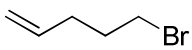
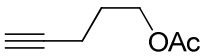
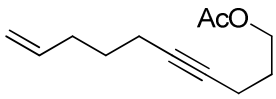
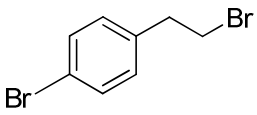
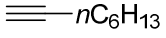
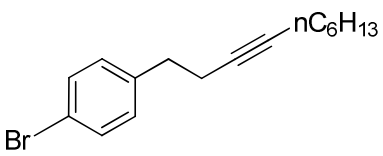
Entry	Alkyl[1]-X	—R[2]	Product	Yield (%)[b]
1	Octyl—I	—*n*C$_6$H$_{13}$	Octyl—*n*-C$_6$H$_{13}$	83
2	Octyl—I	—TMS	Octyl—TMS	74[c]
3				84
4				73[c]
5		—*n*C$_6$H$_{13}$		68
6		—*n*C$_6$H$_{13}$		61
7		—Ph		84

Table 3. (Continued)

Entry	Alkyl[1]-X	—R[2]	Product	Yield (%)[b]
8				89
9				73
10				70
11				79
12				76
13				59
14				69

[a]For coupling of iodides, no NaI was added as additive; for coupling of bromides, 20 mol% of NaI was added as additive. [b]Isolated yields relative to alkyl halide. [c] 1.5 equiv. of alkyne was used.

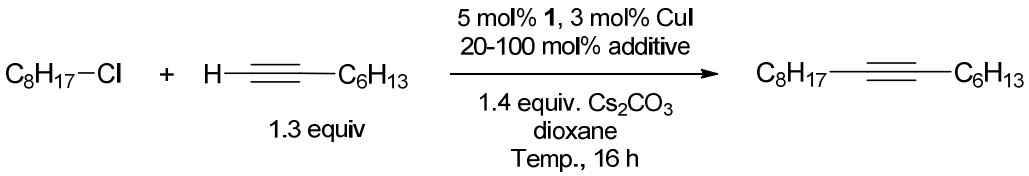
6.3. Sonogashira coupling of alkyl chlorides

6.3.1. Optimization of reaction conditions

Compared to alkyl bromides and iodides, alkyl chlorides are more challenging substrates. The bond strength increases in a range C-Cl > C-Br > C-I, making the cleavage of a very strong carbon-chloride bond difficult in cross-coupling reactions. In fact, we are not aware of any prior example of Sonogashira coupling of non-activated alkyl chlorides. Gratifyingly, the results obtained for the Sonogashira coupling of alkyl bromides helped us to solve the difficult problem for the coupling of alkyl chlorides. In combination with an *in situ* and catalytic Cl/I exchange process, complex **1** might also catalyze the coupling of alkyl chlorides.

A strategy similar to the one employed for Sonogashira coupling of alkyl bromides was used for alkyl chlorides. 20 mol% of *n*-Bu_4NI was used as an additive and the reactions were carried out at 140^0C, while keeping all other reaction parameters the same as in the coupling of alkyl iodides (entry 7, Table 4). Other iodide salts were not efficient (entries 1-4, Table 4) and only a small conversion was observed. The efficiency of *n*-Bu_4NI is probably due to its higher solubility in organic solvents then other inorganic iodide salts. The bond strength between cations and anions is weaker in *n*-Bu_4NI, making it a good source of iodide anions in organic solvents. At 100^0C or 120^0C, the Cl/I exchange was slower, and the coupling yields were lower (entries 5-6, Table 4). This reaction was also carried out in the absence of [($^{Me}N_2N$)Ni-Cl] and/or CuI. The yields were much lower and unsatisfactory (entries 8-10, Table 4).

Table 4. Choice of the best conditions for Alkyl-Cl and control experiments.[a]



Entry	Additive	Solvent	Temp.	Yield
1	20% NaI	Dioxane	120	5
2	100% NaI	Dioxane	120	5
3	20% KI	Dioxane	120	4
4	20% LiI	Dioxane	120	6
5	20% NBu_4I	Dioxane	120	39
6	20% NBu_4I	Dioxane	100	35
7	**20% NBu_4I**	**Dioxane**	**140**	**76**
8	20% NBu_4I	Dioxane	140	3.1[b]
9	20% NBu_4I	Dioxane	140	22.5[c]
10	20% NBu_4I	Dioxane	140	14[d]

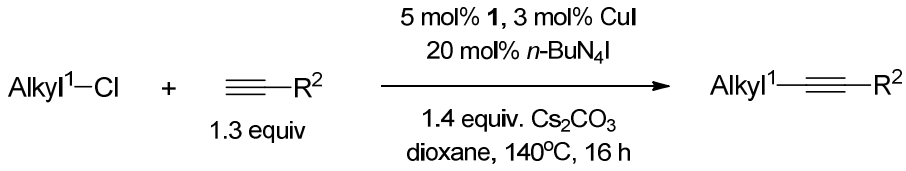
[a] Reactions were performed with 0.5 mmol of octyl-Cl, 1.3 equiv. of octyne, 5 mol% of cat [($^{Me}N_2N$)Ni-Cl], 1.4 equiv. of Cs_2CO_3, 3 mol% of CuI in absence of oxygen. [b]Without Ni catalyst nor Cu-I. [c]With Ni catalyst but not Cu-I. [d]Without Ni catalyst but with Cu-I.

6.3.2. Sonogashira coupling of functionalized alkyl chlorides

The Sonogashira coupling of terminal alkynes with a series of functionalized alkyl chlorides was studied. Even at the relatively elevated temperature of 140^0C, the reaction tolerated a wide range of functional groups. The sensitive keto, amide and ester groups were tolerated (entries 3-5, 9, Table 5). Some substrates with nitrile group could be also used. A steric hindrance between the nitrile group and the alkyl chloride bond was beneficial (entries 9-10, Table 5). Ether and acteal groups did not pose problems and the substrates containing these groups could be coupled in high yields (entries 7-8, Table 5). A wide range of aromatic

heterocycles were also tolerated (entries 6, 11-12, Table 5). The coupling of alkyl—Cl bond was selective over aryl—Cl and even usually reactive aryl—Br bond (entries 13 and 14, Table 5). Alkynes containing alkyl, aryl, Si(*i*-Pr)$_3$, and acetate groups were all viable coupling partners.

Table 5. Sonogashira coupling of alkyl chlorides.



Entry	Alkyl^1-Cl	—R^2	Product	Yield (%)[a]
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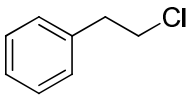
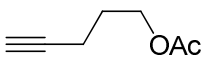
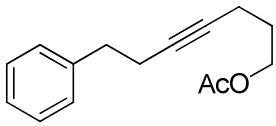
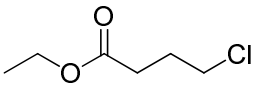
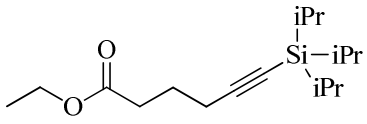
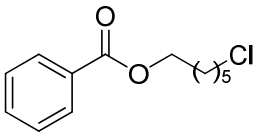
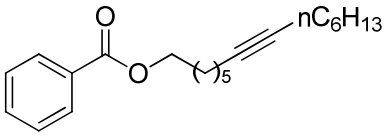
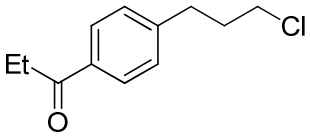
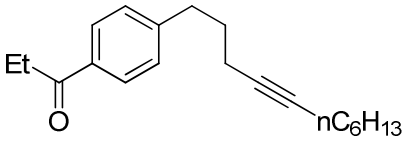
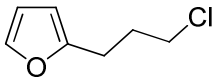
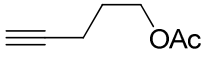
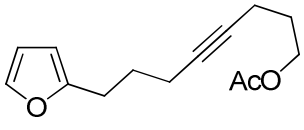
2				66
3		—Si(*i*-Pr)$_3$		62
4		—*n*C$_6$H$_{13}$		70
5		—*n*C$_6$H$_{13}$		57
6				64

Table 5. (Continued)

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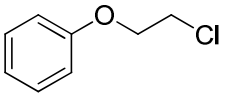
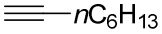
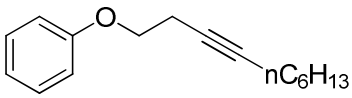
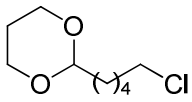
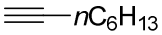
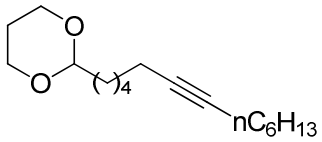
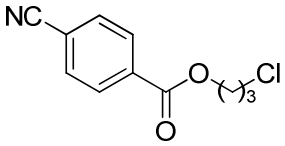
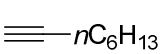
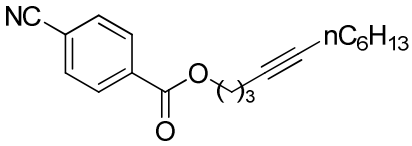
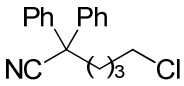
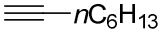
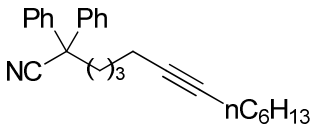
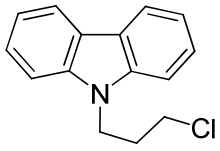
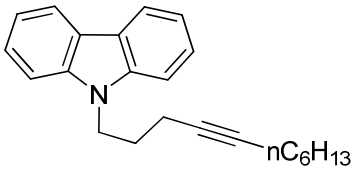
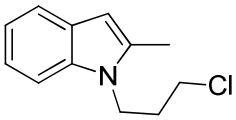
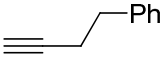
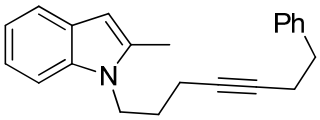
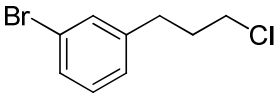
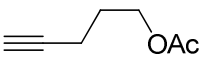
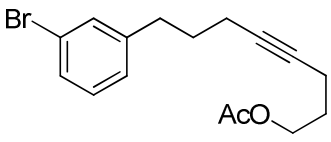
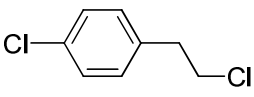
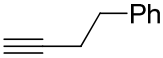
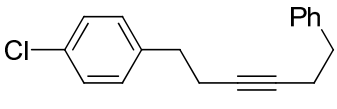
7				88
8				73
9				63
10				66
11				85
12				75
13				58
14				72

[a]Isolated yields relative to alkyl chloride.

6.4. Combination of several [($^{Me}N_2N$)Ni-Cl]-catalyzed cross-coupling reactions

A very useful property of the described Ni-catalyzed Sonogashira coupling is a very high selectivity in the reactions with substrates containing different alkyl halide bonds. Depending on the reaction conditions (additive and temperature), selective coupling of a specific type of carbon-halide bond can be done. For example, no conversion was observed for alkyl bromides when the conditions for coupling of alkyl iodides were employed. A conversion of less than 5% was obtained for alkyl chlorides when the conditions for coupling of alkyl bromides were used. On the other hand, only small modifications of reaction conditions are needed to switch the cross-coupling process between different alkyl halide bonds. This property can be used as an advantage for the application of [($^{Me}N_2N$)Ni-Cl]-catalyzed Sonogashira coupling in the synthesis of complex organic molecules.

Thus, selective coupling of C—Br bond in the presence of C—Cl bond, and of C—I bond in the presence of both C—Br and C—Cl bonds can be done. It is therefore possible to carry out sequential Sonogashira coupling reactions of the substrates containing more than one type of alkyl—halide bonds. A series of experiments were carried out to test this assumption. 1-bromo-6-chlorohexane was chosen as the test substrate, containing both C—Br and C—Cl bonds. The coupling conditions for alkyl bromides were employed for the first Sonogashira coupling of this substrate (Figure 1). The product of the first step was separated, purified and its structure confirmed by spectroscopic methods. There are a carbon-carbon triple bond and a C—Cl bond in this molecule. The C—Cl bond could be further used for the Sonogashira reaction when the coupling protocol for alkyl chlorides was employed. The separation and purification by a chromatography column resulted in the formation of the final product. This example illustrates sequential Sonogashira couplings for the synthesis of compounds with more than one triple bond.

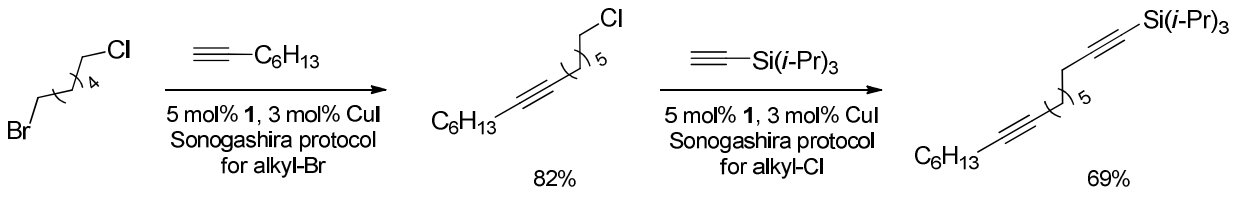


Figure 1. Consecutive Sonogashira coupling of the substrates, containing different carbon-halide bonds.

Furthermore, the protocol for the Sonogashira coupling can be combined with the Kumada-Corriu-Tamao (KCT) coupling protocols, described in the previous chapters.[8] The cross coupling of alkyl bromides and iodides with alkyl Grignard reagents gave good to excellent yields; however, alkyl chlorides were not efficient substrates in these reactions. This feature allows a sequential Kumada-Corriu-Tamao and Sonogashira coupling of certain substrates. 1-bromo-4-chlorobutane was used as a substrate (Figure 2). The desired product was obtained in 2 steps synthesis with a total yield of 78%.

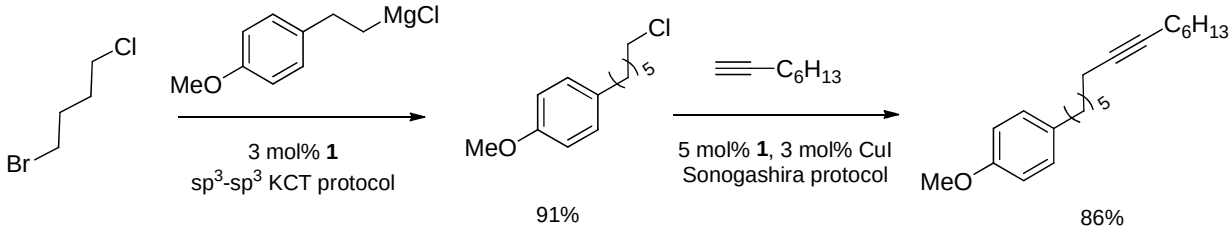


Figure 2. Combination of Sonogashira coupling with alkyl Kumada-Corriu-Tamao coupling.

Aryl or hetero-aryl Grignard reagents can also be used in the sequential coupling. The test reactions were performed on 1-chloro-3-iodopropane. The functionalized Knochel-type Grignard reagents were used for the reaction at the first step of the synthesis. The products were separated and then further utilized for the Sonogashira coupling. The results are represented in Figure 3.

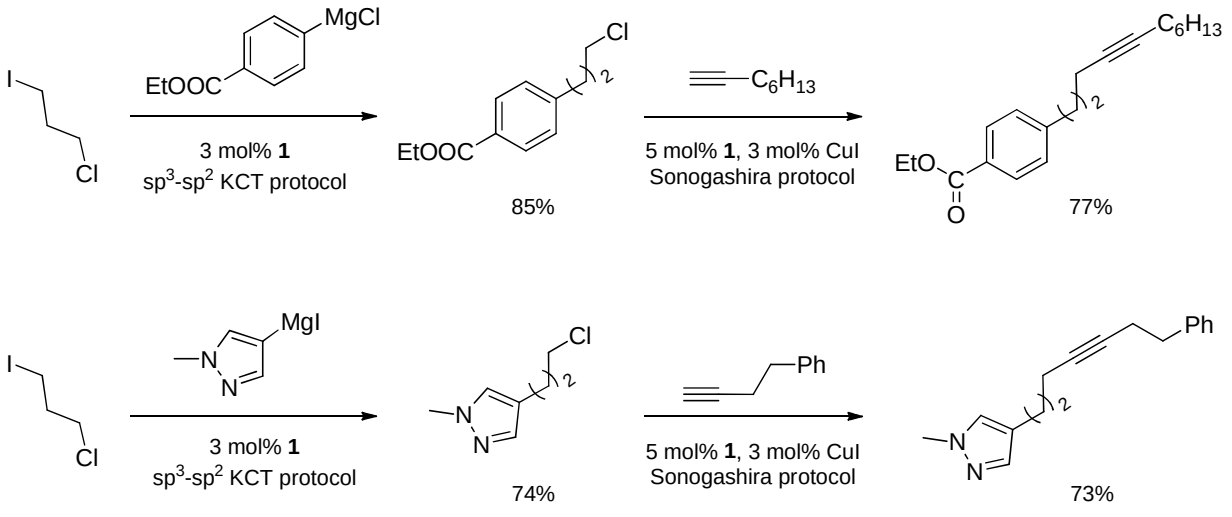


Figure 3. Combination of Sonogashira coupling with aryl and heteroaryl Kumada-Corriu-Tamao coupling.

6.5. Mechanism of the reaction

The base and a relatively high reaction temperature can cause the decomposition of the nickel complex. An Hg-test was done in order to discard the possibility of catalysis by Ni particles. Cross-coupling of octyl iodide and octyl chloride with octyne was done in the presence of 100 equiv. (to Ni catalyst) of Hg. The results are shown in the Figure 4.

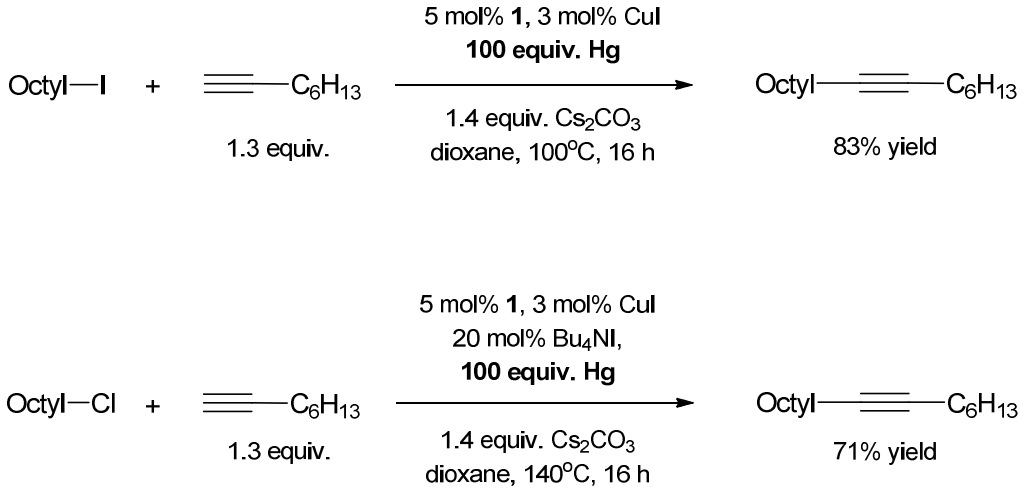


Figure 4. Sonogashira coupling in the presence of 100 equiv. of Hg.

The results show that addition of Hg doesn't influence on the reaction yield, making the possibility of catalysis by Ni particles unlikely.

Further tests were done on the Sonogashira coupling of (bromomethyl)cyclopropane substrate. When the usual conditions for the alkyl bromides were used, the open-structure product was obtained in a high yield (Figure 5). This result suggests the presence of the radical intermediates during the catalytic process.

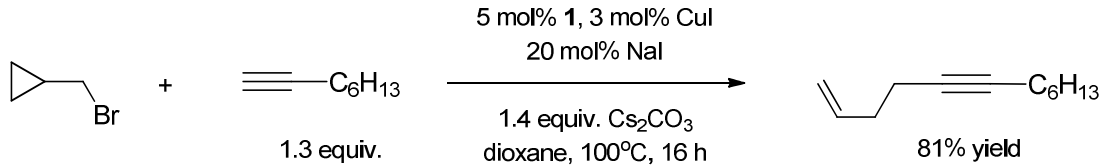


Figure 5. Sonogashira coupling of (bromomethyl)cyclopropane.

[($^{Me}N_2N$)Ni^{II}-alkynyl] complex is proposed as a key intermediate for the Sonogashira coupling reactions. This complex reacts with alkyl halide to form the coupling product via sequential oxidative addition and reductive elimination, similar to the mechanism of KCT coupling, described in previous chapters.

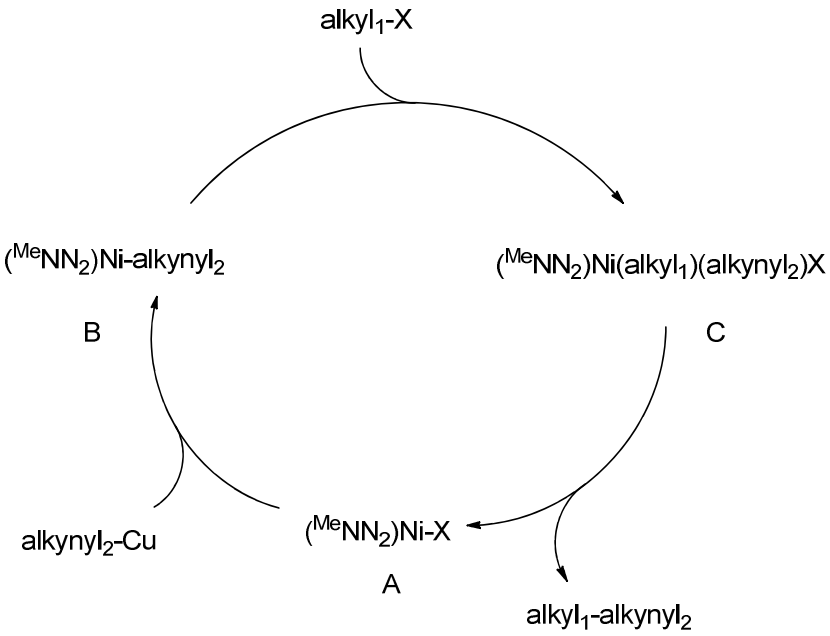


Figure 6. A possible catalytic cycle for the Sonogashira reactions.

6.6. Failed substrates

A wide range of substrates were tested for the [($^{Me}N_2N$)Ni-Cl]-catalyzed Sonogashira coupling of alkyl halides. No particular problems were met in most cases and the desired products were obtained and separated in high yields. However, in some cases this method was not efficient because of the particular functional groups or the specific structures of the substrates. A list of failed substrates with the explanations of the appeared problems is represented in the Table 6.

Table 6. Failed substrates in Sonogashira coupling.

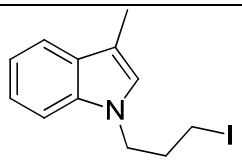
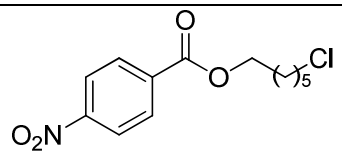
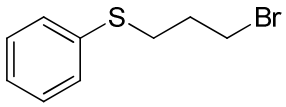
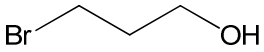
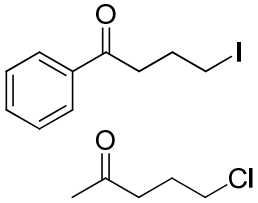
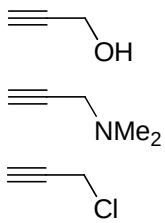
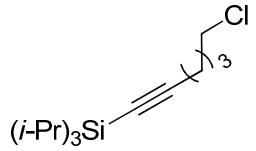
Substrates	Possible problem with this substrate
	2-H is too reactive. If the 2-position is methylated, then coupling occurs properly (see entry 12, Table 5).

Table 6. (Continued)

Substrates	Possible problem with this substrate
	NO_2 group is not tolerated.
	Thioether group is not tolerated.
	Alcohol group is not tolerated.
	Substrates with only alkyl groups between keto and halide groups could not be coupled. However, if there is an aryl group between keto and halide groups, then coupling occurs (see entry 5, Table 5).
	These alkyne substrates could not be coupled. Electronically they are different from normal alkynes.
	Alkyne-containing alkyl halides could not be coupled, possibly due to the formation of 5- or 6-member rings. If there are 6 CH_2 groups between the alkyne and Cl groups, then coupling occurs (see Figure 1). In that case, formation of 7- or 8-member rings is not very favorable.

6.7. Conclusions

In summary, the first Ni-based catalytic system for the Sonogashira coupling of non-activated and β-H containing alkyl halides was developed. This also appears to be the first time that alkyl chlorides have been used in Sonogashira reactions. The coupling tolerates a

wide range of functional groups in both coupling partners. Substituted alkynes could also be prepared in comparable yields to those from reactions of alkyl halides with alkynyl anions in liquid ammonia solutions.[9] However, the latter methods require a strong base, and thus have limited functional-group tolerance for both alkyl halides and terminal alkynes. Therefore, the current Sonogashira protocols are advantageous for the preparation of highly functionalized alkynes. By judicious choices of coupling conditions, different alkyl—halide bonds can be differentiated, leading to orthogonal functionalization of alkyl iodides, bromides, and chlorides.

6.8. Experimental part

The coupling products are fully characterized, and their characterization data can be found in the Chapter 9 and in the supporting information (available free online) of the paper.[10]

Chemicals and Reagents

All manipulations were carried out under an inert N_2(g) atmosphere using glovebox techniques. Solvents were purified using a two-column solid-state purification system (Innovative Technology, NJ, USA) and transferred to the glove box without exposure to air. Deuterated solvents were purchased from Cambridge Isotope Laboratories, Inc., and were degassed and stored over activated 3 Å molecular sieves. Unless noted, all other reagents were purchased from commercial sources and used without further purification. Liquid compounds were degassed by standard freeze-pump-thaw procedures prior to use in the glovebox. The following starting materials were prepared according to literature procedures: ethyl 4-iodobutanoate (entry 4, Table 3,) from ethyl 4-chlorobutanoate and NaI in acetone by a standard method, N,N-diethyl-6-iodohexanamide (entry 5, Table 3) from 6-bromo-*N*,*N*-diethylhexanamide[11] and NaI in acetone by a standard method, 1-[1-(3-iodopropyl)-1*H*-pyrrol-2-yl]ethanone (entry 6, Table 3),[12] 2-(3-iodopropyl)furan (entry 7, Table 3),[13] 6-chlorohexyl benzoate (entry 4, Table 5),[14] 1-chloro-4-(2-chloroethyl)benzene (entry 14, Table 5),[15] 9-(3-chloropropyl)-9H-carbazole (entry 12, Table 5).[16] In two step reactions the first steps in Figures 2 and 3 were done according to procedure described in our previous work.[8]

Physical methods

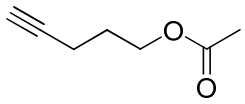
The ^{1}H and ^{13}C NMR spectra were recorded at 293 K on a Bruker Avance 400 spectrometer. ^{1}H NMR chemical shifts were referenced to residual solvent as determined relative to Me_4Si (δ = 0 ppm). The $^{13}C\{^{1}H\}$ chemical shifts were reported in ppm relative to the carbon resonance of $CDCl_3$ (77.00 ppm). GC-MS measurements were conducted on a Perkin-Elmer Clarus 600 GC equipped with Clarus 600T MS. GC measurement was conducted on a Perkin-Elmer Clarus 400 GC with a FID detector. HRCI-MS measurements were conducted at the EPFL ISIC Mass Spectrometry Service at Micro Mass QTOF Ultima. Elemental analyses were performed on a Carlo Erba EA 1110 CHN instrument at EPFL. The temperature of reactions below room temperature was regulated by a Julabo FT-902 chiller.

General procedure for Sonogashira coupling

[($^{Me}N_2N$)Ni-Cl] (26 mg, 0.075 mmol), CuI (9 mg, 0.045mmol), Cs_2CO_3 (684mg, 2.1mmol), Alkyl-X (1.5 mmol) and alkyne (1.95 mmol) were placed in a vial and 6 mL of dioxane was added. NaI (45 mg, 0.3 mmol) was added in case of Alkyl-Br or NBu_4I (120 mg, 0.3 mmol) was added in case of Alkyl-Cl. After addition the mixture was heated in absence of oxygen during 16h at 100^0C for Alkyl-I and Alkyl-Br and at 140^0C for Alkyl-Cl. After this time reaction was cooled to r.t., quenched with 15 mL of water and 1 mL of 1M HCl, extracted with ether (3 times, 20 mL each), dried over Na_2SO_4, filtered, and finally evaporated under a reduced pressure. The residue was purified by flash chromatography on silica-gel.

Synthesis of substrates

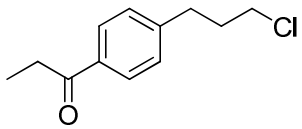
pent-4-ynyl acetate



This compound was synthesized according to a general method described in the literature[17] starting from pent-4-yn-1-ol and acetic anhydride.

^{1}H NMR (400MHz, $CDCl_3$): 4.16 (t, J = 6.2 Hz, 2H), 2.29 (td, J_1 = 7.0 Hz, J_2 = 2.6 Hz, 2H), 2.05 (s, 3H), 1.97 (t, J = 2.6 Hz, 1H), 1.85 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 170.9, 82.9, 68.9, 62.8, 27.4, 20.8, 15.1. HRCI-MS: calculated for ($C_7H_{11}O_2$, M+H), 127.0759; found, 127.0755.

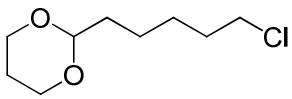
1-(4-(3-chloropropyl)phenyl)propan-1-one



This compound was synthesized by the same way as 1-(4-(2-chloroethyl)phenyl)propan-1-one[18] from (3-chloropropyl)benzene and propionyl chloride.

^{1}H NMR (400MHz, $CDCl_3$): 7.90 (d, *J* = 8.2 Hz, 2H), 7.28 (d, *J* = 8.5 Hz, 2H), 3.52 (t, *J* = 6.5 Hz, 2H), 2.98 (q, *J* = 7.3 Hz, 2H), 2.83 (t, *J* = 7.3 Hz, 2H), 2.09 (m, 2H), 1.21 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 200.3, 146.1, 135.0, 128.6, 128.2, 43.9, 33.5, 32.6, 31.6, 8.2. HRCI-MS: calculated for ($C_{12}H_{16}ClO$, M+H), 211.0890; found, 211.0880.

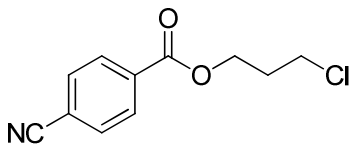
2-(5-chloropentyl)-1,3-dioxane



6-chlorohexanal[19] (5.1 g, 37.7 mmol) and propane-1,3-diol (6.0 mL, 83.02 mmol) in dry toluene (50 mL) were placed in a round-bottom flask equipped with a Dean-Stark under nitrogen. The reaction mixture was refluxed in presence of catalytic amount of $TsOH*H_2O$ (200mg) for 3h. The reaction was quenched at room temperature by the addition of aqueous saturated solution of $NaHCO_3$. The organic layer was washed with water, dried over Na_2SO_4 and solvent was removed in vacuum to give the desired protected aldehyde in quantitative yield.

^{1}H NMR (400MHz, $CDCl_3$): 4.50 (t, *J* = 5.3 Hz, 1H), 4.08 (dd, J_1 = 10.9 Hz, J_2 = 5.0 Hz, 2H), 3.74 (m, 2H), 3.51 (t, *J* = 6.7 Hz, 2H), 2.04 (m, 1H), 1.75 (m, 2H), 1.58 (m, 2H), 1.41 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): 102.0, 66.8, 44.9, 34.9, 32.4, 26.6, 25.7, 23.1. HRCI-MS: calculated for ($C_9H_{18}ClO_2$, M+H), 193.0995; found, 193.0996.

3-chloropropyl 4-cyanobenzoate

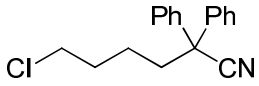


4-cyanobenzoyl chloride (4g, 24.1 mmol) was added slowly to a solution of 3-chloropropan-1-ol (2.04 g, 21.58 mmol) in dry pyridine (20 mL) cooled to 0^0C. The reaction was stirred at

0^0C for 1h and then at r.t. overnight. The crude solution was partitioned between saturated aqueous $NaHCO_3$ (60 mL) and EtOAc (50 mL). The organic layer was further washed with water (30 mL) and 1M aqueous HCl (2 x 30 mL), dried over Na_2SO_4 and concentrated in *vacuo*. The crude product was purified by flash chromatography to give a white solid in 75% yield.

^{1}H NMR (400MHz, $CDCl_3$): 8.13 (d, *J* = 8.2 Hz, 2H), 7.74 (d, *J* = 7.9 Hz, 2H), 4.51 (t, *J* = 6.2 Hz, 2H), 3.69 (t, *J* = 6.2 Hz, 2H), 2.25 (quint, *J* = 5.9 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 164.6, 133.7, 132.1, 130.0, 117.8, 116.4, 62.4, 41.0, 31.4. HRCI-MS: calculated for ($C_{11}H_{11}ClNO_2$, M+H), 224.0478; found, 224.0475.

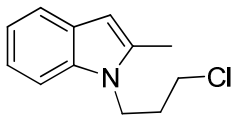
6-chloro-2,2-diphenylhexanenitrile



To a solution of diphenylacetonitrile (2.0 g, 10.3 mmol) in 100 mL of *N,N*-dimethylformamide was carefully added sodium hydride (0.5 g, 12.4 mmol, 60% in oil) in small portions. The mixture was stirred at ambient temperature for 15 min, and then 1-chloro-4-iodobutane (3.28 g, 15 mmol) was added in one portion. The mixture was stirred at ambient temperature. After 20 h, the reaction was quenched with 200 mL of water and extracted with two portions of ethyl acetate (200 mL). The combined organic extracts were washed with water (2 x 400 mL) and then brine (400 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo* to yellow oil. Purification by flash column chromatography on silica gel afforded 1.9 g of 6-chloro-2,2-diphenylhexanenitrile as a viscous liquid.

^{1}H NMR (400MHz, $CDCl_3$): 7.40 (m, 8H), 7.31 (m, 2H), 3.51 (t, *J* = 6.7 Hz, 2H), 2.41 (m, 2H), 1.85 (m, 2H), 1.58 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 139.9, 128.8, 127.8, 126.7, 122.1, 51.6, 44.2, 38.9, 32.2, 23.1. HRCI-MS: calculated for ($C_{18}H_{19}ClN$, M+H), 284.1206; found, 284.1219.

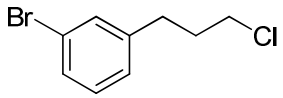
1-(3-chloropropyl)-2-methyl-1H-indole



This compound was synthesized according to a general method described in the literature[3] starting from 2-methyl-1H-indole.

^{1}H NMR (400MHz, $CDCl_3$): 7.57 (d, *J* = 7.6 Hz, 1H), 7.35 (d, *J* = 8.2 Hz, 1H), 7.19 (m, 1H), 7.12 (m, 1H), 6.30 (s, 1H), 4.28 (t, *J* = 7.0 Hz, 2H), 3.55 (t, *J* = 6.2 Hz, 2H), 2.49 (s, 3H), 2.25 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 136.5, 136.3, 128.1, 120.5, 119.7, 119.3, 108.8, 100.3, 42.0, 39.9, 32.7, 12.7. HRCI-MS: calculated for ($C_{12}H_{15}NCl$, M+H), 208.0893; found, 208.0888.

