Tetrahedron 128 (2022) 133135

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Pd-catalyzed functionalization of alkenes and alkynes using removable tethers

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ARTICLE INFO

Article history:
Received 9 May 2022
Received in revised form
30 October 2022
Accepted 2 November 2022
Available online 5 November 2022

Keywords:
Pd catalysis
Alkenes
Alkynes
Tethers
Asymmetric synthesis

ABSTRACT

The palladium-catalyzed functionalization of alkenes is a versatile transformation in synthetic chemistry, but intermolecular processes often suffer from low reactivity and selectivity. Molecular tethers can be introduced to answer these challenges. They have been used successfully for decades, but their installation and removal normally required multi-step procedures. In this review, we will present progress in this area resulting in more efficient tethering processes. We will start with a brief overview of carbamate- and sulfone-based tethered functionalization of allylic alcohol and amine derivatives. Then the recent development of tethers that can be installed *in situ* on (homo)-allyl/propargyl amines or alcohols for double and triple bond functionalization will be described. The difunctionalization of alkenes and alkynes using trifluoro acetaldehyde based tethers developed by our group will be covered in more details. Finally, we will introduce the concept of tethers as catalytically formed chiral auxiliaries for asymmetric synthesis.

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1. Introduction

The palladium-catalyzed functionalization of alkenes is a versatile transformation in synthetic chemistry, but intermolecular processes often suffer from low reactivity and selectivity. When compared to intermolecular processes, the enhanced reactivity associated with intramolecular reactions is originating mostly from a lower activation entropy. As further advantages, the size and conformation of the produced ring may also be adjusted to regulate regioselectivity and stereoselectivity. However, these advantages come with several drawbacks: Substrate synthesis becomes more complex, requiring multistep sequences and this approach may be limited to cyclic scaffolds with low structural variation, due to the difficulty in modifying the intrinsic regio- or stereoselectivity determined by the ring size.

The use of removable tethers has emerged as a promising method for combining the advantages of intramolecular and intermolecular processes in terms of simplicity, reactivity, and selectivity [1]. In the most common approach, a nucleophilic functionality, such as a hydroxy or an amino group, is required to connect the tether to the substrate prior to intramolecular olefin functionalization. Finally, tether cleavage delivers the desired product (Scheme 1, A). This method needs functionalized raw materials. Given the abundance of numerous alcohols and amines in biomass, this is not a major constraint. As a result, the products obtained through tethering are generally highly functionalized.

The additional synthetic steps necessary to install and remove tethers have reduced their effectiveness. Progress has first been realized by the use of tethers easily introduced in one step, such as carbamoyl or sulfonyl compounds (Scheme 1, **B1** and **B2**). However, these types of tethers required harsh conditions for removal, such as heating in concentrated acid solution or strong reductants ($LiAlH_4$). A further gain in efficiency has then be realized with tethers that can be installed *in situ* onto alcohols or amines. This approach builds on previous advances in the use of removable or non-covalently bound directing groups for the functionalization of olefins or allylation processes [2]. This has been achieved mainly by using CO_2 or an aldehyde as the tether (Scheme 1, B3 and **B4**) [3]. CO_2 is commonly used to access cyclic carbonates or carbamates. In these works, cleavage of the tether has not yet been reported, but the same harsh conditions reported for carbamates obtained using other methods should be applicable. Aldehydes, on the other hand, are promising tethers: 1) Simple aldehydes are inexpensive and abundant; 2) The aldehyde-acetal or aldehyde-aminal equilibrium

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https://doi.org/10.1016/j.tet.2022.133135
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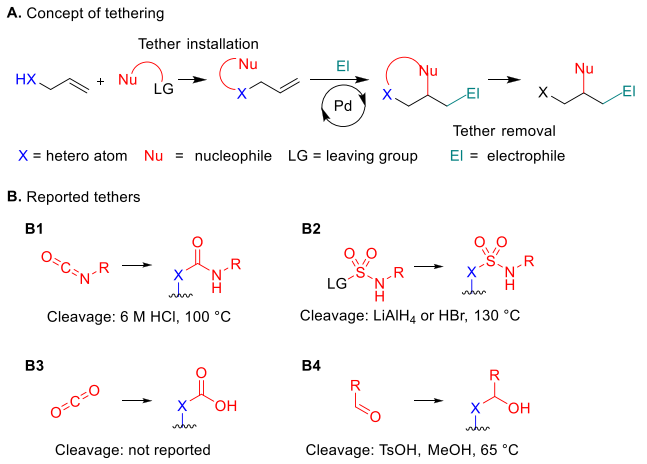


Scheme 1. Concept of tethering and most often used removable tethers.

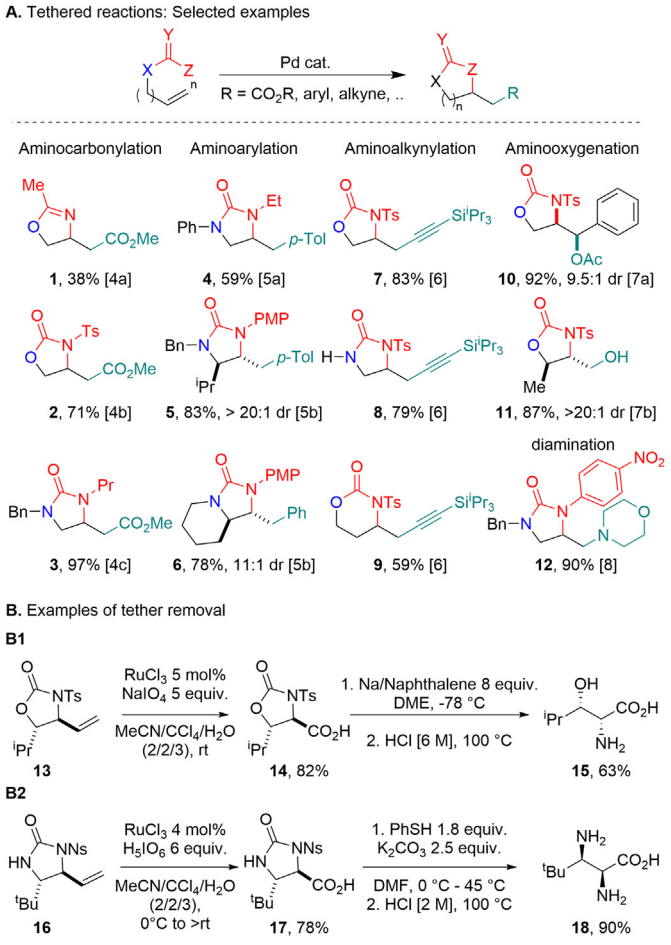
allows for easy tethering and removal. In the case of N,O and N,N acetals, mild acidic condition are sufficient to remove the tether. Nevertheless, the introduction of a new stereocenter on the tether adds a level of complexity to the process.

