ORGANIC CHEMISTRY
FRONTIERS

REVIEW

View Article Online
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Cite this: *Org. Chem. Front.*, 2019, **6**, 1905

Application of dialkyl azodicarboxylate frameworks featuring multi-functional properties

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Received 6th January 2019,
Accepted 4th April 2019

DOI: 10.1039/c9qo00017h

rsc.li/frontiers-organic

Azo-disubstituted derivatives with electron-withdrawing groups, such as acyl, alkoxycarbonyl and nitrile, are widely used as reagents in organic synthesis. Dialkyl azodicarboxylates are the most readily available reagents among them. This review summarizes the utility of dialkyl azodicarboxylates as versatile reagents and essential building blocks for the synthesis of complex molecules. Applications of dialkyl azodicarboxylates in the Mitsunobu reaction, as oxidants in the oxidation of aldehydes, hydrazines, alcohols, hydroxylamines and thiols, and in photocatalytic C–C bond cleavage and C–H bond amination reactions are discussed. In synthetic chemistry, a large number of synthetic procedures use azodicarboxylates as electrophiles. The discussion is also extended toward the enantioselective α-amination of carbonyl, cyanoacetate and heterocycle derivatives. In addition, mechanistic insights are also briefly reviewed.

1. Introduction

Dialkyl azodicarboxylates, as potential reagents, are very useful in organic synthesis, such as in the Mitsunobu reaction.[1] Owing to their unique structural and electronic features, azodicarboxylates are also used in zwitterionic intermediate reactions, as oxidants, and for aldehydic C–H bond functionalization by hydroacylation, amination of C–H bonds, and α-amination of carbonyl and cyanoacetate compounds.[2,3] However, the use of dialkyl azodicarboxylates as carbonylation reagents is very limited. The carbonylation reaction of various substrates involving C–C and C–X (X = N and O) bonds formation has been developed recently. New prospects highlighted its utilities in photocatalytic promoted C–C bond cleavage and C–H bond amination reactions. Azodicarboxylates

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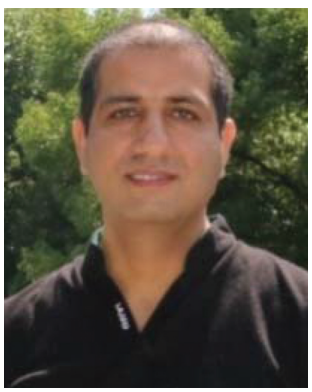
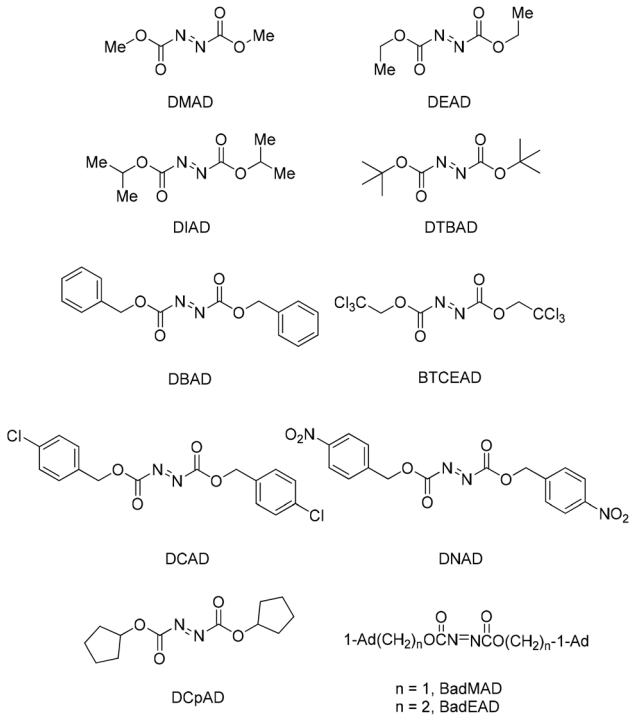


Muhammad Usman

Muhammad Usman was born in Lahore, Pakistan and received his B.Sc. and M.Sc. degrees from the University of Punjab. After working as an analyst in Highnoon Laboratories Pakistan, he joined Prof. Zheng-Hui Guan's group at Northwest University, China, where he obtained his Ph.D degree in 2017. The following year, he commenced his postdoctoral studies with Prof. Wen-Bo Liu at Wuhan University. His current research focuses on the transition-metal-catalyzed formation of carbon–carbon and carbon–heteroatom bonds and green synthetic chemistry.

Xiao-Wen Zhang

Xiao-Wen Zhang was born in Hubei, China. In 2017, he obtained his bachelor's degree from Wuhan University working on heterocycle synthesis under the supervision of Professor Wen-Bo Liu. He is now a graduate student in the same research laboratory. His current research interest is mainly focused on asymmetric desymmetrization reactions.



Scheme 1 Representative dialkyl azodicarboxylates in this review.

also showed applications in the catalytic α-amination of carbonyl and cyanoacetates. Synthetically useful azodicarboxylates are dimethyl azodicarboxylate (DMAD), diethyl azodicarboxylate (DEAD), diisopropyl azodicarboxylate (DIAD), di-*tert*-butyl azodicarboxylate (DTBAD), dibenzyl azodicarboxylate (DBAD), bis-trichloroethyl azodicarboxylate (BTCEAD), di-*p*-chlorobenzyl azodicarboxylate (DCAD), di-4-nitrobenzyl azodicarboxylate (DNAD), dicyclopentyl azodicarboxylate (DCpAD) and adamantyl-tagged azodicarboxylate (BadMAD and BadEAD) *etc.* (Scheme 1).

Comprehensive reviews on the Mitsunobu reaction have been reported by Denton, Fletcher and Brimble.[1] Review articles about pericyclic, oxidation and C–N bond formation reactions were reported by Nair and Zhirov.[3] Our review emphasizes the developments and advances in the field of dialkyl azodicarboxylates as versatile reagents and covers examples about the synthesis of dialkyl azodicarboxylates, brief mechanistic aspects of the Mitsunobu reaction, and their applications in carbonylation, oxidation, electrophilic (enantioselective and C–H) amination, and radical-mediated amination reactions. We hope that this review will be useful for the better understanding of the field and serve as a handy reference for further developments.

2. Synthetic methods for dialkyl azodicarboxylates

Dialkyl azodicarboxylates are generally prepared from commercially available chloroformates and hyarazine.[3] Carboalkoxylation of hydrazine *via* hydrazodicarboxylate formation followed by oxidation delivers the corresponding dialkyl azodicarboxylate (Scheme 2a).

Dialkyl azodicarboxylates with different alkyl groups in the ester functionality can be easily synthesized by using alkyl carbazate instead of hydrazine (Scheme 2b).[3] On oxidation, the unsymmetrical hydrazine intermediates deliver the corresponding azo-compounds.

2.1. Synthesis from alcohol and 1,1′-carbonyldiimidazole

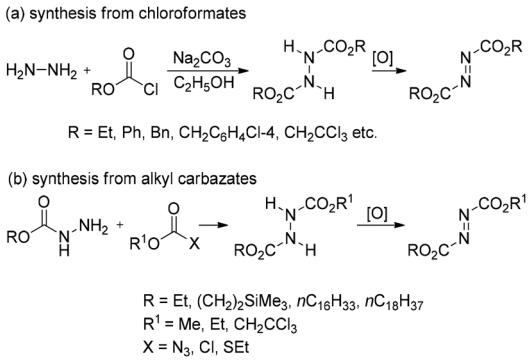
In 2006, Lipshutz and co-workers described a synthesis of di-*p*-chlorobenzyl azodicarboxylate (DCAD).[4] The process com-

Di Wu

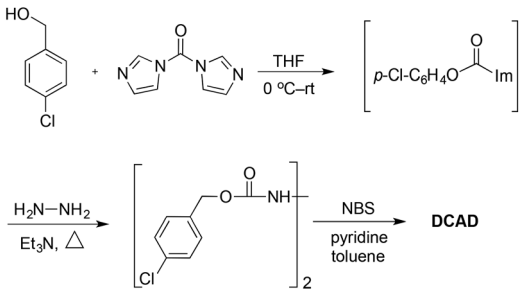
Di Wu was born in Hubei, China. In 2018, she obtained her bachelor's degree from Nankai University working on total synthesis. Then she joined Wuhan University and started working as a research assistant under the supervision of Prof. Wen-Bo Liu. Her current research is mainly focused on iron-catalyzed C–H bond amination reactions.

Zheng-Hui Guan

Zheng-Hui Guan received his BS and PhD degrees from Lanzhou University in 2004 and 2009, respectively, supervised by Prof. Yong-Min Liang. From 2007 to 2008, he was a visiting PhD student at Rutgers University, supervised by Prof. Xumu Zhang. In 2009, he joined the Department of Chemistry at Northwest University to start his independent career as an Associate Professor, and was promoted to Professor in 2014. His research interests currently focus on the development of novel and practical synthetic methodologies. He has published over 50 research papers. He was awarded the Chinese Chemical Society (CCS) Prize for Young Scientists (2015) and the Thieme Chemistry Journals Award (2016).



Scheme 2 General methods for the synthesis of dialkyl azodicarboxylates.



Scheme 3 Synthesis of DCAD by alcohol and CDI.

prised the preparation of carbamate by treating *p*-chlorobenzyl alcohol with 1,1′-carbonyldiimidazole (CDI) in tetrahydrofuran (THF), which was subsequently treated with hydrazine, leading to the formation of dicarboxylate derivative. Finally, oxidation of the corresponding dicarboxylate with *N*-bromosuccinimide (NBS) delivered the DCAD (Scheme 3).

Wen-Bo Liu

Wen-Bo Liu was born in China and received his Bachelor's degree in chemistry from Nankai University in 2006. He obtained his Ph.D. in organic chemistry (2011) from Shanghai Institute of Organic Chemistry (SIOC) under the supervision of Prof. Li-Xin Dai and Prof. Shu-Li You. After working as a postdoctoral scholar with Professor Brian M. Stoltz at Caltech, Wen-Bo became a professor of chemistry at Wuhan University in 2016. His group's research interests include silicon chemistry and asymmetric catalysis.

2.2. Synthesis from chloroformate and hydrazine hydrate

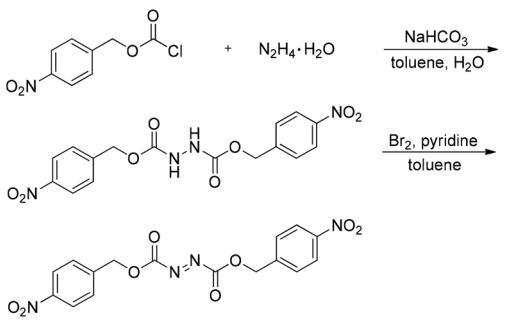
In 2011, Dai and co-workers reported an approach for the synthesis of DNAD and DCpAD, which were used as alternative Mitsunobu reagents.[5,6] DNAD was prepared in two steps. The first step involved the synthesis and separation of di-*p*-nitrobenzyl hydrazinedicarboxylate by the treatment of *p*-nitrobenzyl chloroformate and hydrazine hydrate with an aqueous solution of $NaHCO_3$ in toluene at room temperature. Subsequently, the purified hydrazine intermediate was oxidized by treating with Br_2 and pyridine in toluene at room temperature, which transformed the di-*p*-nitrobenzyl hydrazinedicarboxylate to bright yellow solid DNAD (Scheme 4).

2.3. Synthesis from alcohols and phosgene

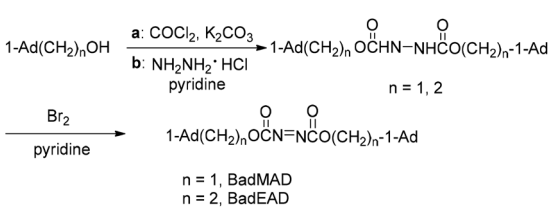
Curran and co-workers documented the synthesis of BadMAD and BadEAD.[7] In their method, the appropriate alcohols were treated with phosgene and hydrazine hydrochloride in the presence of K_2CO_3 and pyridine to form the corresponding dicarbonyl hydrazines. Afterwards, the hydrazine derivatives were oxidized with Br_2 to deliver the corresponding BadMAD and BadEAD (Scheme 5).

3. Mitsunobu reaction

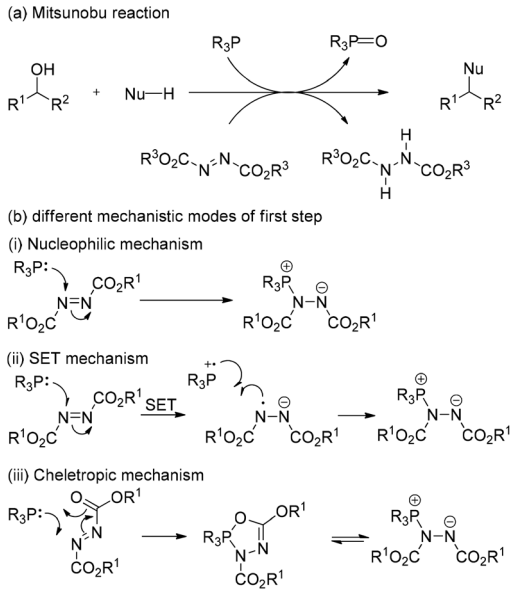
The Mitsunobu reaction was discovered by Oyo Mitsunobu in 1967. It involves the reaction of primary or secondary alcohols with an acidic pronucleophile to generate a variety of functional groups mediated by stoichiometric amounts of triaryl- or trialkyl-phosphine and dialkyl azodicarboxylates, in which



Scheme 4 Synthesis of DNAD from chloroformate and hydrazine hydrate.