1-bromo-3-(3-chloropropyl)benzene



This compound was synthesized from 3-(3-bromophenyl)propan-1-ol[20] by the same procedure as 1-chloro-4-(2-chloroethyl)benzene.[15]

^{1}H NMR (400MHz, $CDCl_3$): 7.35 (m, 2H), 7.16 (m, 2H), 3.53 (t, *J* = 6.2 Hz, 2H), 2.76 (t, *J* = 7.3 Hz, 2H), 2.07 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 143.0, 131.5, 130.0, 129.2, 127.2, 122.5, 43.9, 33.6, 32.3. Elemental analysis: Anal. Calcd for $C_9H_{10}BrCl$: C, 46.29; H, 4.32. Found: C, 46.33; H, 4.45.

6.9. References

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Chapter 7

*Ni/Cu-Catalyzed Direct Alkylation of Heterocyclic C—H Bonds**

*The results presented in this chapter were published in:

Vechorkin, O.; Proust, V.; Hu, X. L. *Angew. Chem., Int. Ed.* **2010**, *49*, 3061-3064.

7.1. Introduction

Aromatic heterocycles are important molecules that have been widely used as synthetic building blocks, bio-active molecules, pharmaceuticals, and organic materials.[1-3] There are now many methods available for the preparation of aromatic heterocycles substituted by aryl, alkenyl, alkynyl, and even activated alkyl groups, most recently by direct C—H functionalization.[4-13] However, the synthesis of heterocyclic compounds substituted by non-activated and β-H containing alkyl groups, remains challenging. Traditional methods such as Friedel-Crafts[14] and radical alkylation reactions[15] pose severe limitation on the electronic properties of the heterocycles, and are often incompatible with sulfur containing heterocycles. Additionally, Friedel-Crafts alkylation requires strong acids, and suffers from side reactions such as multiple alkylation and isomerization. Likewise, the method of deprotonation by strong bases (for example ^{n}BuLi) followed by electrophilic trapping requires cryogenic conditions, active electrophiles, protection of acidic and/or electrophilic groups, or elaborated bases.[16-18]

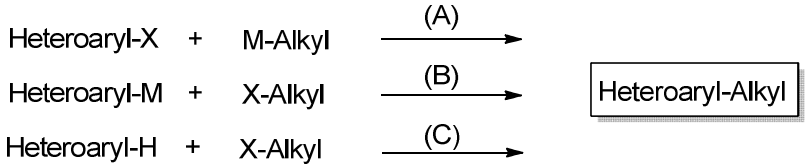


Figure 1. Cross coupling methods for the synthesis of alkylated aromatic heterocycles; X = halide, M = metal.

The development of cross coupling catalysis provides new opportunities in heterocycle synthesis.[19] The alkylated aromatic heterocycles can be produced either by coupling of a heterocyclic halide with an alkyl organometallic nucleophile (path A, Figure 1),[20] or by coupling of a heterocyclic organometallic nucleophile with an alkyl halide (path B, Figure 1).[21] Both methods employ organometallic nucleophiles, and are constrained by the stability and availability of these reagents. Furthermore, extra chemical transformations are required for the preparation of the organometallic reagents. Therefore, direct cross coupling of aromatic heterocyclic C—H bonds with non-activated alkyl halides (path C, Figure 1) represents an attractive alternative. This coupling technology, however, is under-developed due to the difficulties in the coupling of non-activated alkyl halides.[22-24] Alkyl halides are reluctant to oxidative addition; when they do undergo oxidative addition, the resulting metal alkyl intermediates are prone to unproductive β-H elimination. To date, the only reported

example for a successful coupling is the Pd-catalyzed reaction between ethyl oxazole-4-carboxylate with 2 equivalent of n-butyl bromide to form ethyl 2-butyloxazole-4-carboxylate in 60% yield.[25]

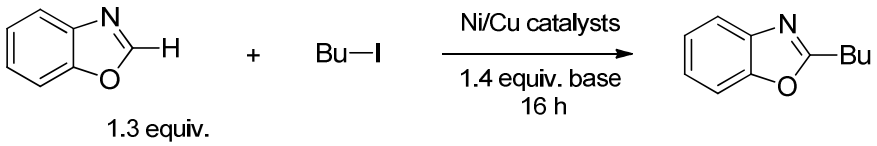
In the course of developing catalysts based on inexpensive and readily available first-row transition metals, we identified a Ni complex, [($^{Me}N_2N$)NiCl] (**1**), as an active (pre)catalyst for the coupling of non-activated alkyl halides.[21, 26-29] In this chapter we show that the combination of this complex and a copper salt leads to efficient coupling of aromatic heterocycles with non-activated and β-H containing alkyl halides. Not only alkyl iodides and bromides, but also alkyl chlorides can be used. The catalysis tolerates a wide range of functional groups in both coupling partners, and has excellent chemo- and regioselectivity.

7.2. Optimization of reaction conditions

7.2.1. Optimization of reaction conditions for alkyl iodides

The cross coupling of benzoxazole with n-butyl iodide was used as a test reaction. After exploration of various experimental parameters, we found that n-butyl benzoxazole could be produced in high yields (ca. 80%) using 5 mol% of [($^{Me}N_2N$)Ni-Cl] (**1**) as the pre-catalyst and 7.5 mol% of CuI as the co-catalyst. A temperature of 140^0C and a reaction time of 16 hours were required for full conversion. The best base was ^{t}BuONa in toluene or ^{t}BuOLi in dioxane (entries 7, 10, Table 1). Other bases were not efficient (entries 16-18, Table 1) or gave diminished yields (entries 1-4, 12, Table 1). Other base/solvent combinations gave lower yields as well. The coupling proceeded even without Cu co-catalyst (entries 13, 15, Table 1), but with a small amount of CuI, the coupling yields were higher. The yields were nearly constant when the loadings of CuI were varied from 2 to 7.5 mol%. The nickel complex **1** was essential for a high efficiency. Without **1**, no coupling occurred (entry 14, Table 1). Replacing **1** with another soluble Ni(II) compound such as $NiCl_2$(dme), $NiCl_2(PPh_3)_2$ led to diminished coupling yields (20-30%) (entries 19-20, Table 1).

Table 1. Optimization of the reaction conditions for Alkyl-I.[a]



Entry	CuI	Base	Solvent	Catalyst	Temp.	Time	Yield[b]
1	7.5mol%	Cs_2CO_3	Dioxane	[($^{Me}N_2N$)Ni-Cl]	100	16h	12
2	7.5mol%	Cs_2CO_3	Dioxane	[($^{Me}N_2N$)Ni-Cl]	140	16h	20
3	7.5mol%	^{t}BuOK	Dioxane	[($^{Me}N_2N$)Ni-Cl]	100	16h	22
4	7.5mol%	^{t}BuOK	Toluene	[($^{Me}N_2N$)Ni-Cl]	100	16h	29
5	7.5mol%	^{t}BuONa	Dioxane	[($^{Me}N_2N$)Ni-Cl]	120	16h	68
6	7.5mol%	^{t}BuONa	Toluene	[($^{Me}N_2N$)Ni-Cl]	120	16h	67
7	**7.5mol%**	**^{t}BuONa**	**Toluene**	**[($^{Me}N_2N$)Ni-Cl]**	**140**	**16h**	**75**
8	7.5mol%	^{t}BuOLi	Toluene	[($^{Me}N_2N$)Ni-Cl]	120	16h	29
9	7.5mol%	^{t}BuOLi	Dioxane	[($^{Me}N_2N$)Ni-Cl]	120	16h	76
10	**7.5mol%**	**^{t}BuOLi**	**Dioxane**	**[($^{Me}N_2N$)Ni-Cl]**	**140**	**16h**	**78**
11	7.5mol%	MeONa	Dioxane	[($^{Me}N_2N$)Ni-Cl]	140	16h	65
12	7.5mol%	K_3PO_4	Dioxane	[($^{Me}N_2N$)Ni-Cl]	140	16h	35
13	0 mol%	^{t}BuONa	Toluene	[($^{Me}N_2N$)Ni-Cl]	140	16h	54
14	0 mol%	^{t}BuONa	Toluene	-	140	16h	0
15	0 mol%	^{t}BuOLi	Dioxane	[($^{Me}N_2N$)Ni-Cl]	140	16h	18
16	7.5mol%	Et_3N	Dioxane	[($^{Me}N_2N$)Ni-Cl]	140	16h	0
17	7.5mol%	DBU	Dioxane	[($^{Me}N_2N$)Ni-Cl]	140	16h	0
18	7.5mol%	4Me-guanidine	Dioxane	[($^{Me}N_2N$)Ni-Cl]	140	16h	0

Table 1. (Continued)

Entry	CuI	Base	Solvent	Catalyst	Temp.	Time	Yield[b]
19	7.5mol%	^{t}BuONa	Toluene	$Ni(dme)Cl_2$	140	16h	36
20	7.5mol%	^{t}BuONa	Toluene	$Ni(PPh_3)_2Cl_2$	140	16h	37

[a] Reactions were performed with 0.5 mmol of butyl-I. [b] GC yields relative to butyl iodide.

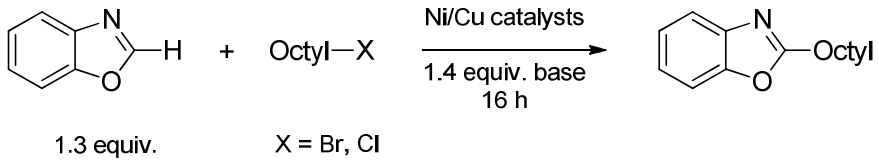
7.2.2. Optimization of reaction conditions for alkyl bromides and chlorides

The coupling of benzoxazole with octyl bromide or octyl chloride was also possible employing similar procedures (Table 2).

The best result with octyl bromide was obtained when the reaction was carried out in dioxane and with ^{t}BuOLi as the base and in presence of 0.2 equiv. of an additive NaI (entry 4, Table 2). 20 mol% of NaI was beneficial, probably by promoting a halide exchange process. Reaction without additive was sometime efficient (entry 5, Table 2), possibly due to the presence of iodide anions from CuI, but the results were not often reproducible. When ^{t}BuONa was used as base in toluene (entries 1-3, Table 2), lower yields were obtained, probably because the Br/I exchange was slower in a less polar solvent.

Octyl chloride can be also coupled with benzoxazole. The same conditions employed for octyl bromide can be used for octyl chloride (entry 6, Table 2). Utilization of ^{t}BuONa in toluene was inefficient (entries 9-11, Table 2), due to difficulty in Cl/I exchange in this solvent. n-Bu_4NI can be also used as additive for the Cl/I exchange (entry 8, Table 2). But the more efficient and cheaper salt NaI was used for the further reaction with alkyl chlorides.

Table 2. Optimization of the reaction conditions for alkyl-Br and alkyl-Cl.[a]



Entry	X	Additive	Base	Solvent	Temp.	Time	Yield[b]
1	Br	-	^{t}BuONa	Toluene	140	16h	22
2	Br	0.2 equiv. NaI	^{t}BuONa	Toluene	140	16h	35
3	Br	0.2 equiv. Bu_4NI	^{t}BuONa	Toluene	140	16h	27
4	**Br**	**0.2 equiv. NaI**	**^{t}BuOLi**	**Dioxane**	**140**	**16h**	**85**
5	Br	-	^{t}BuOLi	Dioxane	140	16h	83
6	**Cl**	**0.2 equiv. NaI**	**^{t}BuOLi**	**Dioxane**	**140**	**16h**	**72**
7	Cl	-	^{t}BuOLi	Dioxane	140	16h	66
8	Cl	0.2 equiv. Bu_4NI	^{t}BuOLi	Dioxane	140	16h	68
9	Cl	-	^{t}BuONa	Toluene	140	16h	0
10	Cl	0.2 equiv. NaI	^{t}BuONa	Toluene	140	16h	0
11	Cl	0.2 equiv. Bu_4NI	^{t}BuONa	Toluene	140	16h	5

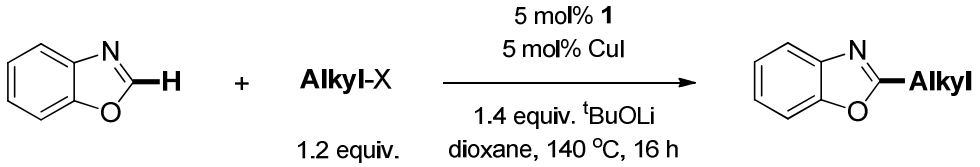
[a] Reactions were performed with 0.5 mmol of octyl-X, 0.65 mmol benzoxazole, 5 mol% [($^{Me}N_2N$)Ni-Cl] catalyst, 7.5 mol% CuI. [b] GC yields relative to octyl halides

7.3. Direct alkylation of benzoxazole with alkyl halides

The optimized conditions are applicable to the coupling of benzoxazole with other non-activated alkyl halides (Table 3). Branching at the β-position of the halide was tolerated (entry 1, Table 3). The coupling of alkyl chloride is selective in the presence of aryl-Cl bond (entry 3, Table 3). Potentially coordinating groups such as ether, thioether, and nitrile groups did not pose much problem (entries 4-6, Table 3). Acetal group was tolerated (entry 7, Table

3). Olefin and ester groups did not interfere with the coupling (entries 8 and 9, Table 3). Encouragingly, a substrate containing a base sensitive keto group could be coupled in a modest yield (entry 10, Table 3). Coupling of substrates containing important heterocyclic groups such as indole, carbazole, and furan was also successful (entries 11-13, Table 3). No coupling occurred with secondary alkyl halides such as cyclohexyl iodide and cycloheptyl bromide. Whereas base-induced elimination from some alkyl halides (e.g., 2-bromoethylbenzene) was indeed observed, this side reaction did not pose a problem for all substrates in Table 3.

Table 3. Direct alkylation of benzoxazole with alkyl halides.[a]



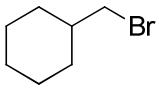
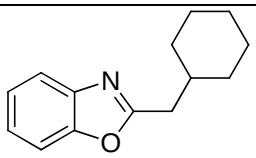
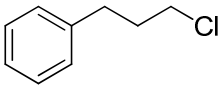
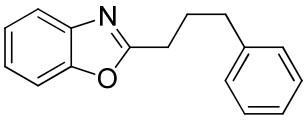
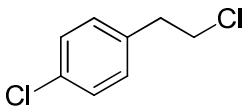
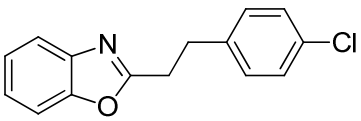
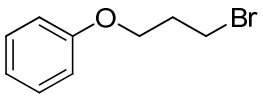
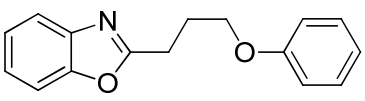
Entry	Alkyl-X	Product	Yield, (%)[b]
1			79
2			70
3			75
4			84

Table 3. (Continued)

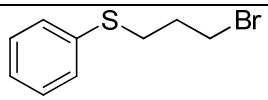
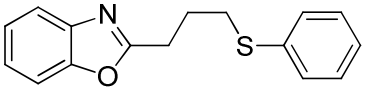
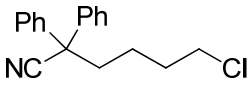
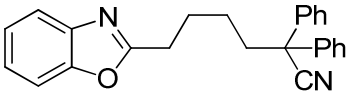
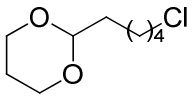
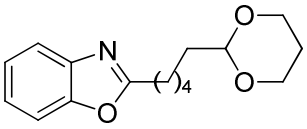
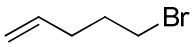
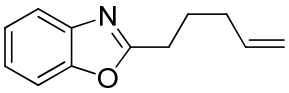
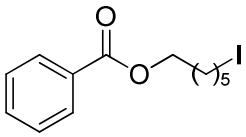
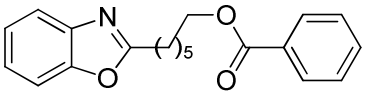
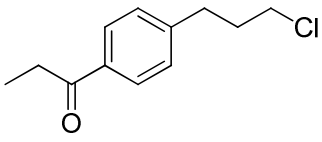
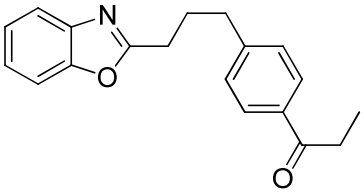
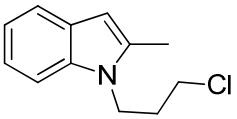
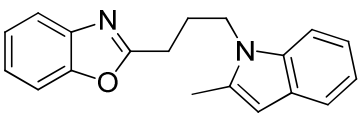
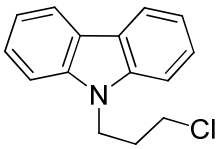
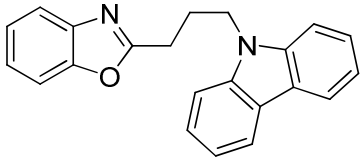
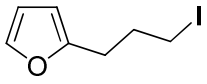
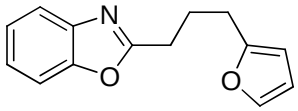
Entry	Alkyl-X	Product	Yield, (%)[b]
5			65
6			56
7			86
8			70
9			71
10			44
11			74

Table 3. (Continued)

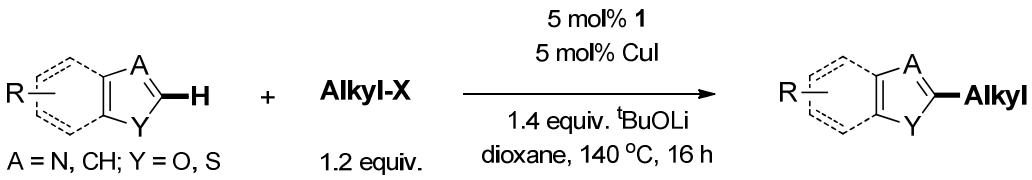
Entry	Alkyl-X	Product	Yield, (%)[b]
12			75
13			73

[a] 1.5 mmol of benzoxazole was used; for coupling of alkyl bromides and chlorides, 0.3 mmol of NaI was added.
[b] Isolated yields relative to the heteroarenes.

7.4. Direct alkylation of other aromatic heterocycles with alkyl halides

Similar procedure can be used for the direct alkylation of other aromatic heterocycles with non-activated alkyl halides (Table 4). Various 5-aryloxazoles could be readily coupled at the 2-position (entries 1-4, Table 4). Aryl-Br moiety in the oxazole did not interfere with the coupling (entry 4, Table 4). Gratifyingly, molecules containing important pharmacophores such as thiazole and thiophene were also suitable substrates, giving rise to 2-alkylated products (entries 5-16, Table 4). In some cases, the more bulky base Et_3COLi was required for higher yields (entries 14-16, Table 4). The catalysis is tolerant to carbazole, ether, olefin, ester, indole, NBoc, aryl- and heteroaryl-halide groups. For unsubstituted substrates (e.g., entries 1-4, 11, table 2), no significant amounts of double alkylation products were observed.

Table 4. Coupling of heterocycles with non-activated alkyl halides.[a]



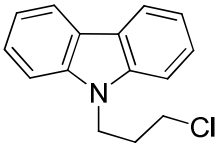
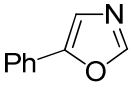
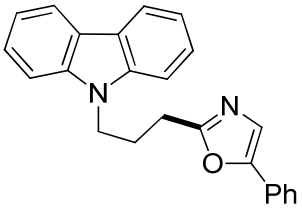
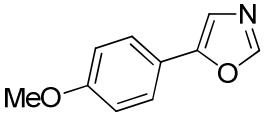
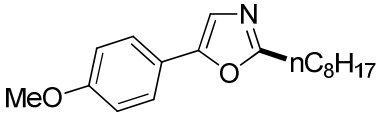
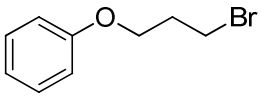
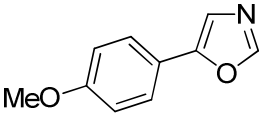
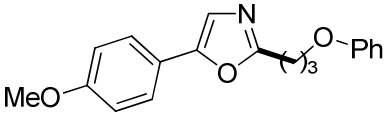
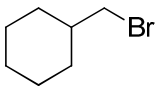
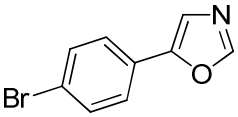
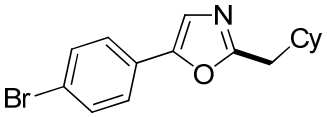
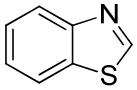
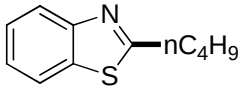
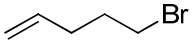
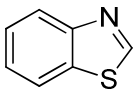
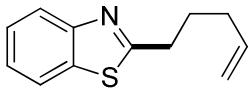
Entry	Alkyl-X	Heteroaryl	Product	Yield (%)[b]
1				74
2	Octyl—I			86
3				81
4				76
5	Butyl—I			78
6				74

Table 4. (Continued)

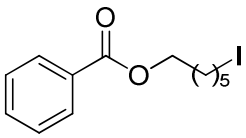
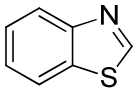
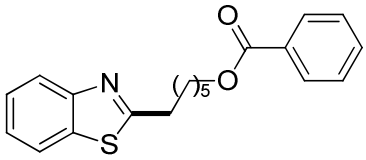
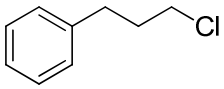
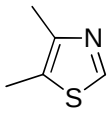
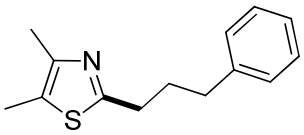
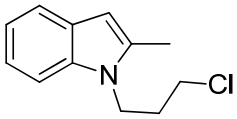
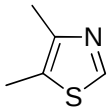
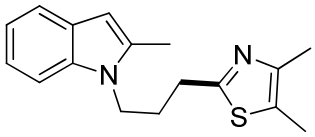
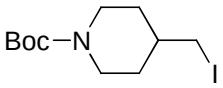
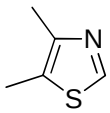
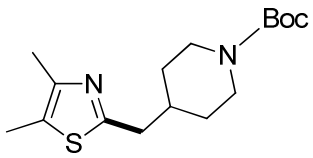
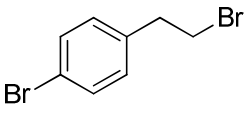
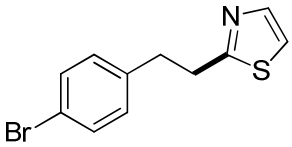
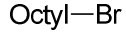
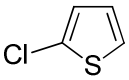
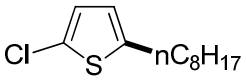
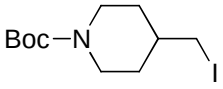
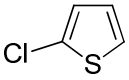
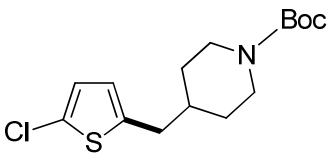
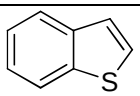
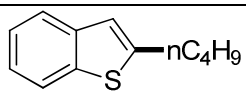
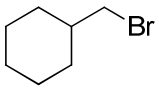
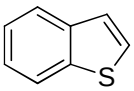
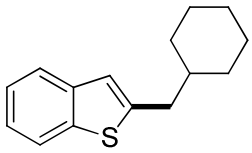
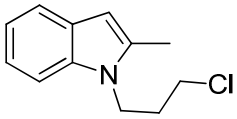
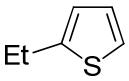
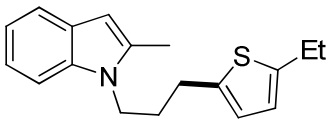
Entry	Alkyl-X	Heteroaryl	Product	Yield (%)[b]
7				72
8				76
9				85
10				79
11				60
12				81
13				62

Table 4. (Continued)

Entry	Alkyl-X	Heteroaryl	Product	Yield (%)[b]
14	Butyl—I			78[c]
15				72[c]
16				66[c]

[a] 1.5 mmol of heteroarenes were used; for coupling of alkyl bromides and chlorides, 0.3 mmol of NaI was added. [b] Isolated yields relative to the heteroarenes. [c] Et_3OLi was used as the base.

7.5. Mechanistic investigations

7.5.1. Hg-test experiment

To check whether heterogeneous Ni particles were responsible for the coupling, the same reaction as in (entry 10, Table 1) was conducted in the presence of 100 equivalent of Hg (relative to Ni catalyst). The coupling yield diminished from ca. 80% to 19%. Hg poisoned the active catalyst, suggesting that metal particles are responsible for the catalysis.

7.5.2. Following the catalysis by NMR

To probe the nature of the active Ni catalyst, the catalysis was followed by ^{1}H NMR (with 20 mol% of Ni pre-catalyst). Free ligand $H^{Me}N_2N$ was the only ligand-containing species observed after 1h (ca. 50% conversion) and after completion of reaction (16h). The ^{1}H NMR spectrum of the reaction mixture after 16h in dioxane-D8 is represented in Figure 2. Thus

pre-catalyst **1** appeared to degrade into the active Ni species and free ligand under the catalytic conditions.

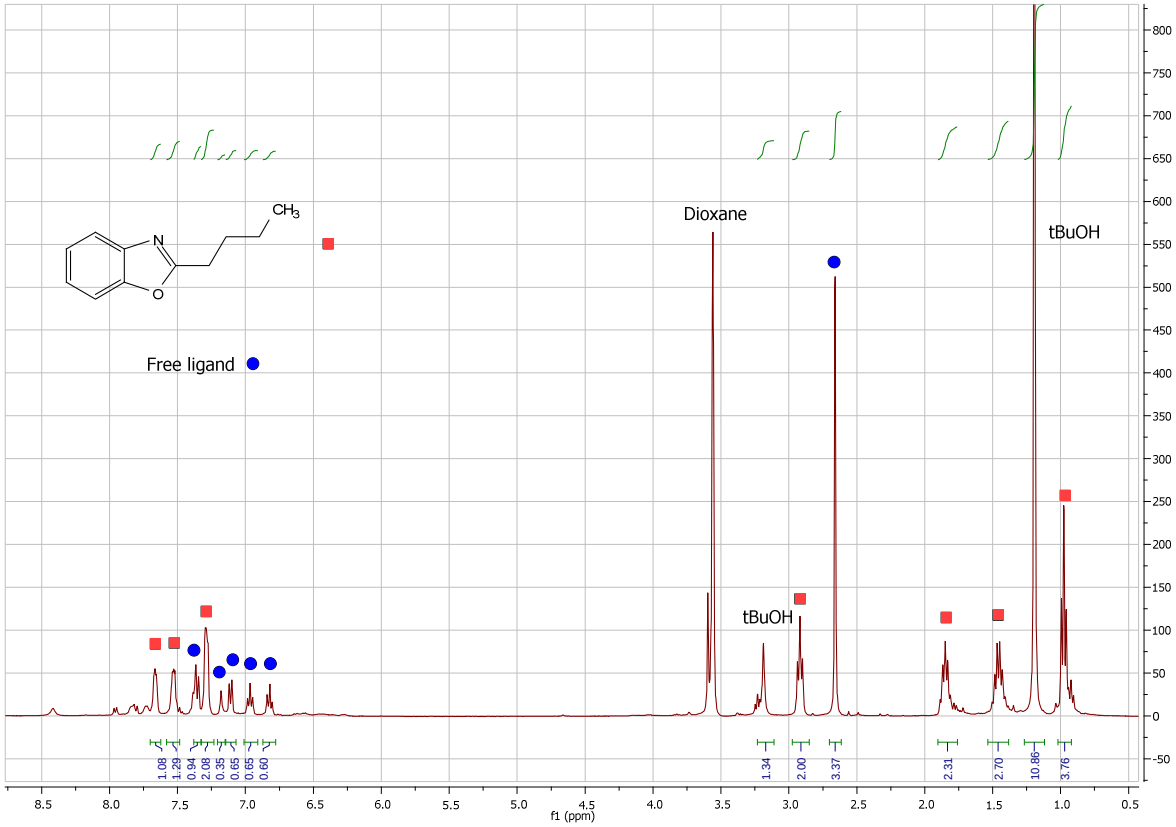


Figure 2. The ^{1}H NMR spectrum of the reaction mixture after 16h.

7.5.3. Filtration experiment

In addition, a filtration experiment was done. A reaction mixture was heated for 1h according to a general procedure. After it was cooled to r.t. and the solids were filtered-off under nitrogen atmosphere. After this, ^{t}BuOLi and CuI were added to the solution again but not [(^{Me}N$_2$N)Ni-Cl] complex and the reaction was heated for further 16h. A low yield of 30% was obtained in the end of the reaction, suggesting that the active catalyst is insoluble and it was removed by filtration after 1h.

7.5.4. D_2O experiment

This experiment was done for the confirmation of the existence of anionic benzoxazole. When the reaction mixture was quenched at a partial conversion with D_2O, 2-deuterated benzoxazole was produced.

This can be seen from the relative intensities of the ^{1}H NMR signals corresponding to the 2-H and the protons on the phenyl ring of benzoxazole. As shown in Figure 3, after 1 hour of the reaction and before D_2O quenching, the ratio of integrations is ca. 1 to 3.7, which is close to the theoretical ratio of 1 to 4 within experimental errors. The broad region between 6.3 and 7.1 ppm corresponds to a deprotonated form of benzoxazole together with the signals of the free ligand. 15 minute after D_2O quenching, the ratio turned into ca. 1 to 5.3 (Figure 4), which was due to the formation of 2-D-benzoxazole (ca. 40% relative to unreacted starting materials). When compared to an internal standard (e.g., from proton residue of d8-dioxane), the intensity of the ^{1}H signal from 2-H remained the same after D_2O quenching, suggesting that 2-H-benzoxazole did not undergo H/D exchange during the 15-minute time period. This H/D exchange did occur when the same mixture was allowed to stay at room temperature overnight, as shown in Figure 5.

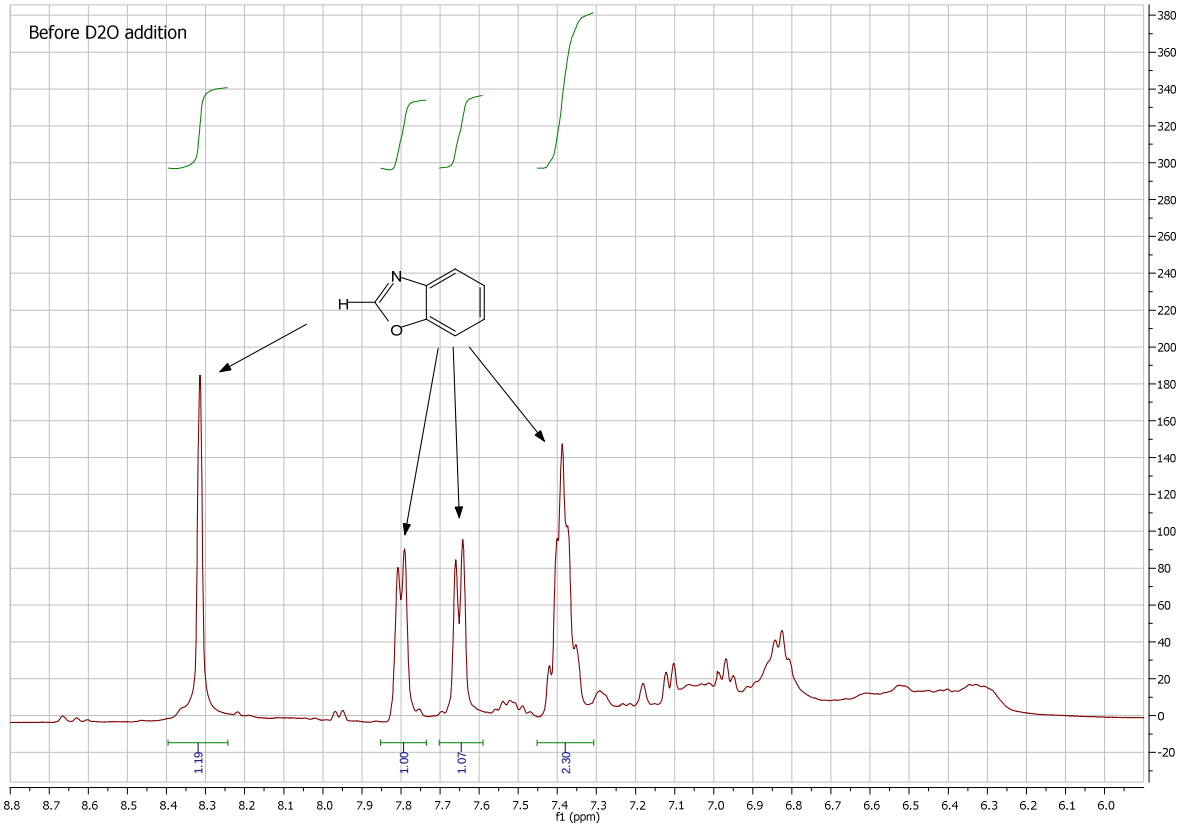


Figure 3. The NMR spectrum of the reaction before D_2O addition.

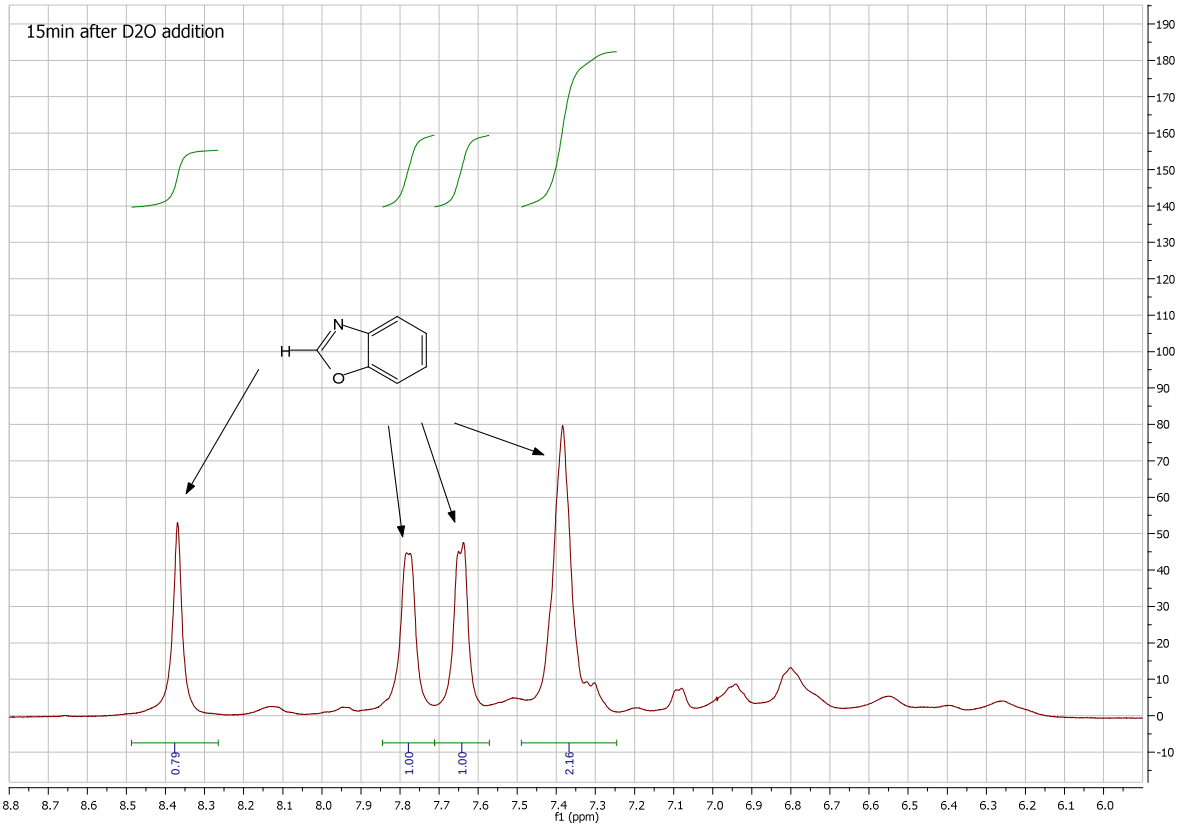


Figure 4. The NMR spectrum of the reaction 15min after D_2O addition.

