Nickamine and analogous nickel pincer catalysts for cross-coupling of alkyl halides and hydrosilylation of alkenes

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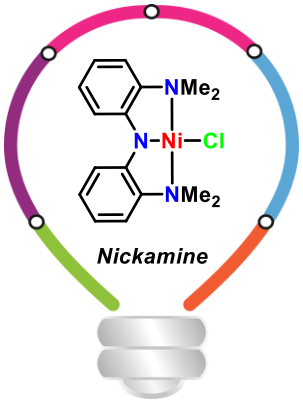
CONSPECTUS Ligand development plays an essential role in the advance of homogeneous catalysis. Tridentate, meridionally-coordinating ligands, commonly referred as pincer ligands, have been established as a privileged class of ligands in catalysis because they confer high stability while maintaining electronic tenability to the resulting metal complexes. Pincer ligands containing "soft" donors such as phosphines are typically used for late transition metal ions, which are considered as "soft" acids. Driven by our interest to develop base metal catalysis and in view of the "hard" character of base metal ions, our group explored a pincer ligand containing only "hard" nitrogen donors. A prototypical nickel complex of this ligand, "Nickamine", turned out to be an efficient catalyst in a wide range of organic reactions.

Due to its propensity to mediate single-electron redox chemistry, Nickamine is particularly suited to catalyze cross-coupling of non-activated alkyl halides through radical pathways. These coupling

partners have been challenging substrates for traditional, palladium-based catalysts due to difficult oxidative addition and non-productive β-H elimination. The high activity of Nickamine for cross-coupling leads to high chemoselectivity and functional group tolerance, even when reactive Grignard reagents are employed as nucleophiles. The scope of the catalysis is broad and encompasses sp^3-sp^3, sp^3-sp^2, and sp^3-sp cross-coupling. The defined nature of Nickamine facilitated the mechanistic study of cross-coupling reactions. Experiments involving radical-probe substrates, presumed intermediates and dormant species, kinetics, and density functional theory computations revealed a bimetallic oxidative addition pathway. In this pathway, two Ni centers each provide one electron to support the two-electron activation of an alkyl halide substrate.

The success of "Nickamine" motivated our systematic structure-activity studies aiming at improved activity in certain reactions through ligand modification. Indeed better catalysts have been developed for cross-coupling of secondary alkyl halides as well as direct alkynylation of alkyl halides. The improvement is attributed to a more accessible Ni center in the new catalysts than in Nickamine. Surprisingly, the improvement could be obtained simply by replacing a dimethyl amino group in Nickamine with a pyrrolidino group.

During the study of the catalytic cycle of Nickamine in cross-coupling reactions, we synthesized the corresponding Ni-H species. Consequently, we explored the catalytic application of Nickamine in Ni-H mediated reactions such as hydrosilylation. To our delight, Nickamine is a chemoselective catalyst for hydrosilylation of alkenes while tolerating a reactive C=O group. An analogous Ni pincer complex was found to catalyze unusual hydrosilylation reactions using alkoxy hydrosilanes as surrogates of gaseous silanes.

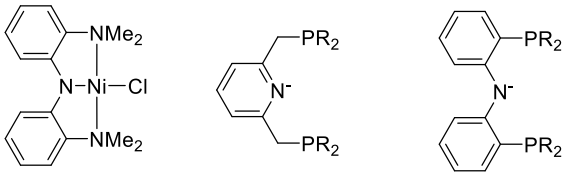

NMe2
N–Ni–Cl
NMe2
Nickamine

1. Introduction

Ligand development occupies a central stage in homogeneous catalysis. Systematic ligand modification is a well-established approach to improving catalysts. However, a promising ligand system needs to be discovered at first before it can be optimized. Ligand discovery might be realized following three paths. The first path is *de novo* design, which is difficult if not impossible at this stage. The second path is screening of ligand libraries. This path is probably the most efficient way to identify a lead ligand for a particular reaction. The obvious limitation of this approach is that no new ligand will be created. In this aspect, a third path becomes important. This path is curiosity-driven ligand development, where a new kind of ligand is first made by intuition and then tested for its destined applications. Here is an account of our journey taking the third path with Nickamine and its analogous.

Nickamine is a Ni(II) complex of a pincer N_2N ligand (**1**, Figure 1). At the time this N_2N pincer was made, pincer ligands had already been firmly established as privileged ligands in coordination chemistry and homogeneous catalysis.[1-3] One of the authors (Hu) was particularly exposed to the chemistry of amido and pyridyl bis(phosphine) (NP_2, **2-3**, Figure 1) ligands[4-8] while he was a postdoctoral researcher thinking about projects for his future independent career (in 2006-2007). He was interested in base metal catalysis, and he thought that the "soft" NP_2 ligands were not the best match for metal ions such as Fe, Co, and Ni. Without resorting to much creativity, he came up with an idea of using amine analogous of the NP_2 ligands, and hence the N_2N ligands.[9] Soon the first ligand was made and so was the first metal complex – a Ni(II) chloride complex, the Nickamine (**1**). The beginner's luck struck. In the following years, our group demonstrated Nickamine as a versatile catalyst for many challenging organic reactions including cross-coupling of alkyl halides and chemoselective hydrosilylation of alkenes. The defined nature of the catalyst

facilitated the mechanistic studies of cross-coupling reactions, which revealed a ubiquitous bimetallic oxidative addition reaction pathway for base-metal catalyzed coupling reactions of alkyl halides. Systematic modifications of the ligand led to a new generation of Ni catalysts with improved performance in certain reactions. This account offers a personal overview of our major developments.



1 2 3

Figure 1. Chemical structures of Nickamine and NP_2 ligands.

2. Nickamine catalyzed cross-coupling of alkyl halides

The pharmaceutical industry currently emphasizes "high-throughput" in its synthetic practices. Metal-catalyzed cross-coupling of sp^2- and sp-carbon fragments is particularly amenable to parallel synthesis. While broad applications of such cross-coupling have contributed to drug discovery, they have also biased discovery efforts towards aromatic compounds. This bias has created a "flatland" in drug development and is partially responsible for the low clinical success rate.[10,11] Because biological targets have 3D structures, compounds with a greater 3D shape than flat aromatics are suggested to have higher chances to succeed as drug candidates. A useful descriptor for saturation, which is related to 3D shape, is the fraction of sp^3 carbon.[10] Cross-coupling reactions of alkyl electrophiles introduce sp^3 carbons in a parallel manner, and thus, they are highly valuable for drug development. These reactions, especially the coupling of non-activated alkyl electrophiles with β-hydrogens, had been challenging due to β-H elimination of

metal alkyl intermediates.[12-14] In recent years, nickel catalysis has been developed to address this challenge.[15-19] Our work using Nickamine as a catalyst contributed to this progress.

2.1 $C(sp^3)$-$C(sp^3)$ cross-coupling

Having made Nickamine, we were eager to explore its catalytic potential. Since organometallic Ni species are frequently invoked as intermediates in various reactions including cross-coupling, we made [($^{Me}N_2N$)Ni-alkyl] complexes (**4**-**5**) by reactions of Nickamine with alkyl Grignard reagents (Figure 2).[20] The methyl derivative **4** reacted cleanly with alkyl halides to give the C-C coupled products (eq 1, Figure 2). These results already pointed to the promise of Nickamine as a catalyst for alkyl-alkyl cross-coupling. But we were sidetracked by the discovery of an unusual transformation: **4** and **5** reacted with CH_2Cl_2 and $CHCl_3$ to give fully C-C coupled products (eqs. 2-3, Figure 2). Partially alkylated products were not formed. The reactions are remarkable because they involve the cleavage of up to three C-Cl bonds to form three new C-C bonds at the same carbon center. After substantial efforts, we were able to develop a catalytic version of the reaction. The double alkylation of CH_2Cl_2 by an alkyl Grignard reagent could be achieved using Nickamine as a catalyst (eq. 4, Figure 2). While the substrate scope of the reaction turned out to be limited,[21] we suggested a potential utility of this reaction in preparing D-labelled alkanes using CD_2Cl_2 as the substrate.

