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Advances in the development of catalytic tethering directing groups for C–H functionalization reactions

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Transition metal-catalyzed C–H bond insertion is one of the most straightforward strategies to introduce functionalities within a hydrocarbon microenvironment. For the past two decades, selective activation and functionalization of certain inert C–H bonds have been made possible with the help of directing groups (DGs). Despite the enormous advances in the field, an overwhelming majority of systems require two extra steps from their simple precursors: installation and removal of the DGs. Recently, traceless and multitasking groups were invented as a partial solution to DG release. However, installation remains largely unsolved. Ideally, a transient, catalytic DG would circumvent this problem and increase the step- and atom-economy of C–H functionalization processes. In this review, we summarize the recent development of the transient tethering strategy for C–H activation reactions.

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1. Introduction

Carbon–hydrogen activation is arguably one of the most active research areas of synthetic chemistry. For the past two decades, selective functionalization of inert C–H bonds has become an indispensable strategy towards structurally diverse molecular architectures.¹ The most noted advantage of C–H



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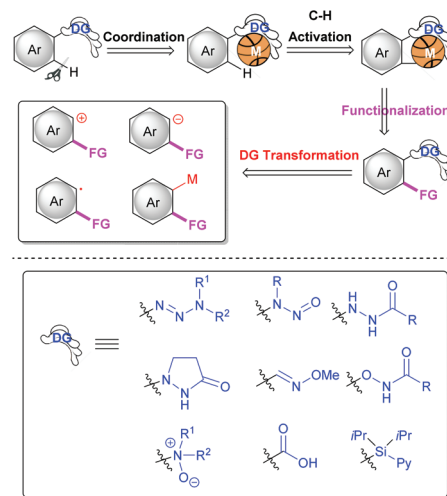
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Nicolas Guimond

Nicolas Guimond was born in Québec city, Canada in 1985. He obtained his BSc degree in 2008 from Laval University (Québec, Canada). He then moved to the University of Ottawa (Ottawa, Canada) to undertake graduate studies under the supervision of Prof. Keith Fagnou, where he worked on Rh(III)-catalyzed C–H functionalization reactions until 2010. After the demise of Keith Fagnou in 2009, Nicolas worked on tethering organocatalysis reactions under the supervision of Prof. André Beauchemin. In 2012, he obtained his PhD degree and moved to Germany for post-doctoral studies in the group of Prof. Dirk Trauner in Munich. He thereby accomplished the biomimetic total synthesis of Betanidin. He was then hired by Bayer Pharma AG, and since 2014, he has been the head of the reaction screening laboratory in the Chemical Development department in Wuppertal, Germany.

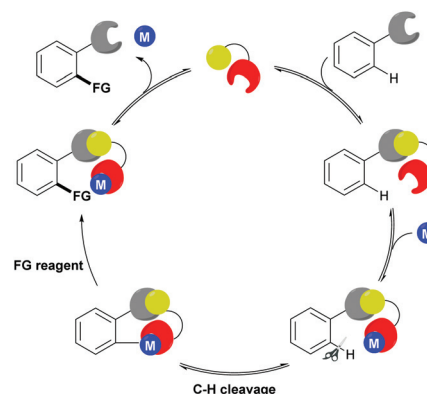
functionalization over cross-coupling reactions is the avoidance of “preactivated substrates” and toxic wastes. Considering the abundance of C–H bonds in organic molecules, selectivity is typically a major issue. Besides reactivity controlled reactions, directing groups have become the most embraced strategy to bias chemoselectivity. In addition, the proximity effect of a DG has proven to be critical for the activation of stable C–H bonds.^{11,1n,2} Although halides and/or organometallic reagents are no longer needed for most C–H functionalization reactions, the problem associated with step- and atom-economy still exists. So far, only a few common functional groups have served as an effective DG by themselves. Often, an extra step is required to enhance metal binding or install additional coordination sites. In this sense, these substrates are preactivated as well. Furthermore, the covalent linkage between a directing group and its substrate often requires harsh removal conditions after functionalization, adding more limitations to the overall process. Recently, a family of labile functionalities emerged as a partial solution to DG removal and derivatization (Scheme 1).³ Groups as such usually consist of a weak N–O or N–N bond.⁴ The nitrogen atom serves as a metal binder, while the weak nature of these bonds offers opportunities for additional transformations such as DG removal, cyclizations and rearrangement. For example, our group developed a series of removable multitasking DGs for this purpose.^{3c,d} Among them, triazene is particularly versatile as it not only can be removed at ambient temperature, but also participates in a number of cationic, radical and organometallic reactions to deliver diverse structures and functionalities.^{5,6} Nitrous amide⁷ and pyrazolidinone⁸ are excellent DGs for redox-neutral C–H functionalization reactions involving Rh, Pd, Co *etc.* *N*-Oxyacetamide shows great multitasking capabilities by undergoing controllable C–H activation cascades.⁹ In addition, *N*-oxides, carboxylic acids, as well as boron- and



