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Perspective

Catalytic β-Functionalization of Carbonyl Compounds Enabled by α,β-Desaturation

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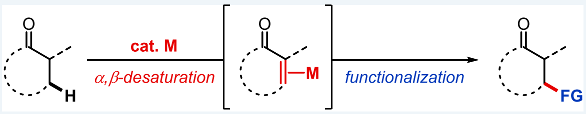
ABSTRACT: Capitalizing on versatile catalytic α,β-desaturation methods, strategies that directly functionalize carbonyl compounds at their less-reactive β-positions have emerged over the past decade. Depending on the reaction mechanism, general approaches include merging with conjugate addition, migratory coupling, and redox cascade. This perspective provides a summary of transition-metal-catalyzed α,β-desaturation methods and in-depth discussions of each β-functionalization strategy with their advantages, challenges, and future directions.



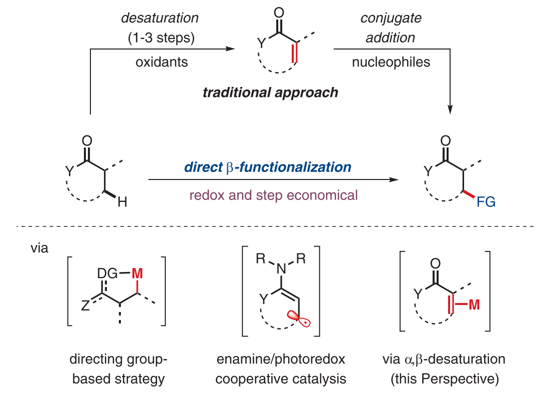
KEYWORDS: *β-functionalization, α,β-desaturation, carbonyl compound, conjugate addition, migratory coupling, redox cascade*

I. INTRODUCTION

Preparation and derivatization of carbonyl compounds are cornerstones in organic synthesis. To date, rich chemistry has been developed to functionalize the ipso and α-positions of carbonyl compounds via nucleophilic addition to carbonyl carbons and enolate couplings with electrophiles.[1] In contrast, direct functionalization at the β position has undoubtedly been a more challenging task, because the β-C−H bonds are significantly less acidic. To access β-functionalized carbonyl compounds, conventional methods mainly rely on conjugate addition of a nucleophile to an α,β-unsaturated carbonyl compound.[2] In many cases, the α,β-unsaturated carbonyl compounds must be synthesized in one or a few steps from the corresponding saturated ones via an oxidation process.[3] Hence, efficient approaches that directly introduce functional groups at β-positions of saturated carbonyl compounds would be attractive, from the redox- and step-economical viewpoints, to streamline complex molecule synthesis (see Scheme 1).[4]

Methods for direct and catalytic β-functionalization of carbonyl compounds have been extensively explored over the past two decades (see Scheme 1).[5] First, directing group-based strategies have been popular, and they typically operate by forming a five-membered metallocycle through C−H activation at the β position.[6] In addition, enamine/photoredox cooperative catalysis provides a creative way to achieve β-functionalization, normally via selective homolytic C−H cleavage to generate a radical species at the β-position.[7] While effective and broadly useful, there are intrinsic requirements associated with these methods, such as the capability of substrates to form five-membered metallocycles or to form enamines. As a complementary approach, the transition-metal-catalyzed desaturation reactions allow for directly forming a reactive center at the β-position of carbonyl compounds,[8] which provides a new platform for β-functionalization, given the versatile reactivity of α,β-unsaturated carbonyls. This Perspective offers a brief overview of transition-metal-catalyzed α,β-desaturation processes and detailed discussion of β-functionalization methods enabled by these processes. In particular, it aims to highlight merits, pitfalls, and potentials of each strategy.

Scheme 1. Direct β-Functionalization of Carbonyl Compounds



II. GENERAL CONSIDERATIONS

To date, numerous strategies have been developed for α,β-desaturation of carbonyl compounds.[3,8] Conventionally, this

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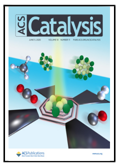

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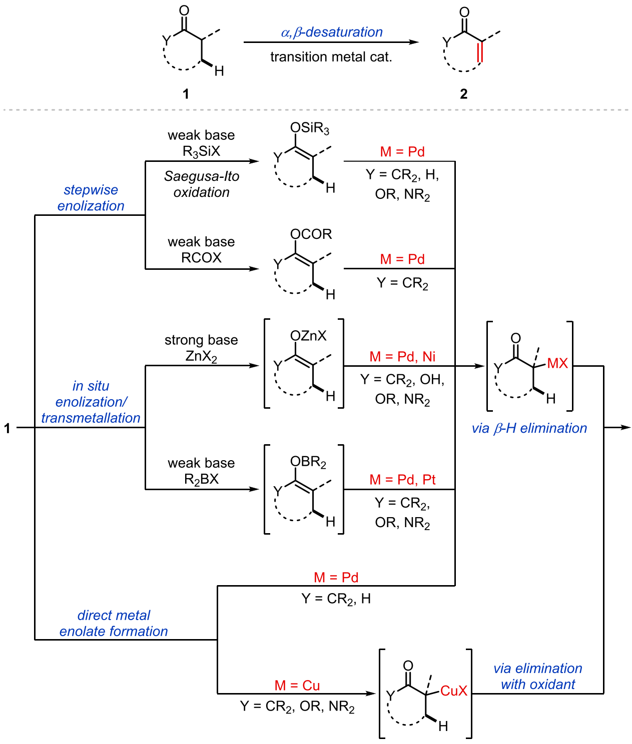
transformation was often achieved through multiple steps by introducing heteroatoms, such as halides,[9] sulfur,[10] and selenium,[11] to the α-position of carbonyl compounds, followed by an elimination process. Direct oxidation methods using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)[12] or 2-iodoxybenzoic acid (IBX)[13] have also been found broadly useful.[14]

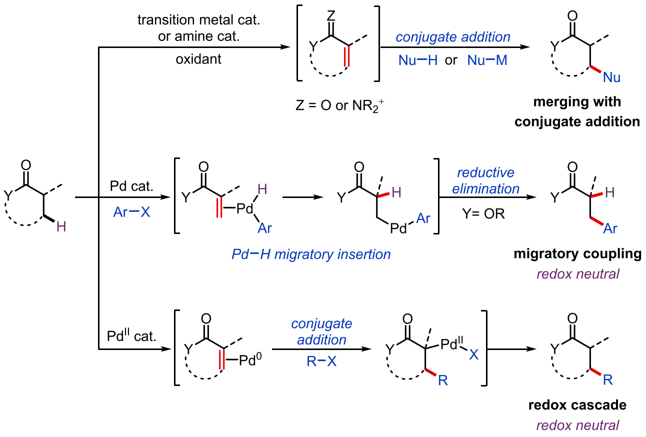
On the other hand, α,β-desaturation strategies based on transition-metal catalysis have been explored since the 1970s,[15] which uses milder oxidants and less-toxic reagents. Generally, almost all transition-metal-catalyzed α,β-desaturation reactions start with the formation of the corresponding metal enolate; thus, according to how enolates are generated, these reactions can be classified into three categories (see Scheme 2). The first category involves stepwise enolization, in which a separate step is used to generate an isolatable enolate precursor. For example, the palladium-catalyzed oxidation of silyl enol ethers, known as Saegusa–Ito oxidation, is a well-established approach and has been widely employed in total synthesis of natural products.[16] Other enolate precursors, such as enol allyl carbonates or enol acetates, could also undergo desaturation via palladium catalysis.[17] The second category involves in situ enolization, followed by transmetalation, which saves one step of operation and sometimes gives a broader substrate scope. Hard enolization via complete deprotonation by a strong base, followed by the formation of a zinc enolate, renders efficient α,β-desaturation of ketones, amides, esters, carboxylic acids, and nitriles, using palladium or nickel catalysts.[18,19] Soft enolization using boron Lewis acids and weak bases has been determined to be effective for the desaturation of ketones, lactams, imides, lactones, and esters catalyzed by palladium or platinum.[20,21] The third category involves direct formation of the reactive metal enolate. Palladium enolates could be directly generated from saturated ketones and aldehydes via α-palladation, which leads to a series of practical desaturation methods, including those using air as the terminal oxidant.[22,23] Copper was recently found to be capable of catalyzing α,β-desaturation of diverse carbonyl compounds through a distinct radical-mediated pathway, with either TEMPO[24] or peroxides[25] as the oxidant.[26]

Scheme 2. Transition-Metal-Catalyzed α,β-Desaturation of Carbonyl Compounds



The versatility of the α,β-desaturation tactics provides rich inspiration and foundation for developing direct β-functionalization of carbonyl compounds through the merger of α,β-desaturation with various coupling approaches. The following content is divided into three sections, and each section is focused on a unique strategy about how functional groups are introduced at the carbonyl β-position (see Scheme 3).

