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Achieving elusive transformations with organocatalysis: direct β-carbon activation of saturated carbonyl compounds

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Abstract: Direct β-carbon activation of saturated carbonyl compounds for carrying out fast forward β-functionalization has been one of the most difficult to achieve tasks in catalysis. In the past few years, this challenging issue has attracted considerable attention among the chemical community that has led to fruitful developments to accomplish this elusive transformation. In this short review, we highlight recent developments for direct β-carbon functionalization of saturated carbonyl compounds based on conceptually new methods including oxidative enamine catalysis, N-heterocyclic carbene (NHC)-assisted catalysis, and photoredox catalysis.

Key words: Organocatalysis, N-heterocyclic carbenes, sp^3 carbon activation, regioselectivity, photoredox catalysis

1. Introduction

Direct α-carbon functionalization of saturated carbonyl compounds through enamine catalysis has been a turning point for the field of organocatalysis (Scheme 1a).[1–4] On the other hand, β-carbon functionalization of α,β-unsaturated carbonyl compounds via iminium catalysis has expanded applications of organocatalysis widely through facile catalytic processes (Scheme 1b).[5,6] Both enamine and iminium catalysis serve as the conceptual basis for an explosive growth of organocatalysis over the past decade and have contributed substantially to the discovery of many unprecedented organic reactions.[7–9] Today, organocatalysis undoubtedly stands as one of the fundamental pillars of catalysis including metal and enzyme catalysis.[10–13] However, organocatalytic activation of typically inert β-carbon of saturated carbonyl compounds remains one of the most difficult challenges for organic chemists (Scheme 1c). Direct β-carbon functionalization of carbonyls has generally been confined to the addition of nucleophiles to α,β-unsaturated carbonyl compounds such as via iminium catalysis[14] and the N-heterocyclic carbene (NHC)-induced Umpolung reactivity of α,β-unsaturated carbonyl compounds that allows β-carbon functionalization with another carbonyl compounds.[15] Several new trends are being introduced for direct β-functionalization of carbonyl compounds.

The traditional approach for β-functionalization of saturated carbonyl compounds involves oxidation of saturated carbonyl compounds to enones or enals (Scheme 1, shaded area), which is followed by the introduction of functional groups on the electron-deficient β-sp^2 carbon atoms through nucleophilic addition reactions. For this purpose, there are two available strategies: first, the Saegusa reaction, which involves the conversion of carbonyl compounds to silyl enol ether prior to its oxidation by Pd^{II},[16–20] and the second protocol dealing

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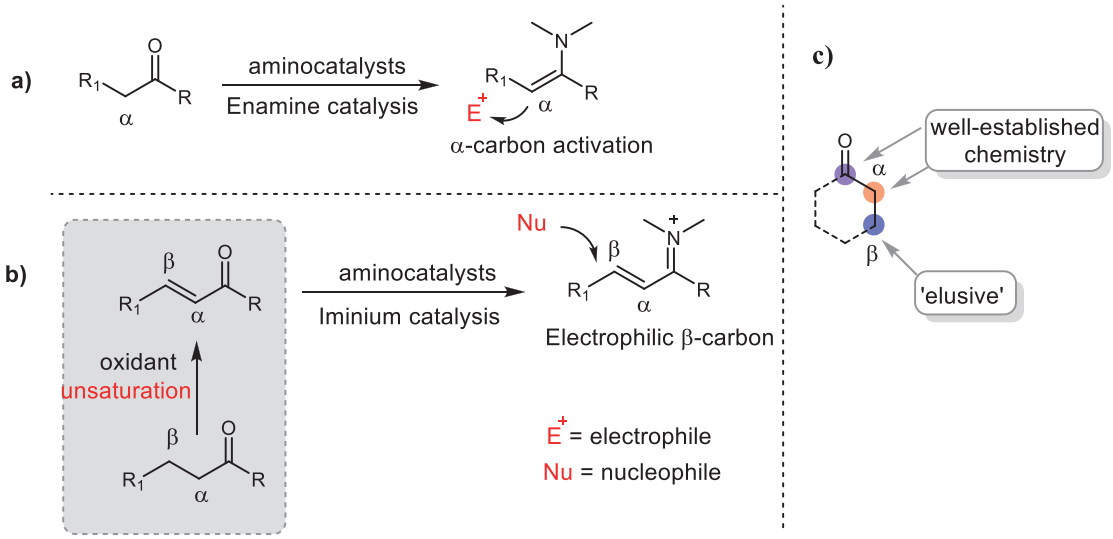


Scheme 1. Common strategies for α and β-carbon functionalization of saturated carbonyl compounds and recent developments for direct β-carbon functionalization of saturated carbonyl compounds.

with the direct dehydrogenation of saturated carbonyl compounds, which can be represented by Nicolaou oxidation.[21–27] However, in these both strategies, the electrophiles (enones or enals) must be prepared prior to subsequent chemical transformations. The whole process is rather time consuming and lacks efficiency in the context of atom economy. Thus, direct β-functionalization of saturated carbonyl compounds that avoids such additional requirements is sought by many chemists.

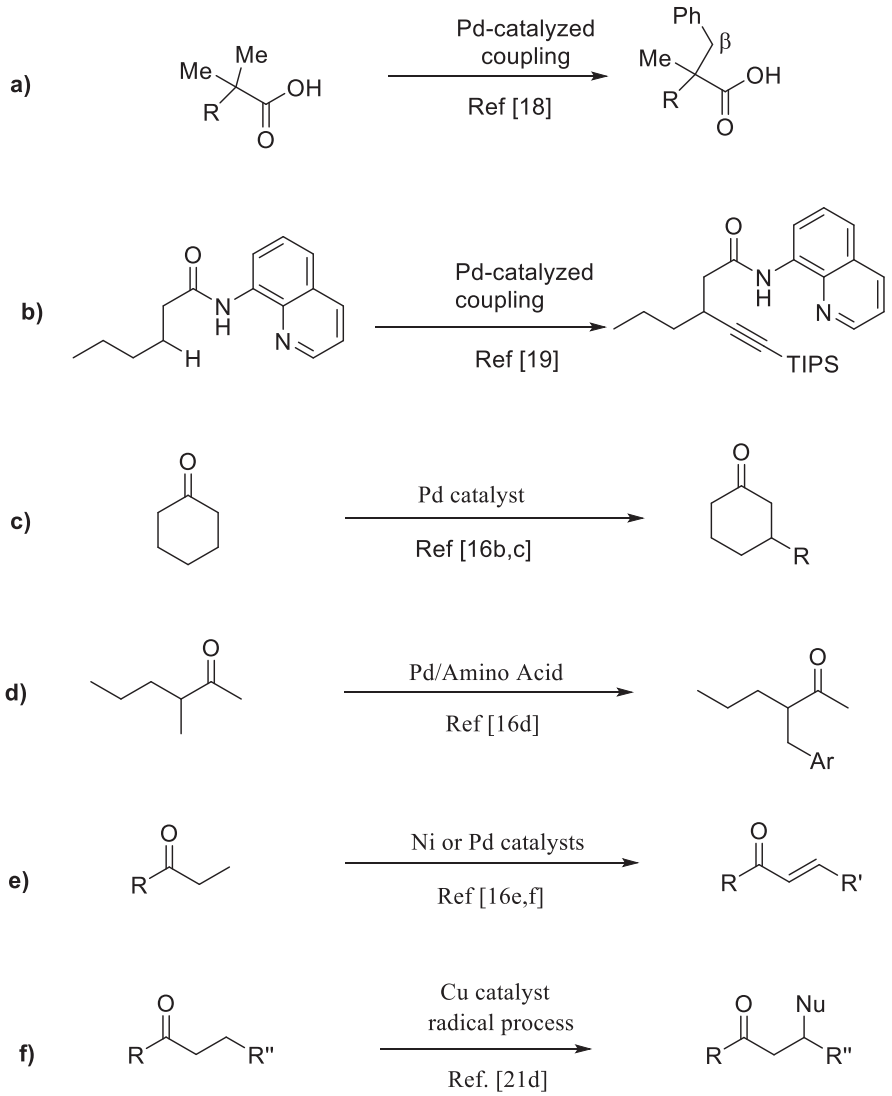
1.1. Advancements in direct β-carbon functionalization of saturated carbonyl compounds

Very few reports have been published involving direct activation of β-carbon in saturated carbonyl compounds, mainly through directing group-assisted transition metal-insertion based strategies (Schemes 2a and 2b).[28–30] Further efforts have been made to develop direct β-functionalization of saturated carbonyl compounds with transition metal-based catalysts by initial substrate dehydrogenation to enone-type intermediate with secondary transformation such as conjugate addition of nucleophiles or radical coupling (Schemes 2c–2f).

