Palladium-Catalyzed Enantioselective β-C(sp³)–H Activation Reactions of Aliphatic Acids: A Retrosynthetic Surrogate for Enolate Alkylation and Conjugate Addition

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Conspectus:

Enolate alkylation and conjugate addition into an α,β-unsaturated system have served as longstanding strategic disconnections for the installation of α or β-substituents on carbonyl-containing compounds. At the onset of our efforts to develop C–H activation reactions for organic synthesis, we set our eye towards developing asymmetric β-C–H activation reactions of aliphatic acids, with the perspective that this bond-forming event could serve as a more flexible retrosynthetic surrogate for both canonical carbonyl-related asymmetric transformations. In this review, we describe our early efforts using strong-coordinating chiral oxazolines to probe reaction mechanism and the stereochemical nature of the C–H cleavage transition state. The characterization of key reactive intermediates through X-ray crystallography and computational studies suggested a transition state with C–H and Pd–OAc bonds being approximately coplanar for optimum interaction. We then moved forward to develop more practical, weakly-coordinating monodentate amide directing groups; a necessary advance towards achieving the β-C–H activation of weakly-coordinating native carboxylic acids. Throughout this journey, gradual deconvolution between a substrate's directing effect and its intimate interplay with ligand properties has culminated in the design of new ligand classes that ultimately allowed the competency of native carboxylic acids in β-C–H activation. These efforts established the importance of ligand acceleration in Pd-catalyzed C–H activation, where the substrate's weak-coordination is responsible for positioning the catalyst for C–H cleavage, while the direct participation from the bifunctional ligand is responsible for enthalpically stabilizing the C–H cleavage transition state. Building upon these principles, we developed five classes of chiral ligands (MPAA, MPAQ, MPAO, MPAThio, MPAAM) to enable enantioselective β-C–H activation reactions, including carbon–carbon and carbon–heteroatom bond formation. The accumulated data from our developed enantioselective C–H activation reactions indicate that ligands possessing point chirality are most

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effective for imparting stereoinduction in the C–H activation step; the application of which enabled the desymmetrization and subsequent C–H functionalization of enantiotopic carbon and protons across a range of weakly-coordinating arylamides, and more recently, with free carboxylic acids. Progress in ligand design, in conjunction with the enabling nature of alkali metal countercations, led to the realization of a suite of β-methyl, and now methylene, $C(sp^3)$–H activation reactions. These advancements also enabled the use of economical oxidants, such as peroxides and molecular oxygen, to facilitate catalyst turnover. In the future, continued progression in designing more efficient bifunctional chiral ligands is likely to provide a myriad of enantioselective β-C–H activation reactions of readily-available native substrates.

Graphical Abstract
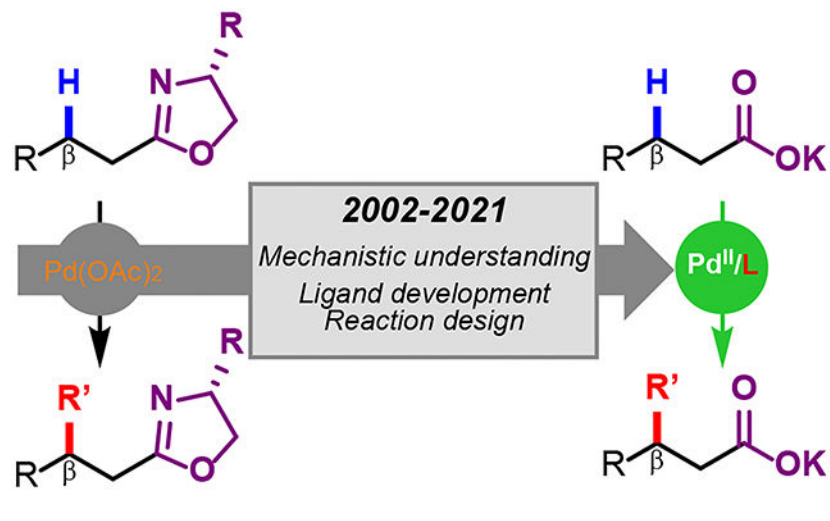
1. Introduction

Since its advent in the early 1800s, synthetic organic chemistry has enabled breakthroughs in medicine, agriculture, and materials science.[5,6] Although modern chemists are well-equipped to construct an immense range of complex molecules, organic synthesis still contains an abundance of unsolved problems. One of the most fundamental limitations of organic synthesis is its dependence on reactive functional groups to forge new chemical bonds. Because organic molecules are composed almost entirely of unreactive C–C and C–H bonds, the transformation of simple starting materials into intricate target molecules can often be circuitous to install or manage reactive functional handles that will ultimately be replaced or removed.

The field of C–H activation has accrued tremendous interest over the past several decades due to its potential to overcome the inefficiencies by redefining the inert C–H bond as a latent source of functionality.[7] However, the ubiquity of C–H bonds in organic molecules poses one of the most formidable regiochemical challenges in transition metal-catalyzed C–H functionalization. To this end, leveraging Lewis basic groups to direct a metal catalyst is a commonly employed strategy to impart regioselection, precisely positioning the catalyst close to a target C–H bond and minimizing the entropic cost of activation required to select

for one of many C–H bonds.[8] Over the years, advancements in directing group, catalyst and ligand design have enabled $C(sp^2)$–H functionalization to become a well-established area of research, and also enabled the previously-elusive aliphatic C–H activation a possibility despite the distinct challenges posed by these systems.[9]

At the outset of our research program, we were particularly interested in developing robust strategies in the β-functionalization of aliphatic free acids, generating products analogous to enolate alkylation in β-methyl functionalization or conjugate addition for β-methylene functionalization (Scheme 1). This was motivated by their ubiquitous presence in chemical feedstocks and natural products, facile diversification, as well as their relative stability compared with carbonyl compounds of lower oxidation states. Such a β-C–H activation approach can widen the versatility of carbonyl functionalization reactions by circumventing the need for: (1) prefunctionalization, and (2) polarity-matching resultant from electronic properties (*e.g.* innately-nucleophilic enolates, or innately-electrophilic α,β-unsaturated systems). In effect, this reconceptualizes canonical d^2/a^3 synthons by avoiding the need for/generation of reactive nucleophilic reagents, while enabling broad compatibility with a range of mild nucleophiles and electrophiles.[10]

Over the decades, fervent research efforts have been devoted toward controlling the π-facial selectivity of enolate or conjugate additions, leading to many established asymmetric variants for these processes. Despite these advancements, free acid asymmetric α-alkylation and conjugate addition into their α,β-unsaturated derivatives represent still to this day, an outstanding methodological gap in the synthetic canon. To this end, β-C–H functionalization provides a unique opportunity in addressing this synthetic shortfall. Contrasting the community's extensive history in controlling π-facial selectivity, enantioselective C–H functionalization processes—where a chiral transition metal complex stereoselectively reacts with a prochiral C–H bond to generate a chiral organometallic intermediate—remained unknown when we initiated this program.[11] These topological differences necessitate the establishment of new stereomodels, given that previously-privileged scaffolds for controlling π-facial selectivity (*e.g.* C_2-symmetic motifs) may not be cross-transferable for the desymmetrization of tetrahedral sp^3 centers. Specifically, β-C–H functionalization could be rendered enantioselective through two main categories: (1) desymmetrization of *enantiotopic carbons* (Scheme 2a), and (2) desymmetrization of *enantiotopic protons* (Scheme 2b). Given the synthetic importance of these carbonyl-related reactions, and in particular their asymmetric variants, we envisioned that the rigorous development of an alternative retrosynthetic disconnection can potentially reconceptualize how carbonyl substitutions are asymmetrically constructed, providing a unified aliphatic retron to access these diverse products.

However, these ambitions were notably challenging at the outset as the reactivity of $Pd(OAc)_2$ for cleaving $C(sp^3)$–H is poor and, at the time, was limited to cyclopalladation directed by nitrogen or sulfur atoms. Native functional groups are often ineffective directing groups for C–H activation owing to their suboptimal catalyst binding abilities, and therefore require the installation of exogenous directing groups to obtain the desired reactivity; the weak coordinative ability of aliphatic acids is no exception to this. Finally, we were also drawn to the potential of using the cyclopalladated intermediate as a linchpin towards its

conversion into a range of C–C or C–X bonds, but recognized that to do so required the development of new ligand scaffolds to enhance the reactivity of the Pd(II) species in order to enable native substrates such as aliphatic acids to direct C–H activation.

In this account, we chronicle the development of palladium-catalyzed β-C(sp^3)–H activation reactions of aliphatic acid derivatives and its diverse reactivity evolution through the lens of ligand development. We begin our discussion with our group's early examples employing chiral oxazolines, highlighting the mechanistic insight into both the redox catalytic cycle and the C–H cleavage transition states established from these initial studies. Next, we describe the progress made towards allowing the use of weakly-coordinating groups in β-C–H activation; a particularly important development towards our ultimate goal: functionalization of free acids. Finally, we cover emerging examples that successfully utilize free acids without requiring exogenous directing group installation—a culmination of a journey since 2002 in ligand design and reaction development. Interwoven through this account, we illustrate how changes in a substrate's directing effect required synergistic modulations in ligand design, and the crucial developments that enable these scaffolds to achieve the required ligand acceleration required for enantioselective aliphatic β-C(sp^3)–H functionalization.[12] We note that this review is not designed to be comprehensive, but rather to summarize key developments and to emphasize ongoing challenges and opportunities for the field at-large.[13]

2. Oxazoline Directing Groups (2002–2007): Mechanistic Insights in Diastereoselective C–H Activation

In our early efforts to develop asymmetric β-C–H activation reactions (supported by a Royal Society Research grant in 2002), we envisioned that a σ-chelating acid-derived chiral auxiliary such as an oxazoline could promote the assembly of a square planar palladium complex poised for cyclometallation. In 2005, our laboratory reported early examples of β-C(sp^3)–H functionalization employing oxazolines as auxiliaries for carboxylic acids.[14] In this report, the iodination of unactivated methyl and cyclopropane C–H bonds was effected under mild conditions, with the pivotal C–H cleavage step mediated by palladium-bound acetates (Scheme 3).[15,16] The C–H functionalization was selective for primary over secondary C–H bonds, and the use of a chiral oxazoline resulted in diastereoselective methyl C(sp^3)–H iodination for substrates where R^1 ≠ R^2. For diastereoselective variants, the oxazoline auxiliary could be cleaved to unveil chiral β-functionalized carboxylic acids in >99% ee. In the same year, we disclosed a related diastereoselective C(sp^3)–H acetoxylation reaction (Scheme 4a).[17] A trinuclear palladium complex bearing an *anti*-configured arrangement was isolated and characterized by X-ray crystallography, an observation that eventually formed the basis of future ligand design for enantioselective β-functionalization (Scheme 4b). We also found that the addition of Ac$_2$O was vital to promote catalyst turnover, regenerating the active Pd(OAc)$_2$ catalyst presumably *via* ligand exchange to afford Pd(IV) diacetate prior to the reductive elimination (Scheme 4c). Subsequent studies on the C–H cleavage step shed light that the Pd–OAc lay approximately coplanar with the target C–H bond, selecting for the C–H bond that minimized substrate steric interactions.[18] These insights gathered from these early examples of aliphatic acid β-C–H

activation established important foundations in ligand and reaction development that guided our eventual successes in the free acid-directed lactonization and acetoxylation processes.

3. Weakly-Coordinating Amide Directing Groups as Acid Surrogates (2007–2020)

3.1 Overview and reactivity development

Amides are commonly employed as exogenous directing groups for the β-C(sp³)–H functionalization of carboxylic acids, and can be roughly divided into two categories: 1) strongly-coordinating, bidentate amides (Figure 1),[19,20] and 2) weakly-coordinating, monodentate amides.[21] While widely employed in transition metal-catalyzed C–H functionalization reactions, strongly-coordinating bidentate amide directing groups are burdened with disadvantages.[22] First, the thermodynamic stability of cyclometallated intermediates is a double-edged sword; although C–H activation is more favored due to the thermodynamic stability of the resulting cyclometallated intermediates, subsequent functionalization of these metallacycles can be challenging due to the a) lack of reactivity of stable strongly-bound intermediates, and b) lack of vacant coordination sites limiting the scope of coupling partners.[22] The latter prohibits downstream transformations such as cross-coupling from being realized, as these intrinsically require two vacant coordination sites on the catalyst to allow transmetallation to occur. Second, employment of external chiral ligands for catalyst-controlled stereoinduction is often not feasible because the strong directing group coordination outcompetes catalyst binding. This critical limitation renders ligand acceleration—necessary for enantioselective catalytic functionalization—particularly challenging.