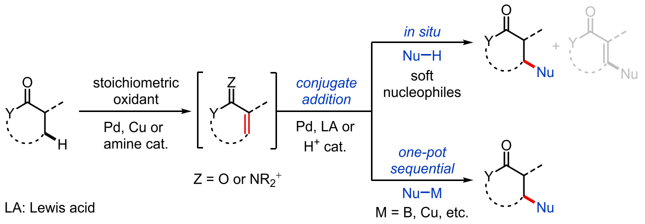
Scheme 3. Three Strategies for Desaturation-Enabled β-Functionalization of Carbonyl Compounds



III. MERGING WITH CONJUGATE ADDITION

Perhaps the most straightforward strategy to access β-functionalized carbonyl compounds is to directly combine α,β-desaturation with conjugate addition of a nucleophile (see Scheme 4). Compared with the conventional stepwise approaches, merging these two processes can save at least one step. The conjugate addition could be coupled with desaturation through either an in situ transformation or a one-pot sequential manner. Generally, if the nucleophiles used are compatible with the desaturation processes, in situ conjugate addition would be feasible and more desirable. One potential pitfall of this approach is that the resulting products could undergo desaturation again, leading to overoxidation. If nucleophiles used are incompatible with the desaturation processes, a sequential desaturation/conjugate addition must be adopted, which, however, typically avoids the overoxidation problem. This section summarizes reactions of these two types,

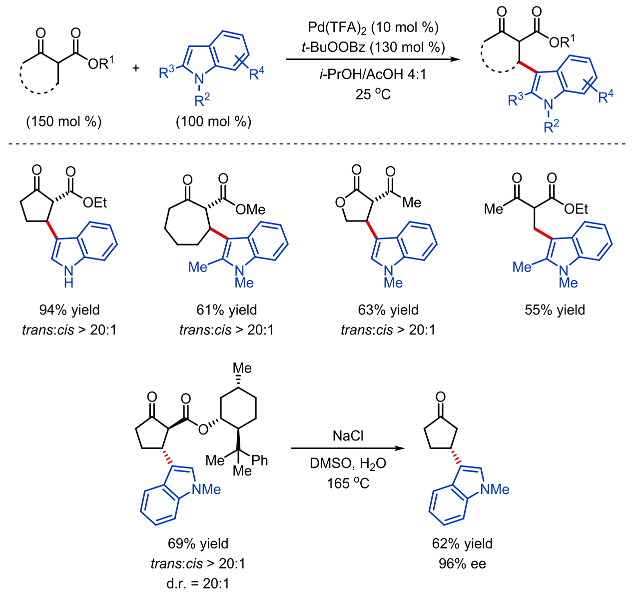
Scheme 4. Merging α,β-Desaturation with Conjugate Addition



and methods that preferentially give overoxidation products, such as β-functionalized conjugated enones, are not included.[27,28]

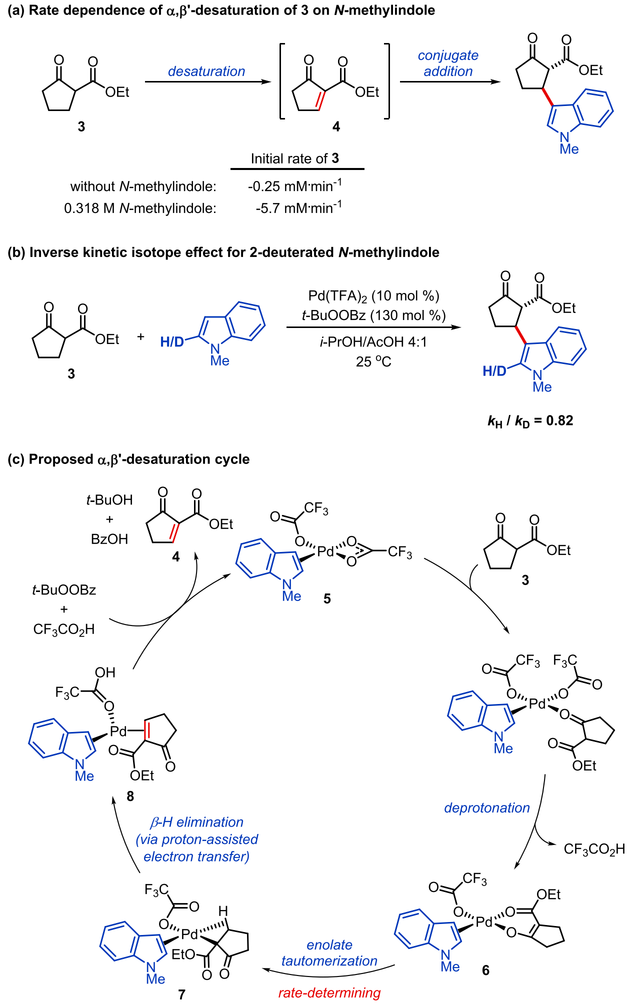
The first Pd-catalyzed β-functionalization of carbonyl compounds using an in situ addition strategy was developed by Pihko and co-workers. In 2012, they reported a Pd-catalyzed β'-arylation of β-keto esters using indoles as nucleophiles (see Scheme 5).[29] The higher acidity of the α-proton in 1,3-dicarbonyl compounds allows facile formation of palladium enolates; thus, this reaction occurred in the absence of bases. *t*-BuOOBz was found to be the optimal oxidant. Both cyclic and linear β-keto esters are viable substrates, and the products predominantly possess *trans* configuration. It is impressive that free indole can be directly used as a *C*-nucleophile. An 8-phenylmenthyl-derived β-keto ester was also determined to be an effective chiral auxiliary, and high enantiomeric excess was achieved after decarboxylation of the arylated product.[30]

Scheme 5. β'-Arylation of β-Keto Esters Using Indoles



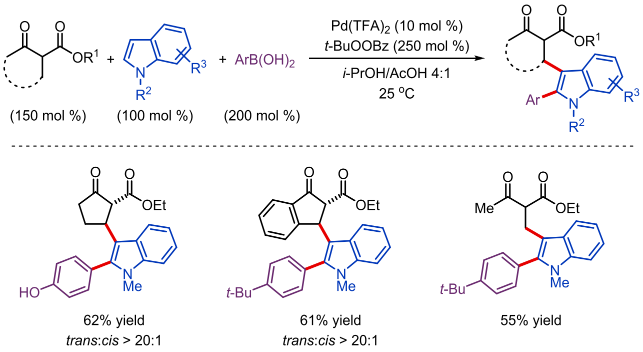
In order to gain deeper understanding of the reaction mechanism, mechanistic studies were performed using β-keto ester **3** and *N*-methylindole as the model substrates (see Scheme 6). First, kinetic studies supported intermediacy of the α,β'-unsaturated β-keto ester **4**. During the initial stage, the concentration of **4** built up and then decayed, and a sigmoidal curve was found for product formation, indicating that α,β'-desaturation and indole conjugate addition could be separate processes. Interestingly, the rate of α,β'-desaturation was highly dependent on the concentration of *N*-methylindole, as *N*-methylindole accelerated the desaturation process (see Scheme 6a).[29] Furthermore, an inverse kinetic isotope effect was detected for the C2-deuterated *N*-methylindole (see Scheme 6b). Combining the results from their computational studies, the authors proposed an indole-assisted desaturation mechanism, in which indole serves as an electron-rich ligand (via 2,3-π-bond) and accelerates the desaturation process (see Scheme 6c).[30] Starting from *N*-methylindole-coordinated $Pd(TFA)_2$ (**5**), substrate coordination and deprotonation delivers an *O*-bound Pd-enolate **6**. Likely due to the stronger bidentate coordination of enolate **6**, the subsequent enolate tautomerization to *C*-bound Pd-enolate **7** was calculated to be the rate-determining step. The β-hydrogen elimination was proposed to occur through proton-assisted electron transfer, which generates a Pd(0) complex **8** that could then be oxidized by *t*-BuOOBz to regenerate complex **5** and release α,β'-unsaturated β-keto ester **4**. During the rate-determining step, tautomerization of the Pd-enolate leads to reduction of electron density at the Pd center in the transition state, which is alleviated by the tightly coordinated electron-rich indole ligand. This also results in a partial C(sp^2) to C(sp^3) rehybridization at the C2 position of the indole, which is consistent with the inverse kinetic isotope effect. After the α,β'-desaturation process, the accumulated α,β'-unsaturated β-keto ester was proposed to undergo a Pd-catalyzed conjugate addition of indole to form the product. Although it was found that acids alone could also catalyze the conjugate addition, a faster reaction rate was detected using the Pd catalyst.