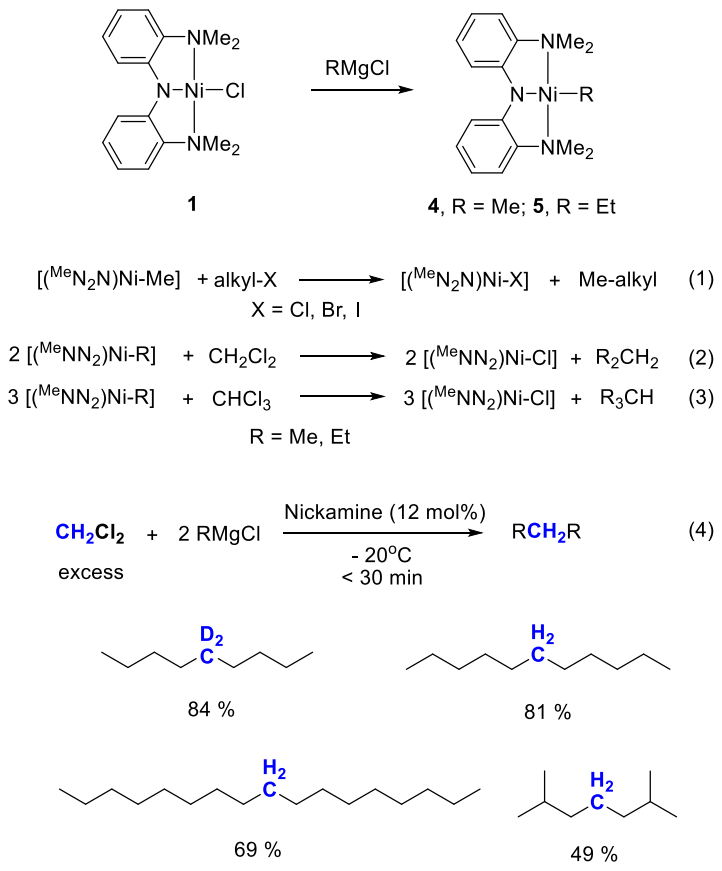


Figure 2. Reactivity of Nickamine and its alkyl analogous as well as cross-coupling of CH_2Cl_2.

Returning to more conventional alkyl-alkyl coupling, we found Nickamine was indeed a catalyst as suggested by the reactions shown in Figure 2.[22] The catalyst worked particularly well with Grignard reagents as the nucleophiles (Figure 3), and the reactions completed rapidly even at -35 to -20 °C. By comparison, the analogous coupling with 9-alkyl-9-borabicyclo[3,3,1]nonane (alkyl-(9-BBN)) reagents required a much higher temperature (80 °C).[23] Primary alkyl bromides and iodides as well as cyclic secondary alkyl iodides were suitable substrates. The mild conditions resulted in high functional group tolerance that was unusual for reactions using Grignard reagents. Indeed, relatively reactive groups such as ester, cyano, alkoxide, ketone, and various heterocycles were well tolerated. The reaction was selective to an alkyl halide moiety over an aryl halide moiety. This coupling method was diastereoselective when 1, 3- and 1, 4-substituted cyclohexyl halides

and tetrahydropyrans were employed as substrates (some examples in Figure 3).[24] The diastereoselectivity originated from the conformational preference of nickel-alkyl intermediates.

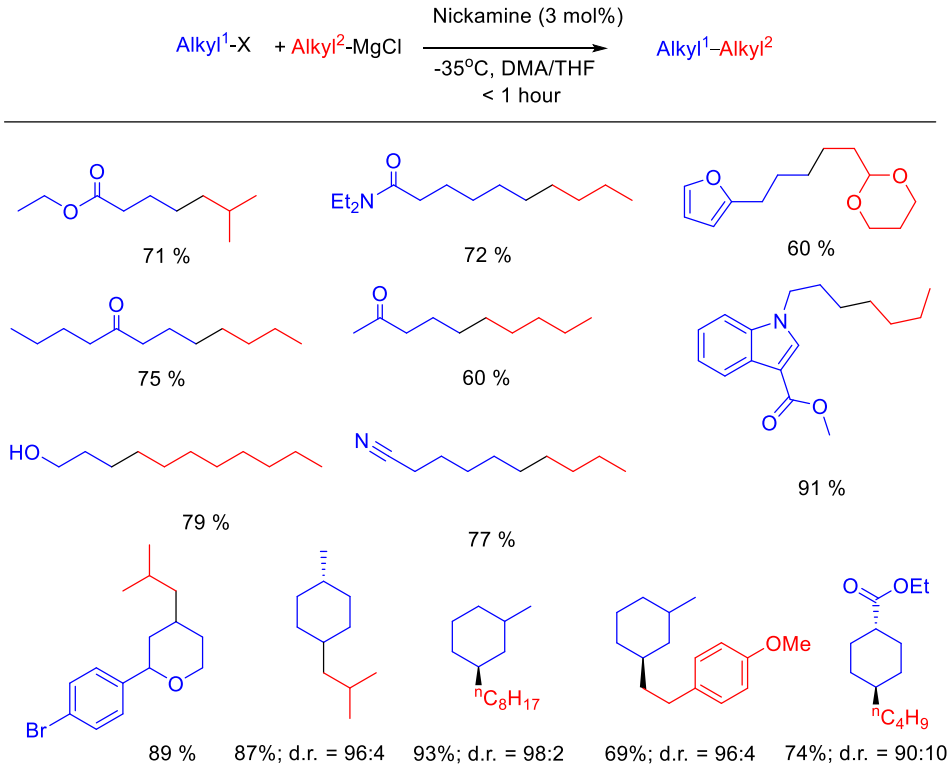


Figure 3. Selected scope of Nickamine-catalyzed alkyl-alkyl Kumada coupling

2.2 C(sp^3)-C(sp^2) cross-coupling

The protocol for alkyl-alkyl coupling described above was inefficient for the analogous alkyl-aryl coupling. By judicious choices of reaction conditions and additives, we were able to develop a new protocol that allowed the coupling of non-activated alkyl halides with aryl and heteroaryl Grignard reagents (Figure 4).[25] An amine additive such as tetramethylethylenediamine (TMEDA) or bis[2-(N,N-dimethylamino)ethyl] ether (O-TMEDA) was essential in suppressing the homo-coupling, although its origin remained unclear. The coupling reactions were rapid at room temperature (< 1 h). Primary iodides and bromides and cyclic secondary iodides were viable electrophiles, and they could contain an ester, amide, nitrile, thioether, acetal, alcohol, indole,

pyrrole, furan, pyrazole, or NBoc group. For the first time, functionalized aryl and heteroaryl Grignard reagents[26-28] could be used as nucleophiles in alkyl-aryl coupling.

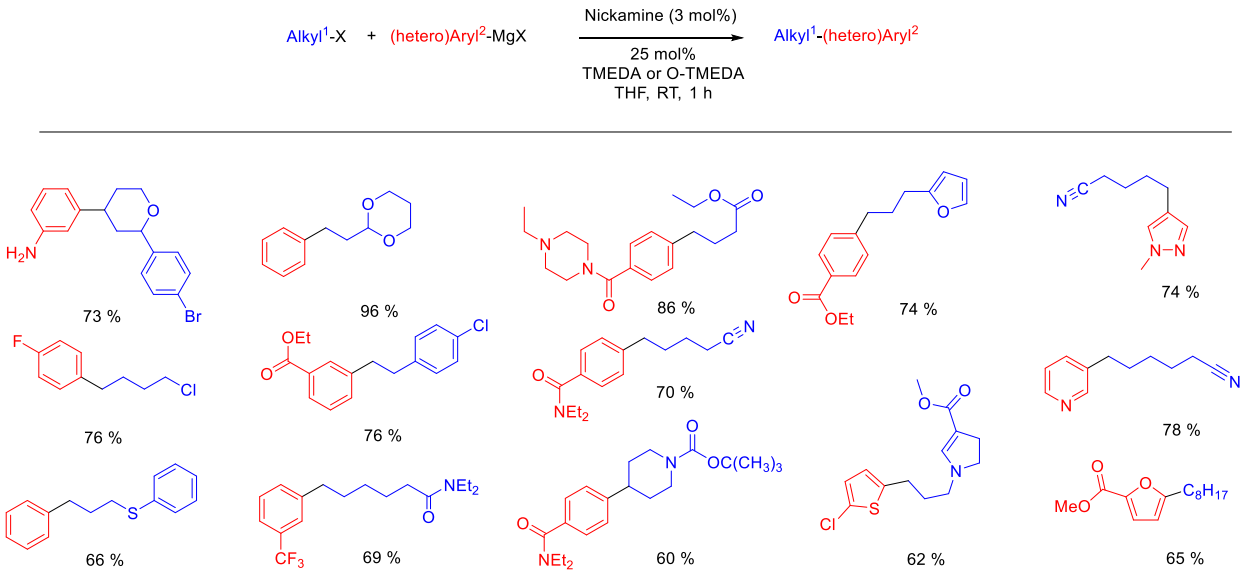


Figure 4. Selected scope of Nickamine-catalyzed alkyl-aryl Kumada coupling

It was perhaps not surprising that Nickamine could catalyze analogous alkyl-alkenyl coupling. This time we decided to employ alkenyl-(9-BBN) reagents as nucleophiles. These reagents can be easily accessed by E-selective hydroboration of terminal alkynes, so a successful coupling would allow the expedited synthesis of functionalized alkyl alkenes from readily available alkynes. Indeed Nickamine was an efficient catalyst for the Suzuki coupling of alkyl halides with alkenyl-(9-BBN) reagents (Figure 5).[29] The stability of Nickamine was essential for the coupling of functionalized alkyl halides. If a mixture of a Ni salt with a bidentate ligand was used, the yield of coupling was low and heterogeneous Ni species was formed. The method worked for both primary and secondary alkyl halides including alkyl chlorides. Sequential hydroboration and cross-coupling was successful. The method was applied to a total synthesis of (±)-Recifeiolide, a natural macrolide in a total of five steps with an overall yield of 35% (Figure 5).

