

# Selectivity Control in the Palladium-catalyzed Cross-coupling of Alkyl Nucleophiles

Olivier Baudoin\*

**Abstract:** Site-selectivity remains a major challenge in metal-catalyzed C–H bond functionalization. Most existing strategies rely on the introduction of a directing group or on the intrinsic reactivity of the substrate. In this account article, we describe the development of an alternative strategy based on the migration of an organopalladium species along an alkyl chain, wherein the phosphine ligand controls the cross-coupling site. This concept was first implemented with lithium enolates, and then extended to  $\alpha$ -zincated alkylamines obtained by directed lithiation and transmetalation. Both the direct and the migrative cross-couplings, which are controlled by simply switching the ligand, furnish synthetically useful organic intermediates.

**Keywords:** C–C coupling · C–H functionalization · Cross-coupling · Palladium

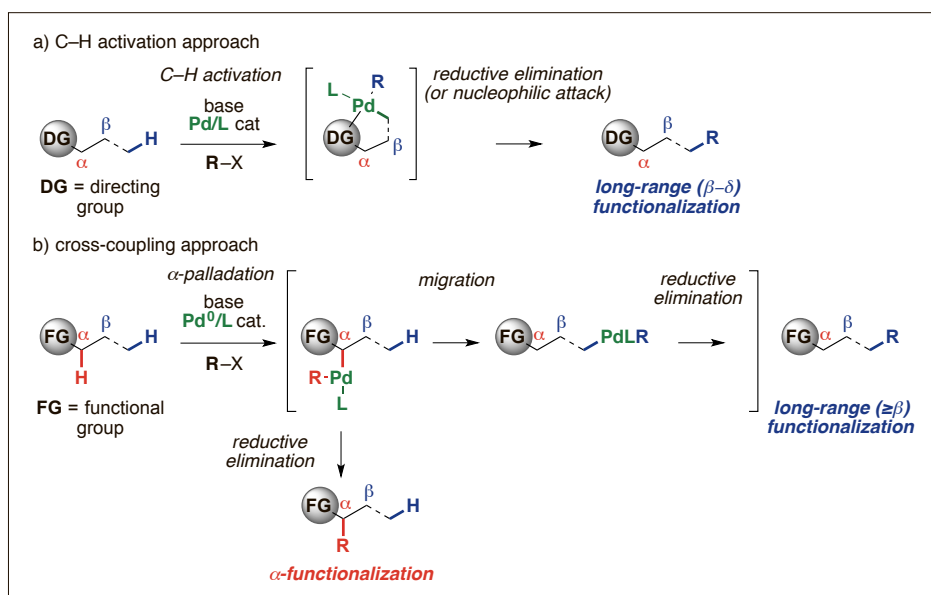


**Olivier Baudoin** completed his PhD in 1998 in the group of Jean-Marie Lehn in Paris. After a post-doctoral stay with K. C. Nicolaou in the Scripps Research Institute, he joined the Institut de Chimie des Substances Naturelles, Gif-sur-Yvette, in 1999 as a CNRS researcher, where he became fully independent in 2004. In 2006, he became a Professor at Université Claude Bernard Lyon 1 and was promoted to First Class Professor in 2011. In 2015, he moved to the University of Basel where he is currently Full Professor of Chemistry. He received the CNRS Bronze Medal in 2005, the Scholar Award of the French Chemical Society, Organic Division, in 2010, and was a junior member of Institut Universitaire de France in 2009–14. His current research focuses on the development of new synthetic methods to functionalize C(sp<sup>3</sup>)-H bonds using transition-metal catalysis, and their application to the synthesis of natural products and active ingredients.

## Introduction

The functionalization of the C–H bond represents a step-economical strategy to synthesize functionalized organic molecules from easily available hydrocarbon feedstock.<sup>[1]</sup> In this context, a large number of new transition metal-catalyzed methods have been disclosed in the past 15 years.<sup>[2]</sup> For obvious reasons, site-selectivity is a challenging aspect in C–H bond functionalization, and it has been mainly addressed by using ‘innate’ reactivity (based on electronic, steric, or stereoelectronic factors), a leaving or directing group, or ligand design.<sup>[3]</sup> In particular, a range of mono- and bidentate directing groups have been developed to perform site-selective C(sp<sup>3</sup>)-H

activation *via* the formation of small (four to six-membered) palladacycles, followed by *ipso* functionalization (Scheme 1a).<sup>[4]</sup> Another strategy that we have been actively pursuing, employs oxidative addition to palladium(0) instead of coordination to palladium(II) in the step preceding C–H activation, and allows the creation of a wide variety of rings.<sup>[5]</sup> More recently, we have designed a different strategy based on a migratory, ‘chain walking’ cross-coupling mechanism (Scheme 1b).<sup>[6]</sup> A functional group bearing a linear alkyl chain is first deprotonated at the acidic  $\alpha$  C–H bond, and the resulting carbanionic species reacts with an *in situ*-generated LPd<sup>II</sup>(R)X organopalladium complex. Reductive elimination from the latter provides the