Scheme 6. Indole-Assisted α,β'-Desaturation of β-Keto Esters



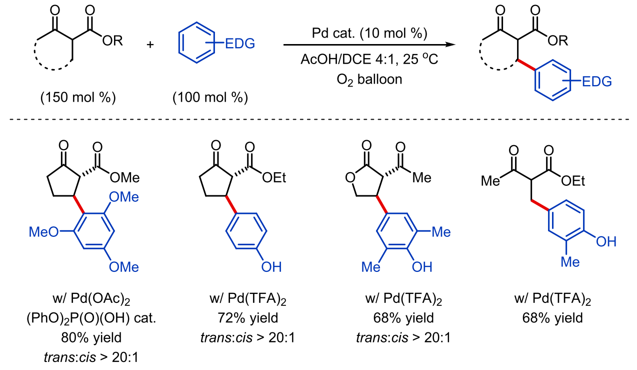
As an interesting extension of this transformation, the same group reported a three-component coupling reaction with β-keto esters, indoles, and arylboronic acids (see Scheme 7).[31] Kinetic studies showed that indoles first underwent fast coupling with arylboronic acids, which accumulated C2-arylated indoles during the initial stage. In addition, β'-arylation of β-keto esters with arylboronic acids was determined to be slower than their reactions with indoles or

Scheme 7. Three-Component Coupling of β-Keto Esters, Indoles, and Arylboronic Acids



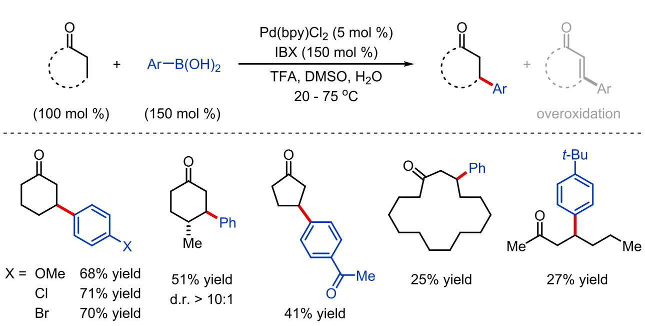
C2-arylated indoles, which became the key for the high chemoselectivity in this three-component coupling reaction. Pihko and co-workers further explored the β′-arylation of β-keto esters, using other electron-rich arenes as the nucleophiles, such as 1,3,5-trimethoxybenzene and phenols (see Scheme 8).[32] In this case, oxygen gas was employed as the terminal oxidant. The addition of electron-rich arenes was also found to accelerate the α,β′-desaturation process, which is consistent with the prior observation in the indole-mediated reactions.[29,30]

Scheme 8. β′-Arylation of β-Keto Esters Using Electron-Rich Arenes



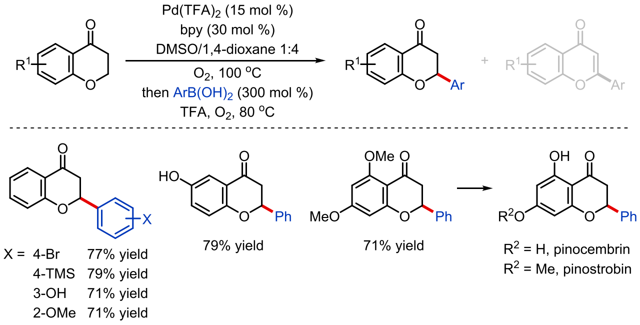
Besides electron-rich arenes, arylboronic acids were later found to be compatible nucleophiles for β-functionalization. In 2017, Li and co-workers reported a Pd-catalyzed β-arylation of simple ketones using IBX as the oxidant (see Scheme 9).[33] Control experiments showed that the ketone desaturation was solely mediated by IBX, while the Pd complex only catalyzed the conjugate addition of arylboronic acids to the enone intermediates. Generation of the overoxidation side products, i.e., arylated enones, was minimized by adding trifluoroacetic acid as the proton source, which promoted protonation of the β-arylated Pd-enolate, thus minimizing the competing β-hydrogen elimination. Cyclohexanones worked the best in this reaction, and a wide range of functional groups on the aryl ring were tolerated. Other cyclic and linear ketones were also viable substrates, albeit in diminished yields.

Scheme 9. Pd-Catalyzed β-Arylation of Ketones Using Arylboronic Acids



In 2019, Kim and co-workers reported the synthesis of flavanones from the Pd-catalyzed β-arylation of chromanones with arylboronic acids (see Scheme 10).[34] While both α,β-desaturation and conjugate addition steps were catalyzed by Pd, addition of arylboronic acids in a sequential fashion after completion of the α,β-desaturation process was crucial for better yields and minimal overoxidation (generating flavone). Trifluoroacetic acid was also found beneficial for suppressing overoxidation. Some sensitive functional groups were tolerated, including aryl bromides, silanes, and free phenols. Natural flavanones such as pinocembrin and pinostrobin were obtained after deprotection of the β-arylated products.

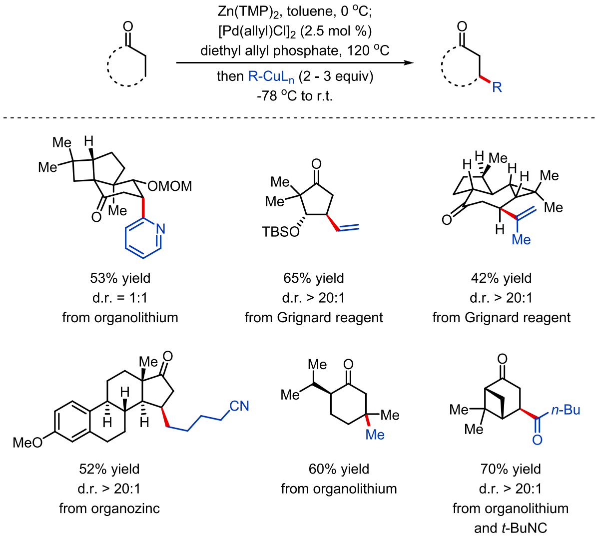
Scheme 10. Pd-Catalyzed β-Arylation of Chromanones Using Arylboronic Acids



In addition to using soft nucleophiles, Newhouse and co-workers in 2017 disclosed a general and practical β-functionalization method that allows for a broadened scope of nucleophiles to be coupled (see Scheme 11).[35] The new protocol was capitalized on the allyl-Pd-catalyzed ketone desaturation, followed by the addition of organocuprate reagents, which enabled β-arylation, alkenylation, alkylation, and acylation of ketones. Benefitting from the robustness of their α,β-desaturation methods,[18] various cyclic ketones with complex fused- and bridged-ring structures were successfully coupled, and decent diastereoselectivity was observed in most cases. It is noteworthy that α,β-vicinal difunctionalization of ketones could also be achieved when electrophiles other than proton were used to quench the enolate generated after the organocuprate conjugate addition.