In this review, we will present recent progress in the area of palladium-catalyzed alkene functionalization using removable tethers. We will start with a brief overview of carbamate- and sulfone-based tethered functionalization of allylic alcohol and amine derivatives. Then the recent development of tethers that can be installed *in situ* on (homo)-allyl/propargyl amines or alcohols for double/triple bond functionalization will be described. The difunctionalization of alkenes and alkynes using trifluoro acetaldehyde based tethers developed by our group will be covered in more details. Finally, we will introduced the concept of tethers as catalytically formed chiral auxiliaries for asymmetric synthesis.

1.1. Carbamate/imidate/urea based tethers

The application of carbamate or imidate-based tethers on alcohols or amines has been first investigated and has resulted in significant advancements in alkene difunctionalization reactions. This type of tethers is easily installed through the use of broadly available reagents such as isocyanates or cyanides. As selected examples of useful transformations developed using this tethering strategy, aminocarbonylation [4], aminoarylation [5], aminoalkynylation [6], aminooxygenation [7] and diamination [8] can be mentioned (Scheme 2, A). The rich diversity of products that can be obtained is based on the fact that the intermediate alkyl-palladium species can undergo either CO insertion, reductive elimination to form a C–C bond, or oxidative functionalization in presence of suitable oxidants (peroxides or hypervalent iodine based reagents like PIDA or Ethynylbenziodoxolones (EBXs)) to give highly functionalized building blocks such as esters **1**–**3**, arenes **4**–**6**, alkynes **7**–**9** or aminoalcohols and diamines **10**–**12**. Nevertheless, the scope of these transformations remained often narrow.

For carbamate/urea tethers, a further challenge resides in controlling O- vs N- cyclization. This can be often realized by the choice of protecting group on nitrogen. Because of the increased nucleophilicity of the oxygen atom, controlling O vs N cyclization is more challenging for urea-based tethers. In addition, removal of the tethers required harsh conditions. In fact, in most publications cleavage is not described and the heterocycles are presented as the final targets. As a representative example, cleavage of the 2-aminooxazoline tether in **14** was achieved by heating at 100 °C in

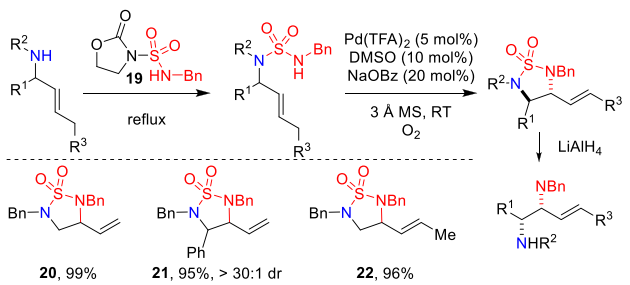


Scheme 2. Overview of transformations using carbamate/imidate/urea-based tethers and representative examples of tether removal.

a solution of 6 M HCl (Scheme 2, B1), while the cyclic urea **17** could be hydrolyzed in a boiling aqueous 2 M HCl solution (Scheme 2, B2) [9]. In both cases, it was required to remove either the tosyl or the nosyl group prior to hydrolysis.

1.2. Sulfone based tethers

Stahl and co-workers developed sulfamide-based tethers as a means of obtaining 1,2- diamines from allylic amines (Scheme 3) [10]. The sulfamide tethers were employed in an oxidative intramolecular aza-Wacker cyclization. The allylic amines can have substituents at the allylic position and on the alkene. The nitrogen introduced via the tether can bear a variety of alkyl, phenyl, and



Scheme 3. Pd-catalyzed aerobic aza-Wacker cyclization with sulfamide tethers.

benzylic groups, delivering sulfamide products such as **20**–**22**. The main limitation of the sulfamide tether is the need for aggressive reductive conditions to cleave the tether and reveal the diamines.

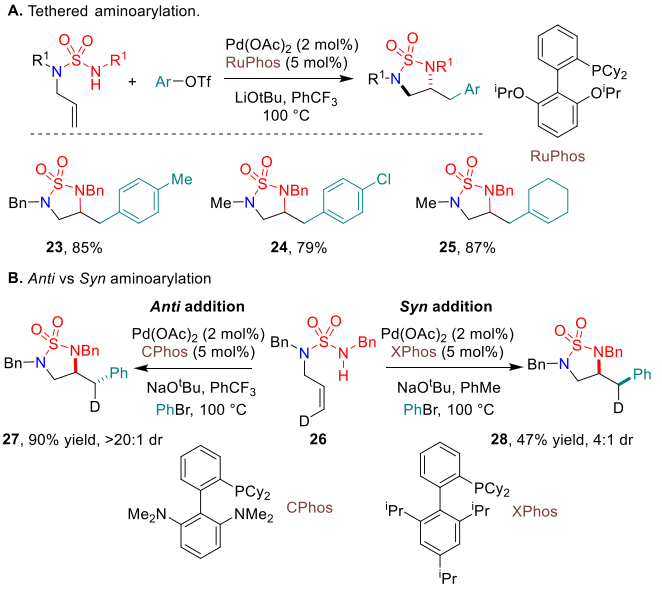
In 2014, the Pd-catalyzed alkene carboamination of *N*-allylsulfamides to give cyclic sulfamides involving aryl electrophiles was reported by Wolfe and co-workers [11] (Scheme 4, **A**). With terminal alkenes, arylation and alkenylation products **23**–**25** were obtained in high yields. However, with the exception of cyclic substrates, 1,2-disubstituted alkenes did not work. To study the stereochemistry of the aminopalladation step, the authors turned to deuterium-labelled allyl amine **26**. They demonstrated that, depending on the reaction conditions, either *syn* or *anti* palladation can be observed (products **27** and **28**) (Scheme 4, B). Many factors influenced the stereochemical outcome of this reaction. Non-coordinating counterions (triflate), biarylphosphines containing electron-donating groups (e.g. CPhos) and polar solvents ($PhCF_3$) preferentially gave the *anti* -addition product. Coordinating counterions (bromide), less polar solvents ($PhCH_3$), and less electron-rich ligands (e.g., XPhos) were employed to get the *syn* addition product, involving in this case neutral palladium intermediates [12].