With our vision towards achieving the enantioselective β-C(sp³)–H functionalization of weakly-coordinating free acids, our laboratory moved away from the established reactivity of strongly-coordinating amides. As a steppingstone, we targeted the development of weakly-coordinating monodentate amide directing groups to facilitate C–H functionalization. We envisaged that the extra vacant coordinating site on the catalyst might enable the use of chiral bidentate ligand scaffolds to impart enantioinduction while broadening transformation scope, thus directly addressing the shortcomings imposed by strongly-coordinating bidentate directing groups. The departure from established directing groups posed energetic challenges we needed to overcome, as the enthalpic contribution from the strong coordination, as well as the conformational restriction from these often-rigid directing groups, all assist in favoring the challenging process of C–H metallation. With only weak-coordination available from the directing motif, the requisite catalytically-relevant substrate-Pd(II) complex poised for cyclometallation is more transient or elusive. This means that a suitably-designed ligand is required to accelerate the C–H cleavage process via reducing the energy barrier (Figure 2). Such ligand acceleration is crucial for achieving asymmetric induction, as any competitive racemic pathway arising from a ligand-free process will erode enantioselectivity.

To this end, we discovered that *N*-methoxyamides were competent weak-coordinating groups, enabling the first example of β-cross-coupling of aliphatic acids with aryl

and alkyl boronic acids (2008, Scheme 5a).[21a] Critically, the shift to monodenticity facilitated cross-coupling, a previously inaccessible transformation, to proceed efficiently. Later, we identified that electron-deficient monodentate *N*-arylamides are privileged weak-coordinating motifs surrogating free acids; particularly noting that the acidic amide proton behaves analogously to the acidic carboxyl proton. The innovations developed to meet the challenges imposed by weakly-directing motifs facilitated the broad discovery of novel transformations across diverse catalytic cycles. One such innovation was reported in 2009, where our laboratory reported the first example of a palladium-catalyzed β-C(sp^3)–H arylation directed by weakly-coordinating *N*-arylamides (Scheme 5b).[21b] The use of CyJohnPhos (**L-1**) in conjunction with CsF enabled the first example of β-methyl C–H functionalization proceeding *via* a Pd(0)/Pd(II) catalytic cycle. Shortly thereafter, we designed a modified *N*-arylamide directing group that proved enabling in the discovery of diverse reactivities. Beyond enabling cross-coupling processes, the weakly-coordinating arylamide directing group proved instrumental in the pioneering discovery of a range of aliphatic β-functionalizations, reporting unprecedented examples in C(sp^3)–H arylation,[1,2,23] alkylation,[24] olefination,[2,23b,e,25] alkynylation,[2,26] carbonylation,[27] borylation,[28] amination,[29] and halogenation[30] (Scheme 5c).

Realizing such a range of transformations validated that diverse functionalization can be enabled by weak substrate coordination. In addition, the shift to a monodentate directing group provided the crucial opportunity for the use of previously inaccessible chiral bidentate ligand scaffolds bearing internal base motifs.[31] These internal base motifs participate in and accelerate C–H cleavage, enabling the catalyst to outcompete against potential background reactivity in the enantiodetermining step.[1,2] The ability for bifunctional chiral bidentate ligands to directly participate in C–H cleavage transition state then allowed us to achieve a range of enantioselective β-C(sp^3)–H activation reactions, with the bidentate binding providing the required spatial organization to enable facile C–H cleavage and the requisite stereoenvironment for enantioinduction *despite* direction by a weakly-coordinating motif.

In the following section, we highlight the number of enantioselective transformations directed by weakly-coordinative amide directing groups, categorizing by the nature of desymmetrization (*i.e.* desymmetrization of enantiotopic carbons *or* enantiotopic protons on the same carbon) during the C–H activation process. These representative examples demonstrate the broad scope of transformations achieved, and highlight key ligand developments that guided our eventual success in achieving free acid functionalization.

3.2 Desymmetrization of Enantiotopic Carbon Atoms

The discovery of bifunctional MPAA ligands—which not only modulate the stereo and electronic environments of the Pd(II) center,[32] but also participate in the C–H cleavage step directly —paved the way for subsequent bidentate ligand design.[33] Beginning in 2011, our group developed several examples of amide-directed asymmetric C–H functionalization *via* desymmetrization of enantiotopic carbons. First, we established the enantioselective C–H arylation, alkylation, and alkenylation of cyclopropanes through cross-coupling with a variety of boronates directed by a weakly-coordinating *N*-arylamide (Scheme 6).[34] Systematic tuning of chiral ligands, especially using the *N*-TcBoc-based protecting group

that was likely involved in the C–H cleavage step, led to the development of a new bidentate MPAA ligand (**L-2**) crucial for high enantioselectivity. Later, our group reported an enantioselective β-C(sp^3)–H arylation of cyclobutanes (Scheme 7),[35] utilizing the same weakly-coordinating *N*-arylamide directing group but employs a chiral *N*-protected bidentate hydroxamic acid ligand (**L-3**).[36] In addition, a small number of acyclic amides were also competent to afford chiral β-aryl amides in moderate yields and ee's.

The desymmetrization of isopropyl groups represents a far more formidable challenge than our previously reported desymmetrative activated β-methylene C–H functionalization due to the more flexible nature of the substrate (Scheme 8a). In 2017, our laboratory established the enantioselective β-C–H arylation, alkenylation, and alkynylation of isobutyramide substrates, directed by a weakly-coordinating perfluorotolyl *N*-arylamide group (Scheme 8b).[2] Inspired by our early studies in oxazoline directing groups, we found success using chiral bidentate *mono*-protected aminomethyl oxazoline (MPAO) ligands. The rigidity and previously-established strong-binding conferred by the oxazoline unit was important to achieve high reactivity and enantioselectivity for this process, with the (*S,S*)-configuration in **L-4** proving optimal for enantioinduction. Importantly, the proposed stereomodel was enabled by our early observations with chiral oxazoline-directed C–H activation, leveraging the *anti*-disposed nature of the substrate and the oxazoline unit to impart enantioinduction. By instead employing a chiral benzoyl-protected MPAO ligand, in conjunction with a weak-coordinating *N*-methoxyamides directing group, 2-aminoisobutyric acid derivatives also underwent enantioselective C–H arylation to afford synthetically valuable chiral α,α-dialkyl α-amino acids. Notably, the prevailing stereomodel proposed for the transformation was enabled by our early observations with chiral oxazolines, noting that sterically-large groups are preferentially *anti*-disposed across the metal catalyst. The remaining α-methyl group in the products could undergo an additional C–H arylation, alkynylation, alkylation, bromination, or borylation to afford diverse α-chiral carboxylic acids.

Taking the success of the MPAO ligand scaffold, our group developed the first enantioselective C(sp^3)–H borylation platform, capable of desymmetrizing methylene C–H bonds in achiral cyclobutylamide substrates using Chiral (*S,R*)-configured bidentate MPAO ligand **L-5** and O$_2$ as the sole oxidant (Scheme 9a).[28b] Enantioinduction was proposed to occur through minimizing steric repulsion between the cyclobutyl ring and the ligand substituents on both MPAO stereocentres (Scheme 9b). Notably, cyclic amides of various ring sizes engaged in the C–H borylation and substrates containing α-tertiary and quaternary carbon centers were tolerated. This study highlights the enabling nature of MPAO ligands in discriminating prochiral carbons for this substrate class given the structural similarity between the isopropyl and cyclobutyl motifs (which can be seen as a constrained isopropyl unit). At the same time, these results illustrated the profound effects on enantioinduction imparted by subtle differences in ligand configuration; the (*S,R*)-MPAO diastereomer effective for cyclobutyl substrates was found to be ineffective for isopropyl desymmetrization.

In 2018, our group extended the applicability of MPAO ligands to enantioselective β-C(sp^3)–H arylation and vinylation of cyclobutylamides using **L-6** (Scheme 10).[23e] This new transformation overcame several of the key limitations associated with our earlier

work (Scheme 7, *vide supra*). First, cyclobutane substrates possessing α-hydrogen atoms were now compatible, and vinylation reactions were performed in addition to arylation. To demonstrate the utility of the transformation, sequential C–H arylation and vinylation were carried out to rapidly construct substituted chiral cyclobutanes bearing three contiguous stereocenters challenging to construct using traditional means.

In addition to examples developed by our laboratory, the Colobert group has also reported amide-directed enantioselective β-C(sp^3)–H activation reactions. Inspired by their previous work utilizing chiral sulfoxides as auxiliary directing groups,[37] the Colobert group recently designed a new family of bidentate chiral *N*-protected aminosulfoxide ligands (**L-7**) for enantioselective β-C(sp^3)–H activation (Scheme 11).[38] *N*-Arylamide derivatives of cyclopropanecarboxylic acid underwent enantioselective C–H arylation in good yields and enantioselectivities utilizing a broad scope of aryl iodides. The proposed stereochemical model invokes key π-stacking interactions between the substrate and ligand, as well as minimized steric interactions between the aryl substituent and *N*-Ac moiety on the ligand.

3.3 Desymmetrization of Enantiotopic Protons

Compared to the desymmetrization of enantiotopic carbons, the enantioselective activation of enantiotopic protons represents a far greater challenge, owing both to the precision required to select for only one of two target protons (rather than differentiating *sets* of several protons), as well as the higher energetic barrier of methylene C–H activation especially for unactivated aliphatic substrates. In 2016, our group developed the enantioselective β-C(sp^3)–H arylation of aliphatic amides, enabled by the discovery of chiral bidentate acetyl-protected aminoethyl quinoline (MPAQ) ligands (**L-8**, Scheme 12).[1,39] The design of MPAQ ligands was inspired by combining features from quinoline ligands, previously employed by our group to stabilize and reliably speciate the active catalyst,[23a,33] and MPAA ligands, previously utilized to accelerate C(sp^3)–H activation and imbue enantioselection.[31,32] In a similar manner, the quinolyl motif was incorporated to provide strong σ-coordination to the metal catalyst, positioning the internal base to favorably cleave the target C–H bond. Extensive ligand evaluation revealed that scaffolds that generated a six-membered Pd chelate was crucial for reactivity. This was later rationalized computationally noting that the five-membered chelate favors the formation of a catalytically incompetent dimeric Pd species, as well as accruing disfavored steric interactions between the arylamide unit with the quinoline ligand due to restricted conformational freedom of the smaller chelate.[40] With the optimized MPAQ ligand (**L-8**), this transformation tolerated a broad scope of aryl iodides and aliphatic amides, proceeding in excellent yields and enantioselectivities.

Extending this finding, we developed an enantio- and diastereoselective methylene C–H arylation of unstrained cycloalkylcarboxamides enabled using analogous bidentate MPAQ ligands (Scheme 13),[23f] which represents the first example of diastereoselective C–H activation through catalyst rather than substrate control. By selecting the optimal *N,N*-ligand (**L-9**, **L-10**) differing in its stereochemical nature, the reaction enabled the selective C–H cleavage of any of the four possible β-C–H bonds in the cycloalkylcarboxamides substrate, selectively generating any of the four possible stereoisomers of the 2-arylated products.

4. β-C(sp³)–H Activation Reactions of Free Carboxylic Acids

4.1 Overview

So far, bespoke directing groups previously discussed have been crucial for the advancement of aliphatic C–H activation, though separate installation and often-adverse removal conditions hamper their tractability. While the direct functionalization of free acid is a desirable venture, their weak coordination diminishes the amount of catalyst-bound substrate present, thus abating reactivity.[41] Additionally, competition between κ^1 and κ^2 coordination modes is problematic, as the κ^2-bound complex does not possess adequate geometry required for cyclometallation. Taking lessons learned from studies incorporating weak-coordinating amides, we discuss the developments that has led to the successful β-C(sp³)–H functionalization of native carboxylic acids without exogenous directing groups.