Scheme 1. Two approaches for the long-range functionalization of C(sp<sup>3</sup>)-H bonds.

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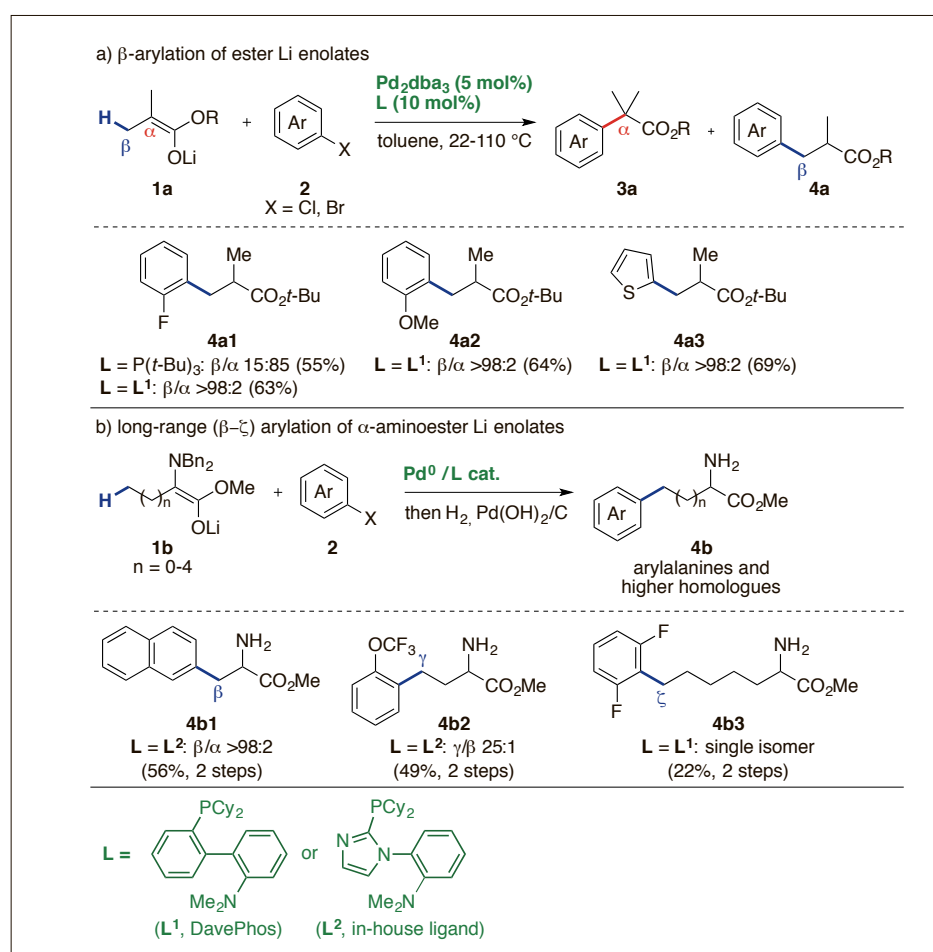
classical  $\alpha$ -functionalized cross-coupling product. Alternatively, ligand-induced migration and reductive elimination may allow to functionalize the alkyl chain at more remote positions. In the ideal case, a simple ligand switch would enable various isomers of the same coupling product to be obtained. Our recent efforts to develop such a divergent strategy using alkyl nucleophiles are described therein.