Scheme 5 Synthesis of adamantyl-tagged derivatives of azodicarboxylate from alcohols and phosgene.



Scheme 6 Mitsunobu reaction and its first step mechanism modes.

the azodicarboxylates are used as key reagents to form the zwitterions.[1,8] In addition, this reaction also provides a convenient strategy that is widely used in the synthesis of natural products.[9] Apart from synthesis of esters, a wide variety of organic compounds, *e.g.* thioesters, azides, amines, ethers, thioethers, thiocyanides and cyanides, can be prepared by the Mitsunobu reaction (Scheme 6a).[9b] As a result, new C–N, C–S, C–O, C–X or C–C bond formations occur through this reaction, and the hydrazinedicarboxamide or hydrazinedicarboxylate and the phosphane oxide are also produced.[9]

The mechanism of the Mitsunobu reaction is equitably complex. Three different mechanistic modes were considered for the first step involving the reaction between phosphine and azodicarboxylate,[10] which results in the formation of the Morrison–Brunn–Huisgen (MBH) betaine (Scheme 6b); (1) a Michael-type nucleophilic mechanism (Scheme 6bi), (2) a single electron transfer process (Scheme 6bii), and (3) a cheletropic (4 + 2 cycloaddition) mechanism involving a ring formation (Scheme 6biii).

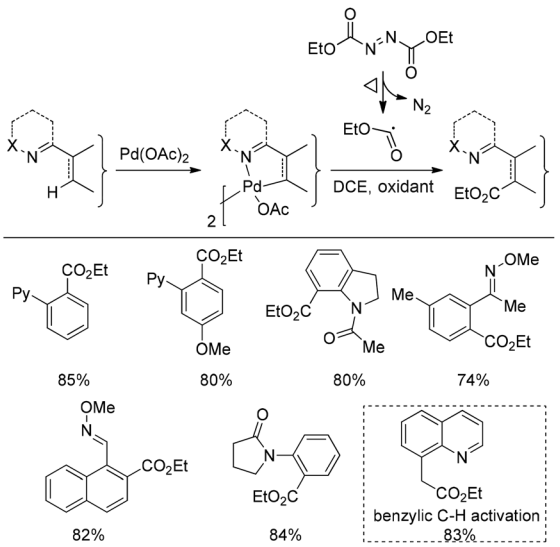
4. Carbonylation reactions

The utility of dialkyl azodicarboxylates as carbonylating reagents is less explored.[11–17] In the last few years, the direct carbonylation reaction has gained significant achievements. The use of dialkyl azodicarboxylates as carbonylating reagents is a complementation to other carboxylation reagents, such as CO and CO_2, which avoids the requisites of harsh reaction conditions (high pressure and temperature).[12–16]

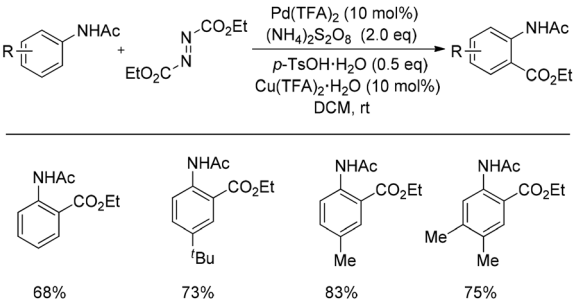
4.1. Carbonylation of aromatic C–H bonds

Yu and co-workers succeeded in developing the *ortho*-selective C–H bond ethoxycarbonylation of 2-arylpyridines, quinolines, 1-phenylpyrrolidin-2-one, 1-(indolin-1-yl)ethanone, and oximes with DEAD by using the palladium catalyst in the presence of an oxidant (Scheme 7).[11] When 8-methylquinoline was used as a substrate along with $Cu(OAc)_2$ employed as the oxidant, the benzylic carbonylated product was obtained in high yield. The reaction was triggered by chelation-assisted C–H bond activation. This procedure provided a unique strategy and an atom-economic alternative method for the synthesis of 8-substituted quinolines in a single step.

In 2014, You and co-workers developed a Pd-catalyzed ethoxycarbonylation of anilides with readily available DEAD *via ortho*-C–H functionalization.[12] A catalytic system consisting of $Pd(TFA)_2$ and an oxidant [$(NH_4)_2S_2O_8$] along with *p*-TsOH as an additive effectively delivered the ester-substituted anilides at room temperature (Scheme 8). Notably, the efficiency of ethoxycarbonylation was significantly improved by the use of $Cu(TFA)_2$ as an additive. The use of the copper(II) salt is believed to facilitate the SET (single electron transfer) process in this reaction. Both electron-donating and electron-withdrawing groups on acetanilides showed good reaction compatibil-



Scheme 7 Ethoxycarbonylation of aromatic C–H bonds with diethyl azodicarboxylate.

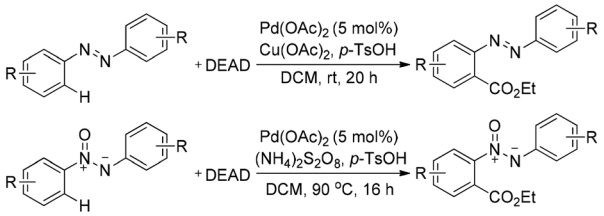


Scheme 8 Pd-Catalyzed *ortho*-C–H ethoxycarboxylation of anilides.

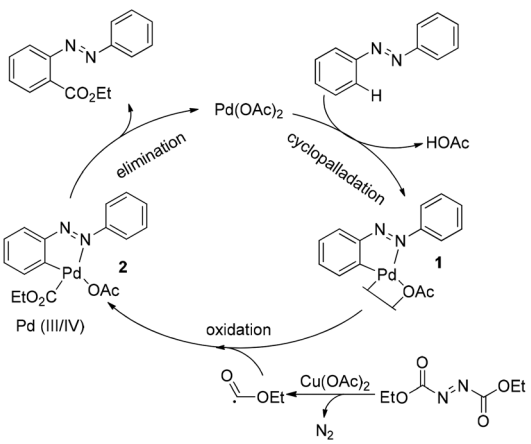
ities and delivered good yields of the corresponding C–H activated products.

Meanwhile, the Wang group established a Pd-catalyzed *ortho*-C–H bond ethoxycarbonylation of azoxybenzenes and azobenzenes (Scheme 9).[13] With $Cu(OAc)_2$ or $(NH_4)_2S_2O_8$ as the oxidant, both azoxybenzenes and azobenzenes with electron-donating and electron-withdrawing groups were found to be compatible with DEAD. Mechanistic investigations indicated that a free radical mechanism is operational. Therefore, a possible mechanism was proposed (Scheme 10). Initially, C–H palladation furnishes the intermediate **1**, followed by coordination with ethoxyacyl radical to generate either the Pd(IV) or Pd(III) intermediate **2**. Finally, reductive elimination of intermediate **2** delivers the desired product and regenerates the Pd(II) for the next catalytic cycle.

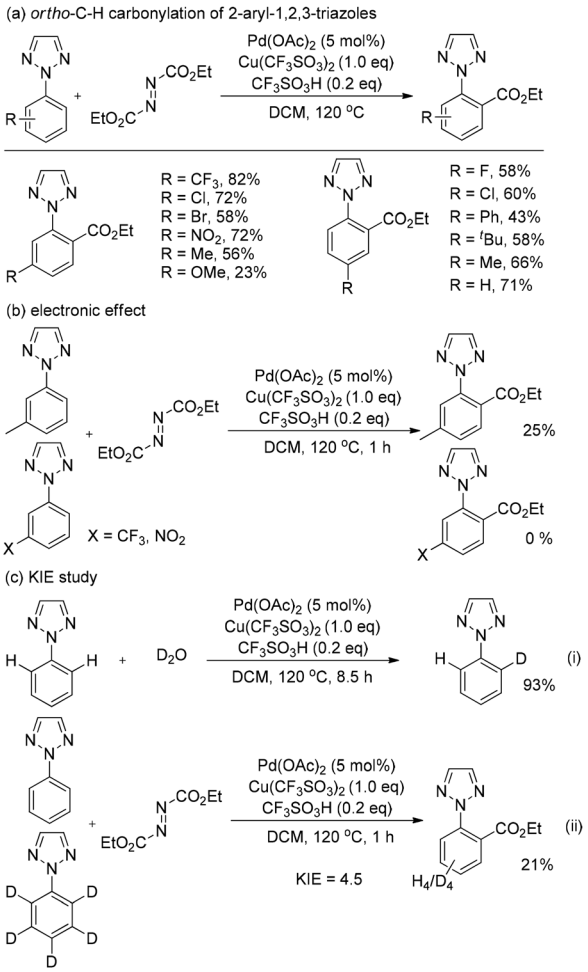
Very recently, Wu and co-workers developed a simple method for the esterification of 2-aryl-1,2,3-triazoles through the use of a palladium complex as the catalyst along with $Cu(CF_3SO_3)_2$ and CF_3SO_3H for the construction of the C–C bonds (Scheme 11).[14] The reaction tolerates a wide range of functional groups on the 2-aryl-1,2,3-triazoles (Scheme 11a). In addition, this method can also be used for the synthesis of the orexin receptor antagonist drug suvorexant. Mechanism elucidation by computational studies showed that an electrophilic C–H activation process may be involved in this process owing to a significant electronic effect (Scheme 11b). Further, a deuterium incorporation experiment indicated that the C–H activation step is reversible (Scheme 11ci). To look deeper into the reaction mechanism, a kinetic isotope effect (KIE) of 4.5 was noted (Scheme 11cii), which suggests that the cleavage of the C–H bond may be involved in the rate-determining step.



Scheme 9 Pd-Catalyzed *ortho*-C–H carbonylation of azobenzenes and azoxybenzenes.

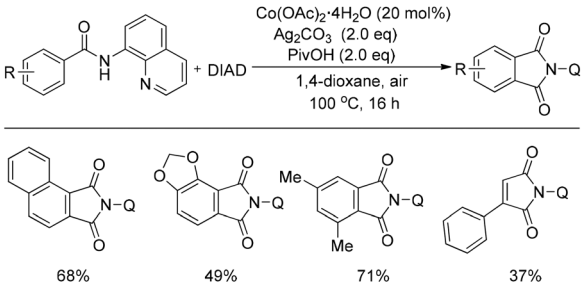


Scheme 10 Proposed mechanism.

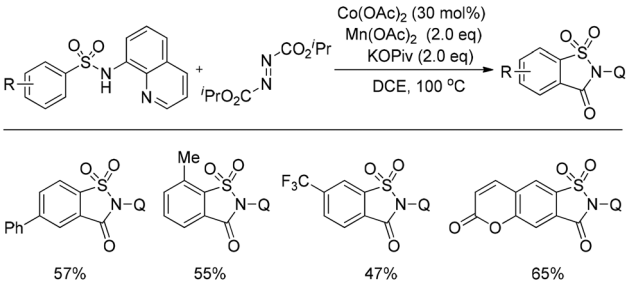


Scheme 11 Pd-Catalyzed *ortho*-C–H carbonylation of 2-aryl-1,2,3-triazoles.

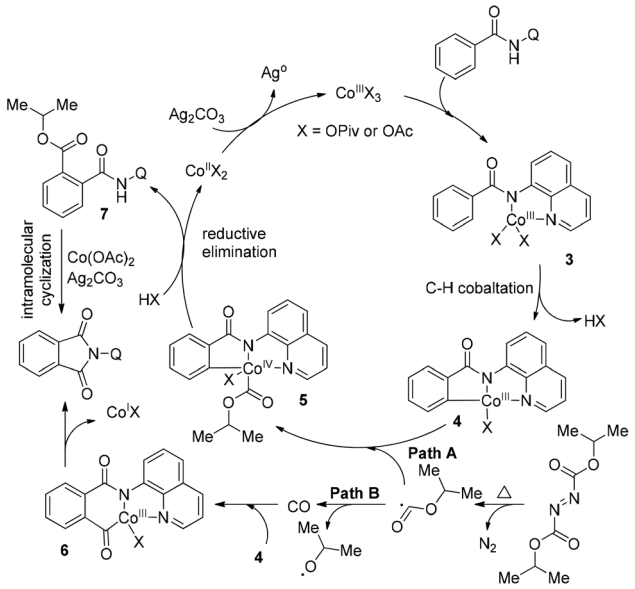
The Co-catalyzed aminoquinoline-directed $C(sp^2)$–H carbonylation of benzamides and sulfonamides was reported by the Zhang and Daugulis groups independently.[15] In 2016, Zhang and co-workers developed a simple procedure for the carbonylation of benzamides with $Co(OAc)_2$ as the catalyst. The chemistry showed excellent functional group tolerance with azodicarboxylates as the carbonyl source (Scheme 12).[15a] Mechanistic investigation indicates that the esteric radical and the CO gas generated by the decomposition of DIAD acted as the carbonylation moiety.[11] Based on the experimental findings, they proposed two mechanistic pathways (Scheme 13): (1) esteric radical formation and intramolecular cyclization of intermediate **7** (Path A); (2) through the generation of CO (Path B) and isopropyloxy radical from esteric radical. These radicals (esteric and isopropyloxy) may combine together to generate diisopropyl carbonate.[11] In Path B, the generated CO inserts the C–Co bond of the intermediate **4** to afford the species **6**.



