Connecting Remote C–H Bond Functionalization and Decarboxylative Coupling Using Simple Amines

Francisco de Azambuja‡$, Ming-Hsiu Yang,‡$, Alexander C. Brueckner,† Paul Ha-Yeon Cheong,‡,* Ryan A. Altman‡,*

†Department of Medicinal Chemistry, The University of Kansas, 1251 Wescoe Hall Drive, Lawrence, Kansas 66045, United States

†Department of Chemistry, Oregon State University, 153 Gilbert Hall, Corvallis, Oregon 97331, United States

#Current Affiliation: The Scripps Research Institute, La Jolla, California 92037, United States

$Both authors contributed equally to this work.
Abstract

Transition metal-catalyzed C–H functionalization and decarboxylative coupling are two of the most notable advances in synthetic strategies developed in the last 30 years. Herein, we connect these two reaction pathways using Et₃N and a simple Pd-based catalyst system to promote a highly para-selective C–H difluoroalkylation reaction from benzylic electrophiles. This base-enabled C–H functionalization transformation not only tolerated electron–rich and –deficient substrates but also a host of functional groups useful for synthetic elaboration. Experimental and computational mechanistic studies suggest a pathway involving an uncommon Pd-catalyzed dearomatization of the benzyl moiety followed by a base-enabled rearomatization through a formal 1,5-hydrogen migration. Critically, this rearomatization was only energetically feasible in the presence of a suitable amine additive. These studies provide an opportunity to develop general para-selective C–H functionalization reactions from benzylic electrophiles, and shows how new reactive modalities may be accessed with careful control of reaction conditions.
In recent decades, transition metal catalyzed cross-coupling reactions\(^1\) and unactivated C–H bond functionalization reactions\(^2\) have emerged as two of the most powerful strategies for constructing C–C bonds. These strategies have enabled the regioselective formation of reactive organometallic species derived from non-reactive groups, which has expanded possibilities for retrosynthetic analysis, and simplified synthetic routes. Additionally, these strategies have enabled the construction of hard-to-form bonds under mild conditions that tolerate a broad spectrum of functional groups. Both strategies have been successfully demonstrated with a variety of transition metal catalyst systems; however, Pd-based systems remain among the most common for both cross-coupling and C–H functionalization reactions, largely due to the low cost relative to other precious metals and well-behaved 2 e\(^-\) chemistry. Typically, decarboxylative coupling reactions occur under mild, neutral, and reductive conditions using a cycle starting with Pd(0), while C–H functionalization reactions occur with complimentary oxidative conditions using a cycle starting with Pd(II). Despite the countless number of catalyst systems designed for these two strategies, simple and creative ways to connect these two reaction paradigms would provide a significant advancement for synthetic chemistry. Herein, we report an unprecedented switch of a classical cross-coupling reaction into a \textit{para}-selective C–H functionalization reaction by a simple additive.

The functionalization of C–H bonds represents an important and powerful strategy for converting simple arenes and hydrocarbons to functionalized molecules, thus providing an efficient atom- and step-economic strategy for increasing structural complexity in simple building blocks, and to modify bioactive molecules at a late stage of synthesis.\(^3\) However, the practical value of such C–H functionalization reactions depends on chemoselective activation of a single C–H bond over others. For aromatic systems, \textit{ortho}-\(^6\)–\(^8\) and even \textit{meta}-selective\(^9\) C–H
bond functionalization reactions normally exploit directing groups and/or specially designed ligands and catalysts. In contrast, the reactions to functionalize C–H bonds at the para position of aromatic rings are frequently restricted to (Fig. 1a): (a) electron-rich substrates that bear nucleophilic character and that typically provide mixtures of ortho- and para-substituted products;11-23 (b) template-assisted reactions of benzyl and phenol derivatives that require extra steps for the installation and removal of the large template, thus restricting broad application;24,25 (c) catalyst-controlled reactions that remain limited to reactions of electron-deficient pyridines and arenes.26-29 Considering the aforementioned challenges, alternate strategies to selectively functionalize the para C–H bond of aromatic rings, preferably through distinct mechanisms, are still highly desirable and rarely realized.
Figure 1. C–H Functionalization vs. Decarboxylative Cross-Coupling

a. Current strategies for para-selective C–H functionalization of arenes. b. Amine additives override conventional decarboxylative coupling and enable para-selective C–H functionalization of arenes.

