Tetrahedron Letters 55 (2014) 5869–5889

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Digest Paper

Catalytic C—C bond forming transformations via direct β-C—H functionalization of carbonyl compounds

Zhongxing Huang, Guangbin Dong *

Department of Chemistry, University of Texas at Austin, Austin, TX 78712, United States

ARTICLE INFO

Article history:
Received 2 July 2014
Revised 1 September 2014
Accepted 1 September 2014
Available online 6 September 2014

Keywords:
C—H functionalization
Carbonyl compounds
β-C—H bonds
C—C bond formation

ABSTRACT

Strategies have emerged over the past decade to enable the direct functionalization of the remote and inert β-C—H bonds of carbonyl compounds. Based on these strategies, a wide collection of novel β-C—C bond formation transformations have been developed, including arylation, alkylation, alkenylation, alkynylation, and carbonylation. This review summarizes these recent methods for C—C bond formations via direct β-C—H functionalization of carbonyl compounds. The scope and limitation of each strategy are also discussed.

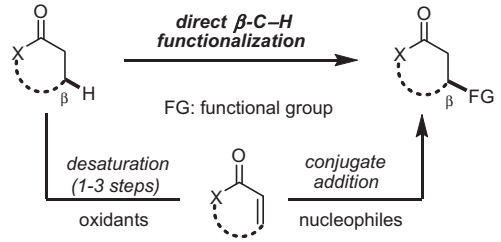
Contents

Introduction

Functionalization of carbonyl compounds represents a cornerstone of organic chemistry. The inherent electrophilicity of the carbonyl group and acidity of the α-C—H bond provide convenient handles for the installation of various functional groups at the *ipso* and α-position of carbonyl compounds, respectively. However, the β-C—H bond is usually considered inert and thus less facile to functionalize directly. On the other hand, such β-substituted motifs are frequently found in a wide array of bioactive compounds, including pesticides, anti-oxidants, and drug candidates.[1] Traditionally, functionalization of the β-position is often accomplished with conjugate addition of nucleophiles to the corresponding α,β-unsaturated carbonyl compounds (Scheme 1).[2] However, α,β-unsaturated carbonyl compounds are often prepared from their saturated derivatives using stoichiometric oxidants.[3] Thus, direct

* Corresponding author.

http://dx.doi.org/10.1016/j.tetlet.2014.09.005
0040-4039/



Scheme 1. β-C—H functionalization of carbonyl compounds.

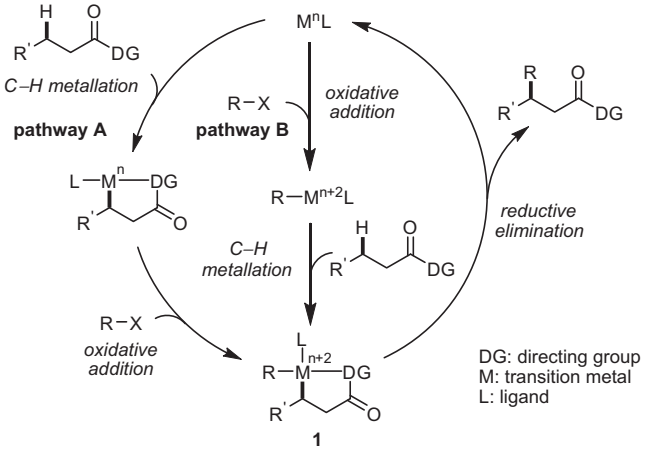
methods to convert the β-C—H bond to the desired functional group would considerably increase the efficiency of preparing β-substituted carbonyl compounds. During the last decade, significant efforts have been devoted toward direct β-C—H functionalization of carbonyl compounds. In this digest, we primarily focus on discussing the transformations that directly replace a β-C—H bond of carbonyl compounds with a C—C bond. While not intended to comprehensively cover all literature references, it rather offers a perspective on strategy design and discovery through selected examples to highlight representative reaction types.

Cyclometallation via directing groups

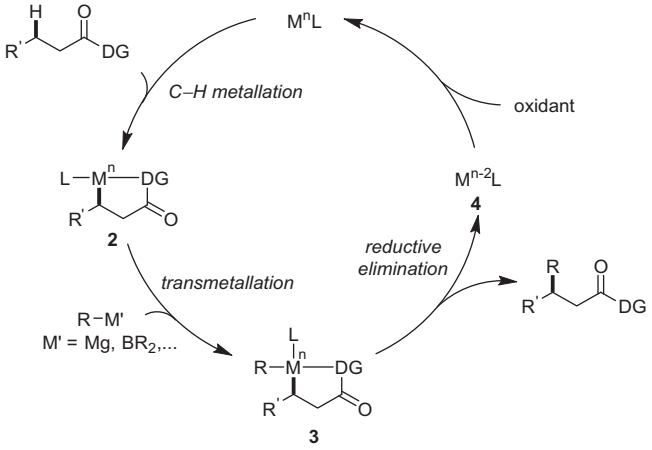
Directing-group strategies have been widely applied in transition-metal-mediated site-selective C—H activation, through which a significant number of catalytic transformations have been developed. Nevertheless, compared with sp^2 C—H bonds, the sp^3-hybridized β-C—H bond of carbonyl compounds is less prone to be cleaved by transition metals from both kinetic and thermodynamic prospectives,[4] which presents a significant challenge for design and development of new directing groups.

General mechanisms

Regarding the mechanism of these cyclometallation-type transformations, two general classes can be imagined based on the coupling partners employed. When an electrophile, such as an aryl halide, is involved, a typical reaction pathway proceeds through a selective metallation at the β-position assisted by the directing group, followed by oxidative addition of the electrophile to the metal giving intermediate **1** (Scheme 2, pathway A). It is also possible that the C—H metallation and oxidative addition occur in a reverse order (pathway B). Under either pathway, reductive elimination of intermediate **1** delivers the β-functionalization product and restores the active catalyst.



Scheme 2. Cyclometallation-type β-C—H functionalization via oxidative addition of electrophiles.



Scheme 3. Cyclometallation-type β-C—H functionalization via transmetallation of organometallic reagents.

When an organometallic reagent (i.e., arylboronic acids) is used, the coupling proceeds through a different mechanism (Scheme 3). After the C—H metallation step, transmetallation between the organometallic reagent and intermediate **2** installs the functional group on the metal center while the oxidation state of the metal remains unchanged. Subsequent reductive elimination affords the product, and oxidation of the reduced catalyst (**4**) by an external oxidant regenerates the catalyst.

According to the types of the directing groups employed, the β-functionalization through cyclometallation can be classified into two categories: type A is with strong bidentate directing groups; type B is with weaker coordinating directing groups.

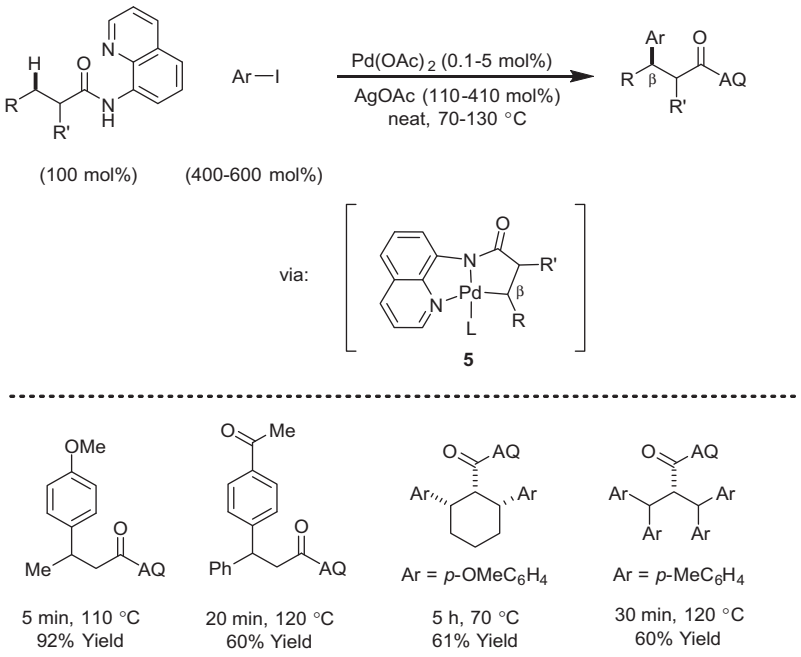
Type A: Bidentate directing group

Arylation

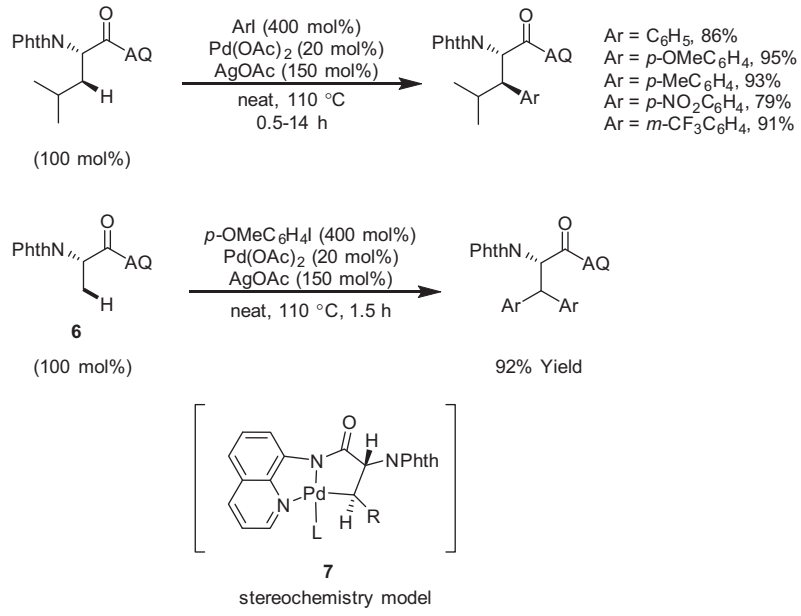
In 2005, Daugulis and co-workers disclosed a palladium-catalyzed β-arylation of amides using 8-aminoquinoline (AQ) as a directing group (Scheme 4).[5] In their proposed intermediate, the 8-aminoquinoline auxiliary provides an L-type (quinoline) and an X-type (amide) ligand to chelate with palladium in a bidentate fashion. The 5–5 fused palladacycle **5** was formed after the selective palladation of the β-C—H bond. Methyl, methylene, and benzylic C—H bonds β to the carbonyl can be arylated selectively with aryl iodides as the aryl source under neat conditions. Silver salts are likely used as an iodide scavenger. When activating a methyl group, the arylation occurred twice to give diarylation products.

Soon after the seminal work by Daugulis, Corey and co-workers successfully applied this strategy to prepare non-natural amino acids (Scheme 5).[6] With the 8-aminoquinoline moiety as the directing group, *N*-phthaloyl valine and phenylalanine derivatives underwent diastereoselective β-arylation through coupling with a range of aryl iodides. The diastereoselectivity could be explained by the formation of a less sterically hindered *trans*-palladacycle (**7**). When alanine derivative **6** was submitted to the reaction conditions, a diarylation product was selectively formed, which is consistent with the observation by Daugulis.[5]

Daugulis and co-workers subsequently discovered that the use of silver salts and neat conditions can be avoided by using a combination of main-group inorganic salts and alcoholic solvents (Scheme 6).[7] In addition, while the diarylation product dominates when 8-aminoquinoline was used as the directing group, 2-methylthio aniline was found to afford selective monoarylation of primary β-C—H bonds. This new directing group also works for



Scheme 4. Palladium-catalyzed β-arylation of amides using 8-aminoquinoline as the directing group.



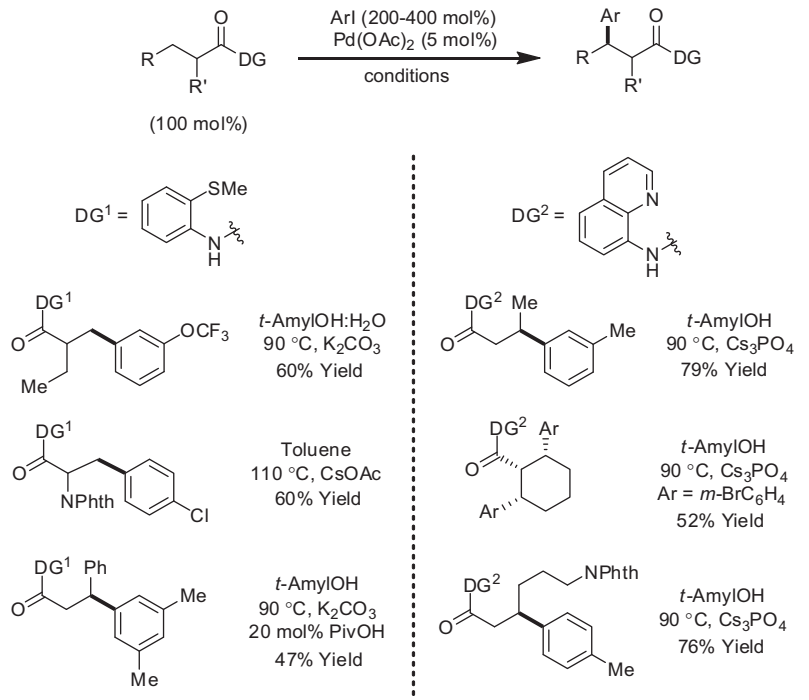
Scheme 5. Synthesis of non-natural amino acid derivatives.

a secondary benzylic C—H bond albeit with a moderate yield when a catalytic amount of pivalic acid was employed as a proton shuttle. In contrast, the 8-aminoquinoline directing group is more efficient for secondary C—H bonds; a number of cyclic and acyclic methylene β-C—H bonds can be arylated in good yields. Notably, Daugulis and co-workers later demonstrated that these complementary reaction conditions could also be nicely applied to the syntheses of non-natural amino acids via diastereoselective β-C—H arylation of N-protected amino acid derivatives.[8]

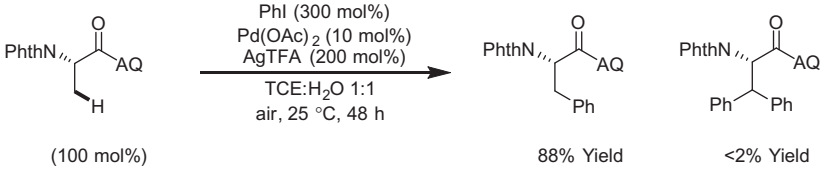
Recently, Chen and co-workers reported a mono-selective β-arylation of *N*-phthaloyl alanine derivatives using 8-aminoquinoline as the directing group (Scheme 7).[9] With the assistance of the trifluoroacetate anion, the β-arylation reaction proceeded under room temperature to afford the monoarylation product in a high selectivity. The authors also demonstrated that the monoarylation products could be further arylated, alkylated, or amidated at the β-position using the same directing group under different reaction conditions.