The first example of native acid-directed aliphatic C–H activation was reported by the Sen group in 1991 (Scheme 14a).[42] This C–H oxidation reaction was stoichiometric in platinum and required superstoichiometric amounts of the substrate. Despite these shortcomings, this work served as an early proof-of-concept that free carboxylic acids could direct a transition metal-catalyzed C–H functionalization reaction at the β-position of an aliphatic substrate. In 2007, our laboratory reported the first catalytic carboxylic acid-directed β-C(sp³)–H activation reaction under ligand free conditions (Scheme 14b).[43] A key finding we discovered was the dramatic acceleration in reactivity through the use of alkali metal carboxylate-derivatives of free acids; noteworthily, the use of a preformed palladium carboxylate substrate *in the absence of* an alkali metal cation was not reactive.[43,44] This remarkable effect in reactivity was later ascribed to the alkali metal preferentially binding to the carboxylate in a κ^2 manner, facilitating carboxylate-catalyst binding in a productive κ^1 fashion.[45] This finding was a major enabler for subsequent reaction development, with nearly all future discoveries requiring a source of alkali metal cation to promote reactivity. Simple α-quaternized aliphatic acids were functionalized with arylboron reagents with good *mono* selectivity under ligand-free conditions, albeit in low yields. β-Functionalization was also achieved with aryl iodides as coupling partners in good yields and with moderate selectivity for monoarylation. In addition, one example was demonstrated for the arylation of a cyclopropyl C–H bond, notable due to the rarity of methylene C–H activation reactions at the time.

4.2 Carboxylic acid directed methyl functionalization (2017–present)

Carboxylic acid-directed aliphatic β-C–H activation remained dormant until a decade later, when several examples of β-C(sp³)–H arylation of substrates without α-quaternary centers were developed. In 2017, our laboratory disclosed the β-C–H arylation of α-amino acids employing aryl iodides as coupling partners (Scheme 15a and b),[46] where a strongly-coordinating pyridine-type ligand **L-11** was crucial for the success of our C–H arylation reaction. Zhao group found that our bidentate MPAA ligand could also effect this arylation reaction.[47] In the same year, the van Gemmeren group reported the β-C(sp³)–H arylation of simple, unfunctionalized carboxylic acids with aryl iodides to afford hydrocinnamic acid derivatives (Scheme 15c).[48] This transformation again employed a bidentate β-MPAA

ligand, tolerated a wide variety of aryl iodides, and performed well with carboxylic acids bearing α-secondary, tertiary, and quaternary centers.

Over the years, cumulative advances have broadened the scope of free acid functionalization to include olefination, carbonylation, alkynylation, acetoxylation, lactonization, and acyloxylation reactions, with these reactions uniformly enabled by bidentate MPAA and related ligands.[3,49–54] In 2018, our laboratory reported the β-C(sp^3)–H olefination, and subsequent lactonization, of aliphatic carboxylic acids to afford γ-lactones (Scheme 16a).[3] This transformation was enabled by the development of a new class of bifunctional acetyl-protected aminoethyl phenyl thioether ligand (**L-12**), with the thioether motif anchoring the catalyst through strong σ-coordination to favorably position the NHAc internal base for C–H cleavage. The use of this novel ligand later also permitted the carboxylic acid-directed β-C(sp^3)–H carbonylation to afford acid anhydrides, giving a rapid entry point to a range of β-carboxylated products (Scheme 16b).[49] Alongside our initial disclosure in 2018, the van Gemmeren group developed the β-C(sp^3)–H acetoxylation of aliphatic carboxylic acids (Scheme 16b).[50] This transformation, though scalable to 5 mmol, was mostly limited to carboxylic acids bearing α-quaternary centers, although one example with an α-tertiary center was demonstrated in low yield.

Recently, our laboratory discovered a carboxylic acid-directed β-C(sp^3)–H lactonization to afford β-lactones using an inexpensive *tert*-butyl hydroperoxide (TBHP) oxidant enabled by β-MPAA ligand **L-13** (Scheme 17a).[51] This provided a modular synthetic route toward β-substituted carboxylic acids by nucleophilic ring-opening of β-lactones to construct diverse C–C and C–X bonds. This C–H lactonization could be carried out on gram scale, catalyst loading could be lowered to 1% and the β-lactone product could be isolated with a simple aqueous wash without chromatography. Modification of these conditions next enabled the discovery of carboxylic acid-directed β-C(sp^3)–H acyloxylation and intramolecular lactonization (to generate γ-, δ-, and ε-lactones), enabled by a new cyclopentane-based β-MPAA ligand (**L-14**).[52] Such conditions also facilitated a free acid-directed dehydrogenative cross-coupling reaction, whereby an initial methyl β-C(sp^3)–H activation generates a weakly bound alkylpalladium species that could then activate and cross-couple with a second aryl C–H bond (Scheme 17b).[53] This discovery enabled a range of tetralin, chromane and indane motifs to be generated, and facilitated a four-step total synthesis of (±)-russujaponol F. Coming full circle, the use of inexpensive TBHP oxidant in conjunction with Ac$_2$O was inspired by our early mechanistic studies in oxazoline-directed C–H acetoxylation; both requiring a similar combination of peroxide oxidant with Ac$_2$O for their success.

4.2. Current Challenges: Enantioselective and β-Methylene Functionalization Functionalization of Carboxylic Acids

Beyond its weak directing ability, the utilization of free carboxylic acids as directing groups for enantioselective C–H activation is especially challenging due to the flexibility of the metal-carboxylate complex, demanding the design of new chiral ligands to promote the desired reactivity *and* stereoselectivity. The first examples of carboxylic acid-directed enantioselective β-C(sp^3)–H activation reactions *via* differentiation of enantiotopic carbon have been reported by our laboratory. In 2018, we reported the carboxylic acid-directed

C(sp^3)–H arylation of cyclopropanes, enabled by a new chiral *mono*-protected aminoethyl amine (MPAAm) ligand **L-15** (Scheme 18a);[55] the replacement of the planar azines (*e.g.* **L-8**) with the sterically more hindered dialkylamino group was crucial for achieving enantioselectivity. More recently, we reported the carboxylic acid-directed cross-coupling of cyclopropanes and cyclobutanes to introduce β-aryl or vinyl groups, enabled by chiral MPAAm (**L-16**) and MPAA ligands (**L-17, Scheme 18b**).[56] In light of these promising results and the challenges highlighted above, the development of diverse enantioselective carboxylic acid-directed functionalizations of unbiased methylene C(sp^3)–H bonds forms an ongoing ambition within our laboratory.

Advancing bifunctional ligand design and incorporating peroxide-mediated reaction conditions inspired from our early stoichiometric studies enabled a growing number of functionalizations directed by free acids. However, these successes tend to be limited to substrates bearing β-methyl or highly activated β-methylene groups, even though deuteration of β-methylene C–H bonds has been observed using MPAAm type ligands.[57] As unactivated methylene C–H bonds are more recalcitrant towards cyclopalladation, an enduring challenge relates to their effective β-methylene C–H activation and downstream functionalization. Building on its enabling ability in free acid-directed C(sp^2)–H oxygenations,[58] we discovered that a new class of pyridine-pyridone (PyriPyri) ligand scaffold (**L-18** and **L-19**) uniquely enabled the β-methylene dehydrogenation of free acids in the presence of other enolizable motifs (Scheme 19).[4] Through this discovery, we further demonstrated that this dehydrogenated intermediate can be intercepted with alkynyl bromides as a second coupling partner, generating diverse butenolide scaffolds. These emerging results augur hope that diverse β-methylene C(sp^3)–H functionalization of native carboxylic acids is indeed possible, and we project that further development along this enabling class of ligand could unveil new reactivities, and achieve enantioselection, for free acid-directed unactivated methylene C(sp^3)–H activation.

6. Summary and Outlook

Over the past two decades, significant advances have been made towards the diverse β-functionalization of aliphatic acids and their derivatives. These transformations typically circumvent the need for prefunctionalization, generation of reactive intermediates and polarity-matching constraints that characterize traditional enolate or conjugate addition transforms, highlighting the potential flexibility of C–H activation as an alternative retrosynthetic strategy. The early oxazoline β-C(sp^3)–H activation reaction reported by our laboratory in 2005 provided a valuable framework for subsequent reaction and chiral ligand design. To overcome the limitations posed by the well-established reactivity of strongly-coordinating bidentate directing groups (*e.g.* unreactive cyclometallated intermediates and limited use of external ligands), our group first developed β-C–H activation reactions that employ weakly-coordinating *N*-arylamide directing groups as free acid surrogates. These studies establish that the combination of weak substrate coordination and bifunctional ligand acceleration is a promising approach for advancing C(sp^3)–H activation, which is essential for realizing the β-C–H activation/functionalization of aliphatic acid substrates.

Central to these advances are the concomitant development of new ligand topologies, enabled both by increased mechanistic understanding and a shift to substrate monodenticity. Through this, specific ligand motifs were engineered to enable productive ligand participation at various steps within the catalytic cycle. Through these developments, we broadened the range of coupling partners possible through diverse catalytic cycles, and established the ability to impart ligand acceleration in these processes. The latter providing the framework necessary for the development of enantioselective variants, where we designed chiral ligands to facilitate enantioselective β-C(sp^3)–H activation reactions. Transformations which desymmetrize both enantiotopic carbon atoms and protons have been established, though the latter remaining less developed. To date, emerging examples show that challenging free acid-directed methylene and enantioselective transformations are possible, though significant research effort is necessary to broaden substrate and transformation scopes for these reactions. Through gaining insight into their reactivity, continued advances will be reliant on the development of new ligand scaffolds to address current shortfalls, which we project can improve the practicality, imbue stereoselectivity, surpass the current site-selectivity and enable further iterative functionalizations for diverse free acid-directed transformations (Scheme 20). These achievements can allow C(sp^3)–H functionalization of free acids to firmly stand beside or even *exceed* enolate and conjugate addition as a venerable strategy for the facile synthesis of diversely β-substituted carbonyl compounds.

Acknowledgement

Biographies

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Examples of Strongly-Coordinative Bidentate Amide Directing Groups

Daugulis, 2005

Daugulis, 2010

Chatani, 2011

Sahoo, 2012

Shi, 2013

Ackermann, 2014

Baran, 2014
Shi, 2015

Shi, 2015

Babu, 2016

Zhou, 2016

Yu, 2018

Ji, 2019
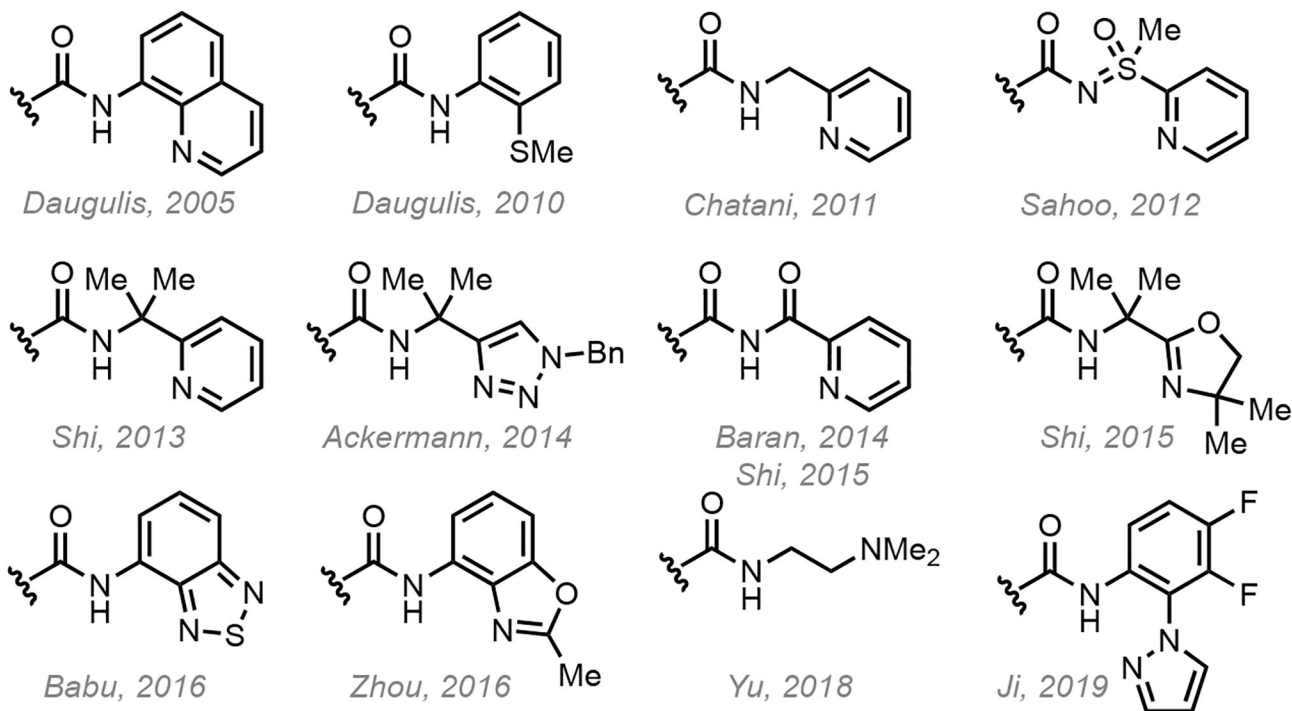
Figure 1.