Besides palladium,[36] copper catalysis has also been found effective to merge conjugate addition and α,β-desaturation of ketones. In 2016, Su and co-workers developed an efficient Cu/TEMPO system that allows for direct β-functionalization of linear ketones by merging α,β-desaturation with the addition of soft nucleophiles (see Scheme 12a).[24a] In this reaction, copper catalyzed both the ketone desaturation and the conjugate addition steps. One merit of this catalytic system is that overoxidation side products were only observed in a trace amount. A wide range of nucleophiles, including amines,

Scheme 11. Telescoped Ketone Desaturation and Conjugate Addition with Organocuprates



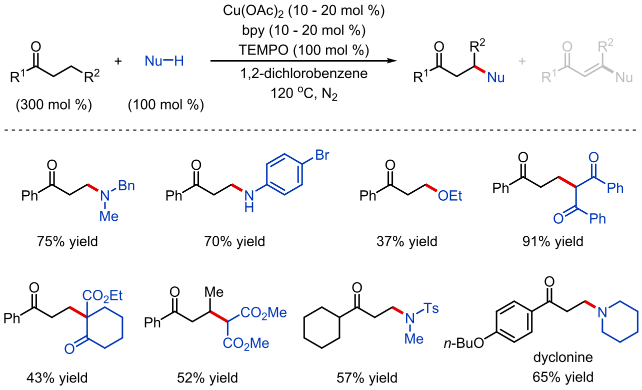
amides, alcohols, and 1,3-dicarbonyl compounds, could be employed. Beyond propiophenone, other linear ketones with β-substituents and dialkyl ketones were also viable substrates.

Given that the Cu-catalyzed α,β-desaturation of ketones using TEMPO as the oxidant was unprecedented, the authors performed detailed mechanistic studies to understand the reaction mechanism.[37] 3-Phenylpropiophenone was found to be a superior substrate that undergoes α,β-desaturation under the standard conditions (without a nucleophile) in an excellent yield, giving 2,2,6,6-tetramethylpiperidine as a byproduct (see Scheme 12b). In addition, the involvement of ketone α-radical species was supported by a radical clock experiment, and its combination with TEMPO could generate a TEMPO-bound ketone (**9**) that was found to be a reaction intermediate. Consequently, a novel catalytic cycle was proposed (see Scheme 12c). The reaction starts with forming Cu(II)-enolate **10** from the Cu(II) salt and ketone, which is likely the rate-determining step, because of the first-order kinetic dependence on both the ketone substrate and the copper catalyst but zero order on TEMPO. In addition, a significant primary kinetic isotope effect was observed for the α-deuterated ketone, but not for the β-deuterated one. The subsequent step involves homolytic cleavage of the C−Cu bond to deliver the Cu(I) salt and an α-radical species **11**, which further recombines with TEMPO to deliver intermediate **9**. It was proposed that the following β-elimination step is assisted by another molecule of TEMPO, which delivers enone and TEMPOH that can further oxidize Cu(I) to Cu(II).

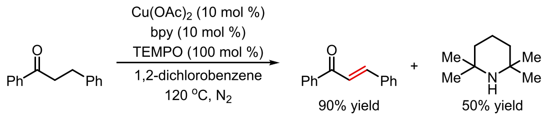
In the same year, Guo, Fang, and co-workers reported a similar Cu/TEMPO system that catalyzed α,β-desaturation of propiophenones, followed by conjugate addition of indoles (see Scheme 13a).[38] Later, Su and Goossen developed a β-arylation and alkenylation of ketones through Cu/Rh cooperative catalysis (see Scheme 13b).[39] While the Cu/TEMPO system was still responsible for the α,β-desaturation, the aryl nucleophile in the conjugate addition step was generated via a Rh-catalyzed carboxyl-directed C(sp^2)−H activation. Notably, while the C(sp^2)−H activation process can also be catalyzed by palladium or other rhodium complexes instead of [Rh(cod)Cl]$_2$, these catalyst systems predominantly

Scheme 12. Cu-Catalyzed α,β-Desaturation and β-Functionalization of Ketones Using TEMPO Oxidant

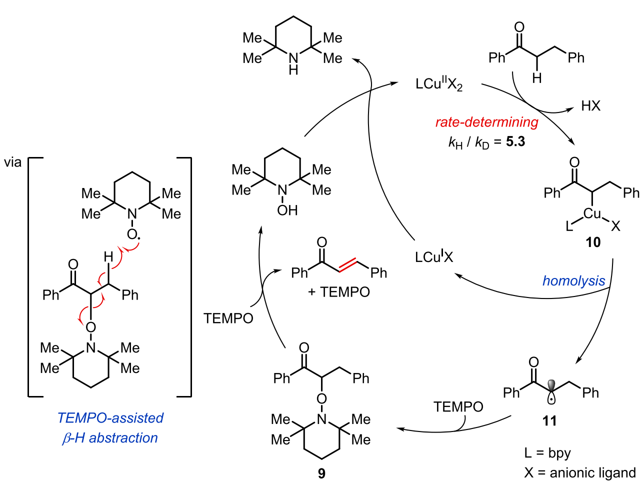
(a) Cu-catalyzed β-functionalization of ketones



(b) Direct Cu-catalyzed desaturation of 3-phenylpropiophenone with TEMPO oxidant

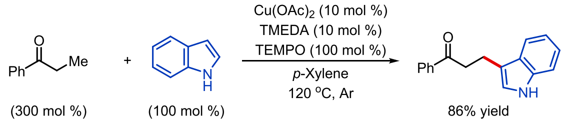


(c) Proposed catalytic cycle for Cu-catalyzed desaturation of ketones

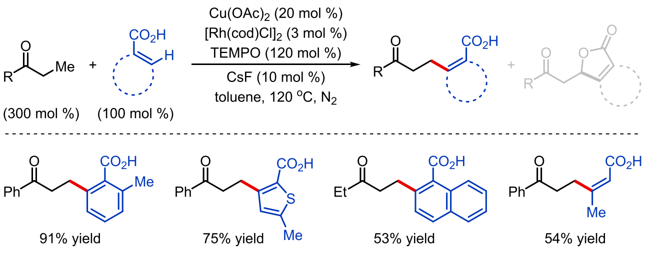


Scheme 13. Cu-Catalyzed β-Arylation and Alkenylation of Ketones

(a) Cu-catalyzed β-arylation of ketones with indoles



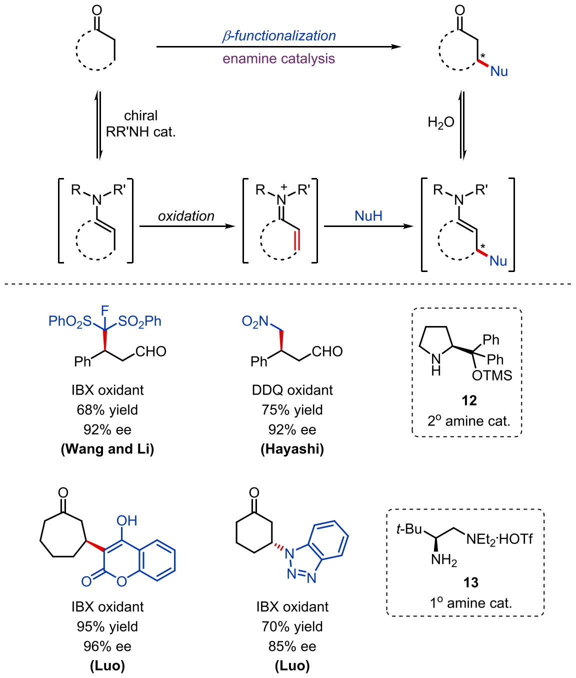
(b) Cu/Rh-cocatalyzed β-arylation or alkenylation of ketones with carboxylic acids



gave an interesting oxa-Michael addition product due to overoxidation of the ketone.