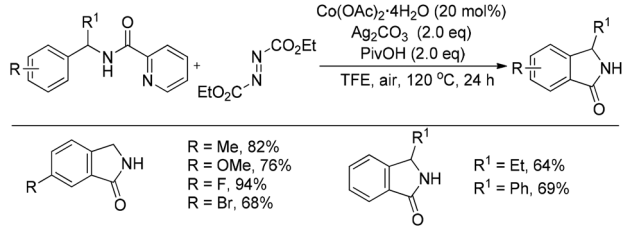
Scheme 12 Co-Catalyzed carbonylation of C(sp^2)–H bonds with azodicarboxylate.



Scheme 14 Co-Catalyzed carbonylation of sulfonamide C(sp^2)–H bonds with DIAD.



Scheme 13 Proposed mechanism.



Scheme 15 Co-Catalyzed C(sp^2)–H carbonylation of benzylamines.

Finally, the corresponding product was obtained *via* reductive elimination.

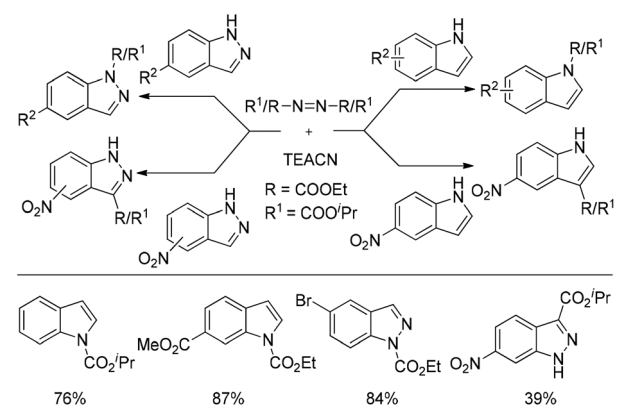
Recently, Daugulis and co-workers reported the carbonylation of sulfonamide with DIAD as the carbonyl source.[15b] The reaction system consisting of $Co(OAc)_2$ as the catalyst and Mn $(OAc)_2$ as the oxidant along with KOPiv in DCE effectively delivered the corresponding products derived from ester, amide and halogen substituted sulfonamides with DIAD (Scheme 14). Importantly, the 5-methoxyaminoquinoline directing group was successfully removed by treatment with BBr_3 and iodine(III) reagent, affording the methyl saccharin derivative in moderate yield.

Isoindolinones are important intermediates for the synthesis of pharmaceuticals and natural products. An interesting traceless directing group-assisted cobalt-catalyzed carbonylation of benzylamines was developed by Zhong and co-workers in 2017.[16] The desired isoindolinones were isolated in moderate to excellent yields (Scheme 15). It is worth pointing out that this carbonylation reaction was found to be compatible with a number of aromatic and hetero-aromatic substituted amines.

4.2. Carbonylation of heteroatoms

In 2013, Lalitha and co-workers documented a simple carbonylation reaction of indazoles and indoles with DEAD or DIAD in the presence of tetraethyl ammonium cyanide (TEACN) at room temperature (Scheme 16).[18] The chemistry of this reaction showed good functional group tolerance with various electron-donating and electron-withdrawing groups and led toward the formation of carbamates. Notably, nitro group-substituted indazoles and indoles resulted in the C–H carbonylation at the C3 position instead of on the nitrogen. However, the mechanism of this unique behavior of nitro-substituted indazoles and indoles is unclear.

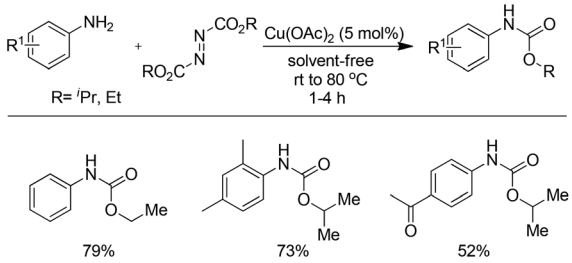
Recently, Guan and co-workers succeeded in the Cu-catalyzed carbonylation of anilines using DIAD and DEAD for the



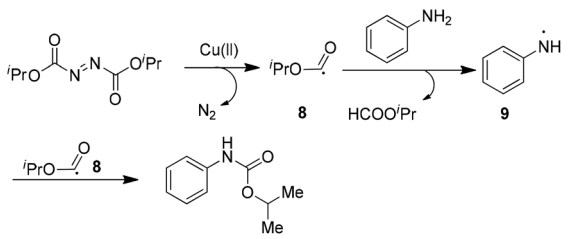
Scheme 16 Carbonylation of indoles and indazoles.

synthesis of carbamates under solvent-free conditions (Scheme 17).[19] Various electron-donating and electron-withdrawing groups on anilines are compatible with this method. However, the scope of the reaction is limited to primary anilines. The utility of heterocyclic analogues (pyridin-4-amine) was also explored, but the desired product was obtained in lower yield. They proposed a plausible reaction mechanism as depicted in Scheme 18. The decomposition of DIAD triggered by the copper catalyst generates the radical species **8**,[13] which abstracts a hydrogen atom from the aniline to form the aminyl radical **9**. The rebound of resulting radicals **8** and **9** delivers the corresponding products.

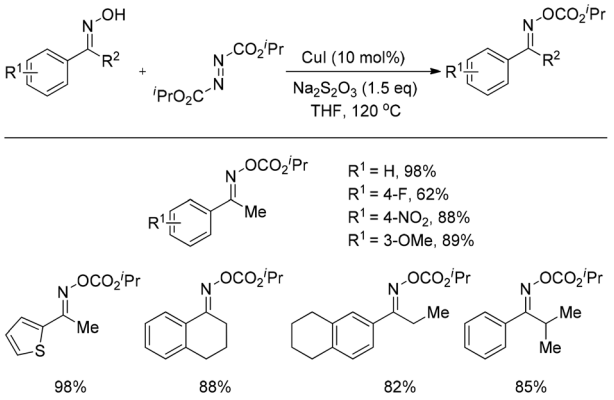
Another approach was reported by Guan and co-workers for the O–H bond carbonylation of oximes.[20] In this reaction, DIAD was involved in a less common isopropoxycarbonylation of ketoximes under a Cu and $Na_2S_2O_3$ catalytic system. DIAD acted as a selective precursor for the synthesis of oxime carbonates in high yields. It is worth noting that $Na_2S_2O_3$ played a very important role in this carbonylation reaction, which might facilitate the C–N bond cleavage of DIAD.[19] Furthermore, this transformation was applicable to a wide range of substituted ketoximes (Scheme 19). However, the reaction with aldoxime (4-methylbenzaldehyde oxime) was found to be less efficient. A mechanism was proposed as shown in Scheme 20. The thermal decomposition of DIAD produces the oxyacyl radical **8**, followed by the double oxidative addition with CuI to generate the copper(III) species **10**. Subsequently, species **10** abstracts a hydrogen atom from the oxime to afford another Cu(III) oxime intermediate **11**, which finally delivered the desired carbonates by the reductive elimination process.



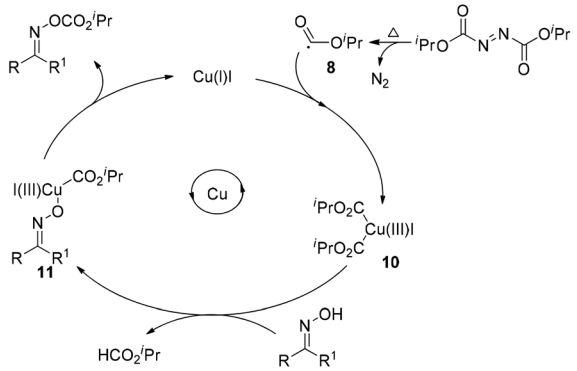
Scheme 17 Copper-catalyzed carbonylation of anilines by azodicarboxylates.



Scheme 18 Proposed mechanism.



Scheme 19 Synthesis of oxime carbonates.

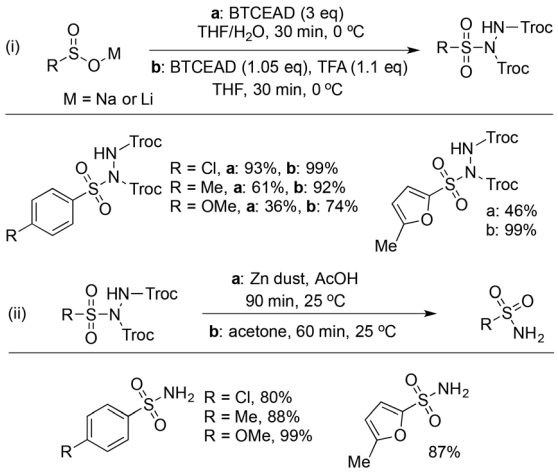


Scheme 20 Proposed mechanism.

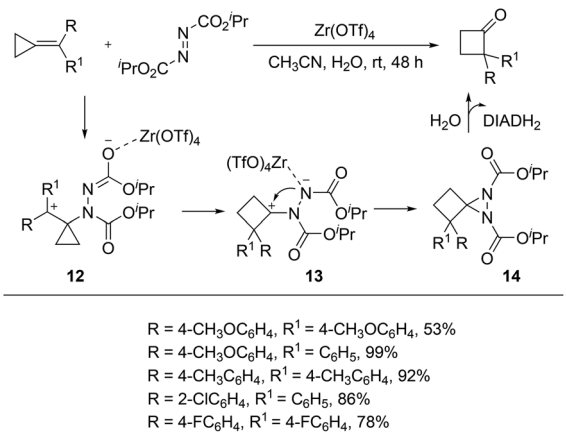
5. Azodicarboxylate as an oxidant

It is well known that dialkyl azodicarboxylates can oxidize different kinds of compounds, *e.g.* alcohols, hydrazines, thiols and hydroxylamines.[21] It is an efficient reagent for the convenient oxidation of compounds containing sulfur (*i.e.* thiols and thiophenols) to symmetrical or unsymmetrical disulfides.[22] The derivatives of aryl- and alkyl-sulfinic acids were easily oxidized to the corresponding sulfonylhydrazides with BTCEAD (Scheme 21i).[23] Sulfonylhydrazides could be further reduced to sulfonamides by treating with zinc dust (Scheme 21ii).

In 2004, Shi and Shao found that methylenecyclopropanes (MCPs) underwent ring expansion when treated with DEAD or DIAD.[24] Optimization of the reaction conditions revealed that a catalytic system consisting of $Zr(OTf)_4$ in CH_3CN/H_2O gave the optimal results. For aromatic substituted MCPs, the reaction proceeded efficiently to deliver the corresponding cyclobutanones in good to high yields (Scheme 22). In this reaction, Lewis acid activates the DIAD toward its reaction with the MCP substrate to generate a zwitterion intermediate **12**, which upon rearrangement gives a ring expansion spirocyclic **14** through **13**. Then the hydrolysis of **14** affords the product and hydrazine.



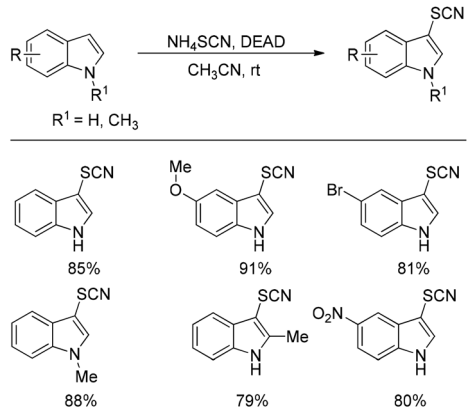
Scheme 21 Synthesis of sulfonylhydrazides and sulfonamides.



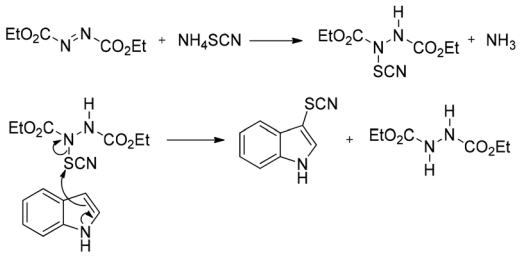
Scheme 22 Methylenecyclopropane ring expansion in the presence of DIAD.

