Carboxylate-Directed C−H Functionalization

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Abstract: As a widely existing functional group in organic molecules, the carboxyl group has numerous advantageous characteristics such as great convenience for further transformation, relatively low toxicity and cost, and weak coordination to transition metal catalysts, which render it an attractive directing group in transition metal-catalyzed C−H bond functionalization reactions. This review surveys transition metal-catalyzed C−H bond functionalization reactions directed by carboxylates, including carbon-carbon, carbon-oxygen, and other carbon-heteroatom bond formation reactions. Reactions directed by the acidic N-arylamides, which are derived from carboxylic acids and have a directing mode similar to that of carboxylates, are also presented here.

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Keywords: amides; carboxylic acids; C−H functionalization; transition metals

1 Introduction

Carbon-hydrogen bonds are ubiquitous in organic molecules, implying the great potential for transforming C−H bonds into a diversity of other functional groups, which is of great significance in organic synthesis. However, due to the inert nature of C−H bonds, direct C−H functionalization made very slow progress until breakthroughs in transition metal-catalyzed C−H activation were made in the past decades.[1] Another great challenge in C−H bond transformation is the intractable problem of achieving the desired selectivities for substrates containing diverse C−H bonds. Currently, the most common strategies for achieving the desired selectivities rely on the use of directing groups, which can bind to transition metal catalysts and induce C−H bond cleavage at appropriate sites. Coordinating groups containing heteroatoms (especially N and O), such as pyridine, oxazoline, amide, carbonyl, and hydroxy groups, etc. are the most common directing groups.[2]

A desired directing group should possess the following characteristics: (i) appropriate coordinating ability to catalysts; (ii) great ease of being installed and removed, (iii) high availability in organic molecules, and (iv) great convenience for further transformation to other functional groups. Unfortunately, the synthetic application of some effective directing groups is limited as they do not fulfil the above requirements.[3]

As a weakly coordinating group, the carboxylate moiety serves as a promising and valuable directing group, due to its possession of numerous advantages. First, it presents weak coordination to catalysts to induce selective C−H bond cleavage and facilitate the release of the catalyst species. Second, carboxyl groups widely exist in organic molecules, and it can be obtained from many other functional groups readily, such as amide, cyano, carbonyl groups and even halides. Third, the carboxyl group can be easily transformed into diverse functional groups or undergo decarboxylation after directed C−H functionalization. Significantly, a range of carboxylic acid derivatives have been developed as effective directing groups in transition metal-catalyzed C−H functionalization, such as amide,[4] oxazoline,[5] hydroxamic acid,[6] etc.

Guang-Fa Shi was born in Anhui, China, in 1990. He obtained his bachelor degree in applied chemistry at Tongji University under the direction of Prof. Yanghui Zhang in 2012. Just after graduation, he joined Yanghui Zhang's group to pursue his PhD studies in organic chemistry in the Department of Chemistry at Tongji University. His current research focuses on transition-metal-catalyzed C−H bond activation.

Yanghui Zhang received his BS and MS in chemistry at Tongji University in Shanghai, China. After 3 years' research experience at Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, he moved to the University of Georgia in Athens, USA to start his PhD studies in carbohydrate chemistry under the direction of Professor Geert-Jan Boons in 2002, and obtained his PhD degree in 2007. He was a postdoctoral fellow working on palladium-catalyzed C−H functionalization in the research group of Prof. Jin-Quan Yu at The Scripps Research Institute in La Jolla, USA for approximately 3 years. Currently, he is a professor in the Department of Chemistry of Tongji University, and his research focuses on the development of highly efficient and step- and atom-economic catalytic transformations for organic syntheses.

The variety of the derivation of carboxylic acids enables compatibility with diverse reaction conditions and greatly expands transformation categories.

In this context, carboxylate-directed C−H activation reactions with diverse coupling partners catalyzed by transition metals are reviewed, as well as those directed by acidic *N*-arylamides, which exhibit similar coordination modes as carboxylates. Unlike the great success in various carboxylate-directed C-(sp^2)−H bond activations, homologous C(sp^3)-H functionalization is more challenging and seems to be less effective.[7] It is comforting that the acidic *N*-arylamide directing groups are valuable complements as they show versatile reactivities in C(sp^3)−H activation with great efficiency.[8] In addition, the general coordination modes of these directing groups with transition metal centers are also presented.

2 Coordination Modes of Carboxylate and *N*-Arylamide Directing Groups with Transition Metal Catalysts in C−H Bond Cleavage

There are a variety of modes for the coordination of carboxylates with metals, which can be collected into several fashions such as κ^1 and κ^2 coordination (Figure 1).[9] In the κ^1 coordination mode, transition metal catalysts coordinate with one carboxyl oxygen atom and cleave the adjacent C−H bond which is spa-

tially favorable, while the catalyst center is sequestered away from target C−H bonds in the κ^2 fashion. For the success of C−H cleavage directed by carboxylates, the κ^1 coordination mode seems to be crucial.

For transition metals such as Rh(I) and Ir(I), a transition from κ^2 to κ^1 coordination may take place to cleave C−H bonds (Figure 2A).[1c,10] However, the car-
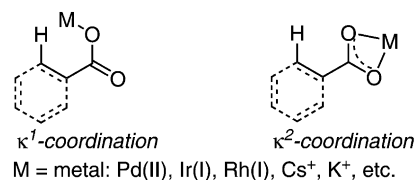

Figure 1. Typical coordination modes of metals with carboxylates: κ^1- and κ^2-coordination.
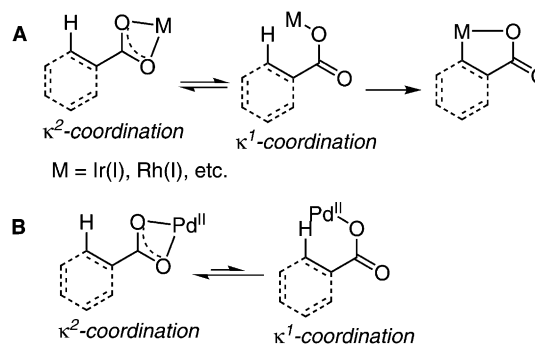

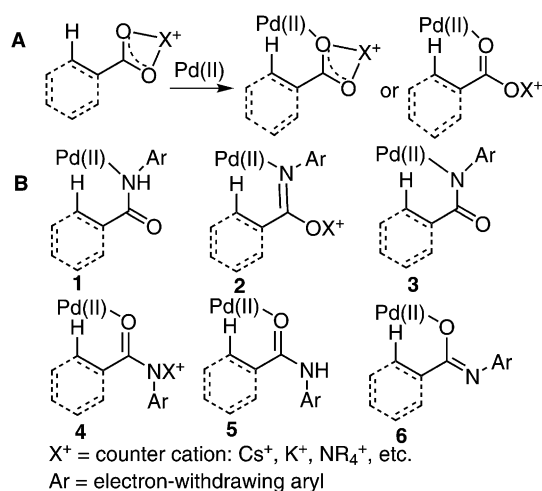**Figure 2.** Coordination modes of Pd(II) and Rh(I)/Ir(I) with carboxylates.

Figure 3. Countercation-assisted coordination modes of Pd(II) with carboxylate and *N*-arylamides.

boxylate-coordinated Pd(II) complex prefers to adopt the κ^2 coordination, which would inhibit C–H cleavage (Figure 2B). Therefore, to make Pd(II)-catalyzed C–H activation take place, the equilibrium must be shifted to the κ^1 coordination by some means.

Remarkably, it has been found that the equilibrium can be shifted from κ^2 to κ^1 coordination simply by the addition of organic or inorganic counter cations such as Cs$^+$, K$^+$, NR$_4^+$, and even protonated amides.[11,12] In this new coordination mode, the counter cations bind to the carboxylate in a κ^2 coordination mode, and the Pd(II) is induced to coordinate in a κ^1 fashion with oxygen lone electron pair (Figure 3A), which enables the Pd(II) to approach and cleave the adjacent C–H bonds.

A similar strategy has been successfully applied to the development of novel *N*-arylamide directing groups.[8a,13] The amides, containing a highly electron-deficient *N*-aryl group, are quite acidic and can be deprotonated with a weak base. The resulting amidates can bind to Pd(II in a κ^1 fashion, which is analogous to that with carboxylates (Figure 3B).[9] The transition metals tend to coordinate with the nitrogen rather than the oxygen atom in many cases (such as the preferred mode 2 or 3 in Figure 3B),[4f] which strengthens the interaction between the catalyst and substrates to facilitate the key C–H bond cleavage step. Remarkably, these novel acidic directing groups have proven to be highly effective in a wide array of C–H activation reactions, especially in the reactions involving C(sp^3)-H activation.

# 3 Carboxylate-Directed C–H Bond Functionalizations with Unsaturated Bonds

Transition metal-catalyzed Heck-type reactions proceeding through C–H bond activation have been widely developed in the past decades. A variety of directing groups prove to be effective for these transformations, such as amide, and amino groups, etc.[14] In this context, carboxylate-directed C–H functionalization with unsaturated bonds has been extensively investigated, and a variety of reactions have been developed.

The initial work of carboxylate-directed C–H olefination was reported by Miura et al. in 1998.[15] In this pioneering work, benzoic acids and naphthoic acids reacted with alkenes such as butyl acrylate or styrene in the presence of Pd(OAc)$_2$ and Cu(OAc)$_2$ in DMF, giving phthalides or isocoumarins in moderate to good yields (Scheme 1). The possible pathway may involve *ortho*-vinylation/nucleophilic cyclization or Wacker-type oxidative cyclization.

Interestingly, the Miura group demonstrated an unusual palladium-catalyzed oxidative coupling of indole-2- or indole-3-carboxylic acids with styrene or acrylates, which gave the corresponding 3-vinylindoles or 2-vinylindoles *via* C–H vinylation and subsequent decarboxylation in the presence of Pd catalyst and Cu(OAc)$_2$·H$_2$O as the oxidant (Scheme 2).[16] The reaction tolerated various heteroaromatic substrates in-
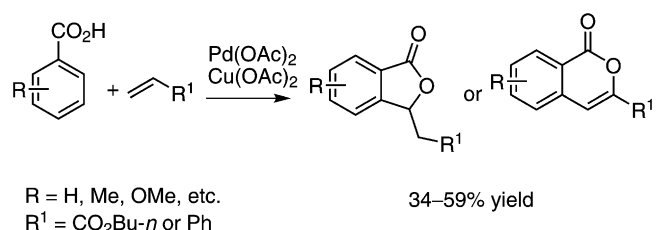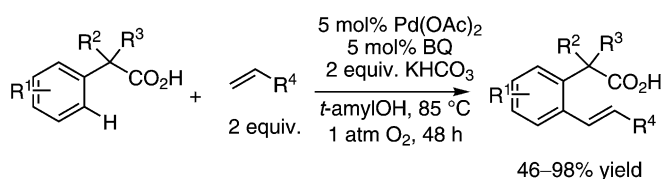

Scheme 1. Pd-catalyzed carboxylate-directed C–H olefination of benzoic acids.
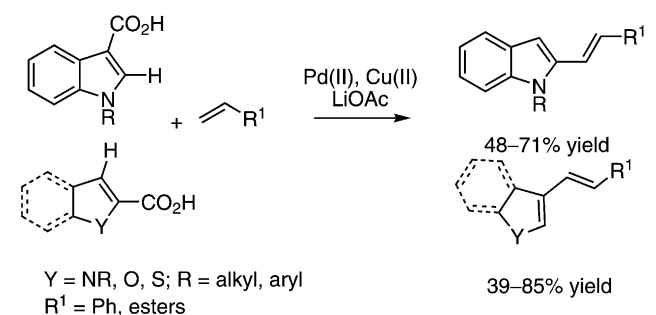
Scheme 2. Pd-catalyzed C–H vinylation of heteroaromatic carboxylic acids.

cluding pyrroles, benzofurans, benzothiophenes, and thiophenes, etc., except for 1-unprotected indole-3-carboxylic acids.

Pd-catalyzed olefinations of C−H bonds of carboxylic acids have been investigated extensively by Yu's group. In 2010, Yu and co-workers developed an efficient Pd-catalyzed C−H olefination of phenylacetic acids under atmospheric oxygen.[17] The atom-economic carboxylate-directed C−H olefination of various substituted phenylacetic acids with different olefin coupling partners was performed with 5 mol% Pd(OAc)$_2$ catalyst, 5 mol% benzoquinone as the additive, atmospheric oxygen as the oxidant, and 2 equiv. of KHCO$_3$ as the base (Scheme 3). A wide range of

Scheme 3. Pd-catalyzed carboxylate-directed C−H olefination under atmospheric O$_2$.

phenylacetic acids bearing F, Cl, or ketones, etc. were compatible with the catalyst system, and the reactions gave the corresponding *ortho*-olefinated products in good to excellent yields. Notably, the transformation was also applicable for the olefination of 3-phenylpropionic acids.

Although the use of directing groups is an effective tool to achieve the desired regioselectivities among different C−H bonds, it is hard to differentiate the two very similar *ortho*-C−H bonds of the directing groups. Ligands often have a great impact on the steric or electronic properties of transition metal catalysts and are utilized to tune the reactivities of the catalysts, which provide new opportunities for selective C−H activation.[17] Recently, a ground-breaking ligand-enabled regioselective C−H activation was achieved by the Yu group, in which amino acid derivatives were introduced as ligands to tune site selectivities.[17] Positional selectivities of multiply substituted aromatic rings with two approximately electronically equivalent *ortho*-C−H bonds were controlled by the addition of mono-*N*-protected amino acids, as a result of the effective catalyst's recognition of the different steric and electronic environments of the two sites (Scheme 4).