Besides transition metals, amines can also be efficient catalysts for direct *β*-functionalization of aldehydes and ketones with soft nucleophiles. Through condensation of amines with aldehydes and ketones, the electron-rich enamine intermediates can undergo subsequent oxidation to realize *α*,*β*-desaturation.[13c,23] Moreover, the resulting iminium ion is also an activated electrophile, which could directly react with various soft nucleophiles to enable *β*-functionalization, and the enantioselectivity could be controlled by using chiral amine catalysts (see Scheme 14). Based on this idea, several innovative methods on asymmetric *β*-alkylation of aldehydes were developed by Wang and Li,[40] and Hayashi[41] using an *L*-proline-derived chiral amine catalyst (**12**). Later, Luo and co-workers employed a powerful chiral primary amine catalyst (**13**) to achieve asymmetric *β*-C−C and C−N forming reactions of ketone substrates.[42] Among these works, IBX was used as the oxidant in Wang/Li and Luo's works and DDQ was employed as the oxidant in Hayashi's study. Notably, Xu and co-workers reported a dual catalytic system with both palladium and chiral amine **12**, which features the use of O_2 as the terminal oxidant (see Scheme 15).[43] Dialkyl malonates were used as effective nucleophiles, and various *β*-arylpropionaldehydes were alkylated in excellent enantioselectivity.

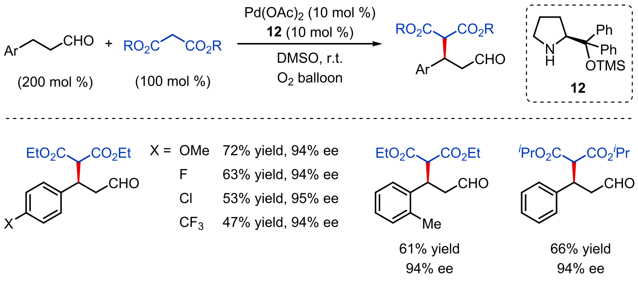
Scheme 14. Enamine Catalysis for Asymmetric *β*-Functionalization of Aldehydes and Ketones



IV. MIGRATORY COUPLING

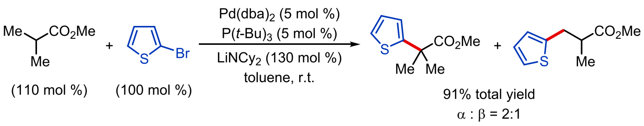
The migratory coupling strategy renders a redox-neutral coupling between aryl halides and linear esters at their *β*-positions. Interestingly, such reactivity arose from an accidental discovery. In 2002, during the study of the Pd-catalyzed *α*-arylation of esters using aryl bromides, Hartwig and co-workers observed the formation of a *β*-arylated ester as a side product in one example (see Scheme 16a).[44] When methyl isobutyrate reacted with 2-bromothiophene, the *α*- and *β*-arylation products were obtained in a 2:1 ratio. The authors reasoned that the unforeseen *β*-arylation product was formed through isomerization of the hindered Pd enolate to the less-hindered homoenolate via a sequence of *β*-hydrogen elimination, reinsertion, and reductive elimination.

Scheme 15. Pd/Enamine Dual Catalysis for Asymmetric *β*-Functionalization of Aldehydes

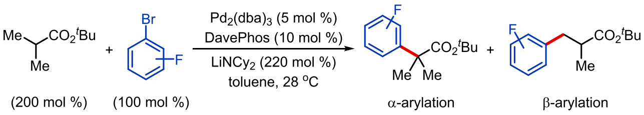


Scheme 16. Pd-Catalyzed *β*-Arylation of Esters via Migratory Coupling

(a) Initial discovery of Pd-Catalyzed β-arylation of esters

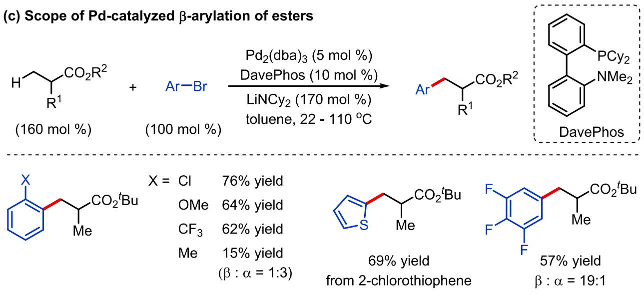


(b) Substrate dependence for Pd-catalyzed β-arylation of esters

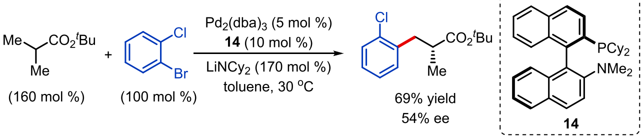


	α / β	total yield
4-F-C_6H_4Br	47:53	91%
3-F-C_6H_4Br	47:53	95%
2-F-C_6H_4Br (50 °C)	<2:98	63%

(c) Scope of Pd-catalyzed β-arylation of esters



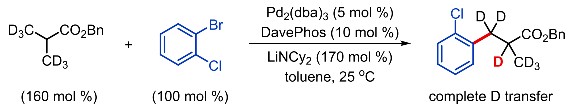
(d) Enantioselective β-arylation of esters



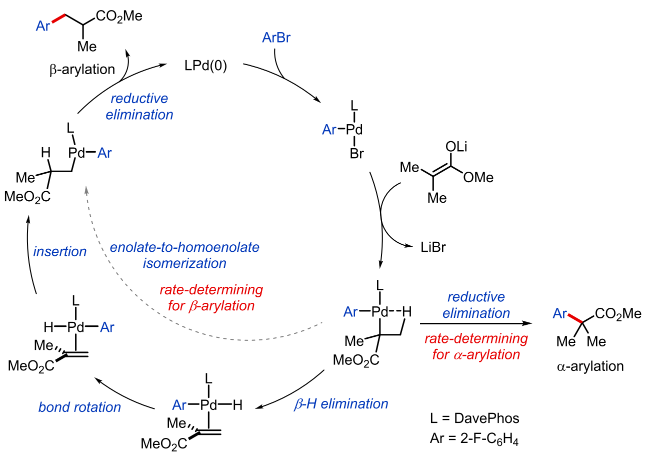
Later, this new pathway toward *β*-functionalization was systematically studied and ultimately promoted to a practical level by Baudoin, Clot, and co-workers. In 2010, they developed a selective *β*-arylation of esters through careful optimization of the catalytic conditions.[45] Both the ligand and the structure of the aryl halide were found to have profound influence on the *β*/*α* selectivity, as DavePhos was superior for *β*-selectivity, and among the three fluorinated phenyl bromides, only the *ortho*-substituted one led to exclusive *β*-arylation (Scheme 16b). This structural dependence was further supported during the following substrate scope study (Scheme 16c).[46] Satisfactory β-selectivity was mostly obtained with aryl bromides containing an electronegative group at the *ortho* position. While the *ortho*-methyl substituent gave poor reactivity and selectivity, 3,4,5-trifluorophenyl bromide still offered high β-selectivity. Moderate enantioselectivity was achieved using chiral ligand **14**, which is structurally similar to DavePhos (Scheme 16d). The deuterium labeling experiment showed that, when the ester with fully deuterated β-positions was subjected to the reaction conditions, complete deuterium transfer to the α-position of the product was detected (see Scheme 17a).