A strategy to synthesize chiral α-amino-β-lactams was developed by Shi and co-workers using a palladium-catalyzed monoarylation/amidation sequence with 2-(pyridine-2-yl)isopropyl (PIP) as the auxiliary (Scheme 8).[10] The PIP directing group is critical for the success of the sequence, because first it displays a high selectivity for the monoarylation step (mono/di > 25:1) and second it is robust enough to survive during the subsequent oxidative amidation step.

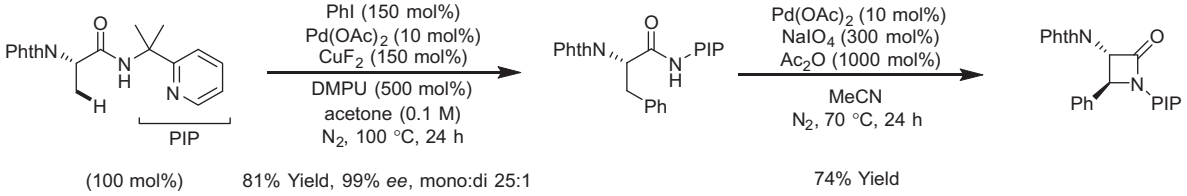
Chen and co-workers developed the first intramolecular version of the β-arylation reaction to construct benzannulated rings in a rapid fashion using 8-aminoquinoline as the directing group



Scheme 6. Palladium-catalyzed β-arylation directed by 2-methylthio aniline or 8-aminoquinoline auxiliary.



Scheme 7. Palladium-catalyzed β-monoarylation of alanine derivatives at room temperature.

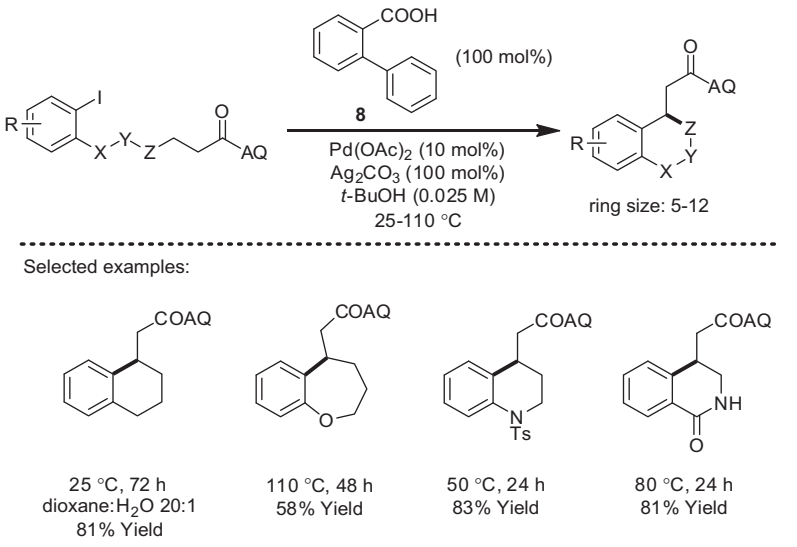


Scheme 8. Palladium-catalyzed synthesis of α-amino-β-lactams via a monoarylation/amidation sequence.

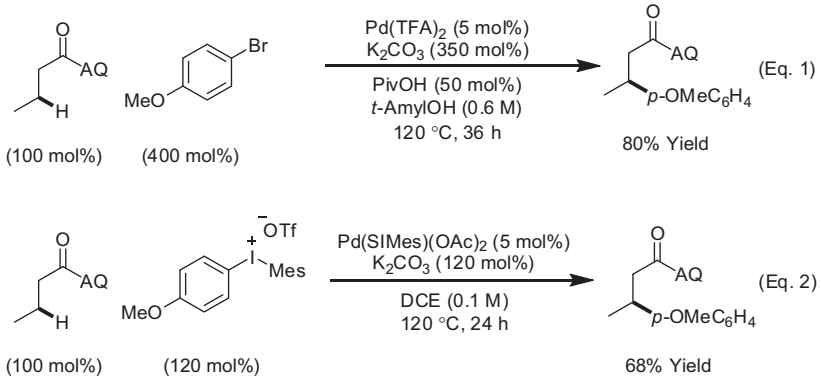
(Scheme 9).[11,12] Through the selective intramolecular coupling of aryl iodides and β-methylene C—H bonds, benzannulated products with different ring sizes were prepared, bearing ether, amine, or amide linkages. The *ortho*-phenyl benzoic acid (*o*-PBA) ligand **8** was found to enhance the overall efficiency, which was proposed to facilitate the oxidative addition of aryl iodides.

Besides using aryl iodides, Zeng and co-workers demonstrated that less reactive aryl bromides are also suitable aryl sources for the palladium-catalyzed β-arylation reactions (Scheme 10, Eq. 1).[13] 8-Aminoquinoline was employed as the directing group. Use of potassium carbonate as the base and pivalic acid as the additive was shown to be critical for the high efficiency. Diaryliodonium salts can be used as an alternative aryl source, reported by Shi and co-workers (Eq. 2).[14] In this case, the NHC-ligated Pd(SIMes)$(OAc)_2$ [SIMes = 1,3-bis(2,4,6-trimethylphenyl)imidazole-2-ylidane)] complex was employed as the catalyst and only a slight excess of diaryliodonium salt was required, which is a notable difference from the reactions with aryl halides.

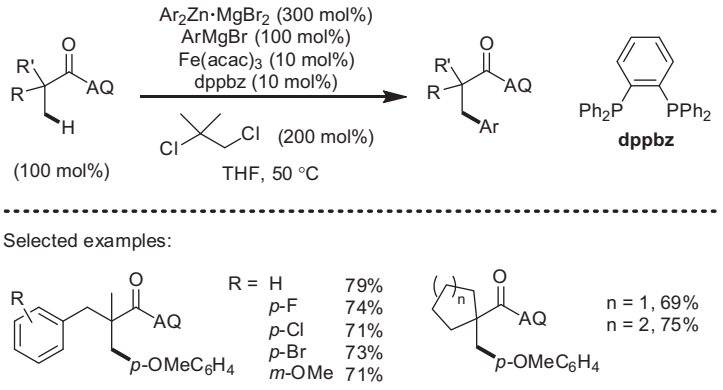
The 8-aminoquinoline auxiliary later proved to be a versatile directing group and readily applicable to C—H activation reactions catalyzed by metals other than palladium. An iron-catalyzed version of the β-arylation reaction was developed by Ilies, Nakamura and co-workers in 2013 (Scheme 11).[15] The iron-catalyzed arylation utilized in situ generated diarylzinc reagents as the aryl source, 1,2-dichloroisobutane (DCIB) as a terminal oxidant, and additional Grignard reagent to deprotonate the amides. A transmetallation-based mechanism was proposed (vide supra, Scheme 3). A high selectivity for methyl over benzylic C—H bonds was observed without 'over arylation' of methyl groups, which is distinct from the palladium-catalyzed reactions. In 2014, Ackermann and co-workers demonstrated the iron-catalyzed β-arylation can be carried out using triazolyldimethylmethyl (TAM) as the



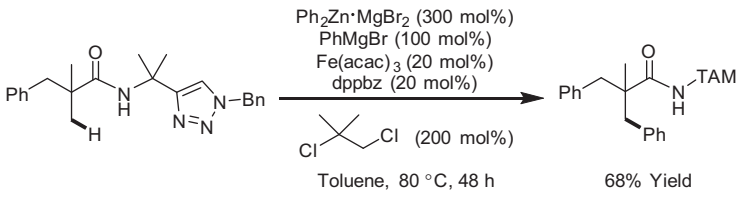
Scheme 9. Palladium-catalyzed intramolecular β-arylation.



Scheme 10. Palladium-catalyzed β-arylation reactions with aryl bromides or diaryliodonium salts.



Scheme 11. Iron-catalyzed β-arylation reaction directed by 8-aminoquinoline auxiliary.



Scheme 12. Iron-catalyzed β-arylation reaction directed by triazolyldimethylmethyl auxiliary.

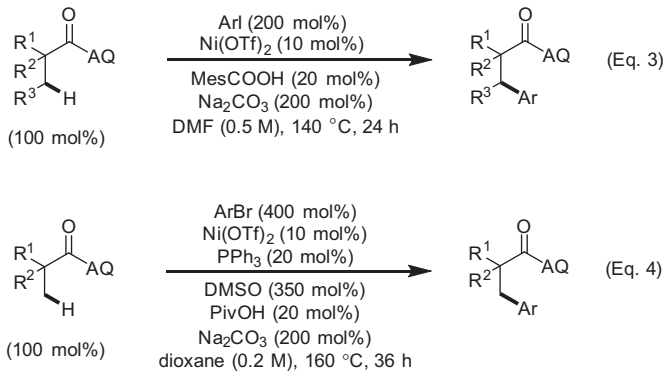
directing group,[16] which can be easily accessed via click cyclization (Scheme 12).[17]

Recently, a nickel-catalyzed β-arylation of amides was reported by the Chatani group using 8-aminoquinoline as the directing group (Scheme 13, Eq. 3).[18] A wide spectrum of sensitive functional groups were tolerated under the reaction conditions, including amines, iodides, indoles, and thiophenes, although substrates with α-protons gave lower yields (or no reaction). Shortly after Chatani's work, You and co-workers developed an analogous arylation reaction using aryl bromides as the coupling partner. With You's method, activation of the methyl group gave monoarylation products (Eq. 4).[19]

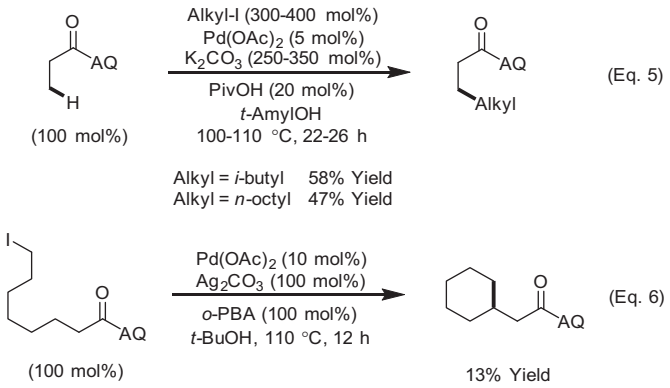
Alkylation

Compared to the arylation reactions, β-alkylation of carbonyl compounds with alkyl halides has been largely underdeveloped. The challenge to realize the β-alkylation stems from the sluggish oxidative addition of alkyl halides and alkyl–alkyl reductive elimination, as well as potential side reactions of alkyl halides, including decomposition and esterification with carboxylate or carbonate bases.

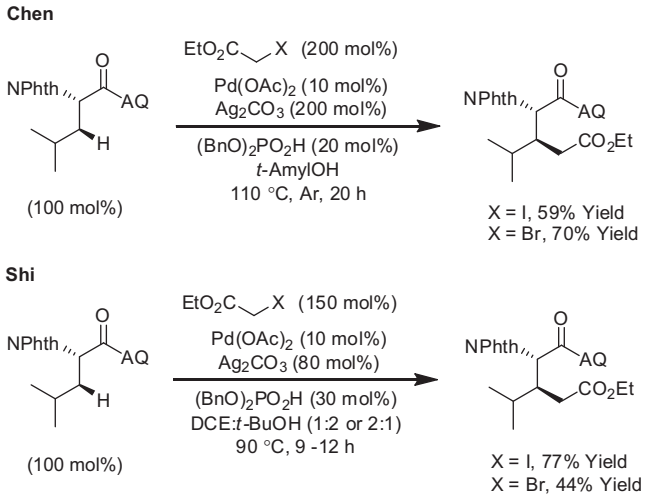
Use of 8-aminoquinoline directing group to facilitate the β-alkylation reaction was first demonstrated by Shabashov and Daugulis in 2010 (Scheme 14, Eq. 5).[7] The palladium-catalyzed coupling of the β-methyl C—H bond of propionic amide and *i*-butyl or *n*-octyl iodide was successful with K_2CO_3 as the base and a catalytic amount of pivalic acid. An example of an intramolecular alkylation of a more challenging β-methylene C—H bond was achieved by Chen and co-workers (Eq. 6).[12]



Scheme 13. Nickel-catalyzed β-arylation reaction directed by 8-aminoquinoline auxiliary.



Scheme 14. Early examples of β-alkylation reaction.