The dehydrogenation of more challenging substrates such as aliphatic esters, nitriles, and amides was achieved using Pd-based catalysts.[31,32] Besides the widely used palladium catalyst, copper, iridium, and ruthenium catalysts have shown their catalytic potential to promote alkane dehydrogenation,[33–36] although ketone dehydrogenation examples are rather rare.[37–39] Undoubtedly, direct β-carbon functionalization of saturated carbonyl compounds is always the desired goal that catalyst specialists pursue and so far only a little success has been achieved and with limited substrate scope. New organocatalytic strategies that facilitate direct β-carbon functionalization of saturated carbonyl compounds are of broad interest in the field of catalysis and might overcome the difficulties associated with such challenging reactions. Various organocatalysis-based novel tools are being developed for achieving elusive transformations in synthetic chemistry.

2. Oxidative enamine catalysis

Iminium catalysis, which involves the transformation of iminium ions to enamines, has been extensively studied and has enjoyed tremendous success in developing many new organic reactions. Recently, the reverse of this

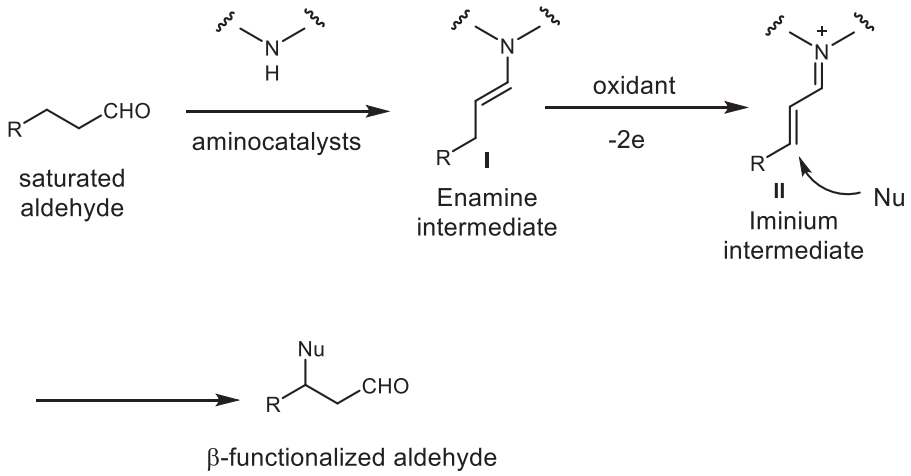


Scheme 2. Examples of direct β-functionalization of saturated carbonyl compounds with transition metal-based catalysts.

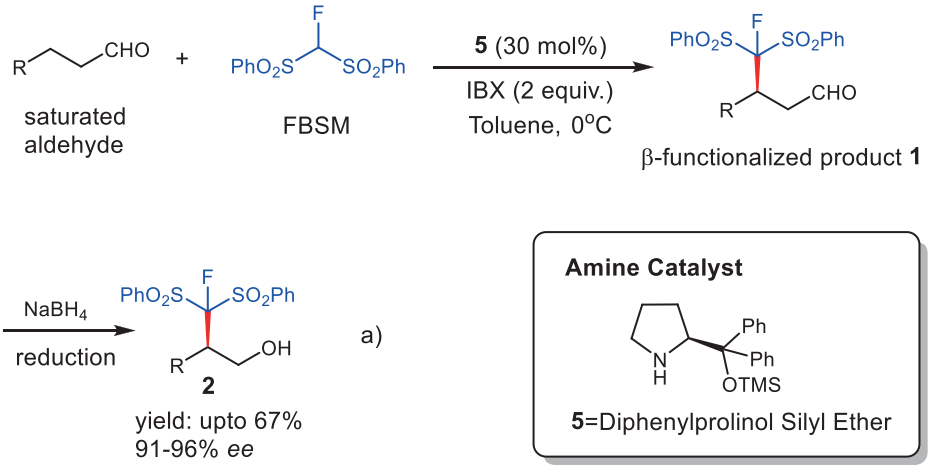
process and conceptually a new strategy, oxidative enamine catalysis that involves conversion of enamines to iminium species, has been disclosed independently by Wang, Li, and Hayashi for direct β-carbon functionalization of saturated carbonyl compounds (Scheme 3). Mechanistically, oxidative enamine catalysis proceeds via direct oxidation of an enamine intermediate **I** to generate an iminium species **II**, which is subsequently intercepted by another nucleophile, resulting in the direct β-functionalization of saturated aldehydes.

The challenging issue for the success of this strategy is the compatibility of enamine with oxidants as oxidants may have deleterious effects on the catalytic activity of organocatalysts through undesired oxidation of the catalyst itself. Wang, Li, and co-workers found *o*-iodoxybenzoic acid (IBX) an ideal candidate for the oxidative coupling of simple aldehydes with fluorobis(phenylsulfonyl) methane (FBSM) (Scheme 4).[40] The asymmetric cascade of enamine-IBX oxidation–iminium-Michael reactions of aldehydes with FBSM proceeded with high enantioselectivity and good to excellent yields with a wide range of substrates.

Hayashi and co-workers developed a one-pot oxidative coupling of aldehydes with nitromethanes in

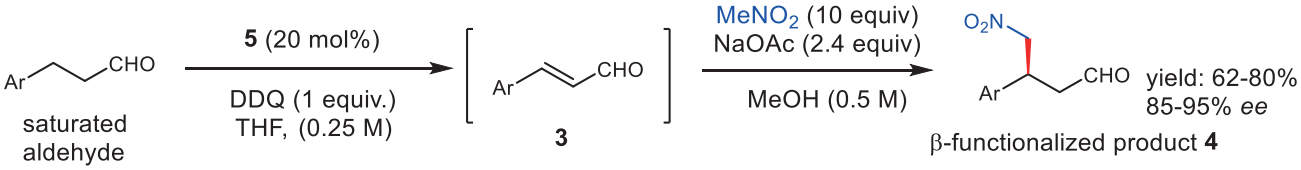


Scheme 3. Schematic representation of steps involved in oxidative enamine catalysis.



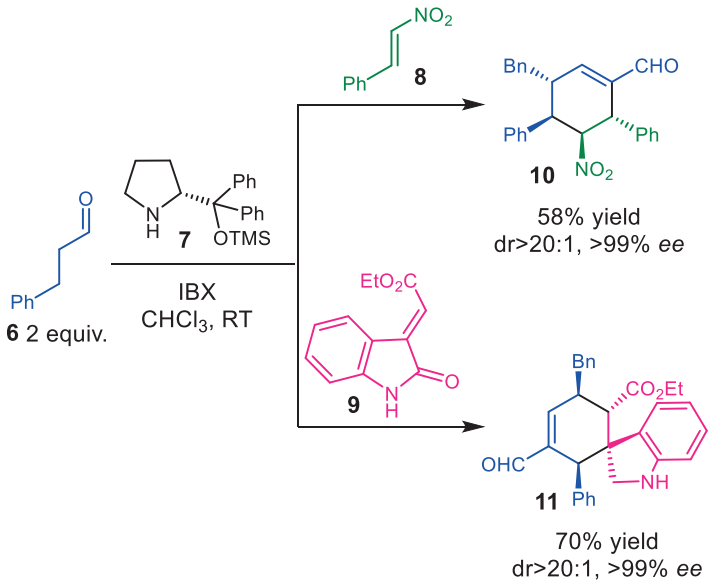
Scheme 4. Oxidative enamine catalysis for β-carbon functionalization of aldehydes.

the presence of diphenylprolinol silyl ether catalyst using 2,3-dichloro-5,6-dicyano-pbenzoquinone (DDQ) as the oxidant (Scheme 5).[41] The key features of this strategy also include, besides being able to carry out direct β-functionalization, the short reaction time, good to excellent yields, and high enantioselectivity of β-functionalized aldehydes **4**.



