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From Mono-*N*-Protected Amino Acids to Pyridones: A Decade of Evolution of Bifunctional Ligands for Pd(II)-Catalyzed C−H Activation

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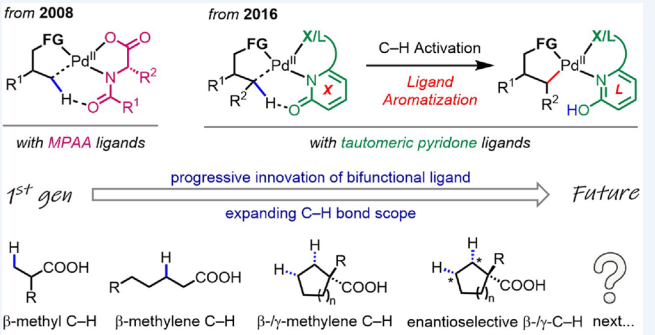
CONSPECTUS: Functionalization of carbon−hydrogen (C−H) bonds has emerged as a powerful strategy in modern organic synthesis, offering efficient routes to build molecular complexity from simple and abundant substrates. Among various transition-metal catalysts, palladium(II) complexes have proven particularly versatile for C−H activation, owing to the diverse reactivity of carbon−palladium bonds. To advance this approach, the discovery of ligands that can accelerate C−H activation as well as subsequent steps in the catalytic cycle is the pivotal driving force. While ligand development has long been integral to Pd(0) catalysts for activating electrophiles, notably in cross-coupling and asymmetric catalysis, the most common electron-donating ligands often inhibit Pd(II)-catalyzed C−H activation, as an electrophilic palladium center is often preferred. Hence the discovery of a suitable concerted metalation−deprotonation (CMD) motif that can be incorporated into bidentate ligands is critical. This design concept led us to discover a series of highly reactive bifunctional ligands that enhance reactivity and control site-selectivity as well as enantioselectivity.



In 2008, our laboratory introduced the first bifunctional mono-*N*-protected amino acid (MPAA) ligands, which incorporate an *N*-acyl group bearing a carbonyl with the required proximity and geometry to serve as an internal CMD base thereby significantly accelerating C−H bond cleavage. Building on this concept, we identified pyridone as a potent CMD-active group capable of further enhancing the efficiency of Pd(II)-catalyzed C−H activation. Following the initial development of monodentate pyridone ligands, a series of bifunctional bidentate pyridone ligands unlocked previously inaccessible transformations of methylene C−H bonds within abundant substrates bearing native functional groups such as carboxylic acids, amides, and alcohols.

In this Account, we summarize our efforts in the rational design of different classes of pyridone-based ligands for Pd(II)-catalyzed diverse C−H functionalization. Emphasis is placed on site-selective and enantioselective functionalization at methylene and remote C−H positions, and we examine how ligand architecture dictates both reactivity and enantioselectivity. Special attention is given to the use of bidentate pyridone ligands in enabling transformations of synthetically valuable native substrates. We conclude with a perspective on the continued design of novel bifunctional bidentate pyridone ligands to achieve the following goals: realization of enantioselective acyclic methylene C−H activation; development of diverse methylene C−H functionalization beyond dehydrogenation and a handful of C−C/C−O bond formations; expanding native substrates to ketones, alcohols, and amines.

KEY REFERENCES

- Wang, P.; Verma, P.; Xia, G.; Shi, J.; Qiao, J. X.; Tao, S.; Cheng, P. T. W.; Poss, M. A.; Farmer, M. E.; Yeung, K.-S.; Yu, J.-Q. Ligand-Accelerated Non-Directed C-H Functionalization of Arenes. *Nature* **2017**, *551*, 489−493.[1] *The first example of monodentate pyridone ligand enabled Pd(II)-catalyzed nondirected C−H activation with arene substrates, demonstrating the concerted metalation−deprotonation (CMD) activity of pyridone ligands.*
- Wang, Z.; Hu, L.; Chekshin, N.; Zhuang, Z.; Qian, S.; Qiao, J. X.; Yu, J.-Q. Ligand-controlled divergent dehydrogenative reactions of aliphatic acids. *Science* **2021**, *374*, 1281−1285.[2] *Pyridine−pyridone ligands enabled the dehydrogenation of free carboxylic acids via β-methylene C−H activation.*
- Kang, G.; Strassfeld, D. A.; Sheng, T.; Chen, C.-Y.; Yu, J.-Q. Transannular C-H functionalization of cycloalkane

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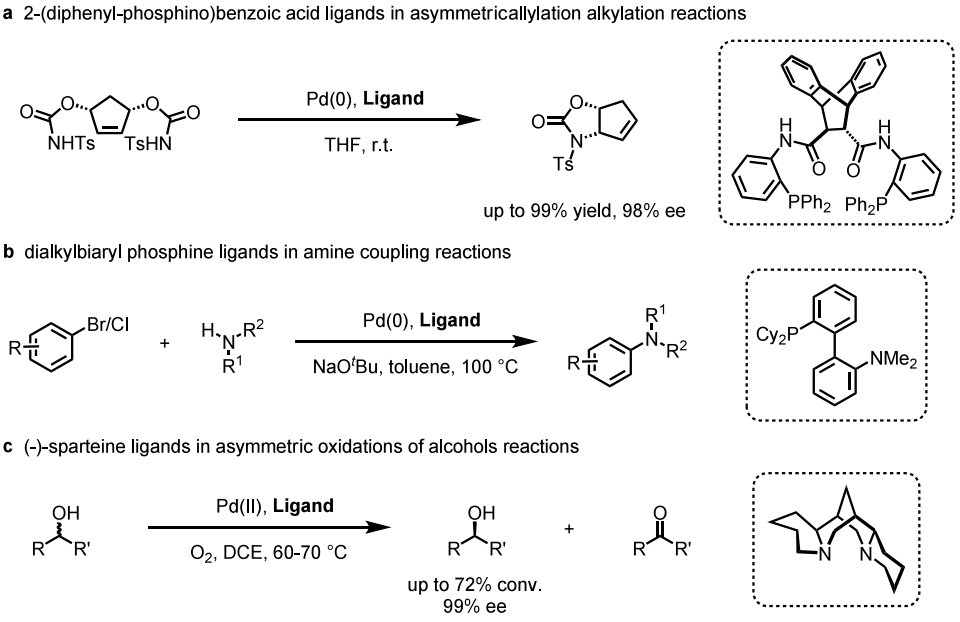
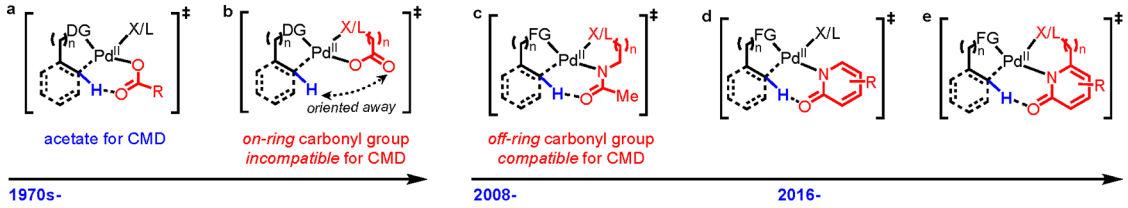


Figure 1. Historic perspective of ligand design for Pd(0) and Pd(II) catalysts.

Scheme 1. Proposed Transition States of CMD Active Ligands in Pd(II)-Catalyzed C−H Activation



carboxylic acids. *Nature* **2023**, *618*, 519−525.[3] *Quinuclidine−pyridone ligands enabled remote methylene C−H arylation at the γ-position of cycloalkane carboxylic acids.*

- Zhang, T.; Zhang, Z.-Y.; Kang, G.; Sheng, T.; Yan, J.-L.; Yang, Y.-B.; Ouyang, Y.; Yu, J.-Q. Enantioselective Remote Methylene C−H (Hetero)arylation of Cycloalkane Carboxylic Acids. *Science* **2024**, *384*, 793−798.[4] *Chiral oxazoline−pyridone ligands enabled highly enantioselective methylene γ- and δ-C−H (hetero)arylation of cyclic carboxylic acids.*

1. INTRODUCTION

Site-selective and enantioselective functionalization of carbon−hydrogen (C−H) bonds with a wide range of native substrates represents a paradigm shift in organic synthesis, providing a new logic of disconnection for the construction of complex molecules.[5] Among the various transition-metal catalysts, palladium(II) complexes have emerged as particularly versatile platforms for C−H activation due to diverse reactivity of carbon−palladium bonds with a wide range of oxidants, electrophiles, and nucleophiles. Discovery of ligands that can accelerate both C−H activation and subsequent functionalization events is crucial for developing broadly useful C−H activation reactions.

Historically, ligand development has been a cornerstone for palladium catalysis, most notably, Pd(0)-catalyzed cross-coupling and allylic substitution reactions. The remarkable reactivity of palladium catalysts arises from their unique versatility to alternate between Pd(0) and Pd(II) oxidation states, enabling a wide range of selective and efficient bond-forming transformations. For example, Trost's bisphosphine ligands have set a benchmark for enantioselective allylic alkylation,[6] and dialkylbiaryl phosphine ligands have revolutionized Pd-catalyzed cross-coupling reactions by improving efficiency and functional group tolerance.[7,8] However, the development of ligands to accelerate Pd(II)-initiated C−H activation has met with challenges and achieved limited success. (−)-Sparteine ligand enabled asymmetric oxidation of alcohols is a stand-alone example; nevertheless the ligand acceleration is absent in this catalysis (Figure 1).[9,10]

While ligand development has long been integral to Pd(0) catalysts for activating electrophiles—notably in cross-coupling and asymmetric catalysis—the most common electron-donating ligands often inhibit Pd(II)-catalyzed C−H activation, as an electrophilic palladium center is often preferred. Based on this fundamental constraint, a different approach remains to be established to achieve ligand acceleration. Mechanistically, electrophilic C−H bond cleavage involves a concerted metalation−deprotonation (CMD) process which was first observed by Martinez[11] and elucidated by Fagnou[12] through DFT calculations. Notably, acetate-assisted C(sp^3)−H palladation was discovered with oxime substrates in Shaw's pioneering studies.[13] While these mechanistic hypotheses are illuminating, the design of various carboxylates or related anions as external bases in monodentate ligands has failed to improve C−H palladation in a significant way.

Incorporation of the carboxylate into a bidentate ligand framework has also been extensively explored without success

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because the carbonyl on the chelate ring is oriented away from the C−H bond, rendering the six-membered transition state forbidden. A breakthrough for Pd(II)-catalyzed C−H activation reactions was made by incorporating an *N*-acyl group into bifunctional mono-*N*-protected amino acid (MPAA) ligands in 2008.[14] These ligands and their derivatives feature an *N*-acyl group, which was discovered to function as a highly effective internal CMD active group, enhancing the rate of C−H activation. The superiority of this newly discovered bifunctional ligand compared to simple acetate stems from the well-organized proximity and geometry of the carbonyl in the *N*-acyl group that is off the chelate ring, as external acetamides are not active (Scheme 1).

The next advance followed, as the pyridone (2-hydroxypyridine/2-pyridone) moiety was later identified as a more effective internal base for the CMD step. The aromatization of pyridone to hydroxypyridine during the C−H activation step serves as a distinct driving force to stabilize the C−H palladation intermediates. In 2016, our group first reported the use of monodentate pyridone ligands in C−H activation.[15] A year later, structural analysis and DFT studies revealed that pyridone ligands coordinate to palladium via the nitrogen atom and serve as internal bases, the promoting C−H cleavage step.[1] Subsequently, a series of bidentate pyridone ligands were developed as a transformative platform for C(sp^3)−H activation. Their efficacy is exemplified by the high reactivity in methylene C−H functionalization reactions directed by weakly coordinating native functional groups such as carboxylic acids,[2−4] native amides,[16] and alcohols (Scheme 1).[17]

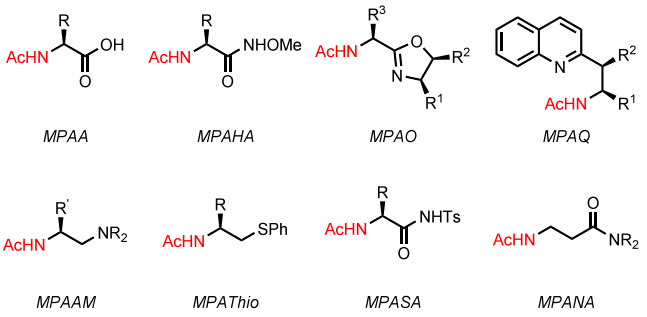
This Account focuses on our development of pyridone ligands for palladium-catalyzed C−H activation reactions. We begin with a summary of our first-generation ligands containing a mono-*N*-protected amino group as a CMD-active base. Next, we provide a background and brief introduction of the pyridone moiety in organometallic chemistry. We then discuss the application of monodentate pyridone ligands in catalytic Pd-catalyzed C−H functionalization reactions. Following this, we present the discovery and development of our second-generation bidentate pyridone ligands, highlighting their effectiveness in C(sp^2)−H and C(sp^3)−H activation, especially with methylene C−H functionalization reactions with weakly coordinating native functional groups. Finally, we offer a future perspective on the pyridone ligand design and the continued advancement of C−H activation strategies.

2. SUMMARY AND RECENT DEVELOPMENT OF BIDENTATE MONO-*N*-PROTECTED LIGANDS

In 2008, we discovered that the bidentate mono-*N*-protected amino acid (MPAA) ligand could enable Pd(II)-catalyzed enantioselective C(sp^2)−H alkylation of diphenyl(2-pyridyl)-methane.[14] Following this study, mechanistic investigations provided important insights into how MPAA ligands influence C−H activation. These studies suggest that the *N*-acyl amide group can act as an internal base in the CMD step. Furthermore, the chiral center adjacent to the *N*-acyl group creates a sterically defined environment that can induce enantioselectivity during C−H cleavage.

Since the initial discovery of MPAA ligands, our group has developed an array of bidentate ligands incorporating the −NHAc scaffold as the CMD-active moiety.[18] These include monoprotected amino hydroxamic acid (MPAHA), mono-*N*-protected amino quinoline (MPAQ), mono-*N*-protected amino oxazoline (MPAO), mono-*N*-protected amino alkyl amine

Scheme 2. Summary of Mono-*N*-Protected Ligands Developed by the Yu Lab

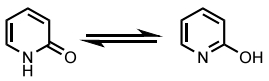


(MPAAM), mono-*N*-protected amino alkyl thioether (MPA-Thio), mono-*N*-protected amino sulfonamide (MPASA),[17,19] and mono-*N*-protected amino neutral amide (MPANA)[20] ligands (Scheme 2).