### Normal and Migrative Arylation of Ester Enolates and Surrogates

Based on an observation from Hartwig and co-workers,<sup>[7]</sup> we initially studied the selectivity control in the Pd<sup>0</sup>-catalyzed arylation of the lithium enolates of isobutyric esters with aryl halides (Scheme 2a).<sup>[8,9]</sup> Whereas bulky ligands such as P(*t*-Bu)<sub>3</sub> favored the direct coupling product **3a**,<sup>[10]</sup> more flexible ligands provided a reversed  $\beta/\alpha$  arylation selectivity, which was optimal with Buchwald's biarylphosphine **L**<sup>1</sup> (DavePhos).<sup>[11]</sup> However, with enolates **1a** only aryl halides bearing an electronegative substituent (Cl, F, CF<sub>3</sub>, OMe) or a heteroatom (O, S) at the adjacent position to the C–X bond provided high  $\beta$ -selectivities. Interestingly, both aryl bromides and chlorides could be employed as electrophiles. An asymmetric desymmetrization was also performed, using a chiral binaphthyl analogue of **L**<sup>1</sup>, with modest enantioselectivities (e.r. up to 77:23).<sup>[8]</sup>

A different selectivity outcome was observed with enolates **1b** derived from  $\alpha$ -aminoesters (Scheme 2b).<sup>[12]</sup> In this case a complete  $\beta$ -selectivity was observed, independent of the nature of the aryl bromide. A second-generation, *N*-phenylimidazole-based<sup>[13]</sup> ligand (**L**<sup>2</sup>) was found to be superior to **L**<sup>1</sup>, and afforded good yields for a range of  $\beta$ -arylated products. Hydrogenation allowed the unveiling of the free amino group, which overall provided an interesting access to analogues of phenylalanine. For instance, aminoester **4b1** is a substructure found in the gonadotropin-releasing hormone agonist Nafarelin. Importantly, extending the length of the alkyl chain undergoing migration turned out to be feasible, but in this case the presence of an electronegative substituent at the *ortho* position of the aryl bromide was again critical to obtain useful levels of selectivity (see **4b2**). Combined with hydrogenation, this method provided an access to valuable homologues of phenylalanine. The most striking example includes a five-carbon linear chain, which led to the  $\zeta$ -arylated product **4b3** as a single isomer, albeit in modest isolated yield.

The pathways leading to  $\beta$  and  $\alpha$  arylation products from isobutyrate **1a** were computed by DFT, and the selectivity fac-



Scheme 2. Migrative arylation of ester enolates.

tors were analyzed using various ligands and aryl electrophiles (Fig. 1).<sup>[9]</sup> The selectivity can be correlated with the difference of the highest transition states in each pathway. It was found computationally that the  $\alpha$ -reductive elimination, which occurs from the O-bound palladium C-enolate, is disfavored by electronegative substituents on the aryl electrophile (forming a stronger Ar–Pd bond),<sup>[14]</sup> and favored by bulky ligands such as P(*t*-Bu)<sub>3</sub> by virtue of steric decompression. On the other hand, and somewhat intuitively, a more flexible ligand such as **L**<sup>1</sup> decreases the energy barrier of the 180° rotation of the  $\pi$ -complex, which arises from  $\beta$ -H elimination and undergoes migratory insertion to give the Pd homoenolate. The biarylphosphine backbone of **L**<sup>1</sup> allows to create a secondary interaction between the non-phosphine-containing phenyl ring and the Pd center, which was shown to lower the transition state of the final reductive elimination step. Although the DFT studies did not allow rationalization of the subtle effects of the substituents on the ligand backbone, they provided a basis for the understanding of the selectivity control, which was further exploited in the subsequently developed migrative couplings. In this regard, more flexible *N*-phenylazole-based ligands such as **L**<sup>2</sup>, initially developed by Beller and co-

workers<sup>[13]</sup> and also known as CataCXium P<sup>®</sup>, were found to provide higher migratory aptitude than their biphenyl counterparts.

Lithium enolates are reactive nucleophiles that allow the above reactions to be performed at low temperatures. However, this reactivity comes along with a basicity and nucleophilicity which limit their functional group tolerance. To solve this issue and extend the scope of the migrative couplings, we turned to the use of silyl ketene acetals (SKAs), which are stable and isolable surrogates of ester enolates, are less reactive than the latter, but provide a higher chemoselectivity.<sup>[15]</sup> Using **L**<sup>2</sup>, ZnF<sub>2</sub> as a Lewis-acidic promoter<sup>[15b]</sup> and DMF as the solvent, a wide variety of  $\beta$ -arylated products containing sensitive functional groups such as ester, cyano, nitro or triflate, were obtained with moderate to good yields (Scheme 3).<sup>[16]</sup> Remarkably, TES-protected  $\beta$ -arylated lactates (**4c3**) were obtained without cleavage of the TES group. Two types of arylated products (*i.e.* R = Me and OTES) were converted to original benzo-fused  $\delta$ -lactones **6–7** in 1–2 steps, thereby providing a straightforward access to these valuable compounds.