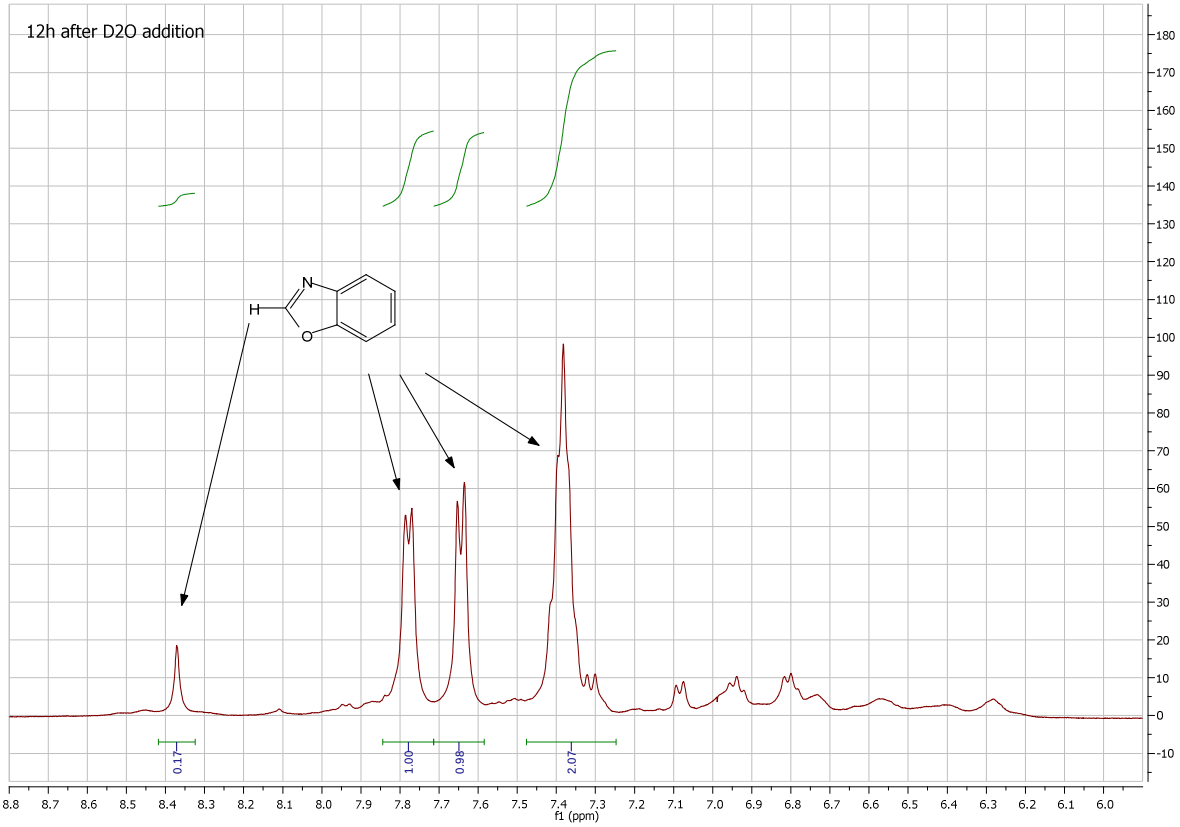


Figure 5. The NMR spectrum of the reaction 12h after D_2O addition.

These results suggest that anionic benzoxazole intermediates exist during the catalysis. These intermediates might exist in the 2-metallated cyclic azole form, or in the ring-opened isocyano phenolate/enolate form, or as an equilibrium mixture (Figure 6). Addition of D_2O converted these anionic species back to 2-D-azoles. An equilibrium between metallated oxazole(thiazole) derivatives and their acyclic isomers is described in the work of Hiff and coworkers.[30]

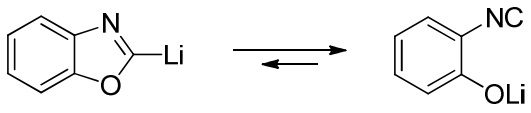


Figure 6. An equilibrium between close- and open-cycle structure of Li salt of benzoxazole.

7.5.5. H/D isotopic effect measurement

H/D isotopic effect measurements were done on the reaction of 2-H-benzoxazole and 2-D-benzoxazole with BuI. Identical reactions conditions including the reaction scale and time were employed. To ensure a relatively high conversion in 1 hour, 20% catalyst loading was used. Two trials were made for each compound. For the coupling of 2-H-benzoxazole, the yields were 49% and 50%, respectively. For the coupling of 2-D-benzoxale, the yields were 46% and 44%, respectively. The difference in yields is very small and almost no isotopic effect is detected.

7.5.6. Proposed mechanism

The first three experiments suggest that the reactions are most likely catalyzed by Ni metal particles. They can be formed by the thermal decomposition of [($^{Me}N_2N$)Ni-Cl]. The ligand exchange with ^{t}BuOLi base is also possible at these conditions, leading to the formation of [($^{Me}N_2N$)Ni-O^{t}Bu]. This complex was also synthesized by the reaction of [($^{Me}N_2N$)Ni-Cl] and ^{t}BuONa in independent experiment. This unstable compound slowly decomposes even at room temperature. A presence of Cu^I salts can be also beneficial for the decomposition reaction.

The existence of an anionic benzoxazole was confirmed, as quenching of the reaction mixture at partial conversion with D_2O produced 2-deuterated benzoxazole. Anionic form of benzoxazole (most likely in ring-opened isocyano enolate form) can be also seen at partial conversion by NMR (Figure 3). Almost no isotopic effect was observed for the coupling of

nBuI with 2-deuterated benzoxazole, thus suggesting that C—H cleavage might not be the turnover limiting step.

The mechanism of the coupling might be similar to those of Ni/Cu- and Cu-catalyzed direct arylation and alkynylation of aromatic heterocycles.[10, 13, 31] Even though the Cu co-catalyst was not necessary for the coupling, it is required for satisfactory yields. We propose that Cu facilitates the transmetallation of anionic azole/thiophene intermediates to Ni (Figure 7).

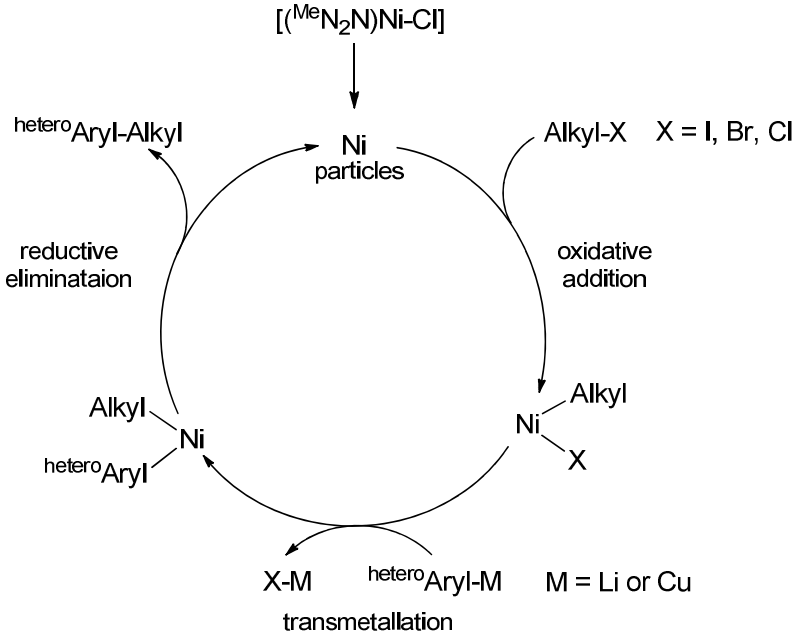


Figure 7. Proposed mechanism for the direct alkylation of aromatic heterocycles.

7.6. Conclusions

In conclusion, we have developed a general and versatile method for the synthesis of alkylated aromatic heterocycles, which are important organic molecules and materials. The chemistry is based on catalytic C—H functionalization using non-activated alkyl electrophiles, a largely under-explored reaction type.[25, 32-34] The Ni/Cu-catalysis enables the coupling of both electron-rich and electron-poor heterocycles, which is difficult to achieve using other synthetic procedures. Various non-activated and β-H containing alkyl halides including the inexpensive chlorides could be coupled, making this method applicable to the synthesis and derivatization of a large number of alkylated heterocycles. The coupling protocol is simple and straightforward, the substrates are readily available, and the pure products can be isolated in high yields. The excellent chemo- and regioselectivity are especially noteworthy. Only alkyl-halide bonds are reactive in the presence of aryl- and

heteroaryl halide moieties, giving possibilities for further functionalization. When the alkyl halides contain heterocyclic groups, no intra- or inter-molecular self-coupling took place. The coupling occurred exclusively on the 2-positions of the aromatic heterocycles, even when there were more than one reaction site on the heterocycles. No multiple alkylation was observed, a desirable feature compared with Friedel-Crafts reactions.

7.7. Experimental part

The coupling products are fully characterized, and their characterization data can be found in the Chapter 9 and in the supporting information (available free online) of the paper.[35]

Chemicals and Reagents

All manipulations were carried out under an inert N_2(g) atmosphere using glovebox techniques. Solvents were purified using a two-column solid-state purification system (Innovative Technology, NJ, USA) and transferred to the glove box without exposure to air. Deuterated solvents were purchased from Cambridge Isotope Laboratories, Inc., and were degassed and stored over activated 3 Å molecular sieves. Unless noted, all other reagents were purchased from commercial sources and used without further purification. Liquid compounds were degassed by standard freeze-pump-thaw procedures prior to use in the glovebox. The following starting materials were prepared according to literature procedures: 2-(3-iodopropyl)furan,[36] 6-iodohexyl benzoate from 6-chlorohexyl benzoate[37] and NaI in acetone by standard method, 1-chloro-4-(2-chloroethyl)benzene,[38] 9-(3-chloropropyl)-9H-carbazole,[39] [(3-bromopropyl)sulfanyl]benzene,[40] (3-bromopropoxy)benzene,[41] tert-butyl 4-(iodomethyl)piperidine-1-carboxylate,[42] lithium 3-ethylpentan-3-olate.[43] Substrates 5-phenyloxazole, 5-(4-methoxyphenyl)oxazole and 5-(4-bromophenyl)oxazole were prepared according to a general procedure.[44] Synthesis of 1-(4-(3-chloropropyl)phenyl)propan-1-one, 1-(3-chloropropyl)-2-methyl-1H-indole, 2-(5-chloropentyl)-1,3-dioxane and 6-chloro-2,2-diphenylhexanenitrile was described in our previous work.[45] 2-Deuteriobenzoxazole was made following literature method.[46]

Physical methods

The ^{1}H and ^{13}C NMR spectra were recorded at 293 K on a Bruker Avance 400 spectrometer. ^{1}H NMR chemical shifts were referenced to residual solvent as determined relative to Me_4Si (δ = 0 ppm). The $^{13}C\{^{1}H\}$ chemical shifts were reported in ppm relative to

the carbon resonance of $CDCl_3$ (77.00 ppm). GC-MS measurements were conducted on a Perkin-Elmer Clarus 600 GC equipped with Clarus 600T MS. GC measurement was conducted on a Perkin-Elmer Clarus 400 GC with a FID detector. HRCI-MS measurements were conducted at the EPFL ISIC Mass Spectrometry Service at Micro Mass QTOF Ultima. Elemental analyses were performed on a Carlo Erba EA 1110 CHN instrument at EPFL.

General procedure for coupling reactions

A mixture of [($^{Me}N_2N$)Ni-Cl] (26 mg, 0.075 mmol), CuI (14 mg, 0.075 mmol), ^{t}BuOLi (168 mg, 2.1 mmol) or Et_3COLi (256 mg, 2.1 mmol), Alkyl-X (1.8 mmol) and heteroarene (1.5 mmol) was placed in a vial and 5 mL of dioxane was added. Additional NaI (45 mg, 0.3 mmol) was added for coupling of Alkyl-Br or Alkyl-Cl. The mixture was heated under N_2 during 16h at 140^0C. The reaction mixture was then cooled to room temperature, quenched with 15 mL of water and 1 mL of 1M HCl, extracted with CH_2Cl_2 (3 times, 20 mL each), dried over Na_2SO_4, filtered, and finally evaporated under a reduced pressure. The residue was purified by flash chromatography on silica-gel.

Hg-test experiment

[($^{Me}N_2N$)Ni-Cl] (9 mg, 0.025 mmol), CuI (5 mg, 0.025 mmol), ^{t}BuOLi (56 mg, 0.7 mmol), Hg (501 mg, 2.5 mmol), Bu-I (57.1 µl, 0.5 mmol) and Benzoxazole (77 mg, 0.65 mmol) were placed in a vial and 2 mL of dioxane was added. After addition the mixture was heated in absence of oxygen during 16h at 140^0C. After this time the reaction mixture was cooled to r.t., quenched with 10 mL of water and 1 mL of 1M HCl. The resulting solution mixture was then extracted with CH_2Cl_2 (3 times, 10 mL each), dried over Na_2SO_4, filtered, and subjected to GC analysis. 60 µL of dodecane was used as an internal standard. The yield of coupling product is 19% (instead of ca. 80% in the absence of Hg).

Following the catalysis by NMR

[($^{Me}N_2N$)Ni-Cl] (36 mg, 0.1 mmol), CuI (5 mg, 0.025 mmol), ^{t}BuOLi (56 mg, 0.7 mmol), Bu-I (57.1 µl, 0.5 mmol) and Benzoxazole (77 mg, 0.65 mmol) were placed in a vial and 1.5 mL of dioxane-D8 was added. After addition the mixture was heated in absence of oxygen during 1h or 16h at 140^0C. After this time the reaction mixture was cooled to r.t., filtered and its NMR-spectrum was recorded.

Filtration experiment

[($^{Me}N_2N$)Ni-Cl] (9 mg, 0.025 mmol), CuI (5 mg, 0.025 mmol), ^{t}BuOLi (56 mg, 0.7 mmol), Bu-I (57.1 µl, 0.5 mmol) and Benzoxazole (77 mg, 0.65 mmol) were placed in a vial and 2 mL of dioxane was added. After addition the mixture was heated in absence of oxygen during 1h at 140^{0}C. Then the reaction mixture was cooled to r.t. and filtered in absence of oxygen to a new vial. CuI (5 mg, 0.025 mmol) and ^{t}BuOLi (56 mg, 0.7 mmol) were added again and the mixture was heated during 16h at 140^{0}C. After this time the reaction mixture was cooled to r.t., quenched with 10 mL of water and 1 mL of 1M HCl. The resulting solution mixture was then extracted with CH_2Cl_2 (3 times, 10 mL each), dried over Na_2SO_4, filtered, and subjected to GC analysis. 60 µL of dodecane was used as an internal standard. The yield of coupling product is ca. 30% (instead of ca. 80% in without filtration of heterogeneous mixture after 1 h).

D_2O experiment

[($^{Me}N_2N$)Ni-Cl] (9 mg, 0.025 mmol), CuI (5 mg, 0.025 mmol), ^{t}BuOLi (56 mg, 0.7 mmol), Bu-I (57.1 µl, 0.5 mmol) and Benzoxazole (77 mg, 0.65 mmol) were placed in a vial and 1.5 mL of dioxane-D8 was added. After addition the mixture was heated in absence of oxygen during 1h at 140^{0}C. After this time the reaction mixture was cooled to r.t., filtered and its NMR-spectrum was recorded. Then D_2O (91 µl, 5 mmol, 99.9% D) was added and the NMR-spectrum was recorded again after 15 minutes and overnight (ca. 12h).

H/D isotopic effect measurement

[($^{Me}N_2N$)Ni-Cl] (36 mg, 0.1 mmol), CuI (5 mg, 0.025 mmol), ^{t}BuOLi (56 mg, 0.7 mmol), Bu-I (68.6 µl, 0.6 mmol) and Benzoxazole-H (60 mg, 0.5 mmol) or Benzoxazole-D (60 mg, 0.5 mmol, contains 89.4% D) were placed in a vial and 1.5 mL of dioxane was added. After addition the mixture was heated in absence of oxygen during 1h at 140^{0}C. After this time the reaction mixture was cooled to r.t., quenched with 10 mL of water and 1 mL of 1M HCl. The resulting solution mixture was then extracted with CH_2Cl_2 (3 times, 10 mL each), dried over Na_2SO_4, filtered, and subjected to GC analysis. 60 µL of dodecane was used as an internal standard.

7.8. References

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Chapter 8

*Carbon Dioxide as the C1 Source for Direct C—H Functionalization of Aromatic Heterocycles**

*The results presented in this chapter were published in:

Vechorkin O.; Hirt N.; Hu, X. L. *Org. Lett.* ***2010****, 12,* 3567-3569.

8.1. Introduction

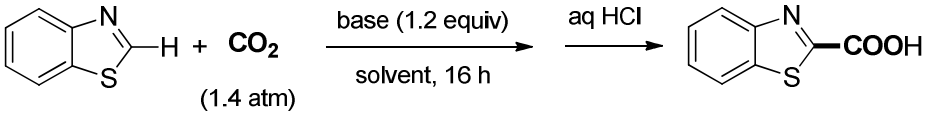
Carbon dioxide (CO_2) is a cheap, abundant, and readily available C1 source.[1-5] Carboxylation of carbon nucleophiles with CO_2 to form new C—C bonds therefore represents an attractive method for the synthesis of carboxylic acids and derivatives, which are in turn valuable organic products. However, due to the high thermodynamic and kinetic stability of CO_2, the carbon nucleophiles have been mostly limited to certain metal-activated unsaturated hydrocarbons[6-8] and reactive organometallic reagents such as Grignard and organolithium compounds.[1,9] Metal catalyzed or assisted coupling of CO_2 with less nucleophilic and more functional group tolerant organometallic reagents such as allylstannanes,[10] aryl- and alkynyl organoboronic esters,[11-13] and organozinc compounds[14,15] has been reported only recently. In addition, several groups have shown that catalytic carboxylation of allenes,[16,17] styrenes,[18] and aryl halides[19] is possible using CO_2 and a reducing agent such as $AlEt_3$ and Et_2Zn. Whereas these newly developed methods improve significantly the scope and group tolerance of carboxylation reactions, stoichiometric amounts of organometallic reagents are still required. Some of these reagents are reactive (e.g., organozincs, $AlEt_3$) and need to be stored and handled under inert atmosphere; others (e.g., boronic esters) are costly and require multiple-step synthesis. A desirable alternative is to directly couple CO_2 with a C—H bond of the organic substrates,[1,4,20] with the best example being the synthesis of salicyclic acid by direct carboxylation of phenol.[1,4] A new method of the transition metal-free carboxylation of the C—H bond of aromatic heterocycles is represented in this chapter.

8.2. Optimization of the reaction conditions

Benzothiazole was chosen as the initial substrate for the optimization of the reaction conditions following our work, described in Chapter 7.[21] Direct C—H functionalization of this heterocyclic compound with sp^2 or sp carbon nucleophiles is now ubiquitous.[22-32] The C(2)—H proton is slightly acidic (pKa = 27 in DMSO)[33] and the formation of carbon anion is possible in the presence of a base such as *tert*-butoxide, phosphate, or carbonate. We hypothesized that coupling of benzothiazole with CO_2 is possible under appropriate reaction conditions and with an active catalyst. As Cu-based catalytic systems are used in many C—H functionalization reactions of heterocycles[22,23,25,29-31,34] and in carboxylation of boronic esters,[11,15] the initial trial with CuI as a catalyst were performed. Indeed, using LiO^tBu as the base, carboxylation of benzothiazole proceeded well at 125^0C in DMF and gave full

conversion of the starting material (entry 1, Table 1). 2-benzothiazolecarboxylic acid was identified as the only organic compound detected by ^{1}H-NMR spectroscopy.

Table 1. Optimization of conditions for direct carboxylation of benzothiazole.[a]



entry	conditions	conversion (%)
1	DMF, 125 ^{o}C, 5 mol % CuI, LiO^tBu	100
2	DMF, 125 ^{o}C, LiO^tBu	100
3	DMF, 125 ^{o}C, NaOMe or NaOH or KOH	0
4	DMF, 125 ^{o}C, K_2CO_3	10
5	DMF, 125 ^{o}C, K_3PO_4	20
6	**DMF, 125 ^{o}C, Cs_2CO_3**	**100 (95[b])**
7	dioxane or toluene, 125 ^{o}C, Cs_2CO_3	0
8	THF or CH_3CN, 90 ^{o}C, Cs_2CO_3	0
9	DMF, 125 ^{o}C, Cs_2CO_3, no CO_2	0

[a] Reaction scale: benzothiazole (1 mmol), base (1.2 mmol), and solvent (2 mL). [b] Isolated yield.

To our surprise, control experiment showed that the same reaction occurred even without CuI under otherwise identical conditions (entry 2, Table 1). Thus, the carboxylation of benzothiazole can be done even without a catalyst. Consistent results were obtained with a 400 mBar of over pressure of CO_2. Both 97% (Sigma-Aldrich) and 99.9% (Alfa Aesar) LiO^tBu worked. Other bases were then tested. NaOMe, NaOH, KOH were ineffective (entries 3, Table 1). The use of K_2CO_3 and K_3PO_4 resulted in low conversions (10% to 20%, entries 4 and 5, Table 1). Cs_2CO_3 (purity from 98% to 99.995%) could be used and gave reproducible results (entry 6, and section 8.4.1.). Since Cs_2CO_3 is less basic than LiO^tBu, it was used for further reactions.[35] No reaction occurred in other solvents (entries 7 and 8, Table

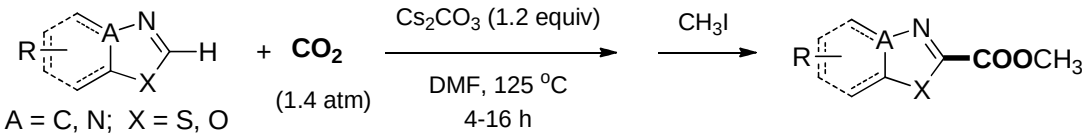
1). And the reaction did not proceed in the absence of CO_2 (entry 9, Table 1), suggesting that the COO moiety in the product does not originate from Cs_2CO_3. The pure product, 2-benzothiazolecarboxylic acid, can be isolated as a white solid in 98% yield from a preparative reaction.

8.3. Carboxylation of different heterocyclic compounds

The water solution of cesium salt of the heterocyclic carboxylic acids can be acidified with the HCl solution to give the desired products. However, the acidic form of the products was found to be not stable and a fast decarboxylation was observed by NMR spectroscopy. It was decided to convert the cesium salts of the heterocyclic carboxylic acids directly to methyl esters by a one-pot reaction with MeI. The stable ester form doesn't undergo carboxylation reaction and the products can be separated by standard methods and in a pure form.

The optimized conditions can be applied for the carboxylation of other heterocycles (Table 2). Substituted benzothiazoles can be carboxylated, including those containing sensitive nitrile and keto groups (entries 1-3, Table 2). Benzoxazoles are suitable substrates, and aryl ester and Cl groups are tolerated (entries 4-7, Table 2). naphtho[1,2-d]oxazole can be coupled (entry 8, Table 2). 5-phenyloxazoles are carboxylated at the C(2) position (entries 9-11, Table 2). 2-Aryl-1,3,4-oxadiazoles can be successfully carboxylated as well (entries 12-16, Table 2). The reactions are compatible with aryl-Cl, Br, CF_3, and OMe groups.

Table 2. Carboxylation of aromatic heterocycles.[a]



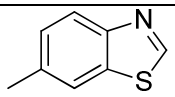
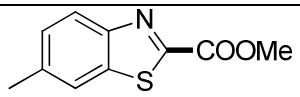
entry	substrate	product	yield, (%)[b]
1			91

Table 2. (Continued)

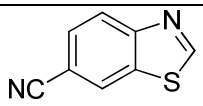
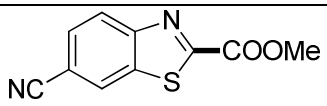
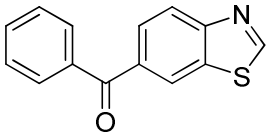
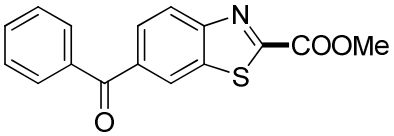
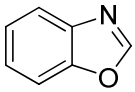
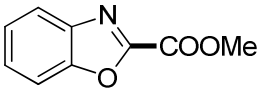
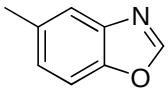
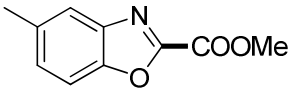
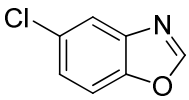
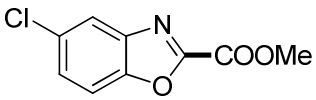
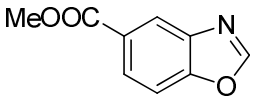
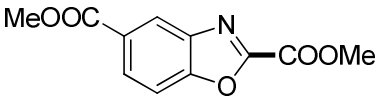
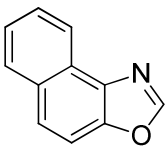
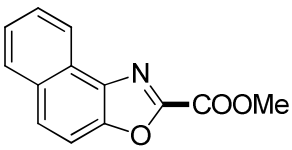
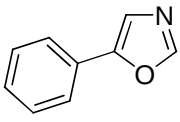
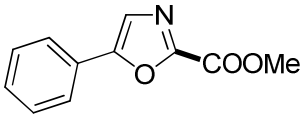
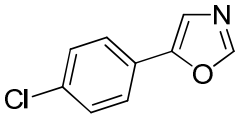
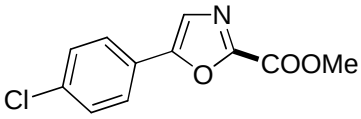
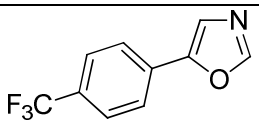
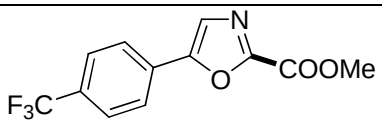
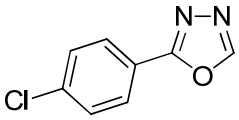
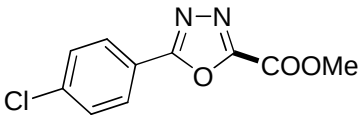
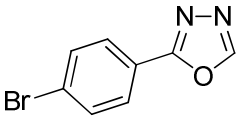
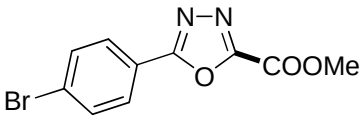
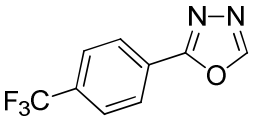
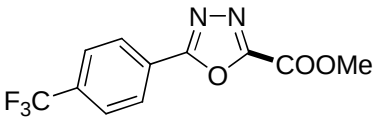
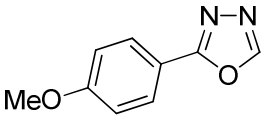
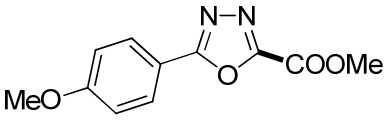
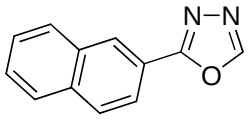
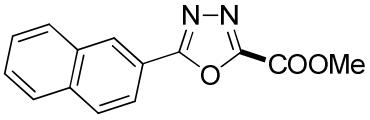
entry	substrate	product	yield, (%)[b]
2			90
3			68
4			91
5			83
6			92
7			92
8			97
9			65
10			55

Table 2. (Continued)

entry	substrate	product	yield, (%)[b]
11			61
12			88
13			83
14			71
15			96
16			64

[a] Reaction scale: heterocycle (2 mmol), base (2.4 mmol), and DMF (3 mL). [b] Isolated yield.

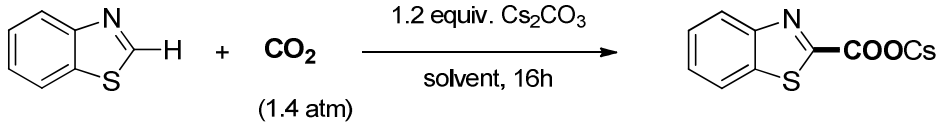
8.4. Investigation and confirmation of Cs_2CO_3 as the valid base for the direct carboxylation

8.4.1. Test of Cs_2CO_3 from different suppliers

To confirm the reproducibility of the carboxylation reactions mediated by Cs_2CO_3, we performed the reaction between benzothiazole and CO_2 using Cs_2CO_3 from different

suppliers and with different purities (metal-based). The results of these reactions are shown in Table 3.

Table 3. Investigation of different commercial Cs_2CO_3 for direct carboxylation.



Entry	Supplier	Purity / % (metal-based)	Conversion[a]
1	Aldrich	98	100
2	Aldrich	99.995	100
3	Acros	99.5	100
4	VWR	Extra-pure	100
5	Chem-Impex	99.9	100
6	Alfa Aesar	99	100
7	Alfa Aesar	99.994 (Puratronic®)	0

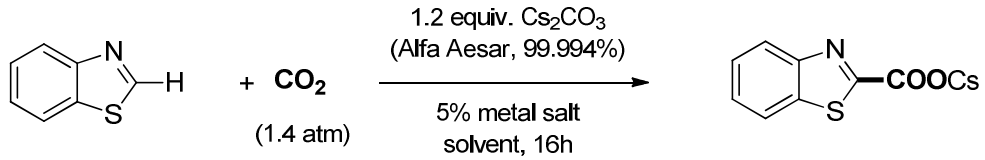
[a] Benzothiazolecarboxylate is the only detectable product.

According to Table 3, six (6) of seven (7) commercial Cs_2CO_3 were effective for the direct carboxylation. Furthermore, 99.995% pure Cs_2CO_3 (Aldrich) could be used, suggesting that the possibility of carboxylation catalyzed by trace metal contaminants is low. Still, we were intrigued by the fact that 99.994% Cs_2CO_3 from Alfa Aesar was not effective.

8.4.2. Influence of the impurities

Some transition metals are active catalysts for the catalytic reactions even in very small quantities. Thus, even small impurities in commercially available compounds were found to be the real catalysts for some processes.[36] The control experiments with 99.994% Cs_2CO_3 from Alfa Aesar were done in order to discard this possibility. This extra pure cesium carbonate was tested in a presence of 5 mol% of different transition metal salts. The results are shown in Table 4.

Table 4. Examination of metal salts in combination with Alfa Aesar's 99.994% Cs_2CO_3 for direct carboxylation.



Entry	Metal salt	Conversion
1	CuI	0
2	Cu_2O	0
3	$FeCl_3$	0
4	$NiCl_2$	0
5	$Pd(OAc)_2$	0
6	LiO^tBu	0

Thus, addition of common metal salts together with Alfa Aesar's 99.994% Cs_2CO_3 did not give any conversion for the carboxylation reaction. These results again suggest that carboxylation is not likely catalyzed by trace metal contaminants in other commercial Cs_2CO_3.

8.4.3. Water content in cesium carbonate

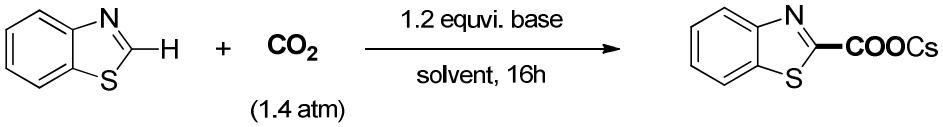
Various commercial Cs_2CO_3 samples were then sent for the chemical analysis. The main difference between Alfa Aesar's 99.994% Cs_2CO_3 and the other sources of Cs_2CO_3 is the bigger content of hydrogen in the first sample. An average result of two experiments of the elemental analysis showed the content of 0.66% of H, which would correspond to about 1 molecule of H_2O per 1 molecule of Cs_2CO_3. The values between 0.1 and 0.3% of H were obtained for the other sources of Cs_2CO_3. These results indicated that the water content might be the origin for the abnormal behavior of Alfa Aesar's 99.994% Cs_2CO_3 in our reactions. It was already shown by Denmark and coworkers that the degree of hydration of Cs_2CO_3 can influence on its activity in cross coupling reactions.[37]

To confirm this hypothesis, the test reactions were performed by manual addition of distilled water to the reaction mixture with Chem-Impex 99.9% Cs_2CO_3 as the base. The

results are shown in Table 5. The conversion of 100% was obtained in this reaction in the absence of water. The inhibition of the reaction was observed by water addition. Adding 0.5 equivalent of water lowered the conversion to 73% (entry 2, table 5); adding 1 equivalent of water completely shut down the reaction (entry 3, table 5). A mixture of Cs_2CO_3 (Chem-Impex, 99.9%) and Cs_2CO_3 (Alfa Aesar, 99.994%) gave reduced yields (entries 5 and 6, Table 5). Thus, the inability of Alfa Aesar's 99.994% Cs_2CO_3 to mediate direct carboxylation could originate from its high water content.

The examination of the morphology of different Cs_2CO_3 samples was done under microscope. Cs_2CO_3 (Alfa Aesar, 99.994%) appears to be less crystalline than all other samples of Cs_2CO_3. The latter samples also seem to be more uniform in terms of particle sizes. The attempts were done to dry Cs_2CO_3 (Alfa Aesar, 99.994%) under vacuum and with heating. However, the samples melted to form a rocky chunk which stuck onto the glassware.

Table 5. Examination of the influence of hydration of Cs_2CO_3 for direct carboxylation.



Entry	Base and hydration	Conversion
1	Cs_2CO_3 (Chem-Impex, 99.9%) + no H_2O	100
2	Cs_2CO_3 (Chem-Impex, 99.9%) + 0.5 equiv. of water	73
3	Cs_2CO_3 (Chem-Impex, 99.9%) + 1 equiv. of water	0
4	Cs_2CO_3 (Chem-Impex, 99.9%) + 4 equiv. of water	0
5	0.6 equiv of Cs_2CO_3 (Chem-Impex, 99.9%) + 0.6 equiv. of Cs_2CO_3 (Alfa Aesar, 99.994%)	65
6	0.3 equiv of Cs_2CO_3 (Chem-Impex, 99.9%) + 0.9 equiv. of Cs_2CO_3 (Alfa Aesar, 99.994%)	0

In summary, most commercial sources of Cs_2CO_3 can mediate direct carboxylation of aromatic heterocycles. Alfa Aesar's 99.994% Cs_2CO_3 is not efficient for the carboxylation reactions, probably due to its high water content. It is unlikely that the traces of other metal salts in commercial sources of Cs_2CO_3 are the catalysts of this reaction.