Scheme 15. Palladium-catalyzed β-alkylation with α-halideacetates.

A general solution to the challenging β-alkylation of methylene groups was independently provided by the Chen and Shi groups in 2013 (Scheme 15).[20,21] A wide range of methylene groups, cyclic or acyclic, were alkylated using α-iodoacetate, methyl iodide, or ethyl iodide. The combination of Ag_2CO_3 and $(BnO)_2PO_2H$, which was first introduced by Chen, appeared to be the key for the success. When alkylating a methyl C—H bond, Shi and co-workers were able to expand the alkyl-halide scope to alkyl iodides or bromides that contain various sensitive functional groups including alkenes, esters, and acetals.[21] Reactions with secondary alkyl iodides did not proceed under either Chen or Shi's conditions.

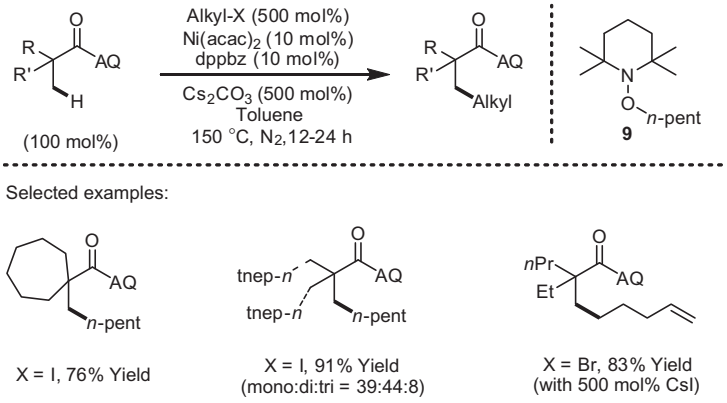
Recently, Ge and co-workers reported that β-alkylation can also be achieved via nickel catalysis using 8-aminoquinoline as the directing group (Scheme 16).[22] A tertiary α-carbon is necessary for the amide substrates to be arylated. Activation of methyl groups tends to be more favorable than methylene groups. It was found that the reaction was sensitive to the sterics of the alkyl halides, as isobutyl iodide and secondary halides did not give any alkylation product. Addition of TEMPO suppressed the reaction and a TEMPO/alkyl adduct (**9**) was also isolated along with the desired product. Therefore, a Ni(II)/Ni(III) catalytic cycle involving alkyl radicals was proposed by the authors for this reaction.

Alkynylation

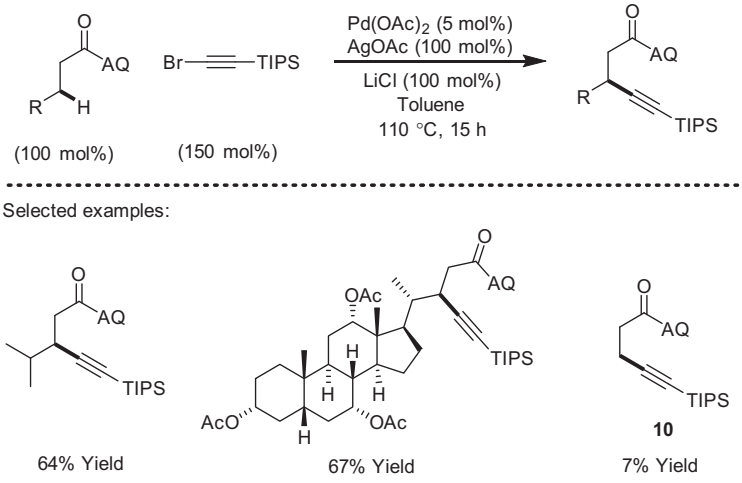
A palladium-catalyzed β-alkynylation reaction with the 8-aminoquinoline directing group was published by Tobisu, Chatani, and co-workers in 2011 (Scheme 17).[23] Bromotriisopropylsilylacetylene was used as the alkyne source. Interestingly, while secondary C—H bonds reacted effectively under the reaction conditions, reactions with methyl C—H bonds only gave a trace amount of product (**10**). This method offered a straightforward and site-selective approach to install alkyne motifs onto the carboxylic derivatives.

Carbonylation

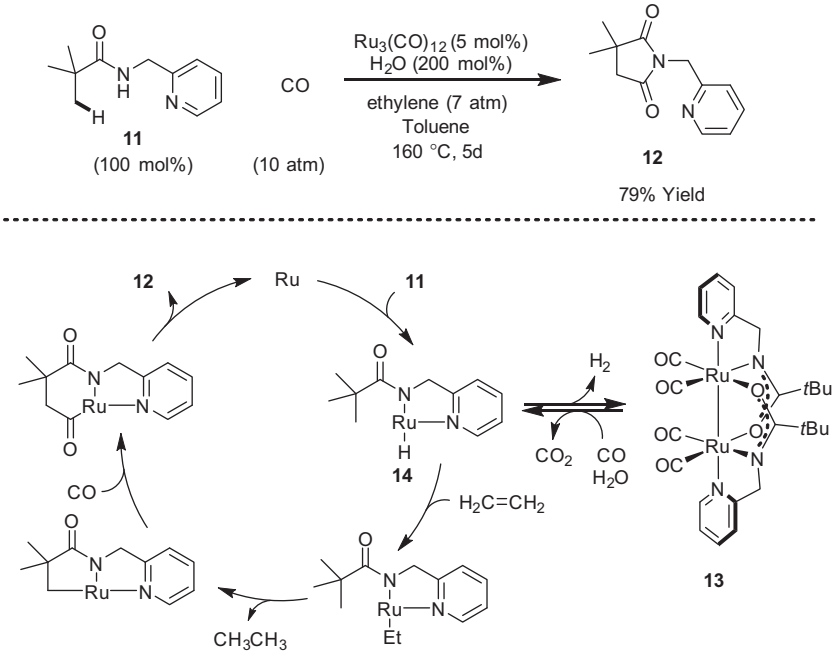
The Chatani group also published a ruthenium-catalyzed β-carbonylation reaction directed by a 2-pyridylmethylamine auxiliary (Scheme 18).[24] A range of succinimide derivatives were formed using this approach. The reaction was proposed to go through a sequence of β-C—H activation, CO migratory insertion, and C—N reductive elimination. In the proposed catalytic cycle, ethylene serves as the H_2 acceptor, and water reacts with complex **13** (the resting state of the catalyst) to generate active species **14**.



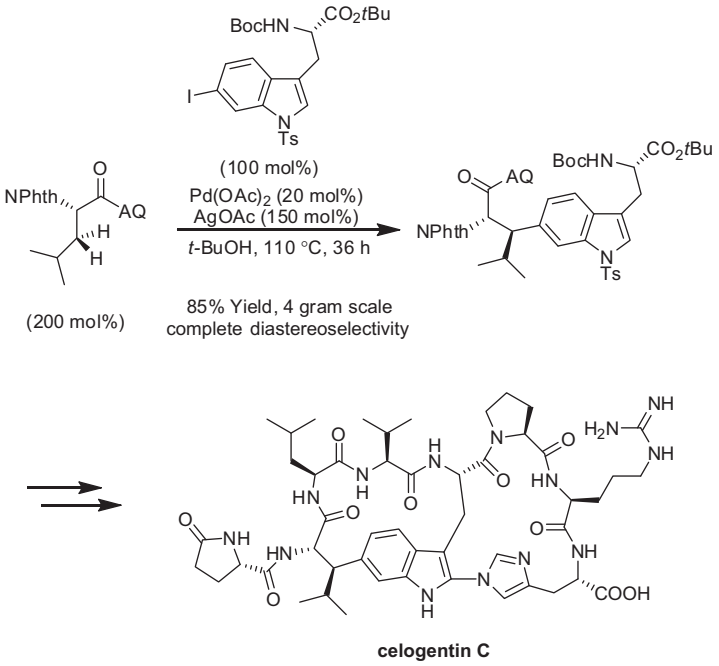
Scheme 16. Nickel-catalyzed β-alkylation with alkyl halides.



Scheme 17. Palladium-catalyzed β-alkynylation reaction directed by 8-aminoquinoline auxiliary.



Scheme 18. Ruthenium-catalyzed synthesis of succinimides via β-carbonylation



Scheme 19. Synthesis of celogentin C via palladium-catalyzed β-arylation directed by 8-aminoquinoline.

Application in total synthesis

When applied in a much more complex setting, the bidentate directing-group strategy still proved to be versatile and reliable. The first total synthesis using this transition-metal-catalyzed direct β-C—H functionalization was reported by Feng and Chen in 2010 (Scheme 19).[25] In the synthesis of the bicyclic peptide natural product, celogentin C, 8-aminoquinoline was used as the directing group in the palladium-catalyzed β-arylation reaction to construct the key C—C bond between the Leu Cβ and Trp C6 position. This β-arylation reaction proceeded smoothly to give the coupling product on a multi-gram scale with complete diastereoselectivity.

Similar C—H functionalization strategies were utilized by Baran and co-workers in construction of the unsymmetrical cyclobutane cores of piperarborenines (Scheme 20).[26] Cyclobutane **15** containing a 2-methylthio aniline directing group underwent efficient β-arylation with 3,4,5-trimethoxyliodobenzene under the optimized conditions. Bis-arylation on both methylene groups was not observed presumably due to the sterically hindered all-*cis* orientation of the tri-substituted cyclobutanes **16**. Different epimerization conditions were then applied to invert either the ester or amide stereocenter on the cyclobutane ring to afford diastereoisomers **17** and **18**. With reduced steric hindrance, the second arylations with 3,4-dimethoxyiodobenzene proceeded smoothly to give tetra-substituted cyclobutane core structures **19** and **20**, which, upon further modifications, led to piperarborenine B and the proposed structure of piperarborenine D, respectively. Later, the same group applied this C—H functionalization logic to the synthesis of the proposed structure of pipercyclobutanamide A, where a C—H arylation/olefination sequence was accomplished (Scheme 21).[27]

Recently, Ting and Maimone reported a concise synthesis of aryltetralin lignan podophyllotoxin via a palladium-catalyzed β-C—H arylation reaction (Scheme 22).[28] The major competing reaction of the arylation step was the β-lactam formation through a C—N bond reductive elimination. The authors discovered that the conformation of the rigid polycyclic system was important to control the selectivity between the C—C bond formation and C—N bond formation.

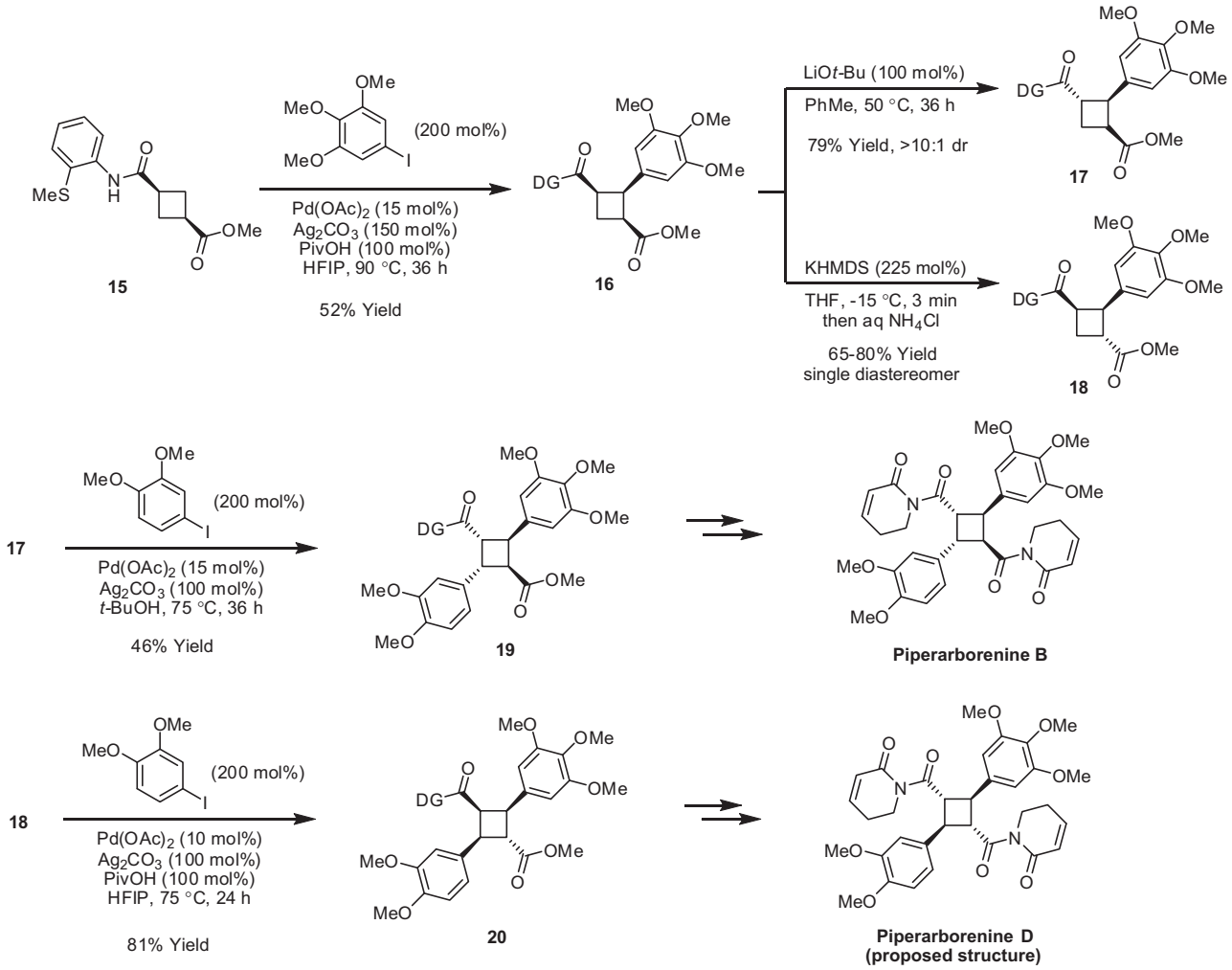
Type B: Weaker coordinating directing group

The use of weaker coordinating non-pyridine-type directing groups in the β-C(sp^3)—H functionalization of carbonyl compounds was pioneered by Yu and co-workers.[29] Compared to bidentate directing groups, such as 8-aminoquinoline, using a monodentate directing group should form a less thermodynamically stable thus more reactive metallacycle after the C—H metallation (Scheme 23). The enhanced reactivity of the metallated intermediate has enabled a collection of challenging C—H functionalization transformations. Furthermore, since an extra coordination site becomes available when using monodentate directing groups, the role of ligand is expected to be more important in controlling the reactivity and selectivity of the C—H functionalization reaction.