The utility of SKAs in arylation reactions was further exploited through a collaboration with Bayer CropScience.<sup>[17]</sup> The  $\alpha$ -arylation of sterically hindered  $\alpha$ , $\alpha$ -

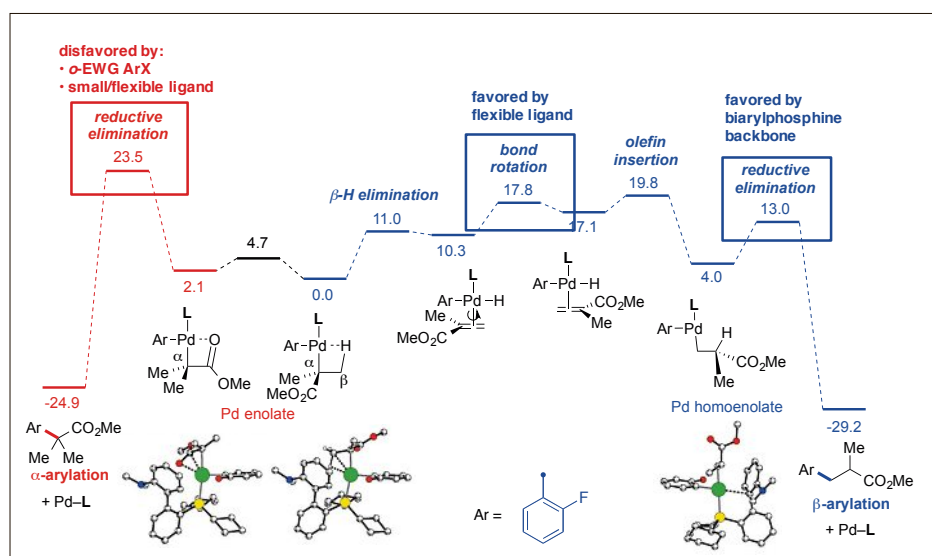
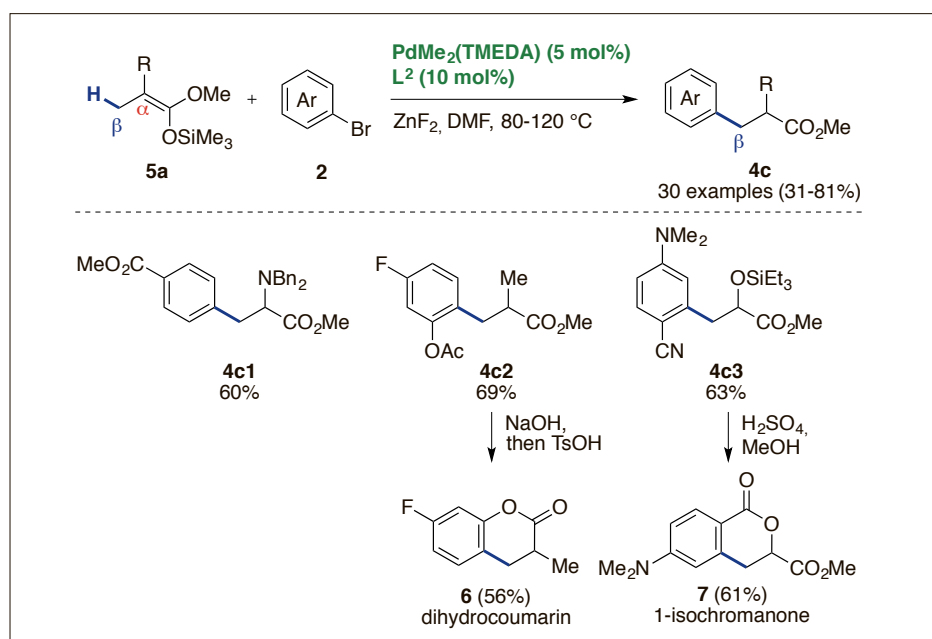
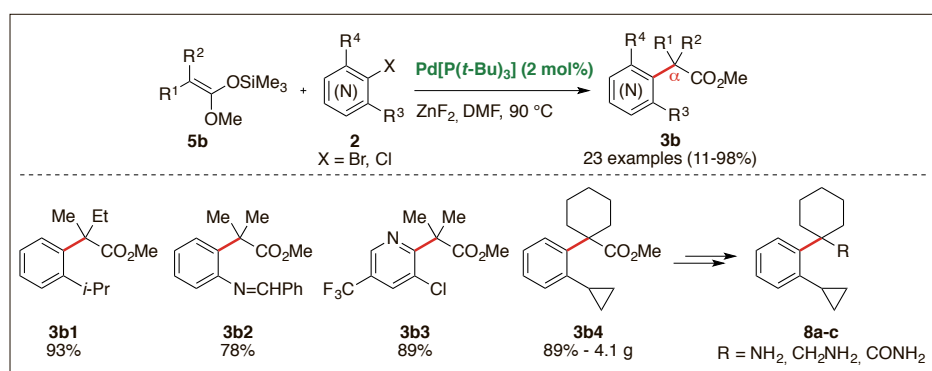