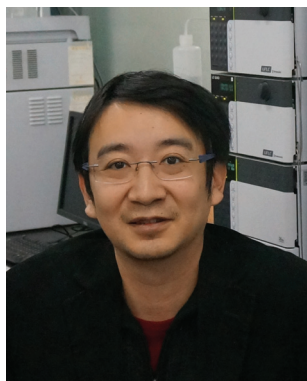
Scheme 1 The multitasking strategy partially addresses the issue of DG removal.

silicon-derived reagents were also utilized as modifiable or traceless directing groups.^{3b,10}

Despite this progress, these DGs are generally not commercially available, especially for substrates bearing additional substituents. Besides, the installation of DGs is not always trivial due to pre-existing sensitive fragments on the substrate. Ideally, a directing group should be installed, utilized and released in a catalytic fashion within a single operation. Steps concerning DG installation and removal would thus be eliminated and C–H functionalization reaction would truly become a one-step transformation with better atom economy. Conceptually, the substrate binds covalently, but reversibly to a bifunctional catalytic tether that contains a metal-binding tail (DG). By carefully controlling the conformation of the substrate–tether–metal complex, a specific C–H bond of the substrate may be activated selectively. Subsequently, the tether can dissociate from the product and enter the next cycle (Scheme 2). This rather simple concept seems to have been overshadowed by the progress of stationary directing groups.



Scheme 2 The tethering strategy using a catalytic directing group.



Yong Huang

Yong Huang received his B.S. degree in chemistry from Peking University in 1997. He received his M.S. and Ph.D degrees from the University of Chicago in 1998 and 2001, respectively. He worked as a postdoctoral fellow at Caltech (the California Institute of Technology) from 2002 to 2004. He subsequently worked as a senior medicinal chemist at Merck Research Laboratories in Rahway, NJ, until 2009. In 2009, he started his independent academic career as a professor at Peking University, Shenzhen Graduate School. He is the recipient of the 2014 Organic Letters Outstanding Author of the Year Award, the Bayer Investigator Award, the Roche Chinese Young Investigator Award, and the Asian Core Program Lectureship Award (2013, 2014 and 2015).

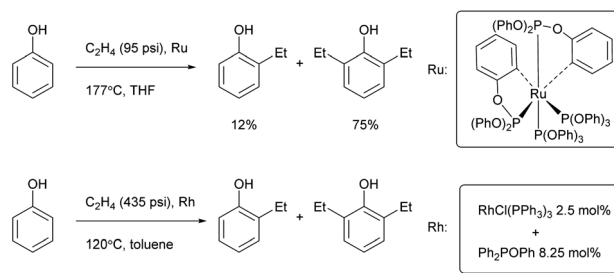
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The most important issue for catalytic tethering groups is the tether turnover. It is difficult to identify reaction conditions promoting rapid substrate-tether conjugation/dissociation without affecting C-H metalation. Thanks to tremendous advances in organocatalysis,¹¹ many reversible bond forming reactions can now be performed under very mild conditions. This progress recently propelled the discovery of catalytic tethers for C-H functionalization reactions. This review covers recent development of catalytic directing groups for carbon-hydrogen activation reactions. The following sections are organized based on tether turnover mechanisms.