Scheme 5. A one-pot oxidative coupling of aldehydes with nitromethane.

To generalize this conceptually new approach, oxidative enamine catalysis has been employed to develop interesting asymmetric cascade processes to produce intriguing complex molecular architectures. The potential of this strategy can be clearly understood from the accomplishment of two-component four-step branched domino reactions by Dieter Enders and his group, facilitating 'one-pot' formation of polyfunctionalized cyclohexene derivatives **10** and **11** in good yields and excellent stereoselectivities (Scheme 6).[42]



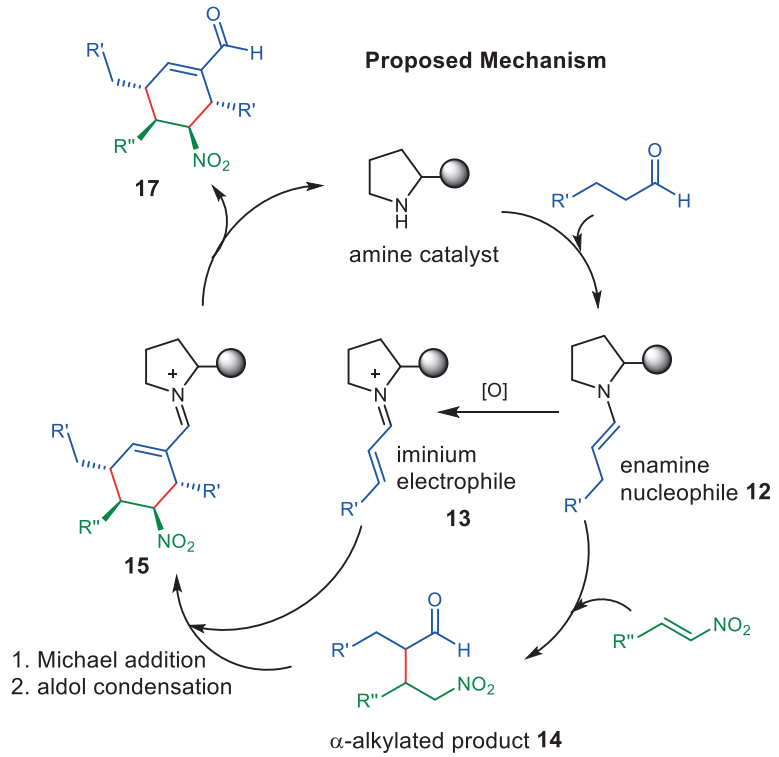
Scheme 6. Synthesis of polyfunctionalized cyclohexene derivatives via oxidative enamine catalysis.

This organocatalytic cascade reaction involves a Michael addition of enamine intermediate **12** with nitroalkenes to give β-alkylated product **14** while parallelly undergoing oxidation to generate **13**. A consecutive second Michael addition of **14** proceeds to trap iminium species **13** and the catalytic cycle concludes with an aldol cyclization step to give polyfunctionalized products (Scheme 7). Interestingly, both the enamine nucleophiles **12** and the iminium electrophiles **13** reacting with each other in this reaction are in situ generated from the same parent aldehyde precursor, which is certainly a key feature of this strategy.

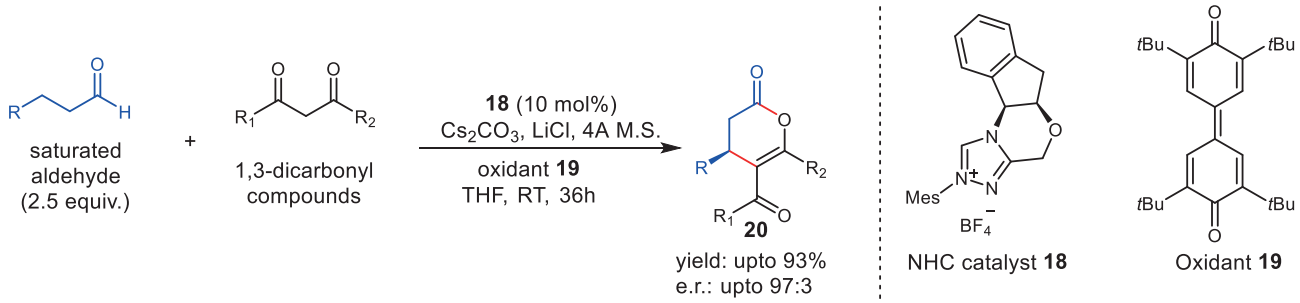
From these examples, it can be realized that oxidative enamine catalysis stands as a new potential strategy expanding the scope of aminocatalysis beyond already well-established activation modes in organocatalysis. The novel strategy holds great potential for future applications in catalytic chemical processes.

3. *N*-Heterocyclic carbene catalysis

To this novel area of oxidative direct β-functionalization, an intriguing addition was reported involving powerful *N*-heterocyclic carbenes (NHCs) as catalysts. NHCs were first reported nearly four decades ago by Öfele and Wanzlick.[43–45] Interest in the area of NHCs surged after the first synthesis of an isolable carbene species. This led to remarkable success in finding applications of these species in organometallic chemistry and catalysis and NHCs are now ubiquitous in the catalysis research field. NHCs have enabled a great variety of organic reactions, such as nucleophilic acylation, β-alkylation, transesterification, hydroacylation, polymerization, ring-opening reaction, carbon–carbon cross coupling such as Suzuki–Miyaura, Mizoroki–Heck, Sonogashira, C-N cross coupling in Buchwald–Hartwig reactions, and so on.[46–52] Further establishing importance of NHCs in catalysis, Chi and co-workers disclosed the first direct activation of the β-carbon of saturated aldehydes by oxidative NHC catalysis (Scheme 8).[53] This strategy reports the first oxidation of NHC-bound enolate intermediates to α,β-unsaturated ester intermediates that are able to react as formal Michael acceptors. Under very mild reaction conditions, various β-lactone products were obtained in good yields and high enantioselectivity using triazolium NHC **18** as catalyst and quinone **19** has played the role of an oxidant in this method, which has better solubility in nonpolar solvent than IBX.



Scheme 7. Mechanistic hypothesis for the synthesis of polyfunctionalized cyclohexene derivatives via oxidative enamine catalysis.

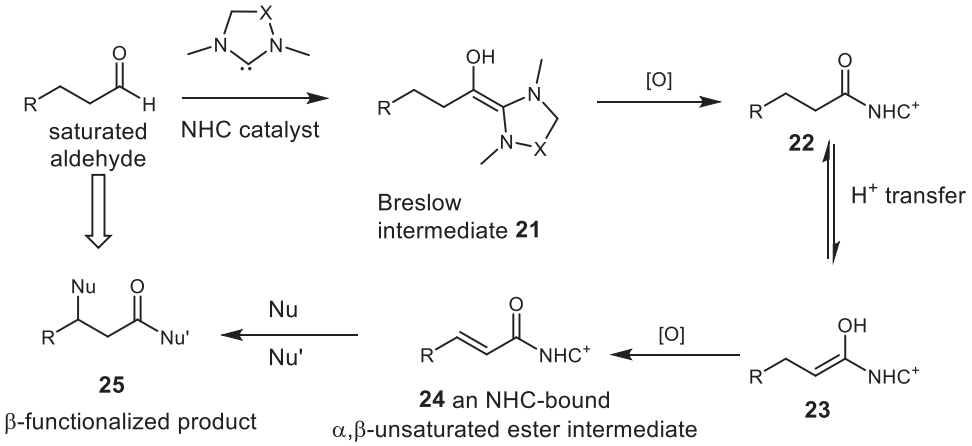


Scheme 8. Direct β-activation of saturated aldehydes through oxidative NHC catalysis.

Two consecutive oxidative processes are proposed to be involved in this mechanistic pathway: first is the well-known oxidation of Breslow intermediates **21** to NHC-bound ester intermediates **22** and the other oxidation is of the NHC-bound enolate intermediates **23** to corresponding α,β-unsaturated ester intermediates **24**, which are vulnerable to undergo Michael addition reaction with nucleophiles to produce β-functionalized products **25** (Scheme 9).