Wolfe and co-workers demonstrated that similar concepts may be applied to substrates other than sulfonamides [13]. Indeed, under similar reaction conditions, deuterated N-allylurea derivative **29** gave *syn* addition product **30** with comparable selectivity (Scheme 5). Conditions developed for the *anti* carboamination of sulfonamide **26** could also be used for the *anti* carboamination of urea **29** to give compound **31**.

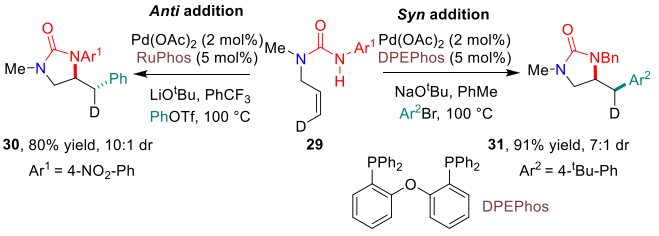
The use of the sulfonamide tether was further extended to an asymmetric transformation using (*S*)-SiPhos-PE as ligand (Scheme 6) [14]. The reaction provided good yields and up to 88% *ee*. Allyl amines with *tert*-butyl as a protecting group such as **32** are required for high enantioinduction. To cleave the sulfamide in product **33**, HBr in phenol at 130 °C was used to give diamine **34**.

1.3. Tether formation with CO_2

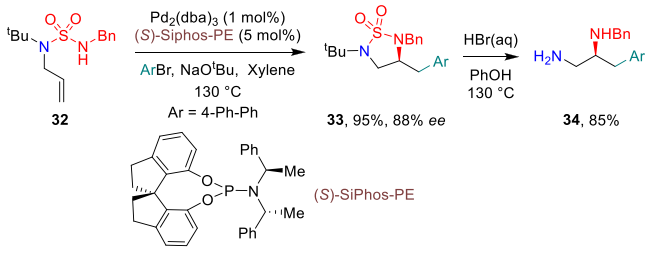
The use of carbon dioxide to generate a tether is highly attractive as it is one of the most broadly available C1 unit. However, the low



Scheme 4. Tethered aminoarylation and deuterium labeling experiments to explore syn vs. anti aminopalladation.



Scheme 5. Deuterium labeling experiments to explore syn vs. anti aminopalladation with urea tethers.



Scheme 6. Palladium catalyzed asymmetric carboamination of allylic amine **32** via a sulfonamide tether.

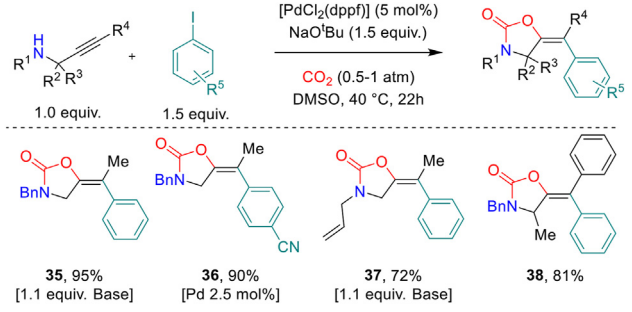
reactivity of CO_2 makes its use limited to the formation of tethers on amines. In particular, propargylic amines can be converted to oxazolidinones in presence of CO_2 under a broad range of conditions, but palladium catalysis has been only rarely used [15,16].

In 2016, Nevado and co-workers reported the first palladium-catalyzed *trans* oxy-arylation of propargylic amines using CO_2 and aryl iodides as electrophiles (Scheme 7) [17]. A broad range of oxazolidinones such as **35**–**38** could be obtained using gaseous CO_2 at atmospheric pressure.

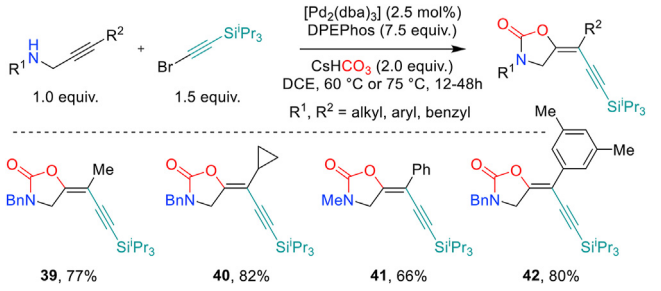
In 2019, our group developed the corresponding oxy-alkynylation reaction (Scheme 8) [18]. Interestingly, cesium hydrogen carbonate could be used directly as carbon dioxide source. *Trans*-substituted electron-rich enynes products **39**–**42** were obtained in 66–82% yield with high selectivity. Although the use of carbon dioxide or carbonates to introduce a tether is highly attractive, it has to be mentioned that cleavage of the tethers in the formed products has not yet been reported.