Examples of strongly-coordinative bidentate amide directing groups commonly used for β-C(sp^3)–H functionalization

Strongly-Coordinative Bidentate Directing Group

Ligand acceleration challenging due to being limited to mono-dentate ligands
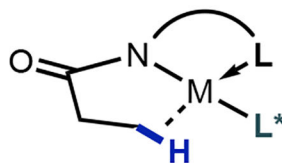
High stability and single vacant coordination site of the intermediate constrains diverse transformations

Weakly-Coordinative Monodentate Directing Group (X = COOH, OH, NHAr, *etc.*)
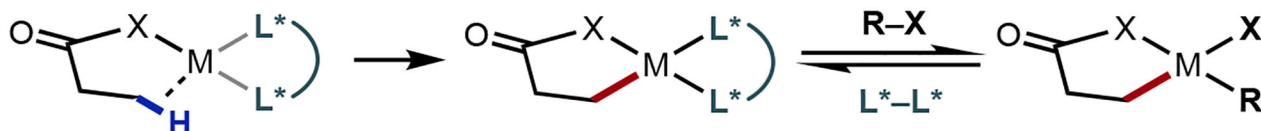
Weak coordination renders catalyst binding/positioning more challenging, but allows the design of both mono- and bidentate ligands for acclerating C–H activation

Figure 2.
Challenges associated with strongly-coordinating bidentate directing groups and rationale for moving towards weakly-coordinative monodentate directing groups

Scheme 1.
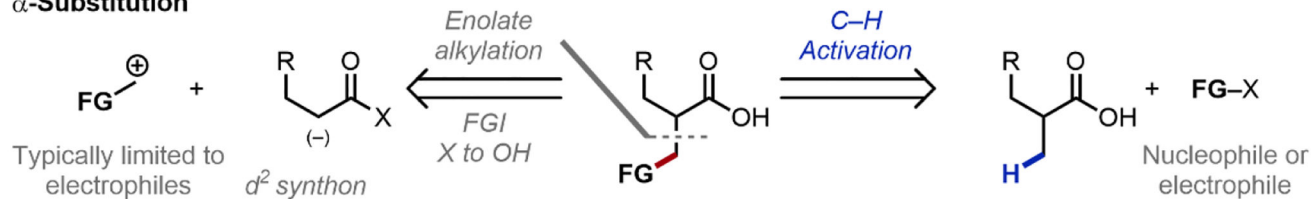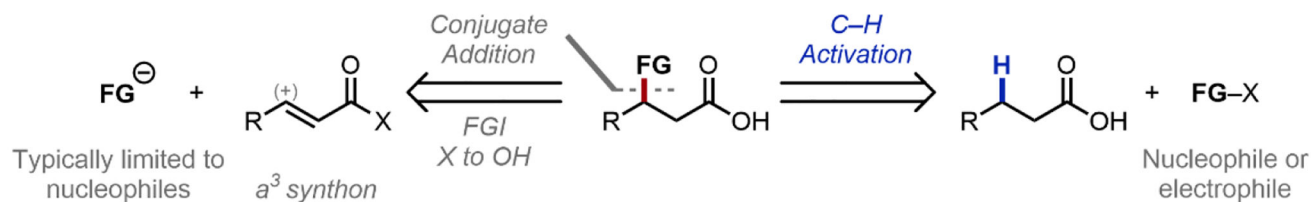
β-C–H functionalization provides an alternative disconnection for the synthesis of functionalized carbonyl derivatives that avoids reactive reagents. FG: Functional group; FGI: functional group interconversion.

(a) Desymmetrization of enantiotopic carbon atoms

C–H functionalization site

New stereocenter

Different carbon atoms

(b) Desymmetrization of enantiotopic protons

C–H functionalization site **and** new stereocenter on the **same carbon atom**
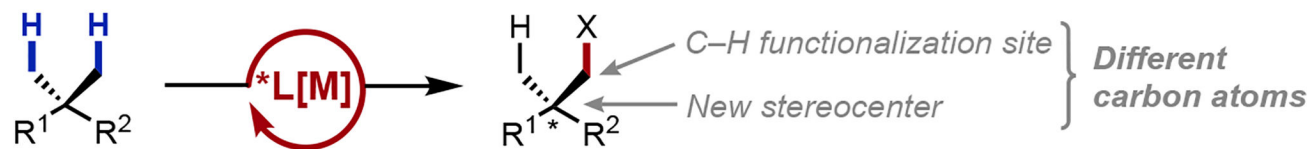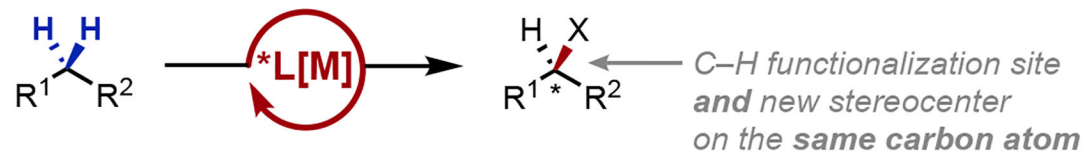
Scheme 2.
Desymmetrization of (a) enantiotopic carbon atoms vs. (b) enantiotopic protons
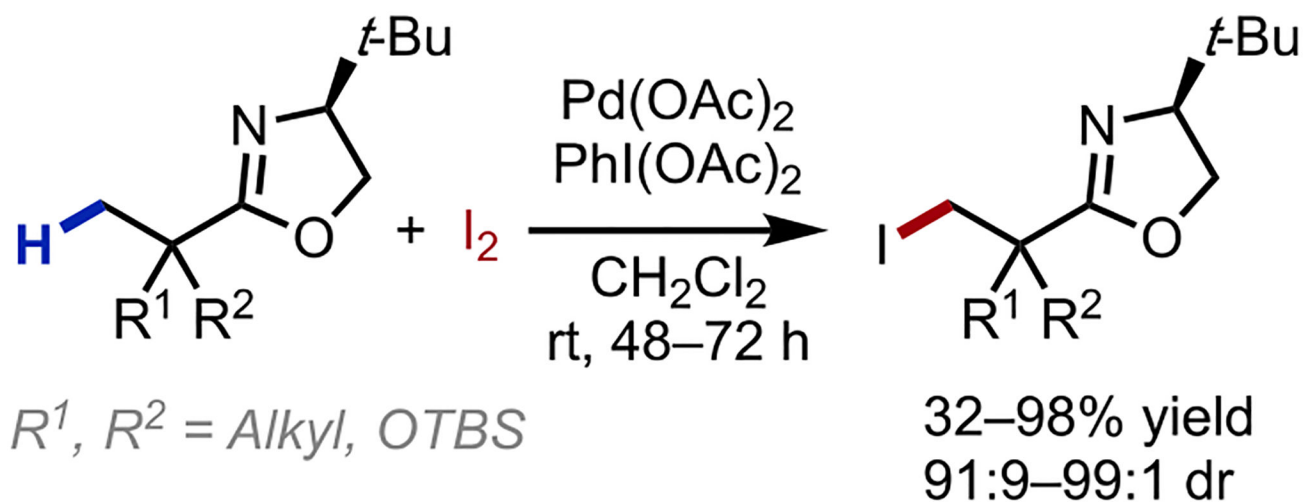
Scheme 3.
Oxazoline-directed diastereoselective β-C(sp^3)–H iodination reaction

(a) Oxazoline-directed C–H acetoxylation (Yu)

R¹, R² = Alkyl, NPhth

$$\text{Pd(OAc)}_2 \quad \text{AcOO}t\text{-Bu} \quad 65\ °\text{C},\ 48\text{–}72\ \text{h}$$

50–90% yield

R¹, R² = Alkyl, OTBS, NPhth

$$\text{Pd(OAc)}_2 \quad \text{lauroyl peroxide} \quad 50\ °\text{C},\ 48\ \text{h}$$

38–73% yield
12–82% de

(b) Key reactive intermediate

•Anti isomer
•Confirmed by X-ray crystallography

(c) Proposed catalytic cycle

trinuclear complex (X-ray)

AcOO*t*-Bu
(Ac₂O is required)

Scheme 4.
Oxazoline-directed diastereoselective β-C(sp³)–H acetoxylation reaction

(a) Weakly-Coordinating *N*-Methoxyamide-Directed Cross-Coupling
First protocol for alkyl cross-coupling with boronic acids

R^1, R^2 = Alkyl, NPhth
R^3 = Aryl, Alkyl

Pd(OAc)$_2$
Ag$_2$O, BQ, K$_2$CO$_3$

t-BuOH *or*
2,2,5,5,-tetramethylTHF
70 °C, 18 h

40–94% yield
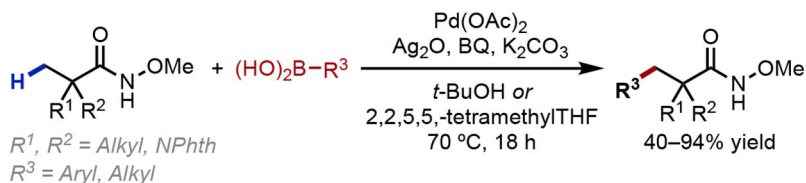
(b) Weakly-Coordinating *N*-Arylamide-Directed Arylation
Enabled the first example of directed Pd(0)/(II) catalysis

R^1, R^2 = Aryl, Alkyl, H

Pd(OAc)$_2$, **L-1**
ArI, CsF

3Å, PhMe
100 °C, N$_2$, 24 h

58–84% yield

L-1
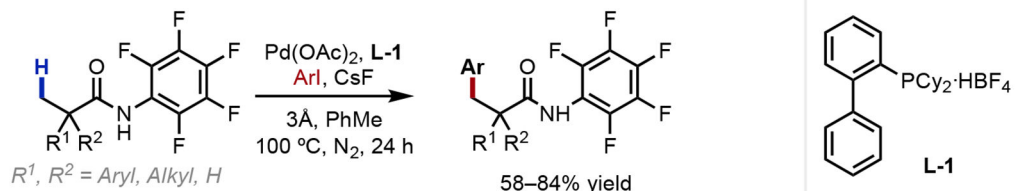
(c) New Transformations of C(sp^3)–H bonds Enabled by Weakly-Coordinating *N*-Arylamide Directing Group
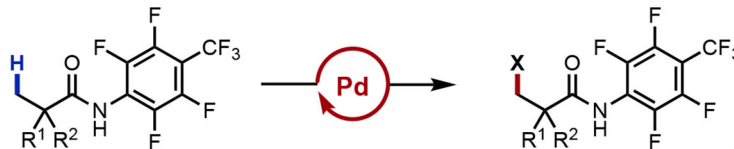
• □-methyl C–H activation
• Pd(0)/(II), Pd(II)/(0), Pd(II/IV) catalytic cycles
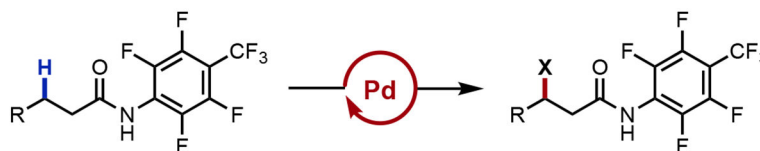
• □-methylene activation
• cyclic and acyclic substrates