Fig. 1. Analysis of selectivity factors using DFT calculations (B3PW91/6-31G\*\*, SDD, PCM). The present case features  $L^1$  as the ligand and 2-FC<sub>6</sub>H<sub>4</sub> as the aryl group. Values refer to Gibbs free energies in kcal mol<sup>-1</sup>.



Scheme 3. Migrative arylation of silyl ketene acetals and application to the synthesis of benzofused  $\delta$ -lactones.

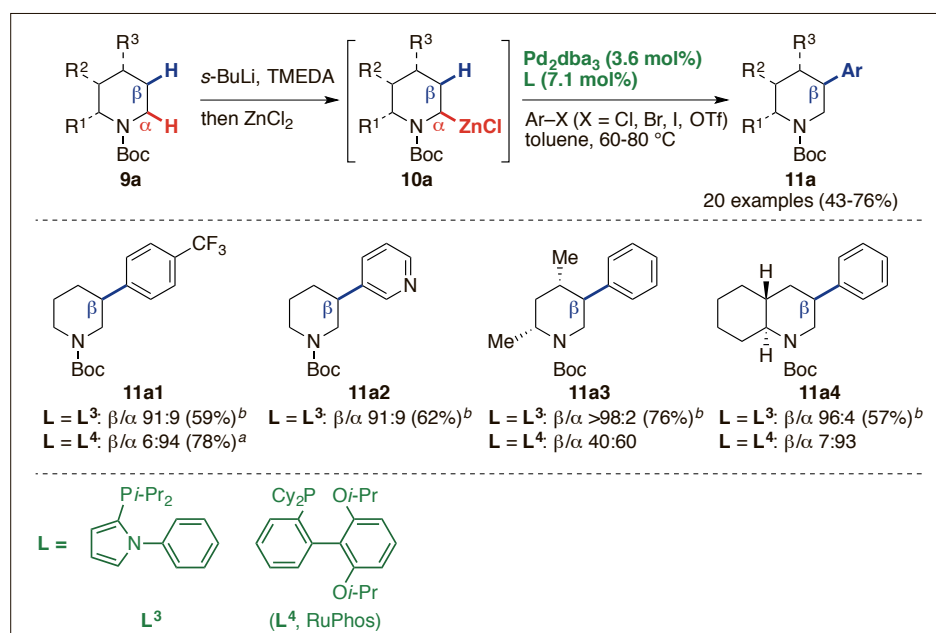


Scheme 4.  $\alpha$ -Arylation of hindered silyl ketene acetals and (hetero)aryl halides.

disubstituted SKAs **5b** with sterically hindered (hetero)aryl bromides or chlorides **2** succeeded in providing a wide range of very bulky (hetero)arylacetates **3b** in generally good yields, whereas the reaction of the corresponding lithium enolates was much less efficient (Scheme 4). The nature of the Pd pre-catalyst was found to significantly impact the reaction efficiency, with the well-defined Pd[P(*t*-Bu)<sub>3</sub>]<sub>2</sub> complex furnishing the highest activity and yield among other pre-catalysts containing the same ligand. The reaction leading to ester **3b4** was successfully performed on multigram scale, and **3b4** was further transformed into the corresponding benzylamine **8a**, phenethylamine **8b** and primary amide **8c** via standard chemistry. The latter are valuable conformationally-constrained building blocks for the synthesis of new potential agrochemicals.