This innovative catalytic protocol paves the way to a conceptually new chemical strategy to introduce β-carbon of saturated carbonyl compounds as a reactive electron-deficient center, the overall strategy resembling that of oxidative enamine catalysis, and offers a powerful concise alternative route for the development of novel reactions and practically useful chemical transformations.

The success of oxidative NHC catalysis in β-functionalization of saturated carbonyl compounds has widened the scope of NHCs in target-selective catalysis. The potential of NHC catalysts have further been



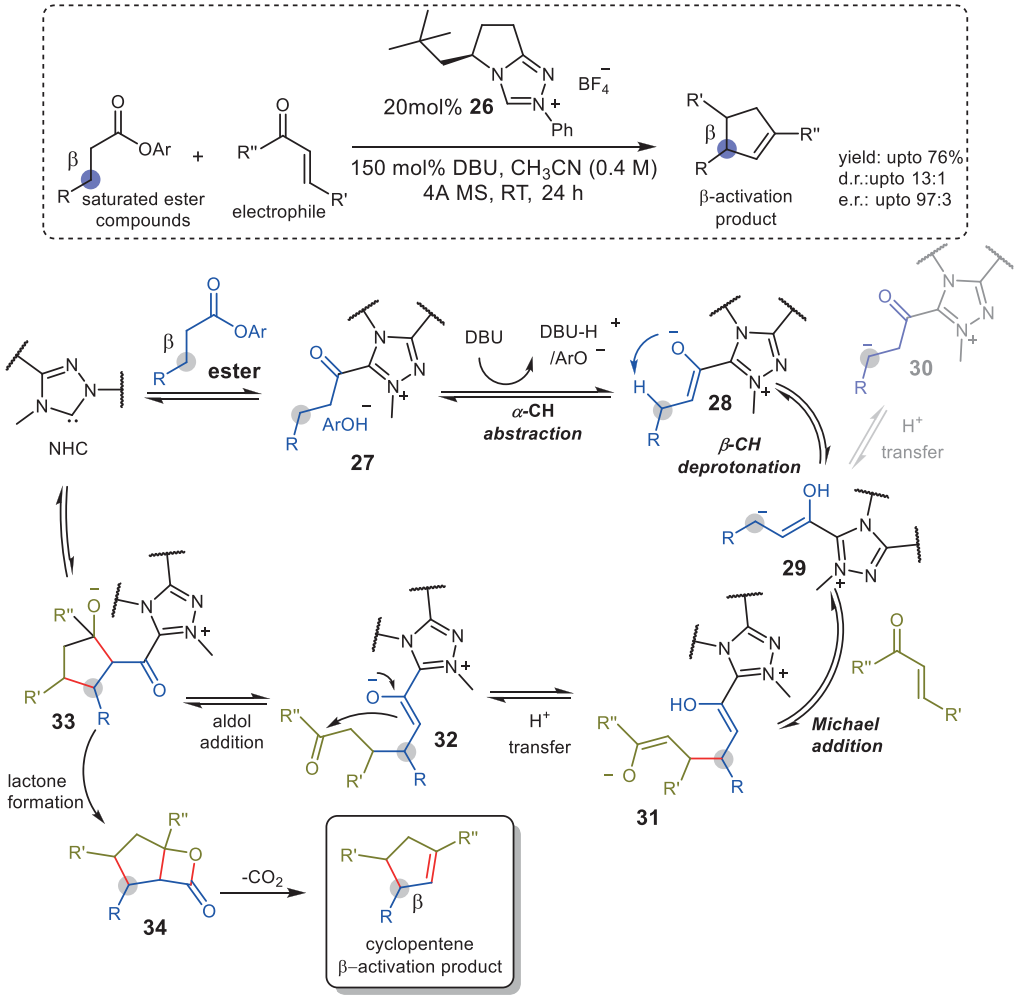
Scheme 9. Mechanistic hypothesis for oxidative NHC catalytic cycle.

tested by the Chi group through screening of various imidazolium-derived NHCs to uncover a remarkably simple and practical direct β-carbon activation of saturated carboxylic esters (Scheme 10).[54] Contrary to oxidative NHC catalysis, this oxidant-free strategy involves the generation of nucleophilic β-carbon. The direct β-functionalization of esters with α,β-unsaturated compounds was carried out in the presence of NHC catalyst **26** with a stoichiometric amount of an organic base, 1,8-diazabicycloundec-7-ene (DBU), to deliver multifunctionalized cyclopentene derivatives. The stoichiometric amount of the base is needed for the β-deprotonation of intermediate **27**, leading to **28**, which possesses the acidic C(sp^3)-H bond at the β-position to ester moiety. An intramolecular β-C-H abstraction of intermediate **28** generates **29** carrying a nucleophilic β-carbon center that undergoes nucleophilic additions with electrophiles, such as enones. As shown in Scheme 10, the mechanistic pathway involves nucleophilic attack of intermediate **29** on enones, followed by an intramolecular aldol condensation, lactone formation, and finally decarboxylation of formed lactone **34** to eventually produce a cyclopentene product.

Although the method suffered with some shortcomings such as ester hydrolysis, lower yields with β-alkylated esters, and, specifically, the deactivation of the nucleophilic catalyst, it offered a practical solution for the enantioselective formation of cyclic compounds in a domino-type transformation by NHC-catalyzed reaction of esters with electrophiles such as enones to produce cyclopentenes, trifluoroketones to produce γ-lactones, and hydrazones to deliver γ-lactams (Scheme 11).[55] Good to excellent yields and high enantioselectivity of structurally complex and intriguing molecular structures are obtained from this very efficient direct activation of β-carbon through NHC catalysis.

The Chi group has further utilized this activation for the synthesis of multicyclic oxoquinoline-type derivatives **36**, where NHC-catalyzed β-carbon activation plays a crucial role (Scheme 12a).[56] The work involved β-carbon functionalization of anhydrides **37** bearing β-alkyl substituents with α,β-unsaturated ketones **39** and isatins **42** to produce cyclopentene derivatives of type **40** and spiro-lactone products **43**, respectively (Scheme 12b).[57]

Furthermore, the Chi group also has performed recent work in this direction involving NHC-catalyzed β-sp^3 carbon activation of propionic acid to generate the smallest homoenolate intermediate with a reactive nucleophilic β-carbon to furnish lactone products **44** (Scheme 13).[58] Mechanistically, two possible pathways are considered for this strategy: Pathway A would proceed through formation of EDC-bound propionic acid

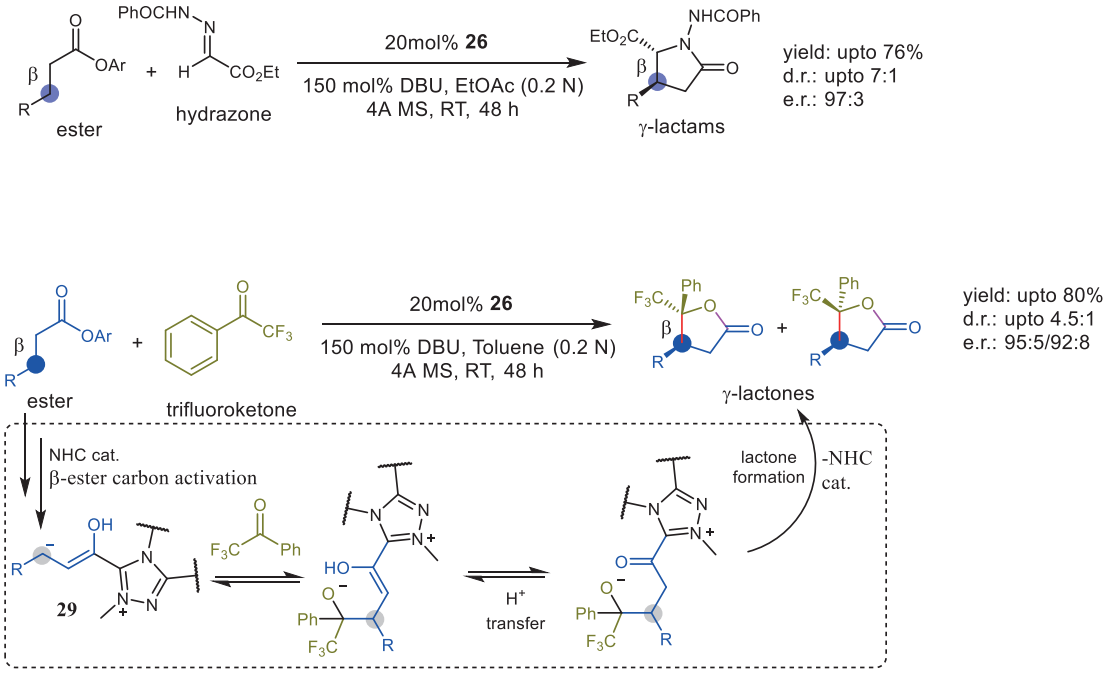


Scheme 10. NHC-catalyzed direct β-activation of esters to produce cyclopentenes; Intermediate 5 undergoes Michael reaction followed by aldol reaction, lactone formation and decarboxylation to give final product. Adapted with permission from Ref. 34 copyrights: Nature Publishing Group.

ester intermediate **45**, whereas pathway B would involve anhydride intermediate **46** prior to proceeding through NHC-bound intermediate **47**.