Remarkably, the amino acid ligands also have a great impact on the reactivities of palladium in carboxylate-directed C−H olefination reactions. For instance, the otherwise unreactive 3-phenylpropionic
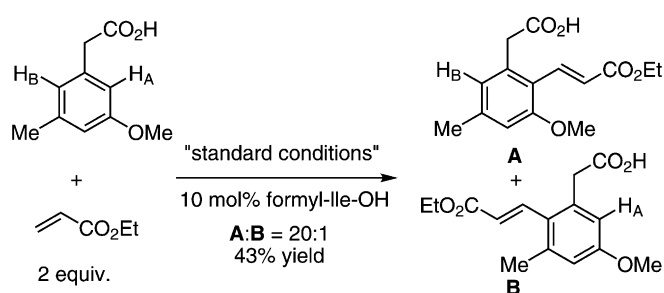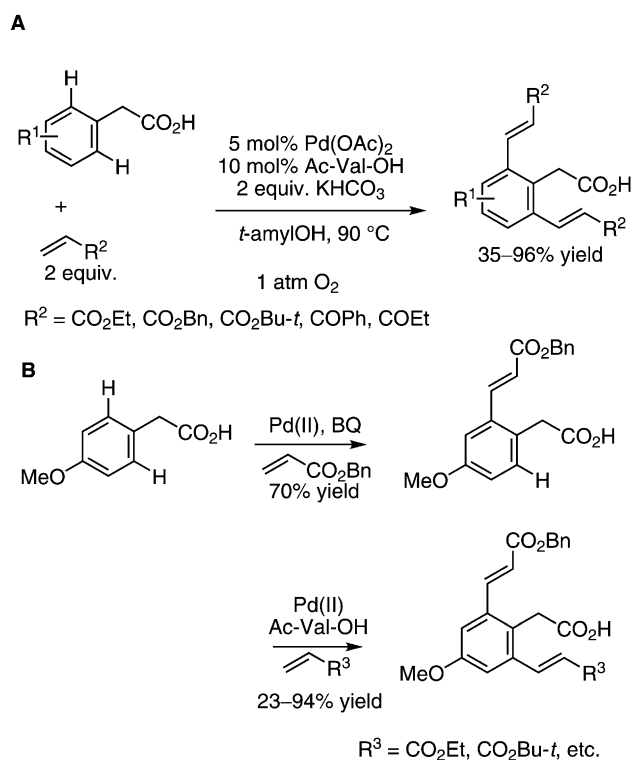

Scheme 4. Pd-catalyzed carboxylate-directed regioselective C−H olefination enabled by ligand.

acids and electron-deficient phenylacetic acids underwent olefination reactions efficiently under the ligand-assisted conditions.[17] Notably, while phenylacetic acids are mono-olefinated in the absence of the amino acid derivatives,[17] the reactions can form di-*ortho*-olefinated products with the aid of optimized ligands (Scheme 5A).[12a] By taking advantage of the two complementary methods, different olefins could be introduced to the *ortho*-positions of phenylacetic acids as desired sequentially (Scheme 5B).

It is noted that the ligand-enabled versatile C−H olefination proved synthetically useful. The reactions have successfully been applied to the synthesis of nat-

Scheme 5. Pd-catalyzed carboxylate-directed *ortho*-C−H di-olefination of phenylacetic acids.
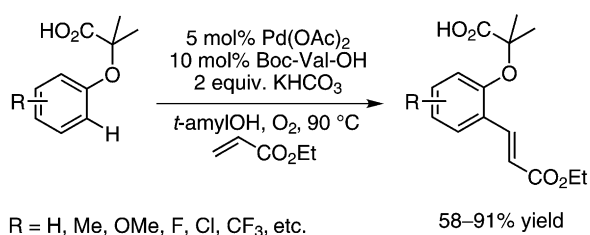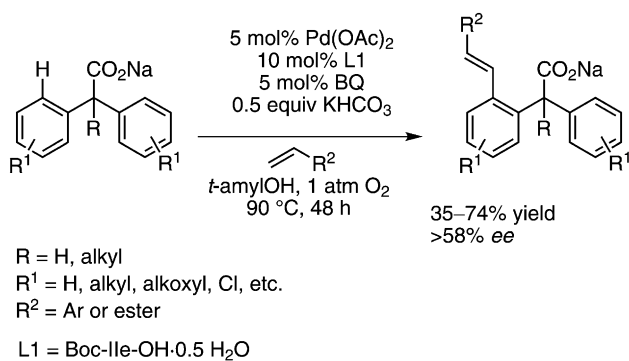
Scheme 6. Pd-catalyzed *ortho*-C−H olefination of phenol derivatives.

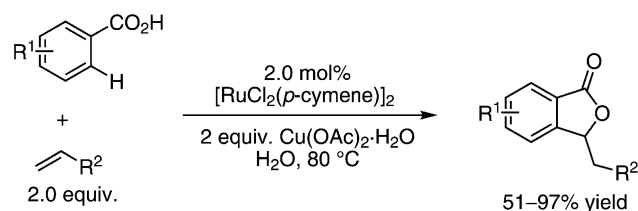**Scheme 8.** Ru-catalyzed oxidative C−H alkylation of benzoic acids in water.

ural products such as 2-tetralones and naphthoic acids in a concise way.[17]

Recently, the Yu group reported the *ortho*-olefination of α-phenoxyacetic acids, in which the carboxylate group acted as a weakly coordinating auxiliary to induce *ortho*-C−H activation.[18] Therefore, phenol derivatives were olefinated with acrylates in the presence of Pd(OAc)₂ and KHCO₃ under atmospheric oxygen, using Boc-Val-OH as the ligand (Scheme 6). The reaction tolerated both electron-donating and electron-withdrawing substituents. The acetic acid directing group can be readily removed to afford *ortho*-olefinated phenols.

Enantioselective C−H activation is quite a challenge, because ligands may inhibit transition metal-catalyzed C−H activation. The discovery that amino acids can promote C−H activation opened a new avenue for developing enantioselective C−H activation reactions. Actually, the Yu group reported a revolutionary mono-*N*-protected amino acid-induced enantioselective C−H alkylation of 2-benzylpyridines in 2008.[19] This pioneering work was successfully extended to carboxylate-directed enantioselective C−H vinylation of α,α-diphenylacetic acid derivatives (Scheme 7).[20] Substrates with alkyl, electron-donating, or moderately electron-deficient substituents on the benzene rings coupled with olefin partners such as styrenes or acrylates efficiently, affording *ortho*-vinylated products in good to excellent yields and enantio-

selectivities. Unfortunately, the selectivities were poor for the substrates containing α-hydrogen.

Besides palladium, other transition metal catalysts have also been developed as effective catalysts in carboxylate-directed C−H functionalization reactions with olefins. In 2011, Ackermann's group disclosed the first example of Ru-catalyzed carboxylate-directed C−H alkenylation of benzoic acids in water, which is an environmentally benign reaction medium (Scheme 8).[21] Versatile phthalides were produced from the corresponding benzoic acids and acrylates or acrylonitriles in the presence of 2.0 mol% Ru catalyst and 2 equiv. of Cu(OAc)₂ as the oxidant. Mechanistic studies suggested that the C−H activation was the rate-limiting step and was irreversible.

Unlike the Pd/Cu-catalyzed C−H bond vinylation of heteroaromatic carboxylic acids,[16] in the presence of Ru catalyst, heteroarenecarboxylic acids coupled with acrylates to afford the vinylated products without decarboxylation (Scheme 9).[22] Substrates including thiophene-, benzothiophene-, benzofuran-, pyrrole-, and indole-2-carboxlic acids were reactive for the regioselective vinylation, as well as indole- and thiophene-3-carboxylic acids. *N*-(*tert*-Butyl)acrylamide and acrylonitrile were also effective coupling partners.

In the same year, the Ison group described an unusual Ir-catalyzed carboxylate-directed reaction of C−H bonds with benzoquinone, affording the benzochro-

Scheme 7. Pd-catalyzed carboxylate-directed ligand-induced enantioselective C−H olefination.
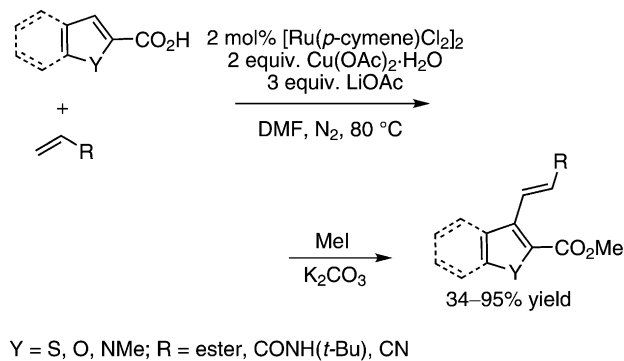
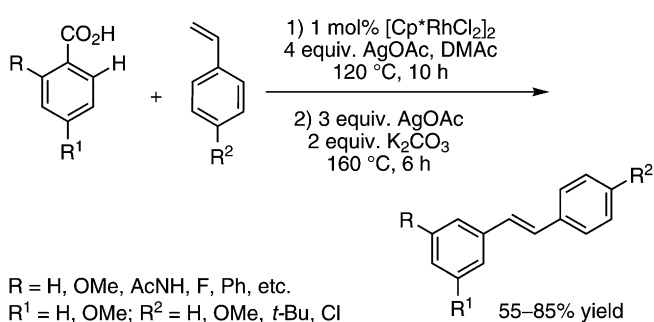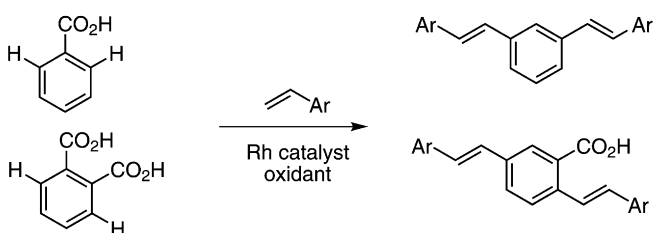**Scheme 9.** Ru-catalyzed carboxylate-directed vinylation of heteroaromatic carboxylic acids.
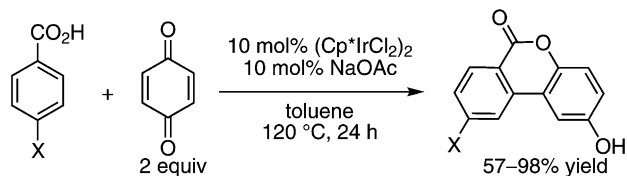
Scheme 10. Ir-catalyzed syntheses of benzochromenones from benzoic acids and benzoquinone.

menones as final products (Scheme 10).[23] Mechanistically, it was proposed that intramolecular proton transfer took place and resulted in the aromatization of benzoquinone ring after the insertion of aryl-Ir species to the double bond, rather than a common β-H elimination. No other oxidants were needed to regenerate the active catalyst species as benzoquinone acted as an internal oxidant. A catalytic amount of sodium acetate played a key role in promoting the reaction, indicating that it may participate in the catalytic cycle.

Similar to the Pd-catalyzed C–H bond vinylation/decarboxylation of indole-carboxylic acids reported by the Miura group,[16] benzoic acids can undergo the same reaction sequence in the presence of a rhodium catalyst (Scheme 11).[24] Thus, various *ortho*-substituted benzoic acids were converted to the corresponding *meta*-substituted stilbenes under the conditions as shown in Scheme 11. 1,3- and 1,4-distyrylbenzenes can be produced from simple benzoic acids and phthalic acids. The transformation proceeds *via* two independent steps: (i) Rh/Ag-catalyzed olefination of

C–H bonds and (ii) decarboxylation of the resulted styrylbenzoic acids in the presence of an Ag salt.

Besides benzoic acids, α,β-unsaturated carboxylic acids and heteroarenecarboxylic acids could also undergo the Rh-catalyzed carboxylate-directed regioselective olefination effectively (Scheme 12).[25] Notably, the carboxyl groups could be readily removed during the reaction or post-treatment with AgOAc/K$_2$CO$_3$. Especially for heteroarenecarboxylic acid, the reactions tended to form decarboxylated products. A wide range of heteroarenes were compatible, including thiophene, pyrrole, benzothiophene, benzofuan, and indole.

Interestingly, the carboxyl groups of heteroarenecarboxylic acids could be retained by using silver oxidants. Therefore, under the conditions shown in Scheme 13, a wide range of thiophene- and furan-2-carboxylic acids underwent C-3 alkenylation, with the carboxyl groups intact.[26]

Rh-catalyzed C–H olefination with alkynes assisted by carboxylate groups has also been developed. As shown in Scheme 14, a range of benzoic acids reacted with internal alkynes in *o*-xylene under air using a Rh/Cu catalyst system efficiently (Scheme 14).[27]

Y = O, S, NMe; R = ester, aryl
R^1 = H, Me, OMe, Ph, Ac, Cl, Br, CF$_3$; R^2 = H, Me

Scheme 12. Rh-catalyzed regioselective olefination of benzoic acids, α,β-unsaturated and heteroarenecarboxylic acids.
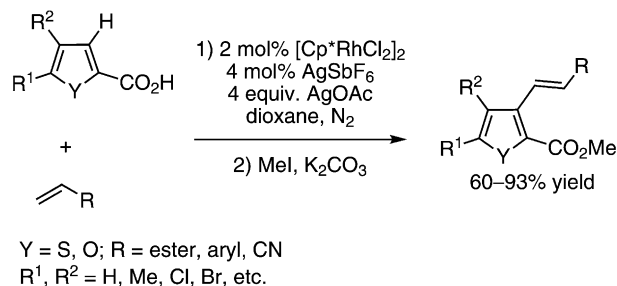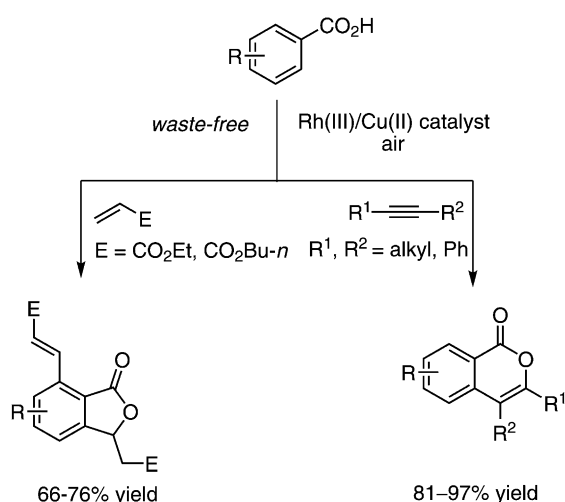

R = H, OMe, AcNH, F, Ph, etc.
R^1 = H, OMe; R^2 = H, OMe, *t*-Bu, Cl

Scheme 11. Rh/Ag-catalyzed precisely ordered *ortho*-olefination/decarboxylation of benzoic acids.

Y = S, O; R = ester, aryl, CN
R^1, R^2 = H, Me, Cl, Br, etc.

Scheme 13. Rh/Ag-catalyzed carboxylate-directed C–H bond alkenylation of heteroaromatic carboxylic acids.

Scheme 14. Rh/Cu-catalyzed carboxylate-directed C−H functionalization reactions with alkynes and acrylates.

The reaction formed isocoumarins and proceeded regioselectively with respect to substituted benzoic acids and unsymmetrical internal alkynes.

Noticeably, benzoic acids also reacted with alkenes efficiently under the similar conditions (Scheme 14).[27] It is interesting that both of the *ortho*-C−H bonds were vinylated in the presence of 2 equiv. of acrylates. The subsequent nucleophilic cyclization afforded 7-vinylphthalides as the final products.