To complement these known transformations, we report an unexpected catalytic para-selective C–H difluoroalkylation reactions of arenes controlled by a simple and common amine base (Fig. 1b). In this reaction, the use of an amine additive overrode the conventional decarboxylative benzylaion pathway, and provided products from a C–H functionalization pathway. Extensive screening, mechanistic studies (quantum mechanical computations, cross-
over experiments, kinetic isotopic effect measurements, and isotopic labeling studies) suggest a mechanism involving an uncommon reversible Pd-catalyzed dearomatization event to access a previously “hidden” dearomatized intermediate. In this process, the base differentiates the decarboxylative benzylation and C–H functionalization pathways by enabling an irreversible 1,5-proton migration that rearomatizes the system providing the final product. Despite scattered reports of analogous reactions of electron-rich substrates (e.g. furan, naphtalenes) controlled by ligands\textsuperscript{31,32} or substrates,\textsuperscript{33-39} the present work only exploits a single additive to convert the reaction pathway from cross-coupling to C–H functionalization of a broad set of substrates. Additionally, the experimental and computational studies provide new insights to support a previously speculative mechanism, and demonstrate the specific role of the amine in rendering the aforementioned selectivity. Finally, this mechanism provides an alternate to classical C(enolate)–C(sp\textsuperscript{2}) bond-forming reductive elimination at a metal center.\textsuperscript{49}

**Results and Discussion**

_Brønsted Basicity Controls Selectivity._ Several factors, including solvents, ligands, and basic additives, affected the known decarboxylative coupling process and enabled the unusual C–H functionalization reaction. In early probing experiments, use of various Pd-based pre-catalysts afforded the α-aryl-α,α-difluoroketone product 2 in polar-coordinating solvents, as well as when exploiting electron-rich P-based ligands [e.g. P(p-C\textsubscript{6}H\textsubscript{4}OMe)\textsubscript{3}] (see the Supplementary Information for the details). Although these catalyst systems improved the ratio of arylation to benzylation, the yield of arylated product 2 remained less than 40%, and provided varying yields of protonated enolate 4. However, the use of basic additives improved both the selectivity and yield of the reaction (Fig. 2a). Nitriles, inorganic bases, and weak bases, such as pyridine (Pyr)
and anilines, exclusively provided benzylated product 3 (entries 2–7). In contrast, more basic amines, including N,N-dimethylaminopyridine (DMAP), tripropylamine (Pr3N), triethylamine (Et3N), and N,N,N′,N′-tetramethylethylene diamine (TMEDA), favored arylated product 2 (entries 8–11). Further exploration of aliphatic amines demonstrated a correlation between rigidity/hindrance and selectivity. The conformationally constrained base, quinuclidine, provided low yield of arylated product 2 (entry 12), while the bulkier N,N-diisopropylethylamine (iPr2NEt) favored benzylated product 3 (entry 13). Thus, Et3N, with a compromise between basicity and steric hindrance, afforded arylated product 2 in the highest yield (entries 10). Additionally, the stoichiometry of Et3N also influenced the yields of arylated product 2, with an increased amount of Et3N improving the selectivity of 2 (entries 10, and 14–16). However, more than 1 equivalent of Et3N did not further increase the yield (entries 10 and 17). After further optimization, the final conditions [2.5 mol% of Pd(PPh3)4/1.0 equiv of Et3N/1,4-dioxane/100 °C] provided the desired arylated product 2 in 75% isolated yield (entry 18).
a.

\[
\begin{align*}
\text{H} & \quad \text{O} & \quad \text{O} & \quad \text{Ph} \\
\text{Me} & \quad \text{F} & \quad \text{F} & \quad \text{1} \\
\text{Ph} & \quad \text{F} & \quad \text{F} & \quad \text{O} \\
\end{align*}
\]