2. Phosphite/phosphinite tethers via *in situ* transesterification

Direct *ortho*-functionalization of phenols is a long-standing problem.¹² Although the phenol oxygen can bind to transition metals, subsequent C-H cleavage would yield a high-energy 4-membered metallacycle, which is quite uncommon.¹³ As a result, *ortho*-functionalization of phenols generally requires extra steps to convert the OH group to an *N*-oxyacetamide,⁹ an ester¹⁴ or a silanol^{10j,15} that can generate a stable 5- or 6-membered metallacycle (Scheme 3).

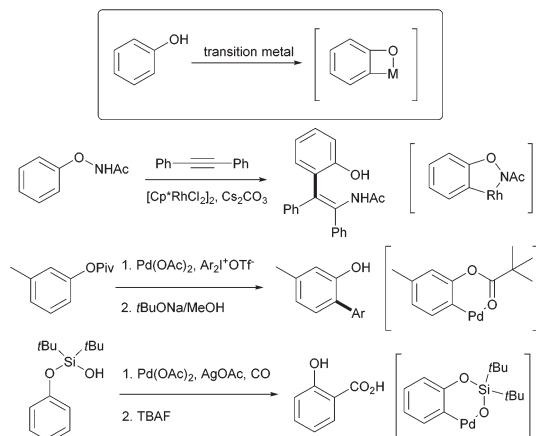
In the 1980s, Lewis demonstrated that ruthenium triarylphosphite complexes can act as active catalysts for *ortho*-specific deuteration and ethylation of phenols.¹⁶ In this reaction, P(OAr)₃ acts as a “sponge” to absorb the phenol substrate and release the ethylated phenol product *via* transesterification. Although the reaction conditions were rather harsh and limited to simple phenol, it opened the doors to the use of P(OAr)₃ as an effective catalytic tether for direct functionalization of phenols. In 2006, Cole-Hamilton discovered that Ph₂POPh could also function as a catalytic tether to promote the same phenol ethylation reaction using Wilkinson's catalyst (Scheme 4).¹⁷ The reaction proceeded smoothly with as low as 2.5 mol% RhCl(PPh₃)₃ and 3.3 times more phosphinite tether (Ph₂POPh), giving 2,6-diethylphenol in 93% GC yield. No reac-



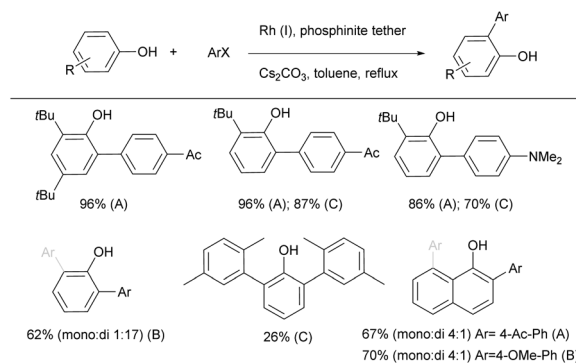
Scheme 4 Ethylation of phenol using phosphinite ligands as transient DGs.

tion was observed in the absence of the phosphinite. When Et₂P(OPh) was used, [RhCl(Et₂P(OPh))₃] was detected by NMR and proposed as the active catalytic species. The reaction was sensitive to substituents on phenol. Palladium showed no catalytic activity and RuH₂(CO)(PPh₃)₃ gave low yields at 30 mol% catalyst loading. Analogously, simple aniline was also ethylated using Ph₂PNHPh, albeit with low efficiency.