In 2010, Iranpoor and Firouzabadi's group reported the thiocyanation of aromatic amines with NH_4SCN and DEAD.[25] In this reaction, indoles substituted with electron-donating/-withdrawing groups delivered the corresponding product in good to excellent yields (Scheme 23). The scope of this reaction was not only limited to indoles, but various substituted anilines were also found to be compatible and were converted into the corresponding 4-thiocyanatoanilines in high to excellent yields. Notably, under the standard reaction conditions, phenol and anisole failed to deliver the corresponding product. They proposed a reaction mechanism as shown in Scheme 24, in which DEAD is activated by NH_4SCN to result in the generation of diethyl 1-thiocyanatohydrazine-1,2-dicarboxylate. Then nucleophilic attack of indole to this species delivers the desired product and diethyl hydrazodicarboxylate (2H-DEAD).

The synthesis of N-heterocyclic compounds is one of the most important processes in organic chemistry. This process leads toward the synthesis of fundamental organic compounds



Scheme 23 Thiocyanation of aromatic amines.



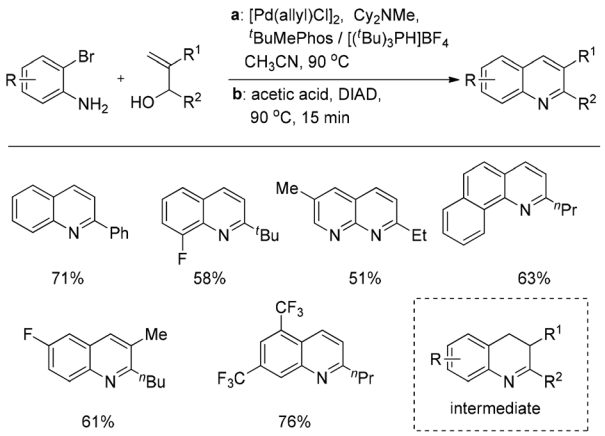
Scheme 24 Proposed mechanism.

that are prevalent in pharmaceutical and natural products.[3] In this regard, indoles and quinolines constitute a biologically important class of organic compounds.[26] Dialkyl azodicarboxylate as a versatile reagent play an important role in the synthesis and transformation of such N-heterocycles.[27,28]

In 2011, Stone reported a modified version of the Larock method *via* a Heck reaction for the synthesis of substituted quinolines.[26b] The first step of this process is a palladium-catalyzed Heck reaction of *ortho*-bromo-anilines with allylic alcohols followed by an intramolecular imine formation that leads to a dihydroquinoline intermediate or a mixture of quinoline and tetrahydroquinoline formed by disproportionation (Scheme 25). The second step involves the dehydrogenation of hydroquinoline by the addition of DIAD in the reaction mixture after a specific interval, which delivered the desired substituted quinoline. This one-pot, two-step method was applicable to various substituted 2-bromoanilines as well as various allylic alcohols.

5.1. Oxidation of alcohols

The conversion of alcoholic groups to their corresponding carbonyl groups *via* oxidation is one of the widely used fundamental transformations in synthetic chemistry.[29,30] Large numbers of useful methods have been developed. Oxidation of alcohols by DEAD to the corresponding carbonyl compounds was first reported by Yoneda and co-workers in 1966.[31] This method generated 2H-DEAD as a single by-product, which could be easily separated by chromatographic technique.



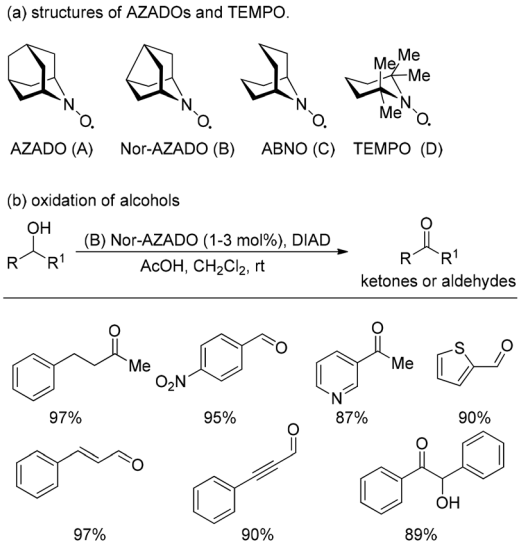
Scheme 25 Synthesis of substituted quinolines.

Importantly, the hydrazodicarboxylate by-product can be easily reoxidized with iodobenzene diacetate (IBD) in methylene chloride at room temperature to generate the DEAD (Scheme 26a).[32]

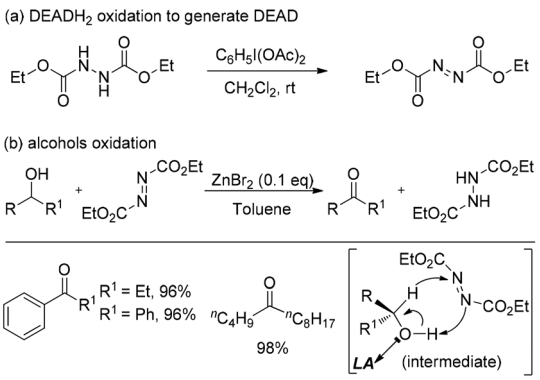
In 2009, Grée and Cao reported the oxidation of alcohols to their carbonyl products by the combination of DEAD and a Lewis acid.[21] Optimization studies revealed $ZnBr_2$ to be an ideal choice (Scheme 26b). The scope of the reaction was demonstrated with primary and secondary alcohols, but propargylic or allylic alcohols were not tolerated. The reaction is proposed to proceed *via* a six-membered cyclic transition state formed by the DEAD and the $ZnBr_2$-activated alcohol (Scheme 26b).

The chemistry of the oxidative transformation of hydroxylamines to nitroso derivatives with DEAD under mild reaction conditions is already known.[33] Inspired by this work, Iwabuchi and co-workers reported that nitroxyl radicals catalyzed the oxidation of alcohols to the corresponding carbonyl derivatives by DIAD.[34] 2-Azaadamantane-, 9-azanoradamantane-, and 9-azabicyclo[3.3.1]nonane-type nitroxyl radicals (AZADOs; AZADO (A),[35a,f] Nor-AZADO (B),[35c] and ABNO (C);[35d] Scheme 27a), which constitute the less sterically hindered class of nitroxyl radicals, were revealed to have potentially higher reactivity as compared with TEMPO (D).[35] Optimization studies found Nor-AZADO to be an ideal catalyst for the oxidation of alcohols to aldehydes or ketones with DIAD (Scheme 27b).[34] This method was applicable to a variety of alcohols, including double- or triple-bond containing alcohols and 1,2-diols. In light of control experiments, AZADOH and DIAD in the absence of acetic acid delivered no alcohol oxidation product except the formation of AZADO. However, oxidation of alcohol proceeded smoothly in the presence of acetic acid. These results suggest that the oxoammonium salt was generated by an acid-catalyzed disproportionation of AZADO (Scheme 28). The oxoammonium salt oxidizes the alcohol to generate the corresponding carbonyl compound and AZADOH. DIAD acted as an efficient oxidant for generating an AZADO from AZADOH to continue the catalytic cycle.

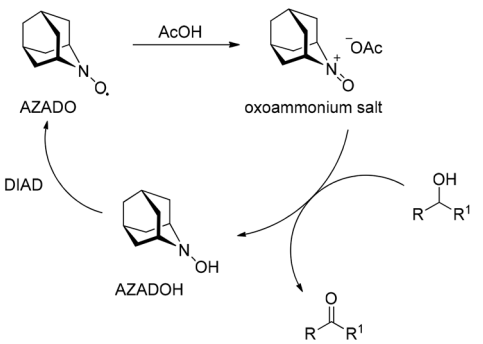
From the environmental perspective (*i.e.* green synthetic techniques), oxidation reactions through oxygen or air are the



Scheme 27 Oxidation of alcohols to carbonyl compounds with DIAD and Nor-AZADO and structures of nitroxyl radicals.



Scheme 26 Hydrazodicarboxylate oxidation to generate DEAD and the oxidation of alcohols to carbonyl compounds.

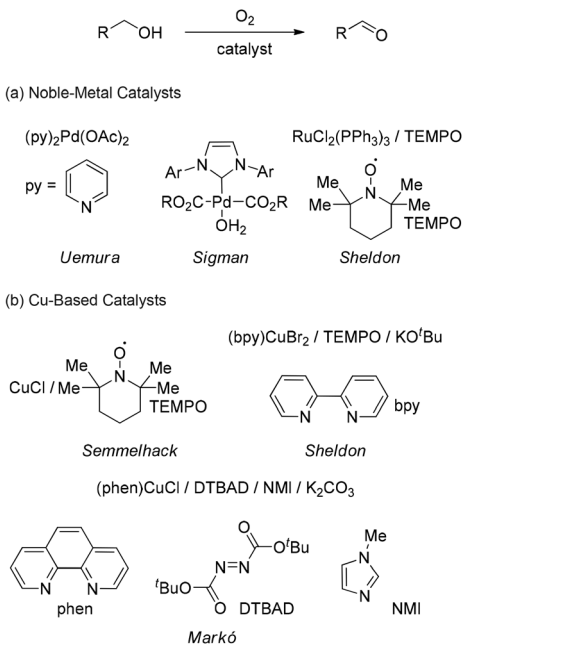


Scheme 28 Proposed mechanism.

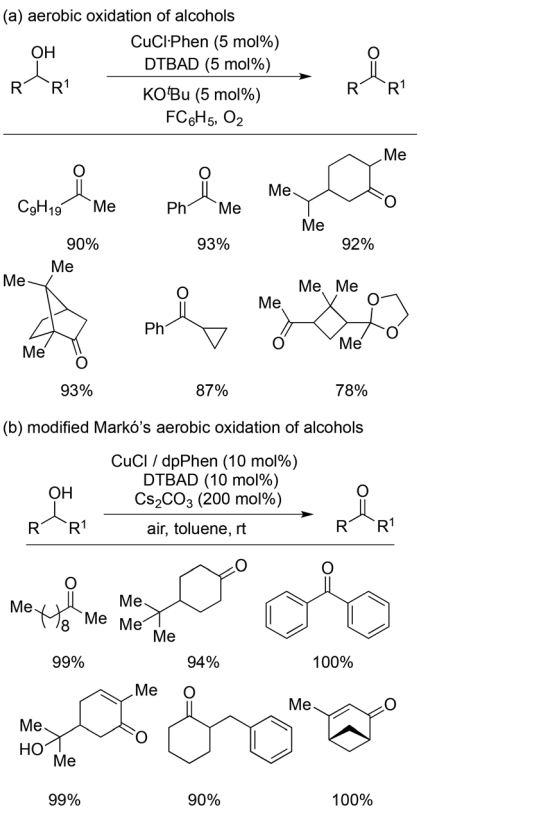
most environmentally friendly methods for the oxidation of alcohols.[35b,36] However, metal-catalyzed reactions are the key toolbox for organic chemistry. They have been widely applied in organic synthesis (such as drug synthesis, natural product synthesis and green chemistry).[37] In the past few decades, transition metal-catalyzed functionalization reactions have gained attention in the field of organic synthesis for challenging transformations.[38] However, most of these reactions require noble metal catalysts (such as Pd, Rh, or Ru).[38,39] Recent studies have highlighted copper as a versatile reagent.[40] Copper-catalyzed reactions have gained significant attention because of two important advantages: (1) copper is inexpensive, insensitive to air, robust and readily available as compared to other transition metal catalysts; (2) it is an efficient and environmentally friendly catalyst for the oxidation of alcohols to aldehydes and ketones.[41]

Recently, a number of catalytic systems have been developed for the aerobic oxidation of alcohols through complexes of precious metals, *i.e.* Pd[42,43] and Ru[44] (Scheme 29a).[41e] These catalytic systems work effectively with a broad range of alcohols, including primary and secondary benzylic, allylic and aliphatic substrates. Aerobic alcohol oxidation by first-row transition metals exhibits wider functional group tolerance (*e.g.*, Cu,[45,46] Co,[47] Fe[48] and V[49]). However, Cu-catalyzed reactions, specifically those utilizing TEMPO[45] or dialkyl azodicarboxylate[46] as an oxidant (Scheme 29b), have emerged as an effective catalytic system.[41e]

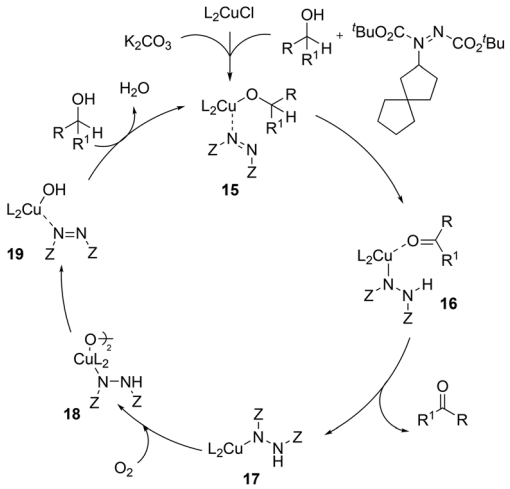
Markó and co-workers have developed a number of methods for the aerobic oxidation of alcohols employing copper catalysts.[41a,46,50,51] Those methods effectively oxidize a variety of functionalized primary and secondary benzylic, allylic and aliphatic alcohols to the corresponding carbonyl derivatives in the presence of a combination of copper catalyst and dialkyl azodicarboxylate. Optimization of the reaction conditions revealed a catalytic system consisting of CuCl·Phen (1,10-phenanthroline), KO^{t}Bu and DTBAD to be suitable for this transformation (Scheme 30a).[51] Based on this work, Tsunoda group documented the modified version of Markó's aerobic oxidation procedure.[52] The reaction conditions including CuCl, 4,7-diphenyl-1,10-phenanthroline (dpPhen), DTBAD (di-*tert*-butyl azodicarboxylate) and Cs_2CO_3 were found to be ideal for oxidizing alcohols to their corresponding carbonyl groups at room temperature (Scheme 30b). This method was applicable to secondary and primary alcohols. A catalytic cycle for this type of oxidation was proposed as shown in Scheme 31.[51] First, copper–alkoxide/azo complex **15** is formed by ligand exchange between the alcohol and the chloride substituent of Phen·CuCl in the presence of a base. A hydrogen-transfer reaction within complex **15** generates the carbonyl-bound hydrazine–copper complex **16**, which upon liberation of the desired ketone reacted with oxygen and produced the binuclear Cu(II) peroxide **18**. Subsequently, hemolytic cleavage of the O–O bond followed by a hydrogen atom abstraction affords the Cu(I) hydroxyl intermediate **19**. Finally, exchange between the OH ligand and the alcohol substrate, with the release of water, regenerates the active catalyst **15**. This work represents an important example whereby the azodicarboxylate



Scheme 29 Catalytic systems for the aerobic oxidation of primary alcohols.