**5% Pd(PPh\(_3\))\(_2\)**  
**Base**  
**toluene, 110 °C**

| Entry | Base (mol%) | 2 (%) | 3 (%) | 4 (%) |
|-------|-------------|-------|-------|-------|
| 1     | --          | 0     | 89    | 0     |
| 2     | Butyronitrile (300) | 0 | 88 | 3 |
| 3     | Na\(_2\)CO\(_3\) (300) | 0 | 91 | 3 |
| 4     | PhONa (100) | 0 | 0 | 18 |
| 5     | PhCO\(_2\)K (100) | 2 | 71 | 6 |
| 6     | Pyridine (100) | 4 | 85 | 0 |
| 7     | N,N-dimethylaniline (100) | 0 | 89 | 2 |
| 8     | DMAP (100) | 54 | 4 | 17 |
| 9     | N\(_2\)(P\(_3\))\(_2\) (100) | 58 | 13 | 6 |
| 10    | Et\(_3\)N (100) | 70 | 5 | 6 |
| 11    | TMEDA (100) | 69 | 5 | 8 |
| 12    | Quinuclidine (100) | 12 | 1 | 10 |
| 13    | t\(_2\)Pr\(_2\)NEt (100) | 12 | 68 | 4 |
| 14    | Et\(_3\)N (50) | 65 | 7 | 5 |
| 15    | Et\(_3\)N (25) | 63 | 11 | 5 |
| 16    | Et\(_3\)N (10) | 49 | 20 | 4 |
| 17    | Et\(_3\)N (300) | 69 | 5 | 5 |
| 18\(^c\) | Et\(_3\)N (100) | 82 (75\(^c\)) | 7 | 6 |
| 19\(^d\) | Et\(_3\)N-Pyr 4-1 (125) | 75 | 5 | 5 |
| 20\(^d\) | Et\(_3\)N-Pyr 1-4 (125) | 75 | 5 | 4 |

---

b.

**Best Combination of Stability and Steric Hindrance**

- **Me**
- **Et**
- **N**
- **TMEDA**

**Not Basic Enough**

**Too Bulky**

- **PhCO\(_2\)K**
- **t\(_2\)Pr\(_2\)NEt**

---

8
Figure 2. 

**Brønsted Basicity Controls Selectivity a.** Amine bases influence selectivity for arylation vs. benzylation. 

b. Unhindered basic amines favored the arylation product. 

Reaction conditions: 1 (0.10 mmol), Pd(PPh₃)₄ (5.0 mol%), base (see Fig. 2a), toluene (0.05 M), 110 °C, 24 h. ¹⁹F NMR yields (α,α,α-trifluorotoluene as standard). 

Optimized conditions: 1 (0.50 mmol), Pd(PPh₃)₄ (2.5 mol%), Et₃N (1.0 equiv.), 1,4-dioxane (0.05 M), 100 °C, 12 h. 

Isolated yield. 

Substrate Scope. A variety of substrates bearing distinct electronic properties and substitution patterns on the benzylic moieties underwent the decarboxylative arylation to incorporate a α,α-difluoroketone group at the para-position of arenes relative to the original benzyl position (Fig. 3). Generally, ortho-substituted electron-rich (5a–b) and -deficient (5e–d) substrates provided the arylated products (6a–d) in good yields and selectivities (> 10:1). Particularly in the case of the substrate 5d, no benzylated product was observed by ¹⁹F NMR. The reaction of the substrate (5e) bearing a bulky phenyl group on the ortho-position of the...
aromatic ring gave the product (6e) in modest yield. This reaction generated 35% of 9H-fluorene as the major side product, which might derive from an intramolecular cyclization reaction. Moreover, substrates bearing an ortho coordinating group (5f–g) and two ortho groups (5h) tolerated the present transformation and produced the arylated products (6f–h) in good yields, though requiring higher catalyst loading and increased reaction temperatures. Even a non-substituted benzylic substrate (5i) was transformed to the arylated product (6i) in good yield and selectivity. This example demonstrated that the selectivity arose from Et₃N rather than a substituent effect. The regioselectivity of the arylation products was confirmed by extensive 2D NMR characterization of adducts 2, 6b, 6d and 6f (see the Supplementary Information for the details).
**Figure 3 Substrate Scope**

*a.* Para-selective C–H difluoroalkylation of substrates bearing distinct benzyl moieties  
*b.* Steric hindrance inhibited arylation.  
*c.* Para-selective C–H difluoroalkylation of substrates bearing distinct ketone moieties.  

*a* Reaction conditions: 5a–o or 8a–f (0.50 mmol), Pd(PPh₃)₄ (2.5 – 5.0 mol%), Et₃N (1.0 equiv.), 1,4-dioxane (0.05 M), 100 °C, 12 – 24 h. Isolated yields.  
*b* 110 °C.  
*c* 120 °C.  
*d* Ratio of isolated product determined by ¹⁹F NMR.  
*e* 1,4-dioxane (0.1 M), 120 °C.  
*f* ¹⁹F NMR yields (α,α,α-trifluorotoluene as standard).