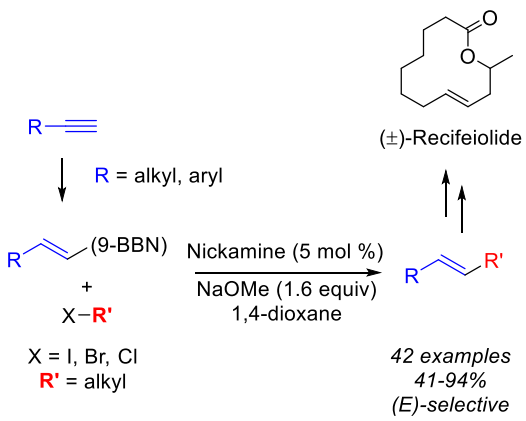


Figure 5. Nickamine-catalyzed alkyl-alkenyl Suzuki coupling.

2.3. C(sp^3)-C(sp) cross-coupling

Alkynes are versatile synthetic intermediates and recurring units in numerous natural products, bioactive molecules, and organic materials.[30,31] During the last decades, Sonogashira coupling has become one of the most widely used methods for the synthesis of internal alkynes.[32-35] However, Sonogashira coupling is generally limited to aryl and vinyl electrophiles. There were few methods for C(sp^3)-C(sp) cross-coupling. We were delighted to find that Nickamine was able to catalyze the coupling of non-activated alkyl halides with alkynyl Grignard reagents (Figure 6).[36] The O-TMEDA additive (1.5 to 3 equiv.) was essential in activating the Grignard reagents. Primary alkyl iodides and bromides were suitable electrophiles. The electronic properties of the alkynyl Grignard reagents had little influence. The coupling had very broad scope (Figure 6). The reactions were conducted at room temperature and completed within several hours. The mild conditions lead to high functional group tolerance (Figure 6).

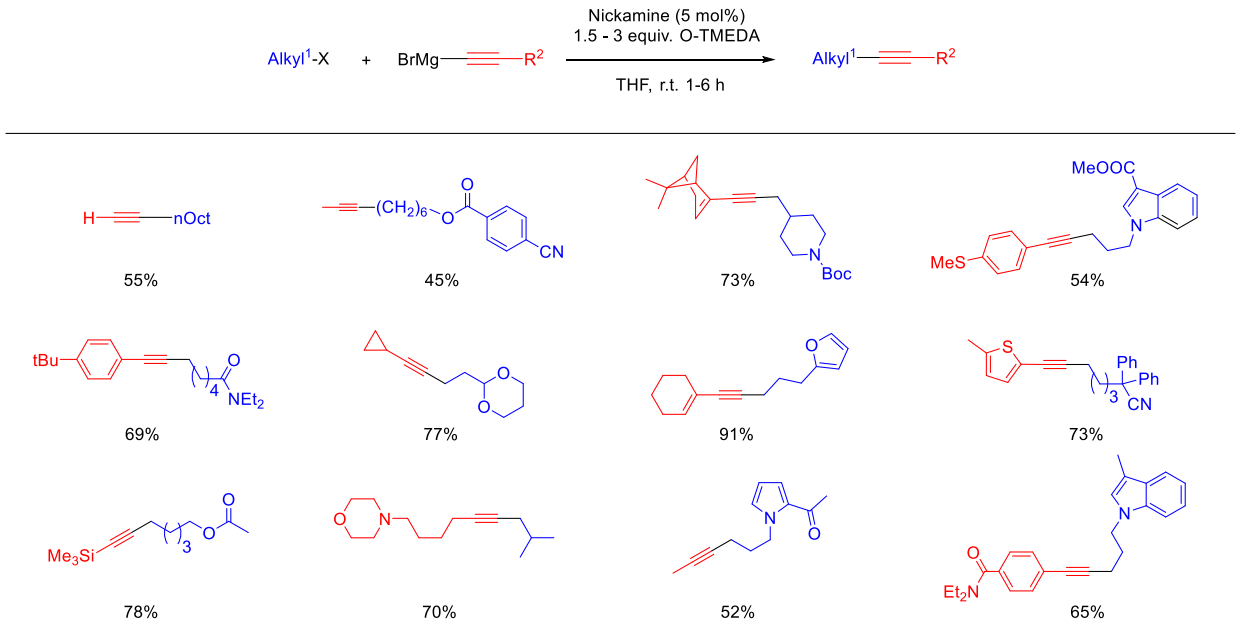


Figure 6. Selected scope of Nickamine-catalyzed alkyl-alkynyl Kumada coupling

The use of Grignard reagents might be inconvenient for some circumstances. Direct C(sp)-H alkylation, using termial alkynes as reagents analogous to Sonogashira coupling, would be an attractive alternative. Prior to our work, there were only two Pd-based protocol for such transformations.[34,37] We found Nickamine to be an excellent catalyst for the direct coupling of primary alkyl halides with terminal alkynes (Figure 7).[38] A simple Cu co-catalyst, CuI, promoted the coupling probably by forming a Cu-alkynyl intermediate. The substrate scope was good. Alkyl iodides, bromides, and chlorides were all suitable electrophiles, but they demand slightly different conditions. For coupling of alkyl bromides, a 20% NaI additive was necessary to in-situ exchange alkyl bromides into alkyl iodides; for coupling of alkyl chlorides, a 20% nBu_4NI was necessary for the same purpose and the reaction temperature needed to be increased from 100 °C to 140 °C. This feature was used to develop sequential coupling of substrates containing more than one type of alkyl-X bond (eqs 5-7, Figure 7).