Scheme 30 Cu-Catalytic aerobic oxidation of alcohols.



Scheme 31 Proposed mechanism; L_2 = Phen.

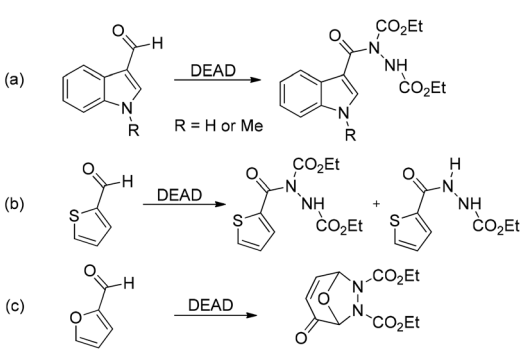
can be regenerated during the reaction and also plays its role as a catalyst rather than a stoichiometric reagent.

5.2. Oxidation of aldehydes

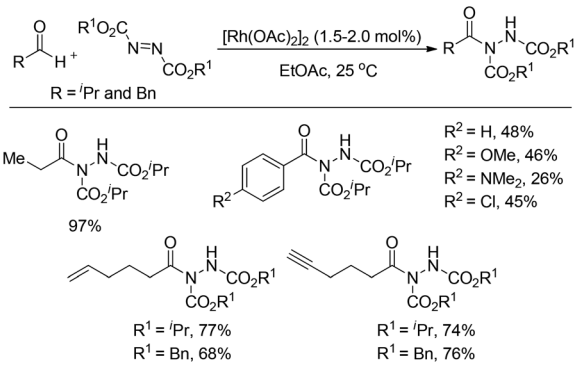
In 1997, Jennings and co-workers reported a hydroacylation reaction of azodicarboxylates by treatment of 3-formylindoles and 2-formylthiophene DEAD (Scheme 32a and b).[53] However, under standard reaction condition, 2-formylfuran delivered a [3.2.1] bicyclic adduct as the major product (Scheme 32c).

In 2004, Lee and Otte reported a rhodium-catalyzed hydroacylation reaction of aldehydes and dialkyl azodicarboxylate for the synthesis of hydrazino imides (Scheme 33).[54] With rhodium acetate $[Rh(OAc)_2]_2$ as the catalyst, the scope of this reaction includes aliphatic saturated aldehydes, as well as unsaturated and aromatic aldehydes. Both DIAD and DBAD showed good compatibility and delivered the corresponding products in good to excellent yields. After this breakthrough, the Ni group and the Caddick group reported the hydroacylation of aldehydes with dialky azodicaboxylate in water.[55,56] Notably, these approaches proceed efficiently without using any catalyst.

A copper-catalyzed method for the hydroacylation of aldehydes with DIAD was reported by Peng and co-workers,[57] in

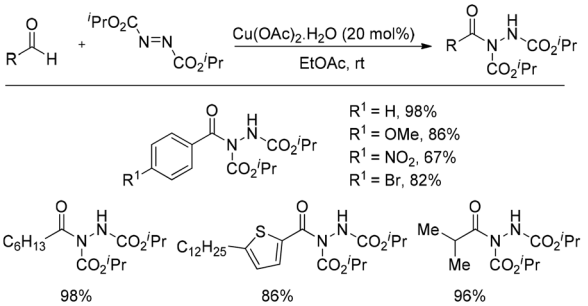


Scheme 32 Transformation of aldehydic C–H bond.

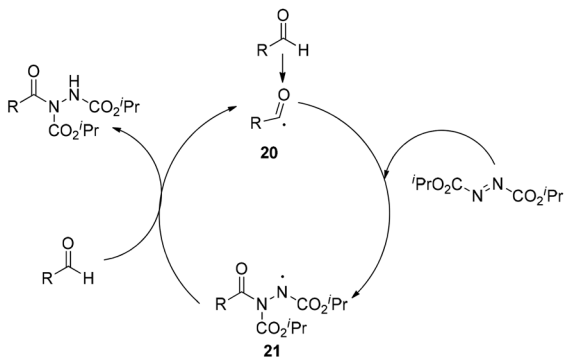


Scheme 33 Hydroacylation of aldehydes.

which $Cu(OAc)_2{\cdot}H_2O$ and EtOAc at ambient conditions were found to be optimal for hydroacylation of aldehydes (Scheme 34). This method was applicable to aromatic as well as aliphatic aldehydes. The reaction tolerates a broad range of substituents on aromatic rings and delivers the corresponding products in moderate to excellent yields. They proposed a radical reaction mechanism (Scheme 35). The mechanism does not provide any related information regarding the copper catalyst. However, it has been recently reported that azodicarboxylate decomposes to generate the acyl radicals in the presence of Cu(II) salts.[13,14,19] The reaction is initiated by the abstraction of a hydrogen atom from aldehyde to generate the



Scheme 34 The Cu-catalyzed hydroacylation reaction of aldehydes with azodicarboxylates.



Scheme 35 Proposed mechanism.

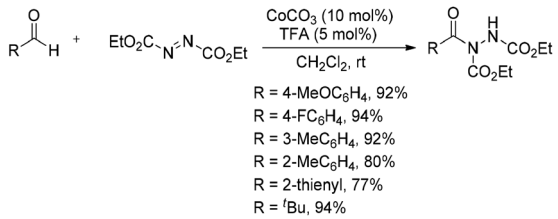
radical species **20**. The addition of **20** to azodicarboxylate resulted in the formation of radical intermediate **21**, followed by the radical abstraction of intermediate **21** and the aldehyde substrate led to the generation of the hydroacylation product.

In 2014, Xu and co-workers developed a new Lewis- and Brønsted-acid-catalyzed strategy for the hydroacylation of aldehydes.[58] The combination of trifluoroacetic acid (TFA) and $CoCO_3$ was found to be crucial to this transformation (Scheme 36). Mechanistic investigation indicated that the reaction involves a radical pathway. Addition of a catalytic amount of TEMPO to the reaction completely suppressed the formation of the corresponding product. ESR (electron paramagnetic resonance) studies also support the presence of a nitrogen-centered radical in the reaction mixture.

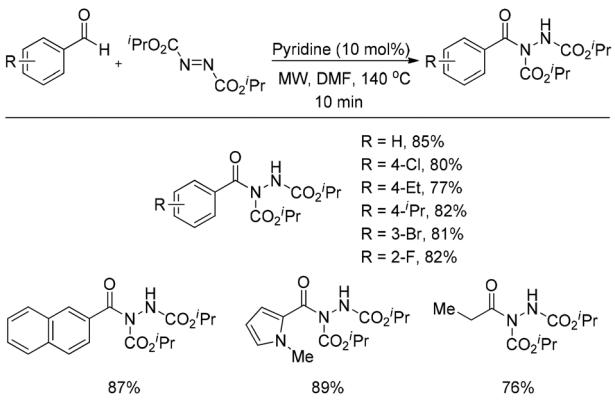
Recently, Muthusubramanian and co-workers documented a microwave-assisted and metal-free approach for the hydroacylation of aldehydes.[59] In this reaction, pyridine was identified as a powerful catalyst in the presence of DMF solvent. This reaction was applicable to a wide range of phenyl-substituted aldehydes (Scheme 37). However, aliphatic aldehyde (*i.e.*, propionaldehyde) and heterocyclic aldehyde (1-methyl-1*H*-pyrrole-2-carbaldehyde) also delivered the corresponding products in high yields. They proposed an ionic reaction mechanism (Scheme 38).

5.3. Amine transformations

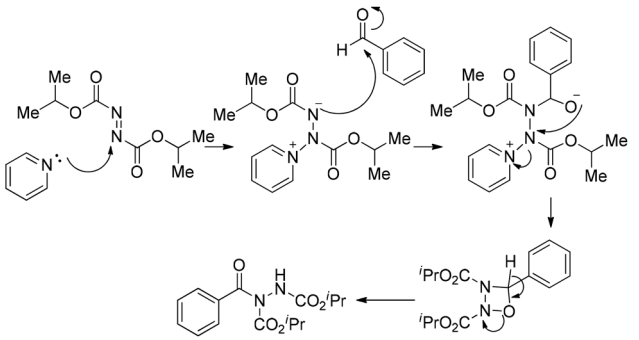
Dialkyl azodicarboxylates are very useful for the transformation of alkylamines to imines by oxidation, which can be



Scheme 36 Lewis- and Brønsted-acid-catalyzed hydroacylation of aldehydes.



Scheme 37 Pyridine-catalyzed hydroacylation of aldehydes with azodicarboxylates.

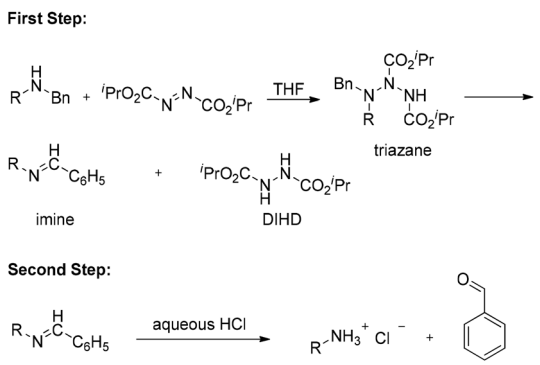


Scheme 38 Proposed mechanism.

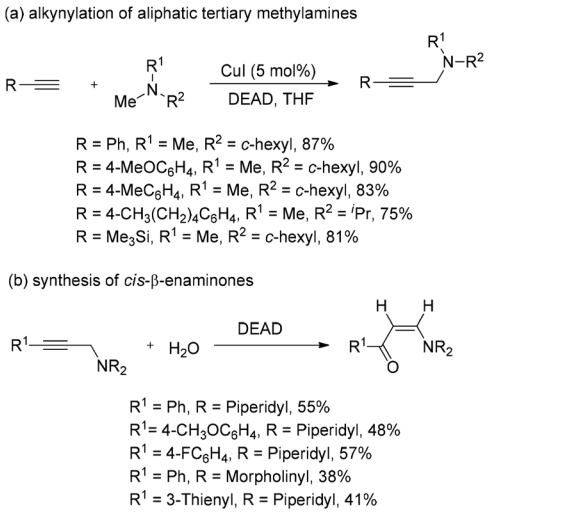
further modified into amines or the corresponding carbonyl derivatives (Scheme 39).[60–62] In this regard, imines furnished by the reaction of dialkyl azodicarboxylate and alkylamines could be used for further transformation with various nucleophiles.

In 2009, Li and Xu established the Cu/DEAD catalyzed alkynylation of aliphatic tertiary methylamines with terminal alkynes.[63] The scope of this reaction covered aryl-substituted terminal alkynes and aliphatic alkynes (Scheme 40a). It is noteworthy that propargylic amine derivatives could be further transformed into *cis*-β-enaminones *via* dehydrogenation by DEAD in the presence of water (Scheme 40b).[64] Based on their studies, a mechanism was proposed (Scheme 41).[63] Initially, tertiary methylamine and DEAD undergo a nucleophilic addition and result in the formation of species **22**. Then transformation of species **22** provides the imine cation species **24** and 1*H*-DEAD **25**. The deprotonation of the terminal alkyne by the nitrogen anion **25** in the presence of Cu-catalyst generates the 2H-DEAD and copper alkynlide (path a). Furthermore, addition of copper alkynlide to imine cation species **24** delivered the corresponding product and generates the copper catalyst. However, for aryl-substituted imines (R^1 or R^2 = ph), preferably the reaction operates through path b where **25** directly adds to **24**.