Steric hindrance on the benzyl moiety influenced the yields and selectivity of the reaction. Specifically, meta-substituted substrates provided lower yields of the arylated products relative to their ortho-substituted counterparts (Fig. 3a: 6j vs 2, 6k vs 6a, and 6l vs 6d). This trend likely arose from the steric hindrance induced by the meta-substituent that disfavored the attack of α,α-difluoroketone enolates at the para position, thus reducing the yields and selectivity of arylated product. Accordingly, substitution of both meta positions, only provided benzylation product 7m (Fig. 3b). Further, substitution of the para position exclusively afforded the benzylation product (7n–o), with no evidence of an expected dearomatized product (Fig. 3b).

The decarboxylative arylation reaction also selectively converted substrates bearing a variety of aryl, heteroaryl, and alkyl α,α-difluoroketones into the products of C–H functionalization (Fig. 3c). Substrates bearing electron-rich (8a), -neutral (8b), and -deficient (8c) aryl α,α-difluoroketone moieties provided the arylated products (9a–c) in high yields and selectivities (>20:1). Even, heteroaryl-containing α,α-difluoroketone substrates (5d–e) worked well under the standard reaction conditions. The tolerance to S- and N-containing heterocycles suggests that the current reaction can apply toward accessing fluorinated analogues of biologically active molecules. Additionally, the reaction of an aliphatic α,α-difluoroketone
substrate (8f) afforded a good yield of the arylated product (9f) without further optimization. For all reactions, products derived from C–C bond formation at the ortho position were not detected (Fig. 3).

*Mechanistic Investigations.* The general mechanism of the C–H functionalization process to furnish α-aryl-α,α-difluoroketone or α-benzyl-α,α-difluoroketone products is depicted in Figure 4. An initial oxidative addition of the Pd(0) catalyst to the substrate formed the **Pd-Benzyl-Carboxylate** ion pair that reversibly dissociates. Upon decarboxylation, the **Pd-Benzyl-Carboxylate** formed **Pd-Enolate** complexes, of which the **O-Bound** and **C-Bound** states exist in equilibrium. The **C-Bound Pd-Enolate** irreversibly reductively eliminates to directly form the **Benzylation Product**. In contrast, the **O-Bound Pd-Enolate** undergoes reversible C–C bond formation at the *para* position to generate the **Dearomatized Intermediate**. Aromatization would provide the **Arylation Product**. At the beginning of this study, the Et₃N-controlled switch of selectivity was not understood; Et₃N could either bind to Pd and facilitate the arylation process over the benzylination process (Pd Ligand Sphere Inset, Fig. 4), or Et₃N could facilitate the rearomatization of the arylation intermediate. To investigate these processes in deeper detail, we conducted several experiments, including cross-over reactions, isotopic labeling experiments, and kinetic isotope effect (KIE), and computational studies.
Figure 4. General reaction mechanism.

*Dissociation of the Pd-benzyl – Carboxylate Ion Pair.* Support for the reversible dissociation of the Pd-Benzyl-Carboxylate ion pair derived from cross-over experiments (Fig. 5a). Subjection of equimolar amounts of substrates 1 and 10 to standard reaction conditions provided all four possible products in equivalent yields. This result implicated a fast scrambling of the Pd-Benzyl-Carboxylate ion pair, as has been previously observed in decarboxylative allylation reactions.41,42
**Figure 5. Mechanistic Experiments**

**a.** Detection of cross-over products supports dissociation of the Pd-Benzyl-Carboxylate ion pair.

**b.** Para hydrogen atom migrated to the benzylic position at a late stage of the reaction.

**c.** H-Migration occurred at a late stage of the reaction and did not involve Pd–H intermediate.

**Nature of C–H Functionalization Step.** In this reaction, the hydrogen atom initially at the para position of the substrate migrated to the benzylic position of the final arylation product. This migration was unequivocally observed using para-deuterated substrate 11, which provided product 12 with full transfer of deuterium to the benzylic position (Fig. 5b). This proton transfer occurred in an intramolecular fashion after the C–C bond forming event, as evidenced by a
second cross-over experiment using deuterated substrate 11 and unlabeled substrate 13. In this experiment, the yields and distribution of cross-over products closely matched those observed previously (Fig. 5a); however, the deuterium label did not cross away from the ‘Pr-bearing benzyl moiety (Fig. 5b). Therefore, the hydrogen atom migration occurred inside the solvent-cage and after formation of the C–C bond. Computational studies suggest that this hydrogen transfer-rearomatization sequence is enabled by the base (vide infra),38,43,44,45 as opposed to hydride transfer mediated by Pd.32 Attempts to detect and/or isolate the Dearomatized Intermediate and study its reactivity were unsuccessful, likely because conversion to the Arylation Product occurs at a sufficiently fast rate to minimize observation under reaction conditions.