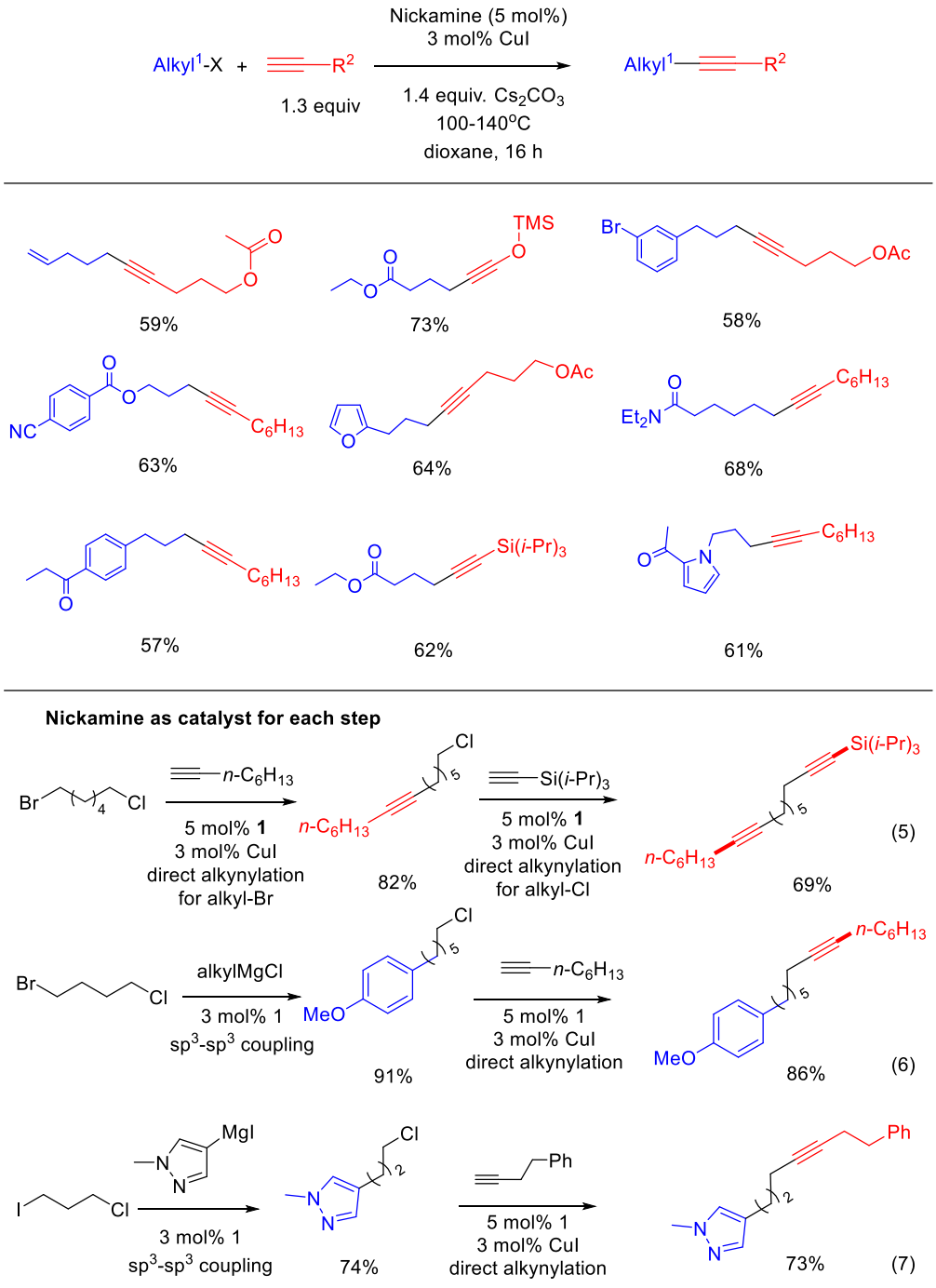


Figure 7. Selected scope of Nickamine-catalyzed direct alkylation of terminal alkynes and orthogonal cross coupling.

3. Mechanistic studies using Nickamine

The mechanistic understanding of cross-coupling reactions of alkyl halides had been limited due to the complexity of these reactions. Moreover, many catalytic systems were composed of mixtures of various Ni salts and ligands, leading to ambiguity in catalytic species. We thought that Nickamine might facilitate the mechanistic studies as we could isolate and test multiple intermediates.

For Nickamine-catalyzed alkyl-alkyl Kumada coupling, reactivity study of presumed intermediates suggested the following simplified reaction sequence (eqs. 8-9): Nickamine first reacted with an alkyl Grignard reagent to form a Ni(II)-alkyl species, which reacted with an alkyl halide to give the coupling product and a Ni-halide species. The latter underwent transmetallation similar to Nickamine to give the Ni(II)-alkyl species again.[20,21]

$$[(^{Me}N_2N)\text{Ni-Cl}] + \text{alkyl}^1\text{-MgCl} \longrightarrow [(^{Me}N_2N)\text{Ni-alkyl}^1] + MgCl_2 \quad (8)$$

$$[(^{Me}N_2N)\text{Ni-alkyl}^1] + \text{alkyl}^2\text{-X} \longrightarrow [(^{Me}N_2N)\text{Ni-X}] + \text{alkyl}^1\text{-alkyl}^2 \quad (9)$$

The coupling of alkyl halides often involves alkyl radicals as intermediates. We had obtained plenty of circumstantial evidence for radical intermediates in Nickamine-catalyzed reactions, for example, by using radical probe substrates such as those containing a pendant cyclopropyl or olefin group.[21] The diastereoselectivity in the coupling of 1, 3- and 1, 4-substituted cyclohexyl halides was also consistent with the formation of cyclohexyl radicals.[24] Nevertheless, non-radical, "organometallic" sequences might give similar outcomes in reactions of radical-probe substrates. A more definitive support for a radical mechanism was obtained in the coupling of a deuterium-labelled radical-probe substrate, **6D** (eq. 10, Figure 8).[39] In a radical mechanism, the insertion of the initial alkyl radical into exo-position of the olefin would give both R and S stereoisomers, and

the following coupling would also give both R and S isomers (Figure 8). The net result is the formation of two diastereoisomers. On the contrary, a concerted "organometallic" mechanism would give only one diastereoisomer. It was found that the actual coupling yielded two diasteroisomers, which confirmed the radical mechanism.

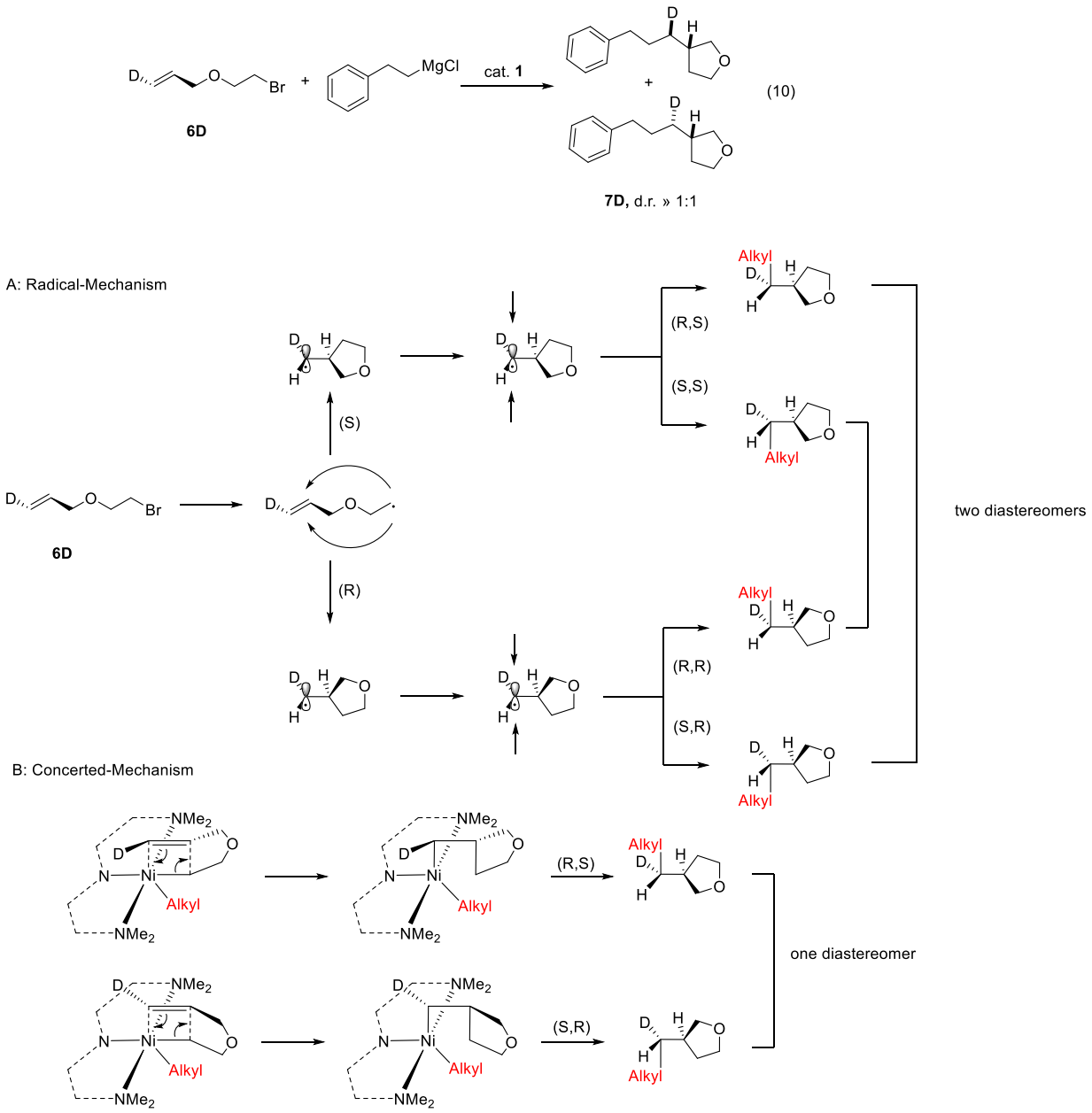


Figure 8. Test for radical intermediates. Reproduced with permission from Ref. 39. Copyright (2013) American Chemical Society.

The C-C coupling step was then subjected to a detailed investigation. At the outset, we considered three reaction pathways (Figure 9).[39] The common first step is the activation of an alkyl halide by a Ni(II) alkyl species (**8**) through a single-electron transfer, resulting in an alkyl radical and an oxidized nickel complex (formally Ni(III); **9**). In a "classic" cage-rebound mechanism (path I) the alkyl radical remains in the solvent cage and recombines with the oxidized nickel complex to give a bis(alkyl) nickel complex (formally Ni(IV); **10**). Reductive elimination from the latter gives the coupling product and a nickel(II) halide complex (**11**), which can re-enter the catalysis through transmetallation. In a bimetallic oxidative addition mechanism (path II), the alkyl radical escapes from the solvent cage and recombines with a second molecule of the nickel(II) alkyl species to give a nickel(III) bis(alkyl) species (**12**). Reductive elimination from **12** gives to the coupling product and a nickel(I) species (**13**), which reacts quickly with **9** to give **8** and **11** through rapid electron-transfer. The third mechanism, called "escape-rebound" (path III), is a twist from the above two mechanisms. Here the alkyl radical escapes from the solvent cage as in the bimetallic oxidative addition mechanism before recombining with the oxidized complex (**9**) as in the cage-rebound mechanism to form the formally Ni(IV) bis(alkyl) intermediates (**10**). The latter reductively eliminates the coupling product to give the Ni(II) halide species (**11**).