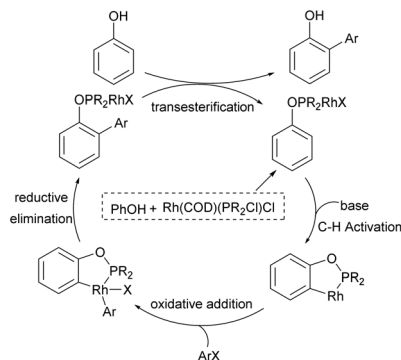
In 2003, Bedford¹⁸ and Oi¹⁹ reported a rhodium-catalyzed direct *ortho*-arylation of phenols using aryl bromides and phosphinite tethers (Scheme 5). The reaction proceeded well for a number of substituted 2-*t*-butylphenols. The use of iPr₂P(O-2-*t*-BuPh) is noteworthy as this particular tether was found to promote *ortho*-metallation much better than other phenoxy analogues. However, iPr₂P(O-2-*t*-BuPh) was only suitable for 2-*t*-butylphenol substrates. Reactions involving other phenols would inevitably generate the corresponding arylated 2-*t*-butylphenol byproducts that were difficult to separate. Consequently, phenols other than 2-*t*-butylphenols would have to employ a tether containing a matching phenoxy residue which needs to be synthesized individually. In order to address this problem, Bedford later found that commercially available iPr₂P(O-2-*t*-BuPh) could serve as a good tether precursor and generate the corresponding phosphinite *in situ*.²⁰ One major limitation



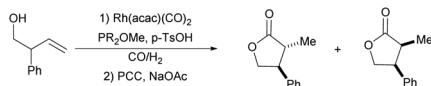
Scheme 3 *ortho*-Functionalization of phenols.



Scheme 5 Arylation of phenols using phosphinites as catalytic tethers. Condition A: Cs₂CO₃ (1.7 eq.), [Rh(PPh₃)₃Cl] (5 mol%), PR₂(OAr') (15 mol%), toluene, reflux, 18 h; B: Cs₂CO₃ (1.7 eq.), [Rh(cod)Cl]₂ (10 mol% Rh), P(NMe₂)₃ (30 mol%), toluene, reflux, 18 h; C: Cs₂CO₃ (1.7 eq.), [Rh(cod)Cl]₂ (2.5 mol%), iPrP(O-2-*t*-BuPh) (10 mol%), toluene, reflux, 18 h. Ar' = phenol starting material.



Scheme 6 Proposed mechanism for the arylation of phenol.



Scheme 7 Hydroformylation of homoallylic alcohols using phosphinite as a catalytic directing group.

for this method is that the reaction does not work well for substrates without an *ortho*-substituent. These substrates could however be arylated using $P(NMe_2)_3$ as the tether precursor.^{18b,19} As a limitation, it was observed that diarylated phenols react much faster due to accelerated C–H metallation.

The proposed mechanism for phosphinite-tethered C–H arylation is illustrated in Scheme 6. Upon ligand exchange with R_2POAr , the corresponding phosphinited Rh undergoes base assisted C–H insertion. Subsequently, aryl halide oxidizes Rh(I) to Rh(III). Reductive elimination generates 2-arylated aryl dialkylphosphite Rh(I), which liberates the arylated phenol product *via in situ* transesterification with the phenol starting material.

This phosphinite tethering strategy was also exploited by Lightburn,²¹ Grünanger and Breit²² for regioselective hydroformylation of homoallylic alcohols (Scheme 7). Although these transformations are not C–H functionalization in nature, the use of a catalytic directing group is clearly related.