8.5. Stability of the acidic form of the products

The acid forms of some products can be separated from the reaction mixture. When a concentrated solution of HCl is added to a water solution of cesium benzothiazole-2-carboxylate, a white precipitate of benzothiazole-2-carboxylic acid can be collected by filtration. Its ^{1}H-NMR spectrum in represented in Figure 1.

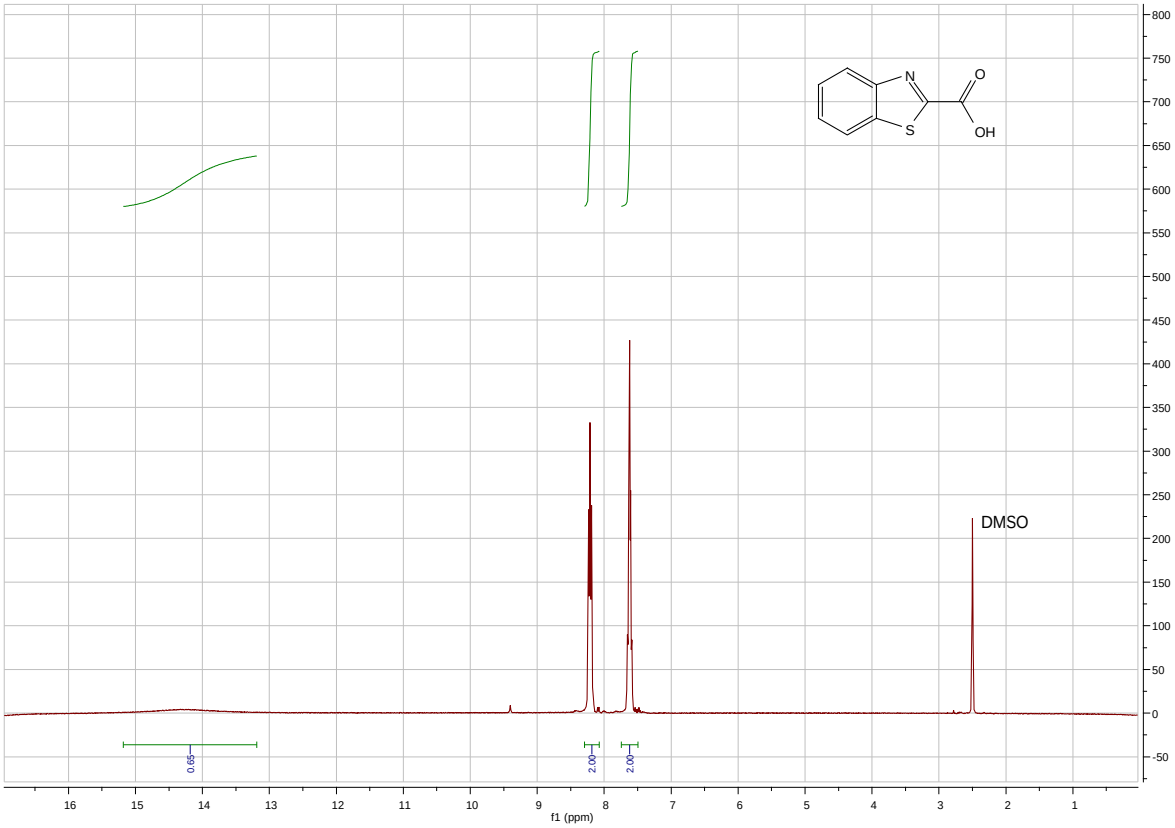


Figure 1. ^{1}H-NMR spectrum of benzothiazole-2-carboxylic acid.

This compound is stable in a solid phase, but fast decomposition occurs when benzothiazole-2-carboxylic acid is dissolved in organic solvents. Decarboxylation of benzothiazole-2-carboxylic acid was studied by NMR spectroscopy in DMSO-D6 solvent (Figure 2). Only small peaks of decarboxylation product benzothiazole are observed on the ^{1}H-NMR spectrum immediately after the solution was prepared. When the solution is kept in

a closed NMR tube for 5h, 20% of benzothiazole-2-carboxylic acid lost CO_2. Almost complete decarboxylation was observed after 24h; an overpressure of CO_2 in the NMR tube was also noticed. Derivatives of other heterocycles are even less stable compound and more than 10% of decarboxylation was observed after 10min. Thus, all the products of carboxylation reactions were converted into a stable ester form, which was separated and characterized.

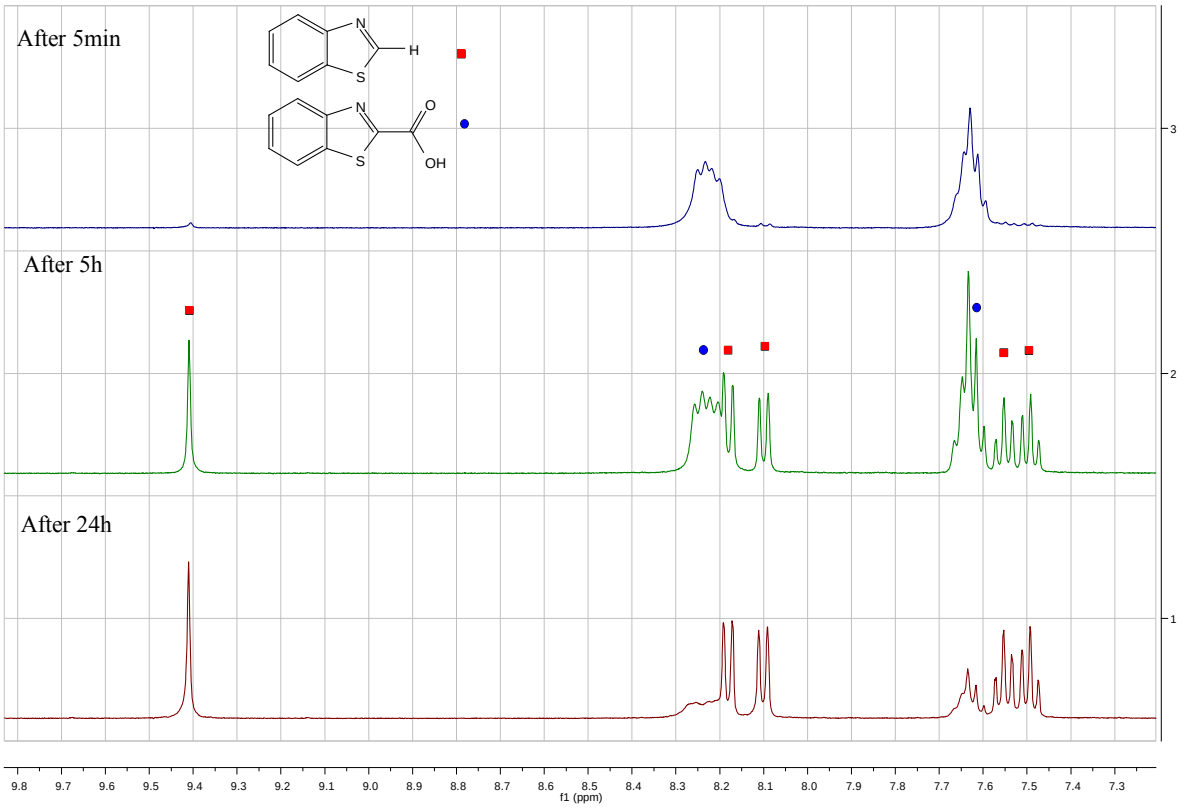
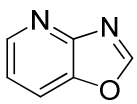


Figure 2. Decarboxylation of benzothiazole-2-carboxylic acid with time.

8.6. Failed substrates

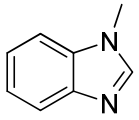
The developed method was also used for the other types of heterocyclic compounds. However, the results were not successful because of the following reasons:

oxazolo[4,5]pyridine



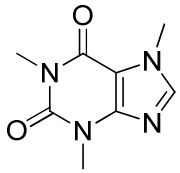
An opening of oxazole cycle was observed during reaction.

1-methyl-benzimidazole



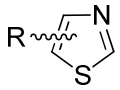
There is no reaction when Cs_2CO_3 is used as a base; however a low conversion was observed with a base LiO^tBu. The product cannot be separated in ester form because the second nitrogen of benzimidazole ring reacts with MeI.

Caffeine



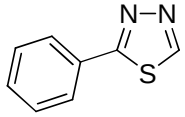
Carboxylation reaction works with LiO^tBu as a base. The conversion of 90% was observed after heating at 150^0C during 8h. However, no ester formation was observed after addition of MeI, not allowing the separation of the product in a stable form.

Thiazole derivatives



No reaction was observed and only starting materials were seen by NMR spectroscopy.

2-phenyl-1,3,4-thiadiazole



An opening of 1,3,4-thiadiazole cycle was observed during reaction.

8.7. Mechanism of the reaction

To probe the mechanism of the reactions, the carboxylation of benzothiazole was followed by NMR. At partial conversion, only benzothiazole and 2-benzothiazolecarboxylate were detected, but not 2-benzothiazolyl anion. In the absence of CO_2, benzothioazole was not deprotonated by Cs_2CO_3 to a detectable degree. Therefore, the following mechanism is

proposed for the carboxylation reaction. The carboxylation proceeds first via an uphill C—H cleavage at the C(2) position, followed by C—C bond formation with CO_2 (Figure 3).

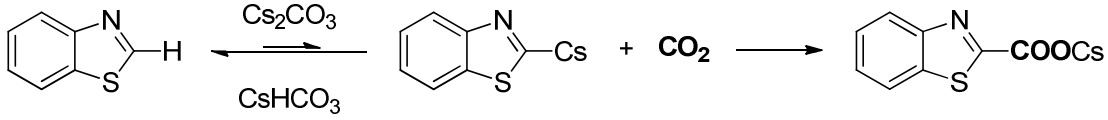


Figure 3. Proposed mechanism for the CO_2 insertion.

8.8. Conclusions

In summary, a simple and straightforward carboxylation method of aromatic heterocycles using CO_2 as the C1 source was described. The resulting heteroaryl carboxylic acids and esters are important compounds for medicinal and materials sciences. Remarkably, direct C—H functionalization is possible without a metal catalyst and with only Cs_2CO_3 as the base. Compared to other carboxylation procedures, the method is more atom- and step-economic, and is practical for industrial use. The use of a mild base results in a high tolerance towards reactive and unsaturated functional groups.

8.9. Experimental section

The coupling products are fully characterized, and their characterization data can be found in the Chapter 9 and in the supporting information (available free online) of the paper.[38]

Chemicals and Reagents

Loading of reagents for carboxylation was carried out under an inert N_2(g) atmosphere using glovebox techniques. Solvents were purified using a two-column solid-state purification system (Innovative Technology, NJ, USA) and transferred to the glove box without exposure to air. Deuterated solvents were purchased from Cambridge Isotope Laboratories, Inc., and were degassed and stored over activated 3 Å molecular sieves. Unless noted, all other reagents were purchased from commercial sources and used without further purification. Liquid compounds were degassed by standard freeze-pump-thaw procedures prior to use in the glovebox. Oxazole substrates were prepared according to a general procedure.[39]

Physical methods

The ^{1}H and ^{13}C NMR spectra were recorded at 293 K on a Bruker Avance 400 spectrometer. ^{1}H NMR chemical shifts were referenced to residual solvent as determined relative to Me_4Si (δ = 0 ppm). The $^{13}C\{^{1}H\}$ chemical shifts were reported in ppm relative to the carbon resonance of $CDCl_3$ (77.00 ppm) or DMSO-D6 (39.52 ppm). GC-MS measurements were conducted on a Perkin-Elmer Clarus 600 GC equipped with Clarus 600T MS. GC measurement was conducted on a Perkin-Elmer Clarus 400 GC with a FID detector. HRCI-MS measurements were conducted at the EPFL ISIC Mass Spectrometry Service at Micro Mass QTOF Ultima. Elemental analyses were performed on a Carlo Erba EA 1110 CHN instrument at EPFL. Melting point measurements were conducted on Buchi Melting Point B-540.

General procedure for the carboxylation to form acids

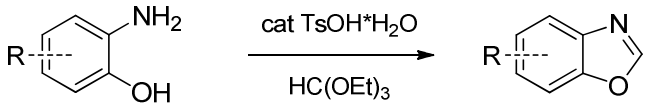
The heterocycle (2 mmol) and Cs_2CO_3 (782mg, 2.4 mmol, Chem-Impex, 99.9%) were placed in a 25 mL Schlenk flask. 3 mL of DMF was then added. The reaction flask was degassed and flushed with CO_2 twice. After this, the reaction mixture was heated at 125 ^{0}C for 16 h under a 400 mbar of overpressure of CO_2. It was then cooled to room temperature and the solvent was evaporated. Water is added to dissolve the solid residue, and the solution was then filtered. 3 mL of 25% aqueous solution of HCl was added slowly to the filtrate. The resulting precipitate was collected by filtration and dried under vacuum.

General procedure for the carboxylation and then esterification

The heterocycle (2 mmol) and Cs_2CO_3 (782mg, 2.4 mmol, Chem-Impex, 99.9%) were placed in a 25 mL Schlenk flask. 3 mL of DMF was then added. The reaction flask was degassed and flushed with CO_2 twice. After this, the reaction mixture was heated at 125 ^{0}C for 16 h under a 400 mbar of overpressure of CO_2. It then cooled to 35 ^{0}C or 65 ^{0}C, and MeI (375 µL, 6 mmol) was added with a syringe. The reaction mixture was stirred for 2 more hours. Then the reaction mixture was cooled to room temperature and the solvent was evaporated. Water was added to make a suspension, and the organic product was extracted with CH_2Cl_2 (3 times, 20 mL each). The organic phase was dried with Na_2SO_4, filtered and the solvent was evaporated under vacuum. In the case that the product was not yet pure, it was purified by a flash chromatography, using hexane/ethyl acetate as a solvent.

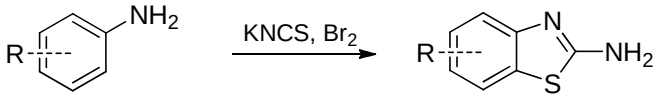
Synthesis of substrates

Synthesis of benzo[d]oxazole type substrates:

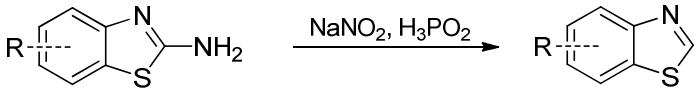


60 mL of triethyl orthoformate was added to a mixture of 2-aminophenol (33 mmol) and p-toluenesulfonic acid monohydrate (3 mol%, 1 mmol, 190 mg). The resulting mixture was heated overnight at 140 ^{0}C. After this, the solvent was evaporated under vacuum and 50 mL of water was added. The organic product was extracted by ethyl acetate (3 times, 40 mL each). The organic phase was dried with Na_2SO_4. Evaporation of solvent under vacuum gave the product in a pure form.

Synthesis of benzo[d]thiazole type substrates:



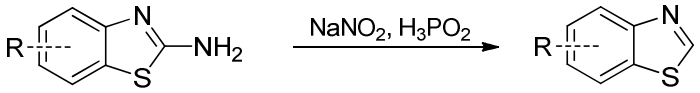
Substituted aniline (22 mmol) and KNCS (3.5 eq, 77mmol, 7.5 g) were dissolved in glacial acetic acid (it takes about 20 min). The solution was cooled with ice bath. Bromine (1.1 eq, 24 mmol, 3.9 g) in 4 mL of glacial acetic acid was then added dropwise, maintaining a reaction temperature below 25 ^{0}C. After addition, the reaction mixture was stirred overnight. Then the reaction mixture was neutralized with 25% solution of ammonia under cooling. The product was collected on the filter, washed with water and small quantity of cold ethyl acetate, and dried under vacuum. The resulting solid product was used without further purification.



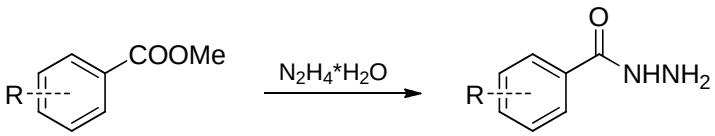
Substituted benzo[d]thiazol-2-amine (12.5 mmol) was dissolved in hot 85% H_3PO_4 (approximately 130 ^{0}C) and the solution was cooled to -8 ^{0}C. A solution of $NaNO_2$ (75 mmol, 5.2 g) in 20 mL of water was added slowly, maintaining a temperature below -4 ^{0}C. Then 30 mL of 50% H_3PO_2 was added slowly and the reaction mixture was stirred overnight. After this time, cold water was added to dissolve all the solid residues of the suspension. The reaction mixture was then neutralized with 25% ammonia solution under cooling. The organic product was extracted with ethyl acetate and purified with a flash chromatography.

Caution: N_2 formed during the reaction, and the volume of the reaction mixture increases considerably. A sufficiently large size of flask should be used.

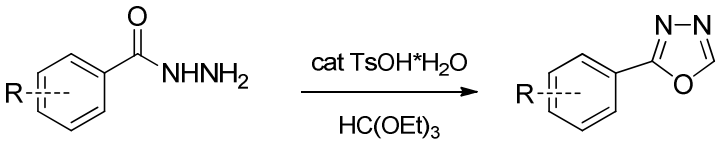
Synthesis of 1,3,4-oxadiazole type substrates:



A mixture of substituted benzoic acid (33 mmol) and catalytic quantity of concentrated H_2SO_4 in methanol was heated at 80 ^{0}C for 4 hours. Then methanol was evaporated under vacuum and 50 mL of water was added. The product was extracted with ethyl acetate (3 times, 40 mL each). The organic phase was dried with Na_2SO_4, and the solvent was evaporated under vacuum, giving the product in a pure form.



The ester was heated in 20 mL of hydrazine monohydrate at 80 ^{0}C during 2 h until the reaction mixture became homogeneous. Then the reaction mixture was cooled to room temperature, and 50 mL of water was added. The organic product was extracted with ethyl acetate (3 times, 40 mL each). The organic phase was dried with Na_2SO_4 and the solvent was evaporated under vacuum, giving the product in a pure form.



60 mL of triethyl orthoformate was added to a mixture of substituted benzohydrazide (33 mmol) and p-toluenesulfonic acid monohydrate (3 mol%, 1 mmol, 190 mg). The resulting mixture was heated overnight at 140 ^{0}C. After this, the solvent was evaporated under vacuum and 50 mL of water was added. The organic product was extracted by ethyl acetate (3 times, 40 mL each). The organic phase was dried with Na_2SO_4. Evaporation of solvent under vacuum gave the product in a pure form.

8.10. References

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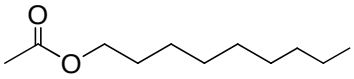
Chapter 9

Characterization data for the products of the catalytic reactions

9.1. Characterization data for the products of the catalytic reactions represented in Chapter 4

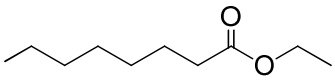


Nonyl acetate (table 6, entry 1-8):[1]

Eluated from the column with hexane-diethyl ether (10:1) in 78% yield as a colorless liquid:

^{1}H NMR (400 MHz, $CDCl_3$): 4.04 (t, *J* = 6.7 Hz, 2H), 2.03 (s, 3H), 1.60 (m, 2H), 1.21-1.35 (m, 12H), 0.87 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 171.3, 64.8, 32.0, 29.6, 29.4, 29.3, 28.7, 26.0, 22.8, 21.1, 14.2.

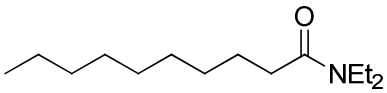


Ethyl octanoate (table 7, entry 1):[2]

Eluated from the column with hexane-diethyl ether (9:1) in 85% yield as a colorless liquid:

^{1}H NMR (400 MHz, $CDCl_3$): 4.11 (q, J = 7.3 Hz, 2H), 2.27 (t, J = 7.3 Hz, 2H), 1.59-1.64 (m, 2H), 1.22-1.33 (m, 11H), 0.86 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 174.0, 60.2, 34.5, 31.8, 29.2, 29.0, 25.1, 22.7, 14.4, 14.2.

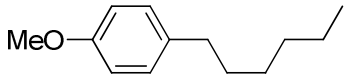


***N*,*N*-diethyldecanamide (table 7, entry 2):**[3]

Eluated from the column with hexane-diethyl ether (15:1 to 6:1) in 78% yield as a colorless liquid:

^{1}H NMR (400 MHz, $CDCl_3$): 3.35 (q, *J* = 7.0 Hz, 2H), 3.28 (q, *J* = 7.3 Hz, 2H), 2.26 (m, 2H), 1.61 (m, 2H), 1.21-1.33 (m, 12H), 1.15 (t, *J* = 7.0 Hz, 3H), 1.08 (t, *J* = 7.3 Hz, 3H), 0.85 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 172.4, 42.0, 40.1, 33.3, 32.0, 29.66, 29.60, 29.4, 25.6, 22.7, 14.5, 14.2, 13.2.

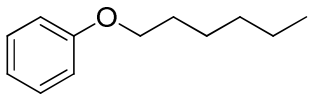


1-hexyl-4-methoxybenzene (table 7, entry 3):[4]

Eluated from the column with hexane-diethyl ether (60:1) in 80% yield as a colorless liquid:

^{1}H NMR (400 MHz, $CDCl_3$): 7.11 (d, *J* = 8.5 Hz, 2H), 6.84 (d, *J* = 8.8 Hz, 2H), 3.80 (s, 3H), 2.55 (m, 2H), 1.59 (m, 2H), 1.32 (m, 6H), 0.89 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 157.8, 135.2, 129.4, 113.8, 55.4, 35.2, 31.90, 31.88, 29.1, 22.8, 14.2.

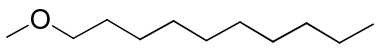


(hexyloxy)benzene (table 7, entry 4):[5]

Eluated from the column with hexane-diethyl ether (60:1) in 97% yield as a colorless oil:

^{1}H NMR (400 MHz, $CDCl_3$): 7.30 (m, 2H), 6.95 (m, 3H), 3.98 (t, *J* = 6.7 Hz, 2H), 1.81 (m, 2H), 1.50 (m, 2H), 1.37 (m, 4H), 0.95 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 159.3, 129.5, 120.6, 114.6, 68.0, 31.7, 29.4, 25.9, 22.8, 14.2.

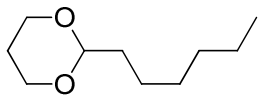


1-methoxydecane (table 7, entry 5):[6]

Eluated from the column with hexane-diethyl ether (10:1) in 98% yield as a colorless liquid:

^{1}H NMR (400 MHz, $CDCl_3$): 3.36 (t, *J* = 6.5 Hz, 2H), 3.32 (s, 3H), 1.56 (m, 2H), 1.22-1.36 (m, 14H), 0.87 (t, *J* = 6.7 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 73.1, 58.7, 32.1, 29.9, 29.8, 29.73, 29.67, 29.5, 26.3, 22.8, 14.2.



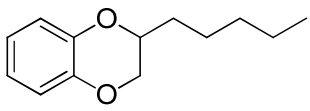
2-hexyl-1,3-dioxane (table 7, entry 6):[7]

Eluated from the column with hexane-diethyl ether (9:1) in 99% yield as a colorless oil:

^{1}H NMR (400MHz, $CDCl_3$): 4.50 (t, *J* = 5.0 Hz, 1H), 4.09 (dd, *J* = 10.9, 4.1 Hz, 2H), 3.75 (m, 2H), 2.07 (q, *J* = 12.6 Hz, 1H), 1.58 (m, 2H), 1.22-1.43 (m, 9H), 0.87 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 102.5, 66.9, 35.3, 31.7, 29.2, 25.9, 24.0, 22.6, 14.1.

HRESI-MS: calculated for ($C_{10}H_{21}O_2$, M+H), 173.1542; found, 173.1547.



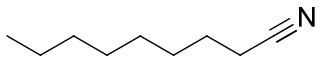
2-pentyl-2,3-dihydro-1,4-benzodioxine (table 7, entry 7):

Eluated from the column with hexane-diethyl ether (60:1) in 71% yield as a colorless liquid:

^{1}H NMR (400MHz, $CDCl_3$): 6.85 (m, 4H), 4.23 (dd, *J* = 11.2, 2.2 Hz, 1H), 4.11 (m, 1H), 3.88 (dd, *J* = 11.2, 7.7 Hz, 1H), 1.31-1.75 (m, 8H), 0.92 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 143.6, 143.4, 121.5, 121.2, 117.4, 117.1, 73.2, 68.2, 31.8, 31.1, 24.8, 22.7, 14.2.

HRESI-MS: calculated for ($C_{13}H_{19}O_2$, M+H), 207.1385; found, 207.1395.

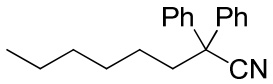


Nonanenitrile (table 7, entry 8):[8]

Eluated from the column with hexane-diethyl ether (9:1) in 77% yield as a colorless liquid:

^{1}H NMR (400 MHz, $CDCl_3$): 2.33 (t, *J* = 7.3 Hz, 2H), 1.65 (m, 2H), 1.44 (m, 2H), 1.20-1.36 (br, 8H), 0.88 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 120.0, 31.8, 29.1, 28.84, 28.78, 25.5, 22.7, 17.2, 14.1.



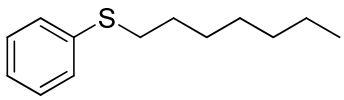
2,2-diphenyloctanenitrile (table 7, entry 9):

Eluated from the column with hexane-diethyl ether (9:1) in 99% yield as a colorless oil:

^{1}H NMR (400 MHz, $CDCl_3$): 7.38 (m, 8H), 7.29 (m, 2H), 2.37 (m, 2H), 1.25-1.48 (m, 8H), 0.87 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 140.4, 128.8, 127.8, 126.9, 122.5, 51.8, 39.7, 31.4, 29.2, 25.6, 22.5, 14.0.

HRESI-MS: calculated for ($C_{20}H_{24}N$, M+H), 278.1909; found, 278.1910.



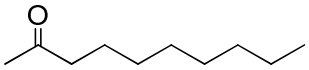
(heptylsulfanyl)benzene (table 7, entry 10):

Eluated from the column with hexane-diethyl ether (100:0 to 30:1) in 56% yield as a colorless liquid:

^{1}H NMR (400 MHz, $CDCl_3$): 7.29 (m, 4H), 7.16 (t, *J* = 7.0 Hz, 1H), 2.92 (m, 2H), 1.65 (m, 2H), 1.41 (m, 2H), 1.22-1.35 (m, 6H), 0.88 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 137.2, 129.0, 128.9, 125.7, 33.7, 31.8, 29.3, 29.0, 28.9, 22.7, 14.2.

Elemental analysis: Anal. Calcd for $C_{13}H_{20}S$: C, 74.94; H, 9.67. Found: C, 75.03; H, 9.77.

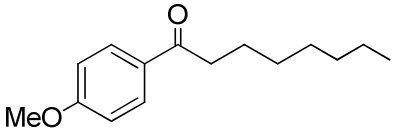


Decan-2-one (table 7, entry 11):[9]

Eluated from the column with hexane-diethyl ether (9:1) in 60% yield as a colorless liquid:

^{1}H NMR (400 MHz, $CDCl_3$): 2.41 (t, *J* = 7.3 Hz, 2H), 2.13 (s, 3H), 1.54-1.60 (m, 2H), 1.22-1.34 (m, 10H), 0.88 (t, *J* = 6.5 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 209.4, 43.9, 31.9, 29.9, 29.5, 29.3, 29.2, 24.0, 22.7, 14.2.

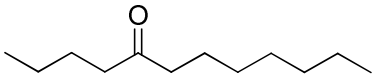


1-(4-methoxyphenyl)octan-1-one (table 7, entry 12):[10]

Eluated from the column with hexane-diethyl ether (6:1) in 68% yield as a slightly yellow solid:

^{1}H NMR (400 MHz, $CDCl_3$): 7.94 (d, *J* = 8.8 Hz, 2H), 6.93 (d, *J* = 8.8 Hz, 2H), 3.87 (s, 3H), 2.90 (t, *J* = 7.3 Hz, 2H), 1.69-1.74 (m, 2H), 1.24-1.37 (m, 8H), 0.88 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 199.4, 163.4, 130.5, 130.4, 113.8, 55.6, 38.5, 31.9, 29.5, 29.3, 24.8, 22.8, 14.2.

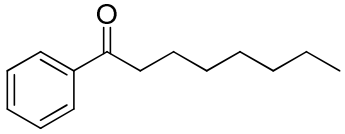


Dodecan-5-one (table 7, entry 13):[11]

Eluated from the column with hexane-diethyl ether (12:1) in 75% yield as a colorless liquid:

^{1}H NMR (400 MHz, $CDCl_3$): 2.27 (td, *J* = 7.7, 1.9 Hz, 2x2H), 1.39-1.48 (m, 4H), 1.10-1.23 (m, 10H), 0.79 (t, *J* = 7.4 Hz, 3H), 0.76 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 211.8, 42.9, 42.6, 31.8, 29.4, 29.2, 26.1, 24.0, 22.7, 22.5, 14.2, 14.0.

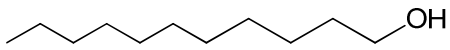


1-phenyloctan-1-one (table 7, entry 14):[12]

Eluated from the column with hexane-diethyl ether (15:1) in 74% yield as a colorless liquid:

^{1}H NMR (400 MHz, $CDCl_3$): 7.98 (m, 2H), 7.57 (m, 1H), 7.48 (m, 2H), 2.98 (t, J = 7.4 Hz, 2H), 1.76 (m, 2H), 1.27-1.42 (m, 8H), 0.91 (t, J = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 200.7, 137.2, 133.0, 128.7, 128.2, 38.8, 31.8, 29.5, 29.3, 24.5, 22.8, 14.2.



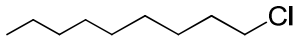
undecan-1-ol (table 7, entry 15):[13]

Eluated from the column with hexane-diethyl ether (9:1) in 79% yield as a colorless liquid:

^{1}H NMR (400 MHz, $CDCl_3$): 3.63 (t, J = 6.7 Hz, 2H), 1.52-1.60 (m, 2H), 1.23-1.36 (m, 16H), 0.88 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 63.2, 33.0, 32.0, 29.8, 29.76, 29.75, 29.6, 29.5, 25.9, 22.8, 14.2.

Elemental analysis: Anal. Calcd for $C_{11}H_{24}O$: C, 76.68; H, 14.04. Found: C, 76.85; H, 13.99.

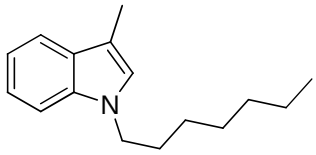


1-chlorononane (table 7, entry 16):[14]

Eluated from the column with hexane-diethyl ether (9:1) in 91% yield as a colorless liquid:

^{1}H NMR (400 MHz, $CDCl_3$): 3.53 (t, J = 6.7 Hz, 2H), 1.77 (m, 2H), 1.42 (m, 2H), 1.23-1.35 (m, 10H), 0.88 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 45.1, 32.7, 31.8, 29.4, 29.2, 28.9, 26.9, 22.7, 14.1.

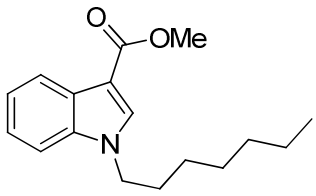


1-heptyl-3-methyl-1*H*-indole (table 7, entry 17):[15]

Eluated from the column with hexane-diethyl ether (20:1) in 95% yield as a colorless oil:

^{1}H NMR (400 MHz, $CDCl_3$): 7.59 (d, *J* = 7.7 Hz, 1H), 7.32 (d, *J* = 7.7 Hz, 1H), 7.22 (t, *J* = 8.0 Hz, 1H), 7.12 (t, *J* = 7.7 Hz, 1H), 6.89 (s, 1H), 4.06 (t, *J* = 7.0 Hz, 2H), 2.36 (s, 3H), 1.82 (quint, *J* = 7.4 Hz, 2H), 1.24-1.36 (m, 8H), 0.90 (t, *J* = 6.7 Hz, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): 136.4, 128.8, 125.6, 121.3, 119.1, 118.5, 110.1, 109.3, 46.2, 31.9, 30.5, 29.1, 27.2, 22.7, 14.2, 9.7.



Methyl 1-heptyl-1*H*-indole-3-carboxylate (table 7, entry 18):

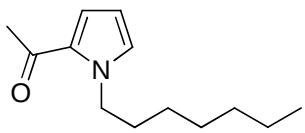
Eluated from the column with hexane-diethyl ether (10:1 to 8:2) in 91% yield as a colorless oil:

^{1}H NMR (400 MHz, $CDCl_3$): 8.18 (m, 1H), 7.83 (s, 1H), 7.37 (m, 1H), 7.28 (m, 2H), 4.13 (t, *J* = 7.0 Hz, 2H), 3.92 (s, 3H), 1.87 (quint, *J* = 7.4 Hz, 2H), 1.29 (m, 8H), 0.87 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 165.7, 136.6, 134.4, 126.9, 122.8, 121.90, 121.88, 110.1, 107.0, 51.1, 47.2, 31.8, 30.0, 29.0, 27.0, 22.7, 14.2.

HRESI-MS: calculated for ($C_{17}H_{24}NO_2$, M+H), 274.1807; found, 274.1820.

Elemental analysis: Anal. Calcd for $C_{17}H_{23}NO_2$: C, 74.69; H, 8.48; N, 5.12. Found: C, 74.97; H, 8.68, N, 5.82.



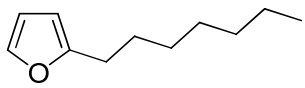
1-(1-heptyl-1*H*-pyrrol-2-yl)ethanone (table 7, entry 19):

Eluated from the column with hexane-diethyl ether (15:1) in 93% yield as a colorless liquid:

^{1}H NMR (400 MHz, $CDCl_3$): 6.95 (dd, *J* = 4.1, 1.8 Hz, 1H), 6.84 (dd, *J* = 2.6, 1.8 Hz, 1H), 6.11 (dd, *J* = 4.1, 2.3 Hz, 1H), 4.29 (m, 2H), 2.43 (s, 3H), 1.71 (m, 2H), 1.27 (m, 8H), 0.87 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 188.3, 130.2, 123.7, 120.3, 107.9, 50.0, 31.9, 31.6, 29.0, 27.5, 26.7, 22.7, 14.2.

ESI-MS: calculated for ($C_{13}H_{22}NO$, M+H), 208.17; found, 208.16.

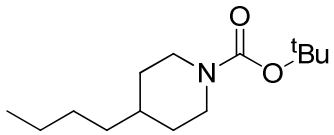


2-heptylfuran (table 7, entry 20):[16]

Eluated from the column with hexane-diethyl ether (100:1) in 99% yield as a colorless oil:

^{1}H NMR (400 MHz, $CDCl_3$): 7.30 (dd, *J* = 2.1, 0.9 Hz, 1H), 6.28 (m, 1H), 5.98 (m, 1H), 2.62 (t, *J* = 7.6 Hz, 2H), 1.64 (m, 2H), 1.25-1.37 (m, 8H), 0.89 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 156.8, 140.7, 110.2, 104.6, 31.9, 29.3, 29.2, 28.2, 28.1, 22.8, 14.2.