Scheme 17. Mechanism of the β-Arylation of Esters via Migratory Coupling

(a) Deuterium transfer experiment



(b) Proposed catalytic cycle

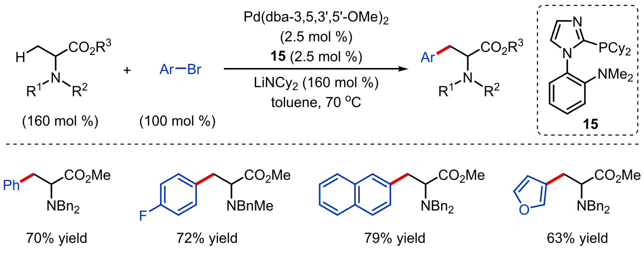


To gain deeper understanding of the reaction mechanism and how the selectivity was affected by different factors, the same team further performed DFT studies.[45,46] Consistent with the deuterium-labeling and computational results, the proposed catalytic cycle starts with oxidative addition of Pd(0) with the aryl bromide, followed by transmetalation to give an aryl Pd-enolate (Scheme 17b). The direct reductive elimination of the aryl and enolate groups would lead to α-arylation; however, if a competing β-hydrogen elimination occurs, after olefin π-bond rotation and reinsertion into the Pd–H bond, a Pd-homoenolate species would be generated, which delivers the β-arylated product upon reductive elimination. The possible olefin dissociation was calculated to possess a higher activation barrier than olefin rotation, which represented a nondissociative mechanism,[47] and was in agreement with the experimental observation that the α,β-unsaturated ester was seldom found as a side product. Alternatively, olefin insertion into the Pd–Ar bond could be another potential pathway, but was found kinetically less favorable than Pd–H migration. The rate-determining step was the Pd-enolate-to-homoenolate isomerization process. Compared with the β-arylation, the competing α-arylation pathway was both kinetically and thermodynamically unfavorable using α-disubstituted esters and DavePhos, with reductive elimination being the rate-determining step. Therefore, any factors that strengthens the Pd–Ar bond (e.g., a more-electron-deficient aryl group) would disfavor the α-arylation pathway by increasing the energy barrier for the reductive elimination from the Pd-enolate, but the β-arylation pathway is less affected by the strength of the Pd–Ar bond. Finally, the higher reactivity of the DavePhos ligand could be attributed to its proper steric bulkiness and the stabilizing interaction between its biaryl backbone and palladium, which rendered easier generation of an active vacant site during transfer of the enolate ligand, as well as a lower overall energy barrier for the β-arylation pathway.

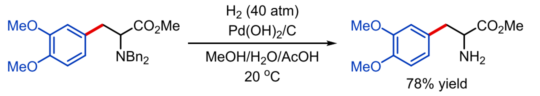
Notably, the β/α selectivity was not always affected by the electronic property of the aryl halides. Baudoin and co-workers later discovered that α-aminoesters were superior substrates for the highly β-selective arylation reaction (see Scheme 18a).[48] In this case, the β-selectivity was not sensitive to the structure and electronic properties of the aryl group, as a wide range of aryl bromides could be coupled, including electron-rich ones. The benzyl protecting group on the amine can be removed under hydrogenation conditions (see Scheme 18b), giving free β-arylated α-aminoesters that are widely found in natural products and drug molecules. It is noteworthy that, attributed to the nondissociative mechanism, a long-range (γ to ζ) arylation of α-aminoesters was also reported using substrates bearing longer chains. The arylation preferentially occurred at the terminal carbon after multiple Pd migrations, although the yield usually decreased after each migration.

Scheme 18. Pd-Catalyzed β-Arylation of α-Aminoesters

(a) Pd-catalyzed β-arylation of α-aminoesters



(b) Deprotection of the benzylamine

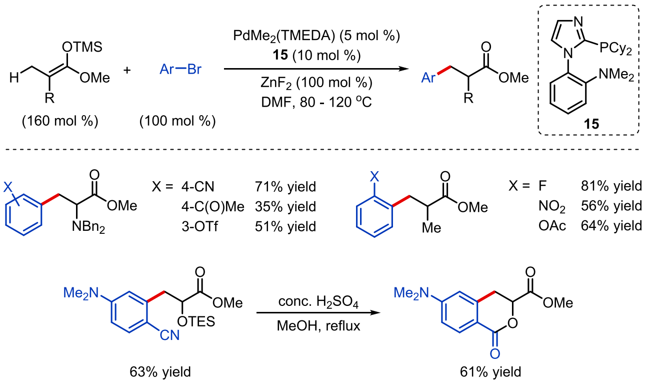


The same team further managed to expand the functional group tolerance by avoiding strong bases. To tackle this issue, they employed silyl ketene acetals as the substrate, which renders Pd-enolate formation simply using zinc fluoride as the activator (see Scheme 19).[49] Indeed, more sensitive substituents on the aryl ring were tolerated, including cyano, nitro, and acetoxy groups, as well as methyl ketones and aryl triflates. This protocol is applicable not only to α-amino and α-methyl esters, but also to α-siloxy esters, which further enables the synthesis of benzo-fused δ-lactones through coupling a 2-cyanoaryl group.

V. REDOX CASCADE

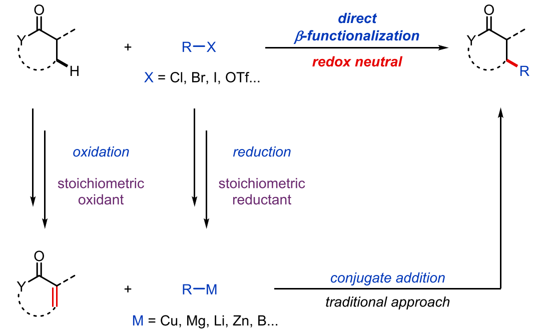
In many C–C forming conjugate addition reactions, the organometallic nucleophiles employed, such as organoboron reagents and organocuprate reagents, are typically generated via reduction of the corresponding organohalides in one or two

Scheme 19. Pd-Catalyzed β-Arylation of Silyl Ketene Acetals



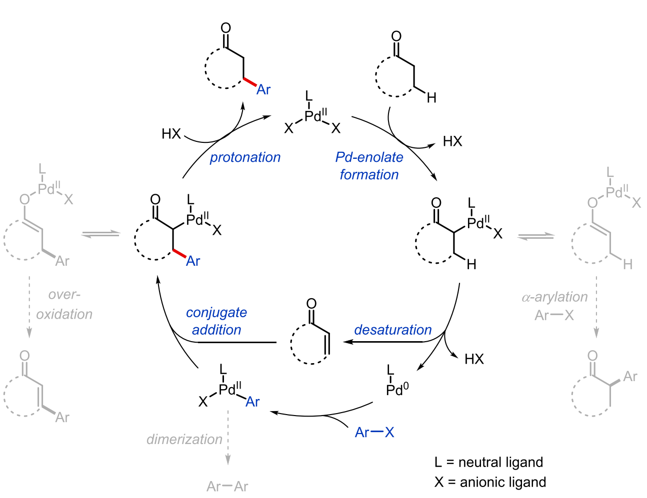
steps. Given that α,β-desaturation is an oxidation process, it would be attractive to merge the generation of organometallic nucleophiles and α,β-desaturation through a catalytic redox cascade (see Scheme 20). Consequently, the direct coupling of saturated carbonyl compounds with organohalides would provide a redox-neutral approach for the desaturation-promoted β-functionalization.

Scheme 20. Redox-Neutral Direct β-Functionalization of Carbonyl Compounds



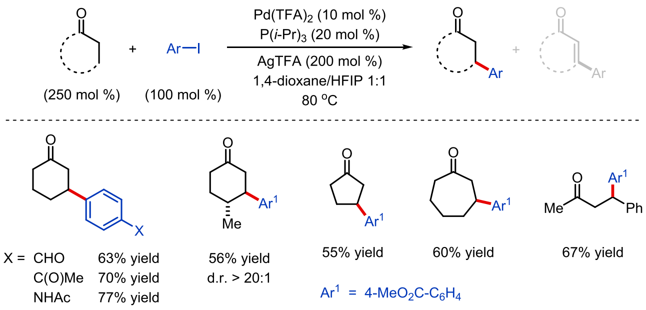
Based on this hypothesis, in 2013, Huang and Dong proposed a Pd-catalyzed redox cascade strategy for the direct β-arylation of ketones with aryl halides (see Scheme 21).[50] It starts with a Pd-mediated ketone desaturation involving formation of the Pd-enolate, β-hydrogen elimination, and Pd(0) formation. The subsequent oxidative addition with aryl halides, followed by conjugate addition (or migratory insertion) of the resulting aryl-Pd species to the enone intermediate, introduces the β-aryl substituent. Finally, protonation of the new Pd-enolate delivers the product and regenerates the Pd(II) catalyst. In this catalytic cycle, the aryl halide serves not only as the carbon source for the C—C bond forming event, but also as the oxidant for the α,β-desaturation; thus, the overall transformation is redox-neutral. Since several side reactions are possible, such as overoxidation, α-arylation, and aryl dimerization, it is crucial to balance the reaction rates of all the steps involved.