Soon afterwards, the Miura group developed a similar Rh(III)/Cu(II) system to synthesize isocoumarins from benzoic acids and internal alkynes (Scheme 15A).[28] Different from the previous work,[27] this catalytic reaction was carried out under N₂ with stoichiometric Cu(OAc)₂ as the oxidant.
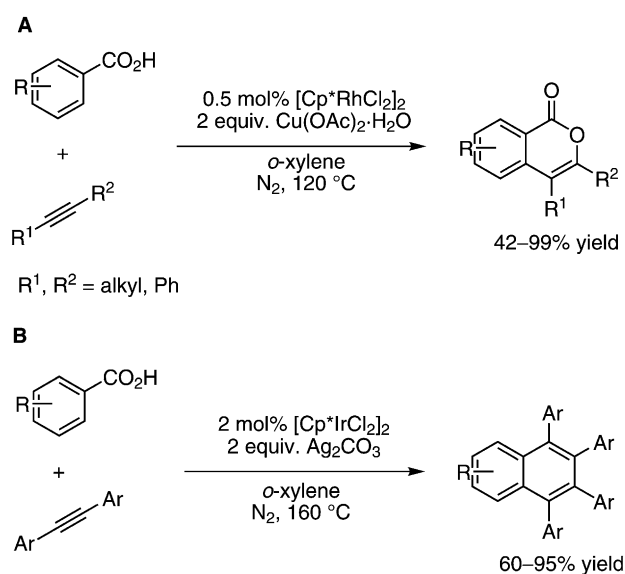
Moreover, the replacement of [Cp*RhCl₂]₂ and Cu(OAc)₂·H₂O with [Cp*IrCl₂]₂ and Ag₂CO₃ provided an efficient way to synthesize naphthalene derivatives *via* the coupling of benzoic acids with alkynes (Scheme 15B). Although the combination of Rh catalyst and Ag₂CO₃ could also deliver the same products, the yields of the reactions were relatively poor. In this reaction, decarboxylation occurred following the first C−H vinylation. The resulting intermediates coupled with a second alkyne to afford naphthalene derivatives as the final products.

An improved catalytic system was reported in 2009 by the same group, which is more suitable for the 2-amino- or 2-hydroxybenzoic acids (Scheme 16).[29] The amount of Cu salt was reduced to 5 mol%, and air was exploited as the terminal oxidant. Furthermore, 4-ethenylcarbazoles could be constructed by using DMF as the solvent, in the presence of 1,2,3,4-tetraphenyl-1,3-cyclopentadiene (C₅H₂Ph₄). Notably, various heteroarene substrates such as indole-, pyrrole-, furan-, thiophene-, and benzothiophene-2-carboxylic acids were accommodated with optimized conditions.

C(sp²)−H bonds of olefins can also be functionalized with alkynes and alkenes in a similar manner. Thus, in the presence of Rh(III) catalyst, substituted acrylic acids reacted with internal alkynes and acrylate esters to afford α-pyrones and butenolides, respectively (Scheme 17).[30] The reaction was performed with 1 mol% [Cp*RhCl₂]₂ catalyst in DMF under nitrogen atmosphere. While internal alkynes coupled with acrylic acids efficiently in the presence of Ag₂CO₃ as the oxidant, Cu(OAc)₂·H₂O was used as the oxidant for acrylate esters in some cases.

In addition to rhodium, ruthenium can also catalyze the oxidative coupling of arylcarboxylic acids with alkynes. In this regard, Jeganmoha's group reported Ru-catalyzed oxidative cyclization of carboxylic acids

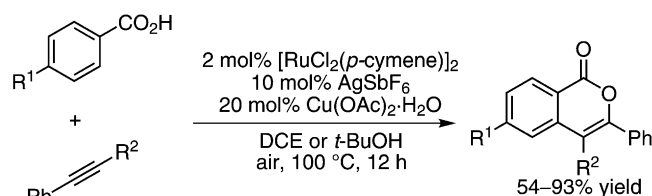**Scheme 15.** Rh- and Ir-catalyzed oxidative coupling of benzoic acids with alkynes.
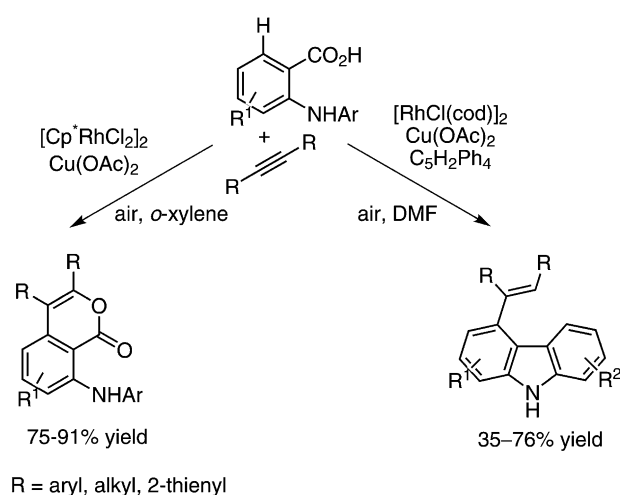
Scheme 16. Rh/Cu-catalyzed oxidative coupling of 2-substituted benzoic acids with alkynes.
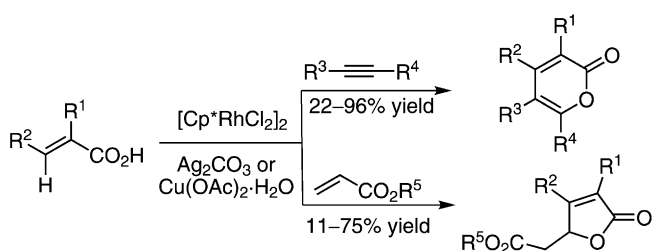
Scheme 17. Rh-catalyzed oxidative coupling of acrylic acids with alkynes and acrylate esters.

R[1] = H, Cl, Br, I, OMe, COMe, etc.
R[2] = alkyl

Scheme 18. Ru-catalyzed regioselective aerobic oxidative cyclization of arylcarboxylic acids with alkynes.

R[2], R[3] = alkyl or aryl

Scheme 19. Ru-catalyzed regioselective oxidative annulation of carboxylic acids with alkynes.

X = O, NMe, NEt, etc.
R[2] = alkyl, aryl

major product
6–83% yield

Scheme 20. Ru-catalyzed oxidative annulation of benzoic acids or benzamides with cyclopropylalkynes.

and alkynes with remarkable regioselectivities in 2012 (Scheme 18).[31] In this reaction, by using the catalyst system of Ru/Ag, isocoumarin was yielded as the final product and no naphthalene derivatives were observed, which showed a great difference from the previous reactions catalyzed by Ir.[28] Interestingly, the reaction formed a single regioisomer with unsymmetrical alkynes as coupling partners. The alkyne carbon bearing a Ph group attached to the carboxylate group with high selectivity. It was shown that AgSbF$_6$ was crucial for the high regioselectivities and completely suppressed the decarboxylation of benzoic acids. The reaction was performed in the presence of a catalytic amount of Cu(OAc)$_2\cdot$H$_2$O, which was proposed to be the source of OAc$^-$ to accelerate the *ortho*-metallation by the Ru catalyst. This catalyst system tolerated a variety of substituents, even sensitive functional groups such as keto and iodo groups on the aromatic ring, and was also effective for the alkenylation of heteroaromatic and even alkenyl acids. However, terminal alkynes and alkynes with trimethylsilyl or organotin groups were not compatible. For unsymmetrically substituted carboxylic acids, the cyclization took place with high regioselectivities, albeit in an unclear rule.

Almost simultaneously, Ackermann et al. reported a similar catalyst system to synthesize isocoumarins and α-pyrones *via* the coupling of carboxylic acids with alkynes, in which AgSbF$_6$ was much less effective than KPF$_6$ for promoting the transformation.[32] Benzoic acids bearing diverse substituents including free hydroxy group could undergo oxidative annulation with aryl- or alkyl-substituted alkynes in the presence of a low-cost Ru catalyst and 2 equiv. of Cu(OAc)$_2\cdot$H$_2$O as oxidant (Scheme 19). Notably, heteroaromatic and alkenyl carboxylic acids were also reactive under the same conditions, and the reactions gave regioselective products when coupling with unsymmetrical alkynes.

The Ru/KPF$_6$ catalyst system was also successfully applied to the oxidative annulation of cyclopropyl-substituted alkynes with benzoic acids and benzamides, affording useful cyclopropyl-substituted isocoumarins and isoquinolones regioselectively (Scheme
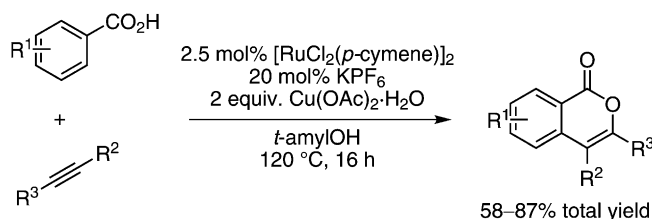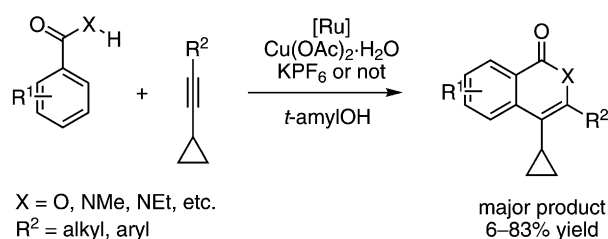
20).[33] In the reactions of benzamides, the addition of KPF$_6$ was not needed.

Allenes proved to undergo oxidative annulation with 1-alkylindole-2-carboxylic acid derivatives at the C-3 position in the presence of a Pd/Ag catalyst system effectively, affording the corresponding indolopyranones, which could also be achieved starting from 3-iodoindole-2-carboxylic acids and allenes under similar conditions (Scheme 21).[34] A wide range of allenes were compatible in the reaction with good reactivities and high regioselectivities.

C(sp^3)−H bond activation/olefination is quite a challenge, due to the competitive coordination of olefin to transition metals and undesired β-H elimination.[35] Pd-catalyzed olefinations of C(sp^3)-H remained undeveloped until the landmark research utilizing *N*-arylamides as directing groups reported by Yu et al. in 2010.[35] In the pioneering work, β-olefination of *N*-ar-
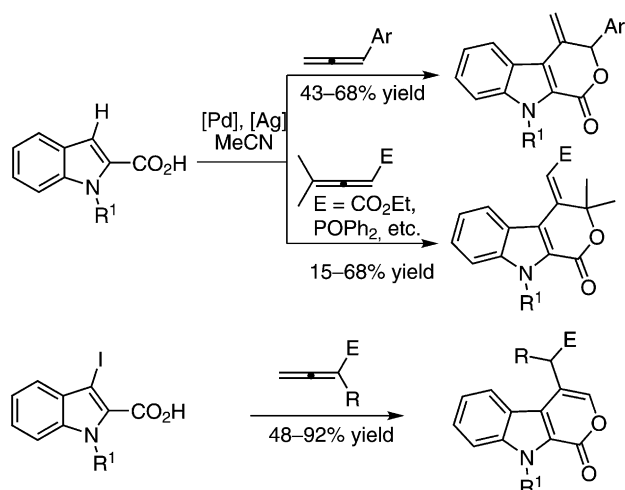
Scheme 21. Pd-catalyzed oxidative annulation of allenes with indole-2-carboxylic acids.

ylamides proceeded in good to excellent yields in the presence of Pd(OAc)$_2$, LiCl, using Cu(OAc)$_2$ and AgOAc as terminal oxidants (Scheme 22). A variety of commercially available carboxylic acids could be converted to arylamides conveniently, which underwent olefination subsequently. Remarkably, the catalytic protocol was also applicable to the olefination of methylene C−H bonds of cyclopropanes and aliphatic carboxylic acids containing α-hydrogens, which often tend to undergo β-H elimination. Significantly, the use of *N*-aryl groups with electron-withdrawing substituents (such as NO$_2$, F, CF$_3$) dramatically improved the reaction yields, and the fine tuning of the *N*-aryl groups can lead to an expansion of the substrate scope.

C−H bonds can be alkynylated with terminal alkyne derivatives. Unlike the initial work on Pd(II)-catalyzed C(sp^3)-H alkynylation with alkynyl halides *via* Pd(II)/Pd(IV) catalytic cycle developed by Chatani,[36] Yu's group reported the first example of Pd(0)/
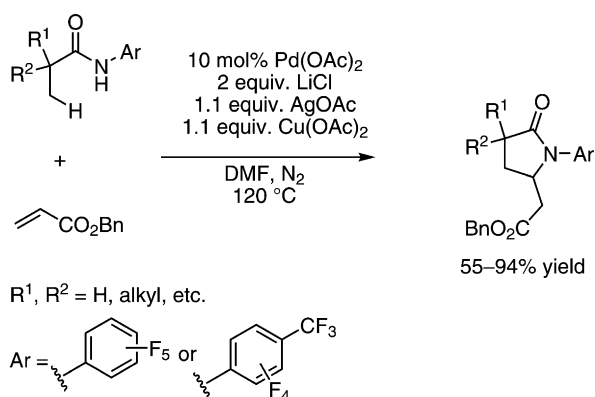

**Scheme 22.** Pd-catalyzed *N*-arylamide-directed C(sp^3)−H olefination.
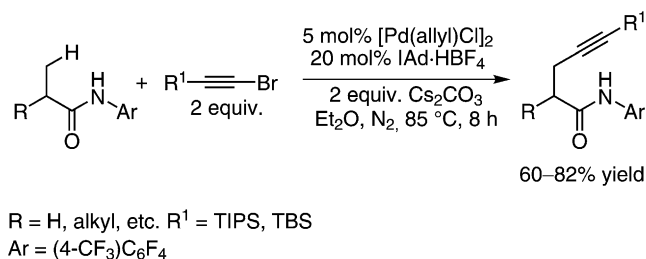
Scheme 23. Pd-catalyzed *N*-arylamide-directed C(sp^3)−H alkynylation with alkynyl halides.