3. 2-Amino pyridine tethers *via* reversible imine/enamine formation

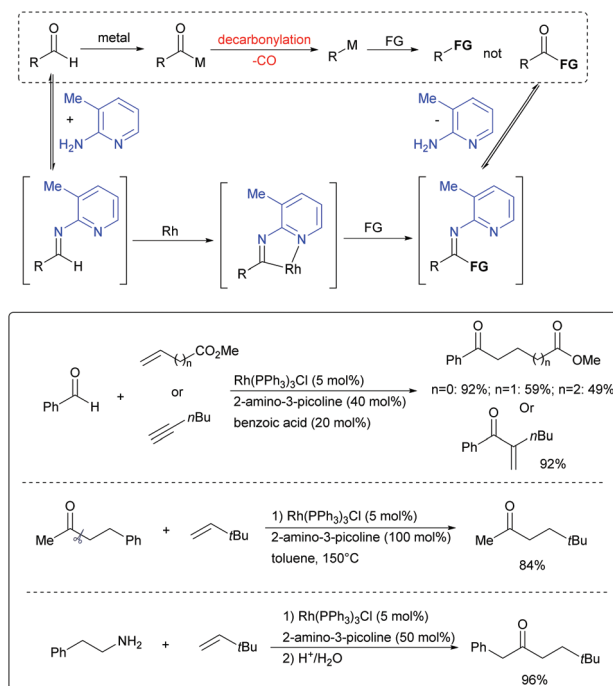
So far phosphinite tethers have been limited to C–H functionalization of phenols. Another well-established reversible bond-forming reaction is enamine/imine formation. Since the pioneering Hajos–Parrish–Eder–Sauer–Wiechert reaction²³ and subsequent contributions by MacMillan, List and Barbas, enamine/imine catalysis has gained tremendous advances.²⁴ Numerous reports have shown that the versatile enamine/imine intermediate can be generated under very mild conditions. The rapid turnover of amine catalysts thus makes

them excellent candidates as catalytic tethers for C–H activation reactions.

The tethering strategy was first explored by Jun for the activation of the formyl C–H bond.²⁵ Although there is no site selectivity issue for these reactions, decarbonylation is often an undesired reaction pathway.²⁶ In order to suppress the loss of CO from the metal center after C–H insertion, 2-amino-3-picoline was used as a catalytic tether. The C–H activation is significantly accelerated for the corresponding imine intermediate, thanks to the directing effect of pyridine. A number of hydroacylation reactions were accomplished using this strategy (Scheme 8).^{25c}

The 3-methyl group on the tether is critical. The pyridine nitrogen is forced into the proximity of the aldimine C–H bond, which enhances the metalation rate. The five-membered imino rhodacycle could be intercepted by either alkenes or alkynes to give the corresponding ketone products.²⁷ It is noteworthy that cleavage of the unstrained C–C bond was also accomplished using the same tether.²⁸ In addition to aldehydes and ketones, alcohols and amines could undergo similar transformations *via in situ* dehydrogenation using the same Rh catalysts.²⁹ The imine formation was proposed as the rate-limiting step for these reactions. Acidic additives were often used to improve the catch and release of the tether.³⁰ Nevertheless, high tether loading was generally required, sometimes in stoichiometric amounts.

In 2012, Dong demonstrated that 2-aminopyridine could be used as a recyclable enamine tether for α -alkylation of cyclic diketones. Instead of forming imines, 2-aminopyridine prefers to form enamines with less hindered cyclic diketones.³¹ In this



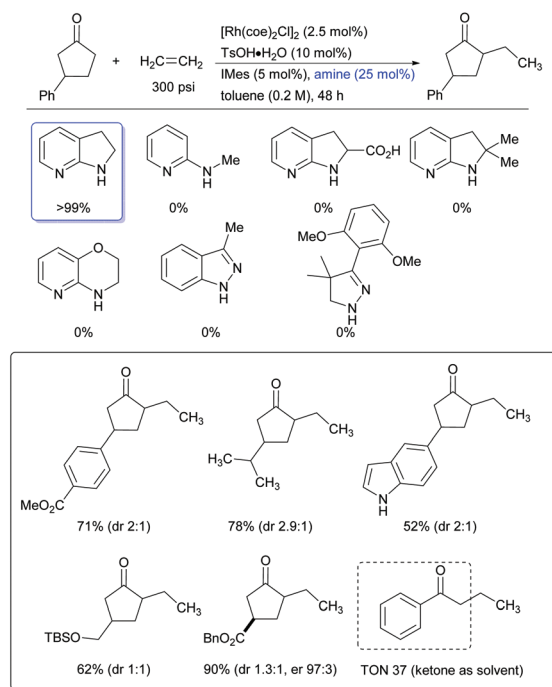
Scheme 8 Hydroacylation using 2-amino-3-picoline as an imine tether.