1.4. Aldehyde based tethers

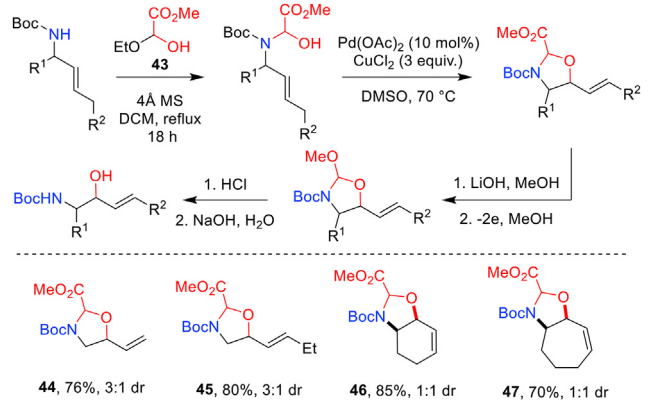
Hiemstra and coworkers were the first to report a Pd-catalyzed Wacker cyclization of hemiaminals in 1992 (Scheme 9) [19]. N-Boc allylamines were heated with aldehyde hemiacetal **43** to access the



Scheme 7. Palladium catalyzed trans oxy-arylation of propargylic amines using CO_2 as tether.



Scheme 8. Palladium catalyzed trans oxy-alkynylation of propargylic amines using CO_2 as tether.

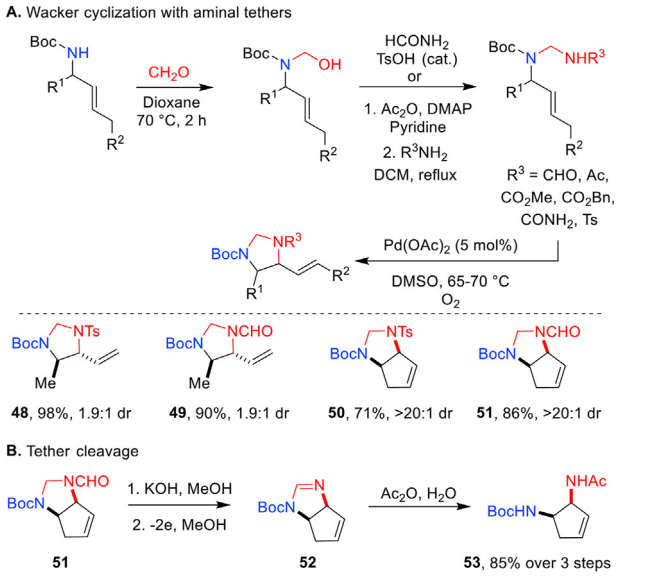


Scheme 9. Synthesis of amino alcohols via the Wacker cyclization of hemiaminals.

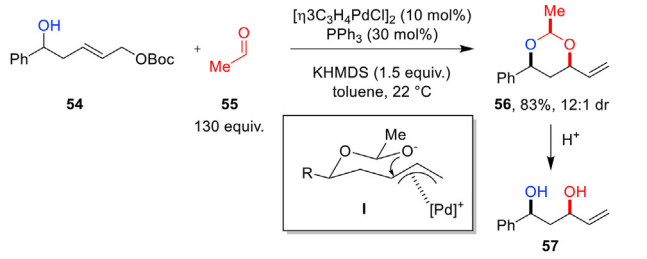
hemiaminal precursors. For acyclic starting materials, oxazolidines such as **44** and **45** were obtained in moderate dr. Cyclic products **46** and **47** were obtained with high *syn* selectivity, but the N,O-acetal center could not be controlled. The tether was cleaved in four steps: the ester was first hydrolyzed, followed by electrochemical oxidation to provide a 2-methoxyoxazolidine derivative. The Boc-protected amino alcohols were then obtained in good yields after acid hydrolysis and basic treatment.

In a follow-up study, the same group demonstrated that molecular oxygen could replace the stoichiometric copper oxidant in the Wacker cyclization, improving the yield [20a]. These conditions were used also for the synthesis of diamines via an aza-Wacker cyclization (Scheme 10, A) [20b]. However, the installation of the aminal tether required two to three steps. A low diastereoselectivity was observed irrespectively of the N-protecting group for acyclic amines (products **48** and **49**), while excellent diastereoselectivities were obtained for the formation of bicyclic diamines such as **50** and **51**. A three-step process was used to cleave the tether (Scheme 10, B). The formyl protecting group on **51** was first cleaved under basic conditions, and subsequent anodic oxidation produced amidine **52**. Finally, after treating amidine **52** with acetic anhydride in water, diamine **53** was obtained in 85% over 3 steps.

After Hiemstra's pioneering work, aldehydes were not used as tethers for a long time, probably because the initially developed approach to install and remove the tether was not efficient enough. However, in the context of palladium catalysis, an interesting Tsuji-Trost reaction employing acetaldehyde (**55**) to form an hemiacetal tether *in situ* was described by Menche and co-workers in 2012 (Scheme 11) [21]. This process converted homoallylic alcohol **54** to *syn* 1,3-diol **56** with good diastereocontrol. The authors proposed that a dynamic kinetic resolution occurred, as the formation of hemiacetal **I** is reversible, to yield the thermodynamically favored



Scheme 10. Synthesis of diamines via an Aza-Wacker cyclization with aminal tethers.



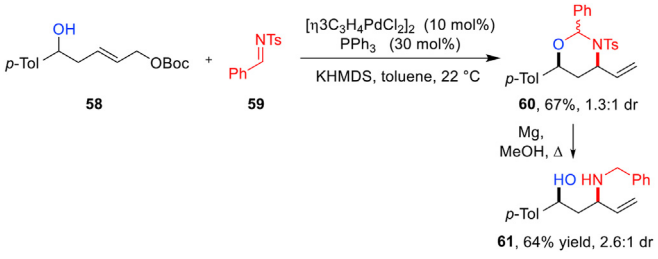
Scheme 11. In situ tethering for Tsuji-Trost type reactions via hemiacetal tether.

all-*syn* product **56**. Although not shown in the article, 1,3-diol acetals may be readily cleaved in presence of acid to yield diol **57** [22].