Further evidence of the late-stage irreversible C–H bond cleavage / hydrogen migration sequence derived from kinetic isotopic effect (KIE) experiments and reactions with a deuterated additive (Fig. 5c). To probe the nature of the C–H bond cleavage, the reaction was run in the presence of CD3OD, a tool widely applied to identify metal hydride intermediates and reversible C–H abstractions.46,47 Unlike many C–H functionalization reactions, the present reaction formed no deuterated product, which discounted mechanisms involving reversible C–H bond activation and/or Pd–H and Pd–Ar intermediates (Fig. 5c). Additionally, KIE’s were explored at both the benzylic and para positions to investigate the sequence of C–C bond formation, C–H bond cleavage, and C–H bond formation. In parallel experiments, a KIE value of 1.0 was measured at both the benzylic and para positions, which suggests that the rate-determining step does not involve C–H bond cleavage (Fig. 5c).46 In competitive experiments, 2° KIE values of 1.3–1.4 at the same positions support a reaction for which the rate determining step does not involve cleavage of the C–H bond, but is sill influenced by the C–H vs. C–D bond strengths. Both
experiments together suggest that the rate-determining step occurs prior to the C–H\textsubscript{\textsubscript{para}} bond cleavage and C–H\textsubscript{\textsubscript{benzyl}} bond formation (Fig. 4).\textsuperscript{34,46,48}
a. **ARYLATION**  
- **Pd-Enolates**  
- **BENZYLATION**

![Chemical Structures and Reactions]

b. **Arylation Product** (C-H Functionalization)

![Chemical Structures and Reactions]
Figure 6. Energetics of key steps. Computed reaction coordinate diagram for the formation of arylation and benzylation products from Pd-enolate complexes.

Computations. An extensive computational investigation clarified the mechanism and the role of the Et₃N in switching the selectivity. These results were validated by crossover experiments, labelling studies, and reactivity trends (see the Supplementary Information for details). All conformational and ligand isomers of species leading from the Pd-Enolates were computed (Fig. 6a). The results revealed that, uniformly, amine-Pd coordination is disfavored over the phosphine-Pd coordination complexes (>5 kcal/mol, see the Supplementary Information for details). Interestingly, the Arylation-TS is kinetically favored by 3.9 kcal/mol over the Benzylation-TS (15.0 kcal/mol vs 18.9 kcal/mol, respectively). Critically, following the Arylation-TS, the barrier for proton transfer to aromatize the system is significant and strongly dependent on the identity of the base.

The critical Dearomatized Intermediate (α-difluoro-α,α-diallyl intermediate) along the arylation pathway bears an acidic methine proton adjacent to two allyl and one fluoroalkyl groups. The pKₐ of this proton suggests the need for stronger amine bases than Pyr (Fig. 2). In the presence of trialkyl amine base, rapid rearomatization favors the Arylation Product (e.g. 15.0 kcal/mol barrier for Me₃N). This distinct dearomatization/H-migration mechanism for reductive elimination complements the recently reported reductive elimination from a [L₉Pd(CF₂COR)(Ar)] complex, which also generates a C(α)–C(sp²) bond though a standard cross-coupling paradigm. In the absence of an appropriate base, the slower rearomatization (e.g. 22.7 kcal/mol for Pyr) favors the formation of the Benzylation Product (18.9 kcal/mol).

These results match experimental observations in which the use of Et₃N provides the arylation products, but the use of Pyr or no base provides the benzylation products. More
specifically, the trialkyl amine base governs the reaction by providing a low-energy pathway for rearomatization, which cannot otherwise occur in the absence of an appropriate base. Further, this mechanism also explains why sterically bulky bases were ineffective in rendering arylation products, because they are likely too hindered to react with the methine proton. Therefore the selectivity of this process is ultimately controlled by the relative kinetics between Benzyla-tion-TS and Deprot-TS.

**Conclusion.** In summary, amine additives transformed a benchmark decarboxylative-coupling benzylation reaction into an unique non-chelation-controlled para-selective C–H functionalization reaction. The two reaction paradigms typically require orthogonal substrates and conditions, but can now be accessed under complementary reaction conditions, namely by simply adding an inexpensive base (Et$_3$N) to a readily available Pd-based catalyst system. Mechanistically, the amine provided a low-energy pathway for rearomatization of a “hidden” dearomatized intermediate. This dearomatized intermediate might exist in other catalytic processes,$^{30}$ and exploitation of this strategy should allow the construction of new and unique products as yet unaccessible by current means.