scenario, pyridine would direct Rh towards oxidative addition into the highly electron-rich enamine C–H bond. Subsequent olefin insertion and C–H reductive elimination deliver α -alkyl ketone products (Scheme 9). This process represents a useful alternative to the traditional Stork ketone alkylation,³² in which halides were used as alkylating agents. Although 2-aminopyridine was used in a stoichiometric amount, it could be recycled under acidic conditions. Furthermore, enamine formation, C–H functionalization and tether removal could be performed in one pot, making the tether a truly traceless directing group. α -Olefination of ketones was accomplished under similar conditions using preformed enamines and alkynes.³³

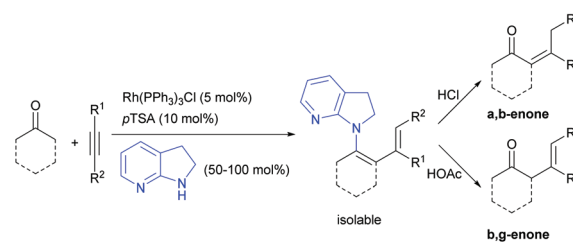
In these cases, the 2-aminopyridine tether strategy seemed to be limited to very active cyclic 1,2-diketones, which form isolable enamines. In addition, the tether did not undergo turnover. In order to address these issues, Dong systematically modified the tether structure and discovered that 7-azaindoline as the catalytic tether is useful to alkylate simple ketone substrates with ethylene (Scheme 10).³⁴ The activity of 7-azaindoline is unique among several closely related tether candidates. Excellent chemo- and moderate diastereoselectivity was observed for ketones bearing a β -substituent. Monoalkylated products were obtained for most substrates. Brønsted acids were used as co-catalysts to facilitate both formation and hydrolysis of the enamine intermediates. This tether was generally used in 25 mol% loading in toluene. Higher turnover numbers were obtained when the ketone substrate was used as a solvent. A catalytic amount of additive such as DABCO, 2,4,4-trimethylpentan-2-amine, was found to accelerate this alkylation reaction.

A similar strategy was used for direct coupling of ketones and alkynes.³⁵ It was found that the enamine formation was also accelerated by the Rh(I) catalyst in the absence of a Brønsted acid. The turnover of 7-azaindoline in these reactions is more difficult due to increased stability of the corresponding dienamine intermediate, which could be isolated. Conjugated and skipped enone products were selectively obtained using HCl and HOAc, respectively (Scheme 11).

Considering the electron-richness of the enamine and the low valent Rh catalyst used, the C–H insertion was proposed to proceed *via* pyridine directed oxidative addition. The corres-

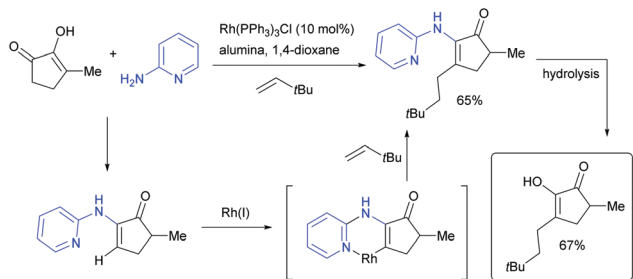


Scheme 10 7-Azaindoline as a catalytic tether for alkylation of simple ketones using alkenes.

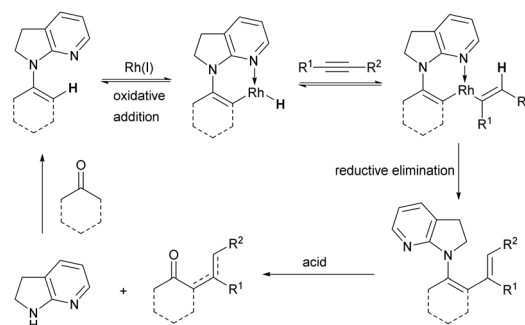


Scheme 11 Internal coupling with simple ketones and alkynes.