• Pd(0)/(II), Pd(II)/(0), Pd(II/IV) catalytic cycles

Transformations Enabled Across Diverse Catalytic Cycles

Pd(0)/(II)	**Pd(II)/(0)**		**Pd(II)/(IV)**	
• Arylation	• Cross coupling	• Heck Olefination	• (Hetero)Arylation	• Alkylation
• Alkynylation	(arylation, vinylation,	• Carbonylation	• Halogenation	• Alkynylation
• Amination	alkylation)	• Borylation		

Scheme 5.
Overview of pioneering transformations facilitated by weak coordination-enabled C–H functionalization
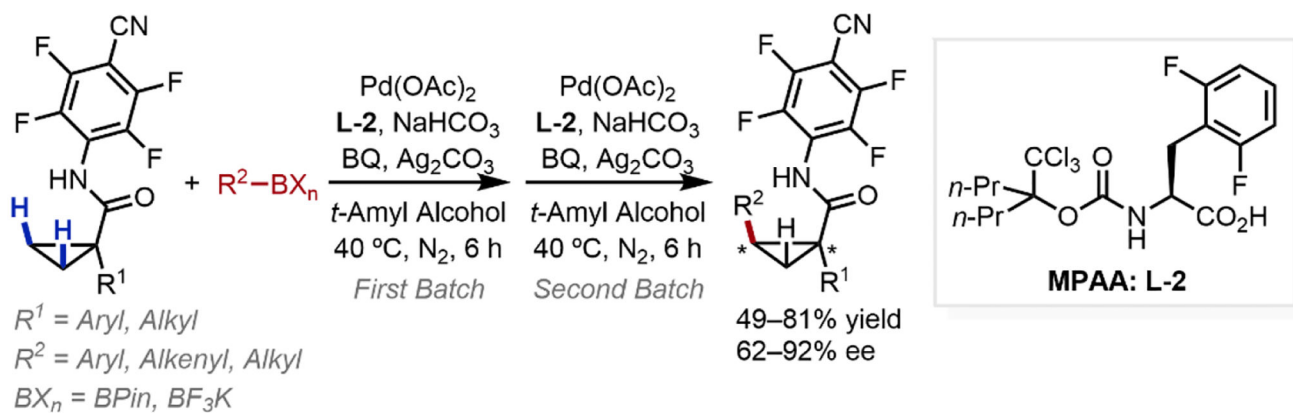
Scheme 6.
Enantioselective C–H Arylation, Alkenylation, and Alkylation of Cyclopropanes
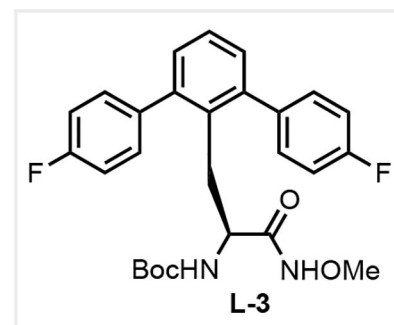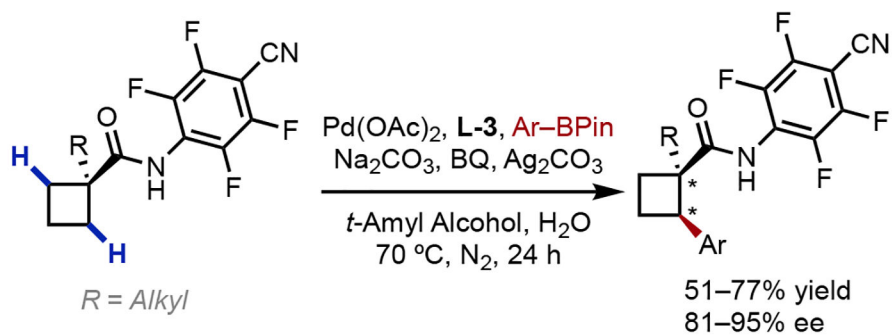
Scheme 7.
Enantioselective C–H Arylation of Cyclobutanes

(a) Challenges in Chiral Differentiation of Geminal Dimethyl C–H Bonds

β-Methylene C–H Activation

Larger, Proximal

α-Gem-Dimethyl C–H Activation

Smaller, Distal
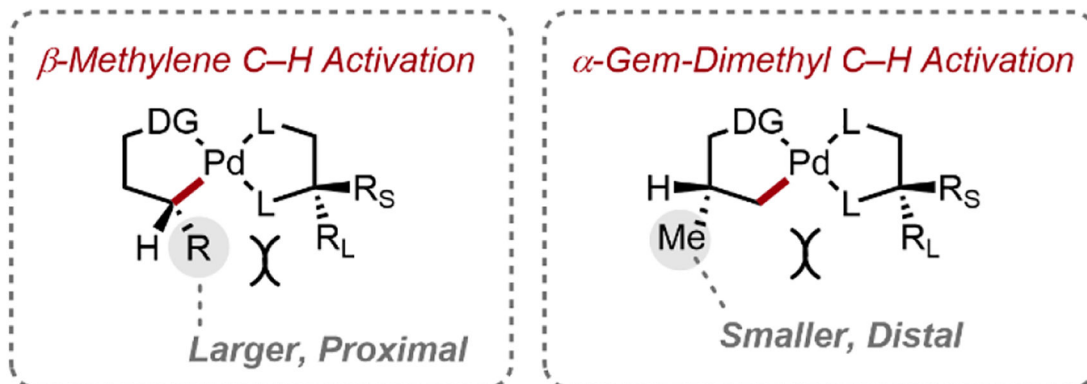
(b) Enantioselective C–H Arylation, Alkenylation, and Alkynylation Reaction

R = Aryl, Alkenyl, Alkynyl

41–85% yield
90:10–99:1 er

MPAO: L-4

anti

Proposed stereomodel
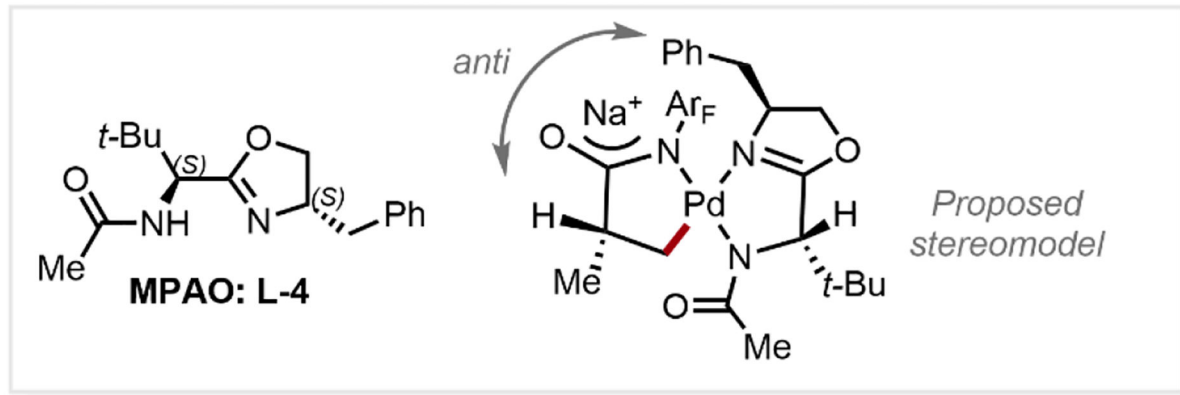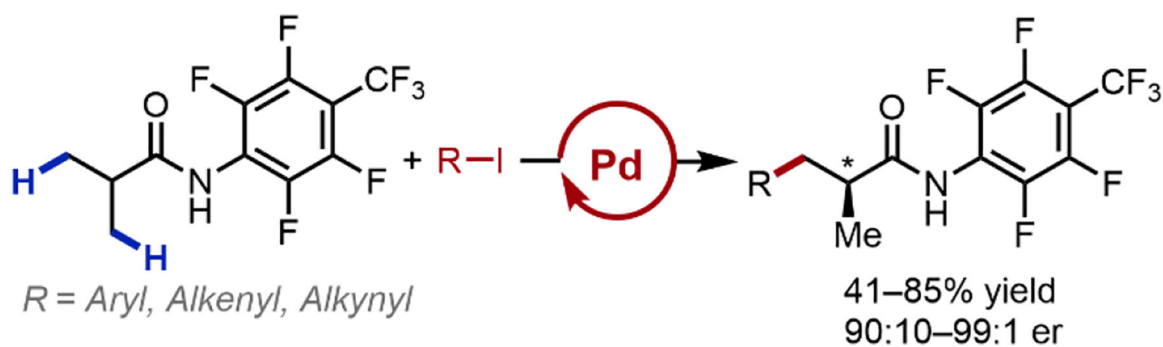
Scheme 8.
Enantioselective C–H Arylation, Alkenylation, and Alkynylation of Isobutyric Acid Derivatives