### Normal and Migrative Arylation of Boc-amines

In addition to enolates and SKAs, other alkyl nucleophiles which would be able to undergo chemoselective migrative cross-coupling were sought after. Following a seminal observation by Knochel and co-workers,<sup>[18]</sup> we investigated the reaction of organozinc compounds, obtained by directed lithiation of Boc-piperidines and Li-Zn transmetalation (Scheme 5).<sup>[19]</sup> In previous work by Coldham and Knochel,  $\alpha$ -zincated Boc-piperidine gave rise to the direct Negishi coupling in the presence of bulky ligands such as P(*t*-Bu)<sub>3</sub>,<sup>[20]</sup> SPhos or RuPhos.<sup>[18]</sup> In contrast, when 2-methyl-Boc-piperidine (R<sup>1</sup> = Me) was employed as the reactant, the  $\beta$ -arylated product was obtained.<sup>[18]</sup> Following our work on the migrative arylation of enolates, we found that more flexible phenyl-azole ligands enabled  $\beta$ -selectivity even from unsubstituted Boc-piperidine (R<sup>1</sup> = R<sup>2</sup> = R<sup>3</sup> = H). Fine-tuning the ligand substituents led to phenyl-pyrrole-based<sup>[21]</sup> phosphine  $L^3$ , which allowed to isolate compound **11a1** with 59% yield and 91%  $\beta$ -selectivity. In contrast, using the more bulky and rigid RuPhos ligand ( $L^4$ ) led to a complete reversal of selectivity consistent with previous work. The nature of the lithium-directing group on the nitrogen atom was also found to influence the arylation selectivity, with the easily removable Boc group being optimal; stronger directing groups such as amides favored the direct coupling product, likely by disfavoring the  $\beta$ -H elimination step in the migration pathway. The reaction was found to tolerate a number of functional groups on the aryl electrophile, thanks to the mild basic and nucleophilic character of organozinc compounds.<sup>[22]</sup> Some substituted Boc-piperidines also gave rise to the

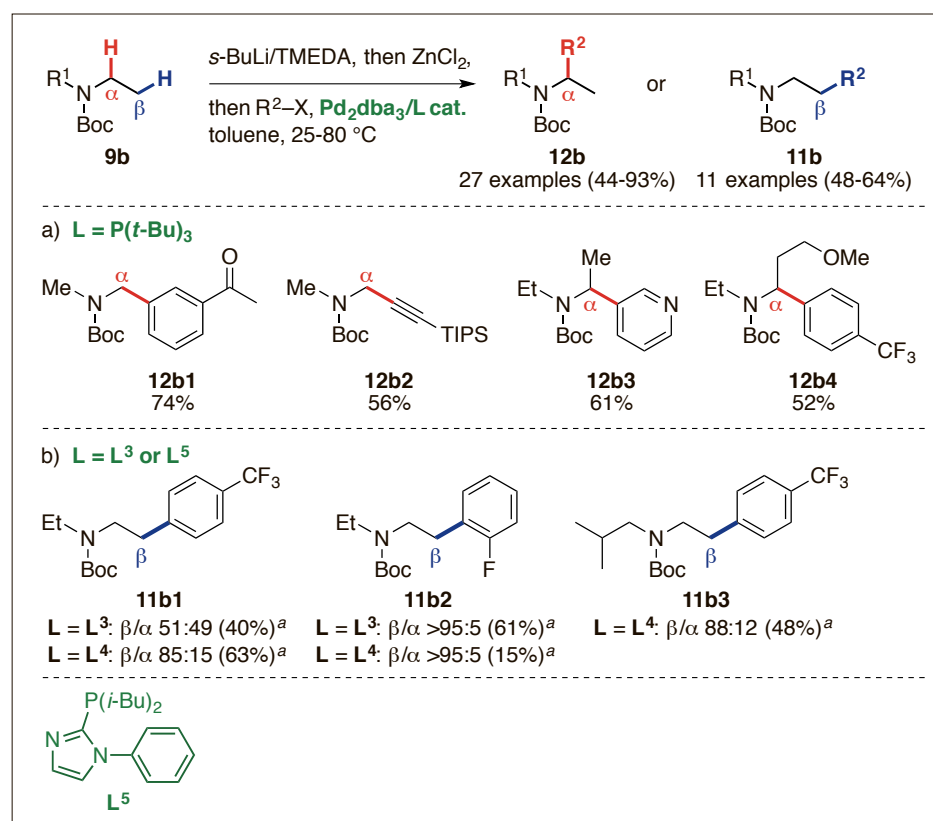
Scheme 5. β-Arylation of Boc-piperidines. <sup>a</sup>Yield of the isolated mixture of α and β isomers.<sup>b</sup>Yield of the isolated β isomer.