Pd(II)-catalyzed coupling of alkynyl halides with C(sp^3)−H bonds in aliphatic carboxamides (Scheme 23).[8c] Therefore, various *N*-arylamides containing α-hydrogens coupled with 2-TIPS- or TBS-alkynyl bromides in the presence of Pd(0)/NHC or Pd(0)/PR$_3$ efficiently. The activation of the methyl C-(sp^3)−H bonds was favored for substrates containing both β-methyl C(sp^3)-H and β-methylene C(sp^3)−H bonds, and amides possessing quaternary α-carbon centers were not reactive. When an α-deutero substrate was subjected to the reaction, the α-deuterium was retained, which indicated that palladation of α-H and subsequent β-H elimination were not involved in the transformation. Mechanistic studies illustrated that [alkynylPd(II)L$_n$] complexes were initially formed *via* the oxidative addition of alkynyl bromides to Pd(0), and then underwent C(sp^3)−H activation/alkynylation to afford the desired products. It should be mentioned that no co-oxidants were required for this Pd(0)/Pd(II) catalyst system, implying that it should be compatible with oxidant-sensitive substrates.

Not only carbon-carbon multiple bonds but also C=O bonds and CO can be inserted by immediate C-metal species generated from transition metal-catalyzed C−H cleavage. In 2012, Li et al. described a novel Rh(III)-catalyzed synthesis of 3-substituted phthalides from benzoic acids and aldehydes, proceeding *via* carboxylate-directed *ortho*-C−H functionalization and subsequent intramolecular cyclization (Scheme 24).[37] Thus, catalyzed by 8 mol% [Cp*RhCl$_2$]$_2$, aromatic aldehydes bearing electron-withdrawing groups and aliphatic aldehydes reacted with benzoic acids containing electron-rich groups to
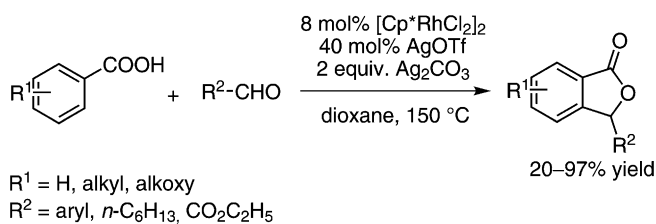
Scheme 24. Rh-catalyzed carboxylate-directed *ortho*-C−H functionalization with aldehydes.
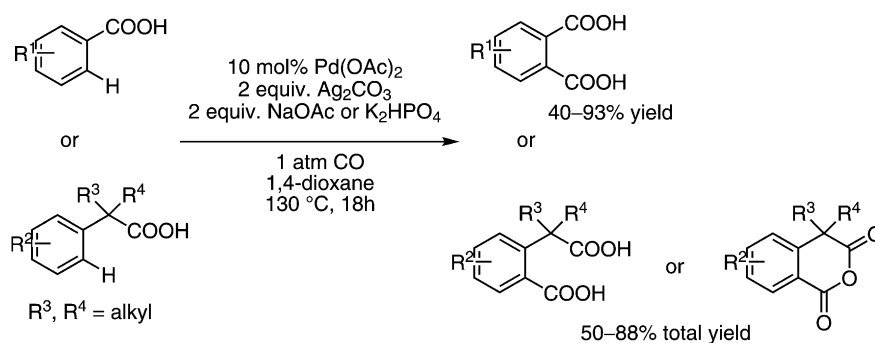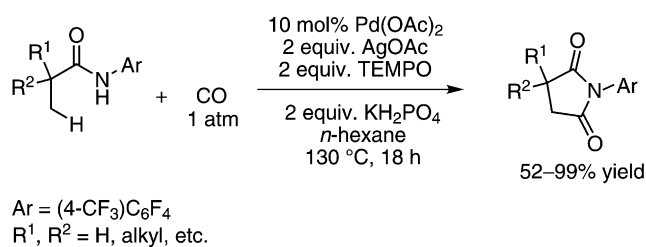
Scheme 25. Pd-catalyzed C−H carboxylation of benzoic acids or phenylacetic acids with CO.

afford the corresponding phthalides in good to excellent yields. A mixture of regioisomers was formed in the case of non-symmetrical *meta*-alkoxy-substituted benzoic acids. AgOTf or AgClO$_4$ played a crucial role in this transformation, which was considered to act as a chloride abstractor to generate the active Rh catalyst species.

The first Pd(II)-catalyzed direct carboxylation of benzoic acids and phenylacetic acids to produce *ortho*-carboxylation products was reported by Yu's group in 2008 (Scheme 25).[12b] Therefore, a range of benzoic and α,α-disubstituted phenylacetic acids underwent C−H activation/CO insertion sequence in the presence of 10 mol% Pd(OAc)$_2$, 2 equiv. of Ag$_2$CO$_3$ as oxidant, and NaOAc or K$_2$HPO$_4$ as base. The reaction tolerated both electron-donating and moderately electron-withdrawing substituent groups. Excellent regioselectivities were achieved in the carboxylation of carboxylic acids with one *meta*-substitutent, as a result of steric effects.[12b] Significantly, the catalytic protocol was applicable to the carboxylation of α-phenylacrylic acid, affording 1-phenylmaleic acid in 68% yield.

In 2010, the same authors investigated more challenging β-C(sp^3)−H carbonylation of aliphatic acid derivatives catalyzed by Pd(II).[38] Using the acidic *N*-arylamide as the directing group, a variety of carboxamides prepared from aliphatic acids underwent β-C(sp^3)−H cleavage, CO insertion, and intramolecular C−N elimination in sequence, releasing succinimides as the final products (Scheme 26). The reaction
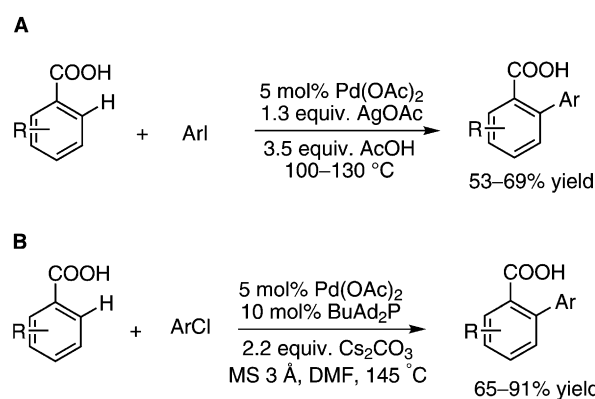
was performed under 1 atm CO with a combination of 2 equiv. of TEMPO and 2 equiv. of AgOAc as the oxidant. It is worth noting that both TEMPO and AgOAc were crucial for the high conversion, probably due to the higher efficiency of oxoammonium salt (oxidized from TEMPO) for the reoxidation of Pd(0) to Pd(II). Substrates containing α-hydrogens were also reactive, as well as the methylene C(sp^3)-H of cyclopropane substrates. Significantly, other directing groups, such as carboxylic acids, oxazolines, pyridines, and hydroxamic acids, failed to enable this type of transformation. In addition, the resulting products can be converted to synthetically useful 1,4-dicarbonyl compounds, demonstrating the synthetic utility of this novel reaction.[38]

4 Carboxylate-Directed C−H Bond Activation/Arylation and Alkylation

As pyridine, anilide, benzamide, and benzylamine,[39] benzoic acids can undergo C−H arylation with aryl iodides (Scheme 27A).[12c] In these reactions, acetic acid was used as the solvent to impede the competitive decarboxylation process, and stoichiometric AgOAc was

Ar = (4-CF$_3$)C$_6$F$_4$
R^1, R^2 = H, alkyl, etc.

Scheme 26. Pd-catalyzed β-C(sp^3)−H carbonylation of carboxamides with 1 atm CO.

Scheme 27. Pd-catalyzed carboxylate-directed C−H arylation of benzoic acids with aryl iodides or chlorides.
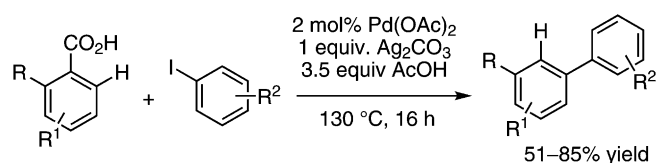
R = F, Cl, CF₃, NO₂, OMe, etc.
R¹ = H, F, Cl, Br, OMe, etc.
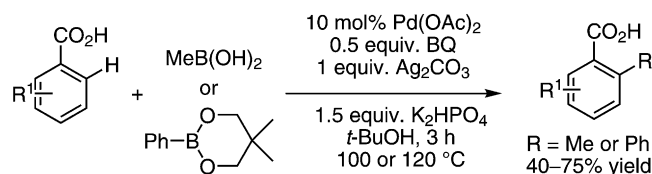R² = F, Cl, Br, Me, CO₂Me

Scheme 28. Pd/Ag-catalyzed *ortho*-C–H arylation/protodecarboxylation of *ortho*-substituted benzoic acids to afford *meta*-arylated arenes.

applied for the removal of iodide. Both electron-rich and electron-deficient aryl iodides could couple with electron-rich and moderately electron-poor benzoic acids, with the toleration of chloride or bromide groups on both of the coupling partners. The reaction was suggested to proceed through a Pd(II)/Pd(IV) pathway.

It is noteworthy that aryl chlorides were also effective C–H arylation reagents for benzoic acids, albeit under different conditions consisting of Pd(OAc)₂, phosphine ligand, Cs₂CO₃, and molecular sieves (Scheme 27B).[12c] A wide array of benzoic acids were *ortho*-arylated in good to excellent yields, but bromide and iodide were not tolerated. While 2- or 3-substituted benzoic acids were monoarylated generally, 3-fluorobenzoic acid and 4- or unsubstituted benzoic acids were diarylated. The catalytic cycle was proposed to consist of a Pd(0)/Pd(II) pathway and heterolytic C–H bond cleavage acted as the overall rate-limiting step.

It should be mentioned that the above arylation products can undergo further decarboxylcation following the method developed by Gooβen et al.[40] which allows for the regioselective synthesis of di- or polyphenyl derivatives.[12c] Therefore, in 2011, Larrosa's group reported an efficient Pd/Ag-catalyzed *ortho*-C–H arylation/decarboxylation of *ortho*-substituted benzoic acids with the carboxylate as a traceless directing group, which provides a novel method for the synthesis of *meta*-arylated arenes, (Scheme 28).[41] Therefore, under the conditions as shown in Scheme 28, a range of benzoic acids underwent C–H arylation and subsequent decarboxylation efficiently. Both electron-withdrawing and electron-donating substituents, including Cl, NO₂, F, CF₃, OMe, Me, etc. on the *ortho*-positions of benzoic acids were tolerated. Notably, the reaction was chemoselective and no protodecarboxylation products of the initial benzoic acids were observed.
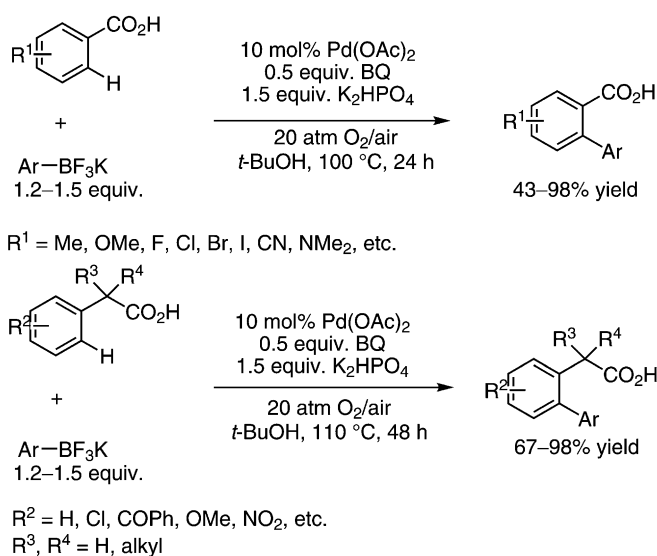
Organoboron reagents have also been developed as coupling partners in carboxylate-directed C–H arylation reactions. In 2007, Yu and co-workers disclosed a Pd-catalyzed arylation of aryl C–H bonds with phenylboronic esters (Scheme 29).[7a] In this pioneering

work, stoichiometric Ag₂CO₃ was used as the oxidant and the use of 0.5 equiv. of benzoquinone was crucial for the success of this transformation. It is worth noting that benzoic acids can be methylated with methylboronic acid under the same conditions. A counterion from an inorganic base was employed to assist the insertion of Pd into C–H bonds.

The above protocol for the Pd-catalyzed C–H arylation of benzoic acids with arylboronic esters suffered from low efficiency and narrow substrate scopes.[7a] Fortunately, the use of aryltrifluoroborates as coupling partners and air or O₂ as the oxidant overcame these drawbacks. Remarkably, the new catalyst system enabled C–H arylation of phenylacetic acids and substrates with electron-deficient substituents (Scheme 30).[42] Excellent regioselectivities were obtained for *meta*-substituted benzoic acids, and only monoarylated products were formed for α-substituted arylacetic acids, in contrast to the diarylation of arylacetic acids without α-substituents. More importantly, the arylation of electron-deficient arenes and phenylacetic acids containing α-H was realized for the first time. Various substituents were tolerated, and 3-pyridyltrifluoroborates were also reactive.

Scheme 29. Pd-catalyzed carboxylate-directed arylation of *ortho*-C–H bond with arylboron reagents.

R¹ = Me, OMe, F, Cl, Br, I, CN, NMe₂, etc.

R² = H, Cl, COPh, OMe, NO₂, etc.
R³, R⁴ = H, alkyl

Scheme 30. Pd-catalyzed arylation of benzoic acids and arylacetic acids with aryltrifluoroborates.