(a) Enantioselective C–H Borylation Reaction

R = Alkyl, H

52–78% yield
88–99% ee

MPAO: L-5

(b) Stereochemical Model

Favored

steric interaction

steric interaction

Disfavored
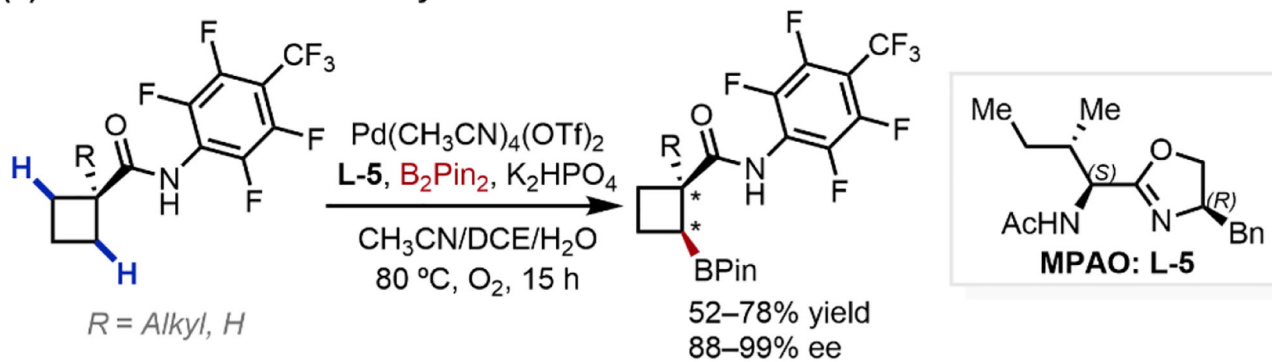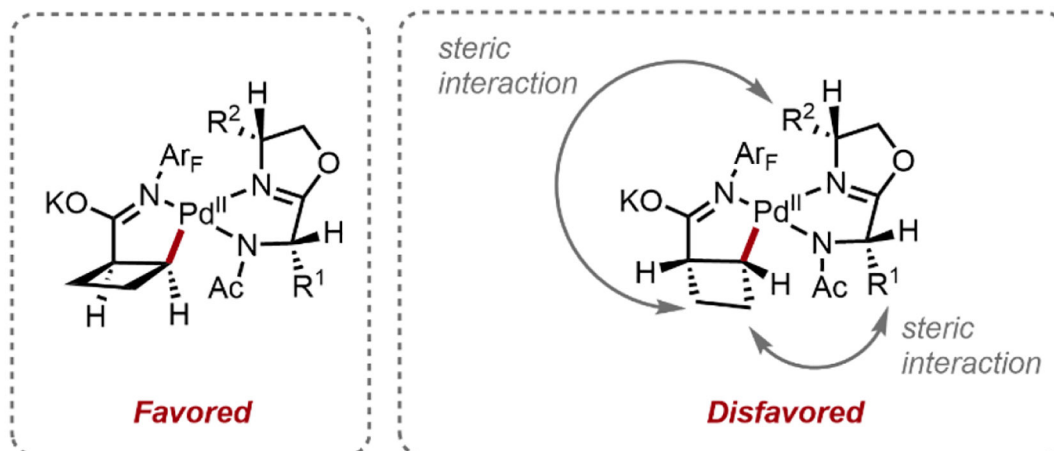
Scheme 9.
Enantioselective C–H Borylation of Cyclobutanylamides
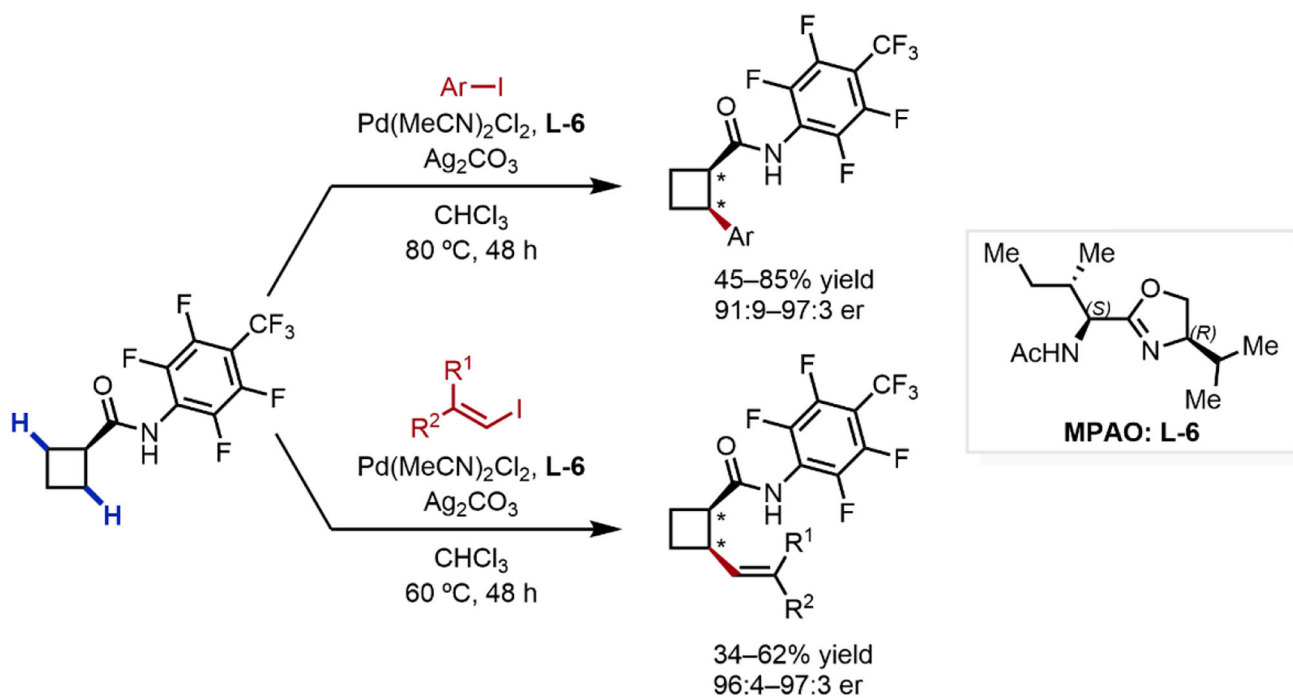
Scheme 10.
Enantioselective C–H Arylation and Vinylation of Cyclobutanes

Chiral *N*-Protected Aminosulfoxide Ligands for Enantioselective C–H Activation (Colobert)

28–92% yield
86.5:13.5–97.5:2.5 er
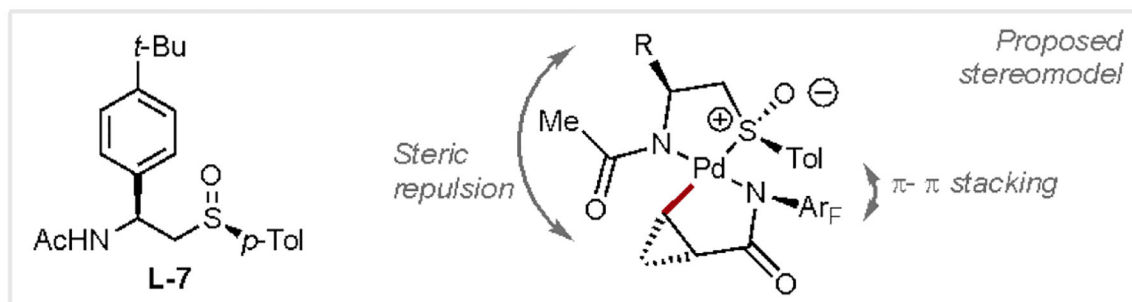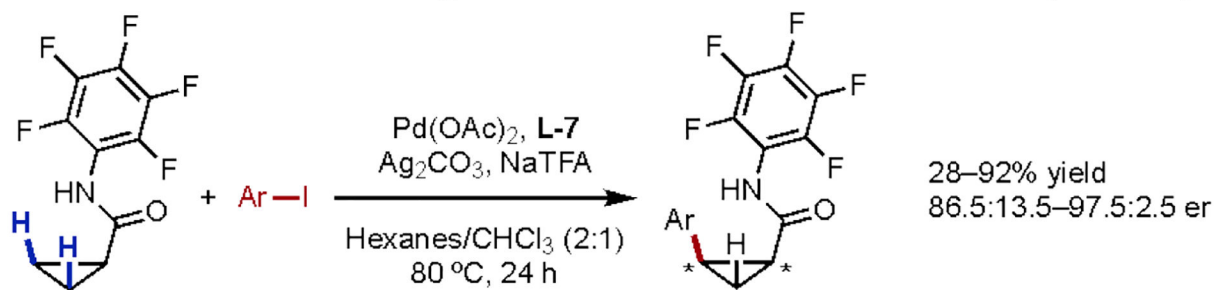
Scheme 11.
Weakly-coordinative Amide-Directed Enantioselective β-C(sp³)–H Arylation Reaction Developed by the Colobert Group

Enantioselective *N*-Arylamide-Directed Methylene C–H Arylation (Yu)
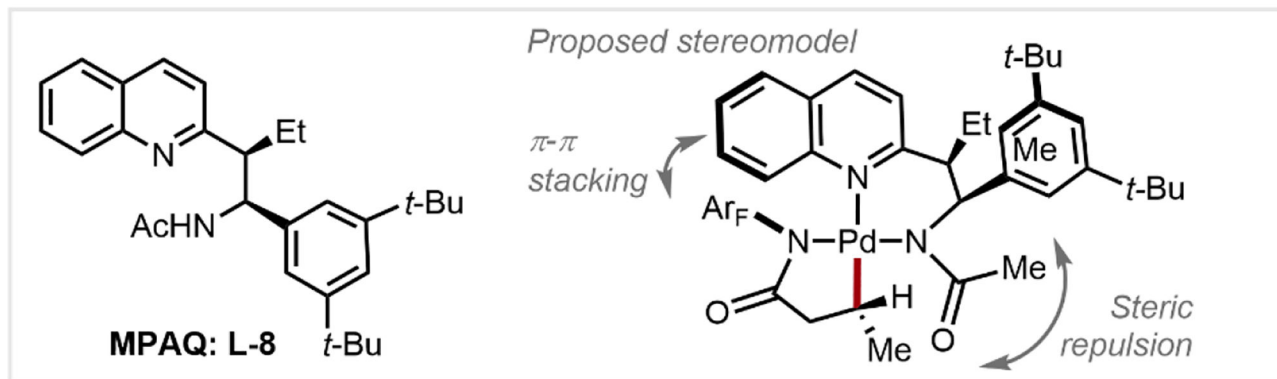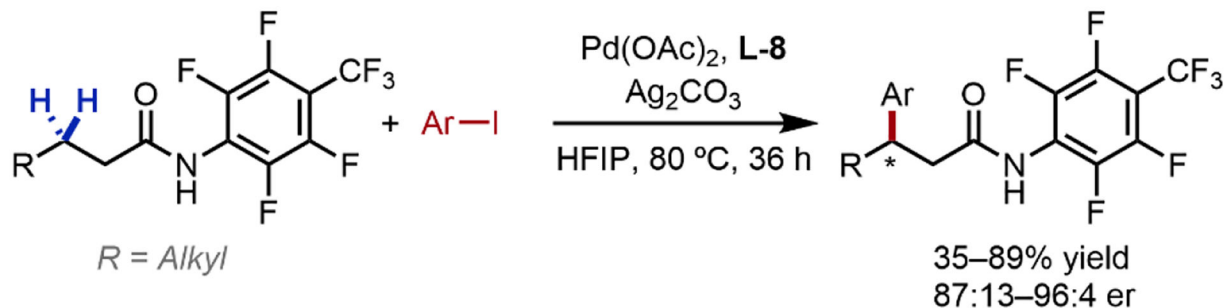
Scheme 12.
Intermolecular Amide-Directed Enantioselective β-C(sp³)–H Activation Reactions
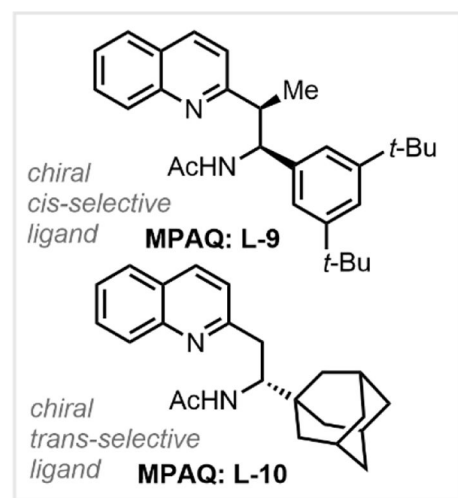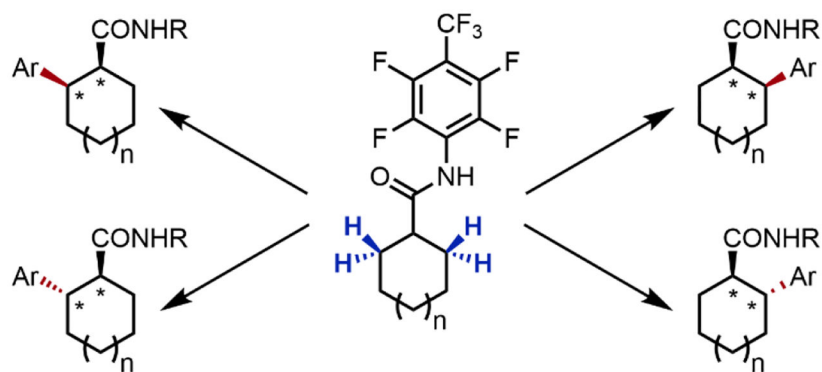
Scheme 13.
Enantio- and Diastereoselective C–H Arylation of Cycloalkylcarboxamides

(a) Pioneering Carboxylic Acid-Directed b-C(sp³)–H Functionalization (Sen)

K₂PtCl₄ (1 equiv)
K₂PtCl₆ (2 equiv)

D₂O, O₂
80–90 °C, 144 h

(6 equiv)

22% yield
relative to
K₂PtCl₄
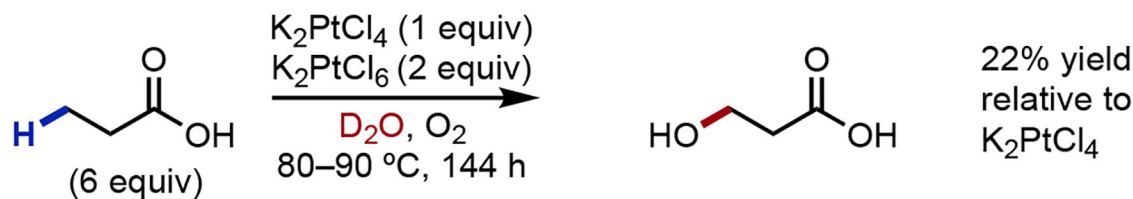
(b) Carboxylic Acid-Directed Arylation (Yu)