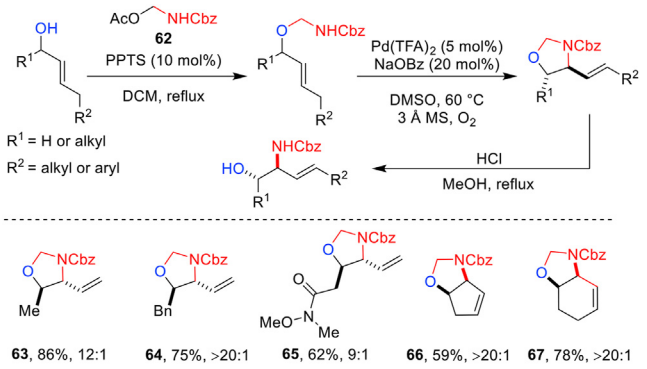
In addition, an allylic amination was also developed via an N,O-acetal tether generated *in situ* by reaction with activated imine **59** (Scheme 12) [23]. A lower diastereoselectivity was observed in this case for the formation of **60**. The tether could be removed to get amino alcohol **61** using Mg/MeOH at reflux.

In 2013, Stahl and co-workers reported a highly diastereoselective aza-Wacker cyclization using N,O-acetals, extending Hiemstra's work (Scheme 13) [24]. The tether was installed on readily available allyl alcohols in a single step using reagent **62**. Products such as **63**–**67** were obtained in 59–86% yield and >9:1 dr with a good functional group tolerance. After treating the cyclic N,O-acetals with an excess of HCl in boiling methanol, free amino alcohols were produced in moderate to good yields.

Our group was interested to apply *in situ* tethering with



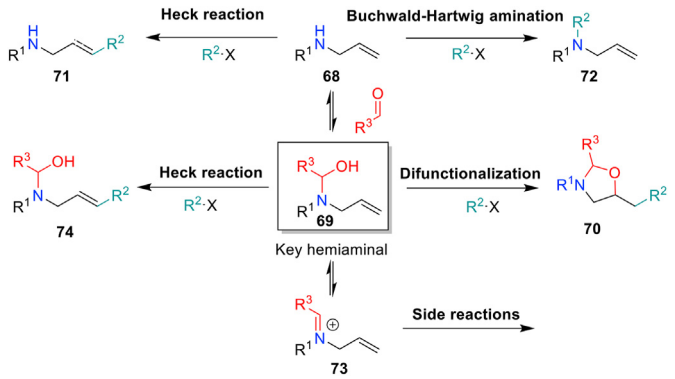
Scheme 12. In situ tethering for Tsuji-Trost type reactions via N,O-acetal tethers.



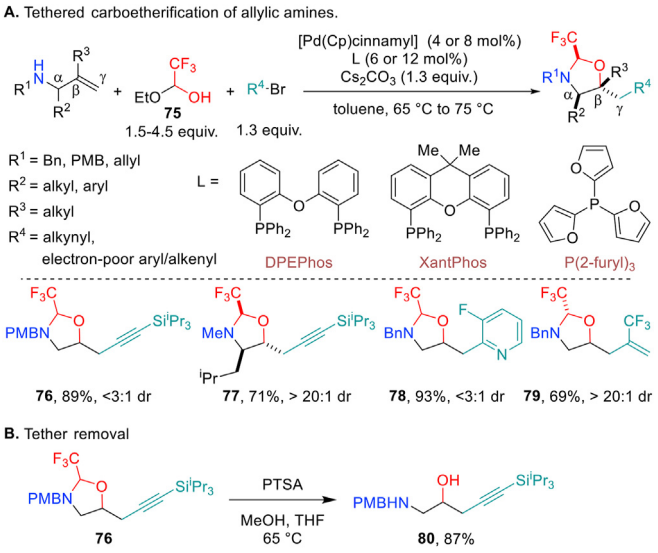
Scheme 13. Aza-Wacker reaction via N,O-acetals.

aldehydes to more complex olefin difunctionalizations (Scheme 14). We postulated that an allylamine **68** and an aldehyde may produce hemiaminal **69** *in situ*, which could then react in a palladium catalyzed carboetherification with an appropriate electrophile to give **70**. In order to achieve this transformation, several side reactions had to be prevented. A quantitative tether formation would be first important to prevent direct Heck reaction and Buchwald-Hartwig coupling to give **71** or **72**, as well as inhibition of the catalyst by the amine. These issues explain probably why there was no example of *in situ* tether formation with aldehydes previous to our work: stoichiometric tether formation and isolation was usually required. In addition, formation of iminium **73** in too large amounts should be avoided, as he could lead to side reactions such as the formation of aminals. Finally, Heck reaction of hemiaminal **69** to give **74** should also be avoided.

In 2015, our group reported the first *in situ* tethering approach for the difunctionalization of alkenes using aldehyde based tethers leading to oxy-alkynylation, -arylation and -alkenylation [25] (Scheme 15). Commercially available trifluoroacetaldehyde derived hemiacetal **75** was used to form a hemiaminal tether. The choice of this particular aldehyde was based on two key considerations: (1) The high electrophilicity of trifluoroacetaldehyde facilitated the rapid condensation with the amine even under basic conditions; (2) The electron-withdrawing character of the CF_3 group made the hydrogen of the hemiaminal OH group more acidic, enabling the use of mild carbonate bases. Electrophilic species such as bromoalkynes or electron deficient aryl and alkenyl bromides could be used to give products such as **76**–**79** (Scheme 15, **A**). Although substituents on the α-and β-positions of the allyl amines were tolerated, ϒ-substituted allyl amines could not be used in this



Scheme 14. Difunctionalization of allylic amines via hemiaminal formation and potential side reactions.

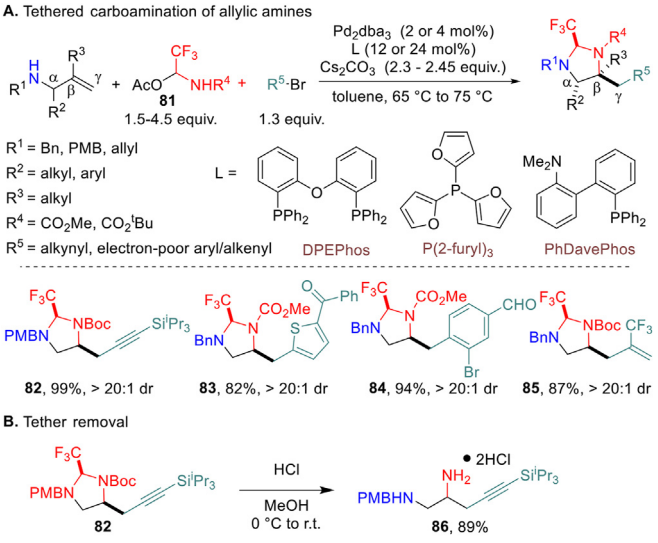


Scheme 15. Synthesis of vicinal amino alcohols via the *in situ* formation of hemiaminal tethers.

transformation. It was important to adjust the ligand on palladium in dependence of the substitution pattern of the allyl amine, with either DPEPhos, XantPhos or P (2-furyl)$_3$ giving the best results. The hydrolysis of the tethered product **76** under mild acidic condition delivered the free amino alcohol **80** in 87% yield, highlighting the ease with which the tether could be removed (Scheme 15, **B**).