**AUTHOR INFORMATION**

Corresponding Author

*E-mail: raaltman@ku.edu, *E-mail: paulc@science.oregonstate.edu

**Author Contributions**
The KU team (FAZ, MHY, and RAA) conducted the all experiments and initiated the project. The OSU team (ACB and PHYC) conducted the computations. Both teams contributed to the mechanistic analyses and the writing of the manuscript.

Notes
The authors declare no competing financial interests.

ACKNOWLEDGMENT
We thank the donors of the Herman Frasch Foundation for Chemical Research (701-HF12), and the National Science Foundation (CHE-1455163) for supporting this work. NMR Instrumentation was provided by NIH Shared Instrumentation Grants S10OD016360 and S10RR024664, NSF Major Research Instrumentation Grants 9977422 and 0320648, and NIH Center Grant P20GM103418. PHYC is the Bert and Emelyn Christensen professor of OSU, and gratefully acknowledges financial support from the Vicki & Patrick F. Stone family. PHYC and ACB acknowledge the National Science Foundation (NSF, CHE-1352663) and the computing infrastructure in part provided by the NSF Phase-2 CCI, Center for Sustainable Materials Chemistry (NSF CHE-1102637).

References:
1 Johansson Seechurn, C. C. C., Kitching, M. O., Colacot, T. J. & Snieckus, V. Palladium-Catalyzed Cross-Coupling: A Historical Contextual Perspective to the 2010 Nobel Prize. Angew. Chem. Int. Ed. 51, 5062-5085 (2012).
2 Labinger, J. A. & Bercaw, J. E. Understanding and exploiting C–H bond activation. Nature 417, 507–514 (2002).
3 Hartwig, J. F. Evolution of C–H Bond Functionalization from Methane to Methodology. J. Am. Chem. Soc. 138, 2-24 (2016).
4 Gensch, T., Hopkinson, M. N., Glorius, F. & Wencel-Delord, J. Mild metal-catalyzed C-H activation: examples and concepts. Chem. Soc. Rev. 45, 2900-2936 (2016).
Yamaguchi, J., Yamaguchi, A. D. & Itami, K. C–H Bond Functionalization: Emerging Synthetic Tools for Natural Products and Pharmaceuticals. *Angew. Chem. Int. Ed.* **51**, 8960-9009 (2012).

Engle, K. M., Mei, T.-S., Wasa, M. & Yu, J.-Q. Weak Coordination as a Powerful Means for Developing Broadly Useful C–H Functionalization Reactions. *Acc. Chem. Res.* **45**, 788-802 (2012).

Neufeldt, S. R. & Sanford, M. S. Controlling Site Selectivity in Palladium-Catalyzed C–H Bond Functionalization. *Acc. Chem. Res.* **45**, 936-946 (2012).

Zhang, F. & Spring, D. R. Arene C–H functionalisation using a removable/modifiable or a traceless directing group strategy. *Chem. Soc. Rev.* **43**, 6906-6919 (2014).

Yang, J. Transition metal catalyzed meta-C–H functionalization of aromatic compounds. *Org. Biomol. Chem.* **13**, 1930-1941 (2015).

Dey, A., Agasti, S. & Maiti, D. Palladium catalysed meta-C–H functionalization reactions. *Org. Biomol. Chem.* **14**, 5440-5453 (2016).

Yamaguchi, J., Yamaguchi, A. D. & Itami, K. C–H Bond Functionalization: Emerging Synthetic Tools for Natural Products and Pharmaceuticals. *Angew. Chem. Int. Ed.* **51**, 8960-9009 (2012).

Engle, K. M., Mei, T.-S., Wasa, M. & Yu, J.-Q. Weak Coordination as a Powerful Means for Developing Broadly Useful C–H Functionalization Reactions. *Acc. Chem. Res.* **45**, 788-802 (2012).

Neufeldt, S. R. & Sanford, M. S. Controlling Site Selectivity in Palladium-Catalyzed C–H Bond Functionalization. *Acc. Chem. Res.* **45**, 936-946 (2012).

Zhang, F. & Spring, D. R. Arene C–H functionalisation using a removable/modifiable or a traceless directing group strategy. *Chem. Soc. Rev.* **43**, 6906-6919 (2014).