R = Alkyl

Pd(OAc)₂
BQ, Ag₂CO₃
K₂HPO₄

t-BuOH
100 °C, 3 h

28–38% yield

Pd(OAc)₂
Ag₂CO₃
K₂HPO₄, NaOAc

t-BuOH
130 °C, 3 h

R = Alkyl

42–72% yield
2.5:1–5:1 mono:di
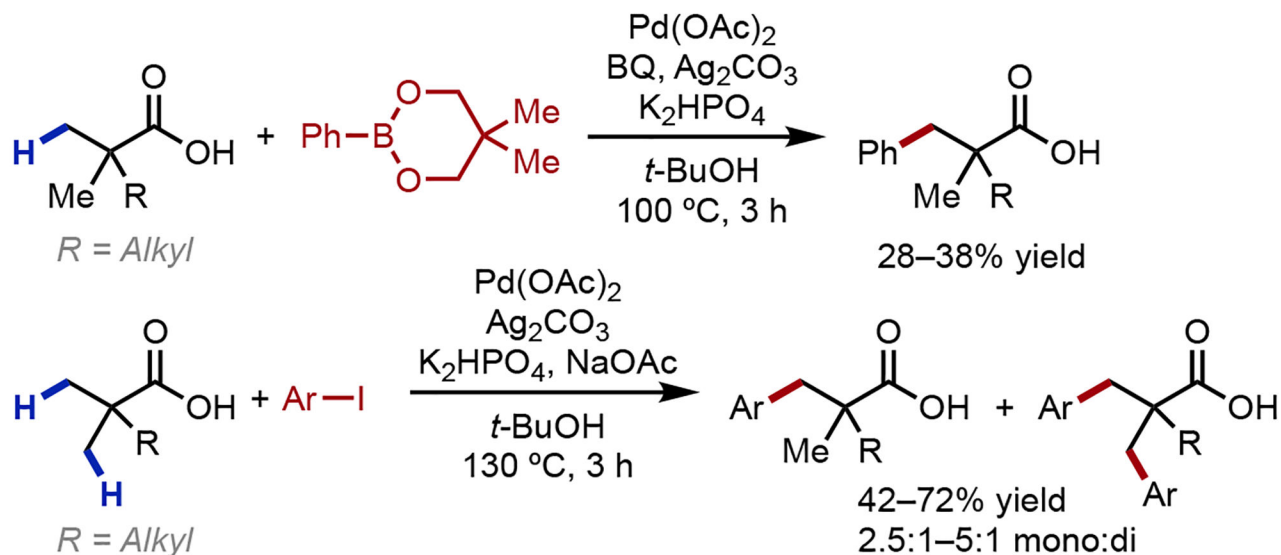
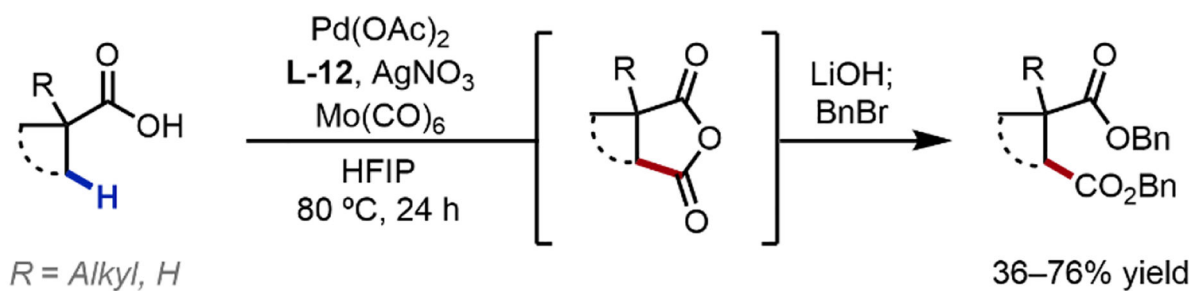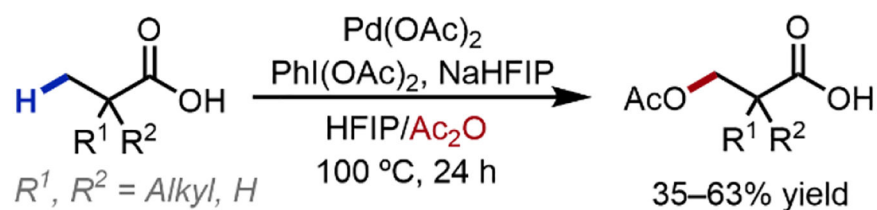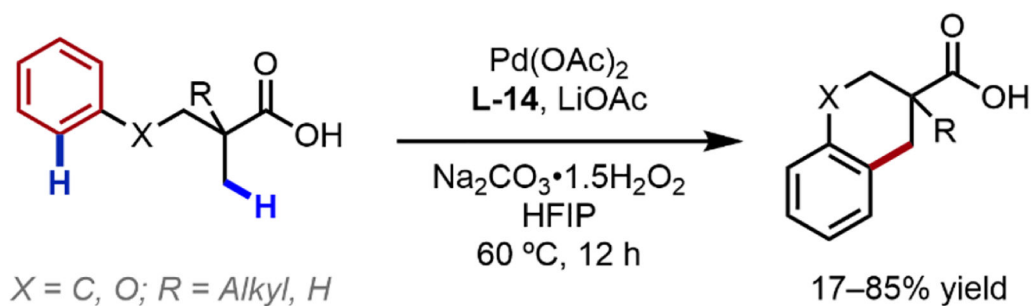**Key finding: the role of the countercation**
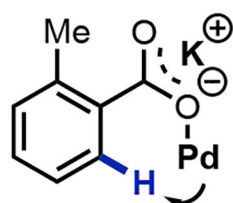
Alkali metal cations
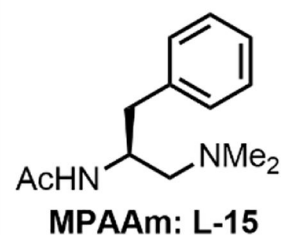enable reactivity
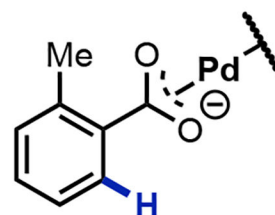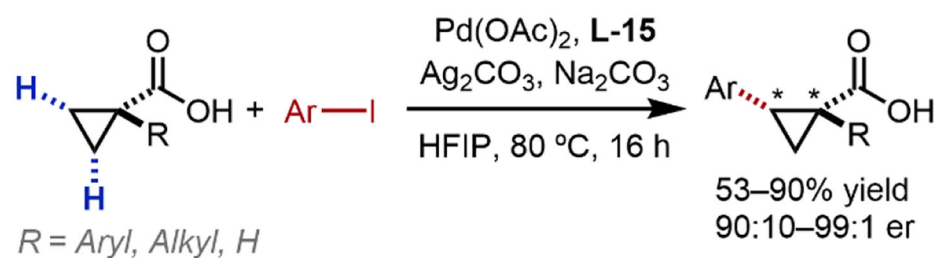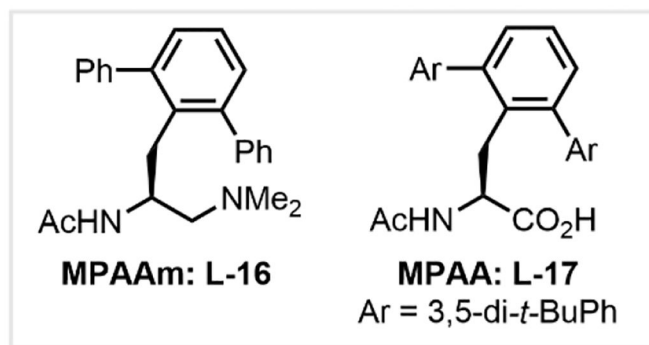
Preformed Pd
carboxylate
not reactive

Scheme 14.
Pioneering Examples of Carboxylic Acid-Directed β-C(sp³)–H Activation Reactions

(a) Arylation of α-Amino Acids with Pyridine-Type Ligand (Yu)

Pd(OAc)$_2$
L-11, AgOAc
Na$_2$HPO$_4$·7H$_2$O

HFIP
100 °C, 24 h

45–84% yield

L-11
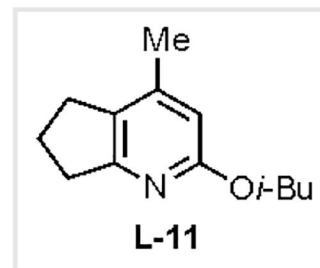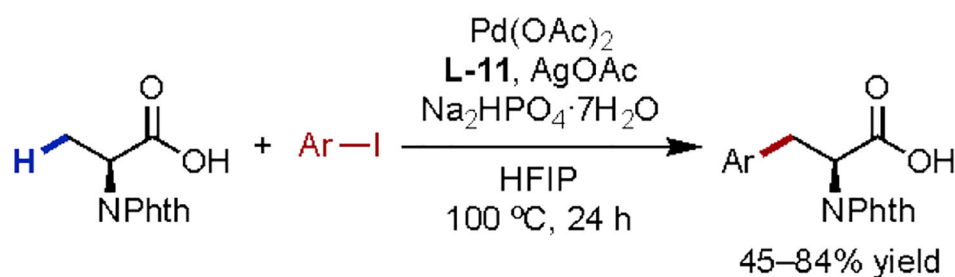
(b) Arylation of α-Amino Acids with MPAA Ligand (Zhao)

Pd(OAc)$_2$
Ac-Gly-OH
Ag$_2$CO$_3$, K$_2$CO$_3$

HFIP
100 °C, 24 h

62–90% yield
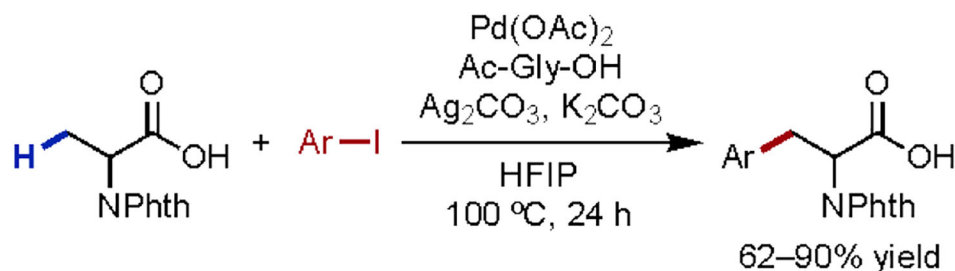
(c) Arylation of Carboxylic Acids with MPAA Ligand (van Gemmeren)

Pd(OAc)$_2$
Ac-β-Ala-OH
Ag$_2$O, Na$_2$HPO$_4$·7H$_2$O

HFIP
80 °C, 24 h

R^1, R^2 = Alkyl, H, NPhth

50–86% yield
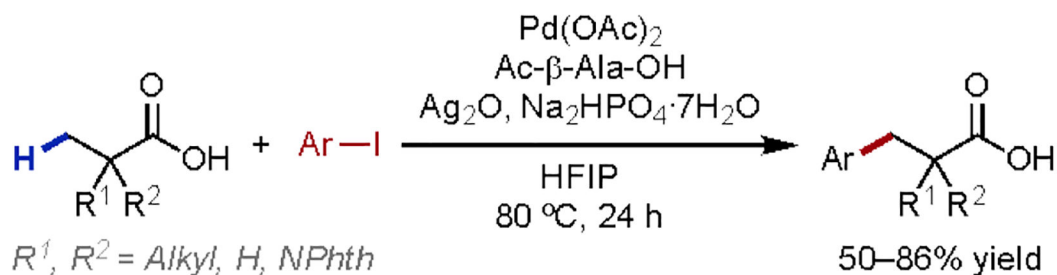
Scheme 15.
β-C(sp^3)–H Arylation of Carboxylic Acids Without α-Quaternary Centers

(a) Carboxylic Acid-Directed Olefination (Yu)