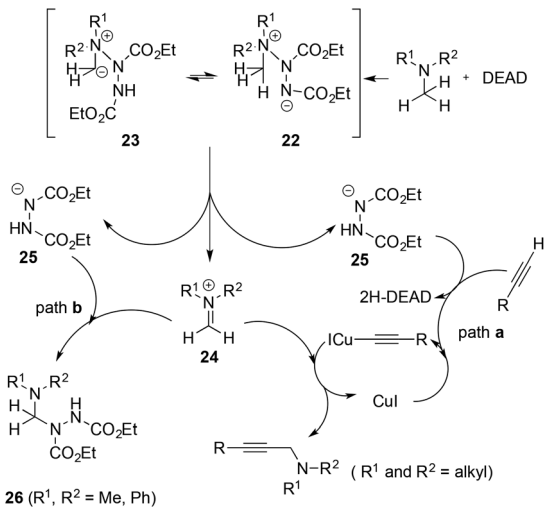
In 2013, Hu and co-workers reported a metal-free dehydrogenative coupling of tertiary amines with α-fluorinated sulfones for the synthesis of β-fluorinated amines by DIAD.[65] This dehydrogenative coupling reaction proceeded in moderate to



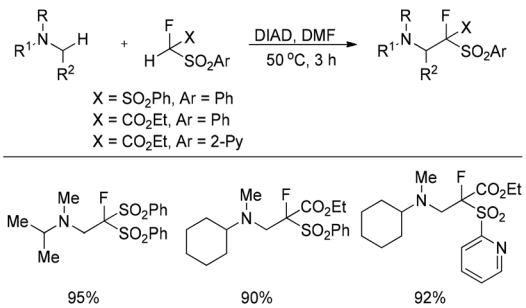
Scheme 39 Amine transformations.



Scheme 40 Alkynylation of aliphatic tertiary methylamines and the synthesis of *cis*-β-enaminones.

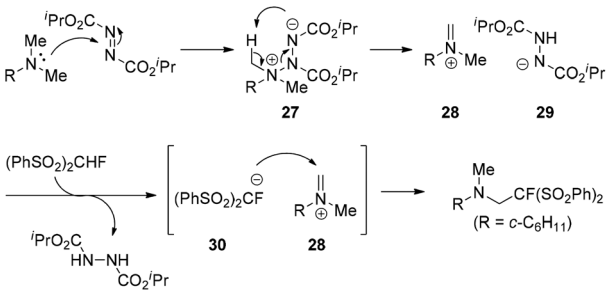


Scheme 41 Proposed mechanism.

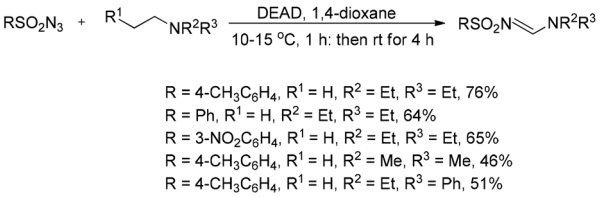


Scheme 42 DIAD-mediated fluoromethylation of tertiary amines.

excellent yields (Scheme 42). They proposed that addition of tertiary amines and DIAD generates a zwitterionic intermediate **27**. A subsequent 1,4-hydrogen shift of the zwitterionic intermediate provides an iminium cation **28** and a nitrogen anion **29**. Subsequently, the deprotonation of α-fluorinated sulfone by **29** forms 2H-DIAD and fluorinated sulfone anion **30**, which adds to the iminium cation **28** to deliver the desired product (Scheme 43).



Scheme 43 Proposed mechanism.

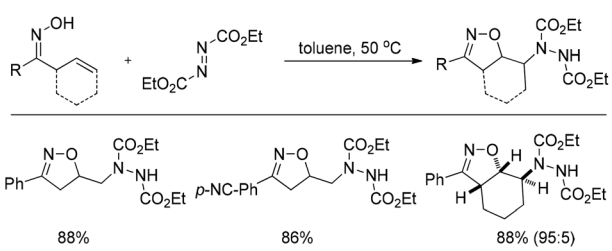


Scheme 44 Synthesis of sulfonyl amides.

In 2008, Li and co-workers reported the DEAD-mediated oxidative dehydrogenation of tertiary amines for the synthesis of sulfonyl amidines from sulfonyl azides.[66] This reaction proceeded smoothly without any assistance of a metal catalyst. This transformation was applicable to a wide range of sulfonyl azides and tertiary amines substrates for the synthesis of *N*-sulfonylamidines in good to excellent yields (Scheme 44).

6. Azodicarboxylates as electrophiles

The large majority of research methods use dialkyl azodicarboxylates as the *N*-electrophiles to produce hydrazines. In 2012, Han and co-workers reported the synthesis of isoxazolines by the reaction of oxime with TEMPO or DEAD.[67] TEMPO or DEAD act as a radical initiator as well as a radical scavenger in the reaction (Scheme 45).

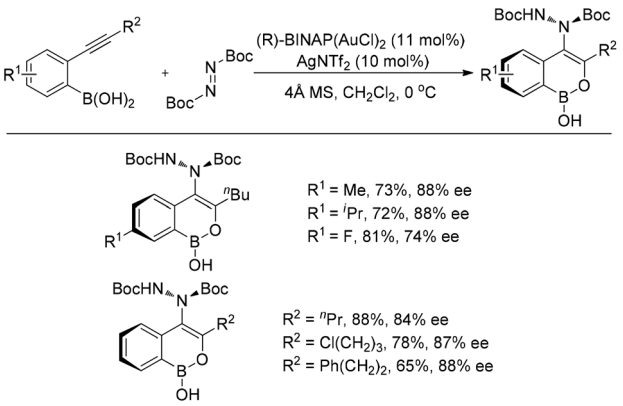


Scheme 45 Amination of alkenes for the synthesis of isoxazolines.

Besides oximes, Han and co-workers also documented the hydrazone radical-promoted synthesis of pyrazolines and tetrahydropyridazines from β,γ-unsaturated and γ,δ-unsaturated hydrazones, respectively.[68] The process involves the addition of hydrazone radicals to C–C bonds to form a new carbon radical followed by trapping with DIAD (Scheme 46).

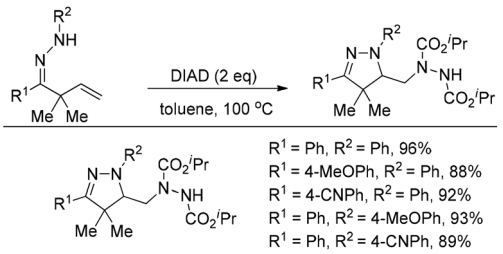
The catalytic enantioselective electrophilic amination reactions using diazocarboxylates are an important application for the construction of nitrogen-containing tetrasubstituted stereogenic carbon centers.[2] These compounds are widely found in natural and biologically active products.[2c] In this regard, an important example of scandium-catalyzed dearomatization of substituted 2-naphthols was reported by Luan and co-workers.[69] The reaction between substituted 2-naphthols and azodicarboxylates proceeded well in the presence of chiral $Sc(OTf)_3$/pybox complex under mild conditions. Various 1,3-disubstituted 2-naphthols and 1-substituted 2-naphthols efficiently participated in this transformation, affording the corresponding dearomatization products in high yields with excellent enantioselectivities (Scheme 47).

Gold- and silver-catalyzed cycloisomerization–amination reactions have been reported by the Gong and He groups.[70,71] In the gold-catalyzed reaction, a chiral gold(I) complex enables the reaction of 2-(alkynyl)phenyl boronic acids and diazenes for the asymmetric synthesis of heteroaryl atropisomers in high yields (Scheme 48).[70] A wide range of substrates bearing different functionalities was tolerated by this method. The chirality of these compounds is relatively stable at ambient temperature but racemization occurs at high temperature.

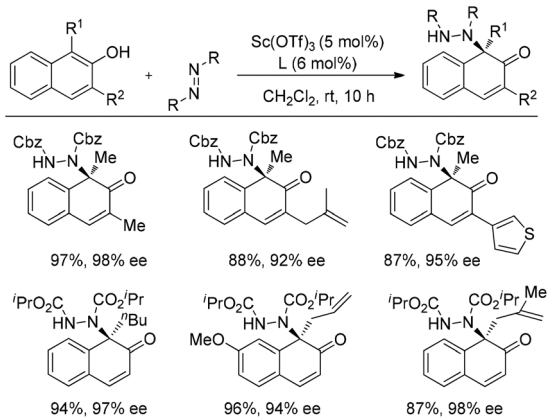


Scheme 48 Cycloisomerization-amination of 2-(alkynyl)phenyl boronic acids.

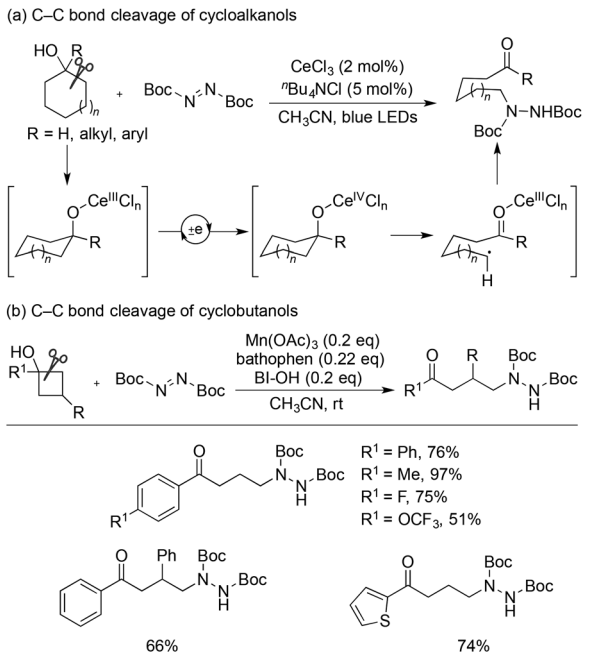
In 2016, Zuo and co-workers reported a visible-light-induced C–C bond cleavage of cycloalkanols by cerium(III) chloride.[72] This reaction not only works well with tertiary cyclic alcohols of varying ring size but secondary cyclic alcohols were also found to be equally compatible. In this reaction system, cerium(III) was oxidized to the cerium(IV) species by visible-light irradiation, followed by C–C bond scission to generate a carbon radical. Subsequently, the addition of DTBAD delivered the aminated product (Scheme 49a). In the same year, Zhu and co-workers reported the Mn-promoted C–C bond cleavage and amination of cyclobutanols for the synthesis of alkyl hydrazines.[73] In this method, cyclobutanol substrate underwent the chain-reaction mechanism to generate



Scheme 46 Synthesis of pyrazolines.



Scheme 47 Dearomatization of 2-naphthols.



Scheme 49 C–C Bond cleavage and amination by DTBAD.

the alkyl carbon radical, which was then followed by DTBAD addition to afford the alkyl hydrazine. The reaction showed excellent regioselectivity and good functional group tolerance under mild reaction conditions (Scheme 49b).

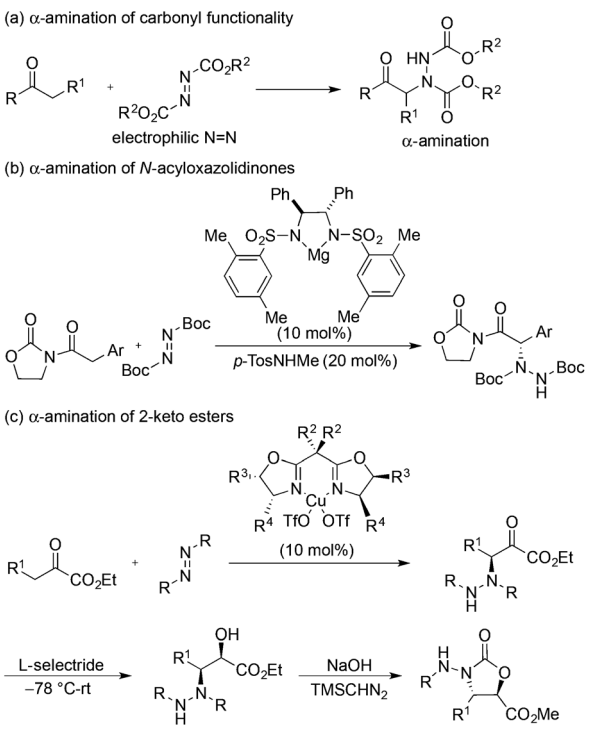
6.1. α-Amination of carbonyl functionalities

Dialkyl azodicarboxylates, are strong electrophiles (electrophilic N=N) owing to the presence of two electron-withdrawing carboxylic groups. The α-amination reaction resulted in the formation of a new C–N bond at the α-position of carbonyl derivatives.[55] A general reaction for α-amination of the carbonyl functionality with dialkyl azodicarboxylates as the electrophilic aminating reagent is shown in Scheme 50a.[74]