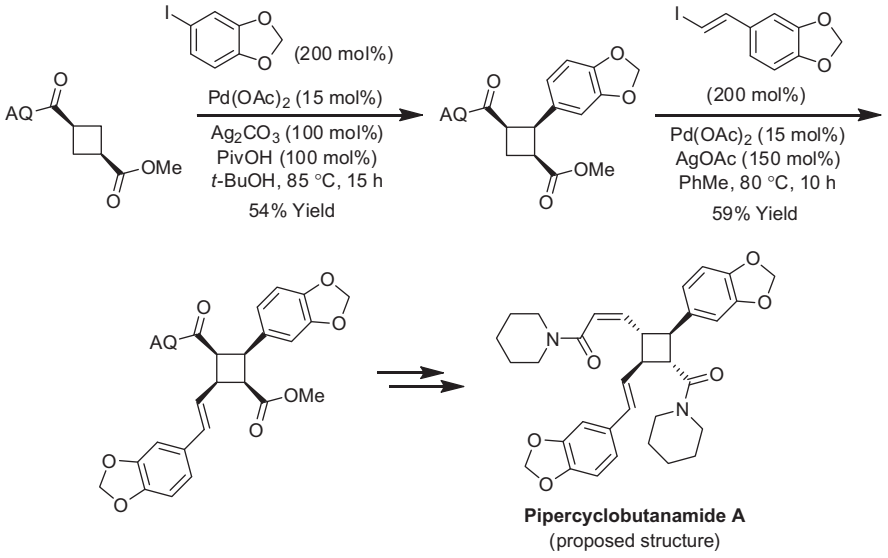
In 2007, Yu and co-workers reported the first β-arylation reaction of simple carboxylic acids with aryl iodides (Scheme 24, Eq. 7).[30] As proposed by the authors, the in situ generated potassium carboxylate guides palladium insertion into the β-C—H bond through a five-membered palladacycle, which, upon oxidative addition of aryl iodide and subsequent C—C bond reductive elimination, gives the β-arylation product. Phenylboronic acid pinacol ester (PhBpin) could also be coupled with the β-C—H bonds in the presence of benzoquinone (BQ) and Ag_2CO_3 as oxidants, albeit with lower efficiency (Scheme 25, Eq. 8).

Later, by employing *O*-methyl hydroxamic acids as the directing group, Yu and co-workers improved the yield of the β-arylation reaction with organoboron reagents (Scheme 25, Eq. 9).[31] Notably, an analogous β-alkylation reaction with alkyl boronic acids was also achieved. In this transformation, 2,2,5,5-tetramethyltetrahydrofuran was used as solvent, which might act as a bulky ligand to inhibit undesired homo-coupling and β-hydride elimination (Scheme 26). Besides silver salts, air was also demonstrated to be a suitable terminal oxidant for the β-arylation and alkylation reactions.

Unfortunately, when the authors attempted the hydroxamic acid-directed β-arylation using aryl iodides as the aryl source, a C—N bond coupling between the amide and aryl iodide proceeded readily (Scheme 27, Eq. 10).[32] To suppress the C—N bond formation



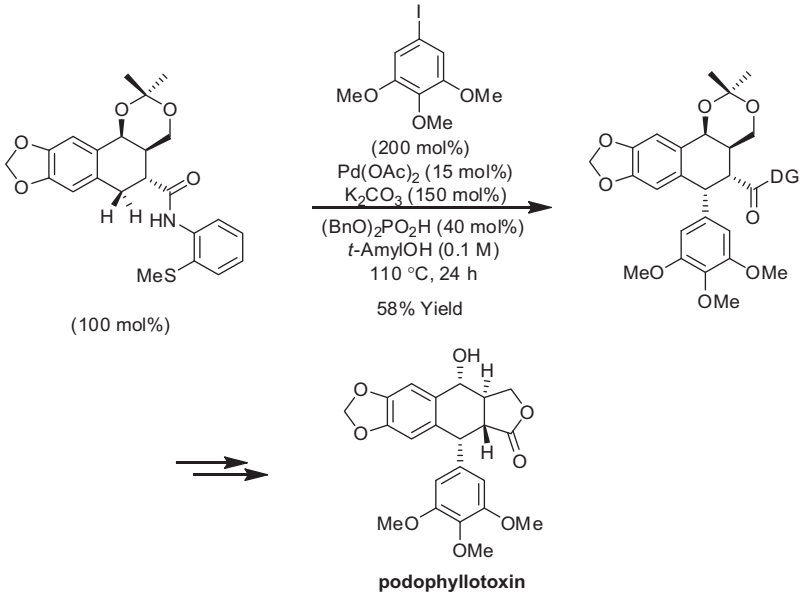
Scheme 20. Synthesis of piperarborenine B and D via sequential β-arylation.



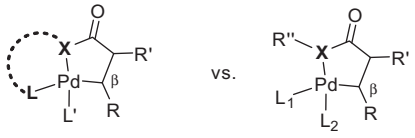
Scheme 21. Synthesis of pipercyclobutanamide A via palladium-catalyzed β-arylation/olefination sequence.

pathway, an acidic but less-nucleophilic *N*-pentafluorophenyl amide was used and found superior as the directing group. A range of β-methyl C—H bonds were arylated efficiently with $Pd(OAc)_2$/Cy-JohnPhos as a precatalyst and CsF as a base.

The acidic *N*-arylamide directing groups later found broad applications in the palladium-catalyzed β-functionalization reactions. A straightforward synthesis of succinimide derivatives via C—H carbonylation was reported by Yu and co-workers in 2010



Scheme 22. Synthesis of podophyllotoxin via palladium-catalyzed β-arylation.

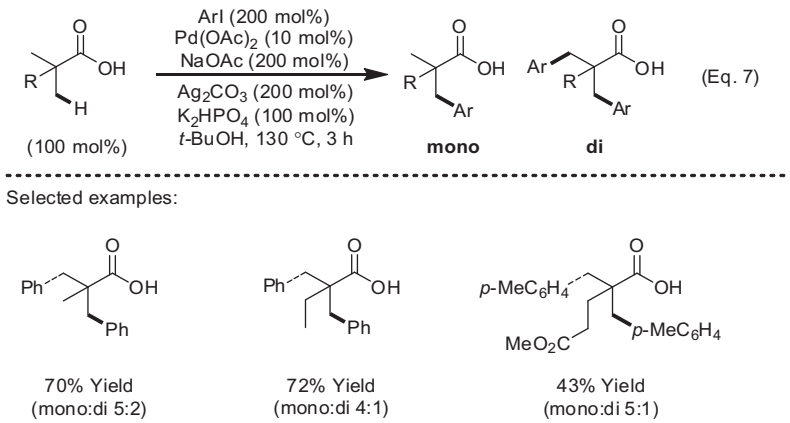


Scheme 23. Palladacycles from bidentate or monodentate directing groups.

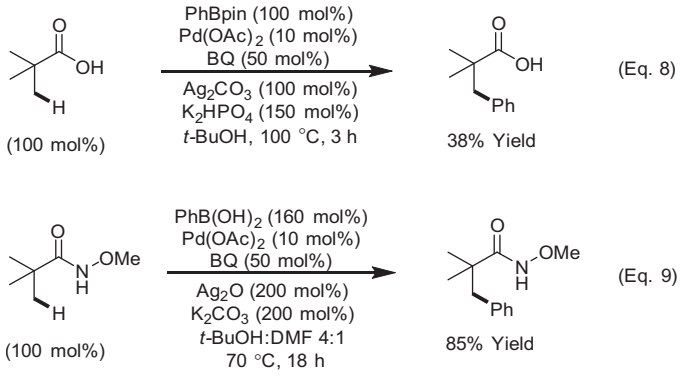
(Scheme 28).[33] Note that a ruthenium-catalyzed analogue was reported by Chatani with a bidentate directing group (vide supra, Scheme 18). Besides primary C—H bonds, cyclopropyl methylene groups are also suitable substrates. A palladium-catalyzed coupling between β-C—H bonds and benzyl acrylates was later developed by the same group (Scheme 29). The in situ generated vinylation intermediate (the oxidative Heck product) underwent an intramolecular 1,4-addition affording the lactam products.[34]

The aforementioned studies with the weaker *N*-arylamide directing groups mainly focused on primary (methyl group) and activated secondary C—H bonds in cyclopropanes. In contrast, methylene C—H bonds are more inert toward palladium insertion due to the unfavorable steric hindrance and enhanced risk for undesired β-hydride elimination.[35] Thus, to achieve a general β-methylene C—H functionalization with the weaker *N*-arylamide directing group, these challenges must be addressed. In 2012, a significant breakthrough was achieved by Yu and co-workers (Scheme 30).[36] The *N*-arylamide-directed β-arylation of various methylene groups was enabled by a bulky and electron-donating quinoline ligand **21**. Only a single ligand was proposed to strongly coordinate to the palladium center due to its steric hindrance, which leaves room for palladium to bind with the *N*-arylamide directing group. Methylene C—H bonds in both cyclic and acyclic substrates were arylated efficiently under the reaction conditions. Later, a Pd(0)-catalyzed alkynylation of β-methylene and methyl C—H bonds with alkynyl bromides was accomplished by the same group. In this case, the bulky and electron-donating NHC ligand **22** was used (Scheme 31).[37]

Recently, toward the synthesis of β-Ar-β-Ar′-α-amino acids with the *N*-arylamide directing group, Yu and co-workers demonstrated that selectivity for mono- versus di-C—H arylation can be determined by the choice of ligands (Scheme 32).[38] Simple 2-picoline ligand **23** afforded the β-monoarylation products with high yield and selectivity while the quinoline-type ligand (**24**) with rigidified oxygen lone pairs was required for the more challenging β-methylene arylation. With this pair of ligands, a sequence to



Scheme 24. Palladium-catalyzed β-arylation of simple carboxylic acids.



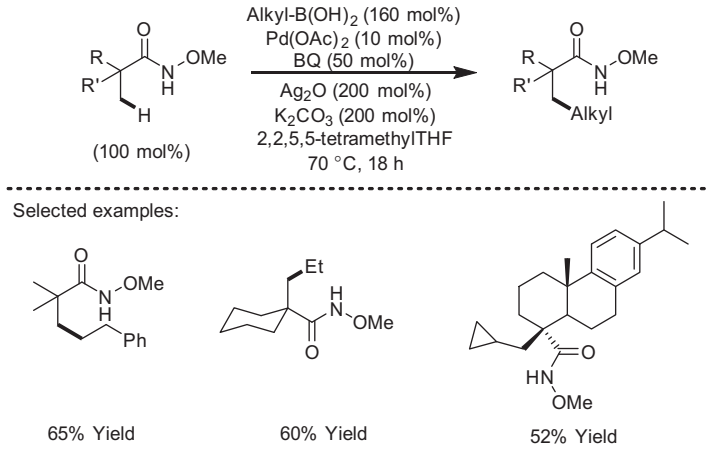
Scheme 25. Palladium-catalyzed β-arylation with aryl organoboron reagents.

incorporate two different aryl groups at the β-position of amino acid derivatives was accomplished in a one-pot fashion without isolating the monoarylation intermediate.

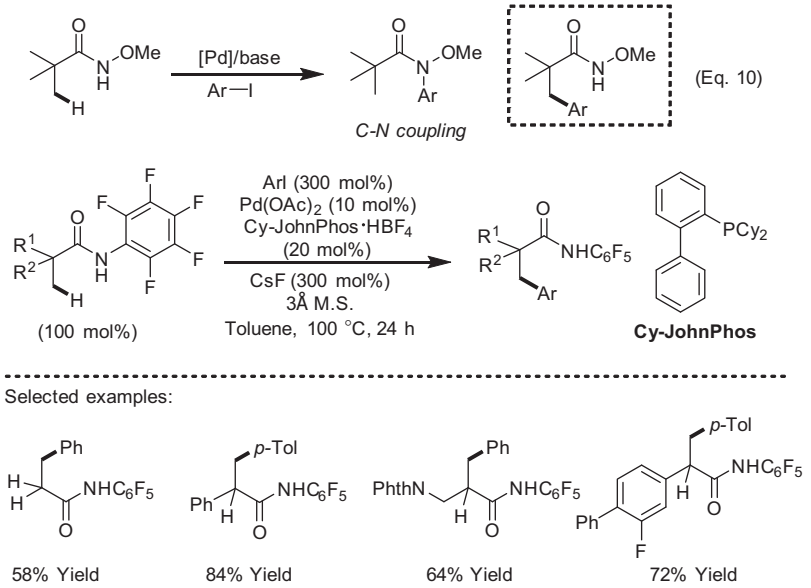
Enantioselective β-C—H functionalization reactions have also been achieved with the acidic *N*-arylamide directing groups (Scheme 33). In 2011, Yu and co-workers reported a desymmetrization-type arylation of cyclopropane methylene C—H bonds with organoboron reagents (Eq. 11).[39] The mono-*N*-protected amino acid ligand (**25**) was found to induce high enantioselectivity for the β-arylation. In contrast, the coupling of alkylboron reagents with the same ligand resulted in a compromised enantioselectivity. An enantioselective β-arylation of cyclobutane methylene groups was later developed by the same group (Eq. 12).[40] In this case, the chiral *O*-methyl hydroxamic acid ligand **26** was employed, which is more Lewis basic than the corresponding amino acid ligands. The desymmetrization of the prochiral β-methyl groups was also demonstrated using a similar ligand **27** (Eq. 13).