NMR studies revealed the dominating presence of propanoic anhydride when propionic acid was treated with DBU. After the addition of NHC catalyst to this mixture, there was no change in NMR spectra, which confirms the formation of anhydride intermediate in the catalytic cycle. Thus, Pathway B was assumed to be involved in the catalytic cycle (Scheme 14). The activation of propionic acid by EDC•HCl led to propionic anhydride **46**, which is intercepted by an NHC catalyst to form intermediate **47**. An α-CH deprotonation of **47** results in the formation of an enolate intermediate **48**, followed by a deprotonation/proton transfer process to form the nucleophilic intermediate **49**. Nucleophilic addition of the β-carbon of intermediate **49** to α-ketobenzhydryl ester or isatins followed by a lactone formation process gave cyclic products **44**, while releasing the catalyst to complete the Pathway B-type catalytic cycle.

Very recently, Xu and co-workers have observed the HOBt-assisted enhancement of diastereoselectivity and enantioselectivity in NHC-catalyzed direct β-functionalization of saturated carboxylic esters **52** (Scheme



Scheme 11. β-Carbon functionalization of saturated carboxylic esters with hydrazones and trifluoroketones through NHC catalysis. The possible mechanistic pathway for trifluoroketone electrophiles involves nucleophilic intermediate 29 obtained from the addition of NHC to saturated ester followed by deprotonations and proton transfer (see Scheme 10 for pathway leading to intermediate 29). The intermediate 29 reacts with trifluoroketone to generate corresponding γ-lactones via an aldol addition and lactonization.

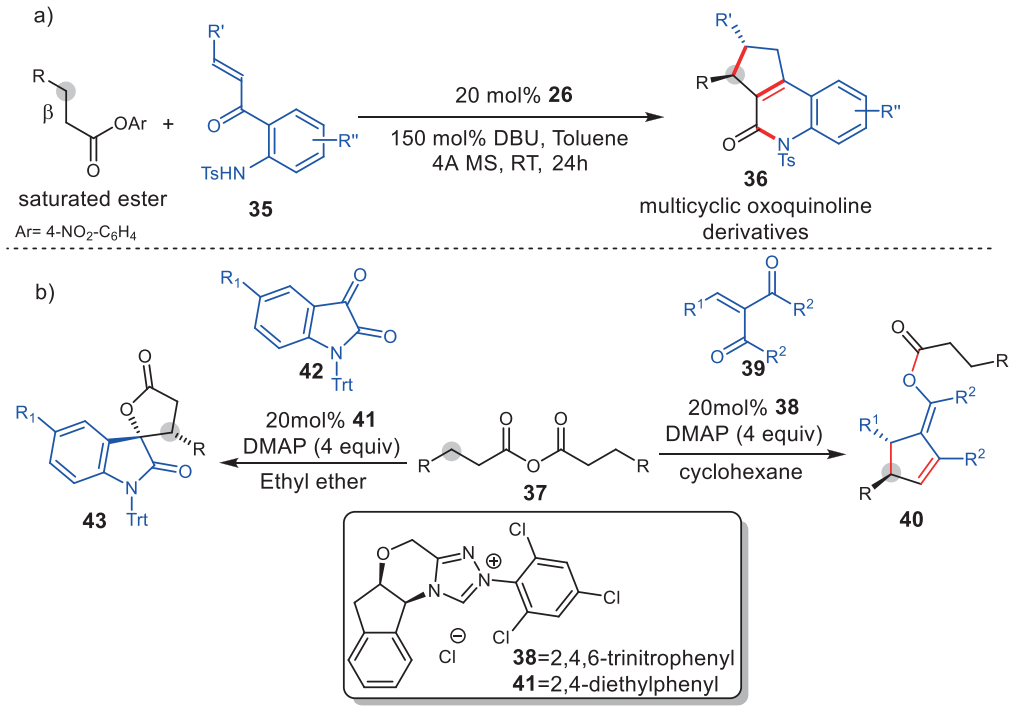
15).[59] The authors have investigated formal [3 + 2] annulations of isatins **53** with saturated carboxylic esters, which proceed in a highly efficient, diastereoselective, and enantioselective manner to afford chiral spirooxindole lactones **54**.

The proposed mechanism depicts a dual role of HOBt (Scheme 16). Firstly, HOBt acts as an ester activating reagent by replacing the 4-nitrophenol moiety of ester **52** to afford reactive benzotriazole ester intermediate **56**, which is intercepted by NHC catalyst **55** to generate acyl azolium intermediate **I**. The intermediate **I** undergoes α-deprotonation to give an enolate intermediate **II**, followed by proton transfer to form homoenolate intermediate **III**. The steric hindrance of bulky substituents on the NHC catalyst causes isatin to react with the intermediate **III** from the opposite face, which is induced due to the second role of HOBt as a hydrogen bonding donor. This nature of transition state **TS** may enhance diastereoselectivity and enantioselectivity of the products. The nucleophilic β-carbon intermediate **III** attacks isatin from the *si* face to provide intermediate **IV**. The lactonization of intermediate **IV** results in the formation of spirooxindole lactone **54** as the annulation product while releasing NHC catalyst for the next catalytic cycle.

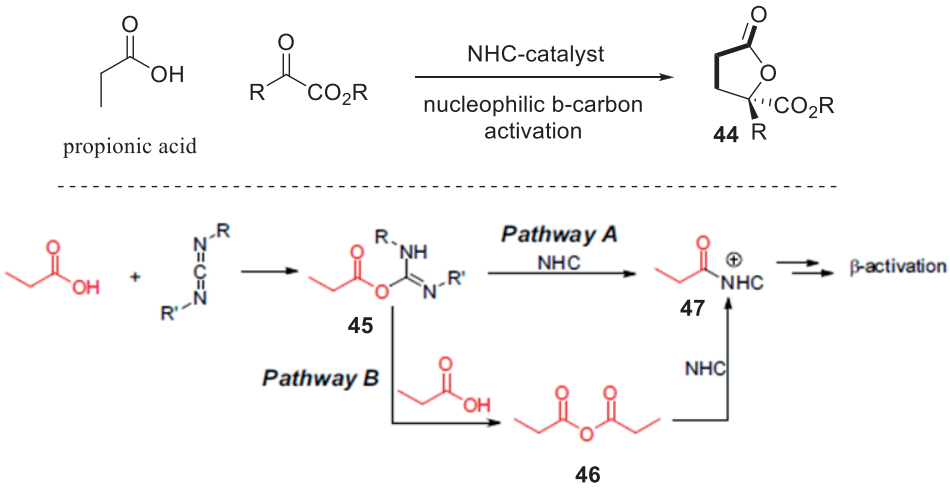
Overall, the NHC-catalyzed direct β-activation strategy represents an excellent alternate to C-H activation strategies of inert chemical bonds.