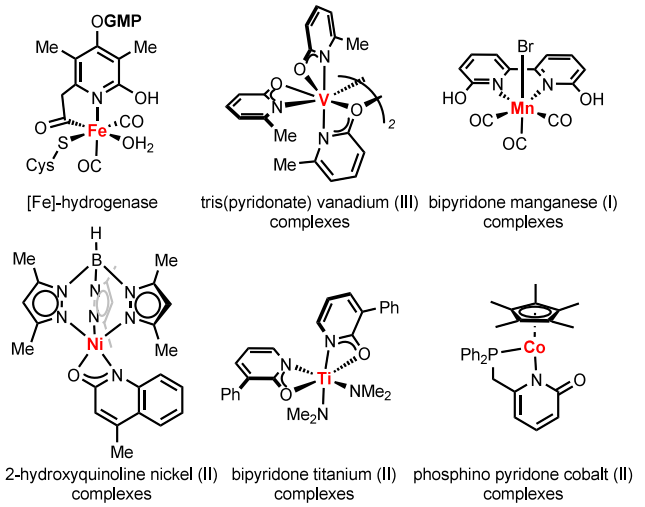
3. HISTORY AND BRIEF INTRODUCTION OF PYRIDONE MOIETY IN ORGANOMETALLIC CHEMISTRY

Since the first discovery of tautomerization of pyridone in 1907 by Baker and Baly, its physical and chemical properties have

Scheme 3. Tautomerization between 2-Pyridone and 2-Hydroxypyridine



Scheme 4. Reactive 3d-Transition Metal Complexes with Pyridone Ligands



been extensively studied.[21] Pyridone exists in equilibrium with its tautomeric form, 2-hydroxypyridine, in both solution and the solid state. Tautomeric distribution depends on the solvent and substituents: polar solvents and electron-withdrawing groups at the 6-position favor pyridone, while nonpolar environments favor 2-hydroxypyridine (Scheme 3).

The versatile coordination modes of pyridonate ligands have enabled the synthesis of various 3d transition metal complexes.[22] A prominent example is naturally occurring [Fe]-hydrogenase, which uses a pyridinol/pyridonate ligand to reversibly catalyze

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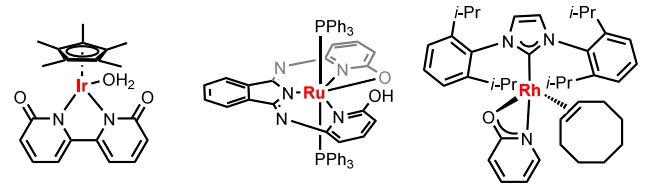
Scheme 5. Noble Transition Metal Complexes with Pyridone Ligands



H_2 activation. Beyond iron, pyridone-based ligands have facilitated hydrogen transfer catalysis with vanadium, manganese, and nickel complexes. Additionally, pyridone ligands have been employed to facilitate other catalytic reactions, such as titanium-catalyzed hydroaminoalkylation of primary aminoalkenes and cobalt-catalyzed alkyne dimerization and selective catalytic reduction of 1,3-enynes to (*E*,*Z*)-1,3-dienes (Scheme 4). Interestingly, following the extensive development of pyridone ligands for Pd(II)-catalyzed C−H activation reactions in the past decade, pyridone ligands have also been successfully developed to improve Cu(I)-catalyzed Ullmann-type coupling reactions.[23]

In addition to 3d transition metals, pyridone-based complexes have also been explored with noble metals. Notable examples include iridium(III) complexes for the hydrogenation of CO_2 to formate, ruthenium complexes for the hydroboration of organic nitriles, and rhodium complexes for linear alkyne dimerization (Scheme 5). In the context of nitrene insertion chemistry, early reports have employed 2-pyridone as a bridging ligand with noble metals, such as Ru. An early insight into coordination of Pd/hydroxypyridine was also obtained when Kong and Rochon synthesized *trans*-[Pd(2-hydroxypyridine)$_2$Cl$_2$] by reacting sodium tetrachloropalladate with 2-hydroxypyridine in aqueous solution.[24]

4. MONODENTATE PYRIDONE FOR PD(II) CATALYZED C−H ACTIVATION

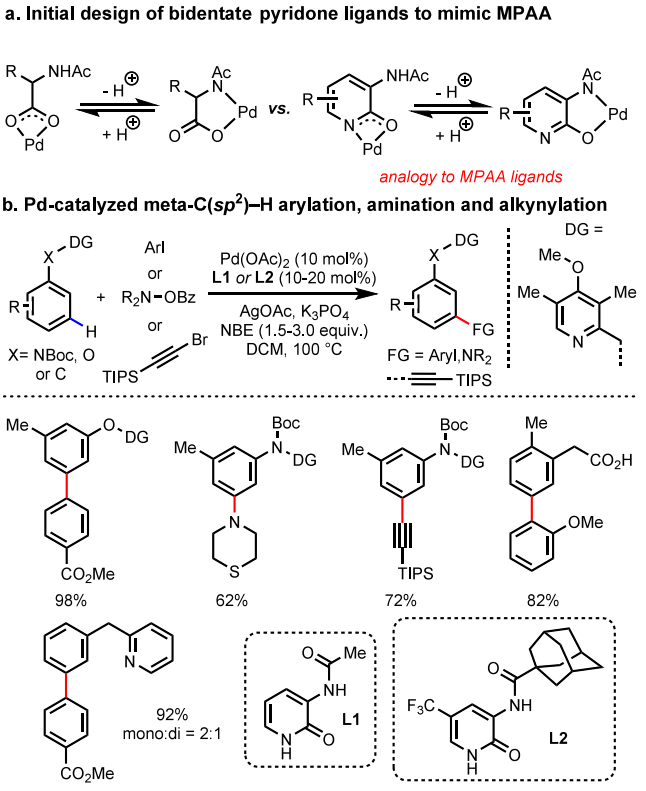
Given the known κ^2-coordination mode of pyridone as a carboxylate surrogate, we wondered whether the carboxylate in our bidentate MPAA-type ligands could be replaced by the pyridone motif. A combination of rational design and experimental investigations on various pyridone structures led to the discovery that pyridone itself could serve as an effective −NHAc surrogate participating in C−H activation. This finding initiated the development of monodentate 2-pyridone ligands as a new class of CMD ligands for Pd(II)-catalyzed C−H functionalization.

4.1. Pd-Catalyzed C(sp^2)−H Functionalization Using External Directing Groups

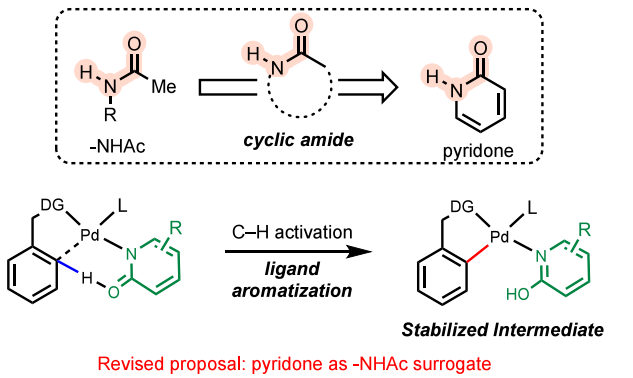
In 2016, our group developed monoprotected 3-amino-2-pyridone ligands (**L1** and **L2**) in which the κ^2-N,O coordination of pyridone emulates the carboxylate (Scheme 6a).[15,25] Compared to MPAA ligands, this class of ligands is more efficient in promoting the norbornene-mediated *meta*-C(sp^2)−H functionalization of a wide range of substrates, including phenols, anilines, heterocycles, and phenylacetic acids (Scheme 6b).[26,27]

Interestingly, it was found that the *N*-acyl group on **L1** was not required for the reactivity, which pointed to a revised binding mode of the ligand. It was proposed that the pyridone ring as a cyclic amide could act as a potent CMD base mimicking the

Scheme 6. Initial Discovery of Pyridone Ligand



Scheme 7. Evolution of Pyridone Design



−NHAc motif. Notably, aromatization accompanying the C−H activation step could provide a strong thermodynamic driving force (Scheme 7).

In 2017, building on this revised proposal, we developed the first simple 2-pyridone enabled *meta*-C(sp^2)−H functionalization of benzylamine substrates (Scheme 8a).[28] We further advanced this *meta*-C−H activation by introducing a chiral transient mediator (CTM) to control the enantioselectivity of the reaction (Scheme 8b).[29]

In addition to benzylamine derivatives, 2-pyridone ligands also displayed similar reactivity for other substrates, including masked aldehydes[30] and 2-cyanobiphenyl.[31] Moreover, the increasing number of reports featuring pyridone-enabled C(sp^2)−H functionalization reactions beyond Pd, such as Mn, Ni, Ru, and Rh, highlights the versatility of the pyridone scaffold across a broader range of transition metals.[32]

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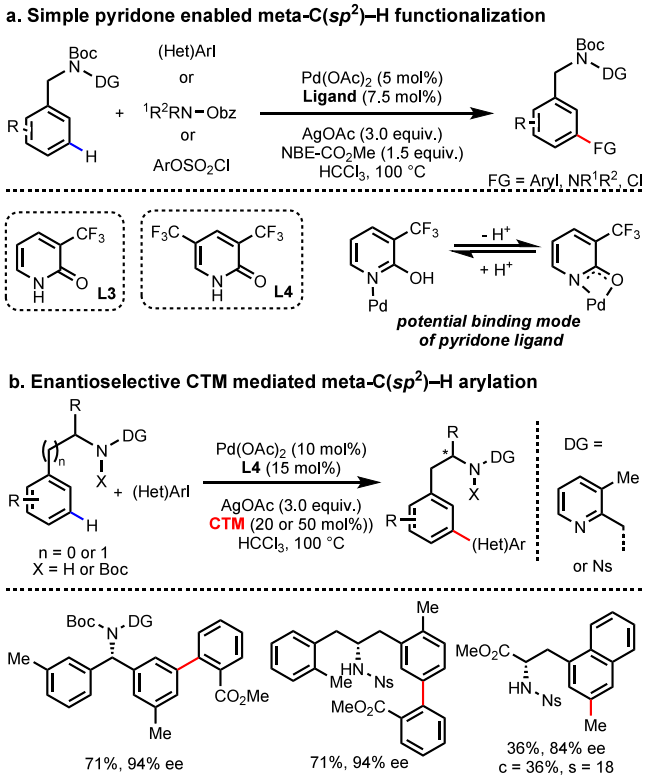
Scheme 8. Pd-Catalyzed *meta*-C(sp^2)−H Functionalizations Enabled by Simple Pyridone Ligands



4.2. Pd-Catalyzed Nondirected C(sp^2)−H Functionalization

Although monodentate pyridone ligands showed promising reactivity, their precise coordination behavior remained ambiguous. This uncertainty was resolved in 2017, when our group reported a Pd(II)-catalyzed C−H olefination reaction enabled by an electron-deficient pyridone ligand (**L4**) (Scheme 9a).[1] To investigate the enabling nature of this ligand, we conducted comprehensive mechanistic studies, including crystallographic, kinetic, and computational analysis. Crystal structures of a Pd(Phen)(**L4**)$_2$ complex and a Pd$_3$(μ_2-OH)(**L4**) complex revealed the κ^2-bridging coordination of pyridone (Scheme 9b). DFT calculations showed that replacing the acetate with pyridone lowers the activation barrier for C−H cleavage. The most favorable CMD transition state features palladium bound with two pyridone ligands: one as an X-type κ^2 ligand and the other as the internal base through coordination with the nitrogen center (Scheme 9c).

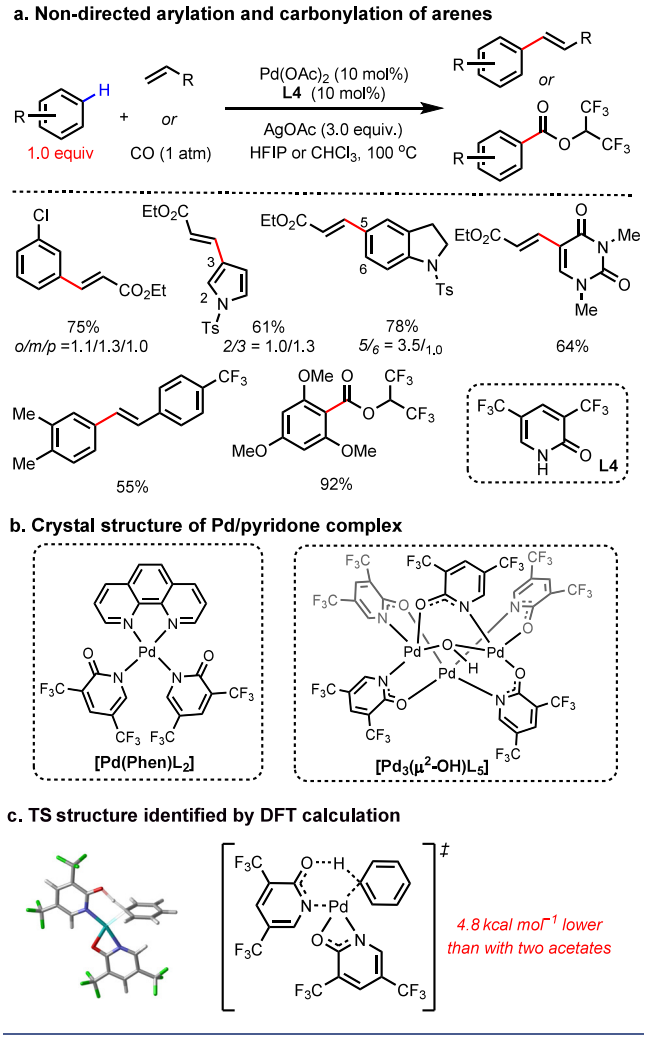
In 2020, this strategy was also employed in *meta*-C(sp^2)−H arylation via Pd/norbornene (NBE) relay.[33] Notably, the reactivity was enhanced by the introduction of an additional pyridine ligand. The dual-ligand system has since been widely adopted for various nondirected C(sp^2)−H functionalization reactions.[34]

4.3. Pd-Catalyzed C(sp^3)−H Functionalization Directed by a Bidentate Auxiliary

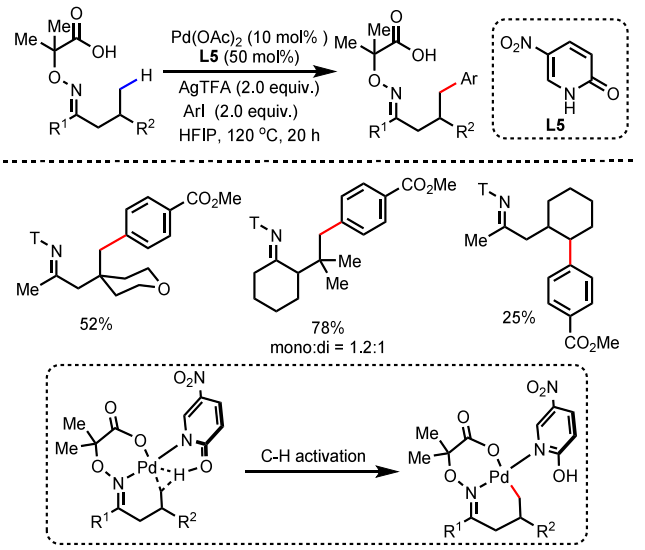
In 2018, the first example of pyridone-enabled C(sp^3)−H activation was demonstrated in Pd(II)-catalyzed γ-C−H activation of ketones directed by a 2,2-dimethyl aminooxyacetic acid auxiliary.[35] The pyridone **L5** was crucial for promoting this unconventional site-selectivity (Scheme 10).