Migratory coupling

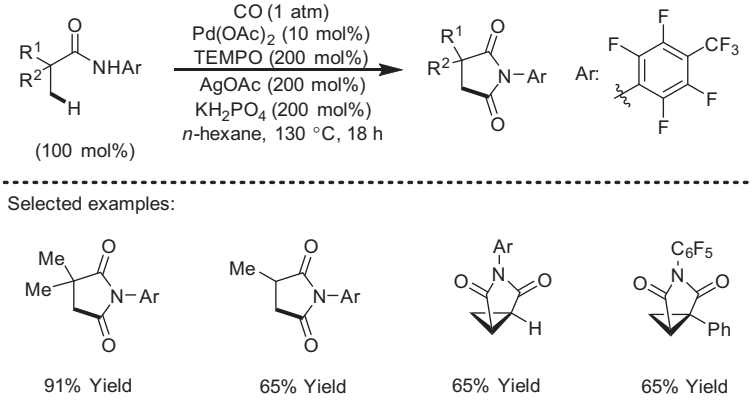
In 2002, while studying the scope of the palladium-catalyzed α-arylation of esters, Hartwig and co-workers discovered that the coupling between methyl isobutyrate and 2-bromothiophene gave



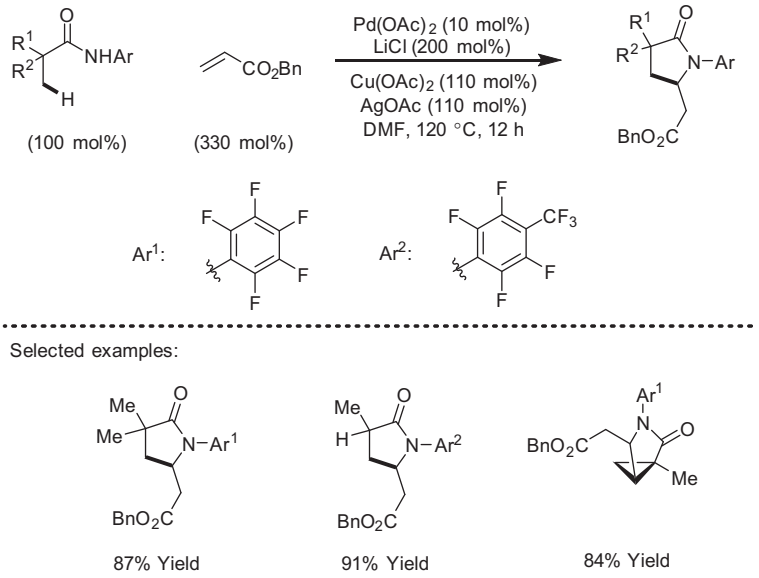
Scheme 26. Palladium-catalyzed β-alkylation of *O*-methyl hydroxamic acids.



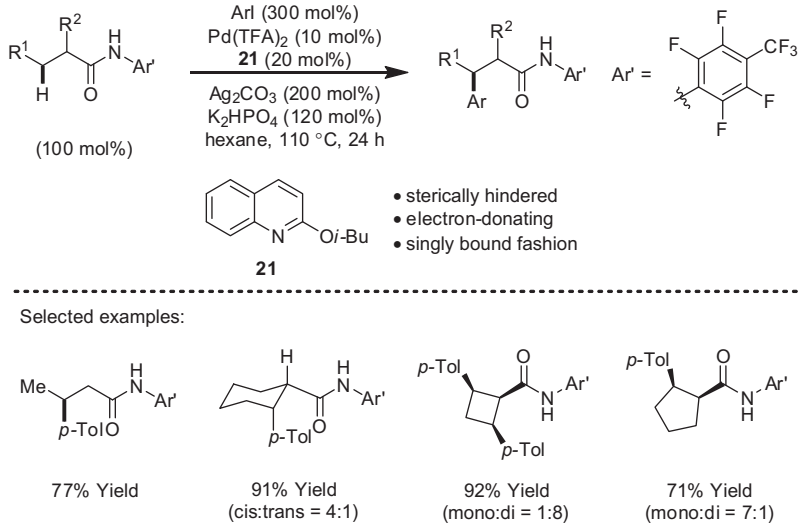
Scheme 27. Palladium-catalyzed β-arylation using acidic *N*-arylamide directing groups.



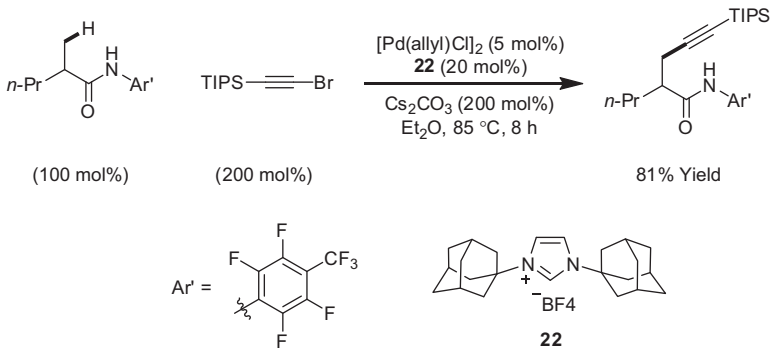
Scheme 28. Palladium-catalyzed synthesis of succinimides via β-carbonylation.



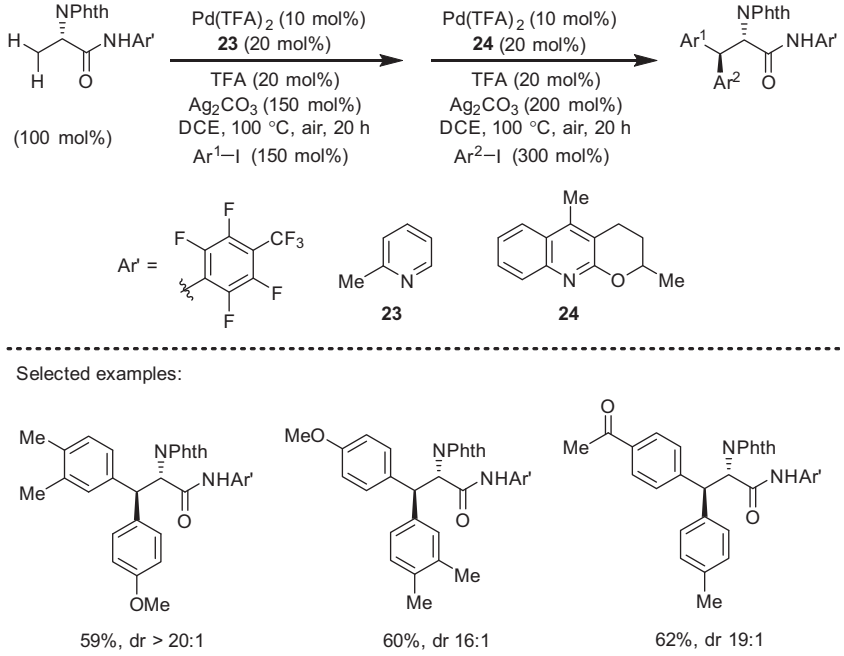
Scheme 29. Palladium-catalyzed β-olefination with benzyl acrylates.



Scheme 30. Palladium-catalyzed β-arylation of methylene C—H bonds.



Scheme 31. Palladium-catalyzed β-alkynylation directed by *N*-arylamide.



Scheme 32. Palladium-catalyzed ligand-controlled synthesis of β-hetero-diaryl amino acid derivatives.

an unexpected 2:1 mixture of α- and β-arylation products (Scheme 34).[41] The novel β-arylation product, as speculated by the authors, came from reductive elimination of a palladium homoenolate, which was rearranged from the hindered palladium enolate.

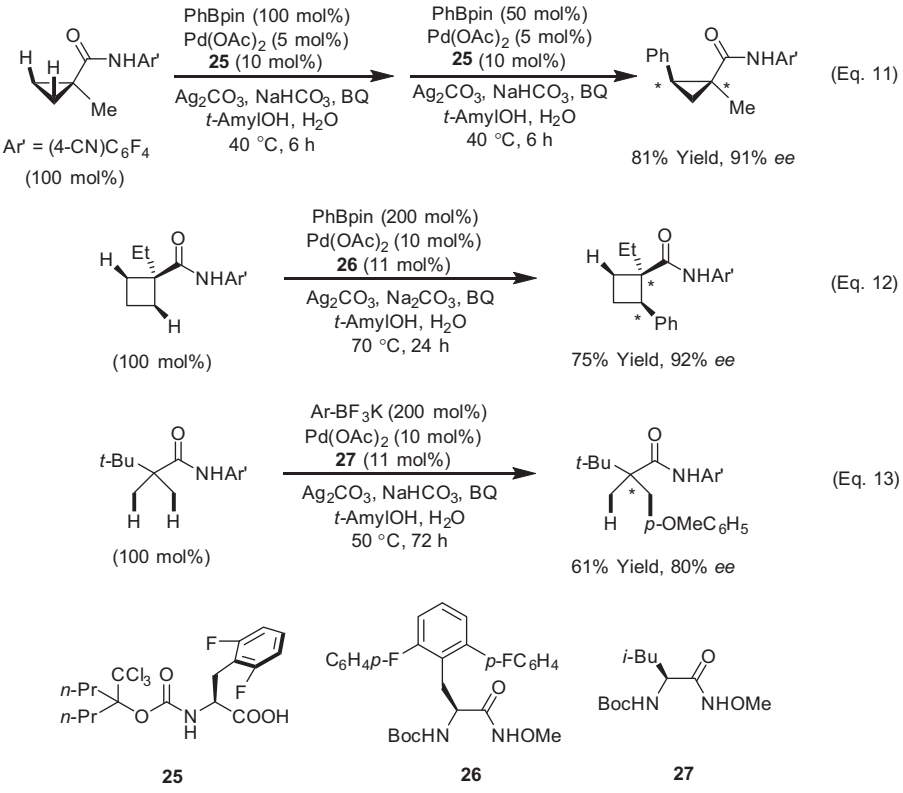
After Hartwig's seminal discovery, Baudoin and co-workers reported a systematic study of the palladium-catalyzed β-arylation reaction of carboxylic esters with aryl halides (Scheme 35).[42] The optimized conditions feature the use of Pd(0)/DavePhos as the pre-catalyst and lithium dicyclohexylamide as the stoichiometric base to generate enolate species. Aryl halides bearing an *ortho* electron-withdrawing group tended to give a high or complete selectivity for the β-arylation instead of the α-arylation. Regarding the ester scope, a tertiary α-carbon is required for the β-selectivity, presumably because the resulting palladium enolate would disfavor a direct reductive elimination to give α-arylation due to the steric hindrance. Notably, moderate *er* values were obtained when a chiral version of the DavePhos ligand (**28**) was used (Scheme 36).

A plausible catalytic cycle, supported by both experimental and computational studies, was proposed by the authors (Scheme 37).[43] Initially, Pd(0) would undergo oxidative addition with aryl bromides and subsequent ligand exchange with the lithium enolate to give palladium enolate **31**. Direct reductive elimination of **31** would afford the α-arylation product **32**. To access the β-arylation product, palladium homoenolate **35** is expected to form via a sequence of β-hydride elimination, olefin rotation and Pd—H reinsertion. Subsequent reductive elimination of the less hindered palladium homoenolate would give the β-arylation product (**36**) and regenerate the Pd(0) catalyst.

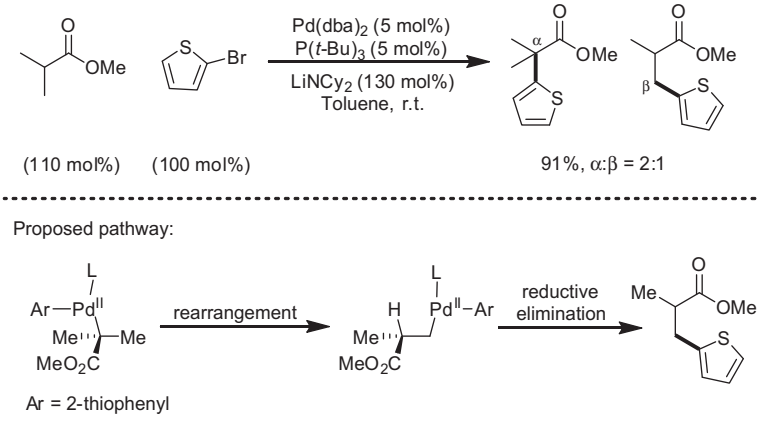
This migratory-coupling type of β-arylation approach has been readily applied to the modification of amino esters utilizing dibenzyl-protected alanine esters as the substrates.[44] Baudoin and co-workers further demonstrated that silyl ketene acetals, surrogates for lithium enolates, can be also adopted for the β-arylation.[45] Under the optimized conditions, a wide range of sensitive functional groups are tolerated, including methyl esters, ketones, acetates, and triflates (Scheme 38).