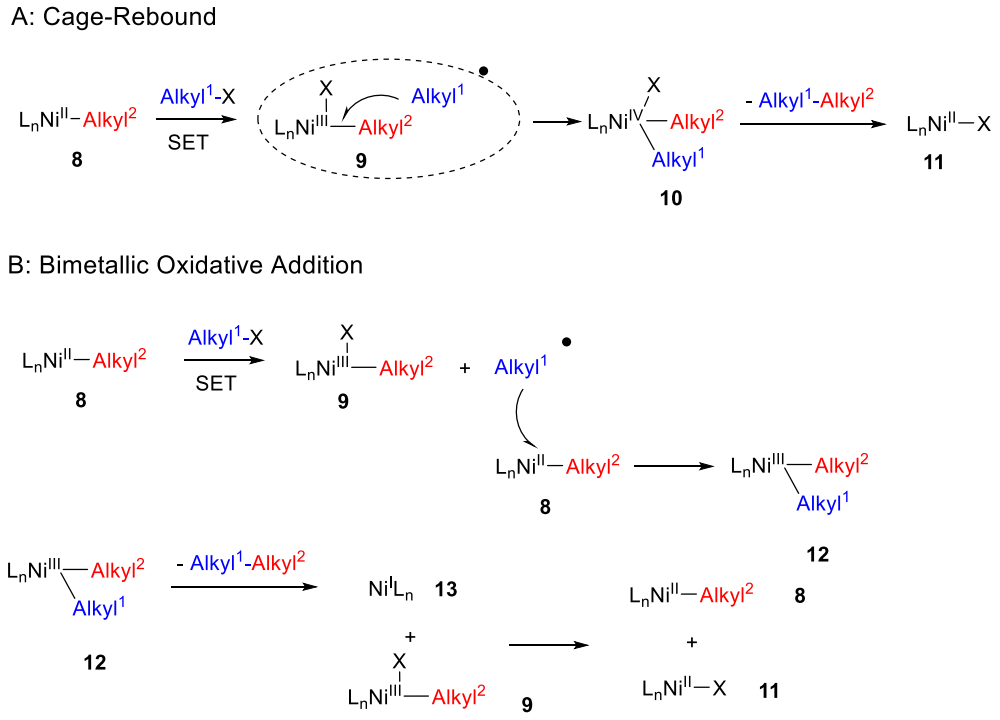


Figure 9. Three possible radical mechanisms for Nickamine-catalyzed alkyl-alkyl Kumada coupling. Reproduced with permission from Ref. 39. Copyright (2013) American Chemical Society.

To differentiate these three mechanisms, the coupling of a radical-clock substrate 3-(2-bromoethoxy)prop-1-ene (**14**) with ^{n}BuMgCl was carried out (Figure 10). The ratio of **17**/**18** was first-order in the loading concentration of the catalyst. This result was inconsistent with a cage-rebound mechanism, which would produce a constant ratio of **17**/**18** regardless of the loading of the catalyst.

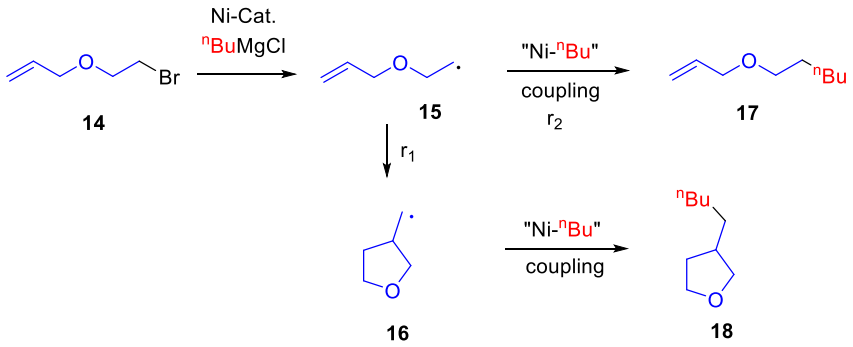


Figure 10. Coupling reaction of a radical-probe substrate. Reproduced with permission from Ref. 39. Copyright (2013) American Chemical Society.

Density functional theory (DFT) computations were conducted to compare the energetics of bimetallic oxidative addition and escape-rebound mechanisms. The results indicate that the combination of an alkyl radical with a Ni(II) alkyl species is exergonic and barrierless, while the combination of the same alkyl radical with a Ni(III) alkyl halide species is endergonic and has a large transition state barrier. Thus, the bimetallic oxidative addition mechanism is favored. Adding to the support of a bimetallic oxidative addition mechanism is a reactivity study which confirms the possibility of the combination of an alkyl radical with an isolated Ni(II)-alkyl species to give an alkyl-alkyl coupled product. Last but not least, during catalysis the concentration of the Ni(II) alkyl species is much higher than that of the Ni(III) alkyl halide species, again favoring the bimetallic oxidative addition mechanism.

Surprisingly, the active Ni(II) alkyl intermediates turned out not to be the initially proposed, isolable [(N_2N)Ni-alkyl] species. [(N_2N)Ni-alkyl] was capable of cross-coupling an alkyl halide, but the rate was slower than the reaction catalyzed by Nickamine. According to a reactivity study, the kinetically relevant species was the doubly alkylated species [(N_2N)Ni-alkyl](alkylMgCl). This species is thermodynamically less stable than its two individual components so its presence cannot be directly detected. The two alkyl groups of [(N_2N)Ni-alkyl](alkylMgCl) could not

exchange at the timescale of the catalysis. The [(N_2N)Ni-alkyl](alkylMgCl) species' enhanced reactivity presumably originates from a more "anionic", electron-rich character compared to the [(N_2N)Ni-alkyl] species.

A painstaking kinetic study showed that the alkyl-alkyl Kumada coupling catalyzed by Nickamine was zero-order in alkyl halide, first-order in catalyst, and second-order in Grignard reagent. The kinetics indicated a turnover determining transmetallation step to produce the active [(N_2N)Ni-alkyl](alkylMgCl) species. This step should be second-order in Grignard reagent, which was supported by kinetic measurements of the stoichiometric transmetallation of Nickamine.

Taking all above results together, a complete catalytic cycle could be proposed (Figure 11). Nickamine, or a halide analogue, reacts with an alkyl Grignard reagent to give [(N_2N)Ni-X](alkylMgCl) in a pre-equilibrium (step i). The latter reacts with another molecule of the alkyl Grignard reagent to give [(N_2N)Ni-alkyl](alkylMgCl) (step ii), which is in equilibrium with the less reactive and isolable [(N_2N)Ni-alkyl] (step iii). [(N_2N)Ni-alkyl](alkylMgCl) then activates an alkyl halide in a bimetallic oxidative addition mechanism described above (step iv-vii) to give the coupling product and a Ni(II) halide species, which re-enters the catalytic cycle by transmetallation.