Scheme 21. Pd-Catalyzed Redox Cascade Strategy for β-Arylation of Ketones



The Pd-catalyzed β-arylation of simple ketones with aryl iodides was found to be general (see Scheme 22).[50,51]

Scheme 22. β-Arylation of Ketones via the Pd-Catalyzed Redox Cascade

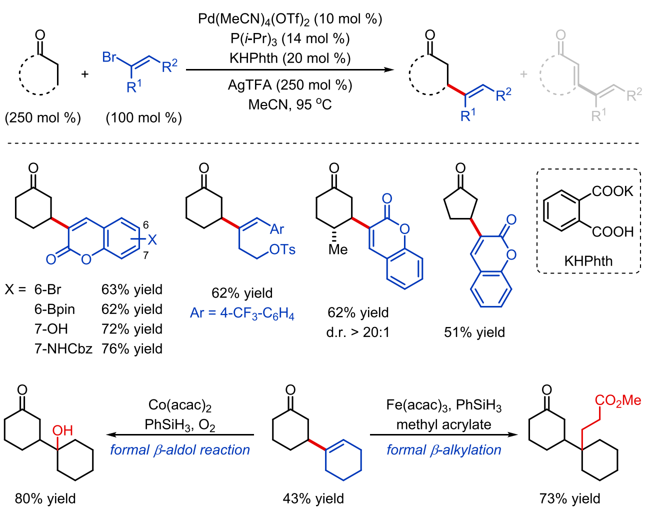


Triisopropylphosphine was a superior ligand for this transformation, and a weakly acidic environment using HFIP was essential to suppress overoxidation and disfavor α-arylation. The Pd-enolate formation step benefitted from a relatively electrophilic Pd center bearing trifluoroacetate (TFA) ligands, and silver trifluoroacetate served as an iodide scavenger to help regenerate the active Pd catalyst. Attributed to the mild reaction conditions, a variety of functional groups, especially base-sensitive ones, were well-tolerated. Other cyclic and linear ketones beyond cyclohexanones could also be smoothly arylated. It should be noted that, during one control experiment of the aforementioned β′-arylation of β-keto esters with electron-rich arene nucleophiles, Pihko and co-workers also observed the β-arylation product using iodobenzene.[32,52]

Recently, Dong and co-workers extended this strategy to the direct β-alkenylation of ketones using readily available alkenyl bromides and triflates (see Scheme 23).[53] Because of the lower stability of alkenyl electrophiles, it became more crucial to balance the reaction rates among the different steps involved. This led them to discover an effective additive—potassium hydrogen phthalate (KHPhth)—which likely promoted both ketone desaturation and protonation of the alkenylated Pd-enolate. Some reactive functional groups were tolerated, such as aryl bromides, boronic esters, and acidic hydrogens. Both linear and cyclic alkenyl bromides were viable substrates. Further transformations of the alkene functionality allowed access to various β-functionalized products, such as formal β-aldol reaction and β-alkylation of ketones.

While these reactions were effective, the use of stoichiometric silver salt under the original reaction conditions not only was less economical, but also complicated the reaction mechanism, since Ag(I) is known to be capable of oxidizing

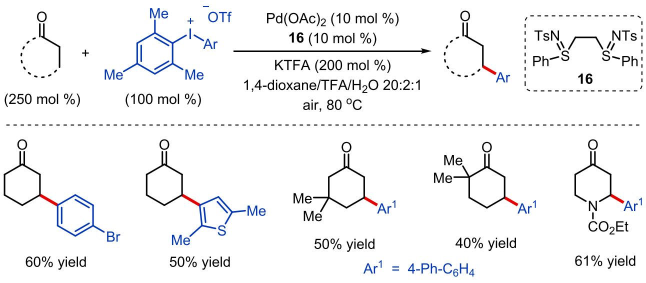
Scheme 23. β-Alkenylation of Ketones via the Pd-Catalyzed Redox Cascade



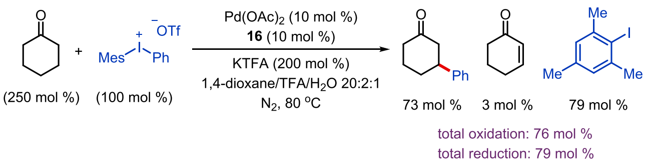
Pd(0) to Pd(II). To enable a β-arylation method free of stoichiometric heavy metals, in 2015, the Dong group developed a complementary catalytic system using diaryliodonium salts as the coupling partner (see Scheme 24a).[54]

Scheme 24. Pd-Catalyzed β-Arylation of Ketones Using Diaryliodonium Salts

(a) β-Arylation of ketones using diaryliodonium salts



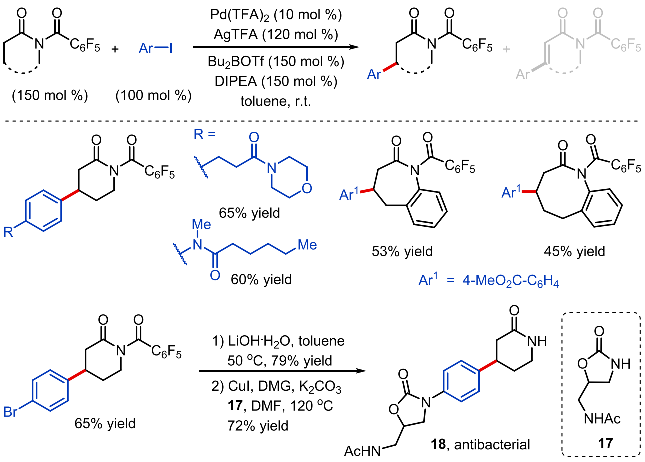
(b) Redox count of the β-arylation reaction under N_2



The use of mesitylaryliodonium salts as the aryl source was beneficial because they generate an inert byproduct, iodomesitylene, that is sufficiently bulky to avoid interfering with the main reaction. A trifluoroacetic acid/potassium trifluoroacetate buffer was used to balance the acidity. Interestingly, a new bis-sulfilimine ligand **16** was found advantageous in this transformation, likely because of its ability to stabilize the Pd nanoparticles that were proven to be the active catalysts in this reaction. Good functional group tolerance was also observed. In addition, a redox count based on the reaction operated under N_2 atmosphere showed that the total amount of ketone being oxidized (the β-arylation product plus the enone intermediate) was consistent with the total amount of the diaryliodonium salt being reduced, which supports the redox-neutral nature of this strategy (see Scheme 24b).

The same team further expanded the carbonyl scope to less-reactive lactams by employing a soft-enolization strategy (see Scheme 25).[55] A combination of dibutylboron triflate and

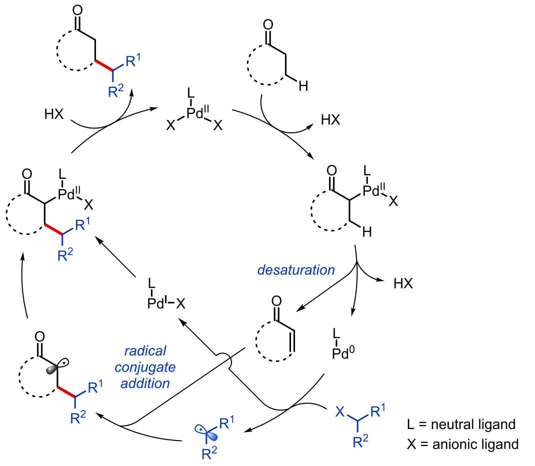
Scheme 25. β-Arylation of Lactams via Pd-Catalyzed Redox Cascade



diisopropylethylamine (DIPEA) enabled enolization of lactams under mild reaction conditions, which promoted the α,β-desaturation process.[20b,21] The reaction selectively occurred at lactams with an acyl protecting group instead of linear amides. The substrate scope could be expanded to seven- and eight-membered lactams. Notably, aryl bromides were well-tolerated, which facilitated the synthesis of an antibacterial compound **18** after protecting group removal and a Cu-catalyzed chemoselective C–N coupling.