Unfortunately, the above transformations have some drawbacks, such as the use of high-pressure O_2 or air, long reaction times, and limited substrate scope for the arylacetic acids.[42] Gratifyingly, these problems were solved by taking advantage of the ligand-acceleration strategy, which was developed by Yu's group.[43] Thus, with the use of mono-*N*-protected amino acid ligands and Ag_2CO_3 as the oxidant, the coupling of phenylacetic acids with aryltrifluoroborates or pinacol esters of arylboronic acids gave arylation products in nearly quantitative yields (Scheme 31A). The quanti-

A

R^1 = Me, OMe, F, Cl, CF$_3$, NO$_2$, COPh, etc.
R^2 = H, alkyl

B
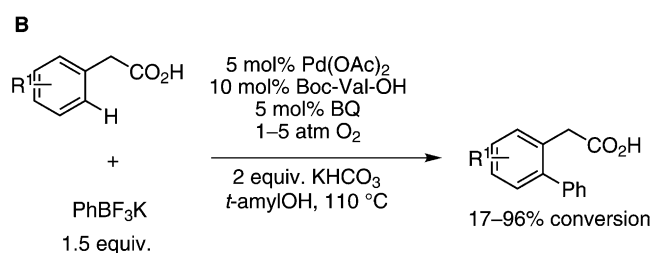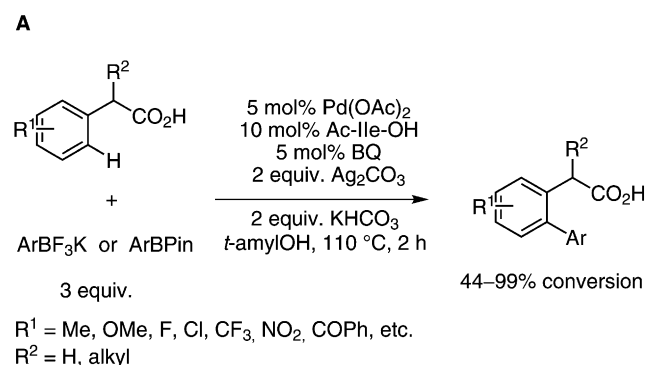
Scheme 31. Ligand-accelerated Pd-catalyzed *ortho*-C−H arylation of phenylacetic acids with organoboron reagents.

ties of Pd(OAc)$_2$ and BQ were reduced to 5 mol%, and the reaction time can be shortened to 2 h. A diversity of substituents including alkyl, alkoxy, halogens, nitro, trifluoromethyl, and ketone groups on the aromatic ring of phenylacetic acids were well-tolerated, and more importantly, substrates containing one or two α-hydrogens were compatible. Control experiments showed that the initial rate of the catalytic cycle was greatly increased by the addition of amino acid ligands.[43] Interestingly, only electron-withdrawing group-protected amino acids were effective.

Amino acid ligands were also successfully applied to meliorate the C−H arylation reactions with O_2 as the oxidant as shown in Scheme 30.[42] Therefore, in the presence of the ligands, the reactions gave high conversions even when the pressure of O_2 was reduced to 5 atm (Scheme 31B).[43] The improvement makes the reaction more applicable and operationally simpler.

Competition experiments between 2-methyl- and 2-trifluoromethylphenylacetic acids were conducted. It was shown that the amino acid ligands improved the initial rate of electron-poor phenylacetic acids while, on the contrary, electron-rich phenylacetic acids gave a lower initial rate in the presence of the ligands. Based on these findings and the reactivities of electron-withdrawing substrates, the catalytic cycle in the presence of amino acid ligands was proposed to proceed *via* a concerted metallation/deprotonation pathway, and an electrophilic palladation process should be involved in the reactions in the absence of the ligands (Figure 4).[43]
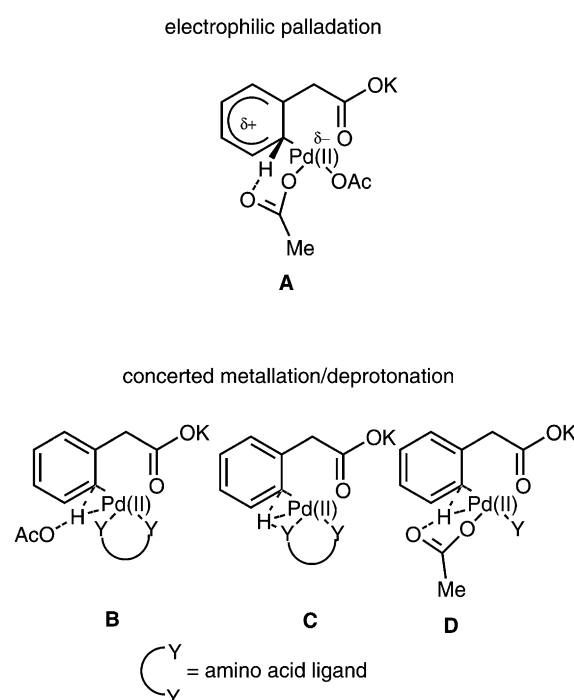
Figure 4. Proposed Pd-mediated C−H bond cleavage. **A**: Electrophilic palladation in the absence of amino acid ligands. **B, C, D**: Concerted metallation/deprotonation in the presence of amino acid ligands.

Interestingly, the Miura group reported the rhodium-catalyzed intramolecular oxidative coupling of two aryl C(sp^2)−H bonds of 2,2-diphenylalkanoic acids (Scheme 32).[44] The coupling products underwent decarboxylation readily to give the corresponding fluorenes. In the reaction, the combination of AgSbF$_6$ and Cu(OAc)$_2$·H$_2$O acted as the oxidant.

N-Arylamide-directed C(sp^2)−H bond arylation reactions have also been developed. Yu's group demonstrated the C−H arylation of nicotinic and isonicotinic acid derivatives to afford the corresponding products, which are of tremendous medicinal importance (Scheme 33).[45] In the presence of Pd(0)/PR$_3$, nicotinamides and isonicotinamides were arylated at the 3-
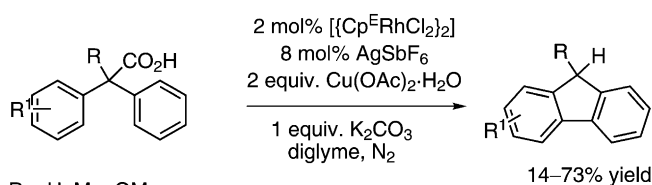
Scheme 32. Rh-catalyzed intramolecular oxidative coupling of 2,2-diphenylalkanoic acids and subsequent decarboxylation.
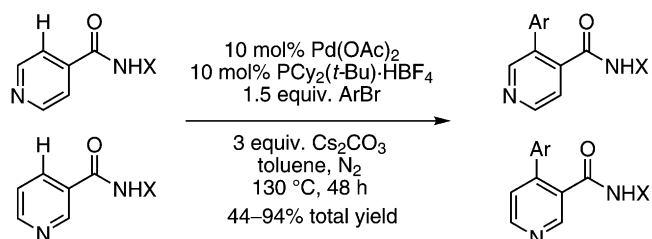
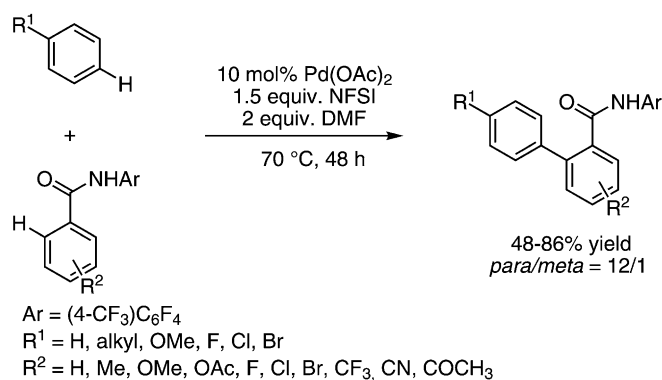**Scheme 33.** Pd/PR$_3$-catalyzed *N*-arylamide-directed C(sp^2)−H arylation of nicotinic and isonicotinic acid derivatives.
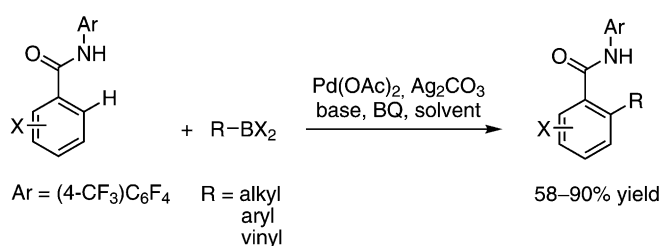
Scheme 34. Pd-catalyzed *N*-arylamide-directed *para*-selective C−H arylation of monosubstituted arenes.

or 4-positions with various aryl bromides. While the directing group of *N*-phenylamides gave a mixture of mono- and diarylated products, *N*-3,5-dimethylphenyl-amide greatly improve the monoselectivities with undiminished yields. Furthermore, ligand screening showed that freshly prepared PCy$_2$(*t*-Bu)·HBF$_4$ ligand could promote the reaction effectively. Notably, this is the first report of C−H activation on the pyridine ring assisted by a directing group, which is challenging due to high electron-deficiency and competitive powerful binding ability to palladium catalysts of pyridyl groups.[45]

Based on the observation of *ortho*-arylation products arising from the coupling of *N*-benzyltriflimides with toluene during the investigation of fluorination,[46] Yu et al. developed the first Pd(II)-catalyzed *N*-arylamide-directed highly *para*-selective C(sp^2)−H/C(sp^2)−H coupling of monosubstituted arenes with *N*-arylbenzamides by using the F$^+$ reagent NFSI (*N*-fluorobenzenesulfonimide) as a by-standing oxidant (Scheme 34).[47] It is noteworthy that K$_2$S$_2$O$_8$ could also act as the oxidant to achieve the coupling products, albeit with low regioselectivities (*para/meta*, 1.7/1). Both electron-donating (alkyl, alkoxy, and OAc) and electron-withdrawing (F, Cl, Br, CF$_3$, CN, and keto) groups on each coupling partner were compatible with the catalytic system, with a *para/meta* ratio of more than 12/1. The kinetic isotope effect between toluene and toluene-d_8 was determined to be 1.0 (Scheme 34), which indicated an electrophilic pallada-
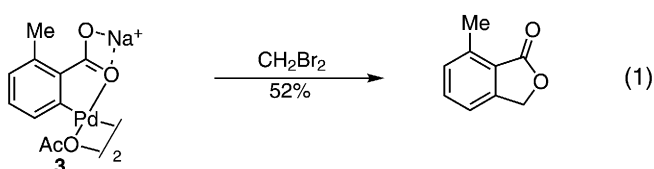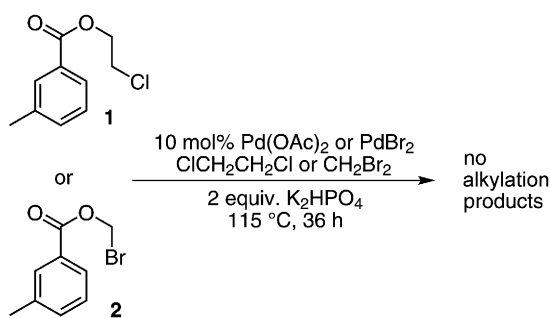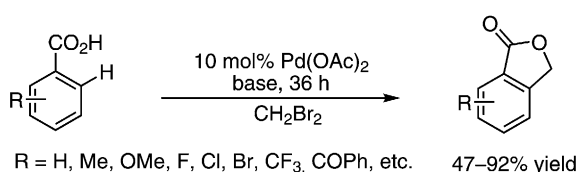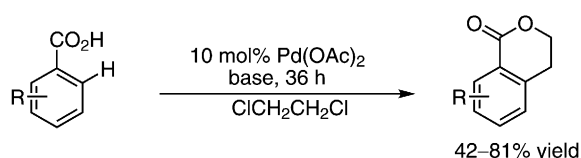
tion mechanism. An [ArPd(IV)F] intermediate was suggested to be formed *via* the oxidation of [ArPd(II)] species, derived from acidic amide-directed C−H cleavage, with the F$^+$ reagent. The [ArPd(IV)F] intermediate was pivotal for the *para*-selective C−H activation of monosubstituted arenes, which probably involved an electrophilic palladation mechanism. Notably, the *N*-arylamide directing groups had a great impact on the regioselectivities.

In 2011, the *N*-arylamide-enabled coupling of C−H bonds with organoboron reagents was also achieved by the Yu group.[48] Therefore, in the presence of a Pd(II) catalyst, a range of benzamides and phenyl-acetamides bearing *N*-2,3,5,6-tetrafluoro-4-(trifluoromethyl)-phenyl group underwent C−H arylation with a variety of organoboron reagents including aryl- or vinylboronic acid pinacol ester and alkyltrifluoroborates (Scheme 35). BQ was a crucial promoter for the reductive elimination of aryl-Pd(II) species, and NaHCO$_3$ was used as the base to facilitate the binding of the amide group to the Pd(II) center. Significantly, this reaction represents the first example of a Pd(II)-catalyzed C(sp^2)−H vinylation with vinylboron reagents.[48]

Interestingly, the Yu group described the Pd(OAc)$_2$-catalyzed *ortho*-alkylation of benzoic acids with alkyl chlorides and bromides, affording lactones as the final products (Scheme 36).[49] Therefore, a range of benzoic acids was reacted with dibromomethane or 1,2-dichloroethane to yield five- or six-mem-
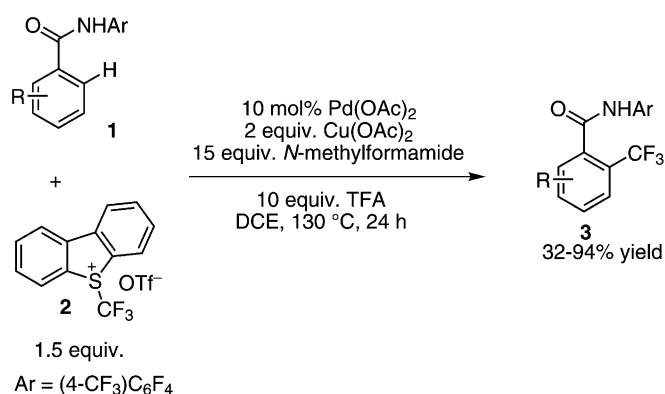
Scheme 35. Pd-catalyzed cross-coupling of $C(sp^2)-H$ bonds with alkyl-, aryl-, and vinylboron reagents.

Scheme 36. Pd-catalyzed *ortho*-C−H alkylation of benzoic acids with alkyl chlorides and bromides.

Scheme 37. Pd-catalyzed trifluoromethylation of *N*-arylbenzamides using an *N*-methylamide as the crucial promotor.

C−H alkylation or arylation reactions involving iodides,[12c,50] were not needed, and only inexpensive inorganic bases were required in this reaction.

The highly efficient *N*-2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenylamide proved to be a versatile directing group in C−H functionalization, as demonstrated by the remarkable work on C−H trifluoromethylation exhibited by Yu's group in 2012.[4f] An array of benzamides bearing the highly electron-withdrawing *N*-phenyl group were successfully trifluoromethylated using trifluoromethylating reagent **2**, with an *N*-methylamide as the crucial promoter (Scheme 37). It was suggested that the *N*-methylamide not only acted as a weak base but also a ligand to promote the coordination of the *N*-arylamide group to the Pd center, and *N*-methylformamide proved to be the most effective. Stoichiometric Cu(OAc)$_2$ was needed to scavenge the free thiophene generated from **2**. A variety of substitutions on the aromatic rings were tolerated, including alkyl, phenyl, methoxy, trifluoromethyl, ester groups and halogen atoms (F, Cl, Br). Notably, the trials with other trifluoromethylating reagents, such as Togni's reagent and TMSCF$_3$, failed to give the desired products.