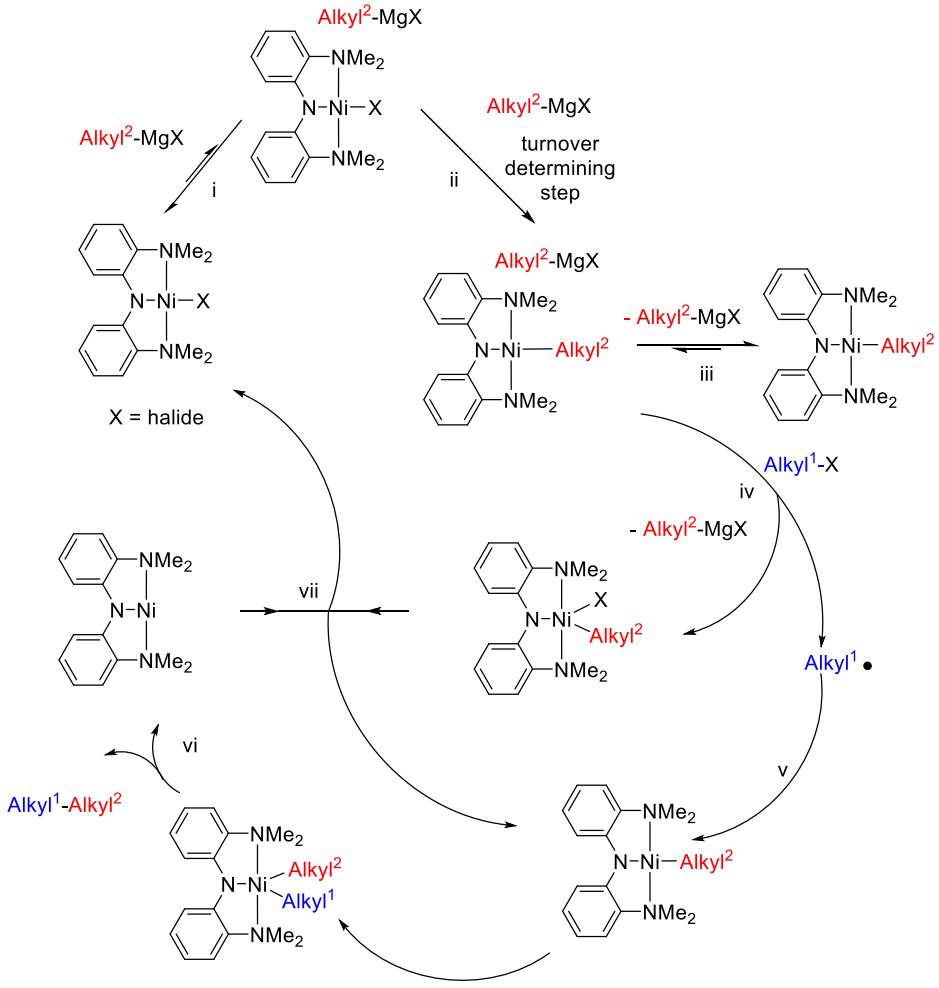


Figure 11. A proposed catalytic cycle for Nickamine-catalyzed alkyl-alkyl Kumada coupling. Reproduced with permission from Ref. 39. Copyright (2013) American Chemical Society.

A follow-up study indicated that a similar mechanism operated for the alkyl-aryl Kumada coupling catalyzed by Nickamine.[40] Again a doubly transmetallated species, [(N_2N)Ni-aryl](arylMgCl), was identified as the key intermediate to activate alkyl halides. Thus, a unified reaction pathway existed in Nickamine-catalyzed coupling reactions of alkyl halides.

4. Ligand development for improved catalysts

The success of Nickamine in the coupling reactions motivated us to develop a next generation of catalysts that overcome its limitations. Our approach was hypothesis-driven ligand design followed by structure-activity studies. We used pre-formed, defined Ni complexes as catalyst candidates to avoid having multiple, unidentified catalyst species.

One of the main limitations in substrate scope for Nickamine is the low efficiency for the coupling of secondary alkyl halides. Only some cyclic secondary alkyl halides were suitable substrates. This limitation is attributed to the steric bulkiness of acyclic secondary alkyl halides, which is problematic for Nickamine which has a rigid pincer ligand. To overcome this limitation, we explored Ni complexes bearing a bidentate mixed amino-amine (NN) ligand (**19-22**, Figure 12).[41] The idea behind this design was that these complexes would be sterically more tolerating. Initially we just wanted an analogue of Nickamine like **22**. It turned out the coordination chemistry of Ni with bidentate ligands was much harder to control, and it took a lot of time before we were able to isolate defined Ni-NN complexes. The positive outcome of this endeavor was that we had a series of complexes with different steric properties, coordination geometries, and spin states (Figure 12). We used two simple alkyl-alkyl Kumada coupling reactions of a cyclic and an acyclic secondary alkyl iodide as the test reactions to compare their catalytic efficiency (Figures 12 and 13). The study showed that a nickel complex (**19**) without a transmetallation site, typically a Ni-halide bond, was completely inactive. All Ni complexes with a Ni-halide bond exhibited some activity. The catalyst needed not to be four-coordinate. For example, 5-coordiante complex **20** had modest activity. Spin did not seem to matter neither, as both low-spin square planar and high spin, 5-coordinate or tetrahedral complexes were active. Overall 4-coordinate Ni-NN complexes were more efficient, and the best catalysts were **21** or **22**, depending on the substrates (Figure 13). These

two catalysts could be used to cross-couple a range of other secondary alkyl halides. Their higher activity compared to Nickamine was attributed to the fact that the fourth ligand, PPh_3 or 2, 4-lutidine, dissociated from the Ni center during catalysis to create 3-coordinate species whose Ni center was more accessible for a bulky substrates. Inhibition study supported this hypothesis.

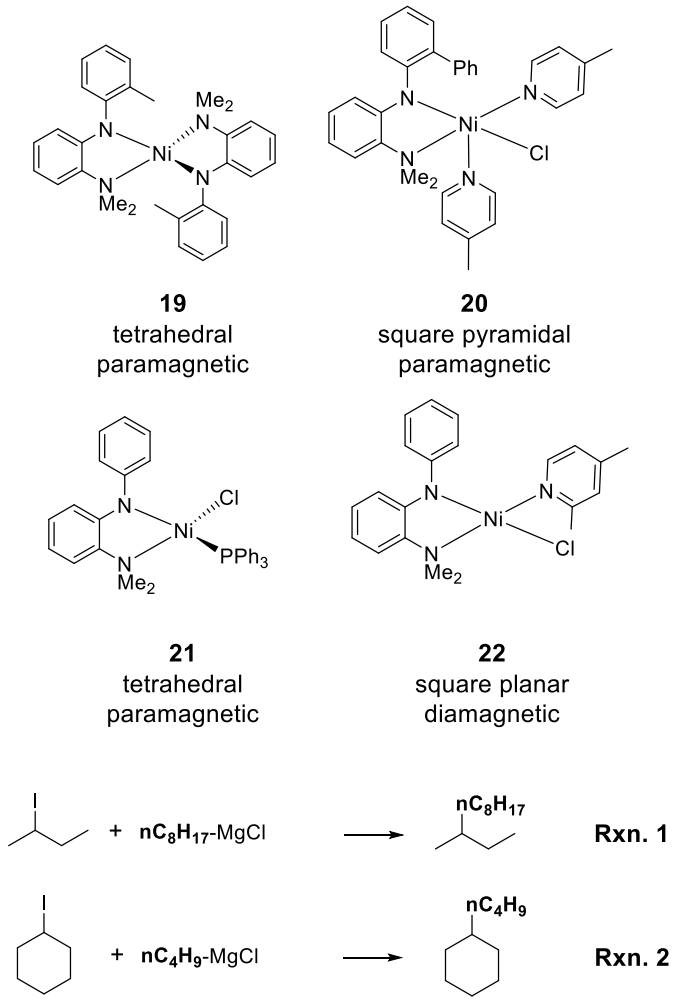


Figure 12. Selected examples of Ni complexes supported by a bidentate NN ligand and the test reactions for their catalytic activity.

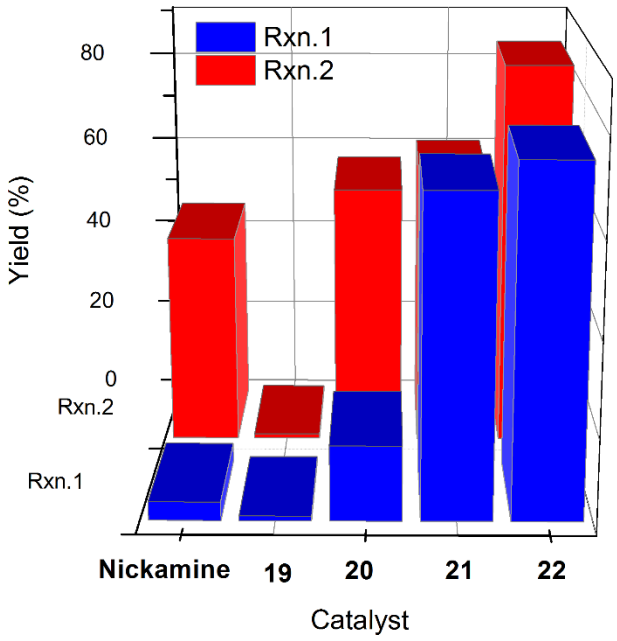
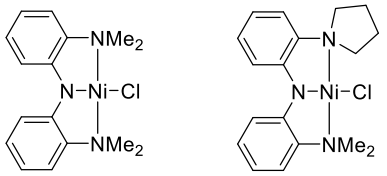


Figure 13. Catalytic activity of selective Ni-NN complexes in comparison to Nickamine.