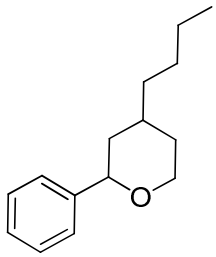
***tert*-butyl 4-butylpiperidine-1-carboxylate (table 7, entry 21):**

Eluated from the column with hexane-diethyl ether (10:1) in 86% yield as a colorless oil:

^{1}H NMR (400 MHz, $CDCl_3$): 4.04 (br., 2H), 2.65 (br., 2H), 1.62 (m, 2H), 1.44 (s, 9H), 1.20-1.35 (m, 7H), 1.05 (m, 2H), 0.88 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 155.1, 79.2, 44.3 (br), 36.4, 36.1, 32.4, 29.0, 28.6, 23.0, 14.2.

HRESI-MS: calculated for ($C_{14}H_{28}NO_2$, M+H), 242.2120; found, 242.2116.



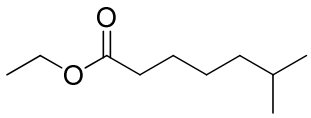
4-butyl-2-phenyltetrahydro-2H-pyran (table 7, entry 22):

Eluated from the column with hexane-diethyl ether (60:1) in 79% yield as a colorless oil:

^{1}H NMR (400 MHz, $CDCl_3$): 7.34 (m, 4H), 7.25 (m, 1H), 4.31 (dd, *J* = 11.4, 2.3 Hz, 1H), 4.17 (m, 1H), 3.60 (m, 1H), 1.89 (m, 1H), 1.65 (m, 2H), 1.29 (m, 8H), 0.90 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 143.4, 128.4, 127.4, 126.0, 80.1, 68.7, 44.1, 36.8, 35.8, 32.8, 28.7, 23.0, 14.3.

HRESI-MS: calculated for ($C_{15}H_{23}O$, M+H), 219.1749; found, 219.1746.

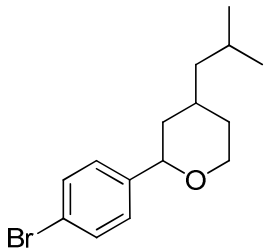


Ethyl 6-methylheptanoate (table 7, entry 23):[17]

Eluated from the column with hexane-diethyl ether (60:1) in 71% yield as a colorless liquid:

^{1}H NMR (400 MHz, $CDCl_3$): 4.10 (q, *J* = 7.2 Hz, 2H), 2.27 (t, *J* = 7.4 Hz, 2H), 1.54 (m, 3H), 1.23 (t, *J* = 7.0 Hz, 3H), 1.18 (m, 4H), 0.84 (d, *J* = 6.5 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): 174.0, 60.2, 38.7, 34.5, 27.9, 27.0, 25.3, 22.7, 14.3.



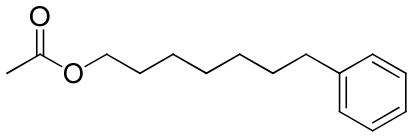
2-(4-bromophenyl)-4-(2-methylpropyl)tetrahydro-2H-pyran (table 7, entry 24):

Eluated from the column with hexane-diethyl ether (60:1) in 89% yield as a colorless oil:

^{1}H NMR (400 MHz, $CDCl_3$): 7.45 (m, 2H), 7.22 (m, 2H), 4.28 (dd, *J* = 11.4, 2.1 Hz, 1H), 4.15 (ddd, *J* = 11.7, 5.0, 1.8 Hz, 1H), 3.59 (m, 1H), 1.73 (m, 4H), 1.28 (m, 2H), 1.12 (m, 2H), 0.88 (dd, *J* = 6.5, 4.4 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): 142.5, 131.5, 127.7, 121.1, 79.3, 68.7, 46.6, 41.3, 33.4, 32.9, 24.4, 23.0, 22.9.

HRESI-MS: calculated for ($C_{15}H_{22}OBr$, M+H), 297.0854 and 299.0835; found, 297.0865 and 299.0830.

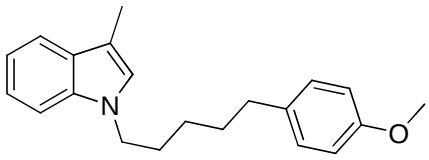


7-phenylheptyl acetate (table 7, entry 25):[18]

Eluated from the column with hexane-diethyl ether (15:1) in 65% yield as a colorless oil:

^{1}H NMR (400 MHz, $CDCl_3$): 7.29 (m, 2H), 7.19 (m, 3H), 4.06 (t, *J* = 6.7 Hz, 2H), 2.62 (m, 2H), 2.05 (s, 3H), 1.28-1.66 (m, 4H), 1.32-1.38 (m, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): 171.3, 142.9, 128.5, 128.3, 125.7, 64.7, 36.0, 31.5, 29.3, 29.2, 28.7, 26.0, 21.1.



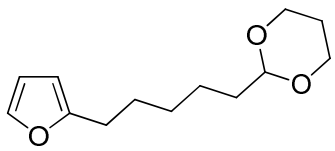
1-[5-(4-methoxyphenyl)pentyl]-3-methyl-1*H*-indole (table 7, entry 26):

Eluated from the column with hexane-diethyl ether (60:1) in 87% yield as a colorless oil:

^{1}H NMR (400 MHz, $CDCl_3$): 7.61 (d, *J* = 7.9 Hz, 1H), 7.32 (m, 1H), 7.24 (m, 1H), 7.14 (m, 1H), 7.09 (d, *J* = 8.8 Hz, 2H), 6.86 (m, 3H), 4.07 (t, *J* = 7.0 Hz, 2H), 3.82 (s, 3H), 2.56 (t, *J* = 7.6 Hz, 2H), 2.37 (s, 3H), 1.86 (m, 2H), 1.64 (m, 2H), 1.38 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): 157.8, 136.4, 134.6, 129.4, 128.8, 125.6, 121.4, 119.1, 118.5, 113.8, 110.1, 109.3, 55.4, 46.1, 34.9, 31.5, 30.3, 26.7, 9.7.

HRESI-MS: calculated for ($C_{21}H_{26}ON$, M+H), 308.2014; found, 308.2015.



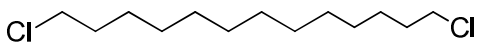
2-[5-(furan-2-yl)pentyl]-1,3-dioxane (table 7, entry 27):

Eluated from the column with hexane-diethyl ether (60:1 to 10:1) in 60% yield as a colorless oil:

^{1}H NMR (400 MHz, $CDCl_3$): 7.27 (dd, *J* = 1.9, 0.9 Hz, 1H), 6.26 (dd, *J* = 3.1, 1.9 Hz, 1H), 5.95 (m, 1H), 4.50 (t, *J* = 5.2 Hz, 1H), 4.09 (m, 2H), 3.74 (m, 2H), 2.60 (t, *J* = 7.6 Hz, 2H), 2.06 (m, 1H), 1.62 (m, 4H), 1.35 (m, 5H).

^{13}C NMR (100 MHz, $CDCl_3$): 156.5, 140.7, 110.1, 104.7, 102.4, 67.0, 35.2, 29.1, 27.99, 27.93, 25.9, 23.8.

GC-MS (EI): 223 (M-H).



1,13-dichlorotridecane (table 7, entry 28):

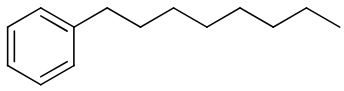
Eluated from the column with hexane-diethyl ether (100:1) in 66% yield as a colorless oil:

^{1}H NMR (400 MHz, $CDCl_3$): 3.53 (t, *J* = 6.7 Hz, 4H), 1.76 (m, 4H), 1.42 (m, 4H), 1.25-1.32 (m, 14H).

^{13}C NMR (100 MHz, $CDCl_3$): 45.3, 32.8, 29.7, 29.66, 29.60, 29.0, 27.0.

GC-MS (EI): 252 (M/Z, EI)

9.2. Characterization data for the products of the catalytic reactions represented in Chapter 5



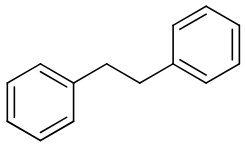
octylbenzene (table 2, entry 1):[19]

Synthesized with TMEDA as an additive.

Eluated from the column with hexane-diethyl ether (100:1) in 92% yield as a colorless liquid:

^{1}H NMR (400MHz, $CDCl_3$): 7,32 (m, 2H), 7,23 (m, 3H), 2,65 (t, *J* = 8,5 Hz, 2H), 1,66 (m, 2H), 1,33 (m, 10H), 0,93 (t, *J* = 6,7 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 142.9, 128.3, 128.1, 125.5, 36.0, 31.9, 31.5, 29.5, 29.3, 29.2, 22.6, 14.1.



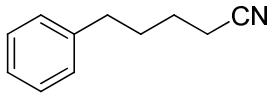
1,2-diphenylethane (table 2, entry 11):[20]

Synthesized with TMEDA as an additive.

Eluated from the column with hexane-diethyl ether (100:1) in 90% yield as a white solid:

^{1}H NMR (400MHz, $CDCl_3$): 7,37 (m, 4H), 7,28 (m, 6H), 3,01 (s, 4H).

^{13}C NMR (100 MHz, $CDCl_3$): 141.7, 128.4, 128.2, 125.8, 37.9.



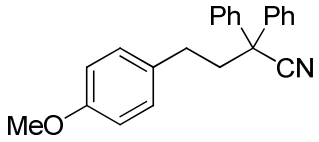
5-phenylpentanenitrile (table 3, entry 1):[21]

Synthesized with TMEDA as an additive.

Eluted from the column with hexane-diethyl ether (30:1 to 10:1) in 80% yield as a colorless liquid:

^{1}H NMR (400MHz, $CDCl_3$): 7.31 (m, 2H), 7.20 (m, 3H), 2.67 (t, *J* = 7.3 Hz, 2H), 2.35 (t, *J* = 7.0 Hz, 2H), 1.80 (m, 2H), 1.69 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): 141.1, 128.3, 128.2, 125.9, 119.5, 34.9, 30.1, 24.7, 16.9.



4-(4-methoxyphenyl)-2,2-diphenylbutanenitrile (table 3, entry 2):

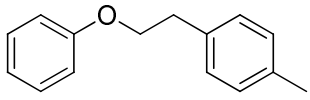
Synthesized with TMEDA as an additive.

Eluted from the column with hexane-diethyl ether (30:1 to 10:1) in 89% yield as a colorless oil:

^{1}H NMR (400MHz, $CDCl_3$): 7.30-7.46 (m, 8H), 7.31 (m, 2H), 7.08 (d, *J* = 8.5 Hz, 2H), 6.83 (d, *J* = 8.5 Hz, 2H), 3.79 (s, 3H), 2.66 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$): 158.0, 139.9, 132.6, 129.2, 128.9, 127.9, 126.8, 122.1, 113.9, 55.2, 51.6, 41.9, 31.1.

HRESI-MS: calculated for ($C_{23}H_{21}NO$, M+H), 328.1701; found, 328.1700.



1-methyl-4-(2-phenoxyethyl)benzene (table 3, entry 3):

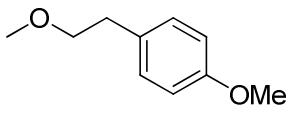
Synthesized with TMEDA as an additive.

Eluted from the column with hexane-diethyl ether (30:1) in 99% yield as a colorless liquid:

^{1}H NMR (400MHz, $CDCl_3$): 7.34 (m, 2H), 7.22 (m, 4H), 6.99 (m, 3H), 4.21 (t, *J* = 7.3 Hz, 2H), 3.13 (t, *J* = 7.3 Hz, 2H), 2.40 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 158.7, 135.9, 135.0, 129.3, 129.1, 128.8, 120.6, 114.5, 68.6, 35.3, 21.0.

Elemental analysis: Anal. Calcd for $C_{15}H_{16}O$: C, 84.87; H, 7.60. Found: C, 84.34; H, 7.58.



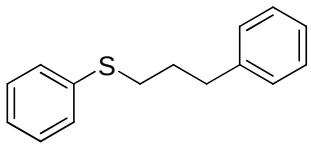
1-methoxy-4-(2-methoxyethyl)benzene (table 3, entry 4):[22]

Synthesized with TMEDA as an additive.

Eluted from the column with hexane-diethyl ether (10:1) in 89% yield as a colorless liquid:

^{1}H NMR (400MHz, $CDCl_3$): 7.15 (d, J = 8.5 Hz, 2H), 6.85 (d, J = 8.5 Hz, 2H), 3.79 (s, 3H), 3.58 (t, J = 7.3 Hz, 2H), 3.37 (s, 3H), 2.84 (t, J = 7.0 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): 158.0, 130.9, 129.6, 113.7, 73.8, 58.5, 55.1, 35.2.



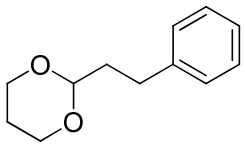
phenyl(3-phenylpropyl)sulfane (table 3, entry 5):[23]

Synthesized with TMEDA as an additive.

Eluted from the column with hexane-diethyl ether (100:1) in 66% yield as a colorless liquid:

^{1}H NMR (400MHz, $CDCl_3$): 7.15-7.40 (m, 10H), 2.94 (m, 2H), 2.78 (t, J = 7.3 Hz, 2H), 1.99 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): 141.2, 136.5, 129.0, 128.8, 128.4, 128.3, 125.9, 125.7, 34.6, 32.8, 30.5.



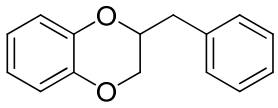
2-phenethyl-1,3-dioxane (table 3, entry 6):[24]

Synthesized with TMEDA as an additive.

Eluted from the column with hexane-diethyl ether (10:1) in 96% yield as a colorless liquid:

^{1}H NMR (400MHz, $CDCl_3$): 7.28 (m, 2H), 7.20 (m, 3H), 4.52 (t, J = 5.3 Hz, 1H), 4.13 (dd, J_1 = 11.4 Hz, J_2 = 5.0 Hz, 2H), 3.76 (m, 2H), 2.73 (m, 2H), 2.11 (m, 1H), 1.93 (m, 2H), 1.35 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): 141.6, 128.4, 128.3, 125.7, 101.4, 66.8, 36.6, 30.0, 25.8.



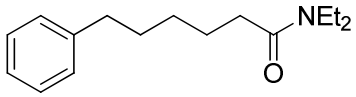
2-benzyl-2,3-dihydrobenzo[b][1,4]dioxine (table 3, entry 7):[25]

Synthesized with TMEDA as an additive.

Eluted from the column with hexane-diethyl ether (20:1) in 85% yield as a colorless liquid:

^{1}H NMR (400MHz, $CDCl_3$): 7.28-7.38 (m, 5H), 6.84-6.94 (m, 4H), 4.38 (m, 1H), 4.20 (dd, J_1 = 11.2 Hz, J_2 = 2.1 Hz, 1H), 3.93 (dd, J_1 = 11.4 Hz, J_2 = 7.0 Hz, 1H), 3.14 (dd, J_1 = 13.8 Hz, J_2 = 6.5 Hz, 1H), 2.91 (dd, J_1 = 14.1 Hz, J_2 = 7.3 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): 143.2, 143.1, 136.3, 129.3, 128.5, 126.7, 121.5, 121.2, 117.3, 117.0, 73.6, 66.9, 37.5.



N,N-diethyl-6-phenylhexanamide (table 3, entry 8):

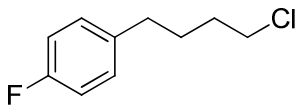
Synthesized with TMEDA as an additive.

Eluted from the column with hexane-diethyl ether (4:6) in 84% yield as a colorless liquid:

^{1}H NMR (400MHz, $CDCl_3$): 7.25 (d, J = 7.3 Hz, 2H), 7.17 (d, J = 6.5 Hz, 3H), 3.36 (q, J = 7.0 Hz, 2H), 3.28 (q, J = 7.3 Hz, 2H), 2.61 (m, 2H), 2.27 (m, 2H), 1.66 (m, 4H), 1.38 (m, 2H), 1.15 (t, J = 7.0 Hz, 3H), 1.10 (t, J = 7.0 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 172.0, 142.5, 128.3, 128.1, 125.5, 41.8, 39.9, 35.7, 32.9, 31.2, 29.0, 25.2, 14.3, 13.0.

HRESI-MS: calculated for ($C_{16}H_{25}NO$, M+H), 248.2014; found, 248.2012.



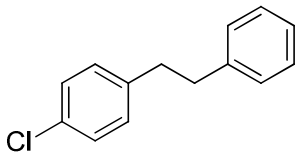
1-(4-chlorobutyl)-4-fluorobenzene (table 3, entry 9):[26]

Synthesized with TMEDA as an additive.

Eluted from the column with hexane-diethyl ether (30:1) in 76% yield as a colorless liquid:

^{1}H NMR (400MHz, $CDCl_3$): 7.14 (m, 2H), 6.98 (m, 2H), 3.55 (t, J = 6.2 Hz, 2H), 2.63 (t, J = 7.3 Hz, 2H), 1.79 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$): 161.3 (d, J = 243.1 Hz), 137.4 (d, J = 3.2 Hz), 129.7 (d, J = 8.1 Hz), 115.1 (d, J = 20.9 Hz), 44.7, 34.2 (d, J = 0.4 Hz), 31.9, 28.7 (d, J = 1.1 Hz).



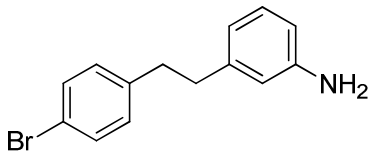
1-chloro-4-phenethylbenzene (table 3, entry 10):[27]

Synthesized with TMEDA as an additive.

Eluted from the column with hexane-diethyl ether (60:1) in 98% yield as a white solid:

^{1}H NMR (400MHz, $CDCl_3$): 7.10-7.35 (m, 9H), 2.93 (s, 4H).

^{13}C NMR (100 MHz, $CDCl_3$): 141.2, 140.0, 131.5, 129.7, 128.4, 128.35, 128.33, 125.9, 37.7, 37.1.



3-(4-bromophenethyl)aniline (table 3, entry 11):

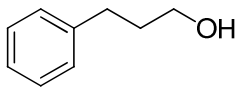
Synthesized with TMEDA as an additive.

Eluted from the column with hexane-diethyl ether (60:1 to 2:1) in 98% yield as a colorless liquid:

^{1}H NMR (400MHz, $CDCl_3$): 7.40 (d, J = 8.2 Hz, 2H), 7.07 (m, 3H), 6.55 (m, 3H), 3.64 (br, 2H), 2.84 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$): 146.2, 142.5, 140.7, 131.2, 130.1, 129.2, 119.5, 118.8, 115.2, 112.9, 37.6, 37.0.

HRESI-MS: calculated for ($C_{14}H_{14}NBr$, M+H), 276.0388 and 278.0368; found, 276.0385 and 278.0377.



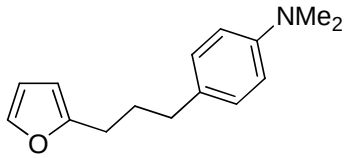
3-phenylpropan-1-ol (table 3, entry 12):[28]

Synthesized with TMEDA as an additive.

Eluted from the column with hexane-diethyl ether (1:1) in 74% yield as a colorless liquid:

^{1}H NMR (400MHz, $CDCl_3$): 7.30 (m, 2H), 7.20 (m, 3H), 3.68 (t, J = 6.5 Hz, 2H), 2.72 (m, 2H), 1.91 (m, 2H), 1.52 (br, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): 141.7, 128.36, 128.38, 125.8, 62.2, 34.1, 32.0.



4-(3-(furan-2-yl)propyl)-N,N-dimethylaniline (table 3, entry 13):

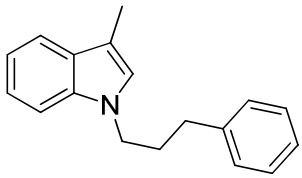
Synthesized with TMEDA as an additive.

Eluted from the column with hexane-diethyl ether (60:1 to 30:1) in 83% yield as a colorless oil:

^{1}H NMR (400MHz, $CDCl_3$): 7.32 (m, 1H), 7.09 (d, *J* = 8.5 Hz, 2H), 6.72 (d, *J* = 8.5 Hz, 2H), 6.29 (m, 1H), 6.00 (m, 1H), 2.93 (s, 6H), 2.66 (t, *J* = 7.3 Hz, 2H), 2.59 (t, *J* = 7.3 Hz, 2H), 1.95 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): 156.2, 148.9, 140.6, 130.2, 129.0, 113.0, 110.0, 104.7, 40.9, 34.1, 29.8, 27.4,

HRESI-MS: calculated for ($C_{15}H_{19}NO$, M+H), 230.1545; found, 230.1552.



3-methyl-1-(3-phenylpropyl)-1H-indole (table 3, entry 14):

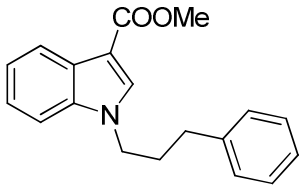
Synthesized with TMEDA as an additive.

Eluted from the column with hexane-diethyl ether (50:1) in 81% yield as a colorless oil:

^{1}H NMR (400MHz, $CDCl_3$): 7.62 (d, *J* = 7.9 Hz, 1H), 7.20-7.35 (m, 7H), 7.14 (m, 1H), 6.90 (s, 1H), 4.10 (t, *J* = 7.3 Hz, 2H), 2.67 (t, *J* = 7.3 Hz, 2H), 2.38 (s, 3H), 2.19 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): 141.0, 136.2, 128.7, 128.4, 128.3, 126.0, 125.3, 121.2, 118.9, 118.4, 110.2, 109.1, 45.3, 33.0, 31.6, 9.5.

HRESI-MS: calculated for ($C_{18}H_{19}N$, M+H), 250.1596; found, 250.1596.



methyl 1-(3-phenylpropyl)-1H-indole-3-carboxylate (table 3, entry 15):

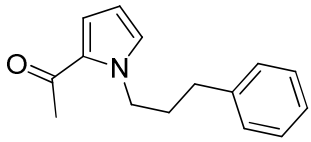
Synthesized with O-TMEDA as an additive.

Eluted from the column with hexane-diethyl ether (2:1) in 81% yield as a slightly yellow liquid:

^{1}H NMR (400MHz, $CDCl_3$): 8.20 (m, 1H), 7.82 (s, 1H), 7.28 (m, 6H), 7.16 (m, 2H), 4.16 (t, J = 7.0 Hz, 2H), 3.92 (s, 3H), 2.66 (t, J = 7.3 Hz, 2H), 2.23 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): 165.4, 140.3, 136.4, 134.1, 128.5, 128.3, 126.7, 126.2, 122.6, 121.8, 121.7, 109.9, 107.0, 50.9, 46.1, 32.7, 31.0.

HRESI-MS: calculated for ($C_{19}H_{19}NO_2$, M+H), 294.1494; found, 294.1492.



1-(1-(3-phenylpropyl)-1H-pyrrol-2-yl)ethanone (table 3, entry 16):

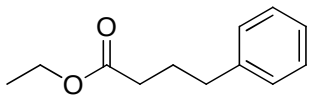
Synthesized with O-TMEDA as an additive.

Eluted from the column with hexane-diethyl ether (20:1 to 10:1) in 62% yield as a colorless liquid:

^{1}H NMR (400MHz, $CDCl_3$): 7.28 (m, 2H), 7.19 (m, 3H), 6.98 (dd, J_1 = 4.1 Hz, J_2 = 1.5 Hz, 1H), 6.83 (m, 1H), 6.14 (dd, J_1 = 3.8 Hz, J_2 = 2.3 Hz, 1H), 4.35 (t, J = 7.0 Hz, 2H), 2.63 (m, 2H), 2.45 (s, 3H), 2.09 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): 188.1, 141.2, 130.1, 130.0, 128.3, 128.2, 125.8, 120.2, 107.8, 49.2, 32.7, 27.2.

HRESI-MS: calculated for ($C_{15}H_{17}NO$, M+H), 228.1388; found, 228.1379.



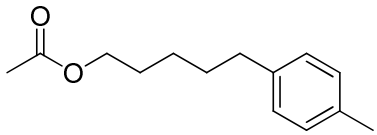
ethyl 4-phenylbutanoate (table 3, entry 17): [29]

Synthesized with O-TMEDA as an additive.

Eluted from the column with hexane-diethyl ether (20:1) in 75% yield as a colorless liquid:

^{1}H NMR (400MHz, $CDCl_3$): 7.30 (m, 2H), 7.20 (m, 3H), 4.14 (q, J = 7.3 Hz, 2H), 2.67 (t, J = 7.6 Hz, 2H), 2.33 (t, J = 7.6 Hz, 2H), 1.97 (quint, J = 7.9 Hz, 2H), 1.26 (t, J = 7.0 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 173.3, 141.3, 128.4, 128.2, 125.8, 60.1, 35.0, 33.6, 26.4, 14.1.



5-p-tolylpentyl acetate (table 3, entry 18):

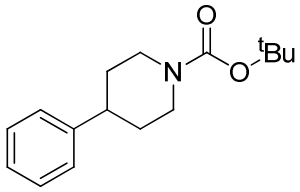
Synthesized with O-TMEDA as an additive.

Eluted from the column with hexane-diethyl ether (30:1 to 10:1) in 63% yield as a colorless liquid:

^{1}H NMR (400MHz, $CDCl_3$): 7.09 (m, 4H), 4.07 (t, J = 6.7 Hz, 2H), 2.59 (t, J = 7.6 Hz, 2H), 2.33 (s, 3H), 2.05 (s, 3H), 1.65 (m, 4H), 1.40 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): 171.1, 139.2, 135.0, 128.9, 128.2, 64.4, 35.2, 31.1, 28.4, 25.5, 20.97, 20.95.

Elemental analysis: Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15. Found: C, 76.44; H, 9.18.



tert-butyl 4-phenylpiperidine-1-carboxylate (table 3, entry 19):

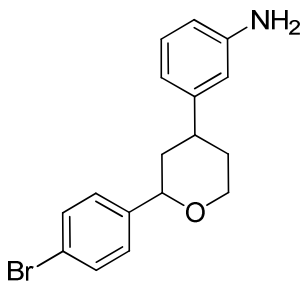
Synthesized with O-TMEDA as an additive.

Eluted from the column with hexane-diethyl ether (30:1 to 10:1) in 65% yield as a colorless liquid:

^{1}H NMR (400MHz, $CDCl_3$): 7.31 (m, 2H), 7.21 (m, 3H), 4.24 (m, 2H), 2.81 (m, 2H), 2.63 (m, 1H), 1.82 (m, 2H), 1.62 (qd, J_1 = 12.6 Hz, J_2 = 3.5 Hz, 2H), 1.49 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): 154.8, 145.7, 128.4, 126.7, 126.3, 79.3, 44.3, 42.7, 33.1, 28.4.

HRESI-MS: calculated for ($C_{16}H_{23}NO_2$, M+H), 262.1807; found, 262.1819.



3-(2-(4-bromophenyl)tetrahydro-2H-pyran-4-yl)aniline (table 3, entry 20):

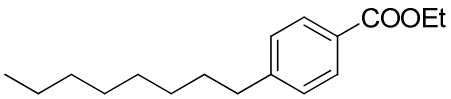
Synthesized with TMEDA as an additive.

Eluted from the column with hexane-diethyl ether (20:1 to 1:1) in 73% yield as a slightly yellow liquid:

^{1}H NMR (400MHz, $CDCl_3$): 7.47 (d, *J* = 8.5 Hz, 2H), 7.27 (d, *J* = 8.2 Hz, 2H), 7.11 (t, *J* = 7.6 Hz, 1H), 6.65 (d, *J* = 7.3 Hz, 1H), 6.55 (m, 2H), 4.44 (m, 1H), 4.28 (m, 1H), 3.45-3.80 (m, 3H), 2.85 (m, 1H), 2.04 (m, 1H), 1.76 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 146.5, 146.4, 141.8, 131.3, 129.4, 127.4, 121.0, 117.0, 113.4, 113.2, 79.1, 68.6, 41.9, 41.2, 33.1.

HRESI-MS: calculated for ($C_{17}H_{18}NBrO$, M+H), 332.0650 and 334.0631; found, 332.0639 and 334.0642.



ethyl 4-octylbenzoate (table 4, entry 2):

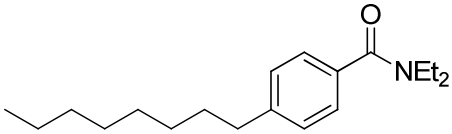
Synthesized by Method A with O-TMEDA as an additive.

Eluted from the column with hexane-diethyl ether (100:1 to 60:1) in 83% yield as a colorless liquid:

^{1}H NMR (400MHz, $CDCl_3$): 7.96 (d, *J* = 8.2 Hz, 2H), 7.23 (d, *J* = 8.4 Hz, 2H), 4.36 (q, *J* = 7.0 Hz, 2H), 2.65 (m, 2H), 1.62 (m, 2H), 1.38 (t, *J* = 7.2 Hz, 3H), 1.20-1.35 (m, 10H), 0.88 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 166.6, 148.3, 129.5, 128.3, 126.3, 60.6, 35.9, 31.8, 31.1, 29.3, 29.2, 29.1, 22.6, 14.3, 14.0.

HRESI-MS: calculated for ($C_{17}H_{26}O_2$, M+H), 263.2011; found, 263.2019.



N,N-diethyl-4-octylbenzamide (table 4, entry 3):

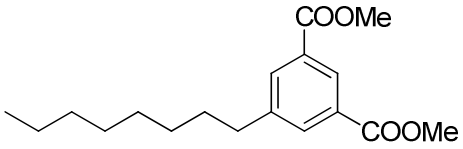
Synthesized by Method A with O-TMEDA as an additive.

Eluted from the column with hexane-diethyl ether (30:1 to 2:1) in 75% yield as a colorless liquid:

^{1}H NMR (400MHz, $CDCl_3$): 7.28 (m, 2H), 7.18 (d, *J* = 7.9 Hz, 2H), 3.14-3.60 (br, 4H), 2.61 (m, 2H), 1.59 (m, 2H), 1.10-1.35 (m, 16H), 0.87 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 171.4, 144.0, 134.4, 128.2, 126.2, 43.2, 39.2, 35.7, 31.8, 31.2, 29.4, 29.22, 29.21, 22.6, 14.1, 14.0, 12.9.

HRESI-MS: calculated for ($C_{19}H_{31}ON$, M+H), 290.2484; found, 290.2475.



dimethyl 5-octylisophthalate (table 4, entry 4):

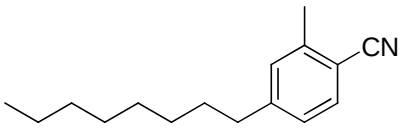
Synthesized by Method A with O-TMEDA as an additive.

Eluted from the column with hexane-diethyl ether (30:1 to 10:1) in 70% yield as a colorless liquid:

^{1}H NMR (400MHz, $CDCl_3$): 8.49 (s, 1H), 8.04 (s, 2H), 3.94 (s, 6H), 2.69 (t, *J* = 7.3 Hz, 2H), 1.64 (m, 2H), 1.22-1.35 (m, 10H), 0.87 (t, *J* = 6.7 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 166.4, 143.7, 133.8, 130.4, 128.1, 52.2, 35.5, 31.8, 31.2, 29.3, 29.18, 29.16, 22.6, 14.0.

HRESI-MS: calculated for ($C_{18}H_{26}O_4$, M+H), 307.1909; found, 307.1923.



2-methyl-4-octylbenzonitrile (table 4, entry 5):

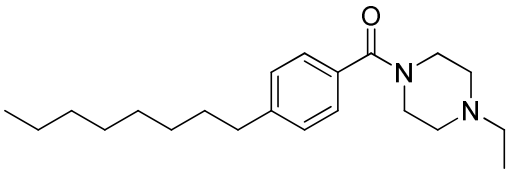
Synthesized by Method A with O-TMEDA as an additive.

Eluted from the column with hexane-diethyl ether (60:1) in 58% yield as a colorless liquid:

^{1}H NMR (400MHz, $CDCl_3$): 7.49 (d, *J* = 7.9 Hz, 1H), 7.11 (s, 1H), 7.06 (d, *J* = 7.9 Hz, 1H), 2.60 (t, *J* = 7.6 Hz, 2H), 2.51 (s, 3H), 1.59 (m, 2H), 1.23-1.35 (m, 10H), 0.88 (t, *J* = 6.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 148.3, 141.7, 132.3, 130.3, 126.3, 118.4, 109.8, 36.0, 31.8, 30.9, 29.3, 29.2, 29.1, 22.6, 20.4, 14.0.

HRESI-MS: calculated for ($C_{16}H_{23}N$, M+H), 230.1909; found, 230.1912.



(4-ethylpiperazin-1-yl)(4-octylphenyl)methanone (table 4, entry 6):

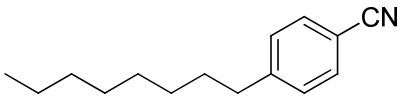
Synthesized by Method A with O-TMEDA as an additive.

Eluted from the column with hexane-ethyl acetate (1:99) in 86% yield as a slightly yellow oil:

^{1}H NMR (400MHz, $CDCl_3$): 7.32 (m, 2H), 7.20 (d, *J* = 8.2 Hz, 2H), 3.40-3.90 (br, 4H), 2.30-2.70 (m, 8H), 1.60 (m, 2H), 1.27 (m, 10H), 1.11 (t, *J* = 7.0 Hz, 3H), 0.87 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 170.4, 144.7, 133.0, 128.3, 127.1, 53.1, 52.5, 52.2, 47.7, 42.2, 35.7, 31.8, 31.2, 29.3, 29.20, 29.19, 22.6, 14.0, 11.8.

HRESI-MS: calculated for ($C_{21}H_{34}N_2O$, M+H), 331.2749; found, 331.2751.



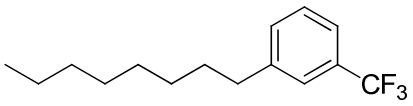
4-octylbenzonitrile (table 4, entry 7): [30]

Synthesized by Method B with TMEDA as an additive.

Eluted from the column with hexane-diethyl ether (100:1) in 62% yield as a colorless liquid:

^{1}H NMR (400MHz, $CDCl_3$): 7.56 (d, *J* = 7.9 Hz, 2H), 7.27 (d, *J* = 7.9 Hz, 2H), 2.65 (m, 2H), 1.61 (m, 2H), 1.25-1.35 (m, 10H), 0.87 (t, *J* = 6.5 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 148.6, 132.1, 129.2, 119.2, 109.4, 36.1, 31.8, 30.9, 29.3, 29.21, 29.20, 22.6, 14.1.



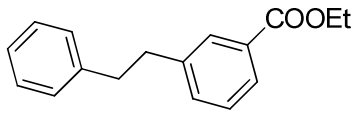
1-octyl-3-(trifluoromethyl)benzene (table 4, entry 8): [31]

Synthesized by Method B with TMEDA as an additive.

Eluted from the column with hexane-diethyl ether (100:1) in 70% yield as a colorless liquid:

^{1}H NMR (400MHz, $CDCl_3$): 7.35-7.46 (m, 4H), 2.66 (t, *J* = 7.6 Hz, 2H), 1.63 (m, 2H), 1.24-1.36 (m, 10H), 0.89 (t, *J* = 6.5 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 143.7, 131.7 (q, *J* = 1.3 Hz), 128.5, 125.0 (q, *J* = 3.8 Hz), 122.4 (q, *J* = 3.8 Hz), 35.8, 31.8, 31.3, 29.4, 29.23, 29.22, 22.6, 14.1.



ethyl 3-phenethylbenzoate (table 4, entry 9):

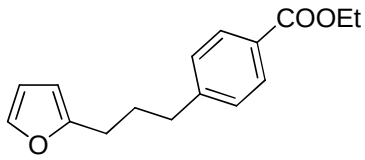
Synthesized by Method A with O-TMEDA as an additive.