Photoredox catalysis

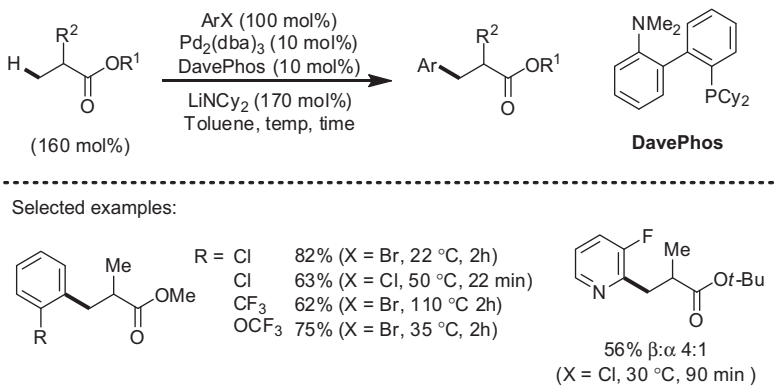
An innovative direct β-arylation of ketones and aldehydes was recently disclosed by MacMillan and co-workers via the combination of photoredox and enamine catalysis (Scheme 39).[46] In the presence of a fluorescent light bulb and 1,4-diazobicyclo[2.2.2]



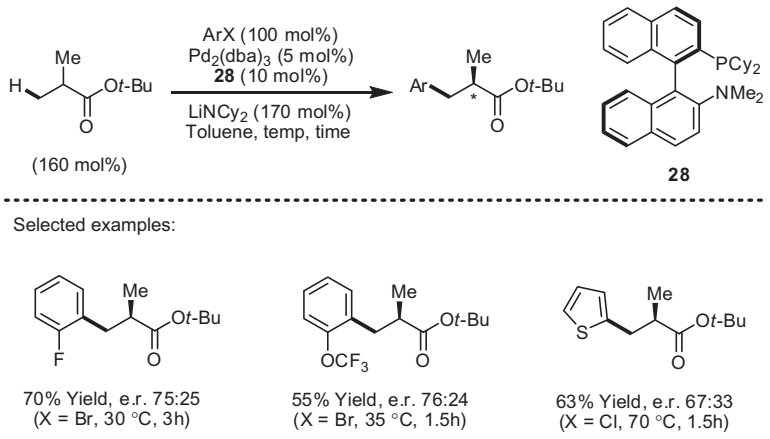
Scheme 33. Palladium-catalyzed enantioselective β-arylations.



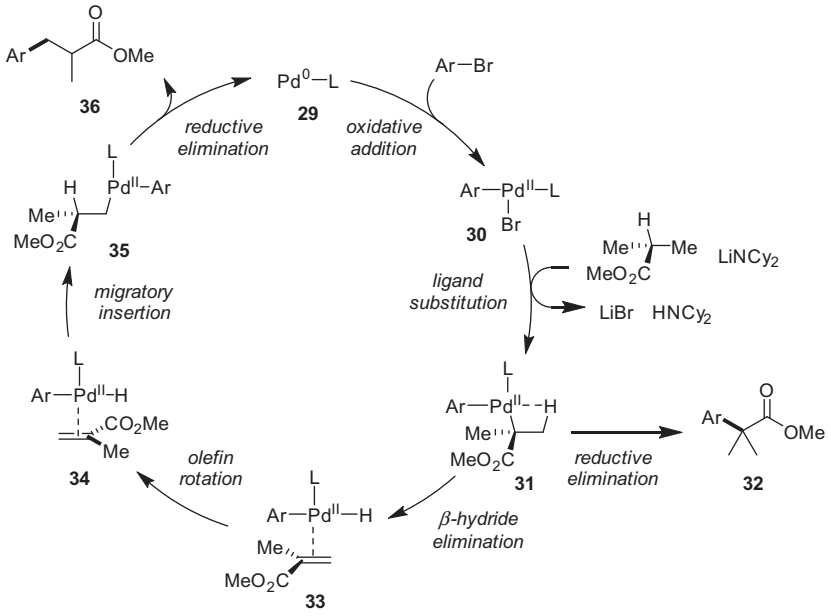
Scheme 34. Hartwig's observation of β-arylation.



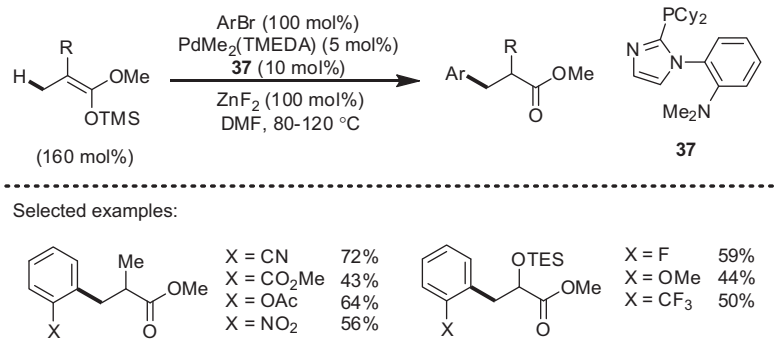
Scheme 35. Palladium-catalyzed β-arylation of carboxylic esters.



Scheme 36. Palladium-catalyzed enantioselective β-arylation of carboxylic esters.

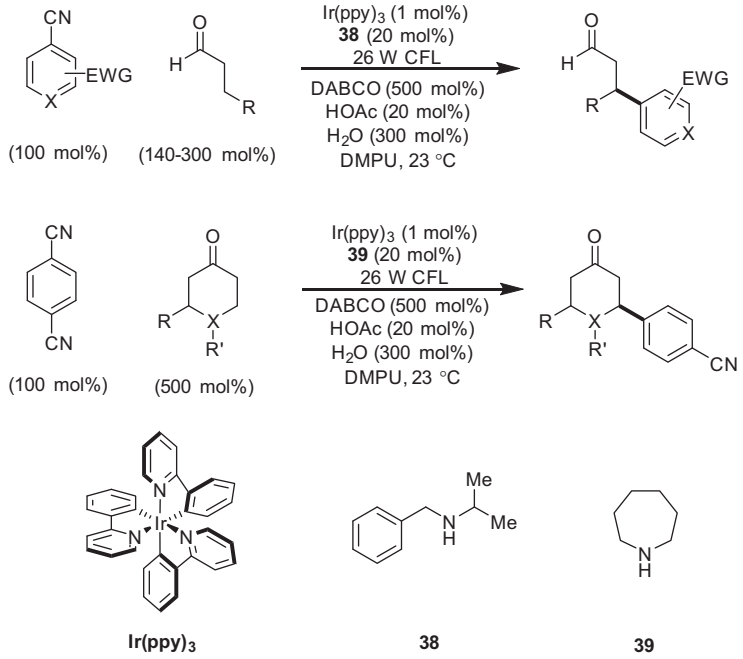


Scheme 37. Proposed mechanism for the palladium-catalyzed β-arylation of carboxylic esters.

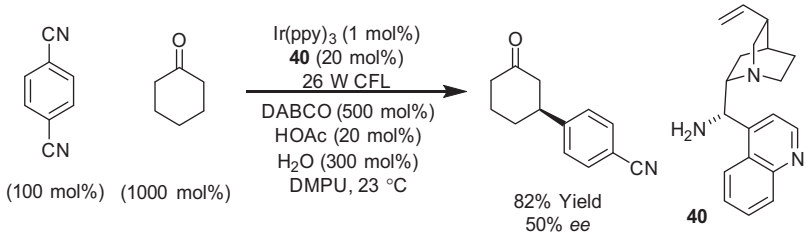


Scheme 38. Palladium-catalyzed β-arylation of silyl ketene acetals.

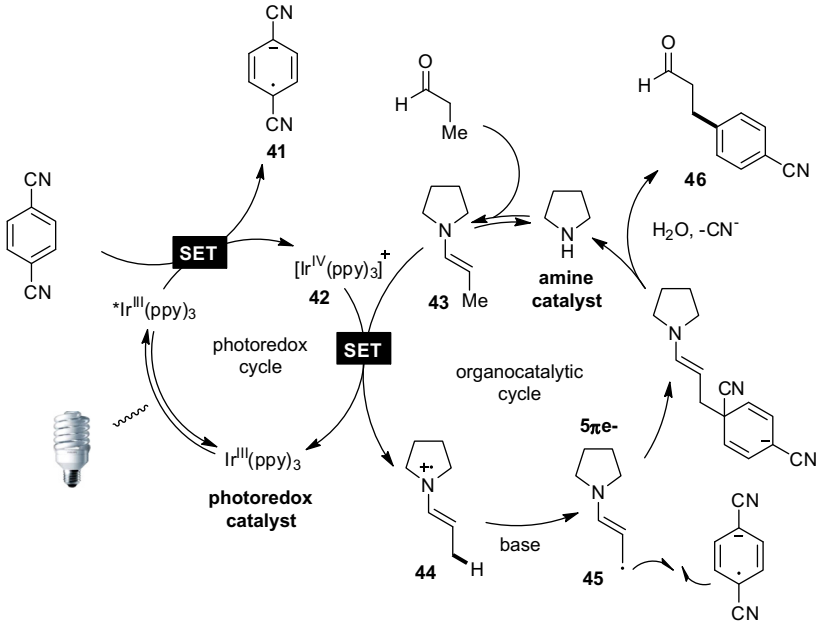
nonane (DABCO) as the base, the coupling between aldehydes and electron-deficient arylnitriles afforded the arylation product with complete β-selectivity. $Ir(ppy)_3$ and *N*-isopropylbenzylamine **38** were used as the photoredox and organocatalyst, respectively. The scope of the aldehyde substrates is broad: primary, secondary, and even tertiary β-C—H bonds can be arylated in good yields. When azepane **39** was employed as the organocatalyst, cyclohexanone derivatives also gave the β-arylation products. The compatibility with cyclic ketone substrates represents a significant advance of the β-functionalization, as the previous directing-group



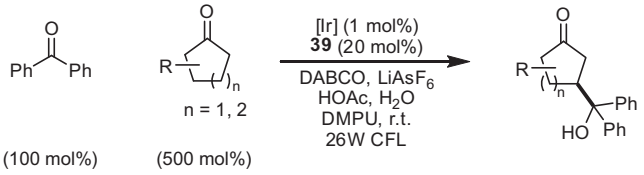
Scheme 39. β-Arylation of aldehydes and ketones via photoredox organocatalysis.



Scheme 40. Enantioselective β-arylation of cyclohexanone using a chiral amine catalyst.



Scheme 41. Proposed mechanistic pathway of photoredox C—H β-arylation.



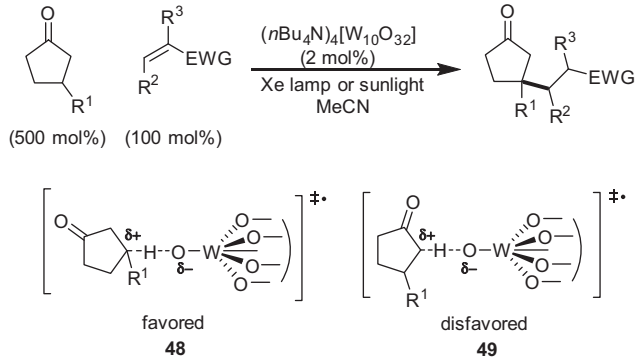
Scheme 42. β-aldol coupling of cyclic ketones with aryl ketones via photoredox catalysis.

or migratory-coupling approaches do not work for cyclic carbonyl compounds. The authors also demonstrated the potential for developing enantioselective β-arylation reactions (Scheme 40). A moderate *ee* value was obtained from the reaction between cyclohexanone and 1,4-dicyanobenzene using a cinchona-derived catalyst (**40**).

In the proposed mechanism, shown in Scheme 41, 1,4-dicyanobenzene is first reduced by the excited catalyst $^{*}Ir(ppy)_3$ via a single-electron transfer to afford radical anion **41** and the oxidized catalyst $[Ir^{IV}(ppy)_3]^{+}$ (**42**). Subsequently, photoredox and organocatalytic cycles would merge: $Ir^{IV}(ppy)_3$ first oxidizes enamine **43** to give radical cation **44** and regenerate the photoredox catalyst. In the presence of a base, the weakened allylic C—H bond in **44** would be deprotonated to give the β-enamine radical **45**, a 5πe system. The coupling between radical anion **41** and β-enamine radical **45**, followed by aromatization and hydrolysis of the enamine, provides the β-arylation product (**46**), releases cyanide (CN—) as a byproduct, and restores the amine catalyst.

Employing a similar photoredox mode, the MacMillan group also realized a formal β-aldol coupling between cyclic and aryl ketones (Scheme 42).[47] The β-enamine radicals from the cyclohexanone or cyclopentanone derivatives could readily couple with the ketyl radical generated from the aryl ketone, which provides access to a range of γ-hydroxyketones. The addition of $LiAsF_6$ was proposed to inhibit the dimerization of the ketyl radicals. Recently, the same group also reported a β-alkylation reaction of aldehydes with Michael acceptors (Scheme 43).[48] In the proposed mechanism, the β-enamine radical generated from the aldehydes is directly intercepted by the Michael acceptor to give an α-acyl radical. Such a radical would then be reduced and protonated to afford the β-alkylation product.