To get an insight into the origin of the reactivity and coordination mode in the acidic amides-directed C−H activation reactions, an X-ray crystallographic analysis was performed to identify the C−H insertion intermediate.[4f] It was speculated that complex **4** should be the C−H insertion species and the reactive intermediate. Although **4** was not observed, an analogous alkali amidate **5** was isolated, which revealed that the acidic amide bonded to the Pd(II) center *via* an imine moiety (Figure 5).[4f] The coordination mode of the amidate is crucial for the superior reactivity of the acidic benzamides in comparison with simple amides. Complex **5** was also allowed to undergo the transformation. The trifluoromethylated product was obtained in a moderate yield in the presence of Cu(OAc)$_2$ and *N*-methylformamide, and the reaction

bered lactones, respectively. The reaction process of nucleophilic substitution followed by C−H activation or Friedel–Crafts-type reactions was ruled out by the observation that **1** and **2** were unreactive (Scheme 36). Furthermore, complex **3** gave the corresponding alkylation product when treated with dibromomethane under the identical conditions [Eq. (1) in Scheme 36]. The mechanism was proposed to involve Pd-catalyzed carboxylate-directed *ortho*-C−H alkylation and subsequent S$_N$2 substitution. It is noted that Ag salts, which are regularly crucial for Pd-catalyzed
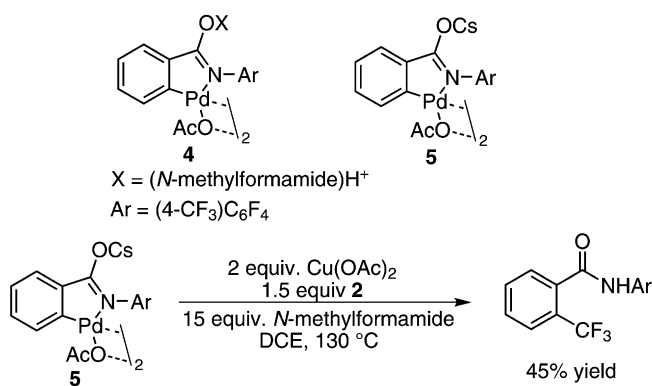
Figure 5. Investigation on the C−H insertion intermediate and coordination mode.

did not occur without Cu(OAc)$_2$ or *N*-methylformamide. However, it is not clear whether the trifluoromethylation proceeded through a Pd(II)/Pd(IV) redox process or a Pd(II)/Pd(II) pathway.
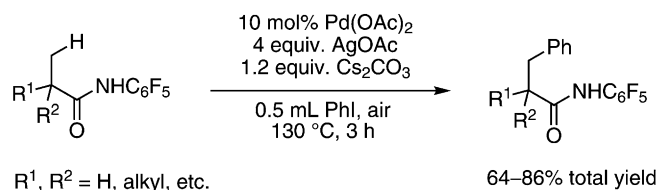
In spite of the huge challenge, the Yu group achieved the first Pd-catalyzed carboxylate-directed β-C(*sp*^{3})−H arylation of simple aliphatic acids,[7a] using organoboron reagents as the coupling partners and stoichiometric Ag$_2$CO$_3$ as the oxidant (Scheme 38A). It should be mentioned that cyclopropylcarbox-
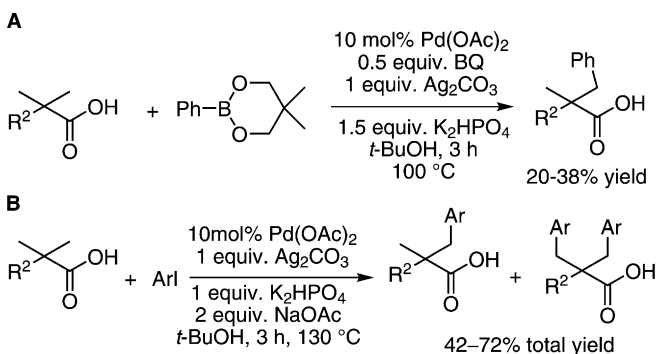
Scheme 38. Pd-catalyzed C−H methylation and arylation of simple aliphatic acids.

ylic acids were also reactive under the same conditions. The C(*sp*^{3})−H arylation of aliphatic acids can also be carried out with aryl iodides as the arylation reagents in the absence of BQ (Scheme 38B).[7a] The reaction gave a mixture of mono- and di-arylated products, and two equiv. of NaOAc were needed to improve yields. A Pd(II)/Pd(IV) catalytic cycle may be involved in the reaction process.

Although the above C(*sp*^{3})−H arylation represents a great progress in the field of C−H activation, it suffered from poor yields and limited substrate scopes.[7a] Most importantly, the carboxylate-directed C(*sp*^{3})−H activation protocol was not compatible with substrates containing α-C−H bonds, which cannot be

remedied by transforming the carboxylate to its derivatives such as oxazoline or hydroxamic acid.[5a,b,51] Fortunately, these limitations can be overcome by using the versatile acidic amide directing group (Scheme 39).[8b] Therefore, in the presence of AgOAc as the co-oxidant and Cs$_2$CO$_3$ as the base, a range of *N*-pentafluorophenyl-substituted aliphatic amides, including those containing α-hydrogens, underwent C(*sp*^{3})−H arylation in high yields. The reaction gave mono- and diarylated products for some substrates.

While the above arylation reactions with aryl iodides in Scheme 38B and Scheme 39[7a,8b] involve a Pd(II)/Pd(IV) pathway, the C(*sp*^{3})−H bonds of the substrate *N*-pentafluorophenyl aliphatic amides, can be arylated with aryl iodides *via* a Pd(0)/Pd(II) mechanism, affording similar arylation products (Scheme 40).[8a] The reaction required the use of


Scheme 39. *N*-Arylamide-directed C(*sp*^{3})−H arylation *via* a Pd(II)/Pd(IV) catalytic cycle.

Scheme 40. Pd/PR$_3$-catalyzed β-C(*sp*^{3})−H arylation of *N*-arylamide.

a phosphine ligand, and the proper choice of bases was crucial for the success of the reactions. While CsF was found to be the only effective base for substrates bearing α-hydrogens, the reactions of substrates containing no α-hydrogens were promoted by Cs$_2$CO$_3$. Mechanistically, the reaction should start with the oxidative addition of aryl iodide to Pd(0) species. The subsequent Pd(II)-mediated C−H cleavage and reductive elimination provide the final arylation product.

As discussed previously, cyclopropylcarboxylic acids can undergo β-C(*sp*^{3})−H arylation with organoboron reagents. However, these reactions suffered from the same limitaions as those with aryl iodides.[7a] In the same way, the limitations can be overcome by using acidic *N*-arylamide directing group. Remarkably, the enantioselective version of this reaction has been achieved by employing amino acid derivatives as the ligands. This ground-breaking work represents the first example of enantioselective C−H arylation of cy-
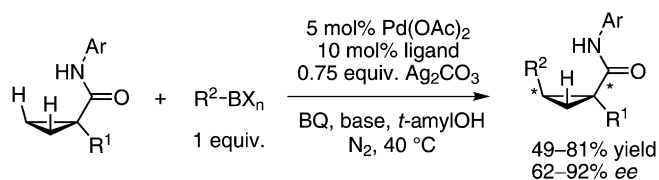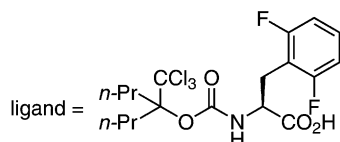
Scheme 41. Pd-catalyzed enantioselective C–H bond functionalization of cyclopropane derivatives enabled by amino acid ligands.

**Scheme 42.** Ligand-enabled Pd(II)-catalyzed arylation of β-methylene C(sp^3)–H directed by N-arylamide.

clopropane rings (Scheme 41).[8d] Ligand screening showed that mono-N-protected amino acids with an aryl group on the amino acid side chain led to high levels of stereoinduction for *cis*-substituted chiral cyclopropanecarboxamides with reasonable yields and high enantioselectivities. A wide range of organoboron reagents, including alkyl-, aryl- and vinylboron reagents, were reactive under the conditions as shown in Scheme 41. While the combination of boronic acid pinacol esters and NaHCO$_3$ was efficient for arylation and vinylation, the alkylation required the use of potassium trifluoroborate salts and Li$_2$CO$_3$ to achieve better results. Unfortunately, substrates with α-hydrogen or α-heteroatoms were not tolerated.

The above protocol is not capable of functionalizing methylene C(sp^3)–H bonds of simple alkyl chains, due to competitive β-H elimination and steric hindrance. The problem was successfully solved *via* the introduction of ligands by the Yu group.[52] Therefore, in the presence of mutually repulsive 2,6-dialkoxypyridine or 2-alkoxyquinoline as the ligand, both acyclic and cyclic alkyl (3- to 6-membered rings) amides could be mono- or diarylated in good to excellent yields (Scheme 42). Both steric bulk and electron-donating properties of the ligands were necessary to achieve the desired reactivities. Interestingly, benzylic C(sp^3)–H arylation occurred prior to that of the aliphatic methylene C(sp^3)–H bond, and the methine C(sp^3)–H bond was not reactive.

The acidic N-arylamide directing group has been successfully extended to the arylation of allylic C(sp^3)–H bonds (Scheme 43).[13a] Thus, in the presence of Pd(OAc)$_2$, PPh$_3$, and *t*-BuONa, N-pentafluorophenyl-substituted acrylamides underwent arylation with a wide range of aryl iodides or bromides at the γ-positions. Interestingly, the double bond in the substrates shifted towards the introduced aryl group
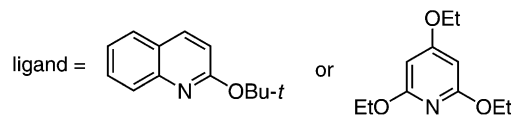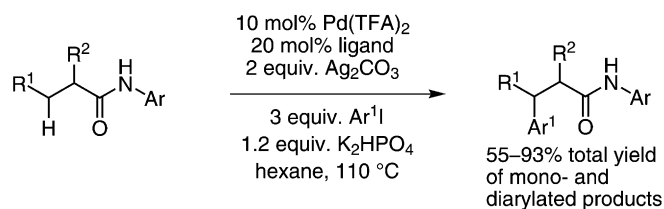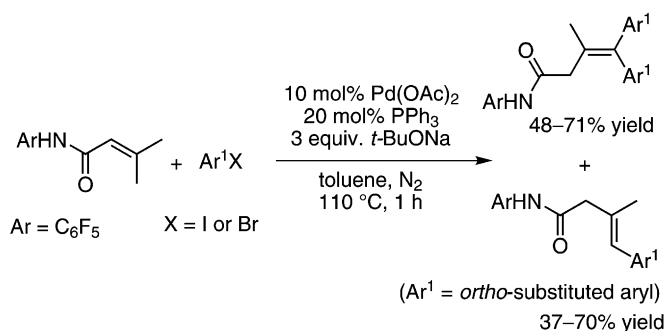

Scheme 43. Pd-catalyzed N-arylamide-directed allylic C–H arylation of acrylamides with aryl iodides or bromides.

which was supported by X-ray diffraction analysis, affording γ-aryl-β,γ-unsaturated acrylamides as the final products. While the reactions gave diarylated products for unhindered aryl halides, *ortho*-substituted aryl halides yielded solely the monoarylation products.

5 Carboxylate-Directed C–H Bond Activation/C–O Bond Formation

The C–O bonds are commonly found in organic structures, including pharmaceuticals and agricultural chemicals, and C–O bond formation has been a research topic of great importance for a long time. Transition metal-catalyzed C–H bond activation/C–O bond formation is a very promising strategy, and great progress has been made in this regard, relying on the use of various directing groups, such as N-containing heterocycle, amide, oxazoline, and oxime, as well as carboxylate groups.[5a,53]

An early example involves Pt-catalyzed C–H hydroxylation of aliphatic acids demonstrated by Sen and Kao in 1991.[7b] Using 25 mol% K$_2$PtCl$_4$ as the catalyst and 0.5 equiv. of K$_2$PtCl$_6$ as the oxidant, the C–H bonds at various positions of aliphatic acids
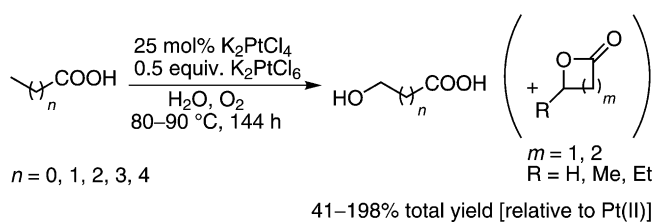
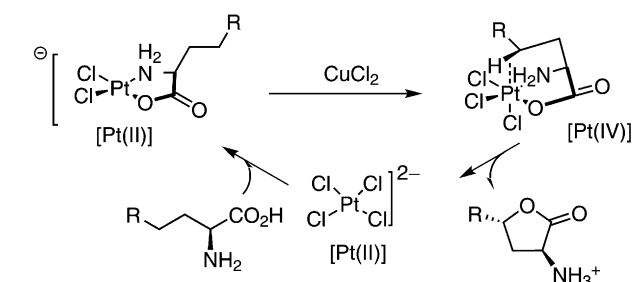**Scheme 44.** Pt-catalyzed carboxylate-directed C−H hydroxylation of aliphatic acids.

Figure 6. The proposed catalytic cycle for Pt-catalyzed C−H functionalization of amino acids.

could be hydroxylated with the carboxylate as the directing group, which could be followed by the cylization to form lactones (Scheme 44). The reactivity of C−H bonds follows the order of preference: α-C−H ≪ β-C−H < γ-C−H ≥ δ-C−H ≈ ε-C−H. The different reactivities were attributed to the favored formation of the less strained metallacycle following C−H bond cleavage by carboxylate-chelated Pt(II) species. Unfortunately, the yields of the reactions are moderate and the substrate scope is limited.

An improved C−O bond formation *via* C−H cleavage was achieved by Sames et al., who reported C−H hydroxylation of amino acids (Scheme 45).[7c] A wide array of α-amino acids with γ- or δ- C−H bonds was hydroxylated with K_2PtCl_4 in the presence of stoichiometric $CuCl_2$ in water, yielding the corresponding γ- or δ-lactones in moderate to good yields.

Noticeably, the catalytic system was also applicable to the hydroxylation of aliphatic amines and simple aliphatic acids.[7c] However, the regioselectivities were distinct from those in the reactions of amino acids. This difference indicated that the functionalization of amino acids proceeded *via* a different mechanism, and it was proposed that the catalytic center Pt was chelated with both the carboxylate and amino groups (Figure 6).