Following the success of using pyridone in enabling distal γ-selectivity, we reported a pyridone ligand enabled arylation of a

Scheme 9. Pyridone Ligands Enabled Nondirected C−H Functionalization of Arenes



Scheme 10. Pd(II)-Catalyzed γ-C(sp^3)−H Functionalization of Ketone Derivatives



distal γ-C−H bond over the proximate β-C−H bonds of alcohol-derived substrates.[36] The unconventional site-selectivity was

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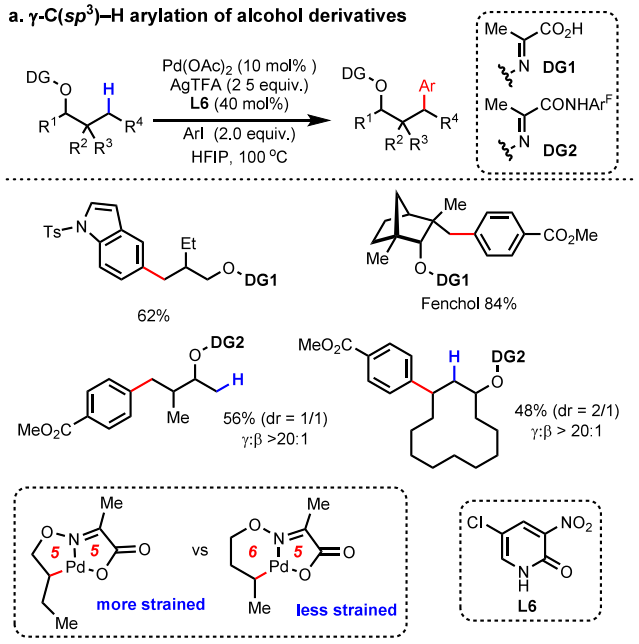
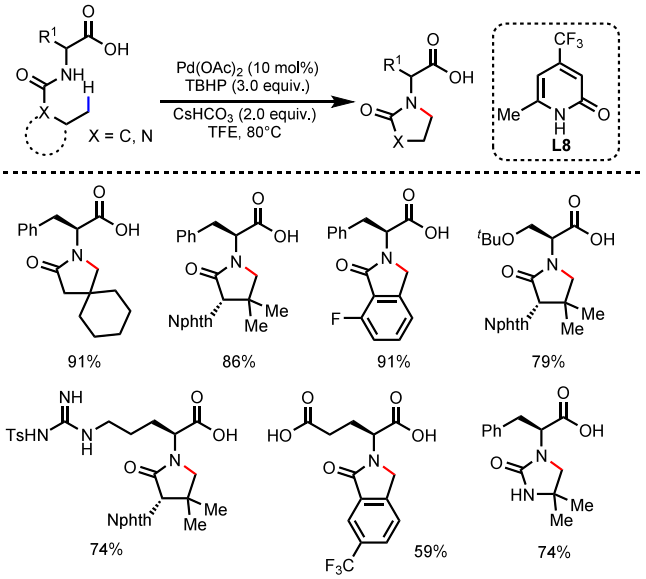
Scheme 11. Pd(II)-Catalyzed C(sp^3)−H Activation of Alcohol Derivatives

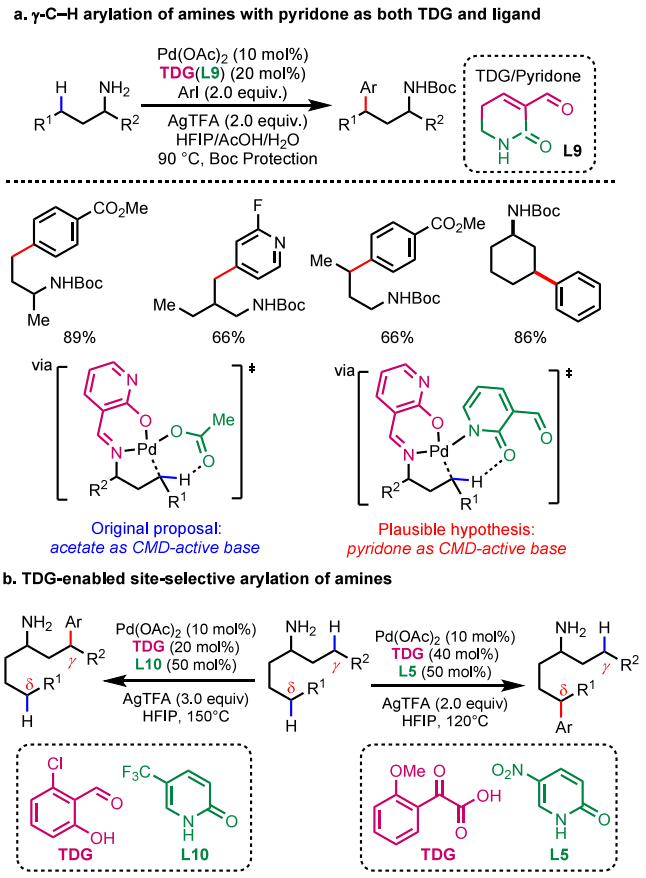


Scheme 12. Pd(II)-Catalyzed γ-C(sp^3)−H Lactamization of Amino Acid Derived Native Amides



controlled by the 5-membered binding bite angle of the auxiliary (Scheme 11a). Later, methylene β-C−H arylation was also

Scheme 13. TDG-Enabled Pd-Catalyzed C(sp^3)−H Arylation of Free Amines with Pyridone Ligands



achieved by utilizing a new bidentate auxiliary (Scheme 11b).[37] The introduction of multiple double bonds to the directing group makes the 5,6-membered palladacycle less strained than the 5,5- or 6,6-membered counterparts, thus making β-/γ-selectivity possible. While only a concise mechanistic rationale is provided here, the original research article offers a full discussion of how different bite angles of the auxiliary govern reactivity and selectivity.[36]

In 2021, the pyridone ligand was employed to promote Pd(II)-catalyzed γ-C(sp^3)−H lactamization of amino acid derived native amides, providing convenient syntheses of γ-lactams, isoindolinones, and 2-imidazolidinones.[38] Notably, a C6-substituted pyridone (**L8**) was most effective in this reaction, probably due to the generation of active monomeric palladium species and promotion of reductive elimination (Scheme 12).

4.4. Pd-Catalyzed C(sp^3)−H Functionalization Enabled by Transient Directing Groups (TDGs)

The development of an L−X-type TDG has emerged as a highly effective approach for the C(sp^3)−H functionalization of carbonyl and amino substrates without the need for preinstallation and removal of directing groups. In 2016, our group reported a γ-C(sp^3)−H arylation of free amines using 2-hydroxynicotinaldehyde (**L9**), a TDG bearing a pyridone-like motif (Scheme 13a).[39] Although acetate was proposed as the CMD base, the pyridone moiety likely also helped the C−H cleavage. In 2018, our group extended this reaction to the even more distal δ-position, achieving both γ- and δ-C(sp^3)−H arylation of free amines.[40] Pyridone was used as a separate ligand

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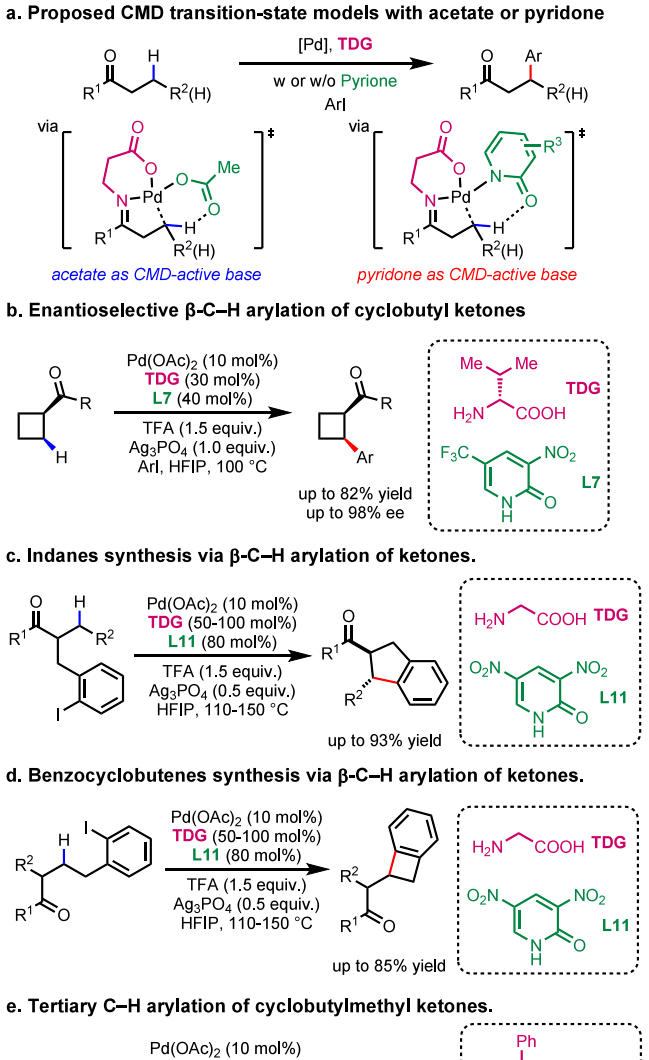
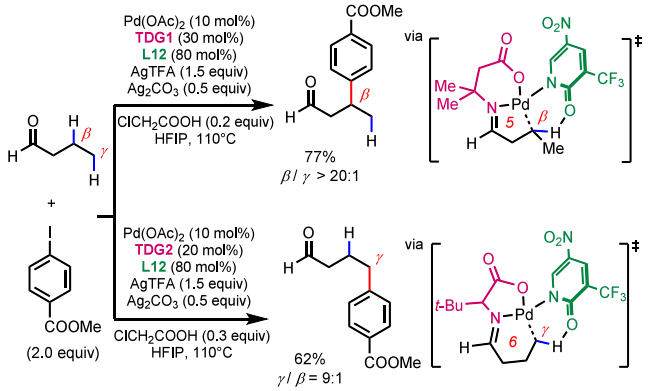
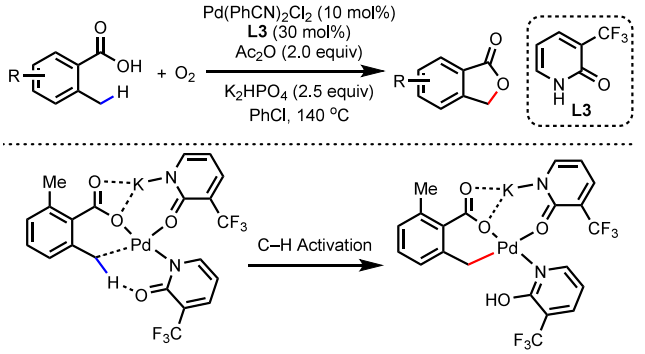
Scheme 14. TDG-Enabled Pd-Catalyzed Methylene and Methine C−H Arylation of Ketones



Scheme 15. TDG-Controlled Pd-Catalyzed Site-Selective β- and γ-C−H Arylation of Aldehydes



Scheme 16. Pd(II)-Catalyzed C(sp^3)−H Lactonization of *ortho*-Methyl Benzoic Acid Derivatives



rather than as part of the TDG, clearly confirming its role in promoting C−H activation (Scheme 13b). Beyond arylation, this strategy also enabled C−O and C−F bond construction.[41,42]

In addition to free amines, pyridone ligands have also been widely applied in the TDG-enabled C(sp^3)−H arylation of ketones and aldehydes (Scheme 14a). Our early TDG work focused on methyl and benzylic C−H bonds using acetate as the CMD base. Following pyridone's success in enabling more inert methylene C−H bonds in free amine systems, we also developed enantioselective β-C−H arylation of cyclobutyl ketones using D-valine as a chiral TDG.[43] The application of **L7** was crucial for promoting both reactivity and enantioselectivity (Scheme 14b). The versatility of pyridone ligands in methylene C−H activation was further highlighted by their application in intramolecular cyclization of ketones (Scheme 14c,d).[44,45] Notably, this strategy was also extended to challenging tertiary C−H bonds, as demonstrated by the β-C−H arylation of cyclobutylmethyl ketones (Scheme 14e).[46]

Apart from β-C−H arylation, our group and the Ge group also reported the pyridone-enabled γ-C−H arylation of ketones and aldehydes, respectively.[47,48] In 2022, we achieved a regiodivergent, site-selective between β- and γ-C−H functionalization by using different TDGs.[49] When six-membered chelating **TDG1** was employed, β-selective arylation of butanal was achieved with excellent selectivity. In contrast, switching to five-membered chelating **TDG2** reversed the selectivity to the γ-position (Scheme 15). A detailed mechanistic discussion can be found in the original research article, where the influence of ligand chelating size on regioselectivity is analyzed comprehensively.[49]

4.5. Pd-Catalyzed C(sp^3)−H Functionalization Enabled by a Monodentate Functional Group

In recent years, Pd(II)-catalyzed C(sp^3)−H activation of monodentate native substrates such as free carboxylic acids and amides has witnessed significant advances owing to the development of several generations of bifunctional ligands based on MPAA.[18] In 2020, our group reported a pyridone-assisted Pd(II)-catalyzed C(sp^3)−H lactonization of *ortho*-methyl benzoic acids using O_2 as the terminal oxidant (Scheme 16).[50] Mechanistic studies revealed dual pyridone coordination: one as an L-type ligand via oxygen and the other as an X-type ligand via nitrogen. This strategy was later extended to C−H amidation and arylation of native amides using Rh(III) and Pd(II) catalysis, respectively.[51] While these findings demonstrate the reactivity of the pyridone ligand for C(sp^3)−H activation of

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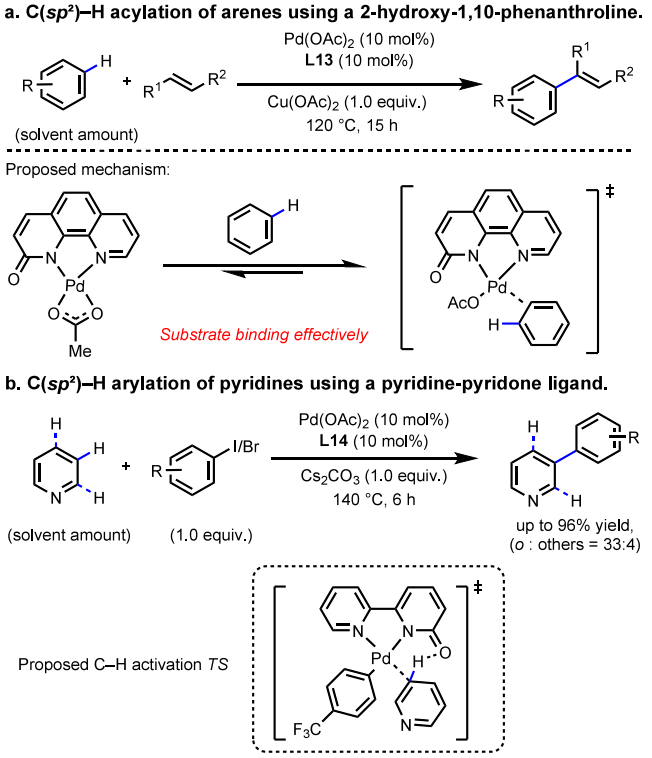
native substrates, a lack of reactivity for methylene C−H bonds points to a need for further development of pyridone ligands.