Eluted from the column with hexane-diethyl ether (100:1 to 60:1) in 88% yield as a colorless liquid:

^{1}H NMR (400MHz, $CDCl_3$): 7.90 (m, 2H), 7.31 (m, 4H), 7.20 (m, 3H), 4.39 (q, J = 7.3 Hz, 2H), 2.98 (m, 4H), 1.41 (t, J = 7.0 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 166.7, 141.9, 141.2, 133.0, 130.5, 129.4, 128.4, 128.3, 128.2, 127.1, 125.9, 60.8, 37.7, 37.6, 14.3.

HRESI-MS: calculated for ($C_{17}H_{18}O_2$, M+H), 255.1385; found, 255.1387.



ethyl 4-(3-(furan-2-yl)propyl)benzoate (table 4, entry 10):

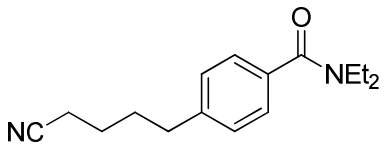
Synthesized by method A with O-TMEDA as an additive, 3.3 of 5eq of Alkyl-I was recovered after reaction with 99% purity.

Eluted from the column with hexane-diethyl ether (100:1 to 30:1) in 74% yield as a colorless liquid:

^{1}H NMR (400MHz, $CDCl_3$): 7.96 (d, J = 8.2 Hz, 2H), 7.31 (d, J = 1.2 Hz, 1H), 7.25 (m, 2H), 6.29 (dd, J_1 = 2.6 Hz, J_2 = 1.8 Hz, 1H), 6.00 (d, J = 2.9 Hz, 1H), 4.37 (q, J = 7.0 Hz, 2H), 2.71 (m, 2H), 2.65 (t, J = 7.3 Hz, 2H), 1.99 (m, 2H), 1.39 (t, J = 7.0 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 166.6, 155.5, 147.3, 140.8, 129.6, 128.4, 128.2, 110.0, 105.0, 60.7, 35.1, 29.3, 27.3, 14.3.

HRESI-MS: calculated for ($C_{16}H_{18}O_3$, M+H), 259.1334; found, 259.1341.



4-(4-cyanobutyl)-N,N-diethylbenzamide (table 4, entry 11):

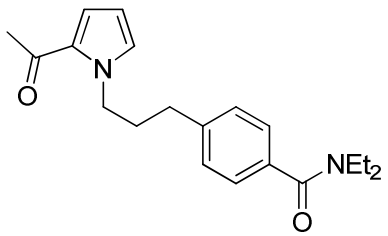
Synthesized by method A with O-TMEDA as an additive, 2.7 of 5eq of Alkyl-I was recovered after reaction with 99% purity.

Eluted from the column with hexane-diethyl ether (10:1 to 1:2) in 70% yield as a colorless liquid:

^{1}H NMR (400MHz, $CDCl_3$): 7.30 (d, *J* = 8.4 Hz, 2H), 7.18 (d, *J* = 7.6 Hz, 2H), 3.20-3.60 (br, 4H), 2.67 (t, *J* = 7.2 Hz, 2H), 2.35 (t, *J* = 7.0 Hz, 2H), 1.79 (m, 2H), 1.67 (m, 2H), 1.05-1.30 (br, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): 171.1, 142.2, 135.0, 128.2, 126.5, 119.4, 43.2, 39.2, 34.7, 30.0, 24.7, 17.0, 14.1, 12.9.

HRESI-MS: calculated for ($C_{16}H_{22}ON_2$, M+H), 259.1810; found, 259.1821.



4-(3-(2-acetyl-1H-pyrrol-1-yl)propyl)-N,N-diethylbenzamide (table 4, entry 12):

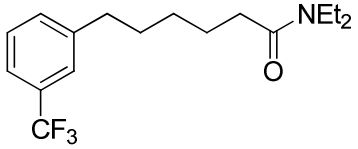
Synthesized by method A with O-TMEDA as an additive, 2.8 of 5eq of Alkyl-I was recovered after reaction with 99% purity.

Eluted from the column with hexane-diethyl ether (20:1 to 3:1) in 72% yield as a slightly yellow liquid:

^{1}H NMR (400MHz, $CDCl_3$): 7.29 (d, *J* = 7.3 Hz, 2H), 7.19 (d, *J* = 7.3 Hz, 2H), 6.97 (dd, J_1 = 4.1 Hz, J_2 = 1.8 Hz, 1H), 6.82 (m, 1H), 6.13 (dd, J_1 = 4.1 Hz, J_2 = 2.6 Hz, 1H), 4.33 (t, *J* = 7.3 Hz, 2H), 3.20-3.60 (br, 4H), 2.63 (m, 2H), 2.44 (s, 3H), 2.07 (m, 2H), 1.05-1.25 (br, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): 188.2, 171.3, 142.4, 134.9, 130.1, 130.0, 128.2, 126.4, 120.3, 107.9, 49.2, 43.2, 39.1, 32.5, 27.3, 14.1, 12.8.

HRESI-MS: calculated for ($C_{20}H_{26}O_2N_2$, M+H), 327.2072; found, 327.2073.



N,N-diethyl-6-(3-(trifluoromethyl)phenyl)hexanamide (table 4, entry 13):

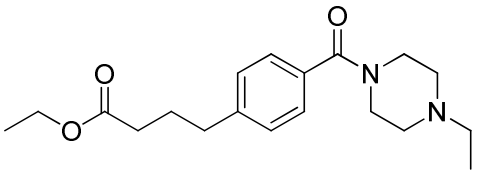
Synthesized by method B with TMEDA as an additive.

Eluted from the column with hexane-diethyl ether (1:1 to 1:2) in 69% yield as a yellow liquid:

^{1}H NMR (400MHz, $CDCl_3$): 7.38 (m, 4H), 3.36 (q, *J* = 7.0 Hz, 2H), 3.28 (q, *J* = 7.0 Hz, 2H), 2.67 (t, *J* = 7.6 Hz, 2H), 2.28 (t, *J* = 7.3 Hz, 2H), 1.67 (m, 4H), 1.38 (m, 2H), 1.15 (t, *J* = 7.0 Hz, 3H), 1.09 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 171.9, 143.4, 131.7, 128.6, 125.0 (q, *J* = 3.7 Hz), 122.4 (q, *J* = 3.8 Hz), 41.8, 40.0, 35.5, 32.8, 31.0, 28.9, 25.1, 14.3, 13.0.

HRESI-MS: calculated for ($C_{17}H_{24}F_3NO$, M+H), 316.1888; found, 316.1891.



ethyl 4-(4-(4-ethylpiperazine-1-carbonyl)phenyl)butanoate (table 4, entry 14):

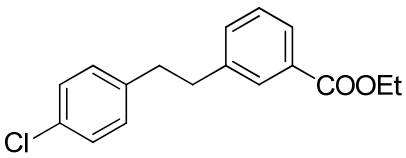
Synthesized by method A with O-TMEDA as an additive, 2.7 of 5eq of Alkyl-I was recovered after reaction with 99% purity.

Eluted from the column with hexane-ethanol (60:1 to 2:1) in 86% yield as a yellow oil:

^{1}H NMR (400MHz, $CDCl_3$): 7.30 (d, *J* = 6.5 Hz, 2H), 7.17 (d, *J* = 6.5 Hz, 2H), 4.09 (q, *J* = 7.0 Hz, 2H), 3.35-3.85 (br, 4H), 2.64 (t, *J* = 7.0 Hz, 2H), 2.30-2.55 (br, 6H), 2.28 (t, *J* = 7.6 Hz, 2H), 1.92 (m, 2H), 1.22 (t, *J* = 7.0 Hz, 3H), 1.06 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 173.1, 170.1, 143.1, 133.4, 128.4, 127.1, 60.1, 53.0, 52.4, 52.1, 47.6, 42.2, 34.8, 33.4, 26.2, 14.1, 11.8.

HRESI-MS: calculated for ($C_{19}H_{28}N_2O_3$, M+H), 333.2178; found, 333.2191.



ethyl 3-(4-chlorophenethyl)benzoate (table 4, entry 15):

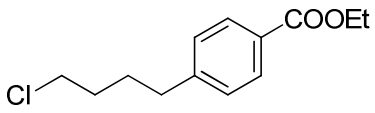
Synthesized by method A with O-TMEDA as an additive, 3.6 of 5eq of Alkyl-I was recovered after reaction with 99% purity.

Eluted from the column with hexane-diethyl ether (60:1 to 30:1) in 76% yield as a colorless liquid:

^{1}H NMR (400MHz, $CDCl_3$): 7.88 (m, 2H), 7.32 (m, 2H), 7.24 (d, *J* = 8.2 Hz, 2H), 7.08 (d, *J* = 8.5 Hz, 2H), 4.38 (q, *J* = 7.3 Hz, 2H), 2.92 (m, 4H), 1.40 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 166.6, 141.4, 139.6, 133.0, 131.7, 130.5, 129.7, 129.4, 128.4, 128.3, 127.2, 60.9, 37.4, 36.9, 14.3.

HRESI-MS: calculated for ($C_{17}H_{17}ClO_2$, M+H), 289.0995; found, 289.0987.



ethyl 4-(4-chlorobutyl)benzoate (table 4, entry 16):

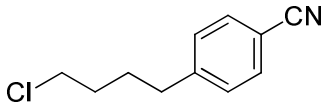
Synthesized by method A with O-TMEDA as an additive, 3.0 of 5eq of Alkyl-I was recovered after reaction with 99% purity.

Eluted from the column with hexane-diethyl ether (60:1 to 30:1) in 86% yield as a colorless liquid:

^{1}H NMR (400MHz, $CDCl_3$): 7.96 (d, *J* = 8.2 Hz, 2H), 7.24 (d, *J* = 8.4 Hz, 2H), 4.36 (q, *J* = 7.0 Hz, 2H), 3.54 (m, 2H), 2.70 (t, *J* = 7.2 Hz, 2H), 1.79 (m, 4H), 1.39 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 166.5, 147.1, 129.6, 128.3, 125.2, 60.7, 44.7, 35.0, 31.9, 28.1, 14.3.

HRESI-MS: calculated for ($C_{13}H_{17}ClO_2$, M+H), 241.0995; found, 241.0985.



4-(4-chlorobutyl)benzonitrile (table 4, entry 17):

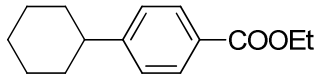
Synthesized by method B with TMEDA as an additive.

Eluted from the column with hexane-diethyl ether (20:1 to 10:1) in 72% yield as a colorless liquid:

^{1}H NMR (400MHz, $CDCl_3$): 7.57 (d, *J* = 8.2 Hz, 2H), 7.28 (d, *J* = 8.2 Hz, 2H), 3.55 (m, 2H), 2.70 (t, *J* = 7.2 Hz, 2H), 1.80 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$): 147.4, 132.1, 129.1, 118.9, 109.7, 44.5, 35.1, 31.8, 27.9.

HRESI-MS: calculated for ($C_{11}H_{12}ClN$, M+H), 194.0737; found, 194.0745.



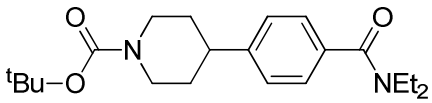
ethyl 4-cyclohexylbenzoate (table 4, entry 18): [32]

Synthesized by method A with O-TMEDA as an additive.

Eluted from the column with hexane-diethyl ether (30:1) in 61% yield as a colorless liquid:

^{1}H NMR (400MHz, $CDCl_3$): 7.96 (d, *J* = 8.2 Hz, 2H), 7.27 (m, 2H), 4.36 (q, *J* = 7.0 Hz, 2H), 2.55 (m, 1H), 1.82 (m, 4H), 1.35-1.45 (m, 6H), 1.38 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 166.6, 153.2, 129.6, 126.7, 126.3, 60.6, 44.6, 34.1, 26.7, 26.0, 14.3.



tert-butyl 4-(4-(diethylcarbamoyl)phenyl)piperidine-1-carboxylate (table 4, entry 19):

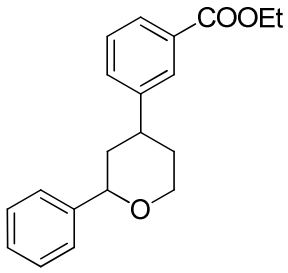
Synthesized by method A with O-TMEDA as an additive, 2.6 of 5eq of Alkyl-I was recovered after reaction with 99% purity.

Eluted from the column with hexane-diethyl ether (10:1 to 1:2) in 60% yield as a colorless liquid:

^{1}H NMR (400MHz, $CDCl_3$): 7.29 (m, 2H), 7.19 (m, 2H), 4.22 (br, 2H), 3.15-3.60 (br, 4H), 2.70 (m, 3H), 1.80 (m, 2H), 1.61 (m, 2H), 1.46 (s, 9H), 1.05-1.25 (br, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): 171.2, 154.7, 146.8, 135.3, 126.7, 126.5, 79.4, 44.2, 43.2, 42.5, 39.1, 33.0, 28.4, 14.1, 12.8.

HRESI-MS: calculated for ($C_{21}H_{32}N_2O_3$, M+H), 361.2491; found, 361.2481.



ethyl 3-(2-phenyltetrahydro-2H-pyran-4-yl)benzoate (table 4, entry 20):

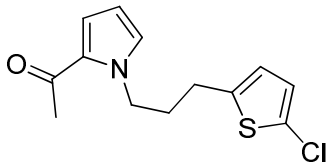
Synthesized by method A with O-TMEDA as an additive, 3.6 of 5eq of Alkyl-I was recovered after reaction with 99% purity.

Eluted from the column with hexane-diethyl ether (20:1 to 10:1) in 58% yield as a colorless oil:

^{1}H NMR (400MHz, $CDCl_3$): 7.95 (s, 1H), 7.91 (d, J = 7.6 Hz, 1H), 7.40 (m, 6H), 7.28 (m, 1H), 4.51 (dd, J_1 = 11.2 Hz, J_2 = 1.8 Hz, 1H), 4.39 (q, J = 7.0 Hz, 2H), 4.31 (m, 1H), 3.79 (td, J_1 = 11.4 Hz, J_2 = 2.9 Hz, 1H), 3.05 (m, 1H), 2.10 (m, 1H), 1.85 (m, 3H), 1.40 (t, J = 7.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 166.6, 145.6, 142.5, 131.2, 130.7, 128.5, 128.3, 127.8, 127.6, 127.4, 125.7, 79.8, 68.5, 60.9, 41.9, 41.2, 33.1, 14.3.

HRESI-MS: calculated for ($C_{20}H_{22}O_3$, M+H), 311.1647; found, 311.1658.



1-(1-(3-(5-chlorothiophen-2-yl)propyl)-1H-pyrrol-2-yl)ethanone (table 5, entry 5):

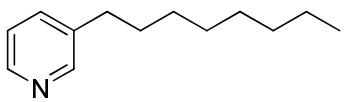
Synthesized by method B with O-TMEDA as an additive.

Eluted from the column with hexane-diethyl ether (30:1 to 20:1) in 62% yield as a slightly yellow liquid:

^{1}H NMR (400MHz, $CDCl_3$): 6.97 (dd, J_1 = 4.1 Hz, J_2 = 1.8 Hz, 1H), 6.82 (m, 1H), 6.71 (d, J = 3.8 Hz, 1H), 6.57 (m, 1H), 6.14 (dd, J_1 = 3.8 Hz, J_2 = 2.3 Hz, 1H), 4.35 (t, J = 7.0 Hz, 2H), 2.71 (t, J = 7.3 Hz, 2H), 2.44 (s, 3H), 2.08 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): 188.2, 142.9, 130.2, 130.0, 126.9, 125.7, 123.7, 120.4, 108.0, 48.7, 32.5, 27.3, 27.2.

HRESI-MS: calculated for ($C_{13}H_{14}OClNS$, M+H), 268.0563; found, 268.0574.



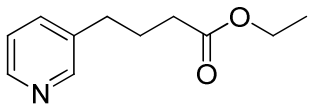
3-octylpyridine (table 5, entry 6): [33]

Synthesized by method B with TMEDA as an additive.

Eluted from the column with hexane-diethyl ether (20:1 to 1:1) in 76% yield as a colorless liquid:

^{1}H NMR (400MHz, $CDCl_3$): 8.42 (m, 2H), 7.48 (m, 1H), 7.19 (dd, J_1 = 7.6 Hz, J_2 = 4.8 Hz, 1H), 2.59 (m, 2H), 1.61 (m, 2H), 1.24-1.36 (m, 10H), 0.87 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 149.8, 147.0, 137.9, 135.7, 123.2, 33.0, 31.8, 31.1, 29.3, 29.2, 29.1, 22.6, 14.0.



ethyl 4-(pyridin-3-yl)butanoate (table 5, entry 7):

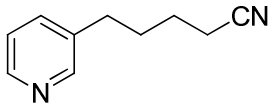
Synthesized by method B with O-TMEDA as an additive.

Eluted from the column with hexane-diethyl ether (1:1 to 1:4) in 69% yield as a colorless liquid:

^{1}H NMR (400MHz, $CDCl_3$): 8.44 (m, 2H), 7.50 (m, 1H), 7.20 (dd, J_1 = 7.4 Hz, J_2 = 5.0 Hz, 1H), 4.12 (q, J = 7.0 Hz, 2H), 2.65 (m, 2H), 2.32 (t, J = 7.4 Hz, 2H), 1.95 (m, 2H), 1.24 (t, J = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 173.0, 149.8, 147.5, 136.6, 135.8, 123.3, 60.3, 33.4, 32.1, 26.1, 14.1.

HRESI-MS: calculated for ($C_{11}H_{15}O_2N$, M+H), 194.1181; found, 194.1183.



5-(pyridin-3-yl)pentanenitrile (table 5, entry 8):

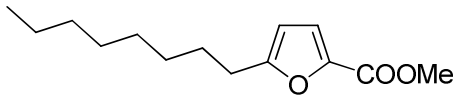
Synthesized by method B with TMEDA as an additive.

Eluted from the column with hexane-ethyl acetate (1:1 to 1:99) in 78% yield as a slightly yellow liquid:

^{1}H NMR (400MHz, $CDCl_3$): 8.45 (m, 2H), 7.49 (d, J = 7.6 Hz, 1H), 7.22 (dd, J_1 = 7.2 Hz, J_2 = 5.0 Hz, 1H), 2.66 (t, J = 7.6 Hz, 2H), 2.36 (t, J = 7.0 Hz, 2H), 1.79 (m, 2H), 1.69 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): 149.7, 147.6, 136.3, 135.6, 123.3, 119.3, 32.0, 29.9, 24.7, 17.0.

HRESI-MS: calculated for ($C_{10}H_{12}N_2$, M+H), 161.1079; found, 161.1074.



methyl 5-octylfuran-2-carboxylate (table 5, entry 9):

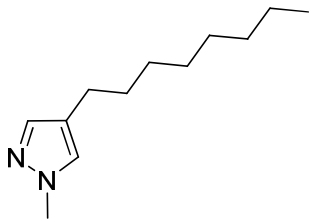
Synthesized by method A with O-TMEDA as an additive.

Eluted from the column with hexane-diethyl ether (60:1 to 30:1) in 65% yield as a slightly yellow liquid:

^{1}H NMR (400MHz, $CDCl_3$): 7.09 (d, *J* = 3.2 Hz, 1H), 6.11 (d, *J* = 3.2 Hz, 1H), 3.87 (s, 3H), 2.67 (t, *J* = 7.3 Hz, 2H), 1.66 (m, 2H), 1.20-1.35 (m, 10H), 0.87 (t, *J* = 6.7 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 161.6, 159.2, 142.7, 119.2, 107.4, 51.6, 31.7, 29.2, 29.14, 29.12, 28.3, 27.7, 22.6, 14.0.

HRESI-MS: calculated for ($C_{14}H_{22}O_3$, M+H), 239.1647; found, 239.1653.



1-methyl-4-octyl-1H-pyrazole (table 5, entry 10):

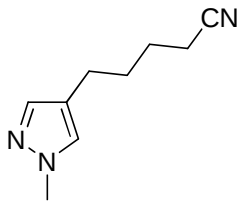
Synthesized by method A with O-TMEDA as an additive.

Eluted from the column with hexane-diethyl ether (1:1) in 91% yield as a slightly yellow liquid:

^{1}H NMR (400MHz, $CDCl_3$): 7.28 (s, 1H), 7.10 (s, 1H), 3.83 (s, 3H), 2.41 (t, *J* = 7.6 Hz, 2H), 1.51 (m, 2H), 1.20-1.35 (m, 10H), 0.86 (t, *J* = 6.5 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 138.5, 127.9, 122.0, 38.6, 31.8, 30.9, 29.3, 29.2, 24.0, 22.5, 14.0.

HRESI-MS: calculated for ($C_{12}H_{22}N_2$, M+H), 195.1861; found, 195.1859.



5-(1-methyl-1H-pyrazol-4-yl)pentanenitrile (table 5, entry 11):

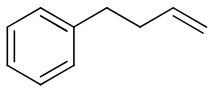
Synthesized by method A with O-TMEDA as an additive, 3.4 of 5eq of Alkyl-I was recovered after reaction with 99% purity.

Eluted from the column with hexane-diethyl ether (20:1 to 1:15) in 74% yield as a colorless liquid:

^{1}H NMR (400MHz, $CDCl_3$): 7.27 (s, 1H), 7.14 (s, 1H), 3.83 (s, 3H), 2.48 (t, *J* = 7.0 Hz, 2H), 2.33 (t, *J* = 6.5 Hz, 2H), 1.68 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$): 138.4, 128.1, 120.5, 119.5, 38.6, 29.8, 24.6, 23.1, 16.8.

HRESI-MS: calculated for ($C_9H_{13}N_3$, M+H), 164.1188; found, 164.1194.

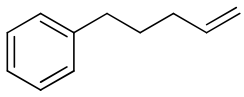


4-phenyl-1-butene **(radical probe experiments, entry 1):** [34]

Eluted from the column with hexane-diethyl ether (100:1) in 78% yield as a colorless liquid:

^{1}H NMR (400MHz, $CDCl_3$): 7.31 (m, 2H), 7.20 (m, 3H), 5.88 (m, 1H), 5.04 (m, 2H), 2.73 (t, *J* = 7.3 Hz, 2H), 2.40 (q, *J* = 7.6 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): 141.8, 138.0, 128.4, 128.2, 125.7, 114.8, 35.5, 35.3.



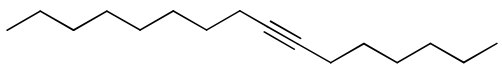
5-phenyl-1-pentene (radical probe experiments, entry 2): [35]

Eluted from the column with hexane-diethyl ether (100:1) in 87% yield as a colorless liquid:

^{1}H NMR (400MHz, $CDCl_3$): 7.30 (m, 2H), 7.20 (m, 3H), 5.87 (m, 1H), 5.04 (m, 2H), 2.65 (m, 2H), 2.12 (q, *J* = 7.0 Hz, 2H), 1.75 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): 142.4, 138.5, 128.4, 128.2, 125.6, 114.6, 35.3, 33.2, 30.6.

9.3. Characterization data for the products of the catalytic reactions represented in Chapter 6

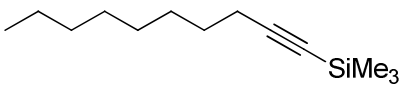


hexadec-7-yne (table 3, entry 1 and table 5, entry 1):[36]

Eluated from the column with hexane-diethyl ether (60:1) in 83% yield as a colorless liquid:

^{1}H NMR (400MHz, $CDCl_3$): 2.13 (t, *J* = 6.2 Hz, 4H), 1.47 (m, 4H), 1.22-1.40 (m, 16H), 0.89 (t, *J* = 6.2 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): 80.2, 31.8, 31.3, 29.2, 29.19, 29.16, 28.8, 28.5, 22.6, 22.5, 18.7, 14.08, 14.03.

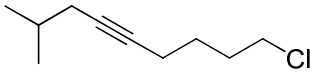


dec-1-ynyltrimethylsilane (table 3, entry 2) :[37]

Eluated from the column with hexane-diethyl ether (100:1) in 74% yield as a colorless liquid:

^{1}H NMR (400MHz, $CDCl_3$): 2.21 (t, *J* = 7.0 Hz, 2H), 1.51 (m, 2H), 1.23-1.40 (m, 10H), 0.88 (t, *J* = 6.5 Hz, 3H), 0.14 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): 107.7, 84.2, 31.8, 29.1, 29.0, 28.7, 28.6, 22.6, 19.8, 14.1, 0.1.



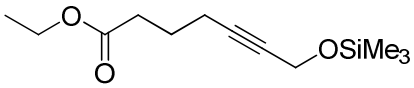
9-chloro-2-methylnon-4-yne (table 3, entry 3):

Eluated from the column with hexane-diethyl ether (60:1) in 84% yield as a colorless liquid:

^{1}H NMR (400MHz, $CDCl_3$): 3.56 (t, *J* = 6.7 Hz, 2H), 2.21 (m, 2H), 2.03 (m, 2H), 1.89 (m, 2H), 1.75 (m, 1H), 1.63 (m, 2H), 0.95 (d, *J* = 6.7 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): 80.0, 79.8, 44.6, 31.5, 28.2, 27.9, 26.2, 21.9, 18.0.

Elemental analysis: Anal. Calcd for $C_{10}H_{17}Cl$: C, 69.55; H, 9.92. Found: C, 69.41; H, 9.96.



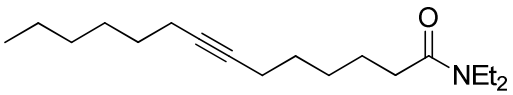
ethyl 7-(trimethylsilyloxy)hept-5-ynoate (table 3, entry 4):

Eluated from the column with hexane-diethyl ether (15:1) in 73% yield as a colorless liquid:

^{1}H NMR (400MHz, $CDCl_3$): 4.25 (t, *J* = 2.3 Hz, 2H), 4.12 (q, *J* = 7.3 Hz, 2H), 2.41 (t, *J* = 7.3 Hz, 2H), 2.27 (tt, J_1 = 7.0 Hz, J_2 = 2.1 Hz, 2H), 1.81 (quint, *J* = 7.3 Hz, 2H), 1.24 (t, *J* = 7.3 Hz, 3H), 0.15 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): 173.0, 84.2, 79.1, 60.3, 51.1, 33.0, 23.7, 18.2, 14.1, -0.3.

HRESI-MS: calculated for ($C_{12}H_{23}SiO_3$, M+H), 243.1416; found, 243.1419.



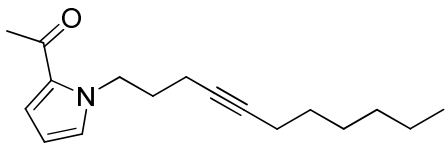
N,N-diethyltetradec-7-ynamide (table 3, entry 5):

Eluated from the column with hexane-diethyl ether (1:1) in 68% yield as a yellow liquid:

^{1}H NMR (400MHz, $CDCl_3$): 3.35 (q, *J* = 7.0 Hz, 2H), 3.28 (q, *J* = 7.0 Hz, 2H), 2.28 (m, 2H), 2.13 (m, 4H), 1.64 (m, 2H), 1.22-1.54 (m, 12H), 1.15 (t, *J* = 7.0 Hz, 3H), 1.09 (t, *J* = 7.3 Hz, 3H), 0.87 (t, *J* = 6.7 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 172.0, 80.3, 79.9, 41.8, 39.9, 33.0, 31.3, 29.0, 28.9, 28.7, 28.5, 25.0, 22.5, 18.7, 18.6, 14.3, 14.0, 13.0.

HRESI-MS: calculated for ($C_{18}H_{34}NO$, M+H), 280.2640; found, 280.2648.



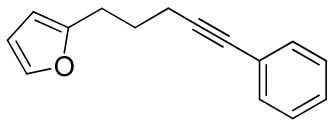
1-(1-(undec-4-ynyl)-1H-pyrrol-2-yl)ethanone (table 3, entry 6):

Eluated from the column with hexane-diethyl ether (20:1) in 61% yield as a colorless liquid:

^{1}H NMR (400MHz, $CDCl_3$): 6.97 (dd, J_1 = 4.1 Hz, J_2 = 1.5 Hz, 1H), 6.92 (m, 1H), 6.13 (m, 1H), 4.42 (t, *J* = 6.7 Hz, 2H), 2.43 (s, 3H), 2.17 (t, *J* = 7.3 Hz, 2H), 2.10 (t, *J* = 6.7 Hz, 2H), 1.90 (m, 2H), 1.50 (m, 2H), 1.24-1.42 (m, 6H), 0.90 (t, *J* = 6.7 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 188.0, 130.7, 129.9, 120.3, 107.7, 81.4, 78.7, 48.3, 31.3, 30.1, 29.0, 28.5, 27.2, 22.5, 18.7, 15.7, 14.0.

HRESI-MS: calculated for ($C_{17}H_{26}NO$, M+H), 260.2014; found, 260.1991.



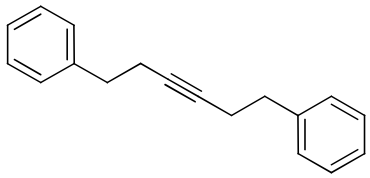
2-(5-phenylpent-4-ynyl)furan (table 3, entry 7):

Eluated from the column with hexane-diethyl ether (60:1) in 84% yield as a colorless liquid:

^{1}H NMR (400MHz, $CDCl_3$): 7.41 (m, 2H), 7.29 (m, 4H), 6.30 (m, 1H), 6.05 (m, 1H), 2.82 (t, *J* = 7.6 Hz, 2H), 2.47 (t, *J* = 7.0 Hz, 2H), 1.96 (quint, *J* = 7.0 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): 155.3, 140.9, 131.5, 128.1, 127.5, 123.8, 110.0, 105.2, 89.4, 81.1, 27.1, 27.0, 18.8.

HRESI-MS: calculated for ($C_{15}H_{15}O$, M+H), 211.1123; found, 211.1124.

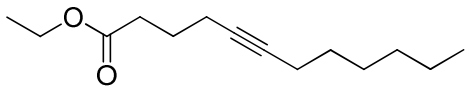


1,6-diphenylhex-3-yne (table 3, entry 8) :[38]

Eluated from the column with hexane-diethyl ether (60:1) in 89% yield as a colorless liquid:

^{1}H NMR (400MHz, $CDCl_3$): 7.32 (m, 4H), 7.23 (m, 6H), 2.81 (t, J = 7.3 Hz, 4H), 2.46 (t, J = 7.6 Hz,4H).

^{13}C NMR (100 MHz, $CDCl_3$): 140.9, 128.4, 128.2, 126.1, 80.2, 35.4, 20.9.



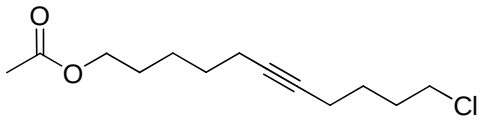
ethyl dodec-5-ynoate (table 3, entry 9):

Eluated from the column with hexane-diethyl ether (30:1) in 73% yield as a colorless liquid:

^{1}H NMR (400MHz, $CDCl_3$): 4.09 (q, J = 7.0 Hz, 2H), 2.38 (t, J = 7.6 Hz, 2H), 2.18 (tt, J_1 = 6.9 Hz, J_2 = 2.4 Hz, 2H), 2.09 (tt, J_1 = 6.9 Hz, J_2 = 2.2 Hz, 2H), 1.76 (quint, J = 7.0 Hz, 2H), 1.43 (m, 2H), 1.27 (m, 9H), 0.85 (t, J = 6.7 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 173.2, 81.1, 78.6, 60.1, 33.0, 31.2, 28.9, 28.4, 24.2, 22.4, 18.6, 18.1, 14.1, 13.9.

HRESI-MS: calculated for ($C_{14}H_{25}O_2$, M+H), 225.1855; found, 225.1846.



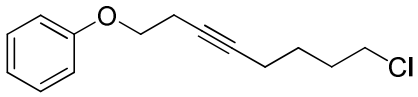
11-chloroundec-6-ynyl acetate (table 3, entry 10):

Eluated from the column with hexane-diethyl ether (15:1) in 70% yield as a colorless liquid:

^{1}H NMR (400MHz, $CDCl_3$): 4.05 (t, J = 7.0 Hz, 2H), 3.55 (t, J = 6.7 Hz, 2H), 2.16 (m, 4H), 2.03 (s, 3H), 1.87 (m, 2H), 1.62 (m, 4H), 1.47 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$): 171.1, 80.4, 79.4, 64.3, 44.5, 31.5, 28.5, 28.0, 26.1, 25.0, 20.9, 18.5, 17.9.

HRESI-MS: calculated for ($C_{13}H_{22}ClO_2$, M+H), 245.1308; found, 245.1309.



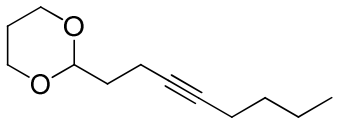
(8-chlorooct-3-ynyloxy)benzene (table 3, entry 11):

Eluated from the column with hexane-diethyl ether (60:1) in 79% yield as a colorless liquid:

^{1}H NMR (400MHz, $CDCl_3$): 7.29 (t, J = 8.2 Hz, 2H), 6.94 (m, 3H), 4.06 (t, J = 7.3 Hz, 2H), 3.56 (t, J = 6.7 Hz, 2H), 2.65 (t, J = 7.0 Hz, 2H), 2.22 (t, J = 7.0 Hz, 2H), 1.89 (m, 2H), 1.65 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): 158.4, 129.4, 120.8, 114.6, 81.0, 76.6, 66.4, 44.5, 31.5, 25.9, 19.8, 18.0.

HRESI-MS: calculated for ($C_{14}H_{18}ClO$, M+H), 237.1046; found, 237.1054.



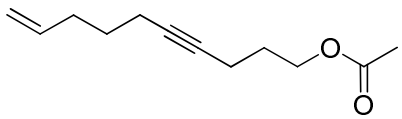
2-(oct-3-ynyl)-1,3-dioxane (table 3, entry 12):

Eluated from the column with hexane-diethyl ether (20:1) in 76% yield as a colorless liquid:

^{1}H NMR (400MHz, $CDCl_3$): 4.94 (t, J = 4.6 Hz, 1H), 4.47 (dd, J_1 = 9.5 Hz, J_2 = 4.4 Hz, 2H), 4.17 (td, J_1 = 10.8 Hz, J_2 = 2.1 Hz, 2H), 2.83 (m, 2H), 2.71 (m, 3H), 2.42 (m, 2H), 2.11 (m, 5H), 1.66 (t, J = 6.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 100.9, 80.3, 79.0, 66.8, 34.4, 31.1, 25.8, 21.8, 18.3, 13.6, 13.5.

HRESI-MS: calculated for ($C_{12}H_{21}O_2$, M+H), 197.1542; found, 197.1547.



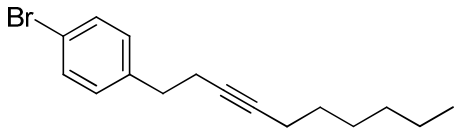
dec-9-en-4-ynyl acetate (table 3, entry 13):

Eluated from the column with hexane-diethyl ether (20:1) in 59% yield as a colorless liquid:

^{1}H NMR (400MHz, $CDCl_3$): 5.78 (m, 1H), 5.00 (m, 2H), 4.15 (t, J = 6.5 Hz, 2H), 2.24 (t, J = 7.0 Hz, 2H), 2.14 (m, 4H), 2.04 (s, 3H), 1.80 (m, 2H), 1.56 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): 171.0, 137.9, 114.9, 80.6, 78.7, 63.2, 32.7, 28.1, 28.0, 20.9, 18.0, 15.4.