Although a two-step formal β-alkylation of ketones can be realized (vide supra), it is more desirable to develop a general and direct β-alkylation method using widely available alkyl halides, which forms a $C(sp^3)-C(sp^3)$ bond at the unactivated carbonyl β-position. However, compared with the β-arylation and alkenylation reactions, it is more difficult to activate $C(sp^3)-X$ bonds through the typical Pd(0)/Pd(II) catalytic cycle. In 2018, a modified redox cascade strategy was reported by Wang and Dong to enable a redox-neutral β-alkylation of ketones with alkyl halides (see Scheme 26).[56] The proposed

Scheme 26. Radical Redox Cascade Strategy for β-Alkylation of Ketones

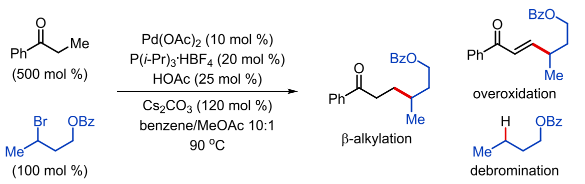


strategy also starts with a Pd(II)-mediated *α*,*β*-desaturation to generate the enone intermediate and Pd(0). The Pd(0) species could then trigger alkyl radical formation from alkyl halides and form a Pd(I) intermediate.[57] Conjugate addition of the alkyl radical and then trapping the resulting ketone *α*-radical species with Pd(I) gives an alkylated Pd(II)-enolate, which, upon protonation, delivers the *β*-alkylation product.

Instead of using Pd as the sole catalyst, a Cu co-catalyst, i.e., Cu(OPiv)$_2$, was found to be essential for enhanced reactivity; as with Pd alone, the reductive debromination of alkyl bromides was the dominant pathway (see Scheme 27a). It was reasoned that, since the enone intermediate was only generated in a catalytic amount from saturated ketones, it became crucial to reversibly stabilize the free alkyl radical species generated; otherwise, side reactions, e.g., C−H abstraction, would be predominant. Here, one role of the Cu co-catalyst could be to stabilize the alkyl radical intermediate. In addition, the amount of overoxidation products also significantly decreased in the presence of Cu, indicating that the second role of the copper co-catalyst was likely to inhibit the undesired *β*-hydrogen elimination after conjugate addition through formation of the corresponding Cu(II)-enolate.

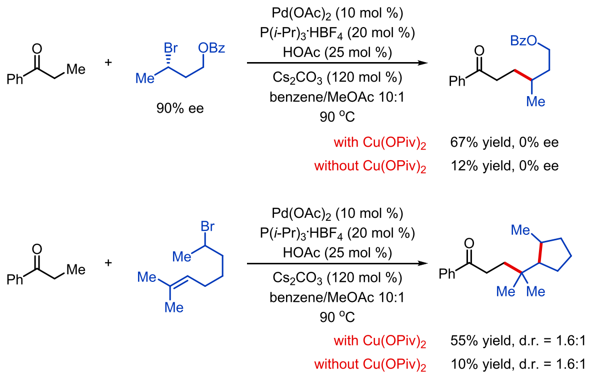
Scheme 27. Pd/Cu Cooperative Catalysis for the *β*-Alkylation of Ketones and Aldehydes

(a) Cu cocatalyst in the β-alkylation of ketones

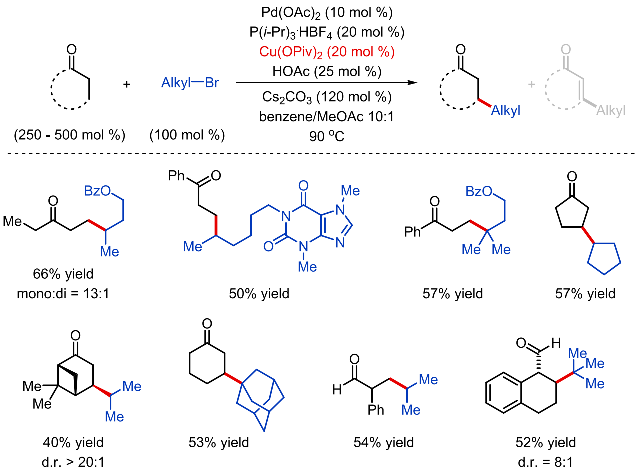


	β-alkylation	overoxidation	debromination
as above	12%	6%	42%
w/ CuOAc (20 mol %)	48%	11%	37%
w/ Cu(OPiv)$_2$ (20 mol %)	68%	7%	23%

(b) Involvement of radical intermediates



(c) Scope of the Pd/Cu-cocatalyzed β-alkylation of ketones and aldehydes



The involvement of the radical intermediate was supported by both the racemization and radical-clock experiments (see Scheme 27b). Notably, regardless of the presence of Cu (except for lower yields), both results were consistent with the fact that Pd is responsible for the radical generation. The reaction conditions avoided stoichiometric heavy metals (silver free) and strong acids/bases; thus, a wide range of functional groups were tolerated. The substrate scope was also broad: linear and cyclic ketones, as well as *α*-branched aldehydes, were all suitable substrates; both secondary and tertiary alkyl bromides could be smoothly coupled (see Scheme 27c).

VI. CONCLUSION AND OUTLOOK

In summary, taking advantage of the *α*,*β*-desaturation process, three distinct strategies for direct *β*-functionalization of carbonyl compounds have been developed. These strategies are classified based on how the *β*-substituent is installed. First, the conjugate addition strategy directly combines *α*,*β*-desaturation and nucleophilic 1,4-addition. Compared with the conventional stepwise processes, this one-pot strategy not only is step-economical, but also avoids handling reactive or sensitive *α*,*β*-unsaturated intermediates. One drawback is that stoichiometric oxidants are indispensable as stoichiometric *α*,*β*-desaturated intermediates need to be formed with this strategy. On the other hand, the migratory coupling strategy permits a redox-neutral *β*-arylation of esters using aryl halides as the reagent. It holds a novel mechanistic pathway through migration of the Pd from the *α*-position to the more remote *β*-position; thus, it has potential to realize enantioconvergent transformations from *α*-substituted racemic esters. The current development of this strategy is still in its early stages. It would be more attractive if the substrate scope could be expanded beyond *α*-branched esters and if the reaction scope could be extended beyond arylation. Finally, the redox cascade strategy is capitalized on reusing the Pd(0) species generated after *α*,*β*-desaturation in a subsequent carbon−halogen bond activation, in which the electrophile serves as both the oxidant and the source for the *β*-substituents. Thus, the overall process is redox-neutral. Both *β*-arylation and alkylation have been realized, and the scope has been expanded beyond more acidic ketones and aldehydes. The current limitation of the redox cascade approach is the requirement of excess carbonyl compounds to avoid overoxidation of the *β*-functionalized product.

As an outlook of the *α*,*β*-desaturation-based *β*-functionalization, there is still plenty of room to extend the scope of carbonyl substrates, which could likely be enabled through creating more efficient and mild *α*,*β*-desaturation methods. In addition, it would certainly be appealing if more and diverse enantioselective versions of these reactions could be developed to allow controlling the absolute stereochemistry at the *β*-position. Careful catalyst and ligand design would probably be the key to address this challenge. Moreover, from the green chemical process and atom-economy viewpoints, it could be highly attractive to realize a byproduct-free *β*-functionalization through direct coupling with olefins, alkynes, or other unsaturated 2π units. This is likely going to require a new mode of activation or a new C−C bond-forming strategy.[58] Lastly, α,β-desaturation may bring new opportunities to functionalize the γ-position of carbonyl compounds through further allylic activation.[59] Overall, the α,β-desaturation-promoted carbonyl functionalization is a relatively young field with much potential. The future development is expected to enrich the carbonyl chemistry and enable more general and efficient methods for streamlined synthesis.

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Notes

The authors declare no competing financial interest.

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