This method was extended to diamine synthesis in 2016, whereby carbamate-based N-protected trifluoroaldimine-derived N,O acetals **81** were employed as tether precursors, offering quick access to functionalized diamines (Scheme 16) [26]. A wide range of alkynyl, aryl, heteroaryl and alkenyl groups were successfully introduced to give aminals such as **82**–**85** (Scheme 16, **A**). In most cases, the diastereomeric ratio was higher than 20:1. ϒ-Substituted allyl amines were also not tolerated in this case. Removing the tether from oxazoline **82** together with Boc deprotection was possible under acidic conditions to yield the hydrochloride salt of diamine **86** in 89% yield.

The carbamate tether **81** might be combined with allyl alcohols

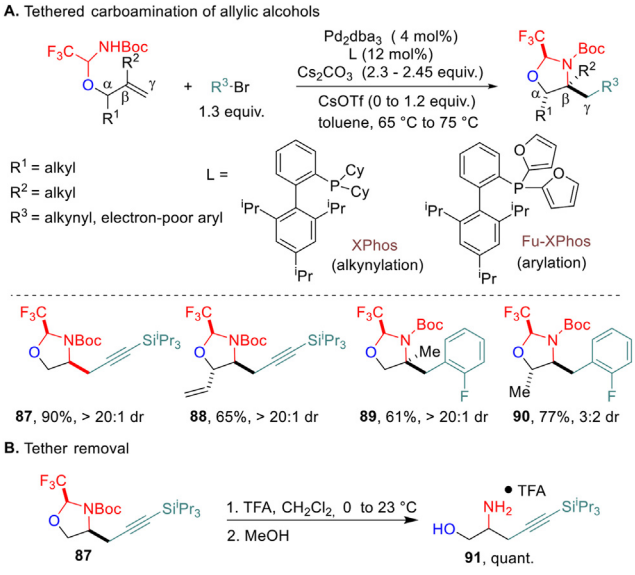


Scheme 16. Synthesis of diamines via the formation of aminal tethers.

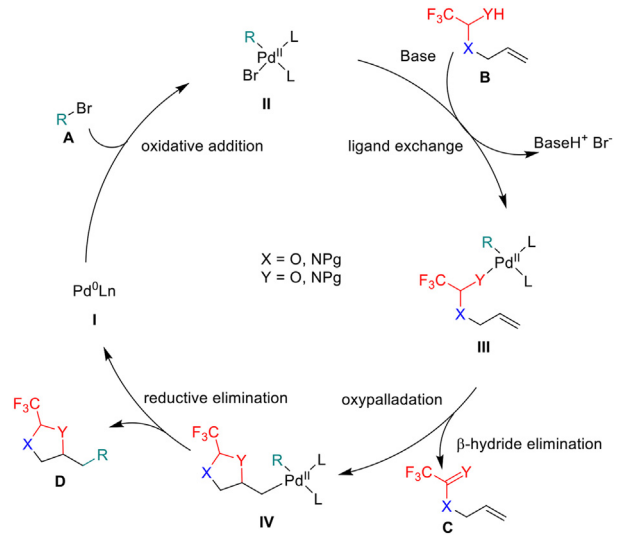
as well (Scheme 17) [27]. The *in situ* tether installation was not as efficient owing to the reduced nucleophilicity of the oxygen, and better results were obtained when the N,O acetals were isolated. Using alkynyl and electron deficient aryl bromides, the tethered alcohols were cyclized to the corresponding oxazolidines in 61–90% yield. The *in situ* installation strategy resulted in a 26% decrease in the yield of alkynylation product **87**. For this transformation, the Heck reaction was a competitive pathway and fine-tuning of the ligand was required to suppress it. A modified Fu-XPhos ligand bearing furyl instead of cyclohexyl groups on the phosphine gave best results. These conditions tolerated substituents on the α-and β-positions, yielding oxazolidines such as **87**–**90** (Scheme 17, **A**). Again, the ϒ-position could not be substituted. The facile release of the tether under acidic conditions was shown with alkyne **87**, which was hydrolyzed to the corresponding amino alcohol **91** in quantitative yield.

A speculative mechanism of the alkene difunctionalizations would begin with the oxidative addition of an organobromide **A** to a Pd (0) complex **I** to generate Pd(II) complex **II** (Scheme 18). The Pd(II)-alkoxide/amino complex **III** (Y = O/NPg) would be formed through base-mediated ligand exchange on **II** with tethered substrate **B**. At this step, either productive oxypalladation/aminopalladation to give intermediate **IV**, or competitive β-hydride elimination occurs, producing amide **C**. A second side reaction would be insertion of the alkene into the Pd–C bond, leading mostly to the Heck product [28]. Finally, reductive elimination leads to the formation of heterocyclic product **D** as well as the regeneration of the palladium (0) complex **I**.