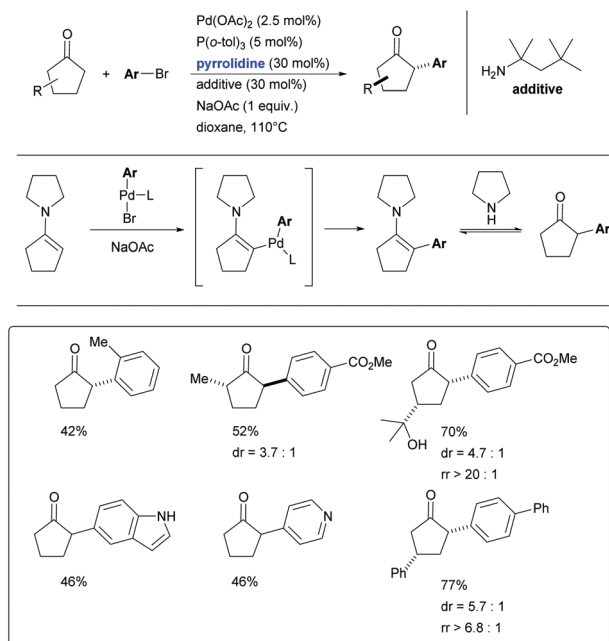
ponding Rh(III) hydride presence was confirmed by X-ray. Subsequent Rh insertion into the triple bond and reductive elimination yields olefinated enamines, which were isolated in moderate to good yields (Scheme 12). Tether recycling was



Scheme 9 Alkylation of ketones using 2-aminopyridine as an enamine tether.



Scheme 12 Proposed mechanism for 7-azaindoline tethered ketone-alkyne coupling.



Scheme 13 Pyrrolidine as a catalytic promoter for α -alkylation of cyclopentanones.

carried out in a separated step, often within the same pot. Although α C–H bonds of ketones are not considered chemically inert. This new functionalization strategy offers obvious advantages over traditional enolate and enamine chemistry, in which the coupling partners are generally electrophiles.

Dong then showed that the pyridine domain of the tether is not required for the palladium-catalyzed selective α -functionalization of cyclopentanones. Simple pyrrolidine acts as an effective promoter for facile electrophilic α -palladation of the cyclic ketones (Scheme 13).³⁶ Reductive elimination yields the desired α -aryl cyclopentanone products. It is remarkable that reductive elimination overrides β -hydride elimination as palladium enolate is prone to give α,β -unsaturated ketone products.³⁷ Interestingly, lower Pd loadings (2.5 mol% vs. 5 mol%) led to higher yield. A hindered primary amine additive was used to improve yield. The role of this additive is however still unclear. When substituted cyclopentanones were examined, decent regio- and diastereoselectivity was obtained.

4. Amino acid tethers via reversible imine formation

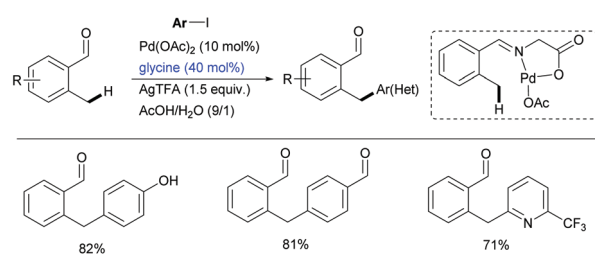
The abovementioned enamine/imine tethering strategy is concentrated on the functionalization of formal or ketone α -C–H bonds. Activation of more inert sp^3 C–H bonds had not been realized until very recently. Yu demonstrated that mono *N*-protected amino acids (MPAA) are excellent bidentate ligands for palladium catalyzed C–H activation of inert sp^3 C–H bonds bearing a neighbouring amide directing group.³⁸ In 2016, the same group discovered that simple non-protected amino acids

could serve as excellent catalytic tethers for direct functionalization of benzylic and ketone β -C–H bonds.³⁹