The Chang group reported a Pt-catalyzed benzylic C(sp^3)−H acetoxylation of *ortho*-alkyl-substituted aromatic carboxylic acids to form aryllactones
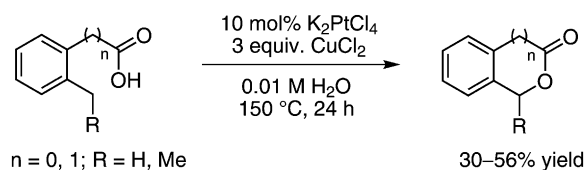

Scheme 46. Pt-catalyzed benzylic C(sp^3)−H acetoxylation of *o*-alkyl-substituted aromatic carboxylic acid derivatives.

(Scheme 46).[54] Therefore, *ortho*-methyl- and ethyl-substituted aromatic carboxylic acids underwent carboxylate-directed C−H oxidation with K_2PtCl_4 and $CuCl_2$ to form the corresponding lactones. The benzylic C−H bond of the *ortho-i*-Pr substituent was unreactive. It should be mentioned that the lactonization was applicable for arylacetic acids in addition to benzoic acids, and the derivatives of carboxylic acids such as esters, amides, and nitriles, which were hydrolyzed to the same carboxylic acids *in situ*, could also undergo the lactonization. The different k_H/k_D values of 2,6-dimethylbenzoic acid between inter- and intramolecular competing reactions in the kinetic isotope effect studies implied that the C−H activation should be assisted by the chelation of the platinum catalyst to the carboxylate group.
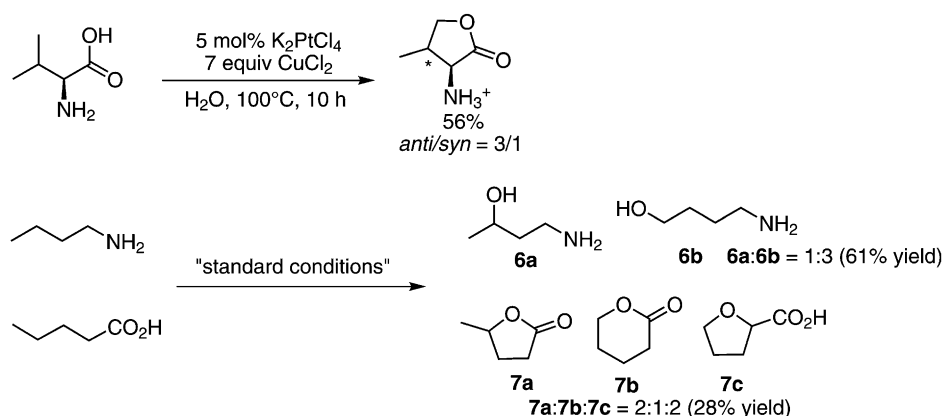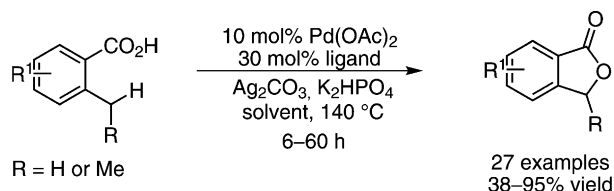

Scheme 45. Pt-catalyzed selective C−H functionalization of amino acids.
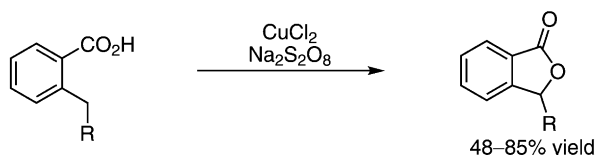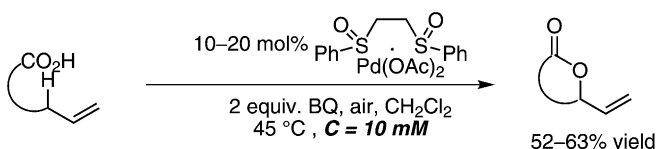
Scheme 47. Cu-catalyzed lactonization of benzylic C−H bonds to synthesize phthalide derivatives.

Scheme 48. Pd-catalyzed C(sp^3)−H activation/C−O bond formation to produce benzolactones.
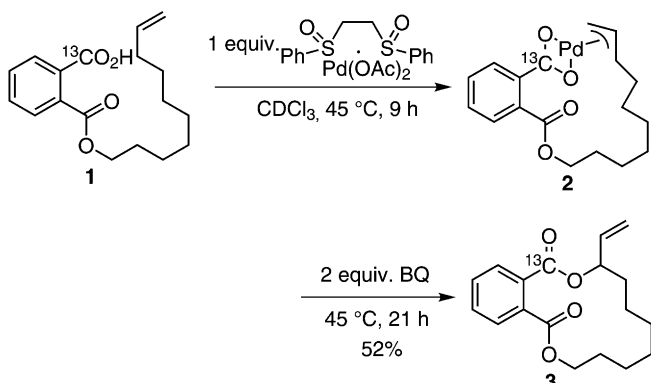
Scheme 49. Pd-catalyzed allylic C−H bond oxidation/macrolactonization.

In 2003, Mahmoodi et al. reported a similar benzylic C(sp^3)−H lactonization, albeit using CuCl$_2$ in the presence of Na$_2$S$_2$O$_8$ in aqueous solution (Scheme 47).[55] The mechanism may involve a benzyl radical intermediate.

Pd-catalyzed lactonization via benzylic C(sp^3)−H oxidation was also achieved by Martin et al. in 2011.[7d] With the use of Pd(OAc)$_2$, K$_2$HPO$_4$, *N*-protected amino acid ligands, and Ag$_2$CO$_3$, a diverse set of *ortho*-alkylbenzoic acids underwent the lactonization process to yield the corresponding benzolactones (Scheme 48). A wide range of substituents, including

ethers, silyl ethers, amides, ketones, acetals, esters, halo, and alkenes was well-tolerated. Mechanistic studies revealed that the transformation proceeded via a Pd(0)/Pd(II) catalytic cycle and the reductive elimination of C(sp^3)−O was the rate-limiting step.

Meanwhile, White and co-workers reported the first example of Pd-catalyzed macrolactonization of ω-alkenoic acids to furnish 14- to 19-membered alkyl- and arylmacrolides via allylic C−H oxidation, with excellent regioselectivity and functional group tolerance (Scheme 49).[56] Heating of the mixture of ^{13}C-labelled alkenoic acid **1** and sulfoxide/Pd(OAc)$_2$ complex afforded π-allyl-Pd complex **2**, which could transform to macrolide **3** in the presence of BQ (Scheme 49). With the support of the mechanistic studies, the formation of a Pd-templated π-allyl carboxylate intermediate was suggested to be crucial for the macrolactonization reaction.

Subsequently, Sasai et al. described a Pd-catalyzed enantioselective allylic C−H functionalization.[57] Therefore, 4-alkenoic acids underwent intramolecular oxidative cyclization in the presence of chiral ligand spiro-bis(isoxazoline) (SPRIX), to give the γ-lactone derivatives with moderate to good enantioselectivities (Scheme 50). It was proposed that a π-allyl Pd intermediate was involved in the catalytic process and the carboxylate group played a crucial role in the enantioselective C−H acetoxylation reaction.

The intramolecular C(sp^2)−H acetoxylation has also been studied quite extensively. Recently, the Wang group disclosed a novel synthetic method for benzofuranones via carboxylate-directed C−H acetoxylation of α,α-disubstituted phenylacetic acids, using Pd(OAc)$_2$ as the catalyst and PhI(OAc)$_2$ as the oxidant (Scheme 51).[58] Amino acid derivatives, which acted as the ligands, exerted a great promotion for the lactonization. Remarkably, one of the phenyl rings of symmetrically substituted diphenylacetic acids was acetoxylated enantioselectively. Boc-Ile-OH proved to be the optimal ligand, and a diverse class of α-alkyl-substituted diphenylacetic acids was desymmetrized with 89–96% *ee*. This reaction is the first example of enantioselective C−H functionalization through a Pd(II)/Pd(IV) redox catalytic cycle.
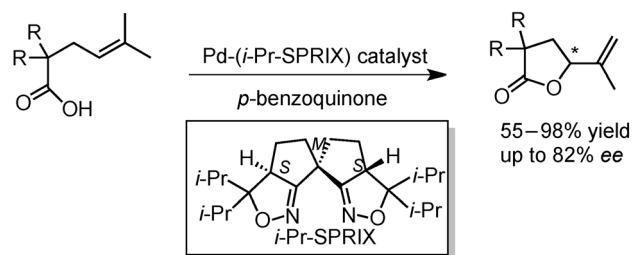
Scheme 50. Pd-catalyzed enantioselective intramolecular oxidative cyclization of 4-alkenoic acids.
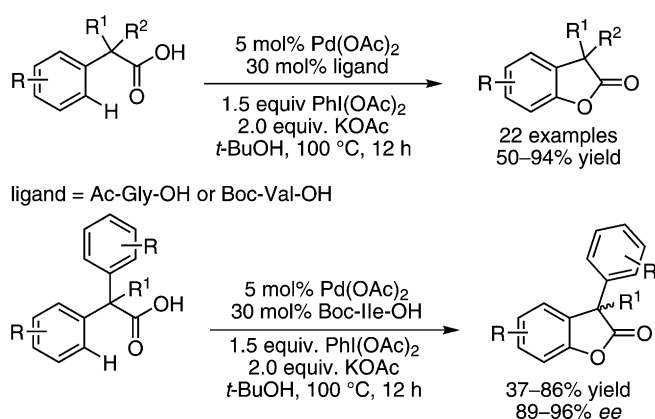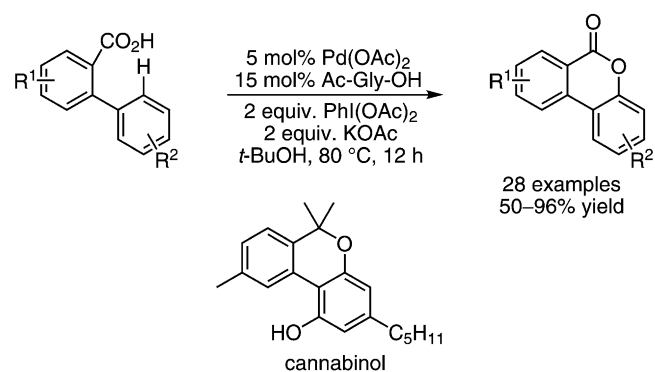
Scheme 51. Pd-catalyzed enantioselective intramolecualr C−H activation/C−O formation of phenylacetic acids.

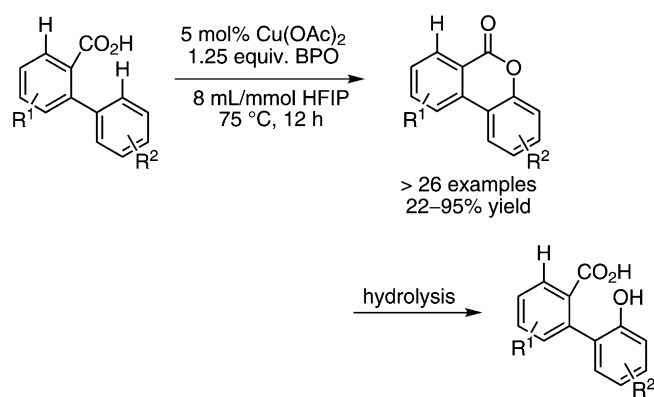**Scheme 53.** Cu-catalyzed carboxylate-directed C(sp^2)−H hydroxylation of 2-arylbenzoic acids.

Simultaneously, the Shi group reported a similar lactonization of phenylacetic acids.[59] However, amino acids were not needed in the reactions. As with Wang's research,[58] phenylacetic acids with α-hydrogens were not compatible.

The protocol of the lactonization of phenylacetic acids[58] developed by Wang and co-workers proved applicable for 2-arylbenzoic acids (Scheme 52).[60] Thus, 2-arylbenzoic acids with a diversity of substituents including halides were transformed into the corresponding biaryllactones in good to excellent yields. However, the cyclization of *ortho*-substituted (R^1 or R^2) substrates gave moderate yields, probably due to the increasing steric hindrance. This reaction provides an efficient method for the synthesis of biaryllactones, which has been demonstrated by its application into the concise total synthesis of the natural product cannabinol with commercially available starting materials.[60]

The lactonization of 2-arylbenzoic acids can also be enabled with copper. Similarly, the carboxylate-directed C−H acetoxylation proceeded efficiently with Cu(OAc)$_2$ and BPO oxidant in the absence of any additives and ligands (Scheme 53).[61] A wide array of

substituents, such as alkoxy, F, I, and even free hydroxyl group, was well tolerated. Interestingly, the hydroxylation occurred on the relatively electron-rich aromatic ring selectively, and the *ortho*-benzyl C-(sp^3)−H bonds were unaffected, which was in contrast to the previous research results.[7d,54,55] Mechanistically, this transformation was expected to be a single electron transfer process, as it could be inhibited by radical scavengers such as TEMPO, BHT, and 1,1-diphenylethylene, etc.

Remarkably, the Yu group discovered a carboxylate-directed C−H oxidation with O$_2$ as the oxygen source.[62] Thus, in the presence of Pd(OAc)$_2$, O$_2$, benzoquinone, and KOAc, benzoic acid derivatives bearing a variety of substituents such as Me, CF$_3$, F, Cl, CN, and NO$_2$, along with amides, ketones, and ethers were oxidized to afford *ortho*-hydroxylation products (Scheme 54). The use of the base and benzoquinone additive were vital to achieve the high yields. Preliminary mechanistic investigations showed that O$_2$ was the source of hydroxy oxygen and the aryl-Pd species, which was formed *via* the carboxylate-directed C−H bond cleavage/cyclometalation, underwent direct oxygenation with O$_2$.

As mentioned previously (Scheme 2 and Scheme 11), the carboxyl group can undergo decarboxylation and be transformed into other functionalities, which makes it a directing group of great utility in organic synthesis. By taking advantages of this at-

Scheme 52. Pd(II)/Pd(IV)-catalyzed carboxylate-directed C−H lactonization for expidient synthesis of biaryl lactones.