5. BIDENTATE PYRIDONE LIGANDS FOR PD-CATALYZED C−H ACTIVATION

Encouraged by our initial success with monodentate pyridone ligands and inspired by the development of bidentate MPAA

Scheme 17. Early Development of Bidentate Pyridone Ligand in C(sp²)−H Functionalization

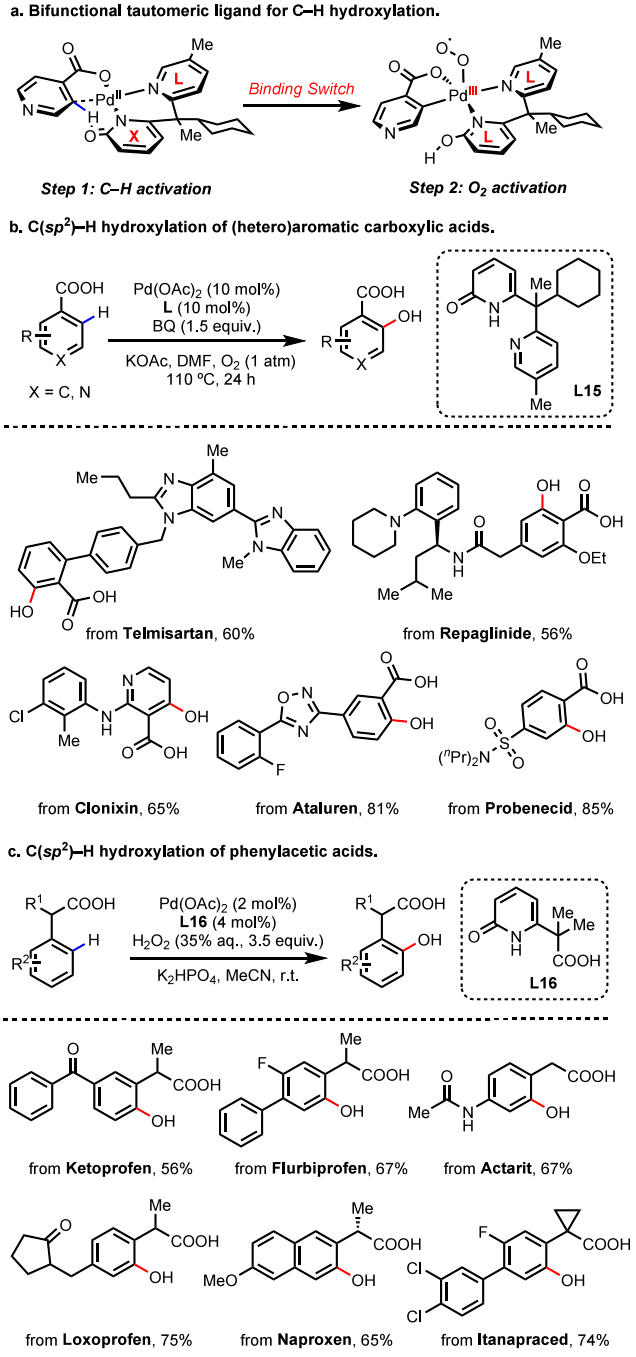


ligand designs, we next focused on the development of bidentate pyridone ligands. The introduction of an additional coordinative motif on the monodentate pyridone ligand can not only help orient the CMD-active pyridone moiety to the proximity of targeted C−H bonds but also facilitate subsequent functionalization via various catalytic cycles.

5.1. Pd-Catalyzed C(sp²)−H Functionalization

Although 2-hydroxy-1,10-phenanthroline (**L13**) has been identified as an effective bidentate ligand for nondirected acylation of arenes by the Duan group in 2013,[52] the pyridone moiety only serves as an amide ligand to help dissociation of the acetate anion from the Pd center without participating in the CMD step (Scheme 17a). Prompted by our first discovery of the dual function of the pyridone motif in C(sp²)−H activation systems,[1] the Albéniz group used a bidentate pyridone ligand (**L14**) to develop a C(sp²)−H arylation of pyridine using solvent quantities in 2018.[53] Although, pyridone was invoked as the internal CMD group, oxidative addition of ArI with Pd(0) was proposed to be the initiating step for the observed C−H arylation, which is mechanistically distinct from our Pd(II)-catalyzed C−H arylation catalytic cycle (Scheme 17b). Moreover, the pyridone moiety was proposed to serve as a CMD-active base in a sulfoxide−pyridone ligand for the C(sp²)−H alkenylation of indoles.[54]

Scheme 18. Pd-Catalyzed C(sp²)−H Hydroxylation of (Hetero)Aromatic Carboxylic Acids and Phenylacetic Acids Using Bidentate Pyridone Ligands



The first breakthrough in developing the Pd(II)-catalyzed C(sp²)−H activation reaction enabled by bidentate pyridone ligand was the discovery of carboxylic acid directed C(sp²)−H hydroxylation.[55] This work established the profound influence of the bite angle of pyridine−pyridone ligands (**L15**) on the reactivity and selectivity in C−H activation (Scheme 18a). Our design of bite-angle-controlled pyridone tautomerization allowed the reductive activation of molecular oxygen as the terminal oxidant (Scheme 18b). Remarkably, this bifunctional ligand significantly expanded the scope of heterocyclic substrates. In our further efforts toward developing scalable oxidation, we reported the CarboxPyridone ligand (**L16**) which

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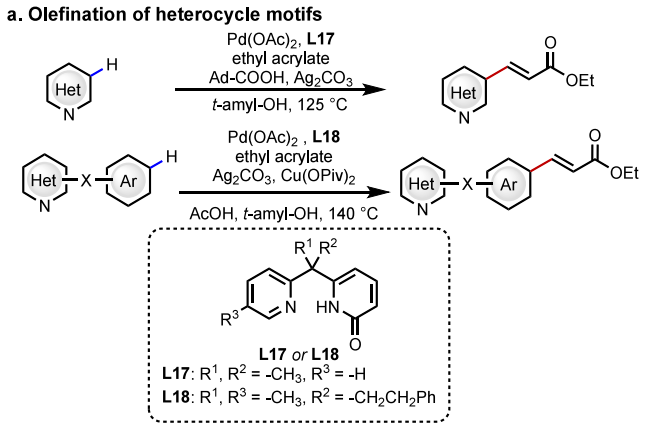
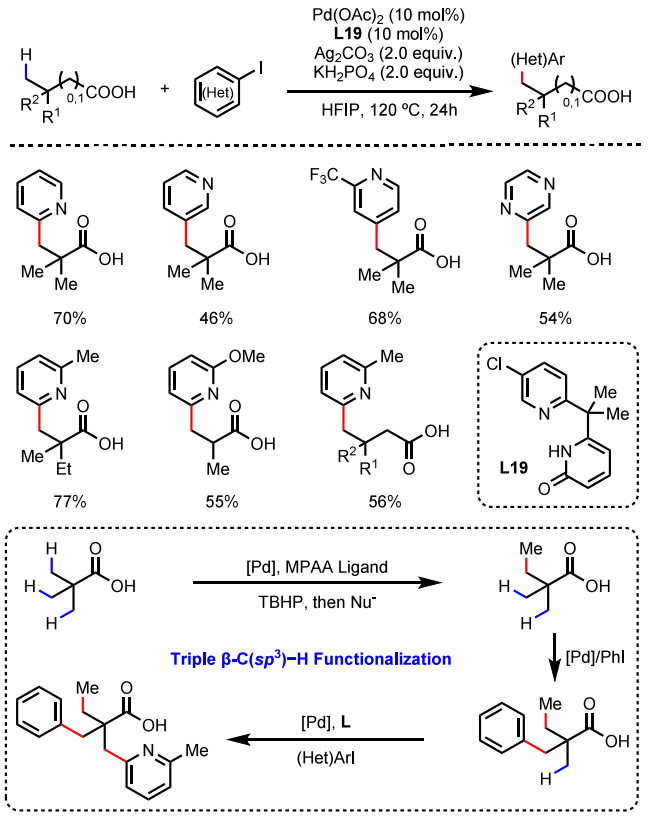
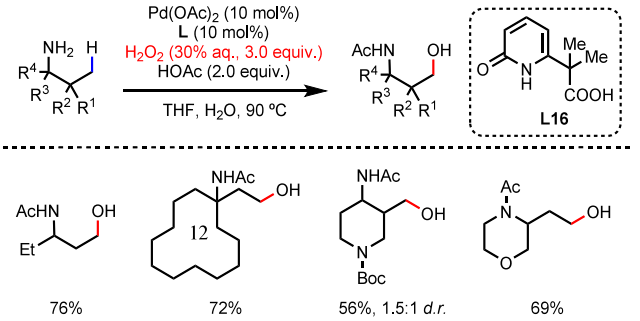
Scheme 19. Pd-Catalyzed Nondirected C(sp^2)−H Olefination of (Hetero)Arenes



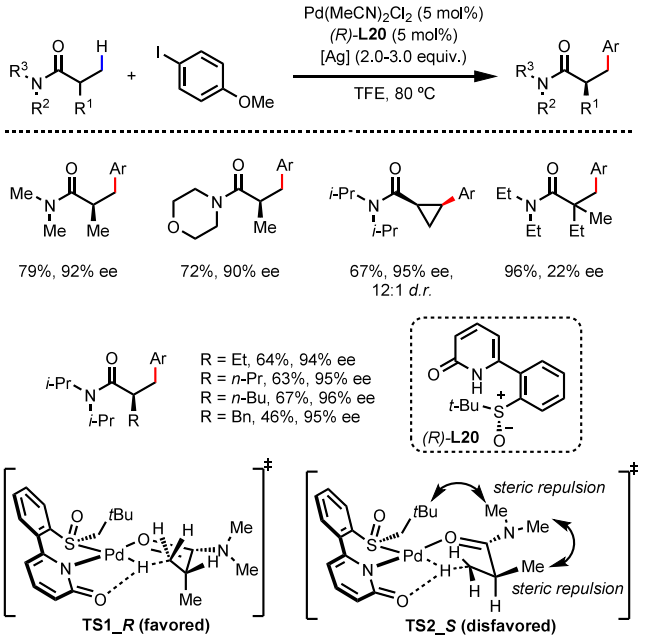
Scheme 20. Pd-Catalyzed C(sp^3)−H (Hetero)Arylation of Carboxylic Acids



Scheme 21. Pd-Catalyzed Methyl γ-C−H Hydroxylation of Amines



Scheme 22. Pd-Catalyzed Enantioselective Methyl β-C−H Functionalization of Native Amides



enabled phenylacetic acid directed C(sp^2)−H hydroxylation using 1−2 mol % loading of Pd catalyst in acetonitrile under air, at room temperature, using cheap aqueous hydrogen peroxide as the oxidant.[56] This reaction remains one of the most process-friendly and scalable protocols for Pd-catalyzed C−H functionalization reported to date (Scheme 18c). Notably, this strategy can be extended to C(sp^2)−H halogenation using three classes of ligands (quinoline−pyridone, quinuclidinone−pyridone, and pyridine−pyridone).[57]

The superior reactivity of bidentate pyridone ligands over their monodentate counterparts led us to explore nondirected C−H activation of heterocycles. In 2023, a dual-ligand system (pyridine−pyridone **L17** or **L18** with lutidine) enabled C3−H olefination of pyridines, and related arenes displayed significantly improved heterocycle compatibility (Scheme 19a).[58] The same system realized *meta*-C−H olefination of silyl-protected phenols, overriding innate para-selectivity.[59] This work highlighted the potential of ligand design to modulate both reactivity and site selectivity (Scheme 19b).