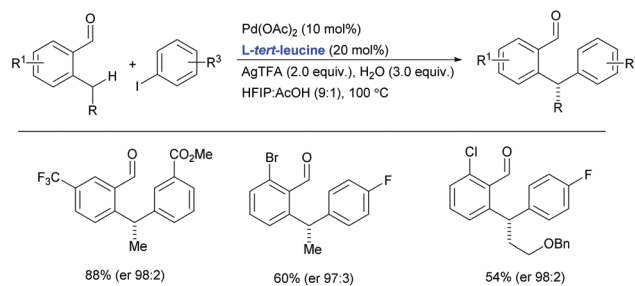
2-Tolualdehyde is known to form a Schiff base with amino acids under mild conditions.⁴⁰ The resulting imino acid resembles MPAA as a bidentate ligand for palladium and can function as a transient directing group for benzylic C–H cleavage. In the presence of Pd(OAc)₂, 40 mol% glycine and aryl iodide, benzylic arylation of 2-tolualdehyde was accomplished. Interestingly, no *ortho*-arylation was reported. A mildly acidic aqueous media was used to control the concentration of the imino acid intermediate and regenerate the transient tether. Various amino acids promoted this reaction with a similar efficiency. The reaction stopped when MPAA were used, due to the lack of coordination sites on the imine nitrogen. Diverse aryl iodides were tolerated, including heteroaryl iodides (Scheme 14).

Chiral amino acids can also be used for highly enantioselective arylation of secondary benzylic carbons. Sterically demanding *L*-*tert*-leucine was found to provide well balanced yield and *er*. Due to the slow imine formation rate, excess *L*-*tert*-leucine tends to poison palladium and erode the yield. Reducing the Pd/ligand ratio to 1/2 led to significantly improved conversion (Scheme 15).

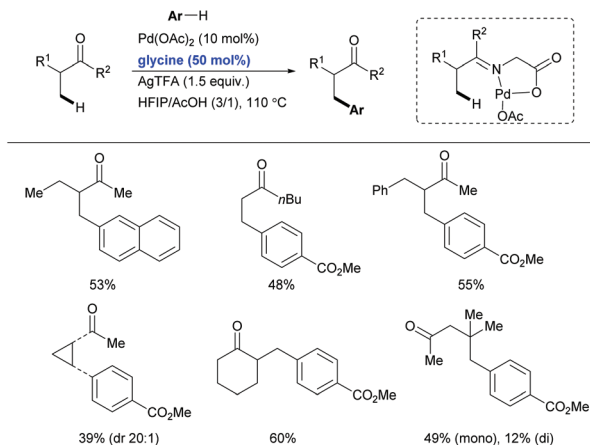
This strategy was further extended to direct β -arylation of aliphatic ketones (Scheme 16). Compared to aldehydes, ketones are much less reactive against imine formation. It was found that only the smallest amino acid tether was productive. A variety of linear, α -branched, and cyclic ketones were tolerated. Interestingly, the γ -C–H bond was functionalized for ketones lacking β -hydrogens. Aliphatic aldehydes failed to undergo analogous transformations due to decomposition.



Scheme 14 Benzylic arylation of tolualdehydes using glycine as a catalytic tether.



Scheme 15 Enantioselective benzylic arylation of 2-alkylbenzaldehydes using *L*-*tert*-leucine as a chiral catalytic tether.



Scheme 16 Arylation of an aliphatic ketone.

5. Conclusions

As directed C–H functionalization research is reaching maturity, focus on converting stationary directing groups to catalytic tethers intensifies. Following the early discovery of phosphinite tethers, enamine/imine catalysis has also made its way into this field. Several amine tethers that show great potential for direct functionalization of substrates without a suitable directing group were recently discovered. However, development of catalytic directing tethers is still on the learning curve. Several obvious challenges remain. Mechanistically, the effect of the metal on the substrate–tether equilibrium is of utmost importance and remains unclear. In addition, the substrate scope is narrow due to difficulty in controlling the tether catch and release. Given the recent encouraging advances in this field combined with the obvious potential advantages of these methods, we expect that this new frontier of C–H activation reactions will continue to thrive.

Acknowledgements

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