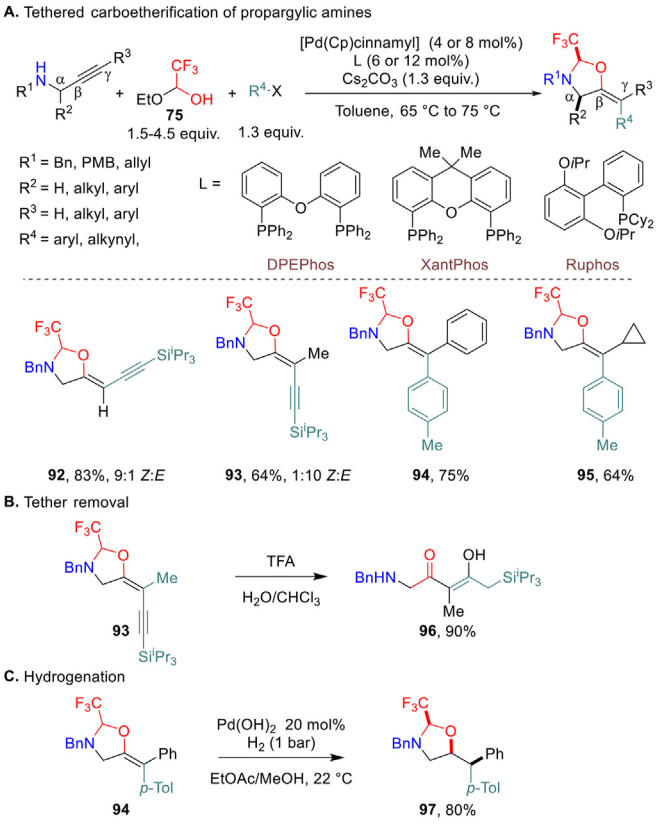
This approach could be further extended to alkyne functionalization. Our group reported in 2019 the palladium catalyzed tethered carbo-oxygenation of propargylic amines (Scheme 19) [29]. Trifluoroacetaldehyde ethyl hemiacetal **75** was used again to access substituted oxazolidines **92**–**95** (Scheme 19, **A**). Bromoalkynes and iodoarenes were used as electrophiles. Interestingly, less reactive electrophiles, such as electron-neutral aryl iodides, could also be used in this case. In contrast to alkenes, substitution at the γ position was well tolerated, leading to more substituted products. For terminal alkynes, *cis*-oxyarylation was observed, whereas substituted alkynes gave *trans*-oxyarylation. Probably, *cis*-oxypalladation happens for terminal propargylic amines, whereas a *cis*-oxypalladation/isomerization sequence or *anti*-palladation



Scheme 17. Tethered carboamination of allylic alcohols via N,O-aminals.



Scheme 18. Postulated mechanism for the Pd-catalyzed alkene difunctionalization via *in situ* tethering.



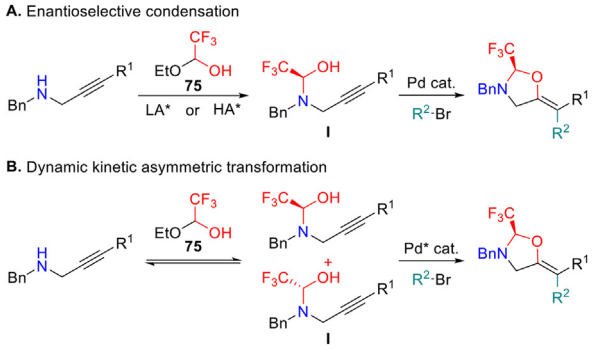
Scheme 19. Pd catalyzed carboetherification of propargylic amines and functionalization of the products.

occurs for internal propargylic amines. Hydrolysis of oxazolidine **93** led to diketone **96** in which hydration of the triple bond had also occurred (Scheme 19, **B**) Hydrogenation of tetrasubstituted alkene **94** occurred with perfect diastereoselectivity to give reduced product **97** (Scheme 19, **C**).

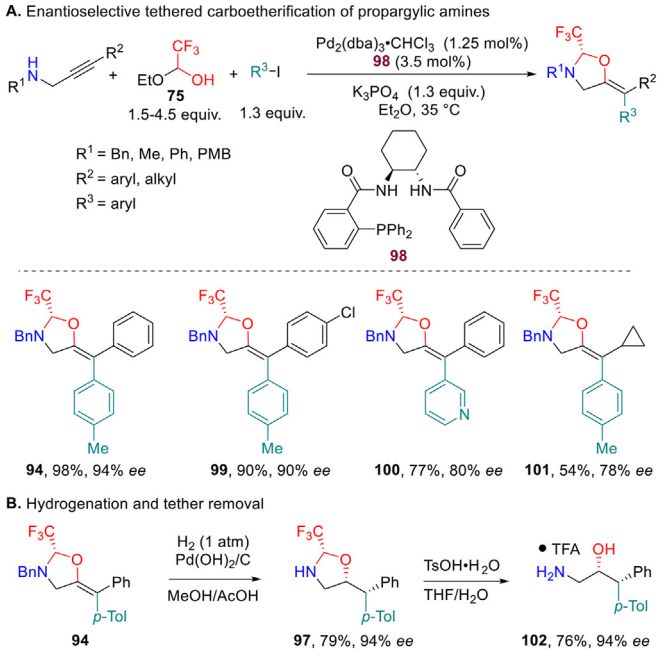
As a result of the high diastereoselectivity observed in the hydrogenation step, an enantioselective installation of the CF_3 chiral

centre would enable access to enantioenriched amino alcohols after removal of the tether. A strategy would then result that would combine the best of catalytic asymmetric transformations and chiral auxiliaries: (a) the chiral auxiliary would be introduced in a synthetically useful step; (b) the absolute configuration would be controlled by a catalytic amount of enantiopure catalyst; and (c) prefunctionalization of substrates would not be necessary thanks to *in situ* tethering. To perform the suggested enantioselective process, two approaches could be exploited depending on the rate of the different elementary steps: a) an enantioselective condensation of the amine with the tether followed by oxyarylation promoted by a non-chiral palladium catalyst if the formation of hemiaminal **I** is irreversible (Scheme 20, A) or b) a Dynamic Kinetic Asymmetric Transformation (DYKAT) via formation of racemic hemiaminal **I** under reversible conditions followed by a resolution with a chiral palladium catalyst (Scheme 20, B). NMR experiments showed that the formation of hemiaminal **I** was reversible and in fast equilibrium under the reaction conditions, making the second strategy the most logical choice.