HRESI-MS: calculated for ($C_{12}H_{19}O_2$, M+H), 195.1385; found, 195.1392.



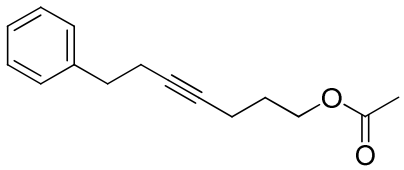
1-bromo-4-(dec-3-ynyl)benzene (table 3, entry 14):

Eluated from the column with hexane-diethyl ether (60:1) in 69% yield as a colorless liquid:

^{1}H NMR (400MHz, $CDCl_3$): 7.40 (d, *J* = 7.9 Hz, 2H), 7.10 (d, *J* = 8.2 Hz, 2H), 2.74 (t, *J* = 7.3 Hz, 2H), 2.42 (t, *J* = 7.0 Hz, 2H), 2.12 (t, *J* = 6.7 Hz, 2H), 1.45 (m, 2H), 1.22-1.38 (m, 6H), 0.90 (t, *J* = 6.5 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 139.8, 131.2, 130.2, 119.9, 81.4, 78.8, 34.8, 31.3, 28.9, 28.5, 22.5, 20.7, 18.6, 14.0.

Elemental analysis: Anal. Calcd for $C_{16}H_{21}Br$: C, 65.53; H, 7.22. Found: C, 65.44; H, 7.33.



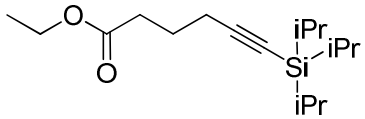
7-phenylhept-4-ynyl acetate (table 5, entry 2):

Eluated from the column with hexane-diethyl ether (9:1) in 66% yield as a colorless liquid:

^{1}H NMR (400MHz, $CDCl_3$): 7.26 (m, 5H), 4.12 (t, *J* = 6.5 Hz, 2H), 2.80 (t, *J* = 7.6 Hz, 2H), 2.44 (t, *J* = 7.6 Hz, 2H), 2.24 (t, *J* = 7.0 Hz, 2H), 2.05 (s, 3H), 1.78 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): 171.0, 140.8, 128.3, 128.2, 126.1, 80.2, 79.3, 63.1, 35.4, 27.9, 20.95, 20.91, 15.4.

HRESI-MS: calculated for ($C_{15}H_{19}O_2$, M+H), 231.1385; found, 231.1386.



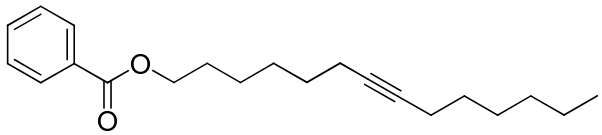
ethyl 6-(triisopropylsilyl)hex-5-ynoate (table 5, entry 3):

Eluated from the column with hexane-diethyl ether (30:1) in 62% yield as a colorless liquid:

^{1}H NMR (400MHz, $CDCl_3$): 4.12 (q, *J* = 7.0 Hz, 2H), 2.45 (t, *J* = 7.6 Hz, 2H), 2.32 (t, *J* = 6.5 Hz, 2H), 1.83 (m, 2H), 1.24 (t, *J* = 7.3 Hz, 3H), 1.05 (m, 21H).

^{13}C NMR (100 MHz, $CDCl_3$): 173.1, 107.6, 81.1, 60.2, 32.8, 24.0, 19.2, 18.5, 14.1, 11.2.

HRESI-MS: calculated for ($C_{17}H_{33}O_2Si$, M+H), 297.2250; found, 297.2255.



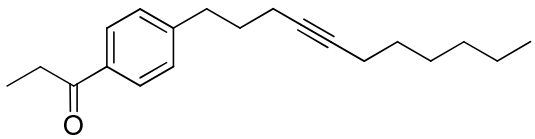
tetradec-7-ynyl benzoate (table 5, entry 4):

Eluated from the column with hexane-diethyl ether (30:1) in 70% yield as a slightly yellow liquid:

^{1}H NMR (400MHz, $CDCl_3$): 8.04 (d, *J* = 7.0 Hz, 2H), 7.55 (t, *J* = 7.3 Hz, 1H), 7.44 (t, *J* = 7.6 Hz, 2H), 4.32 (t, *J* = 6.7 Hz, 2H), 2.14 (m, 4H), 1.78 (m, 2H), 1.40 (m, 14H), 0.88 (t, *J* = 6.5 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 166.6, 132.7, 130.4, 129.4, 128.2, 80.4, 79.8, 65.0, 31.3, 29.1, 28.9, 28.6, 28.5, 28.4, 25.6, 22.5, 18.7, 18.6, 14.0.

HRESI-MS: calculated for ($C_{21}H_{31}O_2$, M+H), 315.2324; found, 315.2309.



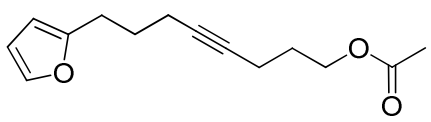
1-(4-(undec-4-ynyl)phenyl)propan-1-one (table 5, entry 5):

Eluated from the column with hexane-diethyl ether (30:1) in 57% yield as a slightly yellow liquid:

^{1}H NMR (400MHz, $CDCl_3$): 7.89 (d, *J* = 8.2 Hz, 2H), 7.27 (d, *J* = 8.2 Hz, 2H), 2.98 (q, *J* = 7.3 Hz, 2H), 2.77 (t, *J* = 7.6 Hz, 2H), 2.16 (t, *J* = 5.6 Hz, 4H), 1.80 (m, 2H), 1.49 (m, 2H), 1.36 (m, 6H), 1.22 (t, *J* = 7.3 Hz, 3H), 0.89 (t, *J* = 6.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 200.4, 147.4, 134.8, 128.6, 128.1, 81.1, 79.2, 34.7, 31.6, 31.3, 30.3, 29.0, 28.5, 22.5, 18.7, 18.1, 14.0, 8.3.

HRESI-MS: calculated for ($C_{20}H_{29}O$, M+H), 285.2218; found, 285.2223.



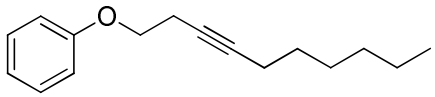
8-(furan-2-yl)oct-4-ynyl acetate (table 5, entry 6):

Eluated from the column with hexane-diethyl ether (20:1) in 64% yield as a colorless liquid:

^{1}H NMR (400MHz, $CDCl_3$): 7.29 (m, 1H), 6.27 (m, 1H), 6.00 (m, 1H), 4.15 (t, *J* = 6.2 Hz, 2H), 2.71 (t, *J* = 7.6 Hz, 2H), 2.25 (m, 2H), 2.18 (m, 2H), 2.05 (s, 3H), 1.80 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$): 171.0, 155.4, 140.8, 110.0, 105.0, 80.1, 79.1, 63.2, 28.0, 27.3, 26.9, 20.9, 18.1, 15.4.

HRESI-MS: calculated for ($C_{14}H_{19}O_3$, M+H), 235.1334; found, 235.1328.



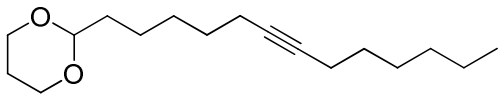
(dec-3-ynyloxy)benzene (table 5, entry 7):

Eluated from the column with hexane-diethyl ether (60:1) in 88% yield as a colorless liquid:

^{1}H NMR (400MHz, $CDCl_3$): 7.29 (m, 2H), 6.95 (m, 3H), 4.07 (t, J = 7.3 Hz, 2H), 2.66 (t, J = 7.3 Hz, 2H), 2.17 (t, J = 7.0 Hz, 2H), 1.50 (m, 2H), 1.25-1.42 (m, 6H), 0.91 (t, J = 6.7 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 158.5, 129.4, 120.8, 114.6, 82.0, 75.7, 66.5, 31.3, 28.8, 28.5, 22.5, 19.8, 18.7, 14.0.

HRESI-MS: calculated for ($C_{16}H_{23}O$, M+H), 231.1749; found, 231.1758.



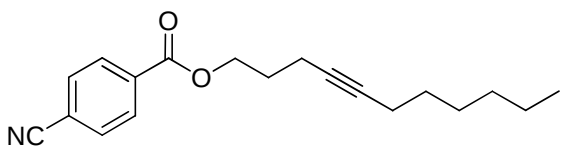
2-(tridec-6-ynyl)-1,3-dioxane (table 5, entry 8):

Eluated from the column with hexane-diethyl ether (20:1 to 9:1) in 73% yield as a colorless liquid:

^{1}H NMR (400MHz, $CDCl_3$): 4.50 (t, J = 5.3 Hz, 1H), 4.09 (dd, J_1 = 11.2 Hz, J_2 = 5.3 Hz, 2H), 3.75 (m, 2H), 2.08 (m, 4H), 1.43 (m, 18H), 0.88 (t, J = 6.7 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 102.3, 80.2, 80.0, 66.8, 35.1, 31.3, 29.1, 29.0, 28.6, 28.5, 25.8, 23.5, 22.5, 18.7, 18.6, 14.0.

HRESI-MS: calculated for ($C_{17}H_{31}O_2$, M+H), 267.2324; found, 267.2314.



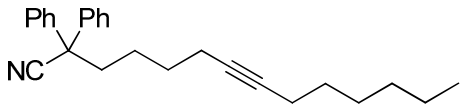
undec-4-ynyl 4-cyanobenzoate (table 5, entry 9):

Eluated from the column with hexane-diethyl ether (15:1) in 63% yield as a colorless liquid:

^{1}H NMR (400MHz, $CDCl_3$): 8.14 (d, *J* = 8.5 Hz, 2H), 7.74 (d, *J* = 8.5 Hz, 2H), 4.45 (t, *J* = 6.5 Hz, 2H), 2.34 (t, *J* = 6.7 Hz, 2H), 2.11 (t, *J* = 6.7 Hz, 2H), 1.95 (quint, *J* = 6.7 Hz, 2H), 1.45 (m, 2H), 1.30 (m, 6H), 0.87 (t, *J* = 6.5 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 164.8, 134.1, 132.1, 130.0, 117.9, 116.3, 81.4, 78.1, 64.6, 31.3, 28.9, 28.5, 28.0, 22.5, 18.6, 15.6, 14.0.

HRESI-MS: calculated for ($C_{19}H_{24}NO_2$, M+H), 298.1807; found, 298.1819.



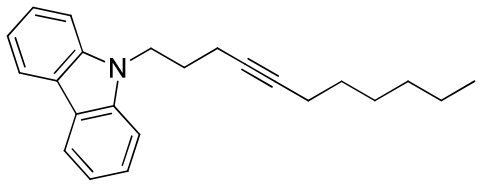
2,2-diphenyltetradec-7-ynenitrile (table 5, entry 10):

Eluated from the column with hexane-diethyl ether (30:1) in 66% yield as a colorless liquid:

^{1}H NMR (400MHz, $CDCl_3$): 7.37 (m, 8H), 7.29 (m, 2H), 2.39 (t, *J* = 7.6 Hz, 2H), 2.16 (m, 2H), 2.10 (t, *J* = 7.3 Hz, 2H), 1.57 (m, 4H), 1.43 (m, 2H), 1.22-1.38 (m, 6H), 0.89 (t, *J* = 6.5 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 140.2, 128.7, 127.7, 126.8, 122.3, 80.8, 79.2, 51.7, 39.1, 31.3, 29.0, 28.8, 28.5, 24.7, 22.5, 18.6, 18.4, 14.0.

HRESI-MS: calculated for ($C_{26}H_{32}N$, M+H), 358.2535; found, 358.2540.



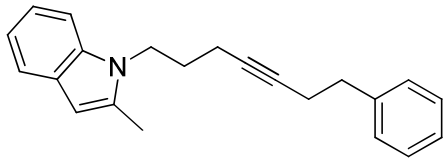
9-(undec-4-ynyl)-9H-carbazole (table 5, entry 11):

Eluated from the column with hexane-diethyl ether (30:1) in 85% yield as a slightly yellow liquid:

^{1}H NMR (400MHz, $CDCl_3$): 8.12 (d, *J* = 7.9 Hz, 2H), 7.50 (m, 4H), 7.26 (m, 2H), 4.46 (t, *J* = 7.0 Hz, 2H), 2.24 (m, 4H), 2.07 (m, 2H), 1.58 (m, 2H), 1.46 (m, 2H), 1.34 (m, 4H), 0.93 (t, *J* = 6.7 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 140.4, 125.5, 122.8, 120.2, 118.8, 108.6, 81.5, 78.9, 41.6, 31.4, 29.1, 28.6, 28.2, 22.5, 18.8, 16.5, 14.0.

HRESI-MS: calculated for ($C_{23}H_{28}N$, M+H), 318.2222; found, 318.2232.



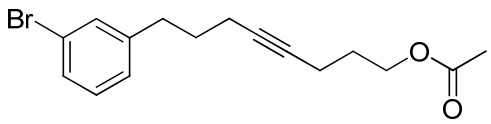
2-methyl-1-(7-phenylhept-4-ynyl)-1H-indole (table 5, entry 12):

Eluated from the column with hexane-diethyl ether (30:1) in 75% yield as a colorless liquid:

^{1}H NMR (400MHz, $CDCl_3$): 7.56 (d, *J* = 8.5 Hz, 1H), 7.31 (m, 6H), 7.17 (t, *J* = 7.0 Hz, 1H), 7.11 (m, 1H), 6.28 (s, 1H), 4.16 (t, *J* = 7.0 Hz, 2H), 2.89 (t, *J* = 7.6 Hz, 2H), 2.56 (t, *J* = 7.3 Hz, 2H), 2.44 (s, 3H), 2.21 (t, *J* = 6.5 Hz, 2H), 1.94 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): 140.7, 136.5, 136.4, 128.38, 128.33, 128.0, 126.2, 120.3, 119.5, 119.1, 108.9, 99.9, 80.6, 79.6, 41.7, 35.3, 29.1, 20.8, 16.2, 12.6.

HRESI-MS: calculated for ($C_{22}H_{24}N$, M+H), 302.1909; found, 302.1899.



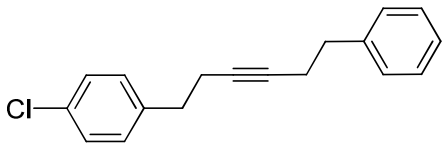
8-(3-bromophenyl)oct-4-ynyl acetate (table 5, entry 13):

Eluated from the column with hexane-diethyl ether (15:1) in 58% yield as a colorless liquid:

^{1}H NMR (400MHz, $CDCl_3$): 7.32 (m, 2H), 7.12 (m, 2H), 4.17 (t, *J* = 6.5 Hz, 2H), 2.67 (t, *J* = 7.3 Hz, 2H), 2.27 (t, *J* = 6.7 Hz, 2H), 2.15 (t, *J* = 7.0 Hz, 2H), 2.05 (s, 3H), 1.80 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$): 171.0, 144.0, 131.4, 129.8, 128.9, 127.1, 122.3, 80.2, 79.3, 63.2, 34.3, 30.2, 28.0, 20.9, 18.0, 15.4.

HRESI-MS: calculated for ($C_{16}H_{20}BrO_2$, M+H), 323.0647 and 325.0628; found, 323.0659 and 325.0643.



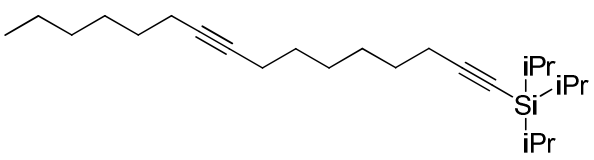
1-chloro-4-(6-phenylhex-3-ynyl)benzene (table 5, entry 14):

Eluated from the column with hexane-diethyl ether (60:1) in 72% yield as a colorless liquid:

^{1}H NMR (400MHz, $CDCl_3$): 7.30 (m, 2H), 7.23 (m, 5H), 7.11 (d, *J* = 8.2 Hz, 2H), 2.77 (m, 4H), 2.43 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$): 140.8, 139.2, 131.8, 129.8, 128.4, 128.3, 128.2, 126.1, 80.5, 79.7, 35.3, 34.6, 20.85, 20.82.

Elemental analysis: Anal. Calcd for $C_{18}H_{17}Cl$: C, 80.43; H, 6.38. Found: C, 80.46; H, 6.57.



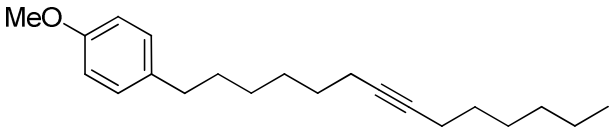
hexadeca-1,9-diynyltriisopropylsilane (2 steps experiments, entry 1):

Eluated from the column with hexane-diethyl ether (100:1) in 69% yield as a colorless liquid:

^{1}H NMR (400MHz, $CDCl_3$): 2.25 (t, *J* = 7.0 Hz, 2H), 2.14 (m, 4H), 1.41 (m, 16H), 1.06 (m, 21H), 0.89 (t, *J* = 6.7 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 109.1, 80.3, 80.05, 80.02, 31.3, 29.1, 29.0, 28.7, 28.5, 28.28, 28.21, 22.5, 19.7, 18.76, 18.70, 18.62, 14.0, 11.2.

HRESI-MS: calculated for ($C_{25}H_{47}Si$, M+H), 375.3447; found, 375.3449.



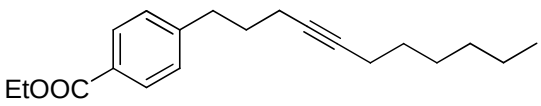
1-methoxy-4-(tetradec-7-ynyl)benzene (2 steps experiments, entry 2):

Eluated from the column with hexane-diethyl ether (30:1) in 86% yield as a colorless liquid:

^{1}H NMR (400MHz, $CDCl_3$): 7.09 (d, *J* = 8.5 Hz, 2H), 6.82 (d, *J* = 8.5 Hz, 2H), 3.79 (s, 3H), 2.55 (t, *J* = 7.6 Hz, 2H), 2.14 (t, *J* = 6.5 Hz, 4H), 1.59 (m, 2H), 1.24-1.52 (m, 14H), 0.89 (t, *J* = 6.5 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 157.5, 134.8, 129.1, 113.6, 80.2, 80.1, 55.2, 34.9, 31.6, 31.3, 29.1, 29.0, 28.7, 28.6, 28.5, 22.5, 18.75, 18.73, 14.0.

HRESI-MS: calculated for ($C_{21}H_{33}O$, M+H), 301.2531; found, 301.2523.



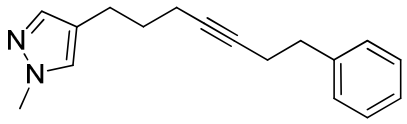
ethyl 4-(undec-4-ynyl)benzoate (2 steps experiments, entry 3):

Eluated from the column with hexane-diethyl ether (60:1) in 77% yield as a colorless liquid:

^{1}H NMR (400MHz, $CDCl_3$): 7.95 (d, *J* = 8.2 Hz, 2H), 7.25 (d, *J* = 7.9 Hz, 2H), 4.36 (q, *J* = 7.0 Hz, 2H), 2.77 (t, *J* = 7.6 Hz, 2H), 2.16 (t, *J* = 6.7 Hz, 4H), 1.80 (quint, *J* = 6.7 Hz, 2H), 1.49 (m, 2H), 1.38 (t, *J* = 7.3 Hz, 3H), 1.26-1.44 (m, 6H), 0.88 (t, *J* = 6.5 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 166.5, 147.2, 129.5, 128.4, 128.1, 81.1, 79.2, 60.7, 34.7, 31.3, 30.3, 29.0, 28.5, 22.5, 18.7, 18.1, 14.3, 14.0.

HRESI-MS: calculated for ($C_{20}H_{29}O_2$, M+H), 301.2168; found, 301.2159.



1-methyl-4-(7-phenylhept-4-ynyl)-1H-pyrazole (2 steps experiments, entry 4):

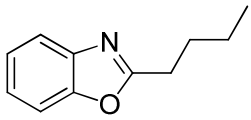
Eluated from the column with hexane-diethyl ether (1:1) in 73% yield as a colorless liquid:

^{1}H NMR (400MHz, $CDCl_3$): 7.26 (m, 6H), 7.10 (s, 1H), 3.85 (s, 3H), 2.82 (t, *J* = 7.3 Hz, 2H), 2.49 (m, 4H), 2.16 (t, *J* = 7.3 Hz, 2H), 1.69 (quint, *J* = 7.3 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): 140.8, 138.6, 128.4, 128.2, 126.0, 120.9, 80.3, 79.9, 38.7, 35.4, 30.0, 22.9, 20.8, 18.0.

HRESI-MS: calculated for ($C_{17}H_{21}N_2$, M+H), 253.1705; found, 253.1695.

9.4. Characterization data for the products of the catalytic reactions represented in Chapter 7



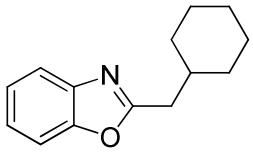
2-butylbenzo[d]oxazole (table 1):

Eluated from the column with hexane-diethyl ether (20:1) in 78% yield as a slightly yellow liquid:

^{1}H NMR (400MHz, $CDCl_3$): 7.67 (m, 1H), 7.47 (m, 1H), 7.29 (m, 2H), 2.93 (t, *J* = 7.6 Hz, 2H), 1.87 (m, 2H), 1.46 (m, 2H), 0.97 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 167.3, 150.7, 141.3, 124.3, 123.9, 119.4, 110.2, 28.8, 28.3, 22.2, 13.6.

HRESI: calculated for ($C_{11}H_{14}NO$, M+H), 176.1075; found, 176.1067.



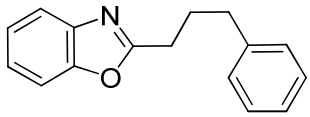
2-(cyclohexylmethyl)benzo[d]oxazole (table 3, entry 1):

Eluated from the column with hexane-diethyl ether (10:1) in 79% yield as a slightly yellow liquid:

^{1}H NMR (400MHz, $CDCl_3$): 7.67 (m, 1H), 7.47 (m, 1H), 7.29 (m, 2H), 2.81 (d, *J* = 7.0 Hz, 2H), 1.97 (m, 1H), 1.72 (m, 5H), 1.15 (m, 5H).

^{13}C NMR (100 MHz, $CDCl_3$): 166.4, 150.7, 141.3, 124.2, 123.9, 119.4, 110.1, 36.5, 36.2, 33.0, 26.0, 25.9.

HRESI: calculated for ($C_{14}H_{18}NO$, M+H), 216.1388; found, 216.1386.



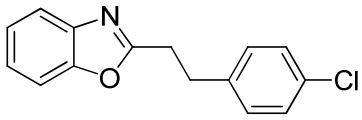
2-(3-phenylpropyl)benzo[d]oxazole (table 3, entry 2):

Eluated from the column with hexane-diethyl ether (10:1) in 70% yield as a slightly yellow liquid:

^{1}H NMR (400MHz, $CDCl_3$): 7.70 (m, 1H), 7.49 (m, 1H), 7.26 (m, 7H), 2.96 (t, *J* = 7.6 Hz, 2H), 2.78 (t, *J* = 7.3 Hz, 2H), 2.24 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): 166.9, 150.7, 141.1, 141.0, 128.4, 128.3, 126.0, 124.4, 124.0, 119.4, 110.2, 35.0, 28.1, 27.9.

HRESI: calculated for ($C_{16}H_{16}NO$, M+H), 238.1232; found, 238.1241.



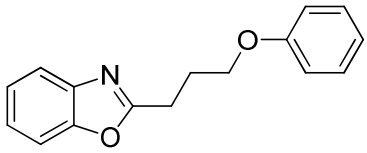
2-(4-chlorophenethyl)benzo[d]oxazole (table 3, entry 3):

Eluated from the column with hexane-diethyl ether (10:1) in 75% yield as a white solid:

^{1}H NMR (400MHz, $CDCl_3$): 7.68 (m 1H), 7.48 (m 1H), 7.31 (m 2H), 7.25 (m 2H), 7.17 (m 2H), 3.20 (s 4H).

^{13}C NMR (100 MHz, $CDCl_3$): 165.7, 150.6, 141.1, 138.4, 132.2, 129.5, 128.6, 124.5, 124.1, 119.5, 110.2, 32.0, 30.2.

HRESI: calculated for ($C_{15}H_{13}NOCl$, M+H), 258.0686; found, 258.0695.



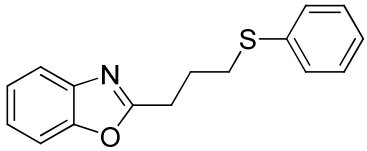
2-(3-phenoxypropyl)benzo[d]oxazole (table 3, entry 4):

Eluated from the column with hexane-diethyl ether (4:1) in 84% yield as a slightly yellow liquid:

^{1}H NMR (400MHz, $CDCl_3$): 7.70 (m, 1H), 7.50 (m, 1H), 7.28 (m, 4H), 6.92 (m, 3H), 4.12 (t, *J* = 5.9 Hz, 2H), 3.17 (t, *J* = 7.3 Hz, 2H), 2.40 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): 166.4, 158.6, 150.7, 141.2, 129.4, 124.5, 124.0, 120.7, 119.5, 114.4, 110.2, 66.3, 26.3, 25.3.

HRESI: calculated for ($C_{16}H_{16}NO_2$, M+H), 254.1181; found, 254.1169.



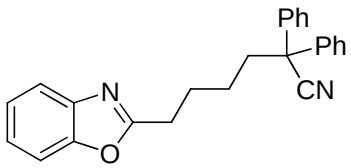
2-(3-(phenylthio)propyl)benzo[d]oxazole (table 3, entry 5):

Eluated from the column with hexane-diethyl ether (4:1) in 65% yield as a slightly yellow liquid:

^{1}H NMR (400MHz, $CDCl_3$): 7.68 (m, 1H), 7.48 (m, 1H), 7.31 (m, 6H), 7.18 (m, 1H), 3.08 (q, *J* = 7.3 Hz, 4H), 2.23 (quint, *J* = 7.0 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): 166.0, 150.6, 141.1, 135.7, 129.3, 128.8, 126.0, 124.5, 124.0, 119.4, 110.2, 32.8, 27.2, 25.9.

HRESI-MS: calculated for ($C_{16}H_{16}NOS$, M+H), 270.0953; found, 270.0953.



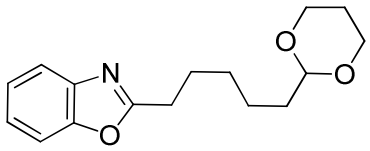
6-(benzo[d]oxazol-2-yl)-2,2-diphenylhexanenitrile (table 3, entry 6):

Eluated from the column with hexane-diethyl ether (2:1) in 56% yield as a yellow oil:

^{1}H NMR (400MHz, $CDCl_3$): 7.67 (m, 1H), 7.37 (m, 13H), 2.92 (t, *J* = 7.6 Hz, 2H), 2.46 (m, 2H), 1.98 (m, 2H), 1.60 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): 166.4, 150.6, 141.1, 139.9, 128.8, 127.8, 126.7, 124.4, 124.0, 122.2, 119.4, 110.2, 51.5, 39.1, 28.1, 26.4, 25.1.

HRESI-MS: calculated for ($C_{25}H_{23}N_2O$, M+H), 367.1810; found, 367.1794.



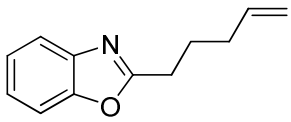
2-(5-(1,3-dioxan-2-yl)pentyl)benzo[d]oxazole (table 3, entry 7):

Eluated from the column with hexane-diethyl ether (2:1) in 86% yield as a yellow oil:

^{1}H NMR (400MHz, $CDCl_3$): 7.65 (m, 1H), 7.46 (m, 1H), 7.28 (m, 2H), 4.49 (t, J = 5.0 Hz, 1H), 4.07 (dd, J_1 = 11.7 Hz, J_2 = 5.0 Hz, 2H), 3.73 (m, 2H), 2.92 (t, J = 7.9 Hz, 2H), 2.06 (m, 1H), 1.88 (m, 2H), 1.59 (m, 2H), 1.40 (m, 5H).

^{13}C NMR (100 MHz, $CDCl_3$): 167.1, 150.7, 141.3, 124.3, 123.9, 119.4, 110.1, 102.1, 66.8, 34.9, 28.9, 28.4, 26.6, 25.7, 23.5.

HRESI-MS: calculated for ($C_{16}H_{22}NO_3$, M+H), 276.1600; found, 276.1601.



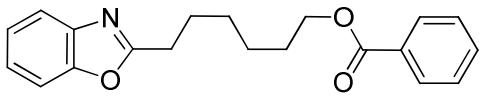
2-(pent-4-enyl)benzo[d]oxazole (table 3, entry 8):

Eluated from the column with hexane-diethyl ether (10:1) in 70% yield as a slightly yellow liquid:

^{1}H NMR (400MHz, $CDCl_3$): 7.67 (m, 1H), 7.47 (m, 1H), 7.28 (m, 2H), 5.82 (m, 1H), 5.04 (m, 2H), 2.93 (t, J = 7.6 Hz, 2H), 2.20 (q, J = 7.0 Hz, 2H), 1.99 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): 166.9, 150.7, 141.3, 137.3, 124.3, 123.9, 119.4, 115.5, 110.1, 32.9, 27.8, 25.7.

HRESI-MS: calculated for ($C_{12}H_{14}NO$, M+H), 188.1075; found, 188.1083.



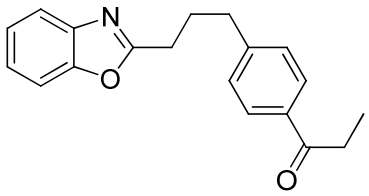
6-(benzo[d]oxazol-2-yl)hexyl benzoate (table 3, entry 9):

Eluated from the column with hexane-diethyl ether (3:1) in 71% yield as a yellow oil:

^{1}H NMR (400MHz, $CDCl_3$): 8.03 (d, *J* = 7.6 Hz, 2H), 7.67 (m, 1H), 7.54 (t, *J* = 6.7 Hz, 1H), 7.44 (m, 3H), 7.29 (m, 2H), 4.32 (t, *J* = 6.5 Hz, 2H), 2.94 (t, *J* = 7.3 Hz, 2H), 1.93 (m, 2H), 1.79 (m, 2H), 1.54 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$): 167.0, 166.5, 150.7, 141.3, 132.7, 130.3, 129.4, 128.2, 124.3, 124.0, 119.4, 110.2, 64.8, 28.7, 28.5, 28.4, 26.5, 25.6.

HRESI-MS: calculated for ($C_{20}H_{22}NO_3$, M+H), 324.1600; found, 324.1588.



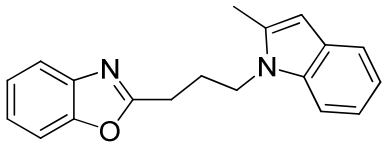
1-(4-(3-(benzo[d]oxazol-2-yl)propyl)phenyl)propan-1-one (table 3, entry 10):

Eluated from the column with hexane-diethyl ether (3:1) in 44% yield as a yellow oil:

^{1}H NMR (400MHz, $CDCl_3$): 7.89 (d, *J* = 8.2 Hz, 2H), 7.67 (m, 1H), 7.47 (m, 1H), 7.30 (m, 4H), 2.97 (m, 4H), 2.82 (t, *J* = 7.3 Hz, 2H), 2.25 (m, 2H), 1.22 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 200.4, 166.4, 150.7, 146.5, 141.2, 135.0, 128.6, 128.2, 124.5, 124.1, 119.5, 110.2, 35.0, 31.6, 27.8, 27.7, 8.2.

HRESI-MS: calculated for ($C_{19}H_{20}NO_2$, M+H), 294.1494; found, 294.1483.



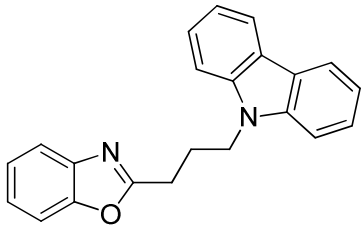
2-(3-(2-methyl-1H-indol-1-yl)propyl)benzo[d]oxazole (table 3, entry 11):

Eluated from the column with hexane-diethyl ether (2:1) in 74% yield as a yellow oil:

^{1}H NMR (400MHz, $CDCl_3$): 7.74 (m, 1H), 7.57 (d, *J* = 7.6 Hz, 1H), 7.51 (m, 1H), 7.34 (m, 3H), 7.17 (t, *J* = 7.0 Hz, 1H), 7.11 (m, 1H), 6.29 (s, 1H), 4.27 (t, *J* = 7.3 Hz, 2H), 2.97 (t, *J* = 7.0 Hz, 2H), 2.45 (s, 3H), 2.41 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): 165.8, 150.6, 141.1, 136.5, 136.1, 128.0, 124.6, 124.1, 120.5, 119.6, 119.5, 119.2, 110.2, 108.8, 100.2, 41.9, 26.6, 25.6, 12.6.

HRESI-MS: calculated for ($C_{19}H_{19}N_2O$, M+H), 291.1497; found, 291.1483.



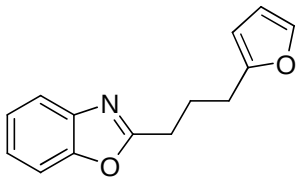
2-(3-(9H-carbazol-9-yl)propyl)benzo[d]oxazole (table 3, entry 12):

Eluated from the column with hexane-diethyl ether (10:1 to 3:1) in 75% yield as a yellow solid:

^{1}H NMR (400MHz, $CDCl_3$): 8.11 (d, *J* = 7.6 Hz, 2H), 7.73 (m, 1H), 7.44 (m, 5H), 7.29 (m, 4H), 4.54 (t, *J* = 7.0 Hz, 2H), 2.97 (t, *J* = 7.3 Hz, 2H), 2.53 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): 165.9, 150.6, 140.9, 140.2, 125.7, 124.7, 124.2, 122.9, 120.3, 119.5, 118.9, 110.2, 108.5, 41.8, 25.8, 25.6.

HRESI-MS: calculated for ($C_{22}H_{19}N_2O$, M+H), 327.1497; found, 327.1497.



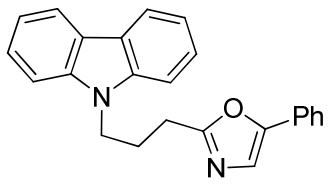
2-(3-(furan-2-yl)propyl)benzo[d]oxazole (table 3, entry 13):

Eluated from the column with hexane-diethyl ether (10:1) in 73% yield as a slightly yellow liquid:

^{1}H NMR (400MHz, $CDCl_3$): 7.68 (m, 1H), 7.48 (m, 1H), 7.30 (m, 3H), 6.28 (m, 1H), 6.05 (m, 1H), 2.98 (t, *J* = 7.3 Hz, 2H), 2.80 (t, *J* = 7.0 Hz, 2H), 2.25 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): 166.6, 154.7, 150.7, 141.0, 124.5, 124.1, 119.4, 110.2, 110.0, 105.4, 27.8, 27.2, 25.0.

HRESI-MS: calculated for ($C_{14}H_{14}NO_2$, M+H), 228.1024; found, 228.1022.