Pd(TFA)$_2$
L-12, Ag$_2$CO$_3$
Na$_2$HPO$_4\cdot$7H$_2$O
HFIP
120 °C, 12 h

R^1, R^2 = Alkyl, H, NPhth

40–99% yield

MPAThio: L-12
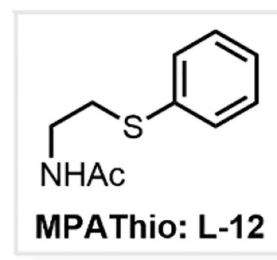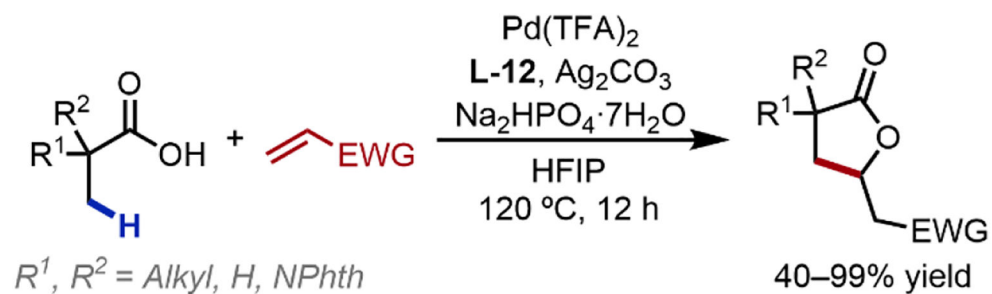
(b) Carboxylic Acid-Directed Carbonylation (Yu)

Pd(OAc)$_2$
L-12, AgNO$_3$
Mo(CO)$_6$
HFIP
80 °C, 24 h

LiOH;
BnBr

R = Alkyl, H

36–76% yield

(c) Carboxylic Acid-Directed Acetoxylation (van Gemmeren)

Pd(OAc)$_2$
PhI(OAc)$_2$, NaHFIP
HFIP/Ac$_2$O
100 °C, 24 h

R^1, R^2 = Alkyl, H

35–63% yield

Scheme 16.
Diverse Carboxylic Acid-Directed β-C(sp^3)–H Activation Transformations

(A) Carboxylic Acid-Directed Lactonization and Acetoxylation (Yu)

38–94% yield

$Nu = C(sp^3), C(sp^2), C(sp), CN,$
$F, Br, N_3, NHNs, OH, SPh$

MPAA: L-13

33–74% yield

MPAA: L-14
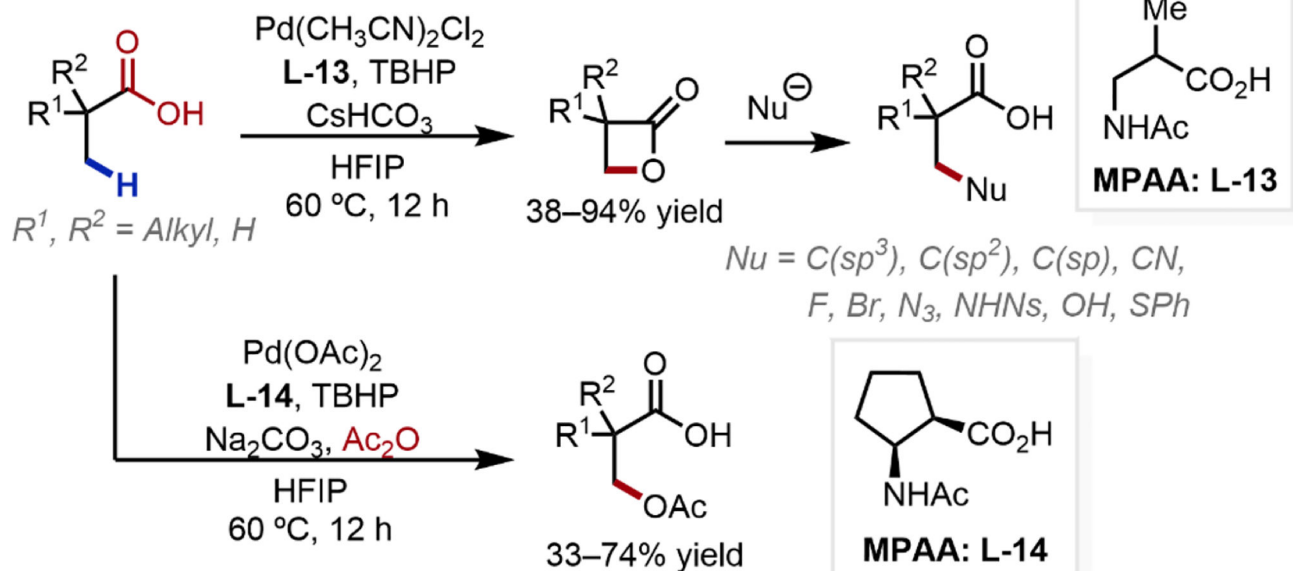
(B) Carboxylic Acid-Directed Cross Dehydrogenative Coupling (Yu)

X = C, O; R = Alkyl, H

17–85% yield

Scheme 17.
Carboxylic Acid-Directed β-C(sp^3)–H Activation Transformations Using Inexpensive Peroxide Oxidants

(a) Enantioselective C–H Arylation of Cyclopropanecarboxylic Acids (Yu)

Reagents and conditions: Pd(OAc)$_2$, L-15; Ag$_2$CO$_3$, Na$_2$CO$_3$; HFIP, 80 °C, 16 h

R = Aryl, Alkyl, H

53–90% yield
90:10–99:1 er

MPAAm: L-15

(b) Enantioselective C–H Cross-Coupling of Cyclobutanes (Yu)

Reagents and conditions: Pd(OAc)$_2$, L-16 or L-17; K$_2$HPO$_4$, BQ, Ag$_2$CO$_3$; t-BuOH, H$_2$O, 60 °C, air, 12 h

Ar—BPin or Vinyl—BPin

R = Alkyl, Aryl, H

42–65% yield
84:16–95:5 er

MPAAm: L-16

MPAA: L-17
Ar = 3,5-di-t-BuPh
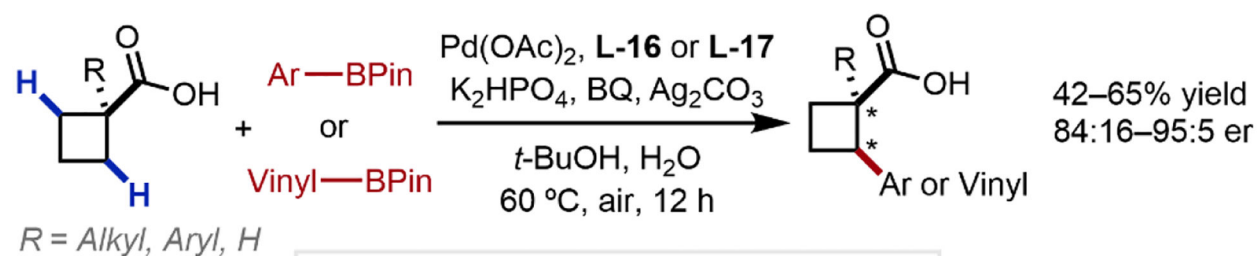
Scheme 18.
Carboxylic Acid-Directed Enantioselective β-C(sp^3)–H Activation Reactions

Dehydrogenation and functionalization of Methylene C–H bonds Directed by Free acids (Yu)
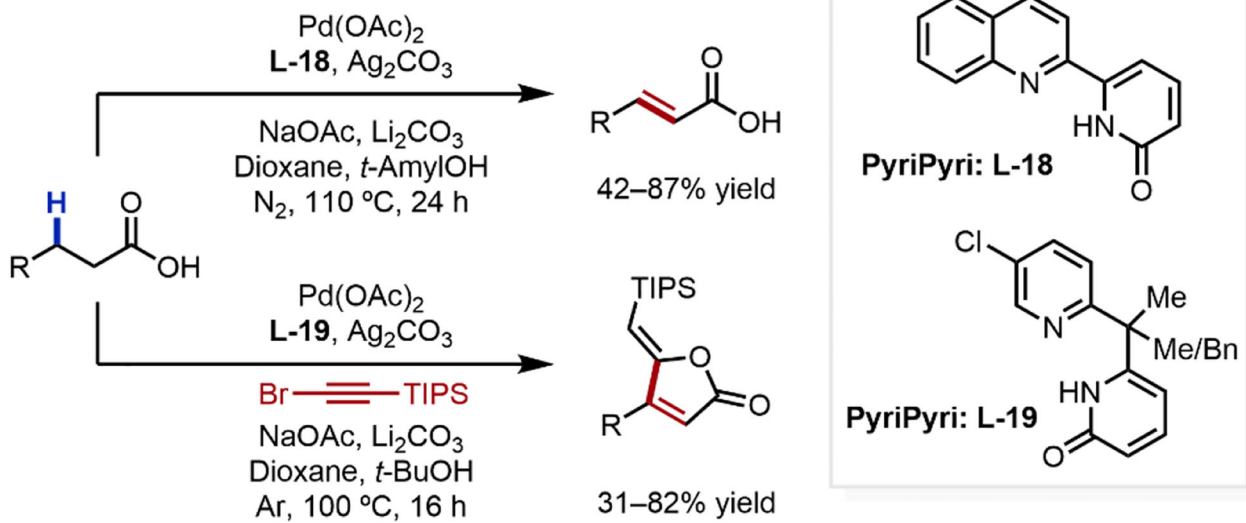
Scheme 19.
Carboxylic Acid-Directed β-Methylene C(sp^3)–H Activation Enables Dehydrogenation and Further Functionalization
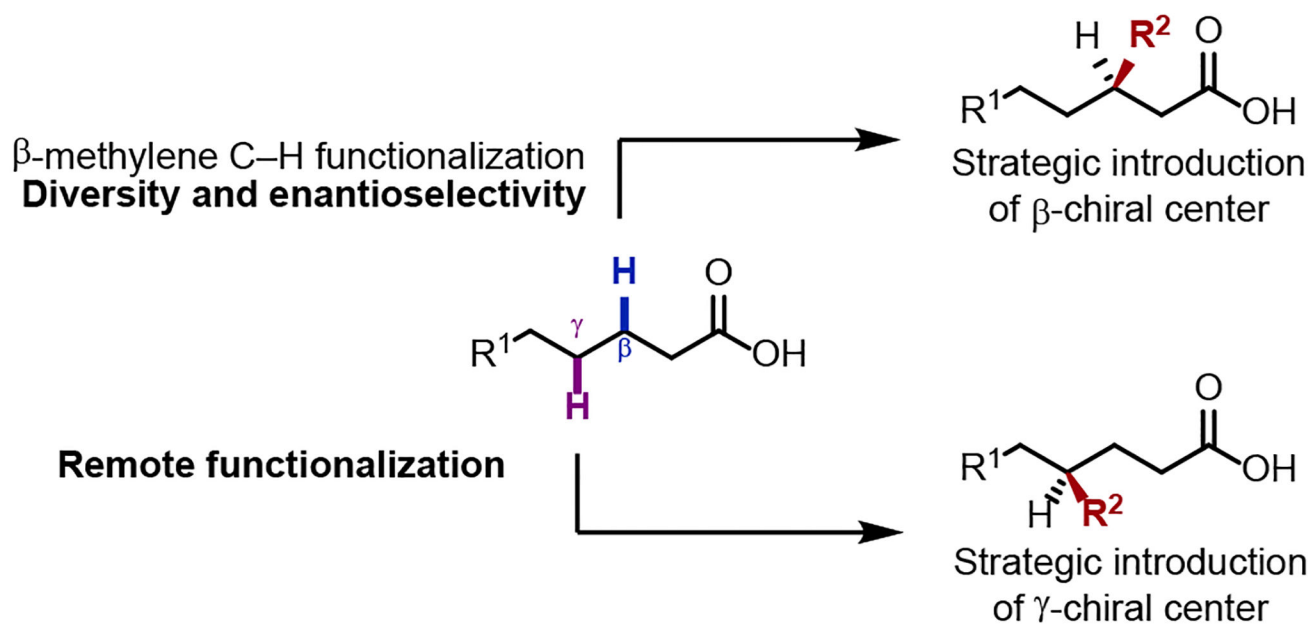
Scheme 20.
Future ambitions for the development of free acid-directed C(sp^3)–H functionalization