Yang, J. Transition metal catalyzed meta-C–H functionalization of aromatic compounds. *Org. Biomol. Chem.* **13**, 1930-1941 (2015).

Dey, A., Agasti, S. & Maiti, D. Palladium catalysed meta-C–H functionalization reactions. *Org. Biomol. Chem.* **14**, 5440-5453 (2016).

Yang, Z., et al. Palladium-catalysed para-selective arylation of phenols with aryl iodides in water. *Chem. Commun.* **49**, 7653-7655 (2013).

Yu, Z., et al. Highly Site-Selective Direct C–H Bond Functionalization of Phenols with α-Aryl-α-diazoacetates and Diazooxindoles via Gold Catalysis. *J. Am. Chem. Soc.* **136**, 6904-6907 (2014).

Berzina, B., Sokolovs, I. & Suna, E. Copper-Catalyzed para-Selective C–H Amination of Electron-Rich Arenes. *ACS Catal.* **5**, 7008-7014 (2015).

Marchetti, L., Kantak, A., Davis, R. & DeBoef, B. Regioselective Gold-Catalyzed Oxidative C–N Bond Formation. *Org. Lett.* **17**, 358-361 (2015).

Xu, H., Shang, M., Dai, H.-X. & Yu, J.-Q. Ligand-Controlled Para-Selective C–H Arylation of Monosubstituted Arenes. *Org. Lett.* **17**, 3830-3833 (2015).

Yang, Z., Qiu, F.-C., Gao, J., Li, Z.-W. & Guan, B.-T. Palladium-Catalyzed Oxidative Arylation of Tertiary Benzamides: Para-Selectivity of Monosubstituted Arenes. *Org. Lett.* **17**, 4316-4319 (2015).

Sokolovs, I. & Suna, E. Para-Selective Cu-Catalyzed C–H Aryloxylation of Electron-Rich Arenes and Heteroarenes. *J. Org. Chem.* **81**, 371-379 (2016).

Ma, B. et al. Highly para-Selective C–H Alkylation of Benzene Derivatives with 2,2,2-Trifluoroethyl α-Aryl-α-Diazoesters. *Angew. Chem. Int. Ed.* **56**, 2749-2753 (2017).

Luan, Y.-X. et al. Amide-Ligand-Controlled Highly para-Selective Arylation of Monosubstituted Simple Arenes with Arylboronic Acids. *J. Am. Chem. Soc.* **139**, 1786-1789 (2017).

Zhang, Z., Tanaka, K. & Yu, J.-Q. Remote site-selective C–H activation directed by a catalytic bifunctional template. *Nature* **543**, 538-542 (2017).

Bag, S. et al. Remote para-C–H Functionalization of Arenes by a D-Shaped Biphenyl Template-Based Assembly. *J. Am. Chem. Soc.* **137**, 11888-11891 (2015).

Patra, T. et al. Palladium-Catalyzed Directed para-C–H Functionalization of Phenols. *Angew. Chem. Int. Ed.* **55**, 7751-7755 (2016).

Nakao, Y., Yamada, Y., Kashiwara, N. & Hiyama, T. Selective C-4 Alkylation of Pyridine by Nickel/Lewis Acid Catalysis. *J. Am. Chem. Soc.* **132**, 13666-13668 (2010).

Tsai, C.-C. et al. Bimetallic Nickel Aluminum Mediated Para-Selective Alkenylation of Pyridine: Direct Observation of η^2,η^1-Pyridine Ni(0)-Al(III) Intermediates Prior to C–H Bond Activation. *J. Am. Chem. Soc.* **132**, 11887-11889 (2010).

Saito, Y., Segawa, Y. & Itami, K. para-C–H Borylation of Benzene Derivatives by a Bulky Iridium Catalyst. *J. Am. Chem. Soc.* **137**, 5193-5198 (2015).
Okumura, S. et al. para-Selective Alkylation of Benzamides and Aromatic Ketones by Cooperative Nickel/Aluminum Catalysis. J. Am. Chem. Soc. 138, 14699-14704 (2016).

Yang, M.-H., Hunt, J. R., Sharifi, N. & Altman, R. A. Palladium Catalysis Enables Benzylation of α,α-Difluoroketone Enolates. Angew. Chem. Int. Ed. 55, 9080-9083 (2016).

Recio, I. I. I. A., Heinzman, J. D. & Tunge, J. A. Decarboxylative benzylolation and arylation of nitriles. Chem. Commun. 48, 142-144 (2012).