An interesting β-alkylation of cyclopentanones was recently reported by Fagnoni and co-workers with tetrabutylammonium decatungstate (TBADT) as the catalyst (Scheme 44).[49] Under Xe-lamp or sunlight irradiation, the electronegative oxygen-centered radical in the excited TBADT catalyst would selectively abstract a β-hydrogen from the cyclopentanone. The resulting β-radical would then be intercepted by a Michael acceptor to give an acyl-radical, which would then receive a hydrogen atom back from the reduced TBADT catalyst to afford the alkylation product. The absence of α-alkylation products was tentatively explained by an unfavorable transition state (**49**) involving an electron-deficient



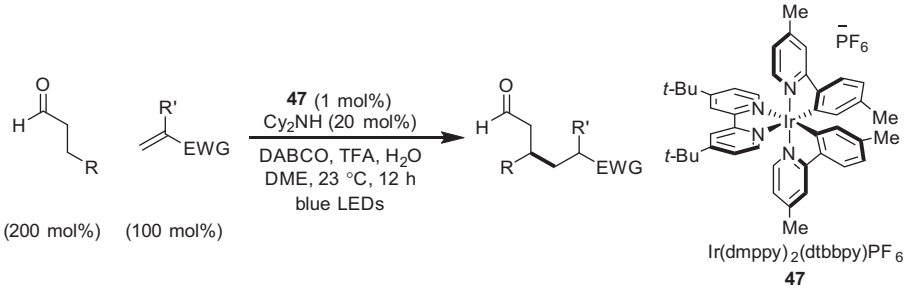
Scheme 44. Photocatalyzed β-alkylation of cyclopentanones.

α-carbon with a partially positive charge. Under a high pressure of carbon monoxide, the β-acylation of cyclopentanones was also accomplished via a sequential addition to the carbon monoxide and electron-deficient alkene. However, the reaction of ketones other than cyclopentanones, including cyclohexanone, cycloheptanone, and 2-pentanone, resulted in a mixture of β- and γ-alkylation products.

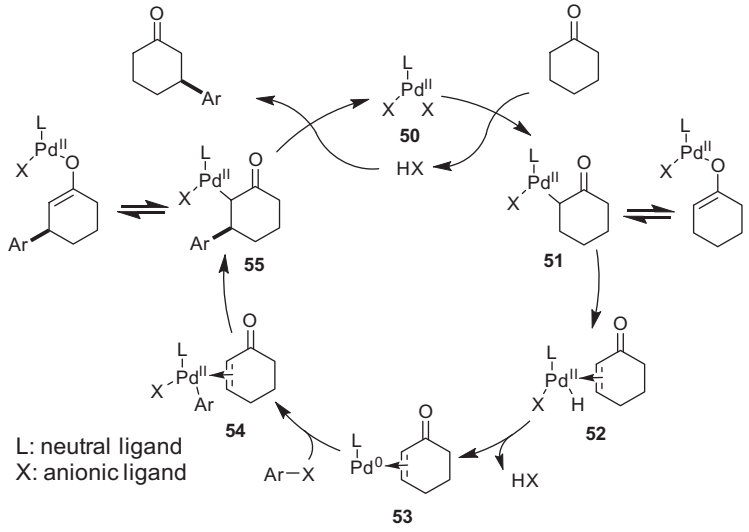
Palladium tandem catalysis

Aiming for a direct β-arylation of simple ketones using readily available aryl halides, the Dong group conceived a tandem catalysis strategy via merging the palladium-catalyzed dehydrogenation and Heck-type reactions. In the designed catalytic cycle (Scheme 45), the ketone substrate would first undergo a Pd(II)-mediated dehydrogenation to give an α,β-unsaturated enone and Pd(0) intermediate **53**. Subsequent oxidative addition of an aryl halide to the Pd(0) species was expected to provide the Pd(II)-aryl complex **54**, which would then undergo migratory insertion into the enone olefin. Protonation of the resulting β-aryl-Pd(II)-enolate **55** with acid would ultimately lead to the β-arylation product and release the Pd(II) catalyst.

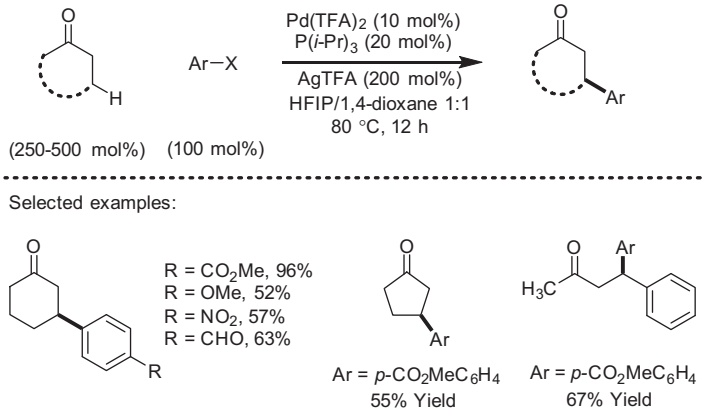
The β-arylation between simple ketones and aryl iodides proceeded smoothly with $Pd(TFA)_2/P(i\text{-}Pr)_3$ as the precatalyst and AgTFA as an additive (Scheme 46).[50] Complete selectivity for the β-position was obtained without forming any α-arylation product. Aryl iodides with various electronic properties can participate in the reaction, representing a distinct feature from the photoredox chemistry. In addition, substrates with base- and nucleophile-sensitive functional groups, which are difficult to handle under conjugate addition conditions, also work well with this Pd tandem catalysis. Aryl bromides can also react but give lower yields. Regarding the scope of ketones, both acyclic and cyclic ketones with different ring sizes were compatible with this β-arylation protocol.



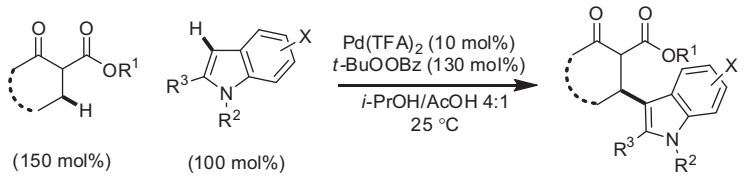
Scheme 43. β-alkylation of aldehydes with Michael acceptors via photoredox catalysis.



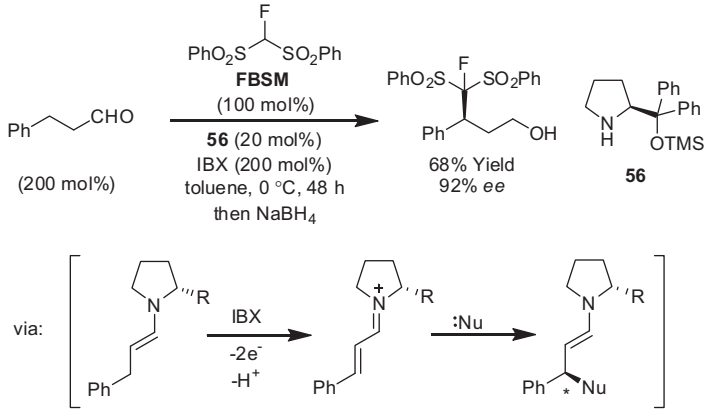
Scheme 45. Proposed strategy for the palladium-catalyzed direct β-arylation of ketones with aryl halides.



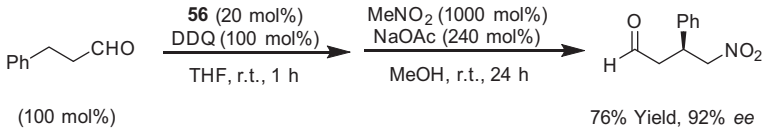
Scheme 46. Palladium-catalyzed direct β-arylation of ketones with aryl halides.



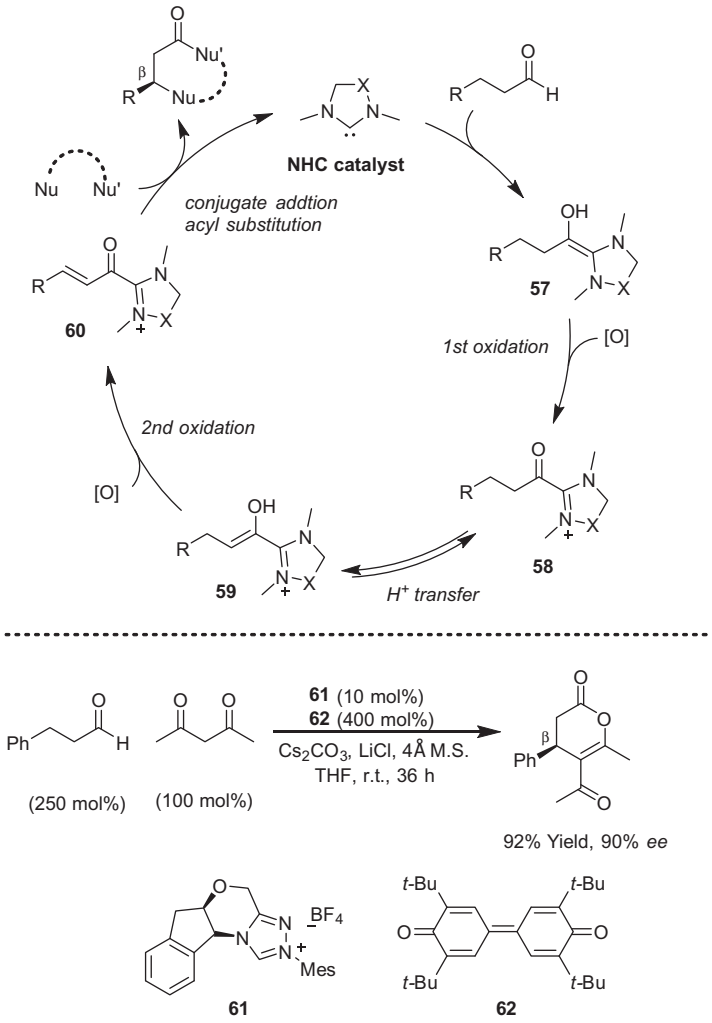
Scheme 47. Palladium-catalyzed β′-indolation of β-keto esters.



Scheme 48. β-C—C bond formation via oxidative enamine catalysis.

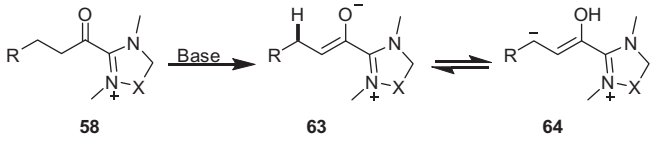


Scheme 49. Synthesis of β-substituted γ-nitro aldehydes via oxidative enamine catalysis.



Scheme 50. β-Functionalization/cyclization of aldehydes via oxidative NHC catalysis.

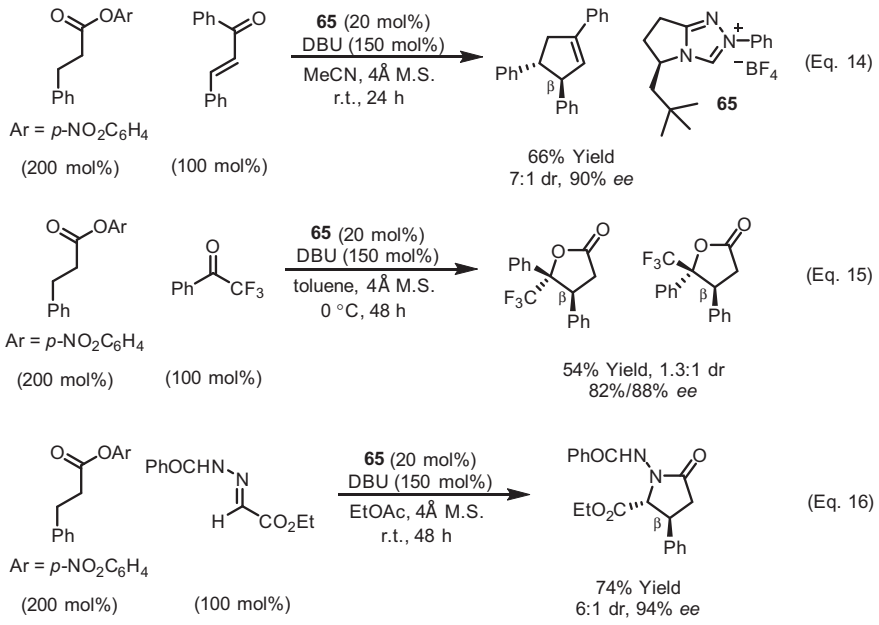
The direct β-arylation of 1,3-dicarbonyl compounds with electron-rich arenes is also viable through an α,β-unsaturated intermediate. In 2012, Pihko and co-workers reported a palladium-catalyzed oxidative β′-indolation of β-keto esters under mild conditions (Scheme 47).[51] The selective coupling between the C3 position of indoles and the β′-position of β-keto esters was achieved using $Pd(TFA)_2$ as a pre-catalyst and *t*-BuOOBz as a stoichiometric oxidant. The authors proposed the reaction proceeds through a palladium-catalyzed dehydrogenation of β-keto esters, followed by a nucleophilic conjugate addition of indoles.[52] Notably, both experimental and computational studies indicated that the indole also functions as a ligand to promote the palladium-catalyzed dehydrogenation of β-keto esters. Later, the same group expanded the scope of arenes to trialkoxybenzenes and phenols assisted by additional Brønsted acids.[53] Under the new conditions, molecular oxygen is used as the sole oxidant.



Scheme 51. Generation of a nucleophilic β-carbon with NHC.