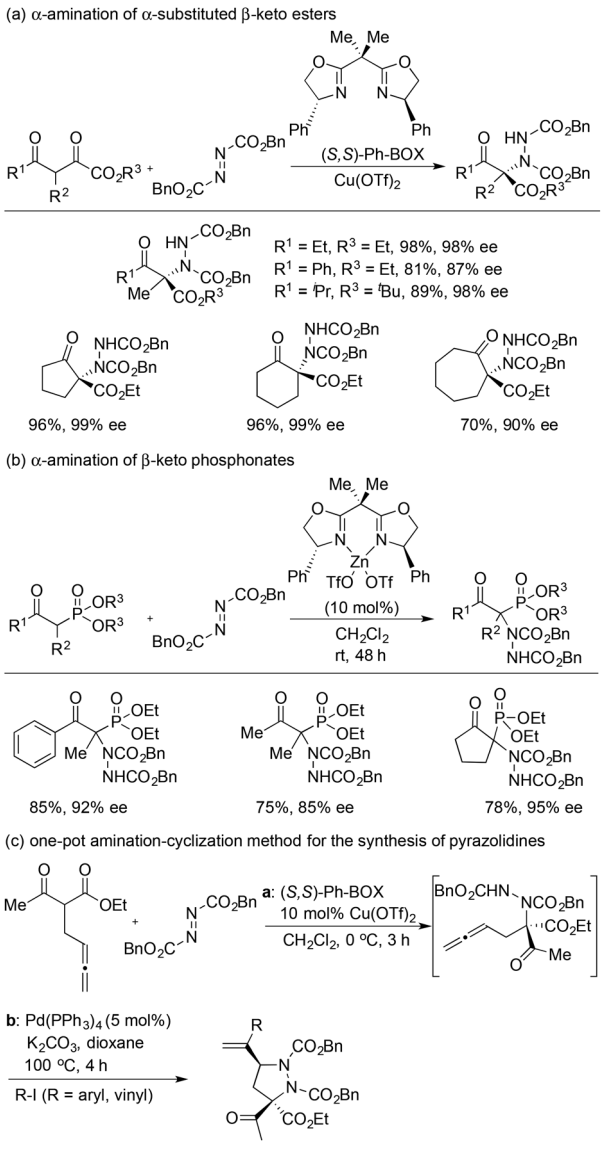
Dating back to 1954, the electrophilic amination of carbonyl compounds was observed by Huisgen while treating cyclohexanone with DEAD.[75] In the last few decades, this strategy has been used for enantioselective synthesis by using chiral organocatalysts or metal complexes. α-Amination of *N*-acyl oxazolidinones with DTBAD was documented by Evans and Nelson by using a chiral magnesium bis(sulfonamide) complex (Scheme 50b).[76a] The turnover of the catalyst was enhanced by using *p*-TosNHMe as an additive, leading toward high enantioselectivity. Later, the same group also demonstrated the enantioselective amination of enolsilanes using a C_2-symmetric copper(II) complex as a chiral Lewis acid.[76b]

Enantioselective α-amination of 2-keto esters with azodicarboxylates using chiral bisoxazoline copper(II) complexes was reported by Jørgensen's group (Scheme 50c).[77] This reaction offers a convenient method for producing optically active *syn*-β-amino-α-hydroxy esters. Jørgensen and co-workers also documented the α-amination of α-substituted β-keto esters with DBAD by a chiral Ph–BOX–Cu(OTf)$_2$ complex.[78a] Notably, by using 0.5 mol% catalyst loading, excellent results were obtained with either cyclic or acyclic β-keto esters (Scheme 51a). Later, this reaction system was also utilized in the amination of α-fluorinated β-keto esters.[78b] Enantioselective amination of β-keto phosphonates with DBAD was also achieved using a zinc bisoxazoline complex (Scheme 51b).[79] High enantioselectivity was obtained with both acyclic and cyclic substrates but required a relatively higher catalytic loading (10 mol%) and an increased reaction time.

By successful tuning of α-amination of β-keto derivatives, it became possible to develop a method for the synthesis of complex structures with diverse chiral centers. In this regard,



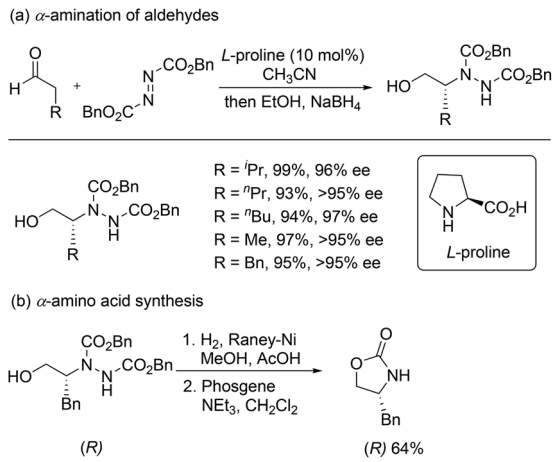
Scheme 50 α-Amination of carbonyl functionalities with dialkyl azodicarboxylates.



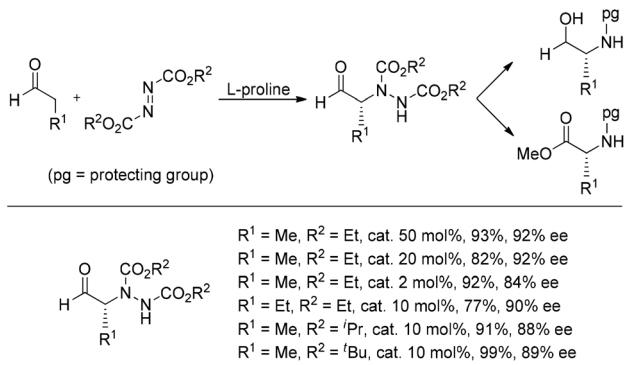
Scheme 51 Amination of β-keto esters and β-keto phosphonates catalyzed by metal complexes.

Ma's group reported a one-pot Cu- and Pd-catalyzed amination method for the synthesis of pyrazolidine derivatives (Scheme 51c).[80] This reaction was first catalyzed by a chiral Ph–BOX–Cu(OTf)$_2$ complex followed by a Pd-catalyzed cyclization.

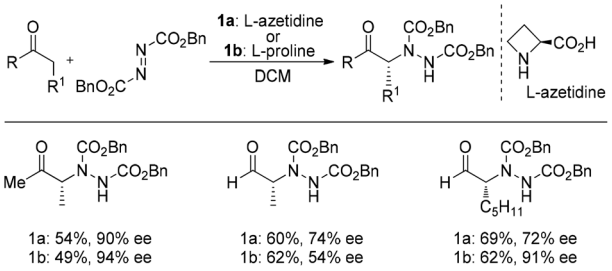
In 2002, List, Jørgensen *et al.* reported the reaction of L-proline-catalyzed α-amination of aldehydes.[81] Stable crystalline 2-hydrazino alcohols were synthesized from aldehydes with dialkyl azodicarboxylate in good yields with excellent enantioselectivities (Scheme 52a[81a] and Scheme 53[81b]). A further new potential application of this method was demonstrated by the synthesis of the α-amino acid derivative from the 2-hydrazino alcohol (Scheme 52b). Notably, this approach proceeded with high enantionselectivity. These results indicated the potential of the amino acid catalyst for α-amination of carbonyl functionality.[82] In addition, this method also provides useful substrates for synthesizing other non-natural or natural α-amino and α-hydrazino acid derivatives.[83] Later, the scope of this reaction was also extended to ketone substrates.[84] In 2006, Greck and co-workers unraveled an L-azetidine carboxylic acid-catalyzed electrophilic α-amination of aldehydes and ketones with dibenzylazodicarboxylate (DBAD) (Scheme 54).[84] In comparison, L-azetidine delivered comparable reaction yields with those delivered by L-proline. Moreover, α-hydrazinoketone derivatives obtained from DBAD can be easily transformed into the corresponding amino ketone in a single step.[85]



Scheme 52 α-Amination of aldehydes with dialkyl azodicarboxylates and the synthesis of α-amino acid derivatives.



Scheme 53 α-Amination of aldehydes for the synthesis of optically active amino aldehydes, amino alcohols and amino acids.

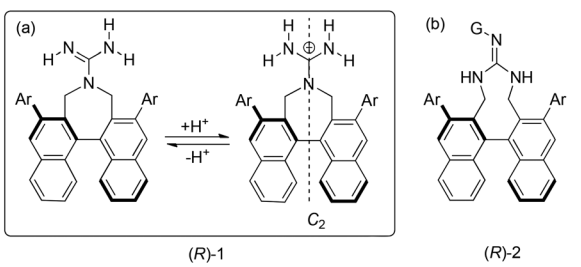


Scheme 54 α-Amination of aldehydes and ketones with DBAD.

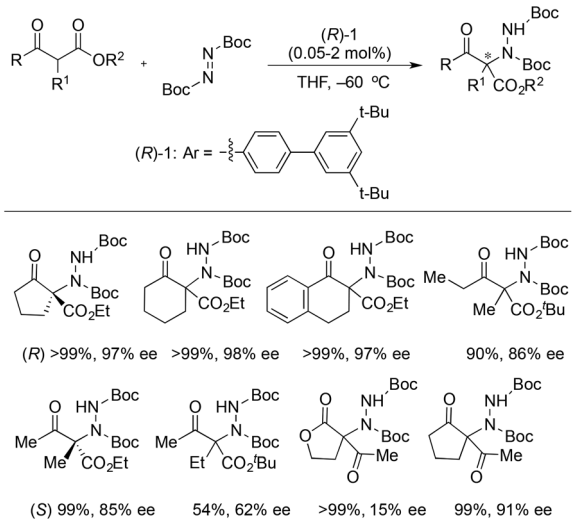
Arginine is known as a conditionally essential or semi-essential naturally occurring amino acid. It was first found in a lupin seedling extract by Ernst Schultze.[86] Guanidine is a functional moiety on the side chain of the arginine with formula $HNC(NH_2)_2$. It acts as a strong base and exists as guanidinium ($C(NH_2)_3^+$) in neutral water. In 2006, Terada and co-workers developed a new axially chiral seven-membered-ring guanidine catalyst (*R*)-1 for the amination of 1,3-dicarbonyl derivatives (Scheme 55).[87] Previously, they had documented that the nine-membered-ring guanidine catalyst (*R*)-2 was an enantioselective and efficient catalyst for the 1,4-addition reaction of 1,3-dicarbonyl derivatives with nitroalkenes (Scheme 55).[88] After optimization of the axially chiral seven-membered-ring guanidine catalyst by changing the aryl group, they found that 4-(3,5-*t*-Bu$_2$C$_6$H$_3$)C$_6$H$_4$, gave the optimal results (Scheme 56).

6.2. Amination of α-cyanoacetates

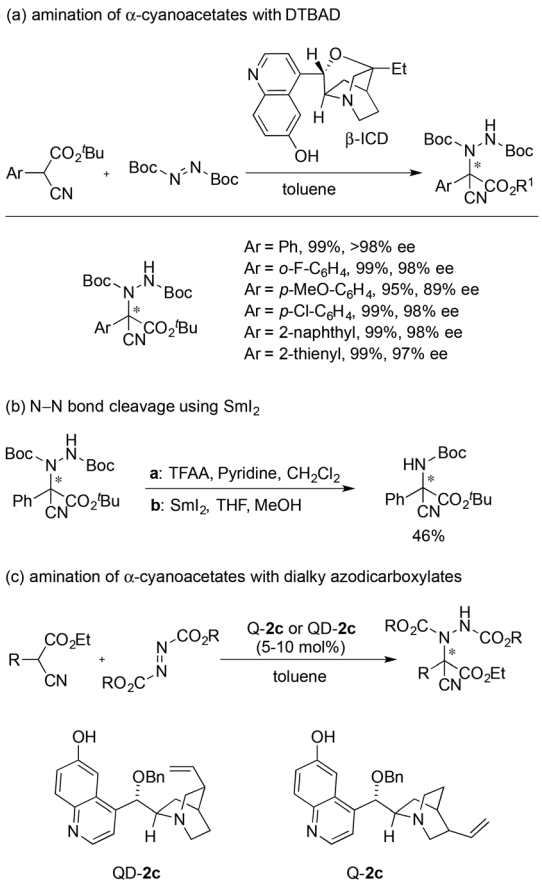
In 2004, Jørgensen and co-workers reported an organocatalytic amination of β-substituted α-cyanoacetates and β-dicarbonyl compounds with a chiral tertiary amine catalyst.[89] A catalytic system consisting of β-isocupreidine (β-ICD) in toluene gave the optimal results (Scheme 57a). It is noteworthy that the asymmetric stereocenter could be further transformed into an α-amino acid derivative *via* cleavage of the N–N bond by the treatment of TFAA, followed by SmI_2 (Scheme 57b). Meanwhile, the Deng group also reported the amination of



Scheme 55 (a) Axially chiral guanidine with a seven-membered ring and its protonated form (*R*)-1; (b) Axially chiral guanidine with a nine-membered ring.



Scheme 56 Electrophilic amination of unsymmetrically substituted 1,3-dicarbonyl compounds.



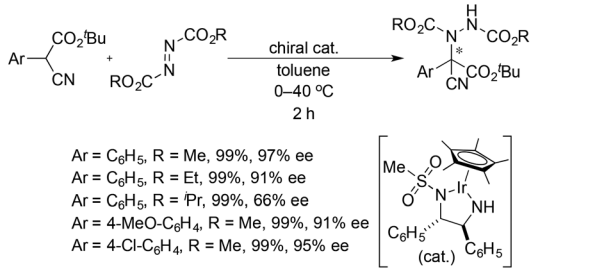
Scheme 57 Organocatalytic amination of α-cyanoacetate compounds and the synthesis of tetrasubstituted α-amino acid.