β-arylated product (**11a3**, **11a4**) with high selectivity and *trans*-diastereoselectivity. A high degree of ligand control was also observed in these cases, as shown with the reversed selectivity obtained with RuPhos as the ligand. Unfortunately, other cyclic Boc-amines such as Boc-pyrrolidine and Boc-azepane mainly gave rise to the α-isomer, which likely reflects the difficulty of these substrates to distort in order to align the C–Pd and C–H elimination, as required in the β-H elimination step. DFT calculations indicated that the two reductive eliminations (α and β) are the selectivity-determining steps in this reaction. In addition, it was shown that with ligand L<sup>3</sup> the reductive elimination at the less crowded C<sub>β</sub> is easier than at C<sub>α</sub>, whereas more bulky ligands similar to L<sup>4</sup> show the opposite trend.

These results were then extended to acyclic Boc-amines **9b** (Scheme 6).<sup>[23]</sup> We first developed general conditions to perform the α-functionalization reaction (product **12b**), and found out that simple P(*t*-Bu)<sub>3</sub> (employed as its bench-stable phosphonium salt) furnished good yields and complete α-selectivity for a range of zincated Boc-amines and carbon electrophiles (Scheme 6a). The latter not only included aryl halides (**12b1**), but also acid chlorides, bromoalkenes and bromoalkynes (**12b2**). The method worked well with a range of Boc-amines containing a primary (**12b1**, **12b2**) or moderately hindered secondary α-carbon (**12b3**), but more hindered substrates failed to undergo α-lithiation and hence cross-coupling. Interestingly, product **12b4** was obtained in a regioselective manner due to the double directing effect of the Boc and OMe groups

in the lithiation step. Then, we looked for appropriate conditions to reverse the selectivity in the arylation of Boc-diethylamine with *p*-trifluoromethylbromobenzene (Scheme 6b). To this purpose, we replaced P(*t*-Bu)<sub>3</sub> with ligand L<sup>3</sup>, which had provided the highest β-selectivities in the arylation of Boc-piperidines (see Scheme 5). However, a 1:1 mixture of the

α- and β-arylated products was obtained, from which the β-arylated product **11b1** was isolated in 40% yield. Replacing the pyrrole subunit of the ligand with imidazole and further decreasing the bulk around the phosphorus atom by replacing the isopropyl with isobutyl groups led to ligand L<sup>5</sup>, which provided an improved selectivity of 85:15 in favor of the β-isomer, together with a yield of 63%. Ligand L<sup>5</sup> was found to give the highest yields and selectivities for a range of *meta* and *para*-substituted bromobenzenes, but ligand L<sup>3</sup> was found to give superior yields with *ortho* substituents (**11b2**). The method was found to be limited to Boc-diethylamine and other moderately bulky secondary amines (**11b3**), on which the lithiation step operates with acceptable efficiency. The reaction mechanism was computed with P(*t*-Bu)<sub>3</sub> and L<sup>5</sup> as the ligands. In contrast to Boc-piperidine, the α-reductive elimination and the rotation of the Pd π-complex (following the β-H elimination step) were found to be the selectivity-determining steps for Boc-diethylamine. With P(*t*-Bu)<sub>3</sub>, the α-reductive elimination had a low energy barrier (16.5 kcal mol<sup>-1</sup>) whereas the barrier of the π-complex rotation was high (23.1 kcal mol<sup>-1</sup>), thus leading to the α-arylated product. With L<sup>5</sup>, these barriers both lay at 21.6 kcal mol<sup>-1</sup>, thus disfavoring the α-reductive elimination and favoring the π-complex rotation en route to the β-arylated product.

Scheme 6. Ligand-controlled α- and β-arylation of acyclic Boc-amines. <sup>a</sup>Yield of the isolated β isomer.