5.2. Pd-Catalyzed Methyl C(sp^3)−H Functionalization

Compared to C(sp^2)−H activation reactions, functionalization of C(sp^3)−H bonds is significantly more challenging. The successful application of monodentate pyridone ligands in

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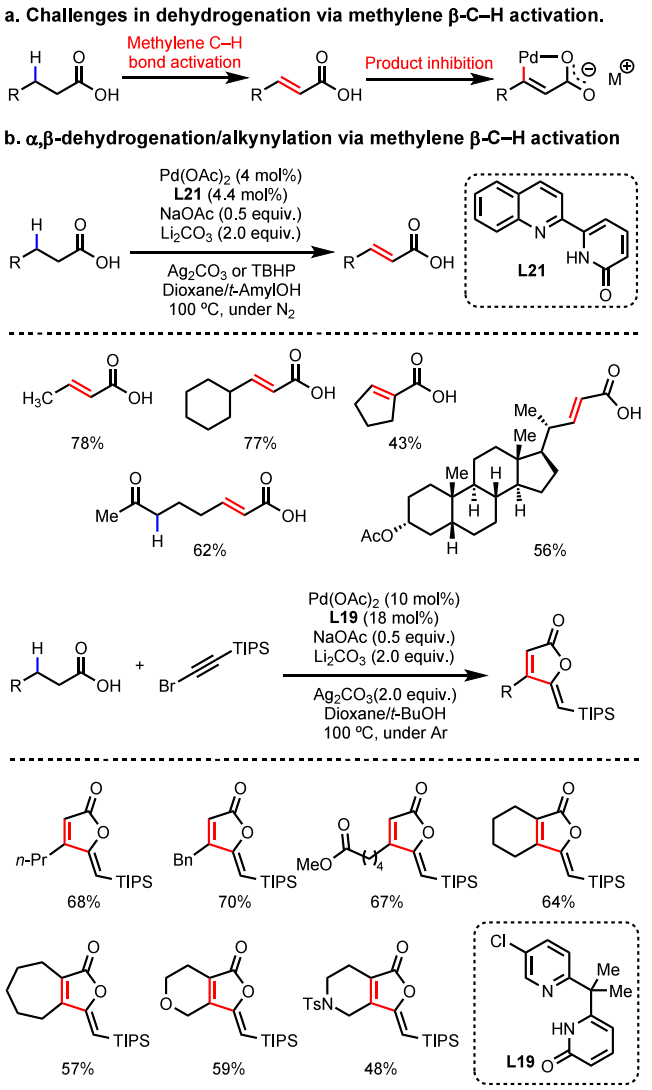
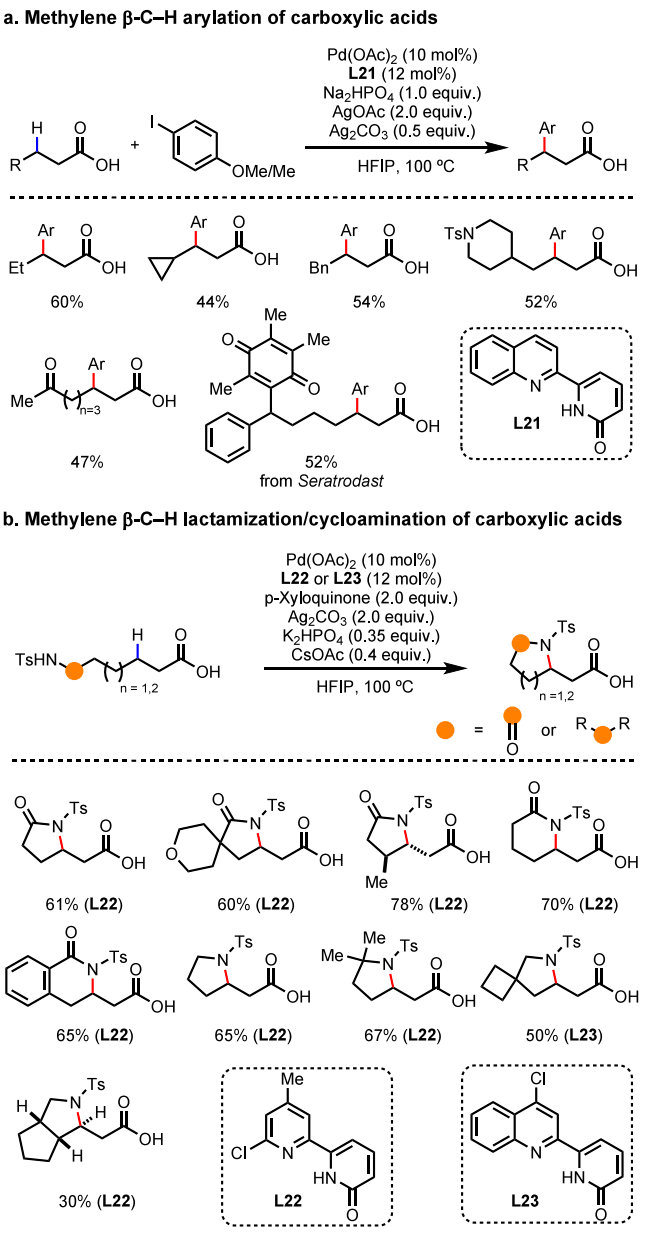
Scheme 23. Pd-Catalyzed α,β-Dehydrogenation and Sequential Alkynylation of Carboxylic Acids via β-Methylene C−H Activation



Scheme 24. Pd-Catalyzed β-Methylene C−H Functionalization of Carboxylic Acids



C(sp^3)−H functionalization paved the way to developing bidentate pyridone ligands for activating previously inaccessible C−H bonds.

Despite the first example of Pd-catalyzed C(sp^3)−H arylation of free carboxylic acid reported in 2007,[60] the development of β-C−H heteroarylation is highly limited. A major challenge in these transformations is the strong coordination of nitrogen atoms in heteroaryl iodides to the palladium center that hampers the reactivity. To overcome this issue, we applied a pyridine−pyridone ligand (**L19**) to promote Pd(II)-catalyzed β- and γ-C−H heteroarylation of carboxylic acids.[61] These ligands successfully suppressed the undesired coordination effects of unhindered pyridine iodides as coupling partners. Moreover, the synthetic utility of this method was highlighted through rapid construction of di(hetero)aryl-containing products via a sequential β-C−H alkylation/arylation strategy (Scheme 20).

Beyond carboxylic acids, our research has also focused on expanding the application of bidentate pyridone ligands to free amines. In 2023, we reported a CarboxPyridone ligand-enabled γ-C−H hydroxylation of amines using aqueous hydrogen peroxide as a sustainable oxidant.[62] This method efficiently delivered γ-hydroxylated *N*-acetyl protected primary amines (1°), piperidines, and morpholines (2°) with excellent monoselectivity (Scheme 21).

In addition to racemic C(sp^3)−H functionalization, efforts have been made toward developing enantioselective C−H activation reactions with chiral bidentate pyridone ligands. In 2023, the Jiao group reported an example of enantioselective methyl β-C−H arylation of native amides employing a chiral sulfoxide−pyridone ligand (**L20**).[63] A broad range of native amides bearing α-stereocenters were successfully arylated at the β-position with high enantioselectivity (Scheme 22). The noncovalent interaction analysis revealed significant steric repulsion between the N-substituent and both the α-methyl group and the ligand's *tert*-butyl group in disfavored **TS2_S**, providing mechanistic insight for the stereocontrol of the ligand.

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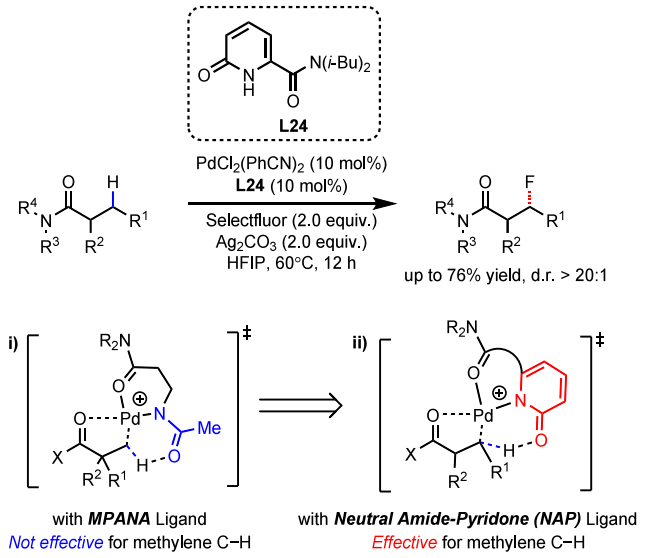
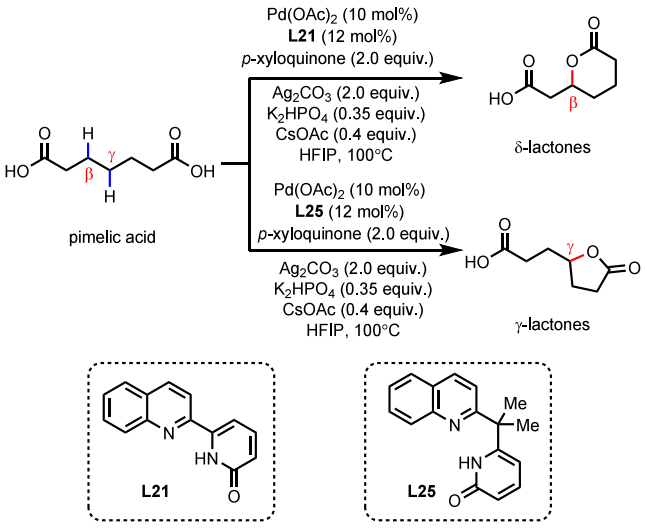
Scheme 25. Pd-Catalyzed Methylene β-C−H Fluorination of Native Amides



Scheme 26. Pd-Catalyzed Ligand-Controlled Site-Selective β- and γ-C−H Lactonization of Dicarboxylic Acids

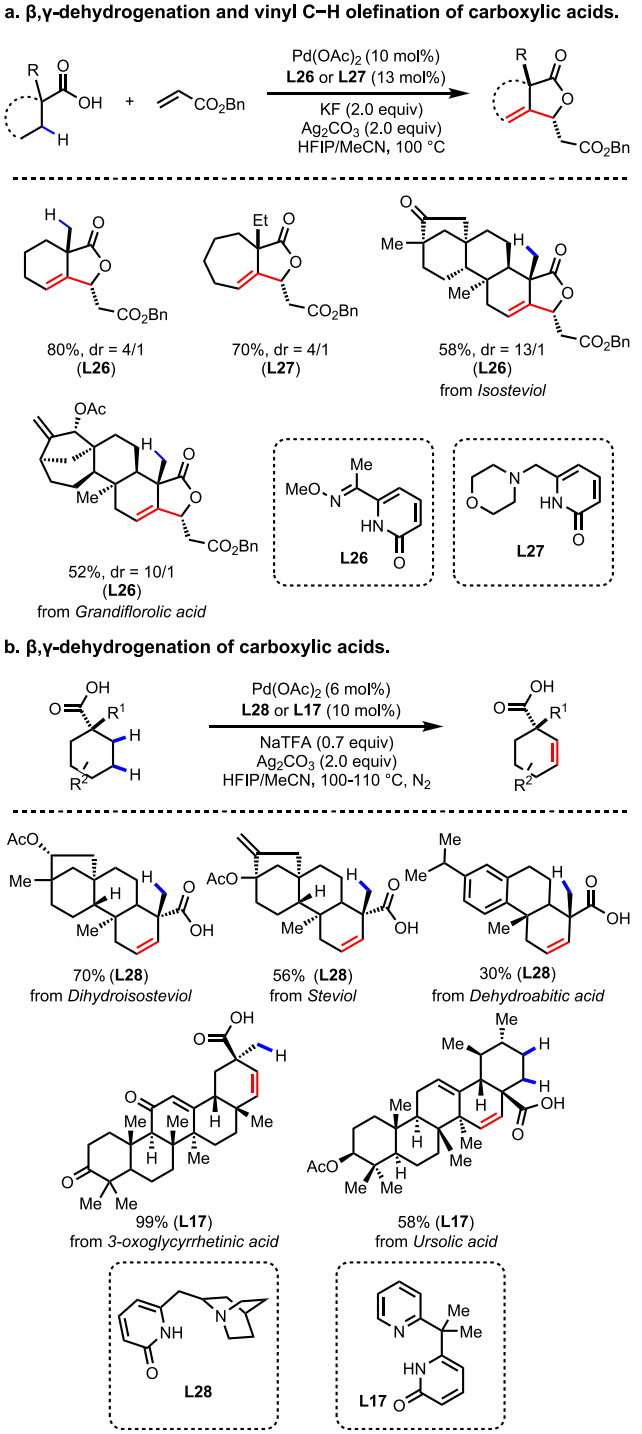


5.3. Pd-Catalyzed Methylene C(sp^3)−H Functionalization

Due to the increased steric hindrance of secondary C−H bonds, Pd-catalyzed methylene C−H activation often relies on strongly coordinating exogenous directing groups. The selective activation and transformation of methylene C−H bonds using weakly coordinating native functional groups has remained as one of the unsolved challenges in the field. We envision that bidentate pyridone ligands, which incorporate a chelating group that positions the pyridone moiety at an optimal distance and geometry to promote the CMD process at the targeted methylene C−H bond, could address this challenge.

5.3.1. Pd-Catalyzed Methylene β-C−H Functionalization of Carbonyl Compounds. In 2021, our group reported the first example of α,β-dehydrogenation of carboxylic acids via Pd-catalyzed methylene β-C−H activation.[2] This transformation posed significant challenges, not only due to the inherent difficulty of methylene C−H activation but also because the olefin products strongly inhibited the catalytic cycle due to the more favorable C(sp^2)−H palladation (Scheme 23a). To address these challenges, two different ligands were employed. First, a planar five-membered chelating quinoline−pyridone ligand (**L21**) with a rigid framework positions the active palladium center close to the methylene β-C−H bond to enhance reactivity while preventing vinyl C−H activation. Second, a six-membered chelating pyridine−pyridone ligand (**L19**) with a larger bite angle not only enables methylene β-C−H activation, but also matches the rigid geometry of acrylic acid to facilitate a tandem vinyl C−H activation, followed by alkynyl bromide coupling (Scheme 23b).