4. Photoredox organocatalysis

Oxidative approaches to direct β-functionalization of saturated carbonyl compounds have removed the barrier to directly achieve β-products in single flask. However, the use of stoichiometric amounts of oxidant still brings some hurdles, especially in industrial applications of these methodologies. The "ideal" direct β-functionalization



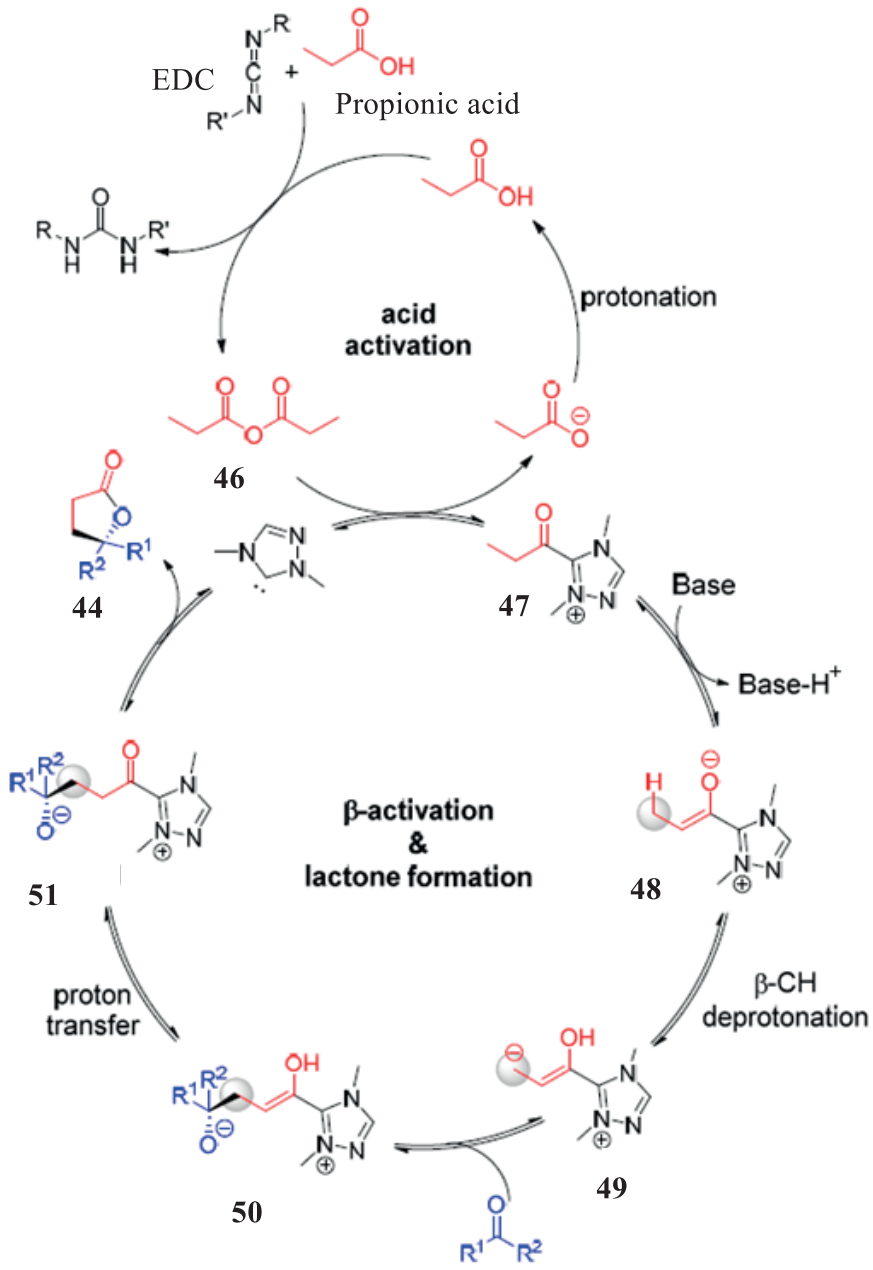
Scheme 12. Further exploitation of NHC-catalyzed direct β-carbon functionalization of saturated carbonyls. a) assembly of structurally complex oxoquinoline derivatives, b) direct β-carbon activation of β-alkylated anhydrides.



Scheme 13. Nucleophilic β-carbon activation of propionic acid by NHC catalysis and prediction of possible two mechanistic pathways. Adapted with permission from Ref. 37. Copyrights: Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim.

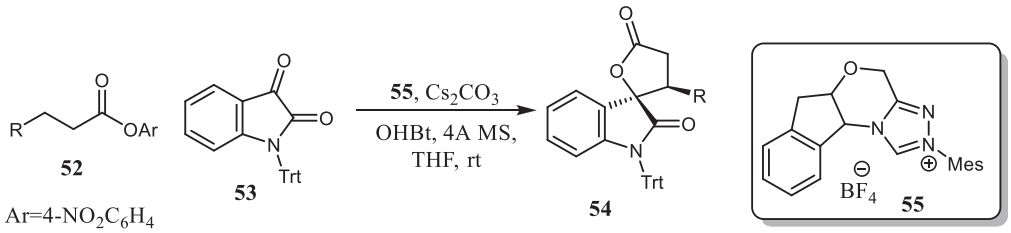
of saturated carbonyl compounds should encompass direct introduction of new C-C bonds without using any oxidants, which may lead to side-reactions and unwanted products. In 2013, MacMillan and co-workers disclosed that photoredox one-electron oxidation of enamine to form a β-carbon radical facilitated direct functionalization of saturated aldehydes and ketones at β-carbon.[60]

In recent years, visible light-mediated photoredox catalysis has rapidly developed and has become an important tool in the field of catalysis.[61,62] Photoredox catalysis has been used in a myriad of synthetic chemical

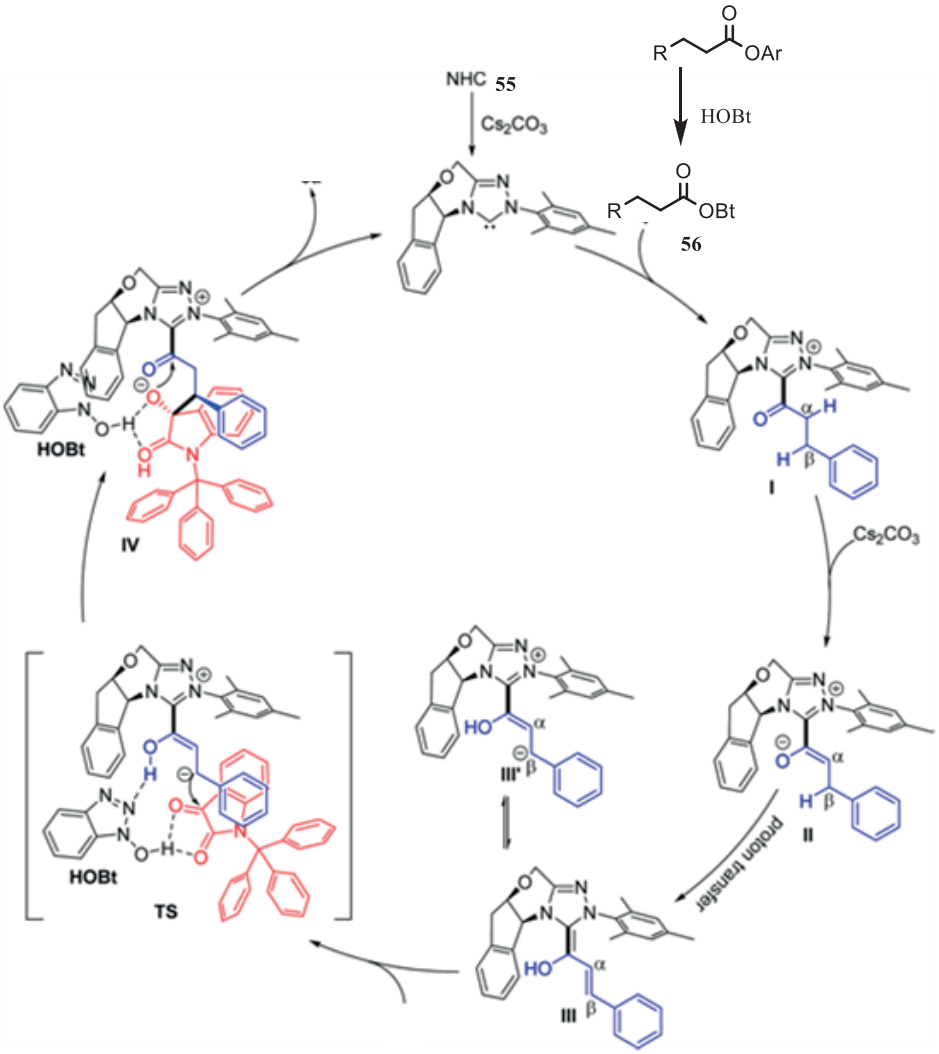


Scheme 14. Plausible mechanism of NHC-catalyzed nucleophilic β-carbon activation of propionic acid. Formation of anhydride intermediate (Pathway B) was proposed based on NMR studies. Adapted with permission from Ref. 37. Copyrights: Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim.