Organocatalysis

The field of using organic molecules as catalysts has experienced explosive growth during the past decade, which has led to the discovery of a number of new transformations. For the functionalization of carbonyl compounds, amines[54] and *N*-heterocyclic carbenes (NHCs)[55] have been extensively applied as catalysts due to their facile reactions with carbonyl groups, highly modulable structures and capability to induce enantioselectivity. Recently,



Scheme 52. NHC-catalyzed β-functionalization reactions of aldehydes with electrophiles.

new modes of activation have been developed to allow β-functionalization directly from saturated carbonyl compounds based on amine or NHC catalysis.

In 2011, Wang and co-workers reported an oxidative enamine catalysis for the direct β-functionalization of aldehydes (Scheme 48).[56] They discovered that the enamine produced by the condensation of the aldehyde and the secondary amine catalyst was first oxidized by *o*-iodoxybenzoic acid (IBX) to give an α,β-unsaturated iminium ion; subsequently, the conjugate addition of carbon nucleophiles followed by hydrolysis afforded the β-substituted aldehydes. Using a chiral amine catalyst (**56**), a range of aldehydes coupled with fluorobis(phenylsulfonyl)methane (FBSM) selectively at the β-position with high enantioselectivity. Shortly after, Hayashi et al. published a cross-coupling of aldehydes and nitromethanes using a similar strategy.[57,58] With 2,3-dichloro-5,6-dicyanoquinone (DDQ) as the stoichiometric oxidant, a sequential enamine oxidation and conjugate addition, in which both steps are catalyzed by the same chiral amine (**56**), proceeds to give a range of β-substituted γ-nitro aldehydes in a one-pot fashion with high enantioselectivity (Scheme 49).

Recently, an oxidative NHC catalysis was developed by Chi and co-workers for the direct β-functionalization of aldehydes (Scheme 50).[59] They proposed the Breslow intermediate (**57**) can be oxidized first to an NHC-bound ester (**58**), which is a tautomer of enol **59**, and a second oxidation process leads to an α,β-unsaturated ester (**60**). The interception of such a Michael acceptor with a carbon nucleophile is expected to introduce a C—C bond at the β-position. Based on this concept, the authors demonstrated an enantioselective synthesis of enol δ-lactones via coupling between saturated aldehydes and 1,3-dicarbonyl nucleophiles. In this transformation, NHC **61** was used as the catalyst and quinone **62** was used as the oxidant.

Later, the same group found that treatment of intermediate **58** with a base (instead of an oxidant) would trigger an α- then β-C—H deprotonation sequence resulting in a nucleophilic β-carbon (Scheme 51).[60] The acidity of the β-C—H bonds in intermediate **63** might stem from the electron-withdrawing nature of the triazolium group, as well as the conjugated system. The reaction of intermediate **64** with chalcone derivatives afforded cyclopentene products through a cascade process involving Michael addition, aldol reaction, lactonization, and decarboxylation (Scheme 52, Eq. 14). Trifluoroketones and hydrazones can also serve as electrophiles to give corresponding lactones and lactams (Eqs. 15 and 16). With chiral NHC **65** as the catalyst, all these products were formed with high enantioselectivity.

Conclusion

During the past decade, the challenge of direct β-functionalization of carbonyl compounds has been a stimulus for new methodology development in organic synthesis. While the toolbox for the direct β-functionalization has been extended dramatically, general and practical methods with broader substrate scope and better functional group tolerance remain to be further developed. Considering the great potential of using direct β-functionalization to streamline complex molecule synthesis, we expect there will be continuing and vigorous development in this area.

Acknowledgement

We thank U.T. Austin and CPRIT for a start-up fund, and also thank the Welch Foundation (F-1781) and Frasch Foundation for research Grants. Dr. Michael Young is acknowledged for proofreading the Letter. G.D. thanks ORAU for a new faculty enhancement award. G.D. is a Searle Scholar.

References and notes

1. For representative examples, see: (a) Fujiwara, M.; Marumoto, S.; Yagi, N.; Miyazawa, M. *J. Nat. Prod.* **2011**, *74*, 86–89; (b) Mancha, S. R.; Regnery, C. M.; Dahlke, J. R.; Miller, K. A.; Blake, D. J. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 562–564; (c) Misawa, N.; Nakamura, R.; Kagiyama, Y.; Ikenaga, H.; Furukawa, K.; Shindo, K. *Tetrahedron* **2005**, *61*, 195–204.
2. Selected reviews on transition-metal-catalyzed conjugate addition: (a) Rossiter, B. E.; Swingle, N. M. *Chem. Rev.* **1992**, *92*, 771–806; (b) Gutnov, A. *Eur. J. Org. Chem.* **2008**, 4547–4554; (c) Hayashi, T.; Yamasaki, K. *Chem. Rev.* **2003**, *103*, 2829–2844.
3. (a) Buckle, D. R.; Pinto, I. L. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, U.K., 1991; Vol. 7, pp 119–149; (b) Larock, R. C. *Comprehensive Organic Transformations*; John Wiley & Sons: New York, 1999. pp 251–256.
4. Hartwig, J. F. *Organotransition Metal Chemistry: From Bonding to Catalysis*; University Science Books: Sausalito, 2010.

5. Zaitsev, V. G.; Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2005**, *127*, 13154–13155.
6. Reddy, B. V. S.; Reddy, L. R.; Corey, E. J. *Org. Lett.* **2006**, *8*, 3391–3394.
7. Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2010**, *132*, 3965–3972.
8. Tran, L. D.; Daugulis, O. *Angew. Chem. Int. Ed.* **2012**, *51*, 5188–5191.
9. Wang, B.; Nack, W. A.; He, G.; Zhang, S.-Y.; Chen, G. *Chem. Sci.* **2014**, *5*, 3952–3957.
10. Zhang, Q.; Chen, K.; Rao, W.; Zhang, Y.; Chen, F.-J.; Shi, B.-F. *Angew. Chem. Int. Ed.* **2013**, *52*, 13588–13592.
11. A selected example of palladium-catalyzed intramolecular α-arylation: Iwama, T.; Rawal, V. H. *Org. Lett.* **2006**, *8*, 5725–5728.
12. Feng, Y.; Wang, Y.; Landgraf, B.; Liu, S.; Chen, G. *Org. Lett.* **2010**, *12*, 3414–3417.
13. Wei, Y.; Tang, H.; Cong, X.; Rao, B.; Wu, C.; Zeng, X. *Org. Lett.* **2014**, *16*, 2248–2251.
14. Pan, F.; Shen, P.-X.; Zhang, L.-S.; Wang, X.; Shi, Z.-J. *Org. Lett.* **2013**, *15*, 4758–4761.
15. Shang, R.; Ilies, L.; Matsumoto, A.; Nakamura, E. *J. Am. Chem. Soc.* **2013**, *135*, 6030–6032.
16. Ye, X.; He, Z.; Ahmed, T.; Weise, K.; Akhmedov, N. G.; Petersen, J. L.; Shi, X. *Chem. Sci.* **2013**, *4*, 3712–3716.
17. Gu, Q.; Al Mamari, H. H.; Graczyk, K.; Diers, E.; Ackermann, L. *Angew. Chem. Int. Ed.* **2014**, *53*, 3868–3871.
18. Aihara, Y.; Chatani, N. *J. Am. Chem. Soc.* **2014**, *136*, 898–901.
19. Li, M.; Dong, J.; Huang, X.; Li, K.; Wu, Q.; Song, F.; You, J. *Chem. Commun.* **2014**, 3944–3946.
20. Zhang, S.-Y.; Li, Q.; He, G.; Nack, W. A.; Chen, G. *J. Am. Chem. Soc.* **2013**, *135*, 12135–12141.
21. Chen, K.; Hu, F.; Zhang, S.-Q.; Shi, B.-F. *Chem. Sci.* **2013**, *4*, 3906–3911.
22. Wu, X.; Zhao, Y.; Ge, H. *J. Am. Chem. Soc.* **2014**, *136*, 1789–1792.
23. Ano, Y.; Tobisu, M.; Chatani, N. *J. Am. Chem. Soc.* **2011**, *133*, 12984–12986.
24. Hasegawa, N.; Charra, V.; Inoue, S.; Fukumoto, Y.; Chatani, N. *J. Am. Chem. Soc.* **2011**, *133*, 8070–8073.
25. Feng, Y.; Chen, G. *Angew. Chem. Int. Ed.* **2010**, *49*, 958–961.
26. Gutekunst, W. R.; Baran, P. S. *J. Am. Chem. Soc.* **2011**, *133*, 19076–19079.
27. Gutekunst, W. R.; Gianatassio, R.; Baran, P. S. *Angew. Chem. Int. Ed.* **2012**, *51*, 7507–7510.
28. Ting, C. P.; Maimone, T. J. *Angew. Chem. Int. Ed.* **2014**, *53*, 3115–3119.
29. Engle, K. M.; Mei, T.-S.; Wasa, M.; Yu, J.-Q. *Acc. Chem. Res.* **2012**, *45*, 788–802.
30. Giri, R.; Maugel, N.; Li, J.-J.; Wang, D.-H.; Breazzano, S.-P.; Saunders, L.-B.; Yu, J.-Q. *J. Am. Chem. Soc.* **2007**, *129*, 3510–3511.
31. Wang, D.-H.; Wasa, M.; Giri, R.; Yu, J.-Q. *J. Am. Chem. Soc.* **2008**, *130*, 7190–7191.
32. Wasa, M.; Engle, K. M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 9886–9887.
33. Yoo, E. J.; Wasa, M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, *132*, 17378–17380.
34. Wasa, M.; Engle, K. M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, *132*, 3680–3681.
35. (a) Baudoin, O. *Chem. Soc. Rev.* **2011**, *40*, 4902–4911; (b) Wasa, M.; Engle, K. M.; Yu, J.-Q. *Isr. J. Chem.* **2010**, *50*, 605–616.
36. Wasa, M.; Chan, K. S. L.; Zhang, X.-G.; He, J.; Miura, M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2012**, *134*, 18570–18572.
37. He, J.; Wasa, M.; Chan, K. S. L.; Yu, J.-Q. *J. Am. Chem. Soc.* **2013**, *135*, 3387–3390.
38. He, J.; Li, S.; Deng, Y.; Fu, H.; Laforteza, B. N.; Spangler, J. E.; Homs, A.; Yu, J.-Q. *Science* **2014**, *343*, 1216–1220.
39. Wasa, M.; Engle, K. M.; Lin, D. W.; Yoo, E. J.; Yu, J.-Q. *J. Am. Chem. Soc.* **2011**, *133*, 19598–19601.
40. Xiao, K.-J.; Lin, D. W.; Miura, M.; Zhu, R.-Y.; Gong, W.; Wasa, M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2014**, *136*, 8138–8142.
41. Jørgensen, M.; Lee, S.; Liu, X.; Wolkowski, J. P.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 12557–12565.
42. Renaudat, A.; Jean-Gérard, L.; Jazzar, R.; Kefalidis, C. E.; Clot, E.; Baudoin, O. *Angew. Chem. Int. Ed.* **2010**, *49*, 7261–7265.
43. Larini, P.; Kefalidis, C. E.; Jazzar, R.; Renaudat, A.; Clot, E.; Baudoin, O. *Chem. Eur. J.* **2012**, *18*, 1932–1944.
44. Aspin, S.; Goutierre, A.-S.; Larini, P.; Jazzar, R.; Baudoin, O. *Angew. Chem. Int. Ed.* **2012**, *51*, 10808–10811.
45. Aspin, S.; López-Suárez, L.; Larini, P.; Goutierre, A.-S.; Jazzar, R.; Baudoin, O. *Org. Lett.* **2013**, *15*, 5056–5059.
46. Pirnot, M. T.; Rankic, D. A.; Martin, D. B. C.; MacMillan, D. W. C. *Science* **2013**, *339*, 1593–1596.
47. Petronijević, F. R.; Nappi, M.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2013**, *135*, 18323–18326.
48. Terrett, J. A.; Clift, M. D.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2014**, *136*, 6858–6861.
49. Okada, M.; Fukuyama, T.; Yamada, K.; Ryu, I.; Ravelli, D.; Fagnoni, M. *Chem. Sci.* **2014**, *5*, 2891–2898.
50. Huang, Z.; Dong, G. *J. Am. Chem. Soc.* **2013**, *135*, 17747–17750.
51. Leskinen, M. V.; Yip, K.-T.; Valkonen, A.; Pihko, P. M. *J. Am. Chem. Soc.* **2012**, *134*, 5750–5753.
52. Leskinen, M. V.; Madarász, Á.; Yip, K.-T.; Vuorinen, A.; Pápai, I.; Neuvonen, A. J.; Pihko, P. M. *J. Am. Chem. Soc.* **2014**, *136*, 6453–6462.
53. Yip, K.-T.; Nimje, R. Y.; Leskinen, M. V.; Pihko, P. M. *Chem. Eur. J.* **2012**, *18*, 12590–12594.
54. Mukherhee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471–5569.
55. Enders, D.; Niemeier, O.; Henseler, A. *Chem. Rev.* **2007**, *107*, 5606–5655.
56. Zhang, S.-L.; Xie, H.-X.; Zhu, J.; Li, H.; Zhang, X.-S.; Li, J.; Wang, W. *Nat. Commun.* **2011**, *2*, 211.
57. Hayashi, Y.; Itoh, T.; Ishikawa, H. *Angew. Chem. Int. Ed.* **2011**, *50*, 3920–3924.
58. Hayashi, Y.; Itoh, T.; Ishikawa, H. *Adv. Synth. Catal.* **2013**, *355*, 3661–3669.
59. Mo, J.; Shen, L.; Chi, Y. R. *Angew. Chem. Int. Ed.* **2013**, *52*, 8588–8591.
60. Fu, Z.; Xu, J.; Zhu, T.; Leong, W. W. Y.; Chi, Y. R. *Nat. Chem.* **2013**, *5*, 835–839.