Scheme 27. Pd-Catalyzed β,γ-Dehydrogenation and Sequential Olefination of Cycloalkane Carboxylic Acids



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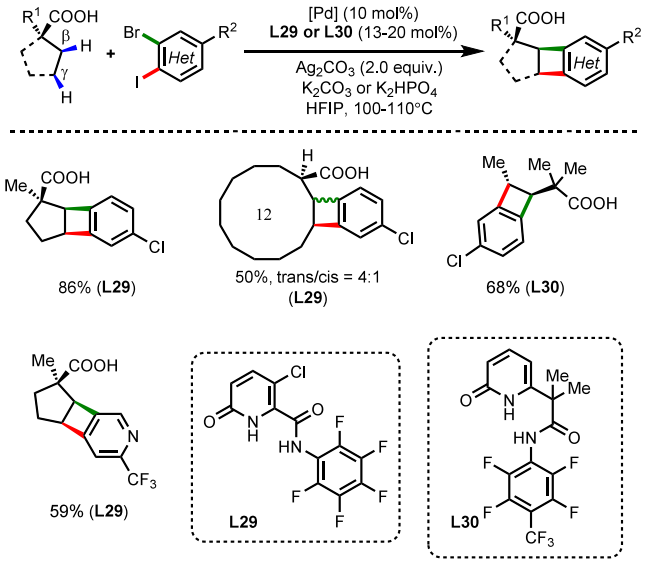
Scheme 28. Regiocontrollable [2 + 2] Benzannulation via Pd-Catalyzed Methylene *β*- and *γ*-C−H Activation



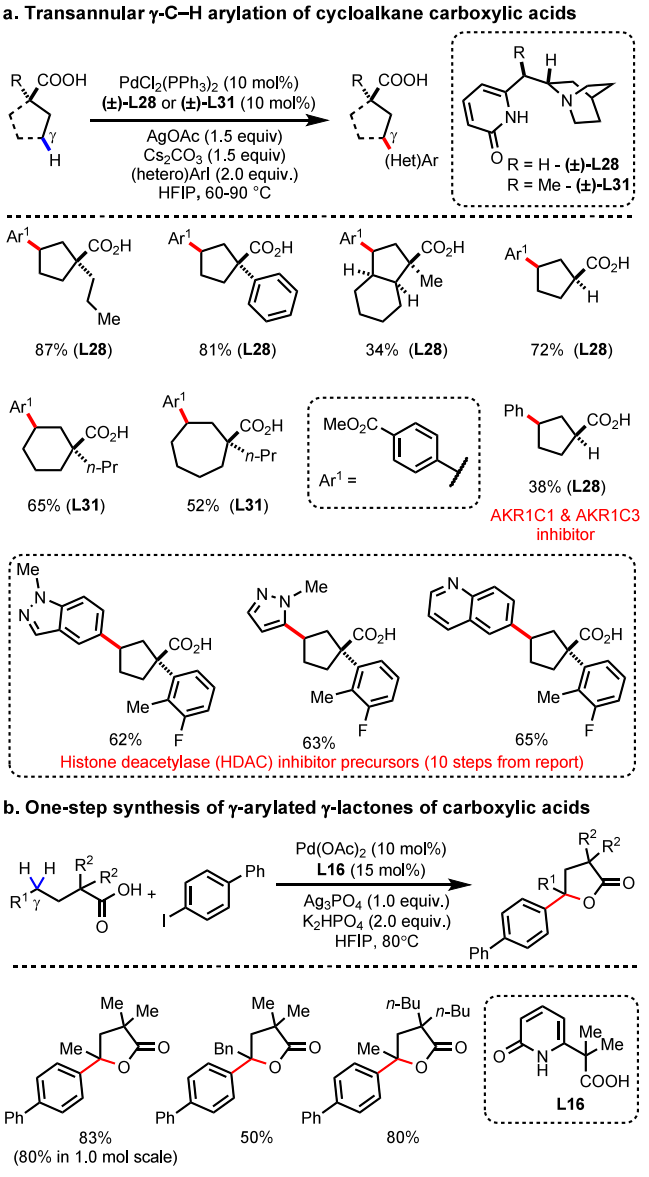
In 2022, we developed the first example of Pd-catalyzed *β*-methylene C−H arylation of carboxylic acids enabled by a quinoline−pyridone ligand (**L21**) (Scheme 24a).[64] Later, our group extended the application of quinoline/pyridine−pyridone ligands to the more challenging C−N bond formation reaction.[65] The development of chlorinated ligands (**L22** and **L23**) was crucial for overcoming *N*-coordination issues and suppressing competing amide-directed pathways (Scheme 24b). Interestingly, a recent synthesis of bicyclo[3.2.0]heptane lactones showcased a valuable use of amine−pyridone ligands.[66]

Beyond carboxylic acids, we are exploring methylene *β*-C−H functionalization of other weakly coordinating carbonyl compounds. Recently, our group developed a neutral amide−pyridone ligand (**L24**) for the Pd-catalyzed methylene *β*-C−H fluorination of native amides.[16] This advancement builds upon our earlier discovery of MPANA ligands, where the carboxylate group of our previously developed MPAA ligand is replaced with a neutral amide, which helps to preserve the cationic character of the palladium center. This electrophilic cationic Pd species enhances both the catalyst−substrate affinity and C−H activation reactivity. We therefore replaced the acetyl amide group in the MPANA ligand with pyridone to accelerate methylene C−H activation (Scheme 25).[20]

5.3.2. Pd-Catalyzed Distal Methylene C−H Functionalization. The discovery of the *β*-C−H functionalization of carboxylic acids encouraged us to explore new reactivity at more remote positions. In 2022, we developed a ligand-controlled strategy for site-selective methylene C−H functionalization of carboxylic acids using a bidentate quinoline−pyridone ligand system.[67] Specifically, a six-membered chelating ligand (**L25**) enabled highly selective methylene *γ*-C−H lactonization of carboxylic acids, forming *γ*-lactones through intramolecular cyclization with the pendant carboxylate. In contrast, a five-membered chelating ligand (**L21**) resulted in exclusive methylene *β*-C−H lactonization. These results highlight the effectiveness of bidentate pyridone ligands in achieving distal methylene C−H functionalization with high site-selectivity (Scheme 26).

Encouraged by this *β*,*γ*-C−H functionalization using bidentate pyridone ligands, we embarked on the development

Scheme 29. Pd-Catalyzed *γ*-C−H Functionalization of Carboxylic Acids



of catalytic *β*,*γ*-dehydrogenation of carboxylic acids bearing *α*-substituents. In 2022, we developed bidentate oxime−pyridone (**L26**) and morpholine−pyridone (**L27**) ligands to enable the synthesis of *β*-alkylidene-*γ*-lactones via *β*,*γ*-dehydrogenation and vinylic C−H olefination of carboxylic acids (Scheme 27a).[68] In a complementary approach, we applied quinuclidine−pyridone (**L28**) and pyridine−pyridone (**L17**) ligands to efficiently catalyze the *β*,*γ*-dehydrogenation of free carboxylic acids without external coupling partners.[69] This method enables the installation of a synthetically versatile double bond at remote positions in a wide array of biologically relevant natural products, such as dihydroisosteviol, steviol, dehydroabietic acid, 3-oxoglycyrrhetinic acid, and ursolic acid (Scheme 27b). Moreover, the use of bidentate quinoline−pyridone ligands has also led to the realization of sequential dehydrogenation of aliphatic acids to access a broad range of *E*,*E*-1,3-dienes.[70]

In 2023, the Pd-catalyzed *β*,*γ*-dehydrogenation pathway was successfully intercepted by coupling to aryl dihalides to form benzocyclobutenes (BCBs). The development of acidic amide−

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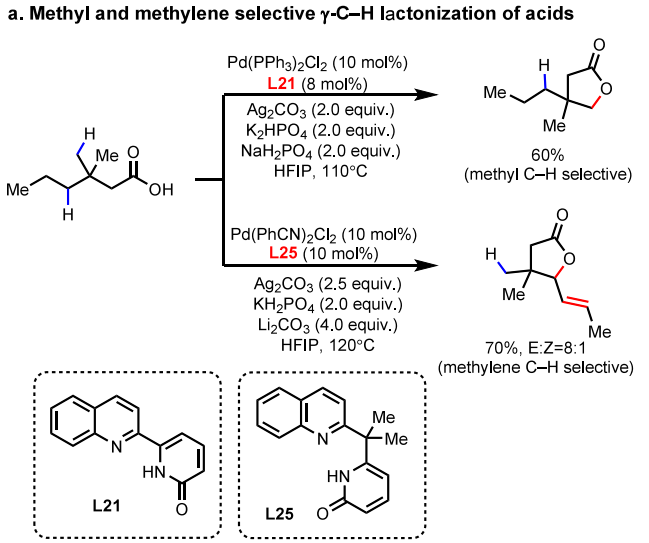
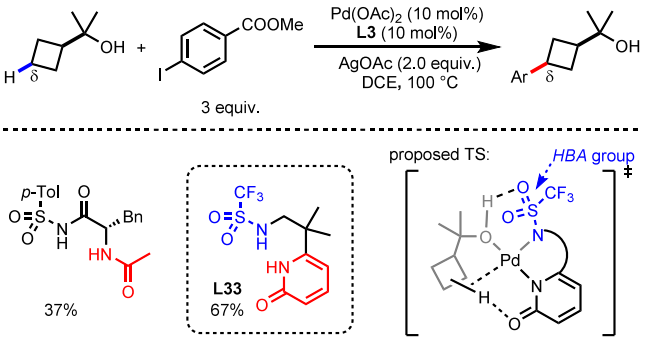
Scheme 30. Pd-Catalyzed γ-C−H Lactonization of Carboxylic Acids



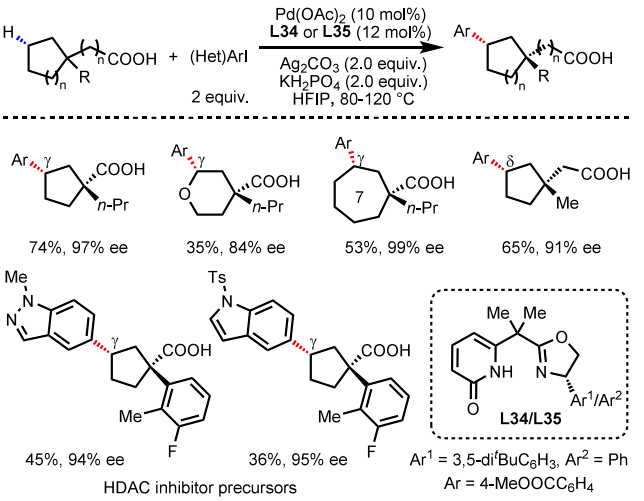
Scheme 31. Pd-Catalyzed Methylene δ-C−H Arylation of Free Alcohols



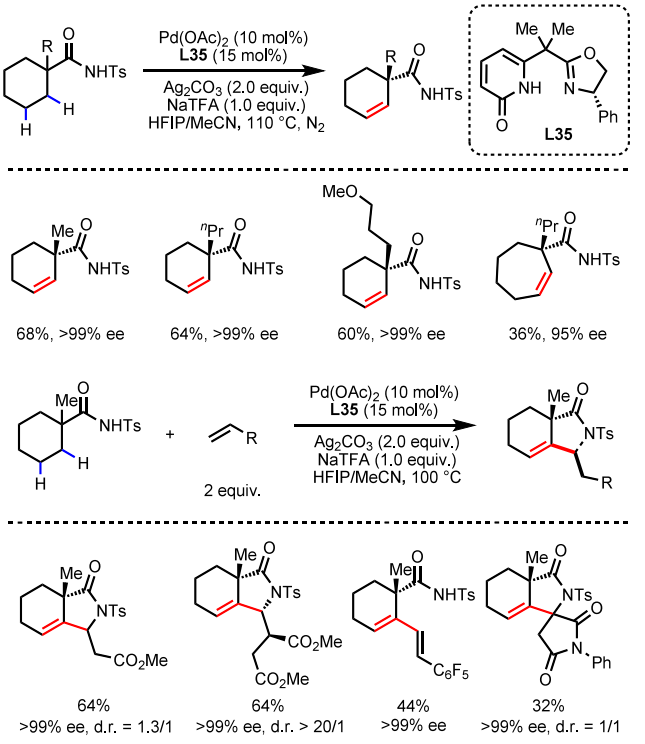
pyridone (**L29** and **L30**) ligands was crucial for this reaction.[71] Notably, the direct use of structurally diverse acyclic and cyclic carboxylic acids without requiring prefunctionalization significantly broadens the synthetic accessibility of BCBs (Scheme 28).

While consecutive functionalization of both β- and γ-C−H bonds within the same molecule has been achieved, site-selective γ-C−H functionalization remains particularly challenging due to the typically higher reactivity of β-C−H bonds. In 2023, our lab

Scheme 32. Pd-Catalyzed Enantioselective Methylene γ- and δ-C−H (Hetero)Arylation of Carboxylic Acids



Scheme 33. Pd-Catalyzed Enantioselective β,γ-C−H Dehydrogenation and Vinyl C−H Olefination of Acidic Amides



reported an example of methylene γ-selective transannular C−H arylation across a broad range of cycloalkane carboxylic acids.[3] Quinuclidine−pyridone (**L28**, **L31**) ligands were essential for the observed reactivity. Importantly, many of these γ-arylated acid products and their derivatives exhibit promising biological activity, underscoring their potential impact in medicinal chemistry (Scheme 29a). In the same year, our group developed a one-step synthesis of γ-arylated γ-butyrolactones via double γ-C−H functionalization of carboxylic acids, enabled by our previously developed CarboxPyridone ligands (**L16**) (Scheme 29b).[72]

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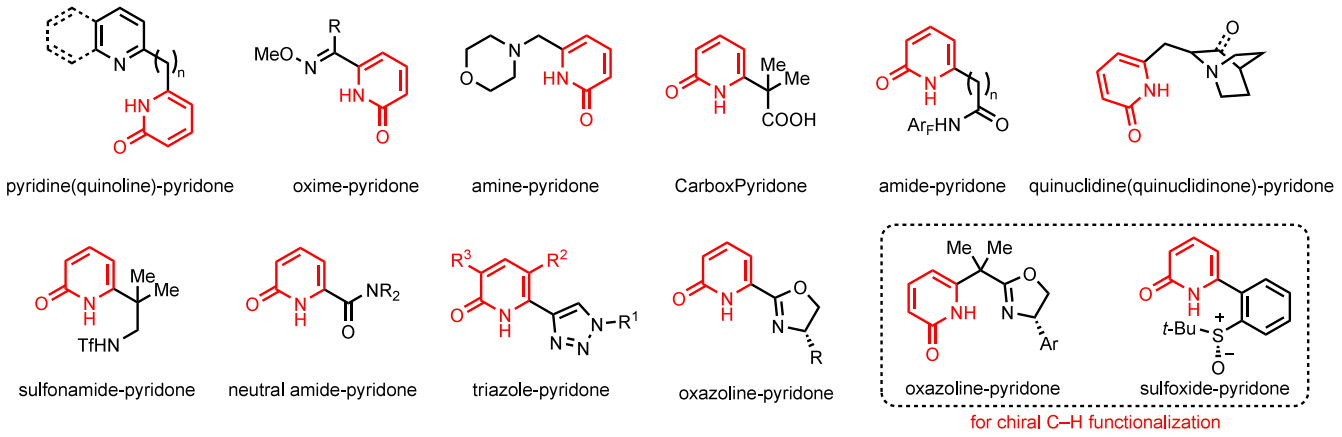
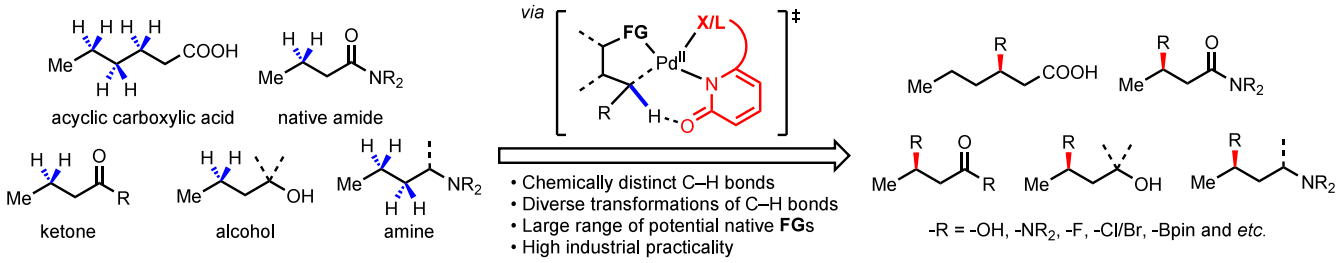
Scheme 34. Bifunctional Bidentate Pyridone Ligands



Scheme 35. Challenges in C−H Functionalization Driving the Development of Pyridone Ligands



In addition to regioselective C−H functionalization reactions, our group developed a chemoselective Pd(II)-catalyzed lactonization of methyl and methylene γ-C−H bonds of carboxylic acids, overcoming the limitation of inherently higher reactivity of primary C−H bonds.[73] Exclusive methyl γ-C−H lactonization was achieved using a five-membered chelating quinoline−pyridone ligand (**L21**), whereas a six-membered chelating quinoline−pyridone ligand (**L25**) led to selective methylene γ-C−H lactonization (Scheme 30a). Remarkably, the synthetic utility of methylene C−H lactonization of carboxylic acids was further demonstrated in our recent report of a Pd-catalyzed one-step butenolide synthesis via triple C−H functionalization enabled by a triazole−pyridone ligand (**L32**).[74] The use of *tert*-butyl hydroperoxide (TBHP) as the sole oxidant offers notable practical advantages in terms of efficiency and operational simplicity (Scheme 30b).