transformations with a range of applications.[63−72] It involves photoinduced electron transfer (PET) steps that allow considerably elusive transformations that are difficult to achieve via traditional two-electron-involving chemical reactions. Moreover, this newly developed trend facilitates an alternative pathway of generating reactive radical intermediates in an operationally simple way and without using toxic precursors that we often come across in photochemistry, requiring high-energy and/or reagent-based radical generation. The potential



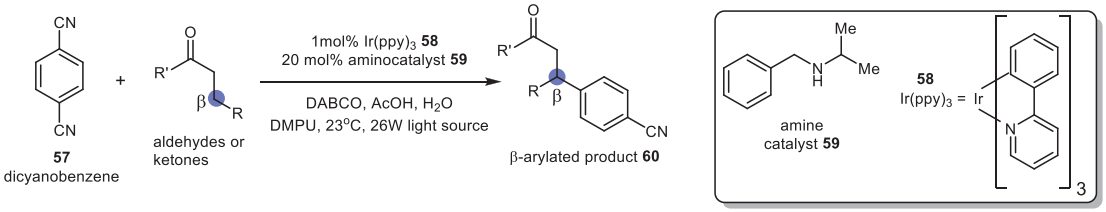
Scheme 15. 1-Hydroxybenzotriazole-assisted NHC-catalyzed β-functionalization of saturated carboxylic esters to produce spirooxindole lactones.



Scheme 16. Proposed mechanistic cycle for HOBt-assisted NHC-catalyzed spirooxindole lactones synthesis. Adapted with permission from Ref. 38 copyrights: American Chemical Society.

of photoredox catalysis in combination with organocatalysis was explored to achieve direct β-carbon activation of saturated carbonyl compounds by MacMillan and his group. Researchers have developed an impressive single electron transfer-mediated transformation that leads to the β-arylation of saturated aldehydes and ketones in good yields (Scheme 17). It was observed that photoredox catalysis coupled with organocatalysis

facilitated direct β-carbon arylation of saturated aldehydes using cyano-substituted arenes and heteroaromatic systems. Moreover, various cyclohexanone derivatives were successfully employed for this photoredox-coupled organocatalytic arylation protocol with significant tolerance to steric variations.



Scheme 17. Direct β-carbon functionalization of aldehydes and ketones by synergistic combination of a photocatalyst, Ir(ppy)3 and an organocatalyst, N-isopropylbenzylamine.

The authors propose a $5e^-$ activation mode via formation of a β-enamine radical **63** generated by one-electron oxidation of enamine intermediate (Scheme 18). The photochemical excitation of $Ir(ppy)_3$ (**58**) causes the generation of a high-energy intermediate, $*Ir(ppy)_3$ (**61**), followed by a single-electron transfer (SET) to dicyanobenzene **57** to produce electron rich radical anion **61**. The intermolecular radical coupling of two active species, β-enamine radical **63** and dicyanobenzene anion radical **61**, results in the formation of a new sp^3-sp^3 C-C bond to yield β-arylated saturated carbonyl products **66**. Notably, in this combined catalytic reaction, the photoredox catalysis is particularly efficient as only 1 mol% of the corresponding catalyst **58** is necessary to run the reaction and requires no preactivation of either coupling partner. Furthermore, use of photoredox catalysis avoids large amounts of oxidants generally needed for oxidative β-functionalization catalytic processes.

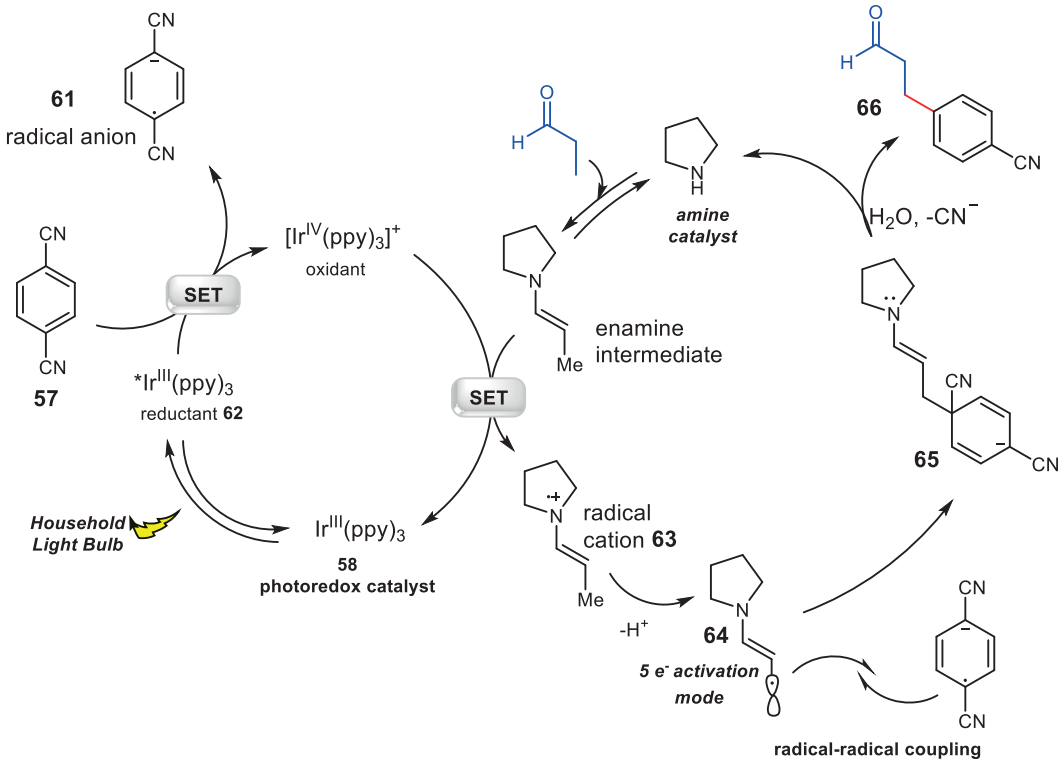
To screen the applicability of this synergistic catalytic method in asymmetric catalysis, enantioselective β-arylation of cyclohexanone was attempted successfully using cinchona-based organocatalyst resulting in intriguing levels of enantioselectivity. This attempt proved that this newly developed activation mode can be further explored in achieving asymmetric variants of these organocatalytic reactions.

Since their initial success in direct β-activation, the MacMillan group have added three examples to this "β-carbon radical" strategy that involved direct β-alkylation of saturated carbonyl compounds with aryl ketones (Scheme 19a),[73] Michael acceptors (Scheme 19b),[74] and imines (Scheme 19c)[75] to produce a wide variety of β-functionalized products.