It is noteworthy that the  $\gamma$ - and longer-range arylation of Boc-amines could not be performed, in contrast to lithium enolates (see Scheme 2b). In order to nevertheless access the corresponding valuable  $\gamma$ -arylated amines, we employed a different, more indirect strategy (Scheme 7).<sup>[24]</sup> Indeed, we found out that the directed lithiation of Boc-allyl amines **13**, followed by Li-Zn transmetalation and Negishi coupling performed in the presence of SPhos **L**<sup>6</sup> provided the  $\gamma$ -arylated enecarbamates **14** with excellent positional selectivity and *E* diastereoselectivity. The other tested ligands furnished a lower yield and/or stereoselectivity. Moderate to good yields were obtained with a range of Boc-allyl amines and aryl electrophiles (**14a-b**), however lower yields were obtained with reactants bearing substituents on the allyl fragment (**14c**). As shown with compound **14a**, a simple hydrogenation of the enecarbamate products provided the initially sought-after  $\gamma$ -arylamine **15** in high yield. Alternatively, acid-mediated hydrolysis of **14a** provided  $\beta$ -arylaldehyde **16** with equally high efficiency. Similar to **15**, this compound could not be directly accessed from the corresponding aldehyde precursor by migrative coupling. Hence the current method employing the more functionalized allylamine precursors provided an indirect solution to synthesize the valuable arylated intermediates **15** and **16**.

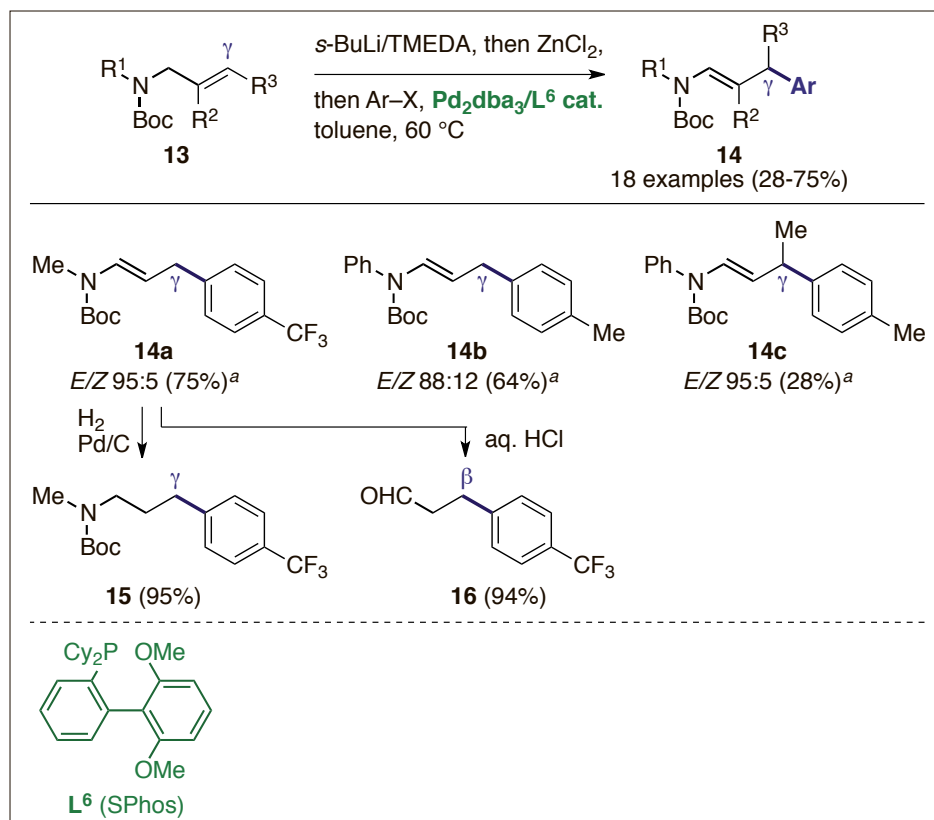
## Conclusion

Migrative cross-couplings provide a new catalytic approach to functionalize unactivated C–H bonds on alkyl chains at remote positions. The selectivity for the migrative vs. normal coupling is largely influenced by the ligand, with flexible biaryl ligands favoring Pd migration and bulky, rigid ligands favoring the direct coupling. Both types of product are valuable organic intermediates that can be accessed from the same precursor by simply switching the ligand. However, selectivities are far from perfect and further work is needed to improve the level of ligand control, as well as to replace the initial and often problematic  $\alpha$ -deprotonation step with more chemoselective alternatives.

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Scheme 7.  $\gamma$ -Selective arylation of allylic Boc-amines. <sup>a</sup>Yield of the isolated *E* isomer.

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