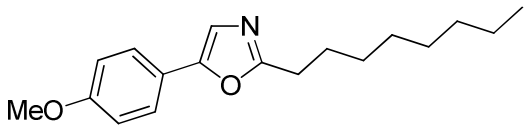
2-(3-(9H-carbazol-9-yl)propyl)-5-phenyloxazole (table 4, entry 1):

Eluated from the column with hexane-diethyl ether (1:1) in 74% yield as a yellow solid:

^{1}H NMR (400MHz, $CDCl_3$): 8.18 (d, *J* = 7.6 Hz, 2H), 7.64 (d, *J* = 7.6 Hz, 2H), 7.49 (m, 6H), 7.34 (m, 4H), 4.49 (t, *J* = 6.7 Hz, 2H), 2.88 (t, *J* = 7.0 Hz, 2H), 2.47 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): 163.0, 151.0, 140.1, 128.7, 128.0, 127.8, 125.6, 123.8, 122.7, 121.6, 120.2, 118.8, 108.4, 41.6, 25.6, 25.3.

HRESI-MS: calculated for ($C_{24}H_{21}N_2O$, M+H), 353.1654; found, 353.1653.



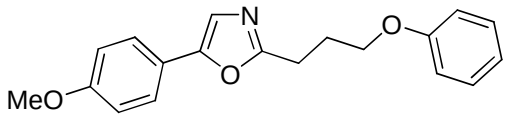
5-(4-methoxyphenyl)-2-octyloxazole (table 4, entry 2):

Eluated from the column with hexane-diethyl ether (2:1) in 86% yield as a yellow solid:

^{1}H NMR (400MHz, $CDCl_3$): 7.51 (d, *J* = 8.8 Hz, 2H), 7.07 (s, 1H), 6.91 (d, *J* = 8.5 Hz, 2H), 3.80 (s, 3H), 2.78 (t, *J* = 7.6 Hz, 2H), 1.79 (m, 2H), 1.22-1.42 (m, 10H), 0.86 (t, *J* = 6.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 163.9, 159.3, 150.6, 125.3, 121.0, 120.0, 114.1, 55.1, 31.7, 29.1, 29.06, 29.05, 28.1, 26.9, 22.5, 14.0.

HRESI-MS: calculated for ($C_{18}H_{26}NO_2$, M+H), 288.1964; found, 288.1977.



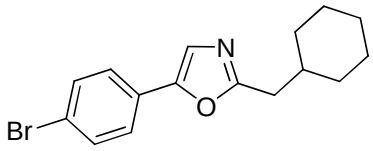
5-(4-methoxyphenyl)-2-(3-phenoxypropyl)oxazole (table 4, entry 3):

Eluated from the column with hexane-diethyl ether (1:1) in 81% yield as a yellow solid:

^{1}H NMR (400MHz, $CDCl_3$): 7.52 (d, *J* = 7.6 Hz, 2H), 7.28 (t, *J* = 7.3 Hz, 2H), 7.11 (s, 1H), 6.93 (m, 5H), 4.08 (t, *J* = 6.2 Hz, 2H), 3.82 (s, 3H), 3.04 (t, *J* = 7.3 Hz, 2H), 2.31 (quint, *J* = 7.0 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): 162.9, 159.4, 158.7, 150.9, 129.3, 125.4, 120.9, 120.6, 120.1, 114.3, 114.1, 66.3, 55.2, 26.6, 24.8.

HRESI-MS: calculated for ($C_{19}H_{20}NO_3$, M+H), 310.1443; found, 310.1427.



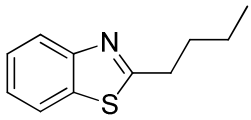
5-(4-bromophenyl)-2-(cyclohexylmethyl)oxazole (table 4, entry 4):

Eluated from the column with hexane-diethyl ether (3:1) in 76% yield as a dark red oil:

^{1}H NMR (400MHz, $CDCl_3$): 7.52 (m, 2H), 7.46 (m, 2H), 7.23 (s, 1H), 2.69 (d, *J* = 7.0 Hz, 2H), 1.75 (m, 6H), 1.24 (m, 3H), 1.04 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): 164.3, 149.8, 131.9, 127.1, 125.3, 122.2, 121.7, 36.7, 35.8, 32.9, 26.1, 26.0.

HRESI-MS: calculated for ($C_{16}H_{19}NOBr$, M+H), 320.0650 and 322.0631; found, 320.0640 and 322.0630.



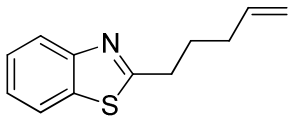
2-butylbenzo[d]thiazole (table 4, entry 5):

Eluated from the column with hexane-diethyl ether (15:1) in 79% yield as a yellow oil:

^{1}H NMR (400MHz, $CDCl_3$): 7.97 (d, *J* = 7.9 Hz, 1H), 7.83 (d, *J* = 7.9 Hz, 1H), 7.44 (m, 1H), 7.34 (m, 1H), 3.12 (t, *J* = 7.6 Hz, 2H), 1.87 (m, 2H), 1.47 (m, 2H), 0.98 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 172.3, 153.2, 135.1, 125.7, 124.5, 122.4, 121.4, 34.0, 31.7, 22.2, 13.7.

HRESI-MS: calculated for ($C_{11}H_{14}NS$, M+H), 192.0847; found, 192.0844.



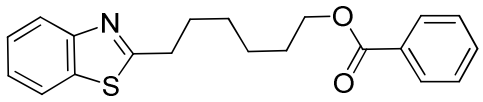
2-(pent-4-enyl)benzo[d]thiazole (table 4, entry 6):

Eluated from the column with hexane-diethyl ether (10:1) in 74% yield as a yellow oil:

^{1}H NMR (400MHz, $CDCl_3$): 7.97 (d, *J* = 7.9 Hz, 1H), 7.82 (d, *J* = 8.2 Hz, 1H), 7.43 (t, *J* = 7.3 Hz, 1H), 7.33 (m, 1H), 5.82 (m, 1H), 5.05 (m, 2H), 3.11 (m, 2H), 2.20 (q, *J* = 7.0 Hz, 2H), 1.98 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): 171.7, 153.1, 137.4, 135.0, 125.7, 124.5, 122.4, 121.3, 115.4, 33.5, 32.9, 28.6.

HRESI-MS: calculated for ($C_{12}H_{14}NS$, M+H), 204.0847; found, 204.0842.



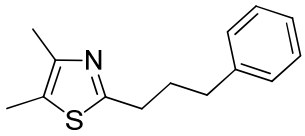
6-(benzo[d]thiazol-2-yl)hexyl benzoate (table 4, entry 7):

Eluated from the column with hexane-diethyl ether (4:1) in 72% yield as a yellow solid:

^{1}H NMR (400MHz, $CDCl_3$): 8.04 (d, *J* = 7.3 Hz, 2H), 7.97 (d, *J* = 7.6 Hz, 1H), 7.83 (d, *J* = 7.9 Hz, 1H), 7.55 (t,*J* = 7.0 Hz, 1H), 7.44 (m, 3H), 7.34 (m, 1H), 4.32 (t, *J* = 6.5 Hz, 2H), 3.13 (t, *J* = 7.6 Hz, 2H), 1.92 (m, 2H), 1.79 (m, 2H), 1.53 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$): 172.0, 166.6, 153.1, 135.0, 132.7, 130.3, 129.4, 128.2, 125.8, 124.6, 122.4, 121.4, 64.8, 34.1, 29.5, 28.7, 28.5, 25.7.

HRESI-MS: calculated for ($C_{20}H_{22}NO_2S$, M+H), 340.1371; found, 340.1369.



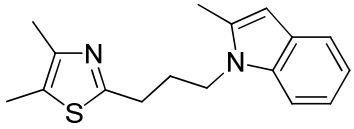
4,5-dimethyl-2-(3-phenylpropyl)thiazole (table 4, entry 8):

Eluated from the column with hexane-diethyl ether (5:1) in 76% yield as a yellow liquid:

^{1}H NMR (400MHz, $CDCl_3$): 7.28 (m, 2H), 7.19 (d, *J* = 7.0 Hz, 3H), 2.92 (t, *J* = 7.6 Hz, 2H), 2.71 (t, *J* = 7.6 Hz, 2H), 2.30 (s, 6H), 2.07 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): 166.0, 147.1, 141.4, 128.3, 128.2, 125.7, 124.8, 35.1, 32.7, 31.6, 14.5, 11.1.

HRESI-MS: calculated for ($C_{14}H_{18}NS$, M+H), 232.1160; found, 232.1161.



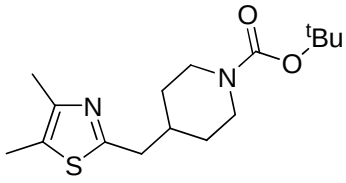
4,5-dimethyl-2-(3-(2-methyl-1H-indol-1-yl)propyl)thiazole (table 4, entry 9):

Eluated from the column with hexane-diethyl ether (2:1) in 85% yield as a yellow oil:

^{1}H NMR (400MHz, $CDCl_3$): 7.53 (d, *J* = 7.6 Hz, 1H), 7.27 (m, 1H), 7.14 (t, *J* = 6.7 Hz, 1H), 7.07 (m, 1H), 6.25 (s, 1H), 4.17 (t, *J* = 7.3 Hz, 2H), 2.96 (t, *J* = 7.6 Hz, 2H), 2.42 (s, 3H), 2.32 (m, 6H), 2.22 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): 164.7, 147.4, 136.5, 136.1, 128.0, 125.2, 120.3, 119.6, 119.1, 108.9, 100.0, 42.2, 30.5, 29.9, 14.5, 12.6, 11.2.

HRESI-MS: calculated for ($C_{17}H_{21}N_2S$, M+H), 285.1425; found, 285.1411.



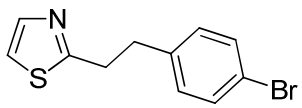
tert-butyl 4-((4,5-dimethylthiazol-2-yl)methyl)piperidine-1-carboxylate (table 4, entry 10):

Eluated from the column with hexane-diethyl ether (1:1) in 79% yield as a yellow oil:

^{1}H NMR (400MHz, $CDCl_3$): 4.06 (br., 2H), 2.78 (d, *J* = 7.0 Hz, 2H), 2.65 (br., 2H), 2.28 (m, 6H), 1.86 (m, 1H), 1.68 (d, *J* = 12.9 Hz, 2H), 1.43 (s, 9H), 1.21 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): 163.9, 154.7, 147.5, 125.1, 79.2, 43.6, 39.8, 37.2, 31.7, 28.3, 14.6, 11.1.

HRESI-MS: calculated for ($C_{16}H_{27}N_2O_2S$, M+H), 311.1793; found, 311.1798.



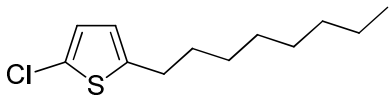
2-(4-bromophenethyl)thiazole (table 4, entry 11):

Eluated from the column with hexane-diethyl ether (3:1) in 60% yield as a slightly yellow liquid:

^{1}H NMR (400MHz, $CDCl_3$): 7.69 (d, *J* = 3.2 Hz, 1H), 7.40 (d, *J* = 8.2 Hz, 2H), 7.18 (d, *J* = 3.2 Hz, 1H), 7.07 (d, *J*= 8.2 Hz, 2H), 3.30 (t, *J* = 7.6 Hz, 2H), 3.08 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): 169.4, 142.3, 139.2, 131.5, 130.1, 120.1, 118.2, 35.2, 34.6.

HRESI-MS: calculated for ($C_{11}H_{11}NSBr$, M+H), 267.9796 and 269.9775; found, 267.9779 and 269.9764.



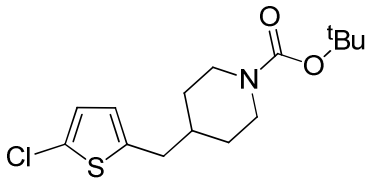
2-chloro-5-octylthiophene (table 4, entry 12):

Eluated from the column with hexane-diethyl ether (30:1) in 81% yield as a colorless oil:

^{1}H NMR (400MHz, $CDCl_3$): 6.70 (d, *J* = 3.8 Hz, 1H), 6.53 (d, *J* = 3.8 Hz, 1H), 2.71 (t, *J* = 7.3 Hz, 2H), 1.62 (m, 2H), 1.30 (m, 10H), 0.88 (t, *J* = 6.5 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 144.7, 126.4, 125.5, 123.1, 31.8, 31.4, 30.3, 29.2, 29.1, 28.9, 22.6, 14.0.

Elemental analysis: Anal. Calcd for $C_{12}H_{19}ClS$: C, 62.45; H, 8.30. Found: C, 62.25; H, 8.43.



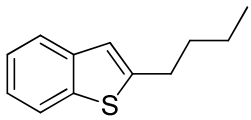
tert-butyl 4-((5-chlorothiophen-2-yl)methyl)piperidine-1-carboxylate (table 4, entry 13):

Eluated from the column with hexane-diethyl ether (10:1) in 62% yield as a colorless oil:

^{1}H NMR (400MHz, $CDCl_3$): 6.71 (d, *J* = 3.5 Hz, 1H), 6.52 (d, *J* = 3.2 Hz, 1H), 4.10 (br., 2H), 2.65 (m, 4H), 1.70 (m, 3H), 1.45 (s, 9H), 1.11 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): 154.7, 141.6, 125.6, 124.5, 79.3, 43.1, 38.3, 37.2, 31.7, 28.4.

HRESI-MS: calculated for ($C_{15}H_{23}ClNO_2S$, M+H), 316.1138; found, 316.1128.



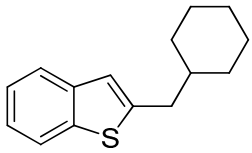
2-butylbenzo[b]thiophene (table 4, entry 14):

Eluated from the column with hexane in 78% yield as a colorless liquid:

^{1}H NMR (400MHz, $CDCl_3$): 7.80 (d, *J* = 8.2 Hz, 1H), 7.70 (d, *J* = 7.9 Hz, 1H), 7.35 (m, 2H), 7.28 (m, 1H), 2.94 (t, *J* = 7.3 Hz, 2H), 1.78 (m, 2H), 1.47 (m, 2H), 1.01 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 146.7, 140.1, 139.2, 123.9, 123.2, 122.5, 122.0, 120.3, 33.1, 30.4, 22.1, 13.8.

Elemental analysis: Anal. Calcd for $C_{12}H_{14}S$: C, 75.45; H, 7.42. Found: C, 75.14; H, 7.43.



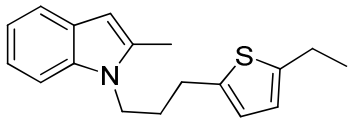
2-(cyclohexylmethyl)benzo[b]thiophene (table 4, entry 15):

Eluated from the column with hexane-diethyl ether (100:1) in 72% yield as a colorless liquid:

^{1}H NMR (400MHz, $CDCl_3$): 7.77 (d, *J* = 7.6 Hz, 1H), 7.67 (d, *J* = 7.6 Hz, 1H), 7.28 (m, 2H), 6.98 (s, 1H), 2.78 (d, *J* = 7.0 Hz, 2H), 1.73 (m, 6H), 1.23 (m, 3H), 1.00 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): 145.2, 140.1, 139.4, 123.9, 123.2, 122.5, 122.0, 121.3, 39.7, 38.6, 33.0, 26.4, 26.1.

Elemental analysis: Anal. Calcd for $C_{15}H_{18}S$: C, 78.21; H, 7.88. Found: C, 77.94; H, 7.59.



1-(3-(5-ethylthiophen-2-yl)propyl)-2-methyl-1H-indole (table 4, entry 16):

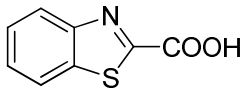
Eluated from the column with hexane-diethyl ether (100:1) in 66% yield as a colorless liquid:

^{1}H NMR (400MHz, $CDCl_3$): 7.53 (d, *J* = 7.3 Hz, 1H), 7.24 (m, 1H), 7.14 (t, *J* = 7.0 Hz, 1H), 7.07 (m, 1H), 6.61 (s, 2H), 6.25 (s, 1H), 4.12 (t, *J* = 7.3 Hz, 2H), 2.83 (m, 4H), 2.41 (s, 3H), 2.13 (m, 2H), 1.30 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 145.4, 141.1, 136.5, 136.2, 128.0, 123.9, 122.7, 120.3, 119.6, 119.1, 108.9, 99.9, 42.3, 31.6, 27.5, 23.4, 15.9, 12.7.

HRESI-MS: calculated for ($C_{18}H_{22}NS$, M+H), 284.1473; found, 284.1468.

9.5. Characterization data for the products of the catalytic reactions represented in Chapter 8



benzo[d]thiazole-2-carboxylic acid (table 1):

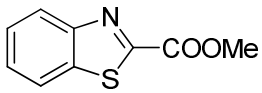
Obtained in 98% yield as a solid:

^{1}H NMR (400MHz, DMSO-D6): 14 - 15 (br., 1H), 8.21 (m, 2H), 7.62 (m, 2H).

^{13}C NMR (100 MHz, DMSO-D6): 161.4, 160.0, 152.9, 136.3, 127.5, 127.2, 124.8, 123.0.

HRESI-MS: calculated for ($C_8H_6NO_2S$, M+H), 180.0119; found, 180.0125.

Elemental analysis: Anal. Calcd for $C_8H_5NO_2S$: C, 53.62; H, 2.81; N, 7.82. Found: C, 53.35; H, 2.66; N, 7.76.



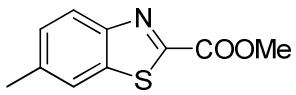
methyl benzo[d]thiazole-2-carboxylate:

Obtained in 95% yield as a solid. Melting point: 95 ^{0}C (lit. value: 90 ^{0}C[39]).

^{1}H NMR (400MHz, $CDCl_3$): 8.24 (d, *J* = 8.2 Hz, 1H), 7.97 (d, *J* = 7.6 Hz, 1H), 7.56 (m, 2H), 4.08 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 161.1, 158.0, 153.1, 136.7, 127.6, 127.1, 125.5, 122.1, 53.6.

HRESC-MS: calculated for ($C_9H_8NO_2S$, M+H), 194.0276; found, 194.0276.



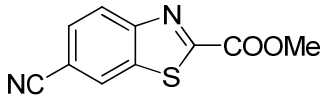
methyl 6-methylbenzo[d]thiazole-2-carboxylate (table 2, entry 1):

Obtained in 91% yield as a solid.

^{1}H NMR (400MHz, $CDCl_3$): 8.05 (d, J = 8.5 Hz, 1H), 7.69 (s, 1H), 7.33 (d, J = 8.5 Hz, 1H), 4.03 (s, 3H), 2.47 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 161.1, 156.7, 151.2, 138.1, 136.9, 128.9, 124.8, 121.4, 53.4, 21.6.

HRESI-MS: calculated for ($C_{10}H_{10}NO_2S$, M+H), 208.0432; found, 208.0428.



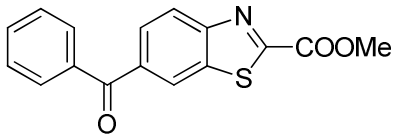
methyl 6-cyanobenzo[d]thiazole-2-carboxylate (table 2, entry 2):

Eluated from the column with hexane - ethyl acetate (2:1) in 90% yield as a solid:

^{1}H NMR (400MHz, $CDCl_3$): 8.35 (dd, J_1 = 1.5 Hz, J_2 = 0.6 Hz, 1H), 8.33 (dd, J_1 = 8.5 Hz, J_2 = 0.6 Hz, 1H), 7.83 (dd, J_1 = 8.5 Hz, J_2 = 1.5 Hz, 1H), 4.12 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 162.1, 160.3, 155.2, 137.0, 129.9, 127.3, 126.4, 118.0, 111.3, 54.1.

HRESI-MS: calculated for ($C_{10}H_7N_2O_2S$, M+H), 219.0228; found, 219.0233.



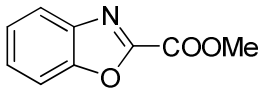
methyl 6-benzoylbenzo[d]thiazole-2-carboxylate (table 2, entry 3):

Eluated from the column with hexane - ethyl acetate (2:1) in 68% yield as a solid:

^{1}H NMR (400MHz, $CDCl_3$): 8.42 (m, 1H), 8.31 (d, J = 8.5 Hz, 1H), 8.01 (dd, J_1 = 8.5 Hz, J_2 = 1.8 Hz, 1H), 7.82 (dd, J_1 = 8.2 Hz, J_2 = 1.5 Hz, 2H), 7.62 (m, 1H), 7.51 (m, 2H), 4.10 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 195.4, 161.1, 160.6, 155.2, 137.1, 136.6, 132.8, 130.0, 128.6, 128.5, 125.2, 124.7, 53.9.

HRESI-MS: calculated for ($C_{16}H_{12}NO_3S$, M+H), 298.0538; found, 298.0518.



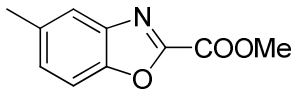
methyl benzo[d]oxazole-2-carboxylate (table 2, entry 4):

Obtained in 91% yield as a solid. Melting point: 99 ^{0}C (lit. value: 100 ^{0}C[40]).

^{1}H NMR (400MHz, $CDCl_3$): 7.87 (d, J = 7.6 Hz, 1H), 7.64 (d, J = 8.2 Hz, 1H), 7.51 (td, J_1 = 7.6 Hz, J_2 = 1.5 Hz, 1H), 7.44 (m, 1H), 4.07 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 156.8, 152.4, 150.8, 140.4, 128.2, 125.8, 122.1, 111.7, 53.6.

HRESI-MS: calculated for ($C_9H_8NO_3$, M+H), 178.0504; found, 178.0506.



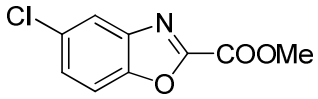
methyl 5-methylbenzo[d]oxazole-2-carboxylate (table 2, entry 5):

Obtained in 83% yield as a solid. Melting point: 97^{0}C (lit. value: 98 ^{0}C[3]).

^{1}H NMR (400MHz, $CDCl_3$): 7.61 (s, 1H), 7.49 (d, J = 8.5 Hz, 1H), 7.29 (dd, J_1 = 8.2 Hz, J_2 = 1.2 Hz, 1H), 4.05 (s, 3H), 2.46 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 156.8, 152.4, 149.1, 140.6, 135.8, 129.6, 121.6, 111.0, 53.5, 21.4.

HRESI-MS: calculated for ($C_{10}H_{10}NO_3$, M+H), 192.0661; found, 192.0660.



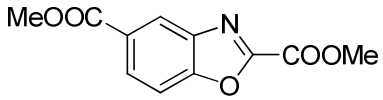
methyl 5-chlorobenzo[d]oxazole-2-carboxylate (table 2, entry 6):

Obtained in 92% yield as a solid. Melting point: 124 ^{0}C (lit. value: 122 ^{0}C[3]).

^{1}H NMR (400MHz, $CDCl_3$): 7.83 (d, J = 2.1 Hz, 1H), 7.57 (m, 1H), 7.47 (dd, J_1 = 8.8 Hz, J_2 = 2.1 Hz, 1H), 4.07 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 156.5, 153.6, 149.4, 141.4, 131.5, 128.8, 121.9, 112.6, 53.9.

HRESI-MS: calculated for ($C_9H_7NO_3Cl$, M+H), 212.0114; found, 212.0116.



dimethyl benzo[d]oxazole-2,5-dicarboxylate (table 2, entry 7):

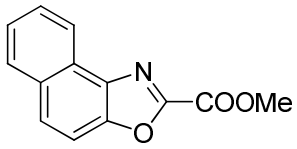
Eluated from the column with hexane - ethyl acetate (1:1) in 92% yield as a solid:

^{1}H NMR (400MHz, $CDCl_3$): 8.56 (s, 1H), 8.26 (d, *J* = 8.5 Hz, 1H), 7.70 (d, *J* = 8.8 Hz, 1H), 4.11 (s, 3H), 3.97 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 166.0, 156.5, 153.7, 153.5, 140.5, 129.8, 128.4, 124.2, 111.7, 53.9, 52.5.

HRESI-MS: calculated for ($C_{11}H_{10}NO_5$, M+H), 236.0559; found, 236.0565.

Elemental analysis: Anal. Calcd for $C_{11}H_9NO_5$: C, 56.17; H, 3.86; N, 5.96. Found: C, 55.73; H, 4.02; N, 5.72.



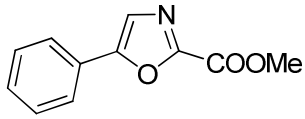
methyl naphtho[1,2-d]oxazole-2-carboxylate (table 2, entry 8):

Obtained in 97% yield as a solid. Melting point: 155 ^{0}C (lit. value: 146 ^{0}C[41]).

^{1}H NMR (400MHz, $CDCl_3$): 8.63 (d, *J* = 8.2 Hz, 1H), 7.97 (m, 2H), 7.73 (m, 2H), 7.61 (m, 1H), 4.13 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 156.8, 151.6, 148.9, 136.5, 131.5, 129.9, 128.8, 128.0, 126.9, 126.4, 122.3, 111.1, 53.7.

HRESI-MS: calculated for ($C_{13}H_{10}NO_3$, M+H), 228.0661; found, 228.0654.



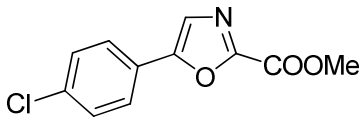
methyl 5-phenyloxazole-2-carboxylate (table 2, entry 9):

Eluated from the column with hexane - ethyl acetate (2:1) in 65% yield as a solid:

^{1}H NMR (400MHz, $CDCl_3$): 7.72 (m, 2H), 7.50 (s, 1H), 7.41 (m, 3H), 3.99 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 156.0, 154.3, 151.3, 129.8, 129.0, 126.5, 125.0, 123.8, 53.0.

HRESI-MS: calculated for ($C_{11}H_{10}NO_3$, M+H), 204.0661; found, 204.0666.



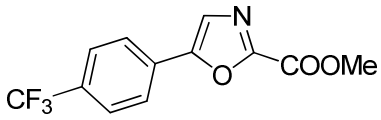
methyl 5-(4-chlorophenyl)oxazole-2-carboxylate (table 2, entry 10):

Eluated from the column with hexane - ethyl acetate (3:1) in 55% yield as a solid:

^{1}H NMR (400MHz, $CDCl_3$): 7.69 (d, *J* = 8.2 Hz, 2H), 7.52 (s, 1H), 7.43 (d, *J* = 8.5 Hz, 2H), 4.02 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 156.0, 153.3, 151.5, 135.9, 129.4, 126.3, 125.1, 124.2, 53.2.

HRESI-MS: calculated for ($C_{11}H_9NO_3Cl$, M+H), 238.0271; found, 238.0271.



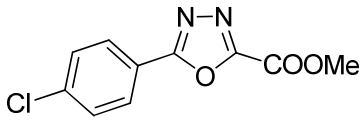
methyl 5-(4-(trifluoromethyl)phenyl)oxazole-2-carboxylate (table 2, entry 11):

Eluated from the column with hexane - ethyl acetate (3:1) in 61% yield as a solid:

^{1}H NMR (400MHz, $CDCl_3$): 7.88 (d, *J* = 8.2 Hz, 2H), 7.72 (d, *J* = 8.2 Hz, 2H), 7.64 (s, 1H), 4.04 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 155.9, 152.8, 152.1, 131.5 (q, *J* = 33 Hz), 129.8 (q, *J* = 1.4 Hz), 126.1 (q, *J* = 3.8 Hz), 125.4, 125.3, 123.7 (q, *J* = 272.3 Hz), 53.3.

HRESI-MS: calculated for ($C_{12}H_9NO_3F_3$, M+H), 272.0535; found, 272.0524.



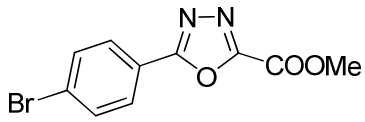
methyl 5-(4-chlorophenyl)-1,3,4-oxadiazole-2-carboxylate (table 2, entry 12):

Obtained in 88% yield as a solid:

^{1}H NMR (400MHz, $CDCl_3$): 8.11 (d, *J* = 8.8 Hz, 2H), 7.54 (d, *J* = 8.8 Hz, 2H), 4.09 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 165.7, 156.3, 154.6, 139.3, 129.7, 128.8, 121.1, 53.8.

HRESI-MS: calculated for ($C_{10}H_8N_2O_3Cl$, M+H), 239.0223; found, 239.0212.



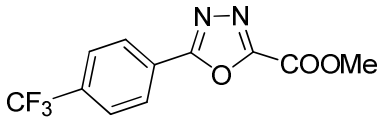
methyl 5-(4-bromophenyl)-1,3,4-oxadiazole-2-carboxylate (table 2, entry 13):

Obtained in 83% yield as a solid:

^{1}H NMR (400MHz, $CDCl_3$): 8.02 (d, *J* = 8.5 Hz, 2H), 7.69 (d, *J* = 8.5 Hz, 2H), 4.08 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 165.8, 156.3, 154.7, 132.7, 129.0, 127.9, 121.5, 53.9.

HRESI-MS: calculated for ($C_{10}H_8N_2O_3Br$, M+H), 282.9718 and 284.9699; found, 282.9726 and 284.9717.



methyl 5-(4-(trifluoromethyl)phenyl)-1,3,4-oxadiazole-2-carboxylate (table 2, entry 14):

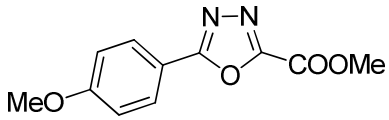
Obtained in 71% yield as a solid:

^{1}H NMR (400MHz, $CDCl_3$): 8.29 (d, *J* = 8.2 Hz, 2H), 7.81 (d, *J* = 8.2 Hz, 2H), 4.09 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 165.2, 156.6, 154.6, 134.4 (q, *J* = 33.1 Hz), 128.0, 126.0 (q, *J* = 268.2 Hz), 126.3 (q, *J* = 3.8 Hz), 125.9 (q, *J* = 1.5 Hz), 53.9.

HRESI-MS: calculated for ($C_{11}H_8N_2O_3F_3$, M+H), 273.0487; found, 273.0489.

Elemental analysis: Anal. Calcd for $C_{11}H_7N_2O_3F_3$: C, 48.54; H, 2.59; N, 10.29. Found: C, 48.25; H, 2.85; N, 9.95.



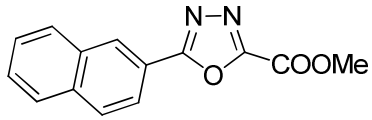
methyl 5-(4-methoxyphenyl)-1,3,4-oxadiazole-2-carboxylate (table 2, entry 15):

Obtained in 96% yield as a solid:

^{1}H NMR (400MHz, $CDCl_3$): 8.07 (d, *J* = 8.8 Hz, 2H), 7.01 (d, *J* = 9.1 Hz, 2H), 4.06 (s, 3H), 3.87 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 166.5, 163.2, 155.8, 154.9, 129.5, 115.0, 114.7, 55.5, 53.7.

HRESI-MS: calculated for ($C_{11}H_{11}N_2O_4$, M+H), 235.0719; found, 235.0710.



methyl 5-(naphthalen-2-yl)-1,3,4-oxadiazole-2-carboxylate (table 2, entry 16):

Eluated from the column with hexane - ethyl acetate (3:1) in 64% yield as a solid:

^{1}H NMR (400MHz, $CDCl_3$): 8.61 (s, 1H), 8.13 (dd, J_1 = 8.8 Hz, J_2 = 1.8 Hz, 1H), 7.93 (m, 2H), 7.85 (d, *J* = 8.2 Hz, 1H), 7.56 (m, 2H), 4.08 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): 166.6, 156.2, 154.8, 135.0, 132.6, 129.2, 128.9, 128.5, 128.5, 127.9, 127.3, 123.1, 119.7, 53.7.

HRESI-MS: calculated for ($C_{14}H_{11}N_2O_3$, M+H), 255.0770; found, 255.0764.

9.6. References

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Curriculum Vitae

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EDUCATION

2007 – Ph.D. student, Ecole Polytechnique Fédérale de Lausanne (Swiss Federal Institute of Technology, Lausanne)
Major: organometallic chemistry
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2002 – 2007 Master degree student, department of chemistry, Kharkov National University, Ukraine
Major: physical and theoretical chemistry
Magna cum laude diploma
Thesis adviser: Prof. Alexander Korobov

Jun. 2004 Summer training, Sovereign SC Company, Antwerp, Belgium
"Meeting the real world needs – chemistry and business contact at polymers, adhesives and lacquers market"

RESEARCH EXPERIENCE

2007 – Organometallic chemistry: development of new synthetic methods for cross coupling of non-activated alkyl halides and direct C-H functionalization

2005 – 2007 Extracurricular undergraduate research project "Simulation of solid state reactions in terms of tiling"

2002 – 2003 Organic chemistry: synthesis of potentially pharmaceutically active heterocyclic compounds

INDUSTRY EXPERIENCE

2003 – 2007 Product development manager at Factorial company (distributor of BASF, Exxon Mobil, Simona, Weis, Sovereign SC products in Ukraine)

TEACHING EXPERIENCE

2007 – 2010	Graduate teaching assistant in general, organic, inorganic and analytical chemistry
2002 – 2007	Preparation of secondary-school students for All-Ukrainian chemistry olympiads

AWARDS AND FELLOWSHIPS

2011	Finalist of the DSM Science & Technology Award 2011
2011	Swiss National Science Foundation fellowship for young researchers
2010	Invited for the Syngenta workshop for talented young chemists 2010
2010	Finalist of the Reaxys Ph.D. Prize 2010
2009	The best poster award in the 2009 CUSO summer school
2009	Student Travel Award from the Swiss Academy of Science
2002, 2003	President of Ukraine fellowship for talented students
2002	Silver medal, 34th International Chemistry Olympiad, Groningen, the Netherlands
2001, 2002	The first place at the 38th and 39th all-Ukrainian chemistry Olympiads

LANGUAGES

English (fluent), French (fluent), German (intermediate), Russian (native)

LIST OF SCIENTIFIC PUBLICATIONS

1. "Bis[(2-dimethylamino)phenyl]amine Nickel(II) Chloride". **O. Vechorkin** and X. L. Hu, e-EROS, *Encyclopedia of Reagents for Organic Synthesis*. Wiley, **2011**

2. "A Structure-Activity Study of Ni-Catalyzed Alkyl-Alkyl Kumada Coupling. Improved Catalysts for Coupling of Secondary Alkyl Halides". P. Ren, **O. Vechorkin**, K. von Allmen, R. Scopelliti, and X. L. Hu *J. Am. Chem. Soc.*, **2011**, **2011**, *133*, 7084 – 7095

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8. “Functional Group Tolerant Kumada–Corriu–Tamao Coupling of Nonactivated Alkyl Halides with Aryl and Heteroaryl Nucleophiles: Catalysis by a Nickel Pincer Complex Permits the Coupling of Functionalized Grignard Reagents”. **O. Vechorkin**, V. Proust and X. L. Hu, *J. Am. Chem. Soc.* **2009**, *131* (28), 9756 – 9766
   - Selected by the journal 'Synfacts' as 'SYNFACT of the month' for October 2009 (*Synfacts*, **2009**, 1139)
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10. “Nickel Complexes of a Pincer Amidobis(amine) Ligand: Synthesis, Structure, and Activity in Stoichiometric and Catalytic C—C Bond Forming Reactions of Alkyl

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11. "Nickel Complexes of a Pincer NN_2 Ligand: Multiple Carbon-Chloride Activation of CH_2Cl_2 and $CHCl_3$ Leads to Selective Carbon-Carbon Bond Formation". Z. Csok, **O. Vechorkin**, S. B. Harkins, R. Scopelliti, X. L. Hu, *J. Am. Chem. Soc.* **2008**, 130, 8156 – 8157

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