Exploiting this concept, our group developed in 2020 an enantioselective tethered oxyarylation of propargylic amines, providing access to enantioenriched chiral amino alcohols (Scheme 21, A) [30]. A "One arm Trost" monophosphine Trost-type ligand **98** was



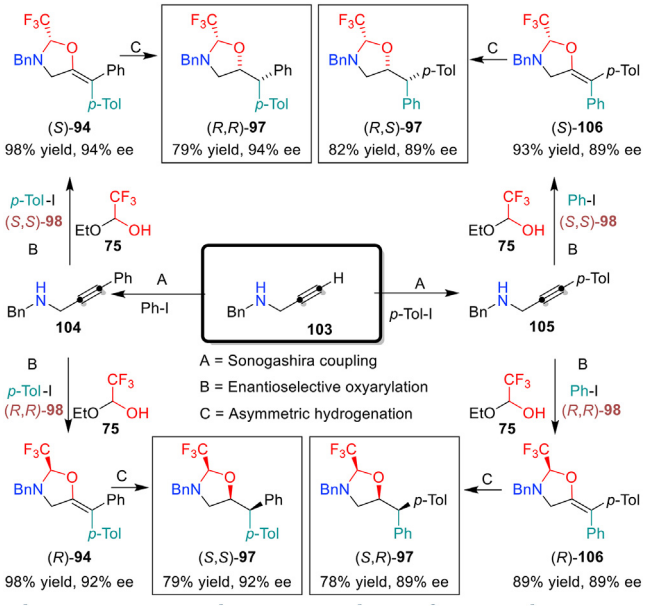
Scheme 20. Different scenarios to achieve enantioselective oxyarylation via tethering.



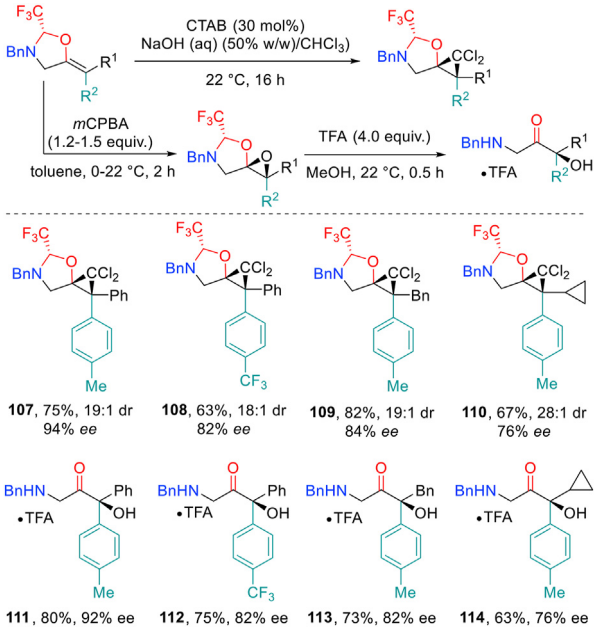
Scheme 21. Pd catalyzed enantioselective carboetherification of propargylic amines.

used in a DYKAT process to induce high enantioselectivity. The product **94** was obtained in 98% yield and 94% *ee*. Halogenated arenes and heterocycles were tolerated in the reaction (products **99** and **100**). A cyclopropyl containing substrate afforded the desired product **101** in 54% yield and 78% *ee*. Hydrogenation with simultaneous benzyl group deprotection proceeded in 79% yield for alkene **94** with perfect diastereoselectivity (Scheme 21, **B**). The tether could be then removed on **97** to give amino alcohol **102** without erosion of the enantiopurity.

All four potential stereoisomers of the amino alcohols could be accessed by carefully selecting the starting material, electrophile, and absolute configuration of the ligand (Scheme 22). A common starting material **103** is readily available. The stereodivergent



Scheme 22. Diastereodivergent synthesis of protected amino alcohol **97**.



Scheme 23. Enantioselective cyclopropanation and epoxidation/hydrolysis sequence via catalytically formed chiral auxiliaries.

synthesis of the four stereoisomers of **97** can be achieved in three steps: Sonogashira cross-coupling (A); enantioselective oxyarylation (B) and stereoselective reduction (C). The amino alcohol precursors could be obtained in 55–60% overall yield from **103** with over 89% *ee* and more than 20:1 dr.

In 2022, our group demonstrated that the catalytically formed chiral auxiliaries can also be used in other transformations than hydrogenation. In particular, the formation of both cyclopropanes and epoxides occurred in high yields and diastereoselectivity (Scheme 23) [31]. The obtained cyclopropanes **107**–**110** were stable, whereas the epoxides could be directly hydrolyzed to form α-hydroxy ketones **111**–**114**.

2. Conclusion

Tethering strategies have been used for the palladium-catalyzed functionalization of olefins to overcome limitations of reactivity and selectivity inherent to intermolecular processes. However, tethering has usually required multi-step sequences for installation and removal, making it synthetically less efficient. Progress has been realized with easier to install tethers based on carbonyl or sulfonyl groups. Although these types of tethers are easily installed using broadly available reagents, their removal requiring strong acidic or reducing conditions remains an important barrier for their applications. Our group further contributed to this area by developing *in situ* tethering strategies for the functionalization of allylic and propargylic amines and alcohols using trifluoroacetaldehyde-derived molecular tethers. The N,O or N,N acetals formed using this approach can be easily removed under mild acidic conditions. At the time of first submission of this review, only carbon-based electrophiles could be used in such processes, but our group in between reported the first example of oxygen-based electrophiles for oxyamination using iodobenzene diacetate as reagent [32]. A general shortcoming of tethered based alkenes functionalization is the lack of enantioselective methods reported with only two examples so far: The aminoarylation reported by Wolfe and coworkers [14] and our concept of catalytically formed chiral auxiliaries [30]. After submission of this review, our group also reported the first example of enantioselective hydroetherification of propargylic amines to access chiral auxiliaries on less substituted alkenes [33]. Further applications of the tethering concept to the palladium-catalyzed functionalization of alkenes and alkynes as well as to other synthetic transformations can be expected in the future.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

Acknowledgments

This work is supported by the European Research Council (ERC Consolidator Grant SeleCHEM, No. 771170) and EPFL. This publication was created as part of NCCR catalysis, a National Center of Competence in Research funded by the Swiss national science Foundation (Grant No. 180544).

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