While the improvement in the coupling of bulky substrates using complexes with bidentate ligands was somewhat expected, we were surprised by the finding that replacement of dimethylamine by pyrrolidine in Nickamine led to a new catalyst with much improved efficiency in the coupling of secondary alkyl halides (Figure 14).[42] This ligand modification was originally made in an unrelated project where our goal was to attach a chiral pyrrolidine moiety in the pincer N_2N ligand for enantioselective cross-coupling. That adventure is fruitless until the present day, producing humbling experience along with much agony. Anyway, when exploring synthetic routes to the designed chiral complexes, we prepared **23** as a model and tested its catalytic activity for the coupling of secondary alkyl halides, substrates of interest for enantioselective coupling. Unexpected, not only cyclic secondary alkyl halides, but also acyclic alkyl halides were coupled. The catalyst was efficient for both Kumada and Suzuki coupling. Notably in Suzuki coupling the

reactions could take place at room temperature, in contrast to a high temperature (< 80 ºC) required when using Nickamine as catalyst.[42]



Nickamine (1) **23**

Figure 14. Comparison of the structures of Nickamine and complex **23**.

Table 1. Comparison of Catalytic Efficiency in Kumada Coupling of Secondary Alkyl Iodides. Reproduced with permission from Ref. 42. Copyright (2016) American Chemical Society.

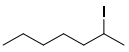
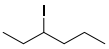
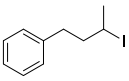
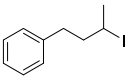
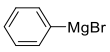
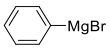
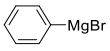
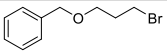
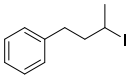
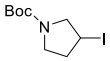
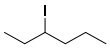
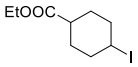
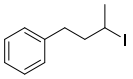
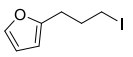
Entry	Alkyl Halide	Grignard Reagent	Yield using **1** (%)	Yield using **23** (%)
1		*n*-Octyl-MgCl	Trace	87
2		*n*-Octyl-MgCl	Trace	50
3		*n*-Octyl-MgCl	Trace	70
4		*n*-Butyl-MgCl	Trace	78
5			Trace	60
6			5	50
7			18	62

Table 2. Comparison of Catalytic Efficiency in Suzuki Coupling of Secondary Alkyl Iodides. Reproduced with permission from Ref. 42. Copyright (2016) American Chemical Society.

Entry	Alkyl Halide	R-(9-BBN)	Yield using **1** (%)	Yield using **23** (%)
1		*n*-Octyl	23	83
2		*n*-Octyl	9	93
3		*n*-Octyl	Trace	68
4		*n*-Octyl	9	53
5		*n*-Octyl	31	86
6		Phenyl	0	59
7		Phenyl	13	83

The drastically improved catalytic efficiency of **23** compared to Nickamine (Tables 1 and 2) was remarkable given the structural and electronic similarities, as revealed by X-ray crystallography and cyclic voltammetry. The catalysis using **23** was significantly inhibited when an exogenous ligand (lutidine, pyridine, or PPh_3) was added to the reaction medium. This result suggests that the pyrrolidino group in **23** is much more "hemilabile" than the dimethylamine group in Nickamine and readily de-coordinate from the Ni center to create a more accessible reaction site.

A follow-up study probed the structure-activity relationship of a series Ni-NNN complexes having one or two cyclic alkyl amine donors (Figure 15).[43] These complexes have no major structural difference except having different C–N–C and '*pseudo'* bite angles. They performed

quite differently in alkyl-alkyl Kumada and Suzuki cross-coupling reactions. But the activity showed no obvious correlation with the redox potential, Lewis acidity (as measured by ^{1}H-NMR data of Ni-NCCH$_3$ complexes), or C-N-C angle of the complexes. This result underlines the complexity of catalyst design even using defined metal complexes. The efficiency of a catalytic process with multiple elementary steps depends on many factors such as catalytic stability, reaction barriers of all steps, and viable reaction pathways. Changing one property of a catalyst might result in a change in more than one of these factors, making non-linear overall change in efficiency.

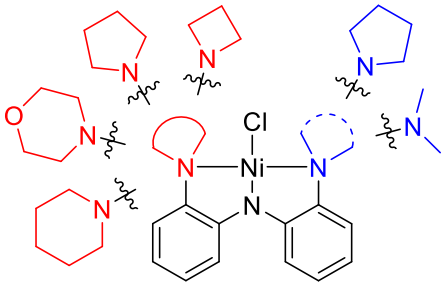


Figure 15. A series of Ni-N$_2$N pincer complexes for structure-activity study in cross coupling reactions.

In another approach to create a more "hemilabile" pincer ligand, we replaced one of the two aryl linkers of the N$_2$N ligand in Nickamine by a more flexible ethylene linker (Figure 16).[44] The resulting Ni-Cl complex **24** behaved similar to Nickamine in Kumada coupling reactions. However, a significant difference was found in their catalytic efficiency for direct alkylation of terminal alkynes. While Nickamine catalyzed this coupling at 100-140 °C, **24** catalyzed the coupling at room temperature. The mild conditions facilitated a kinetic study, which confirmed the "hemilabile" nature of the new pincer ligand (Figure 16). The de-coordination of an amine donor from a catalytic intermediate allows the activation of primary alkyl halides at room temperature.

A Ni(II) bis(acetylide) species (**27**), instead of the isolable Ni-alkynyl complex (**25**), was the intermediate that activated alkyl halides.

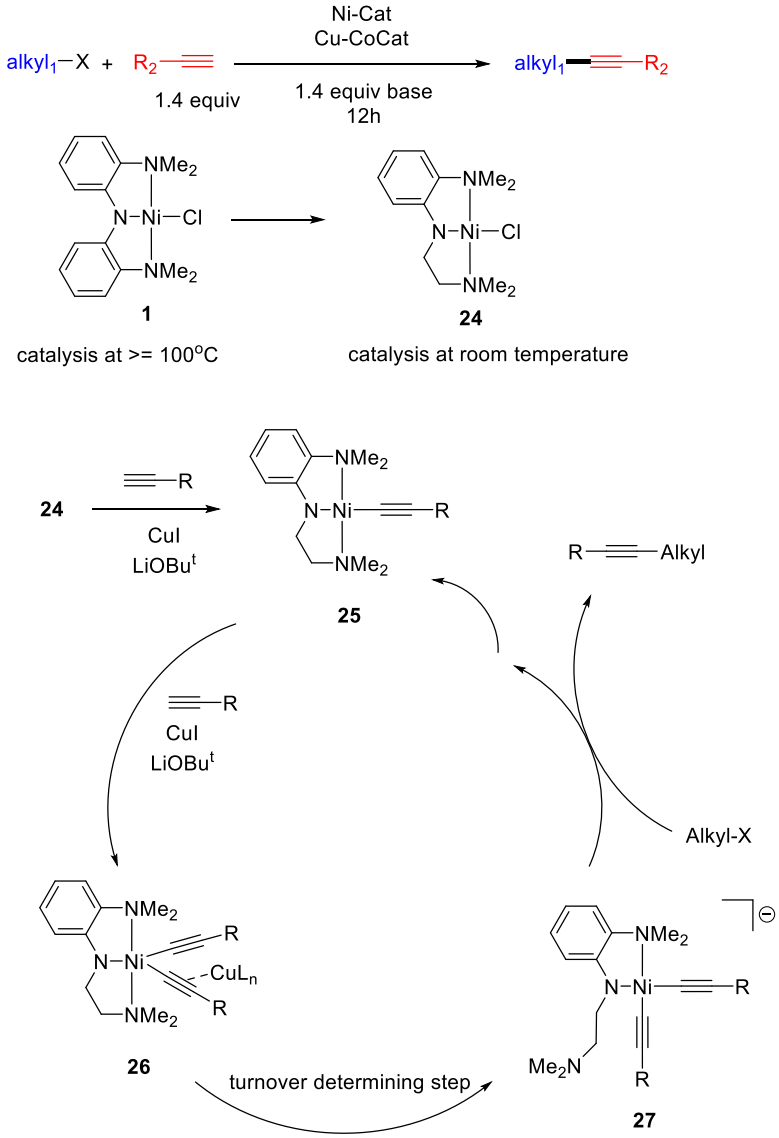


Figure 16. A "hemilabile" Ni pincer complex with improved activity for direct alkylation of terminal alkynes and its proposed catalytic cycle.

5. Hydrosilylation of alkenes catalyzed by nickel pincer complexes

Transition metal catalyzed hydrosilylation of alkenes[45-52] is an efficient and atom economic method to synthesize organosilicons, which have many industrial applications.[45,49,52] Platinum-containing catalysts[53,54] are very efficient for hydrosilylation, but they are expensive and based on a rare metal.[55] The development of base metal catalysts[51,56,57] for hydrosilylation has become an active area of research.