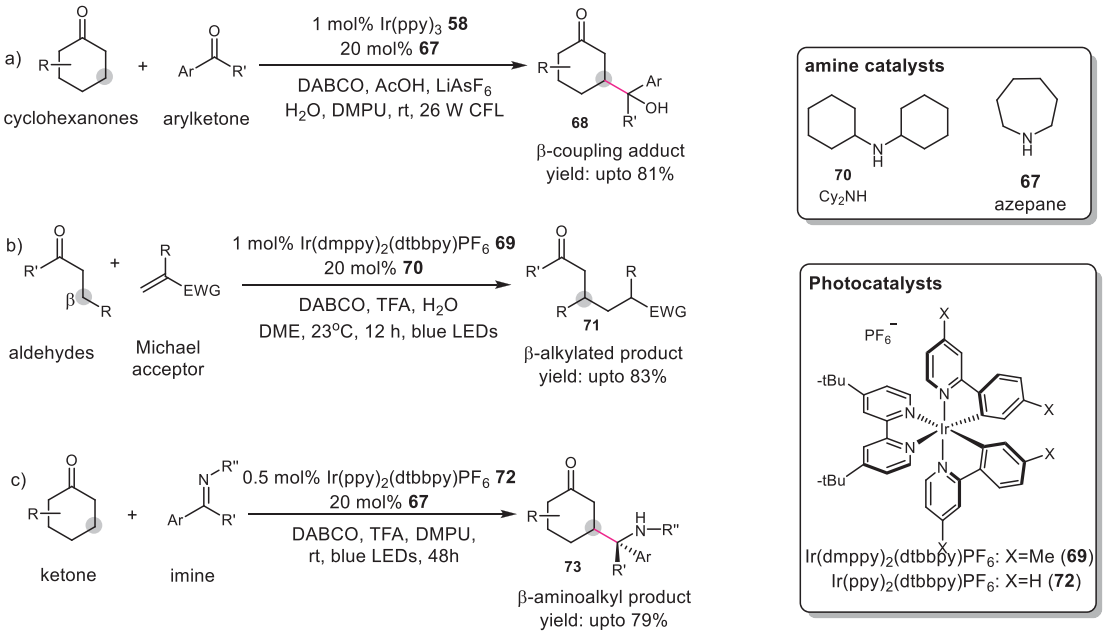
This redox-neutral and atom-economical approach was successfully implemented for a variety of reactions including not just intermolecular reactions but also for intramolecular reactions leading to structurally interesting cyclized products and in one pot three-component reactions leading to products with inspiring yields, expanding the horizons of potential future applications of this activation mode (Scheme 20).

Very recently, Ryu, Fagnoni, and co-workers have developed a very simple and straightforward organocatalyst-free strategy for β-alkylation and acylation of cyclopentanones using electron-deficient alkenes that can be achieved by merely exposing the reaction solution to the sun in a glass vessel on a window ledge in the presence of tetrabutylammonium decatungstate (TBADT) as the photocatalyst (Scheme 21a).[76] This strategy requires no artificial energy and, interestingly, use of either artificial xenon light or natural sunlight irradiation gave mostly similar results. Furthermore, the authors were successful in carrying out TBADT-catalyzed β-acylation of cyclopentanone via a multicomponent reaction using cyclopentanone, CO, and electron-deficient alkenes (Scheme 21b), proving the possible wide scope of this strategy.

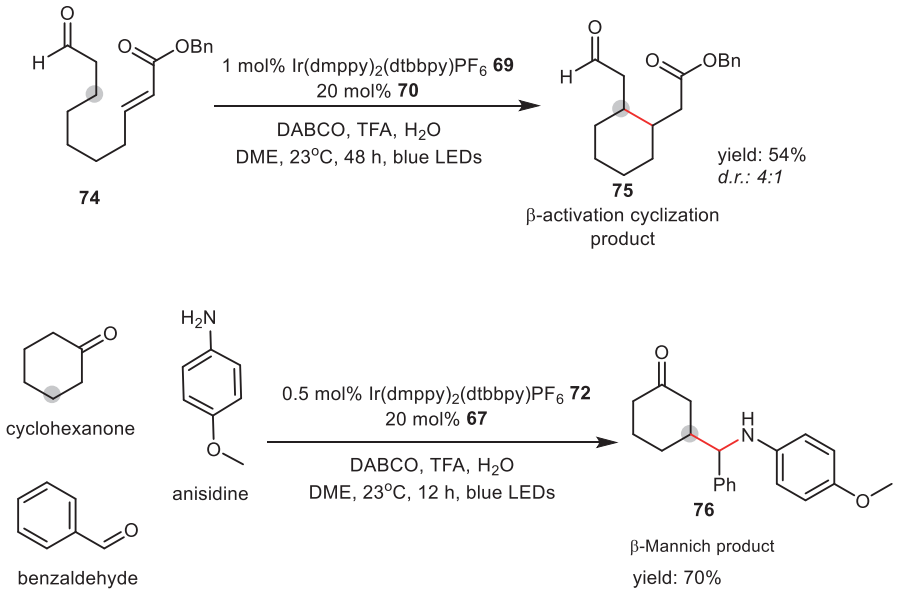
Finally, the direct β-carbon activation approaches highlighted here are highly efficient, and require no preactivation of either (any) of the coupling partners. Moreover, these methods provide a rapid access to



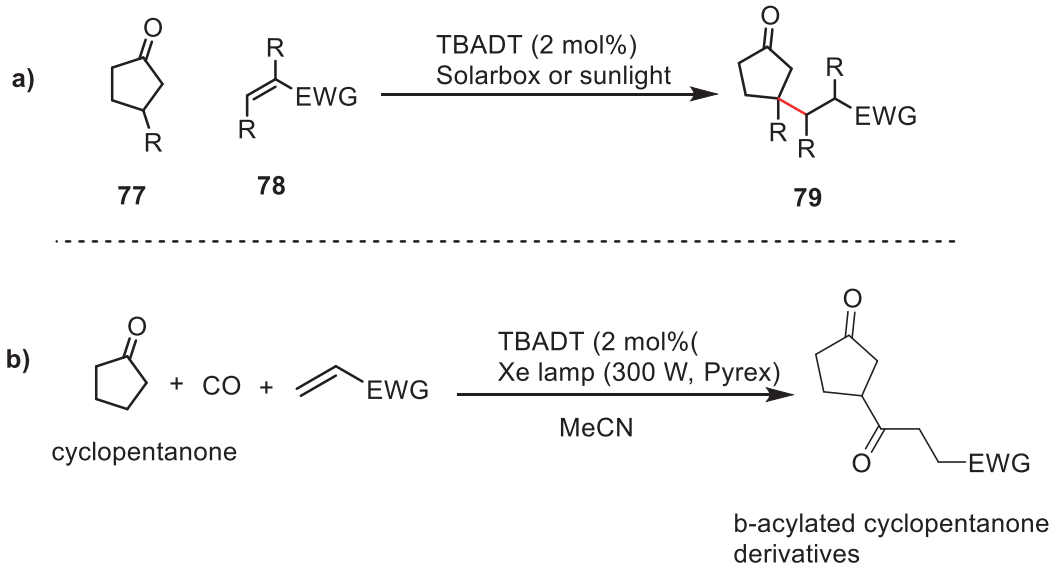
Scheme 18. Direct β-arylation of carbonyl compounds via photo-induced one electron oxidation of enamine intermediates: proposed mechanistic pathway of this synergistic catalysis protocol. From Ref. 39. Adapted with permission from AAAS.



Scheme 19. Direct β-functionalization of saturated carbonyl compounds with Michael acceptors, aryl ketones, and imines through photoredox organocatalytic activation mode.



Scheme 20. Implementation of photoredox organocatalytic approach for intramolecular direct β-alkylation and three-component β-Mannich reactions.



Scheme 21. Photocatalytic regioselective β-functionalization of cyclopentanones including a three-component reaction to achieve regioselective β-acylation of cyclopentanone.

complex structures and thus offer an excellent route to biologically active complex scaffolds. Mechanistically, these methods differ in formation of different species such as oxidative conversion to electrophilic unsaturated moieties, generation of radical coupling partners through SET, and being nucleophilic in nature. This initial success will attract the attention of researchers, leading to further development of novel strategies and modes of activations in organocatalysis.

5. Summary and outlook

In summary, the "elusive" chemical transformations of otherwise inert β-sp^3 carbon of saturated carbonyl compounds have been addressed successfully with organocatalytic activations. Although the direct β-carbon activation of saturated carbonyl molecules is a new addition in asymmetric organocatalysis, the principle has already attracted the attention of the chemical community. Given the possibility of limitless utility of the direct activation of carbonyl β-carbons, this research will significantly expand in the coming days and will contribute to the development of novel methods, perhaps introducing new modes of activation in organocatalysis. In addition, the direct activation of saturated carbonyl β-carbons would expose previously unknown dimensions for the design and synthesis of structurally complex molecules via easy and short synthetic strategies. These versatile approaches significantly increase efficiency and success in finely tuned catalysts with a high degree of activity and selectivity. Further developments will witness remote chemical bond functionalization to construct $C(sp^3)$-$C(sp^3)$, $C(sp^3)$-O, and $C(sp^3)$-N bonds through catalyst designing based on mechanistic understanding of the processes.

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