Beyond carboxylic acids, bidentate pyridone ligands have also proven to be effective for methylene C−H functionalization of alcohols. In 2023, our group reported the first example of free alcohol-directed δ-C−H arylation.[17] Bidentate triflamide−pyridone ligands (**L33**) were crucial for methylene C−H activation, whereas acyl amide ligands prove to be ineffective. Notably, the triflamide group not only serves as a coordination group but also acts as a hydrogen-bond acceptor (HBA), organizing the CMD transition state by restricting rotation around the Pd−O bond (Scheme 31).

5.3.3. Pd-Catalyzed Enantioselective Methylene C−H Functionalization. Although bidentate pyridone ligands have demonstrated excellent activity in promoting methylene C−H functionalization, achieving enantioselective methylene C−H activation of carboxylic acids remains a paramount challenge. Building on the success of chiral bidentate mono-*N*-protected amino acid ligands,[18] we were motivated to develop new chiral bidentate pyridone ligands to enable enantioselective methylene C−H functionalization.

The ability of chiral oxazoline units in bidentate ligands to significantly enhance the enantioselectivity was demonstrated by our previously developed MPAO ligands. Applying chiral oxazoline as a coordinating group, we designed a new class of chiral oxazoline−pyridone ligands (**L34** or **L35**). In 2024, we applied this design to achieve highly enantioselective methylene γ- and δ-C−H (hetero)arylation of a broad range of cyclic free carboxylic acids.[4] This protocol enables the construction of tertiary stereocenters through desymmetrization of α-quaternary centers, delivering chiral products in up to >99% ee (Scheme 32).

The utility of chiral bifunctional oxazoline−pyridone ligands was further demonstrated in the development of enantioselective β,γ-dehydrogenation and sequential olefination of cycloalkyl amides.[75] This protocol accommodates a broad range of carbocyclic substrates with varying ring sizes, efficiently converting them into chiral β,γ-unsaturated amides or β-alkylidene-γ-lactams with excellent enantioselectivity (Scheme 33).

6. CONCLUSION AND FUTURE OUTLOOK

The development of ligands has profoundly influenced the advancement of selective and efficient Pd(II)-catalyzed C−H functionalization in organic synthesis. In this Account, we have highlighted our efforts in the design of pyridone-based ligands that promote a broad array of C(sp^2)−H and C(sp^3)−H functionalization reactions over the past decade. Our initial investigations into monodentate pyridone ligands revealed their superior ability to accelerate nondirected aryl C−H activation and directed methylene C−H activation. Building on these findings, we have developed a second generation of bidentate pyridone ligands incorporating a pyridone moiety, including

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pyridine−pyridone, quinoline−pyridone, oxime-pyridone, CarboxPyridone, amide−pyridone, quinuclidine (quinuclidinone)−pyridone, sulfonamide−pyridone, neutral amide−pyridone, and triazole−pyridone scaffolds. These ligands have emerged as powerful tools for expanding the scope of Pd(II)-catalyzed C−H functionalization, particularly in tolerating heterocyclic substrates and enabling methylene C−H activation of weakly coordinating carboxylic acids and their derivatives. In addition, chiral bidentate pyridone ligands, such as oxazoline−pyridone (developed by our group) and sulfoxide−pyridone (developed by the Jiao group), have enabled highly enantioselective transformations of unreactive C−H bonds, further expanding the utility of pyridone ligand design in asymmetric catalysis. (Scheme 34)

Looking ahead, further advances in pyridone ligand design are anticipated to address the remaining challenges in the field of Pd(II) catalyzed C−H functionalization. These include the development of chiral pyridone scaffolds for enantioselective acyclic methylene C−H activation and the extension of C−H functionalization reactivity beyond conventional C−C and C−O bond formation, such as hydroxylation, amination, fluorination, halogenation, and borylation. In addition, expanding the compatibility of these ligands to a broader range of native functional groups, such as native amides, ketones, alcohols, and amines, will enhance their applicability to complex molecule synthesis. Finally, to enhance the practicality of C−H activation, we aim to utilize cost-effective oxidants and lower catalyst loadings and to explore earth-abundant metals, supported by next-generation pyridone ligands (Scheme 35).

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Jin-Quan Yu received his B.Sc. in Chemistry from East China Normal University and his M.Sc. from the Guangzhou Institute of Chemistry. In 2000, he obtained his Ph.D. at the University of Cambridge with Prof. Jonathan B. Spencer. After some time as a Junior Research Fellow at Cambridge, he joined the laboratory of Prof. E. J. Corey at Harvard University as a postdoctoral fellow. He then began his independent career at Cambridge (2003−2004), before moving to Brandeis University (2004−2007), and finally The Scripps Research Institute, where he is currently the Frank and Bertha Hupp Professor of Chemistry and Bristol Myers Squibb Endowed Chair in Chemistry.

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REFERENCES

(1) Wang, P.; Verma, P.; Xia, G.; Shi, J.; Qiao, J. X.; Tao, S.; Cheng, P. T. W.; Poss, M. A.; Farmer, M. E.; Yeung, K.-S.; Yu, J.-Q. Ligand-Accelerated Non-Directed C-H Functionalization of Arenes. *Nature* **2017**, *551*, 489−493.

(2) Wang, Z.; Hu, L.; Chekshin, N.; Zhuang, Z.; Qian, S.; Qiao, J. X.; Yu, J.-Q. Ligand-controlled divergent dehydrogenative reactions of aliphatic acids. *Science* **2021**, *374*, 1281−1285.

(3) Kang, G.; Strassfeld, D. A.; Sheng, T.; Chen, C.-Y.; Yu, J.-Q. Transannular C-H functionalization of cycloalkane carboxylic acids. *Nature* **2023**, *618*, 519−525.

(4) Zhang, T.; Zhang, Z.-Y.; Kang, G.; Sheng, T.; Yan, J.-L.; Yang, Y.-B.; Ouyang, Y.; Yu, J.-Q. Enantioselective Remote Methylene C−H (Hetero)arylation of Cycloalkane Carboxylic Acids. *Science* **2024**, *384*, 793−798.

(5) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. Palladium(II)-Catalyzed C−H Activation/C−C Cross-Coupling Reactions: Versatility and Practicality. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094−5115.

(6) Trost, B. M.; Breit, B.; Peukert, S.; Zambrano, J.; Ziller, J. W. A new platform for designing ligands for asymmetric induction in allylic alkylations. *Angew. Chem., Int. Ed.* **1995**, *34*, 2386−2388.

(7) Guram, A. S.; Buchwald, S. L. Palladium-Catalyzed Aromatic Aminations with in situ Generated Aminostannanes. *J. Am. Chem. Soc.* **1994**, *116*, 7901−7902.

(8) Paul, F.; Patt, J.; Hartwig, J. F. Palladium-catalyzed formation of carbon-nitrogen bonds. Reaction intermediates and catalyst improve-

ments in the hetero cross-coupling of aryl halides and tin amides. *J. Am. Chem. Soc.* **1994**, *116*, 5969−5970.
(9) Jensen, D. R.; Pugsley, J. S.; Sigman, M. S. Palladium-Catalyzed Enantioselective Oxidations of Alcohols Using Molecular Oxygen. *J. Am. Chem. Soc.* **2001**, *123*, 7475−7476.
(10) Ferreira, E. M.; Stoltz, B. M. The Palladium-Catalyzed Oxidative Kinetic Resolution of Secondary Alcohols with Molecular Oxygen. *J. Am. Chem. Soc.* **2001**, *123*, 7725−7726.
(11) Gómez, M.; Granell, J.; Martinez, M. Variable-Temperature and -Pressure Kinetics and Mechanism of the Cyclopalladation Reaction of Imines in Aprotic Solvent. *Organometallics* **1997**, *16*, 2539−2546.
(12) Lafrance, M.; Rowley, C. N.; Woo, T. K.; Fagnou, K. Catalytic Intermolecular Direct Arylation of Perfluorobenzenes. *J. Am. Chem. Soc.* **2006**, *128*, 8754−8756.
(13) Constable, A. G.; McDonald, W. S.; Sawkins, L. C.; Shaw, B. L. Palladation of dimethylhydrazones, oximes, and oxime O-allyl ethers: crystal structure of [Pd3(ON = CPriPh)6]. *J. Chem. Soc., Chem. Commun.* **1978**, 1061−1062.
(14) Shi, B.-F.; Maugel, N.; Zhang, Y.-H.; Yu, J.-Q. PdII-Catalyzed Enantioselective Activation of C(sp2)−H and C(sp3)−H Bonds Using Monoprotected Amino Acids as Chiral Ligands. *Angew. Chem., Int. Ed.* **2008**, *47*, 4882−4886.
(15) Wang, P.; Farmer, M. E.; Huo, X.; Jain, P.; Shen, P.-X.; Ishoey, M.; Bradner, J. E.; Wisniewski, S. R.; Eastgate, M. D.; Yu, J.-Q. Ligand-Promoted *Meta*-C−H Arylation of Anilines, Phenols, and Heterocycles. *J. Am. Chem. Soc.* **2016**, *138*, 9269−9276.
(16) Li, Y.-H.; Yu, J.-Q. Palladium-Catalyzed Methylene β-C−H Fluorination of Native Amides. *J. Am. Chem. Soc.* **2025**, *147*, 20233−20238.
(17) Strassfeld, D. A.; Chen, C.-Y.; Park, H. S.; Phan, D. Q.; Yu, J.-Q. Hydrogen-Bond-Acceptor Ligands Enable Distal C(sp^3)-H Arylation of Free Alcohols. *Nature* **2023**, *622*, 80−86.
(18) Shao, Q.; Wu, K.; Zhuang, Z.; Qian, S.; Yu, J.-Q. From $Pd(OAc)_2$ to Chiral Catalysts: The Discovery and Development of BifunctionalMono-*N*-Protected Amino Acid Ligands for Diverse C−H Functionalization Reactions. *Acc. Chem. Res.* **2020**, *53*, 833−851.
(19) Ouyang, Y.; Phan, D.; Chekshin, N.; Li, Y.-H.; Qiao, J. X.; Eastgate, M. D.; Yu, J.-Q. Enantioselective β-C(sp^3)−H Nucleophilic Tosylation of Native Amides: A Synthetic Platform for Chiral Methyl Stereocenters. *J. Am. Chem. Soc.* **2025**, *147*, 19559−19567.
(20) Li, Y.-H.; Chekshin, N.; Lu, Y.; Yu, J.-Q. β-C−H Bond Functionalization of Ketones and Esters by Cationic Pd Complexes. *Nature* **2025**, *637*, 608−614.
(21) Baker, F.; Baly, E. C. C. CVI.—The relation between absorption spectra and chemical constitution. Part VII. Pyridine and some of its derivatives. *J. Chem. Soc., Trans.* **1907**, *91*, 1122−1132.
(22) For a recent review on pyridone ligands in organometallic complexes, please see: Fedulin, A.; Jacobi von Wangelin, A. 2-Pyridonates: A Versatile Ligand Platform in 3d Transition Metal Coordination Chemistry and Catalysis. *Catal. Sci. Technol.* **2024**, *14*, 26−42.
(23) Xu, L.; Zhu, J.; Shen, X.; Chai, J.; Shi, L.; Wu, B.; Li, W.; Ma, D. 6-Hydroxy Picolinohydrazides Promoted Cu(I)-Catalyzed Hydroxylation Reaction in Water: Machine-Learning Accelerated Ligands Design and Reaction Optimization. *Angew. Chem., Int. Ed.* **2024**, *63*, No. e202412552.
(24) Kong, P.-C.; Rochon, F. D. Aminobenzonitrile compounds of platinum(II) and palladium(II). *Inorg. Chim. Acta* **1984**, *83*, 65−67.
(25) Wang, P.; Li, G.-C.; Jain, P.; Farmer, M. E.; He, J.; Shen, P.-X.; Yu, J.-Q. Ligand-Promoted *meta*-C−H Amination and Alkynylation. *J. Am. Chem. Soc.* **2016**, *138*, 14092−14099.
(26) Shi, H.; Wang, P.; Suzuki, S.; Farmer, M. E.; Yu, J.-Q. Ligand Promoted *meta*-C−H Chlorination of Anilines and Phenols. *J. Am. Chem. Soc.* **2016**, *138*, 14876−14879.
(27) Li, G. C.; Wang, P.; Farmer, M. E.; Yu, J.-Q. Ligand-Enabled Auxiliary-Free *meta*-C−H Arylation of Phenylacetic Acids. *Angew. Chem., Int. Ed.* **2017**, *56*, 6874−6877.
(28) Wang, P.; Farmer, M. E.; Yu, J.-Q. Ligand-Promoted meta-C−H Functionalization of Benzylamines. *Angew. Chem., Int. Ed.* **2017**, *56*, 5125−5129.
(29) Shi, H.; Herron, A. N.; Shao, Y.; Shao, Q.; Yu, J. Q. Enantioselective Remote meta-C-H Arylation and Alkylation via a Chiral Transient Mediator. *Nature* **2018**, *558*, 581−585.
(30) Farmer, M. E.; Wang, P.; Shi, H.; Yu, J.-Q. Palladium-Catalyzed meta-C−H Functionalization of Masked Aromatic Aldehydes. *ACS Catal.* **2018**, *8*, 7362−7367.
(31) Fan, Z.; Bay, K. L.; Chen, X.; Zhuang, Z.; Park, H. S.; Yeung, K. S.; Houk, K. N.; Yu, J. Q. Rational Development of Remote C−H Functionalization of Biphenyl: Experimental and Computational Studies. *Angew. Chem., Int. Ed.* **2020**, *59*, 4770−4777.
(32) Zhang, P.; Chang, W.; Kang, Y. S.; Zhao, W.; Cui, P. P.; Liang, Y.; Sun, W. Y.; Lu, Y. Rhodium(III)-Catalyzed C(sp^2) − H Chemoselective Annulation to O-Cyclized Isochromen-imines from Benzamides. *Org. Lett.* **2020**, *22*, 9462−9467.
(33) Liu, L.-Y.; Qiao, J. X.; Yeung, K.-S.; Ewing, W. R.; Yu, J.-Q. meta-Selective C−H Arylation of Fluoroarenes and Simple Arenes. *Angew. Chem., Int. Ed.* **2020**, *59*, 13831−13835.
(34) Chen, H.; Wedi, P.; Meyer, T.; Tavakoli, G.; van Gemmeren, M. Dual Ligand-Enabled Nondirected C-H Olefination of Arenes. *Angew. Chem., Int. Ed.* **2018**, *57*, 2497−2501.
(35) Zhu, R.-Y.; Li, Z.-Q.; Park, H. S.; Senanayake, C. H.; Yu, J.-Q. Ligand-Enabled γ-C(sp^3)−H Activation of Ketones. *J. Am. Chem. Soc.* **2018**, *140*, 3564−3568.
(36) Xia, G.; Weng, J.; Liu, L.; Verma, P.; Li, Z.; Yu, J.-Q. Reversing conventional site-selectivity in C(sp^3)−H bond activation. *Nat. Chem.* **2019**, *11*, 571−577.
(37) Xia, G.; Zhuang, Z.; Liu, L.-Y.; Schreiber, S. L.; Melillo, B.; Yu, J.-Q. Ligand-Enabled β-Methylene C(sp^3)−H Arylation of Masked Aliphatic Alcohols. *Angew. Chem., Int. Ed.* **2020**, *59*, 7783−7787.
(38) Liu, S.; Zhuang, Z.; Qiao, J. X.; Yeung, K.-S.; Su, S.; Cherney, E. C.; Ruan, Z.; Ewing, W. R.; Poss, M. A.; Yu, J.-Q. Ligand Enabled Pd(II)-Catalyzed γ-C(sp^3)−H Lactamization of Native Amides. *J. Am. Chem. Soc.* **2021**, *143*, 21657−21666.
(39) Wu, Y. W.; Chen, Y. Q.; Liu, T.; Eastgate, M. D.; Yu, J.-Q. Pd-Catalyzed γ-C(sp 3)−H Arylation of Free Amines Using a Transient Directing Group. *J. Am. Chem. Soc.* **2016**, *138*, 14554−14557.
(40) Chen, Y. Q.; Wang, Z.; Wu, Y.; Wisniewski, S. R.; Qiao, J. X.; Ewing, W. R.; Eastgate, M. D.; Yu, J.-Q. Overcoming the Limitations of γ- and δ-C−H Arylation of Amines through Ligand Development. *J. Am. Chem. Soc.* **2018**, *140*, 17884−17894.
(41) Chen, Y.-Q.; Wu, Y.; Wang, Z.; Qiao, J. X.; Yu, J.-Q. Transient directing group enabled Pd-catalyzed γ-C(sp^3)−H oxygenation of alkyl amines. *ACS Catal.* **2020**, *10*, 5657−5662.
(42) Chen, Y.-Q.; Singh, S.; Wu, Y.; Wang, Z.; Hao, W.; Verma, P.; Qiao, J. X.; Sunoj, R. B.; Yu, J.-Q. Pd-Catalyzed γ-C(sp^3)−H Fluorination of Free Amines. *J. Am. Chem. Soc.* **2020**, *142*, 9966−9974.
(43) Xiao, L.-J.; Hong, K.; Luo, F.; Hu, L.; Ewing, W. R.; Yeung, K.-S.; Yu, J.-Q. Pd^{II}-Catalyzed Enantioselective C(sp^3)−H Arylation of Cyclobutyl Ketones Using a Chiral Transient Directing Group. *Angew. Chem., Int. Ed.* **2020**, *59*, 9594−9600.
(44) Provencher, P. A.; Bay, K. L.; Hoskin, J. F.; Houk, K. N.; Yu, J.-Q.; Sorensen, E. J. Cyclization by C(sp^3)−H Arylation with a Transient Directing Group for the Diastereoselective Preparation of Indanes. *ACS Catal.* **2021**, *11*, 3115−3127.
(45) Provencher, P. A.; Hoskin, J. F.; Wong, J. J.; Chen, X.; Yu, J.-Q.; Houk, K. N.; Sorensen, E. J. Pd(II)-Catalyzed Synthesis of Benzocyclobutenes by β-Methylene-Selective C(sp^3)−H Arylation with a Transient Directing Group. *J. Am. Chem. Soc.* **2021**, *143*, 20035−20041.
(46) Cheng, J.-T.; Xiao, L.-J.; Qian, S.-Q.; Zhuang, Z.; Liu, A.; Yu, J.-Q. Palladium(II)-Catalyzed Selective Arylation of Tertiary C−H Bonds of Cyclobutylmethyl Ketones Using Transient Directing Groups. *Angew. Chem., Int. Ed.* **2022**, *61*, No. e202117233.
(47) Li, B.; Lawrence, B.; Li, G.; Ge, H. Ligand-Controlled Direct γ-C−H Arylation of Aldehydes. *Angew. Chem., Int. Ed.* **2020**, *59*, 3078−3082.