Mendis, S. N. & Tunge, J. A. Decarboxylative dearomatization and mono-α-arylation of ketones. Chem. Commun. 52, 7695-7698 (2016).

Jaeger, C. W. & Kornblum, N. New type of substitution at a saturated carbon atom. J. Am. Chem. Soc. 94, 2545-2547 (1972).

Bao, M., Nakamura, H. & Yamamoto, Y. Facile Allylative Dearomatization Catalyzed by Palladium. J. Am. Chem. Soc. 123, 759-760 (2001).

Lu, S., Xu, Z., Bao, M. & Yamamoto, Y. Carbocycle Synthesis through Facile and Efficient Palladium-Catalyzed Allylative De-aromatization of Naphthalene and Phenanthrene Allyl Chlorides. Angew. Chem. Int. Ed. 47, 4366-4369 (2008).

Peng, B., Zhang, S., Yu, X., Feng, X. & Bao, M. Nucleophilic Dearomatization of Chloromethyl Naphthalene Derivatives via η3-Benzylpalladium Intermediates: A New Strategy for Catalytic Dearomatization. Org. Lett. 13, 5402-5405 (2011).

Ueno, S., Komiya, S., Tanaka, T. & Kuwano, R. Intramolecular SN′-Type Aromatic Substitution of Benzylic Carbonates at their Para-Position. Org. Lett. 14, 338-341 (2012).

Zhang, S., Wang, Y., Feng, X. & Bao, M. Palladium-Catalyzed Amination of Chloromethyl naphthalene and Chloromethylanthracene Derivatives with Various Amines. J. Am. Chem. Soc. 134, 5492-5495 (2012).

Zhang, S., Yu, X., Feng, X., Yamamoto, Y. & Bao, M. Palladium-catalyzed regioselective allylation of five-membered heteroarenes with allyltributylstannane. Chem. Commun. 51, 3842-3845 (2015).

Bordwell, F. G. Equilibrium acidities in dimethyl sulfoxide solution. Acc. Chem. Res. 21, 456-463 (1988).

Trost, B. M., Xu, J. & Schmidt, T. Palladium-Catalyzed Decarboxylative Asymmetric Allylic Alkylation of Enol Carbonates. J. Am. Chem. Soc. 131, 18343-18357 (2009).

Weaver, J. D., Recio, A., Grenning, A. J. & Tunge, J. A. Transition Metal-Catalyzed Decarboxylative Allylation and Benzylolation Reactions. Chem. Rev. 111, 1846-1913 (2011).

Xie, H., Zhang, H. & Lin, Z. DFT Studies on the Palladium-Catalyzed Dearomatization Reaction between Chloromethyl naphthalene and the Cyclic Amine Morpholine. Organometallics 32, 2336-2343 (2013).

Boga, C., Del Vecchio, E., Forlani, L. & Tozzi, S. Evidence of Reversibility in Azo-Coupling Reactions between 1,3,5-Tris(N,N-dialkylamino)benzenes and Arenediazonium Salts. J. Org. Chem. 72, 8741-8747 (2007).

Forlani, L., Boga, C., Del Vecchio, E., Ngobo, A.-L. T. D. & Tozzi, S. Reactions of Wheland complexes: base catalysis in re- aromatization reaction of σ complexes obtained from 1,3,5-tris(N,N-dialkylamino)benzene and arenediazonium salts. J. Phys. Org. Chem. 20, 201-205 (2007).

Simmons, E. M. & Hartwig, J. F. On the Interpretation of Deuterium Kinetic Isotope Effects in C–H Bond Functionalizations by Transition-Metal Complexes. Angew. Chem. Int. Ed. 51, 3066-3072 (2012).

Ma, S., Villa, G., Thuy-Boun, P. S., Homs, A. & Yu, J.-Q. Palladium-Catalyzed ortho-Selective C–H Deuteration of Arenes: Evidence for Superior Reactivity of Weakly Coordinated Palladacycles. Angew. Chem. Int. Ed. 53, 734-737 (2014).

Ariafard, A. & Lin, Z. DFT Studies on the Mechanism of Allylative Dearomatization Catalyzed by Palladium. J. Am. Chem. Soc. 128, 13010-13016 (2006).
Arlow, S. I. & Hartwig, J. F. Synthesis, Characterization, and Reactivity of Palladium Fluorenone Complexes. *J. Am. Chem. Soc.* **139**, 16088-16091 (2017).