During our studies of Nickamine-catalyzed cross-coupling reactions, we were interested in the synthesis and reactivity of [($^{Me}N_2N$)Ni-H], a presumed product after β-H elimination from a Ni(II)-alkyl species.[58] We found that this hydride species could be cleanly generated by reaction of a Ni(II) alkoxide species, e.g., [($^{Me}N_2N$)Ni-OMe], with a silane.[59] The Ni(II) hydride inserted into an olefin much quicker than into a ketone, suggesting chemoselectivity towards non-polar double bonds.

Since metal hydride species are often invoked as intermediates in alkene hydrosilylation, we explored Nickamine and its alkoxide analogous as catalysts. Indeed these complexes were very active, and the most convenient catalyst was [($^{Me}N_2N$)Ni-OMe] which worked under base-free conditions.[60] A turnover number of up to 10000 and a turnover frequency of up to 83000 h^{-1} was achieved. The reactions were *anti*-Markovnikov for terminal alkenes (Figure 17). Not only epoxide, bromo, ester, amine, and amide groups, but also highly reactive ketone and aldehyde groups were tolerated. With internal alkenes as substrates, a tandem alkene isomerization and hydrosilylation occurred to give terminal, *anti*-Markovnikov products.

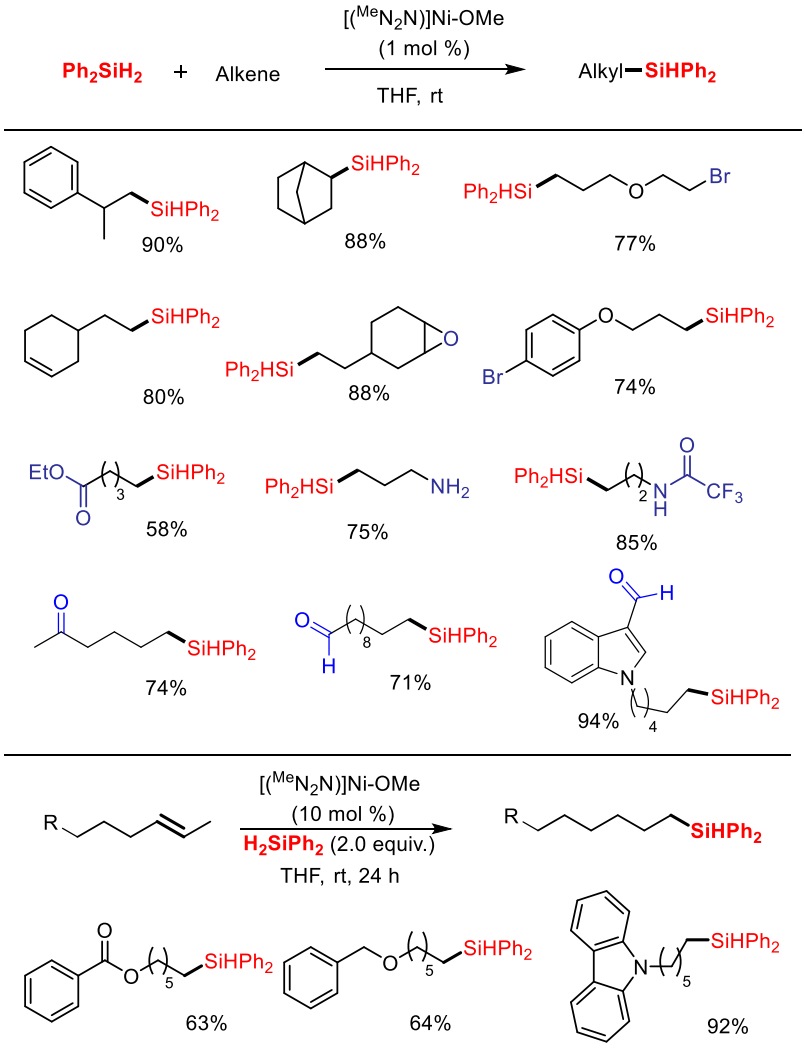


Figure 17. Alkene hydrosilylation catalyzed by a derivative of Nickamine.

When testing other nickel pincer complexes for alkene hydrosilylation, we obtained an unexpected finding using the Ni(II) amido(bisoxazoline) complex **28** as catalyst. In the presence of a catalytic amount of base such as NaO^{t}Bu, **28** catalyzed the hydrosilylation of alkenes with alkoxy hydrosilanes, $Me_2(MeO)SiH$, $Me(MeO)_2SiH$ and $(MeO)_3SiH$, to give alkyl hydrosilanes instead of alkoxy silanes (Figure 18).[61] The net result was that readily available alkoxy hydrosilanes served as safe surrogates of gaseous silanes including Me_2SiH_2, $MeSiH_3$ and SiH_4, which were flammable and inconvenient to handle. A preliminary mechanistic study indicated that

the unusual hydrosilylation occurred by base-catalyzed disproportionation of two alkoxy silanes to give a dihydrosilane followed by conventional hydrosilylation with this dihydrosilane. Thanks to the rapid hydrosilylation step, no buildup of dihydrosilane was observed.

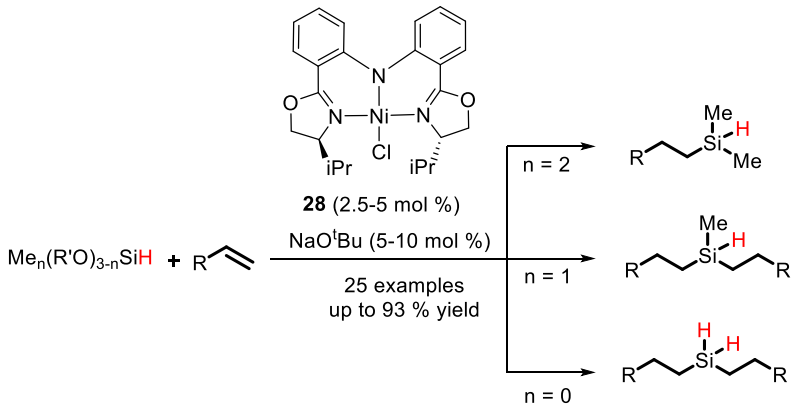


Figure 18. Hydrosilylation of alkenes with alkoxy hydrosilanes to give alkyl hydrosilanes.

6. Conclusion

Driven by a curiosity over all-nitrogen-containing pincer ligands, we made Nickamine. Ten years later, Nickamine is proven not to be just another pincer complex. It is a catalyst in a remarkably broad range of cross-coupling reactions of alkyl halides. It enabled functional-group-tolerant Kumda coupling which was at odds with the common perception at the time. Nickamine also facilitated mechanistic studies which revealed a bimetallic oxidative addition mechanism ubiquitous for many base-metal-catalyzed cross-coupling reactions of alkyl halides. It set the basis for rational designs of next generation catalysts which exhibited improved efficiency for particular reactions or substrates. By summarizing our journey, we hope to advocate for curiosity-driven ligand development as a creative supplement to the increasingly popular screening approach in

catalysis. The application of Nickamine and analogues in hydrosilylation reactions suggests that more are yet to come for these catalysts.

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BIOGRAPHICAL INFORMATION

Renyi Shi was born in 1988 in Jiangsu Province, China. He obtained a Bachelor's Degree in 2011 from Nanjing University, China and a PhD degree in 2016 from Wuhan University, China. His PhD work was conducted under the supervision of Prof. Aiwen Lei. He joined in 2017 Prof. Xile Hu's group at EPFL, Switzerland as a postdoctoral fellow. His research interests focus on bio-mimetic and bio-speculated coordination chemistry and base metal catalysis.

Zhikun Zhang was born in 1990 in Jiangsu Province, China. He obtained a Bachelor's Degree in 2012 from Lanzhou University, China. He completed a PhD study in 2017 at Peking University, China, under the guidance of Prof. Jianbo Wang and Prof. Yan Zhang. In the same year, he joined Prof. Xile Hu's group at EPFL, Switzerland as a postdoctoral fellow. His research interest is asymmetric catalysis using base metals in both homogeneous and heterogeneous systems.

Xile Hu was born in 1978 in Putian, Fijian Province, China. He received a B.S. degree from Peking University (2000; advisor: Prof. Jianhua Lin) and a Ph.D. degree from the University of California, San Diego (2004; advisor: Prof. Karsten Meyer). He carried out a postdoctoral study at the

California Institute of Technology (advisor: Prof. Jonas Peters) before joining the faculty of the École Polytechnique Fédérale de Lausanne (EPFL) as a tenure-track assistant professor in 2007. He was promoted to associate professor in January 2013 and full professor in June 2016. He directs an interdisciplinary research program to develop catalysis for sustainable synthesis of added-value chemicals and for cost-effective production of solar fuels. His group is unifying concepts and methods in homogeneous, heterogeneous, and enzyme catalysis to obtain fundamental understanding of catalysis and novel catalysts.

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