https://doi.org/10.1021/acs.accounts.5c00503
Acc. Chem. Res. 2025, 58, 2910−2926

(48) Li, Y.-H.; Ouyang, Y. X.; Chekshin, N.; Yu, J.-Q. Pd(II)-Catalyzed C(sp^3)−H (Hetero)arylation of Ketones Enabled by Transient Directing Groups. *ACS Catal.* **2022**, *12*, 10581−10586.
(49) Li, Y.-H.; Ouyang, Y. X.; Chekshin, N.; Yu, J.-Q. Pd(II)-Catalyzed Site-Selective β- and γ-C(sp3)−H Arylation of Primary Aldehydes Controlled by Transient Directing Groups. *J. Am. Chem. Soc.* **2022**, *144*, 4727−4733.
(50) Qian, S. Q.; Li, Z.-Q.; Li, M.; Wisniewski, S. R.; Qiao, J. X.; Richter, J. M.; Ewing, W. R.; Eastgate, M. D.; Chen, J. S.; Yu, J.-Q. Ligand-Enabled Pd(II)-Catalyzed C(sp^3)−H Lactonization Using Molecular Oxygen as Oxidant. *Org. Lett.* **2020**, *22*, 3960−3963.
(51) Wakikawa, T.; Sekine, D.; Murata, Y.; Bunno, Y.; Kojima, M.; Nagashima, Y.; Tanaka, K.; Yoshino, T.; Matsunaga, S. Native Amide-Directed C(sp^3)−H Amidation Enabled by Electron-Deficient Rh^{III} Catalyst and Electron-Deficient 2-Pyridone Ligand. *Angew. Chem., Int. Ed.* **2022**, *61*, No. e202213659.
(52) Ying, C.-H.; Yan, S.-B.; Duan, W.-L. 2-Hydroxy-1,10-phenanthroline vs 1,10-Phenanthroline: Significant Ligand Acceleration Effects in the Palladium-Catalyzed Oxidative Heck Reaction of Arenes. *Org. Lett.* **2014**, *16*, 500−503.
(53) Salamanca, V.; Toledo, A.; Albéniz, A. C. [2,2′-Bipyridin]-6(1*H*)-one, a Truly Cooperating Ligand in the Palladium-Mediated C−H Activation Step: Experimental Evidence in the Direct C-3 Arylation of Pyridine. *J. Am. Chem. Soc.* **2018**, *140*, 17851−17856.
(54) Wang, Y.-J.; Yuan, C.-H.; Chu, D.-Z.; Jiao, L. Regiocontrol in the Oxidative Heck Reaction of Indole by Ligand-Enabled Switch of the Regioselectivity-Determining Step. *Chem. Sci.* **2020**, *11*, 11042−11054.
(55) Li, Z.; Wang, Z.; Chekshin, N.; Qian, S.; Qiao, J. X.; Cheng, P. T.; Yeung, K. S.; Ewing, W. R.; Yu, J.-Q. A tautomeric ligand enables directed C−H hydroxylation with molecular oxygen. *Science* **2021**, *372*, 1452−1457.
(56) Li, Z.; Park, H. S.; Qiao, J. X.; Yeung, K. S.; Yu, J.-Q. Ligand-Enabled C-H Hydroxylation with Aqueous H_2O_2 at Room Temperature. *J. Am. Chem. Soc.* **2022**, *144*, 18109−18116.
(57) Zhao, H.; Yu, J.-Q. *J. Am. Chem. Soc.* **2025**, manuscript submitted for publication.
(58) Meng, G.; Wang, Z.; Chan, H. S. S.; Chekshin, N.; Li, Z.; Wang, P.; Yu, J.-Q. A Dual-Ligand Catalyst for the non-Directed C−H Olefination of Heteroarenes. *J. Am. Chem. Soc.* **2023**, *145*, 8198−8208.
(59) Meng, G.; Yan, J.-L.; Chekshin, N.; Strassfeld, D. A.; Yu, J.-Q. Ligand-Controlled Nondirected *meta*- or *para*-C-H Olefination of Silyl-Protected Phenols. *ACS Catal.* **2024**, *14*, 12806−12813.
(60) Giri, R.; Maugel, N.; Li, J.-J.; Wang, D.-H.; Breazzano, S. P.; Saunders, L. B.; Yu, J.-Q. Palladium-Catalyzed Methylation and Arylation of sp^2 and sp^3 C−H Bonds in Simple Carboxylic Acids. *J. Am. Chem. Soc.* **2007**, *129*, 3510−3511.
(61) Meng, G.; Hu, L.; Tomanik, M.; Yu, J. Q. β- and γ-C(sp^3)−H Heteroarylation of Free Carboxylic Acids: A Modular Synthetic Platform for Diverse Quaternary Carbon Centers. *Angew. Chem., Int. Ed.* **2023**, *62*, No. e202214459.
(62) Li, Z.; Yu, J.-Q. Ligand-Enabled γ-C(sp^3)−H Hydroxylation of Free Amines with Aqueous Hydrogen Peroxide. *J. Am. Chem. Soc.* **2023**, *145*, 25948−25953.
(63) Yuan, C.-H.; Wang, X.-X.; Jiao, L. Ligand-Enabled Palladium(II)-Catalyzed Enantioselective β-C(sp^3)-H Arylation of Aliphatic Tertiary Amides. *Angew. Chem., Int. Ed.* **2023**, *62*, No. e202300854.
(64) Hu, L.; Meng, G.; Yu, J.-Q. Ligand-enabled Pd(II)-catalyzed β-methylene C(sp^3)-H arylation of free aliphatic acids. *J. Am. Chem. Soc.* **2022**, *144*, 20550−20553.
(65) Chan, H. S. S.; Lu, Y.; Yu, J.-Q. Palladium-Catalysed Methylene C(sp^3)−H Lactamization and Cycloamination Enabled by Chlorinated Pyridine−Pyridone Ligands. *Nat. Synth.* **2024**, *3*, 752−762.
(66) Fan, Z.; Cai, X.; Sheng, T.; Yu, J.-Q. Synthesis of Bicyclo[3.2.0]-heptane Lactones via a Ligand-Enabled Pd-Catalyzed C(sp^3)−H Activation Cascade. *Chem. Sci.* **2025**, *16*, 9436−9440.
(67) Chan, H. S. S.; Yang, J.-M.; Yu, J.-Q. Catalyst-Controlled Site-Selective Methylene C−H Lactonization of Dicarboxylic Acids. *Science* **2022**, *376*, 1481−1487.
(68) Sheng, T.; Zhuang, Z.; Wang, Z.; Hu, L.; Herron, A. N.; Qiao, J. X.; Yu, J.-Q. One-Step Synthesis of β-Alkylidene-γ-lactones via Ligand-Enabled β,γ-Dehydrogenation of Aliphatic Acids. *J. Am. Chem. Soc.* **2022**, *144*, 12924−12933.
(69) Sheng, T.; Kang, G.; Zhuang, Z.; Chekshin, N.; Wang, Z.; Hu, L.; Yu, J.-Q. Synthesis of β, γ-Unsaturated Aliphatic Acids via Ligand-Enabled Dehydrogenation. *J. Am. Chem. Soc.* **2023**, *145*, 20951−20958.
(70) Meng, G.; Hu, L.; Chan, H. S. S.; Qiao, J. X.; Yu, J. Synthesis of 1, 3-dienes via ligand-enabled sequential dehydrogenation of aliphatic acids. *J. Am. Chem. Soc.* **2023**, *145*, 13003−13007.
(71) Yang, J.-M.; Lin, Y.-K.; Sheng, T.; Hu, L.; Cai, X.-P.; Yu, J.-Q. Regio-controllable [2 + 2] benzannulation with two adjacent C(sp^3)−H bonds. *Science* **2023**, *380*, 639−644.
(72) Hoque, M. E.; Yu, J.-Q. Ligand-Enabled Double γ-C(sp^3)−H Functionalization of Aliphatic Acids: One-Step Synthesis of γ-Arylated γ-Lactones. *Angew. Chem., Int. Ed.* **2023**, *62*, No. e202312331.
(73) Yan, J.-L.; Hu, L.; Lu, Y.; Yu, J.-Q. Catalyst-Controlled Chemoselective γ-C(sp^3)−H Lactonization of Carboxylic Acid: Methyl versus Methylene. *J. Am. Chem. Soc.* **2024**, *146*, 29311−29314.
(74) Lin, Y.-K.; Kim, D.; Ouyang, Y.; Yu, J.-Q. Versatile Butenolide Syntheses via a Structure-Oriented C−H Activation Reaction. *J. Am. Chem. Soc.* **2025**, *147*, 26019.
(75) Sheng, T.; Zhang, T.; Zhuang, Z.; Yu, J.-Q. Synthesis of chiral carbocycles via enantioselective β, γ-dehydrogenation. *Nature Synthesis* **2024**, *3*, 1550−1559.

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