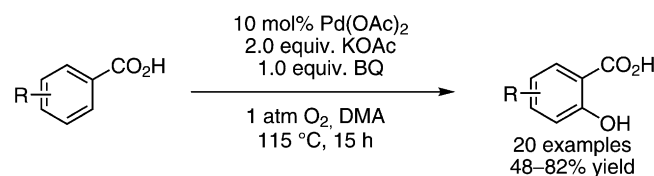Note: 2-naphthol is derived from 1-naphthoic acid

Scheme 54. Pd-catalyzed carboxylate-directed *ortho*-hydroxylation of benzoic acids with O$_2$.
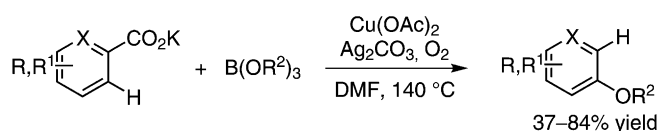
Scheme 55. Cu-catalyzed *ortho*-C−H alkoxylation of benzoates.

Scheme 56. Pd-catalyzed C−H halogenation of benzoic acids assisted by countercations.

tractive reactivity, Gooßen et al. developed a carboxylate-directed Cu/Ag-catalyzed C−H alkoxylation with concomitant protodecarboxylation of benzoates (Scheme 55).[63] The alkoxylation occurred on the *ortho*-site of the carboxylate group to give the corresponding aryl ethers, rather than *ortho*-alkoxybenzoates or the products arising from *ipso*-decarboxylative etherification. Trialkyl borates acted as the efficient alkoxide sources, and Cu(OAc)$_2$ and Ag$_2$CO$_3$ were suggested to be responsible for the C−H bond activation and the decarboxylation process, respectively. Both primary and secondary alkoxides were accommodated, and benzoates containing diverse substituents, such as keto, cyano, sulfonyl, nitro, and Br, were reactive. The reaction occurred at the less hindered positions for *meta*-substituted benzoates selectively, except for 3-nitro-4-methoxybenzoate.

6 Carboxylate-Directed C−H Bond Activation/C−X (X = halogen, N, B) Formation

In addition to C−C and C−O bonds, other C−heteroatom bonds can be formed *via* carboxylate-directed C−H activation. Based on the previous effort of oxazoline-directed Pd-catalyzed C−H iodination,[51] Yu et al. developed a similar reaction by using carboxylates as the directing groups,[11] which is complementary to traditional directed *ortho*-lithiation/halogenation.[64] Thus, catalyzed by 5 mol% Pd(OAc)$_2$, benzoic acids were iodinated or brominated with *in situ* generated IOAc or IBr from IOAc and R$_4$NBr (R = Bu or Me) (Scheme 56). Inorganic or organic bases including NaOAc, DMF, and tetraalkylammonium salts were essential for promoting the reaction. Notably, while *ortho*-diiodinated products were generated consistently in the case of DMF as the base, the addition of tetraalkylammonium salts such as Bu$_4$NI led to high monoselectivities. A wide range of substituents including F, Cl, Br, Me, OMe, OAc, and ester group were tolerated. The crucial role of base was considered to provide an appropriate countercation.

The catalytic system was applied to the iodination of synthetically useful phenylacetic acids, which are incompatible with classic directed *ortho*-lithiation procedures due to the presence of acidic α-hydrogen.[64b,65] The reaction was performed in the dark to suppress undesired competing processes and increase the yields (Scheme 57).[65] Various Pd(II) catalysts were effective, especially Pd(OAc)$_2$, PdI$_2$, etc. A variety of substituents on the phenyl rings was tolerated, including electron-donating (Me, AcO, etc.) and electron-deficient (F, Cl, Br, I, CF$_3$, keto, etc.) groups. *meta*-Substituted substrates were iodinated at the less hindered *ortho*-positions exclusively, and excellent monoselectivities were achieved with simple phenylacetic acids. It is worth noting that catalyst PdI$_2$ can be reused at least five times without a drastic reduction in yields. Furthermore, the transformation showed broad synthetic application, demonstrated by the site selective iodination of drug scaffolds and the subsequent derivatization of iodinated products.
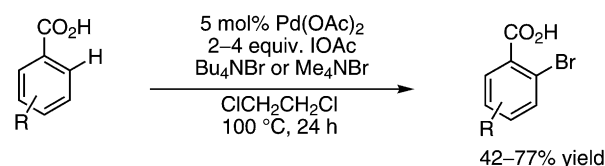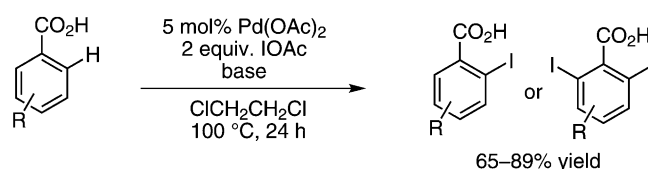
The acidic *N*-arylamide-directed Pd-catalyzed *ortho*-C−H iodination was reported by Yu and co-workers in 2013,[13b] with I$_2$ as the iodination reagent and the sole oxidant. In the presence of 2 mol% Pd(OAc)$_2$, various phenylacetic amides were iodinated with 2.5 equiv. of I$_2$ efficiently (Scheme 58). The use of a combination of CsOAc and NaHCO$_3$ proved to promote the reaction remarkably, probably due to the anionic ligand exchange of unreactive PdI$_2$ with CsOAc to regenerate active Pd(OAc)$_2$ or PdI(OAc) species, and NaHCO$_3$-assisted N−H deprotonation of the acidic amide to form the reactive imidate. Diiodi-
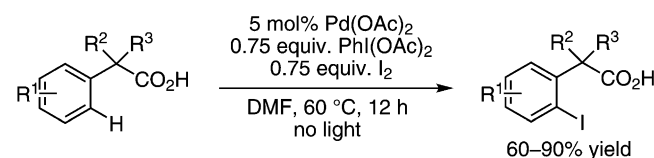
Scheme 57. Pd-catalyzed *ortho*-C−H iodination of phenylacetic acids with recyclable Pd-precatalyst.
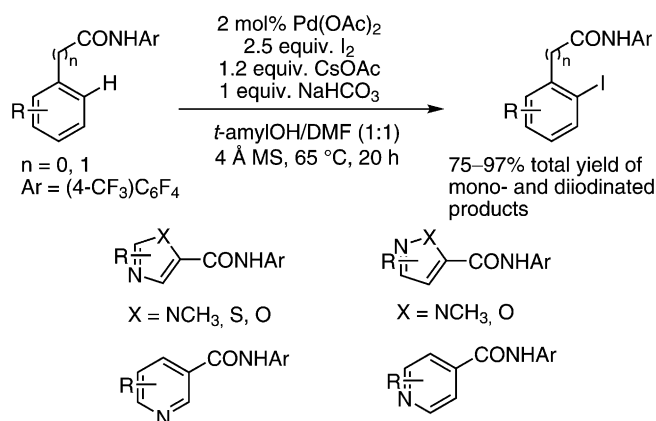
Scheme 58. Pd-catalyzed *N*-arylamide-directed C(sp^2)−H cleavage/iodination of aromatic and heteroaromatic carboxamides.

Figure 7. Assembly of the reactive catalysis precursor.

Scheme 59. Pd-catalyzed *N*-arylamide-directed *ortho*-C−H fluorination by F$^+$ reagent.

nated products were generated exclusively for substrates with two *ortho*-C−H bonds, and even those with *meta*-substituents. However, monoselective iodination may be achieved by using α-substituted phenylacetic amides. The transformation was applicable for benzamides. Therefore, under the same conditions, benzamides were iodinated to give monoiodination products for the substrates with substituents at either *ortho*- or *meta*-positions, and the reaction formed a mixture of diiodination products and undesired dimers of iodinated benzamides for non-substituted benzamides.

Remarkably, a wide array of heterocycles was successfully iodinated for the first time with this protocol,[13b] including pyrazoles, oxazoles, thiazoles, and pyridines etc. As heterocycles can strongly coordinate to transition metals, directed Pd-catalyzed iodination of heterocyclic compounds remained a great challenge. In the catalysis mode, the Pd center binds with the moderately coordinating amide as a result of a strong *trans*-effect and steric effects between the pyridyl groups in [Pd(py)₂] complex **I**, and it becomes sufficiently electrophilic for C−H cleavage with the aid of the acidic amide directing groups (Figure 7).

The direct fluorination of aryl C−H bonds remains a great challenge, and the C−H fluorination of benzoic acid derivatives had not been achieved until the pioneering work of Yu et al. in 2011, using the readily removable *N*-arylamide as directing group.[13c] Pd(OTf)₂(MeCN)₄ was utilized as the catalyst instead of Pd(OAc)₂, to prevent competing C−OAc reductive elimination from the Pd center. *ortho*-Monofluorination products were formed selectively in the presence of 10 mol% catalyst, 20 mol% NMP, and 1.5 equiv. of F$^+$ reagent (*N*-fluoro-2,4,6-trimethylpyridinium triflate) in MeCN at 120 °C, and the reactions gave *ortho*-difluorobenzoic amides using 3 equiv. of F$^+$ reagent and PhCF₃ as the solvent (Scheme 59). Sub-
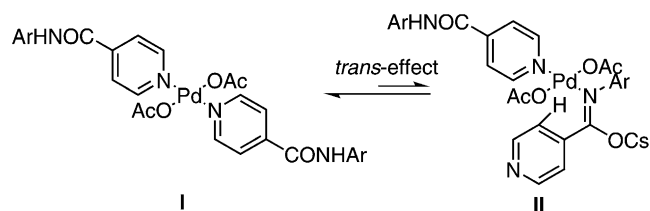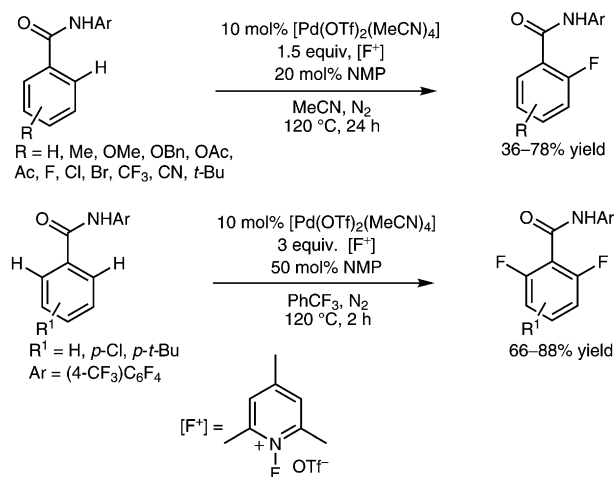
strates bearing alkyl, alkoxy, fluoro, chloro, bromo, cyano, and trifluoromethyl groups furnished the desired products in good yields, while acetoxy and acetyl groups reduced the reactivities. The pyridinium cation from F$^+$ reagent was expected to be the counter cation in the coordination mode, although an X-type coordination mode of the acidic amide could not be ruled out as yet.[13c]

The Yu group also achieved the Pd-catalyzed *N*-arylamide-directed *ortho*-C−H amination of *N*-arylbenzamides using *O*-benzoylhydroxylamines as the electrophilic amination reagent.[66] Therefore, *N*-arylbenzamides were aminated with a range of *O*-benzoylhydroxydialkylamines to give the corresponding arylalkylamines in the presence of stoichiometric Ag salt (AgOAc or Ag₂CO₃) and an inorganic base (CsF or KF) (Scheme 60). Satisfyingly, the intermolecular amination reaction could also be performed with a combination of secondary amines and benzoyl peroxide, which formed the reactive *O*-benzoylhydroxylamines *in situ*.[66] The electron-neutral and electron-rich substituted benzamides underwent the transformation in DCE effectively, while α,α,α-trifluorotoluene was the appropriate solvent for the electron-deficient substrates.

As organoboron compounds tend to undergo transmetallation with transition metals, it is expected to be challenging to perform the transition metal-catalyzed
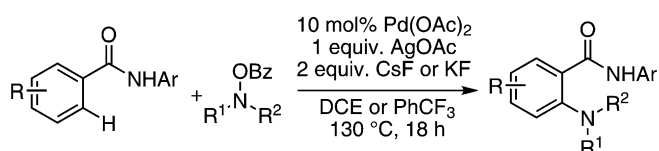
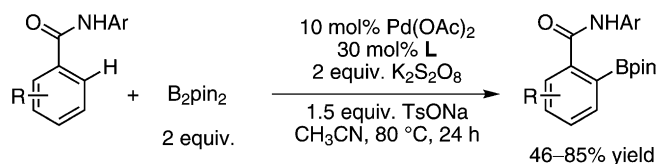**Scheme 60.** Pd-catalyzed *ortho*-C–H amination of benzamides.
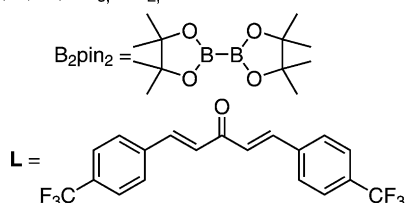
Scheme 61. Pd-catalyzed C(sp^2)–H borylation of benzamides directed by acidic *N*-arylamide group.

direct borylation of C–H bonds.[67] Fortunately, the versatile acidic *N*-arylamide directing group was successfully employed to direct Pd-catalyzed C–H borylation.[67] Diverse *N*-arylbenzamides were efficiently borylated with B$_2$pin$_2$, to afford the corresponding boronic esters, with the tolerance of various groups (Scheme 61). The use of a weak base (TsONa) and strong oxidant K$_2$S$_2$O$_8$ was critical for the success of the borylation reaction, along with modified dibenzylideneacetone ligand **L**. The transformation may proceed *via* a Pd(II)/Pd(IV) or a Pd(II)/Pd(0) process, which remains to be investigated. The borylation products are of great synthetic utility as boronic esters can be transformed into a variety of functional groups by proven methods.[68]

7 Conclusions

In summary, due to its great advantages in transition metal-catalyzed C–H activation, the carboxylate-directed C–H functionalization has gained considerable interest, and a variety of reactions has been developed over the past decade. The cyclometal complexes, which are generated *via* the carboxylate-directed C–H cleavage, may react with a wide range of reaction partners including carbon-carbon/heteroatom multiple bonds, organic halides, organometallic reagents, and miscellaneous reagents. These reactions provide novel

methods for the formation of C–C, C–O, C–N, C–I, C–F, C–B bonds. The acidic *N*-arylamides bearing highly electron-deficient aryl groups have a directing mode similar to that of carboxylate groups, but show novel reactivities in a number of transition metal-catalyzed C–H functionalization reactions, which render otherwise impossible reactions feasible. Based on these breakthroughs and the ubiquity of carboxyl groups, C–H functionalization reactions directed by carboxylate groups and their derivatives are expected to have great application potentials in organic synthesis, and especially in drug discovery, as they provide expedient and efficient ways for the derivatization of organic molecules.

Acknowledgements

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