α-substituted α-cyanoacetate compounds with readily accessible chiral catalysts from both quinine and quinidine.[90] With the optimized reaction conditions, a variety of α-aryl cyanoacetates were successfully converted to the desired products in either the *R* or *S* configuration with QD-2c and Q-2c, respectively (Scheme 57c).

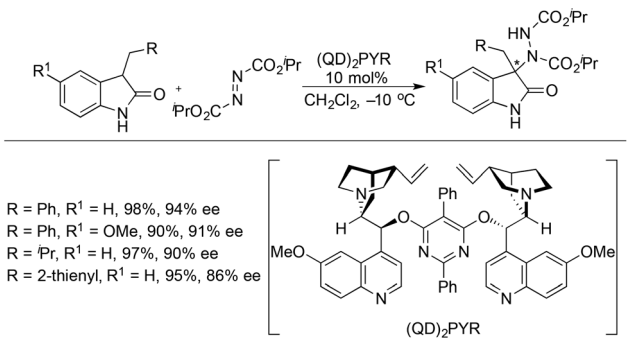
For the amination of α-cyanoacetates with chiral metal complexes, Ikariya and co-workers established the bifunctional chiral Ru and Ir amido complexes-catalyzed amination of α-substituted α-cyanoacetates with dialkyl azodicarboxylate in 2008 (Scheme 58).[91] This reaction provides a useful procedure for the construction of nitrogen-substituted asymmetric stereocenters (*R* configuration) in excellent yields and with high enantioselectivities.

6.3. Amination of heterocycles

Heterocyclic compounds are ubiquitous core structures found in numerous biologically active and functional materials. Their catalytic asymmetric construction is of high significance and interest.[3a,92] In this regard, organocatalytic α-amination of oxindoles has been reported by the Zhou,[93a] Chen,[93b] and Barbas[93c] groups. The Chen and Barbas groups reported the cinchona alkaloid derivative $(DHQD)_2PHAL$-catalyzed amination of 2-oxindoles for the asymmetric synthesis of 3-amino-2-oxindoles. However, Zhou and co-workers reported the construction of tetrasubstituted stereocenters by quinidine derivative $(QD)_2PYR$-catalyzed amination of oxindoles (Scheme 59).[93a] This protocol was applicable to a range of 3-substituted oxindoles to provide the desired products in high yields and with excellent enantioselectivity. Soon after this, chiral nickel and scandium complexes were reported for the



Scheme 58 Amination of α-substituted α-cyanoacetates with a chiral amido Ir complex.



Scheme 59 Organocatalytic amination of oxindoles.

amination of 3-prochiral oxindoles.[94,95] Among the C3 heteroatom-substituted oxindoles (3-alkoxyoxindoles and 3-thiooxindoles), Zhou and co-workers demonstrated an elegant amination of those derivatives with DTBAD in 2013.[96] A catalytic system consisting of β-ICD gave the optimal results for the amination of 3-thiooxindoles while $(DHQD)_2PHAL$ was found to be optimal for the amination 3-alkoxyoxindoles.

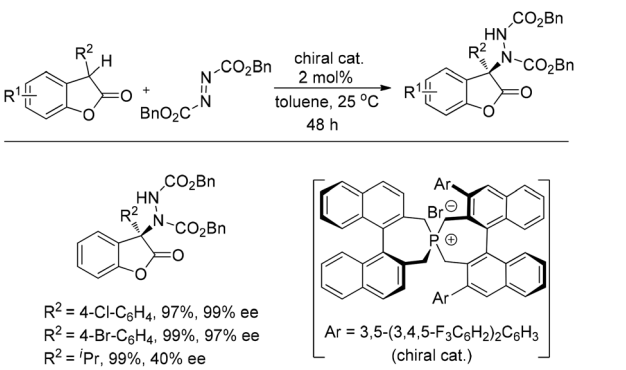
In 2011, Ma and co-workers succeeded in developing an enantioselective amination of benzofuranones with azodicarboxylate (Scheme 60).[97] In this reaction the use of BINOL-derived *P*-spiro quaternary phosphonium salt effectively provided the corresponding chiral benzofuran-2(3*H*)-ones with high enantioselectivities. Meanwhile, Feng and co-workers independently reported the amination of 4-substituted pyrazolones with azodicarboxylates.[98] In this reaction, a Gd complex derived from $Gd(OTf)_3$ and chiral *N*,*N*′-dioxide was used as the catalyst (Scheme 61). This method exhibited high enantioselectivities and delivered tetrasubstituted carbon center-containing products in excellent yields by utilizing only 1 mol% or even 0.05 mol% of catalyst.

6.4. C–H bond amination

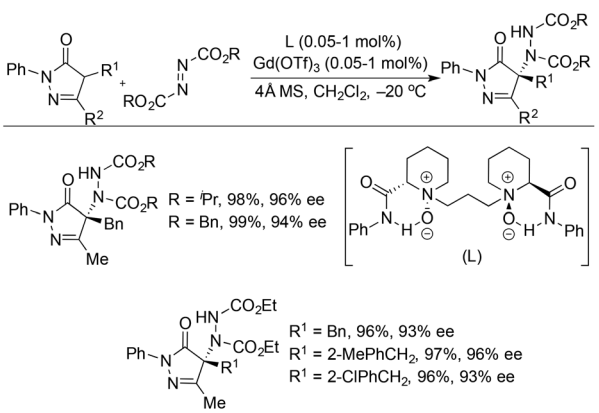
In 2012, Inoue and co-workers reported the amination of benzylic, propargylic and aliphatic C(sp^3)–H bonds by dialkyl azodicarboxylates in the presence of *N*-hydroxyphthalimide (NHPI).[99] Notably, the reaction occurred under neutral conditions and delivered the corresponding hydrazines in an efficient chemoselective manner (Scheme 62). Furthermore, the synthesis of amines was achieved by using BTCEAD instead of DEAD. The first step involved the formation of the corresponding BTCEAD adduct in high yield, then further reduction of this adduct by treating with zinc in the presence of AcOH and acetone delivered the corresponding amine (Scheme 62). The NHPI serves as a catalyst to produce the carbon radical species **31**, which combines with dialkyl azodicarboxylate and generates a nitrogen radical species **32**. Then **32** abstracts a hydrogen from the NHPI delivering the corresponding aminated product and returning the chain cycle (Scheme 63).

The amination of benzoheterocycle C(sp^3)–H bonds by DTBAD in the presence of visible light *via* the formation of α-aminoalkyl radicals was reported by Nishibayashi's group.[100] A well-established photocatalytic system derived from [Ir catalyst][BF_4] in NMP (*N*-methylpyrrolidone) at ambient temperature was found to be optimal for this reaction (Scheme 64). Furthermore, *N*,*N*-acetals obtained by this amination reaction could react with different nucleophiles (Grignard reagents and indoline derivative).

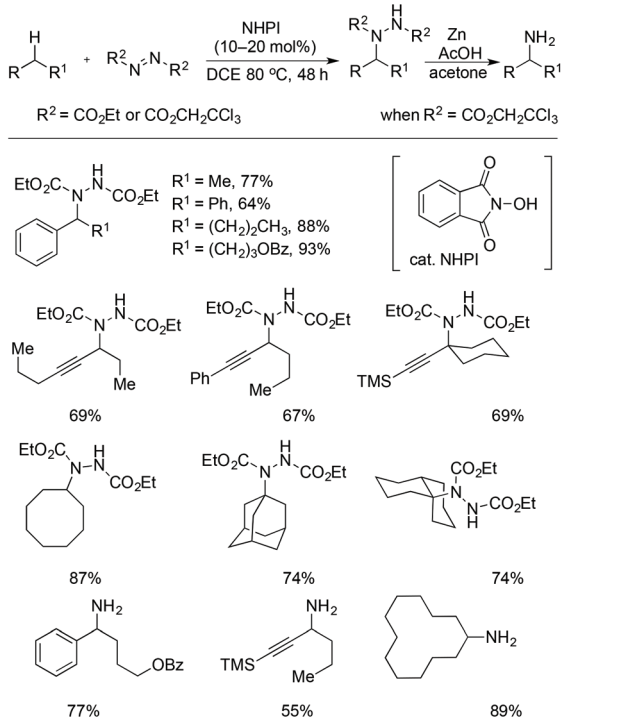
In 2013, Fagnoni and co-workers reported the tetrabutylammonium decatungstate (TBADT)-catalyzed addition of C–H bonds to DIAD under irradiation conditions.[101] This TBADT-photoinduced reaction was found to be suitable for the addition of cyclic alkanes with five- to eight-membered rings,



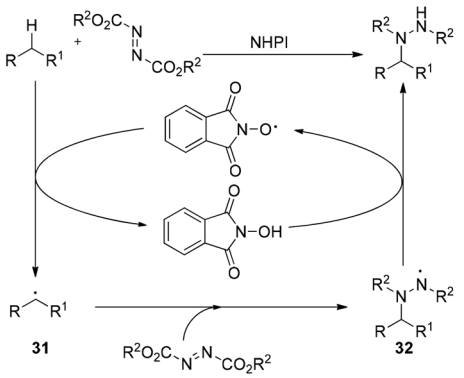
Scheme 60 Organocatalytic amination of benzofuranones.



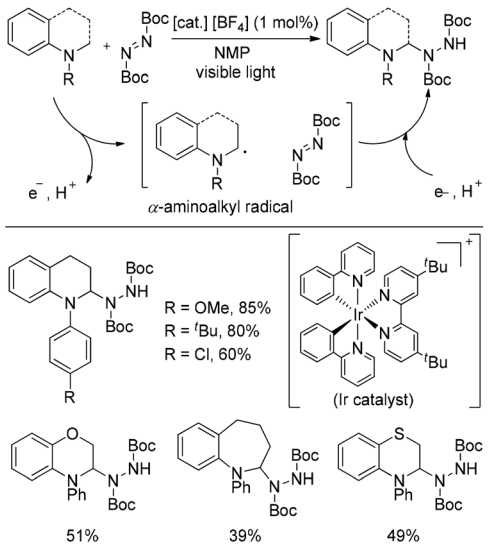
Scheme 61 Amination of pyrazolones.



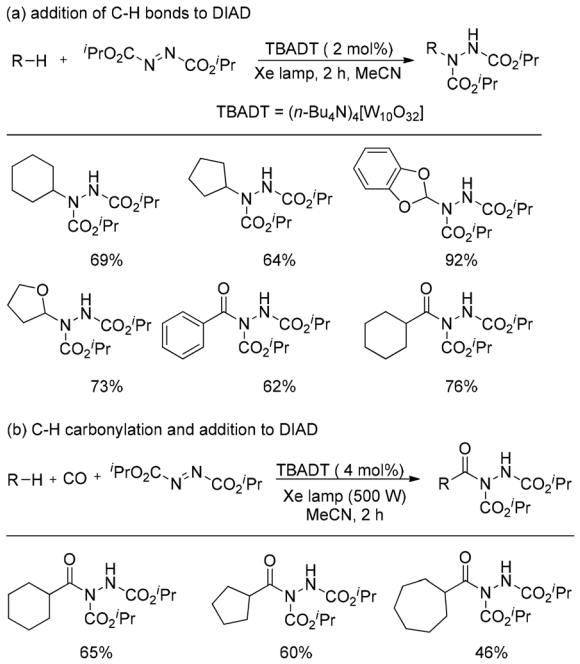
Scheme 62 Amination of C(sp^3)–H bonds by dialkyl azodicarboxylates.



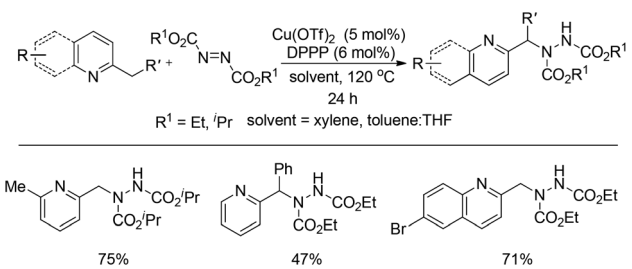
Scheme 63 Proposed mechanism.



Scheme 64 Amination of benzoheterocycle C(sp^3)–H bonds by di-*tert*-butyl azodicarboxylate.



Scheme 65 Alkylation and acylation of diisopropyl azodicarboxylate.

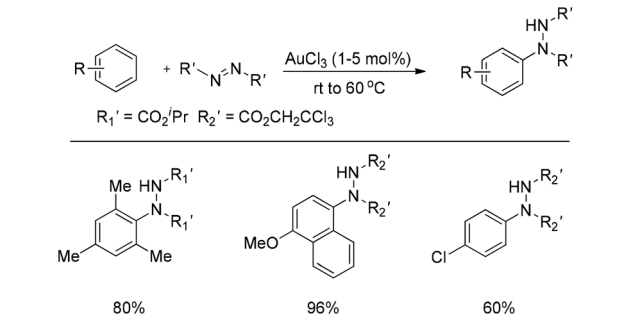


Scheme 66 Cu-Catalyzed C–H bond amination of azaarenes by dialkyl azodicarboxylate.

ether, acetal and aldehydic C–H bonds to DIAD to form C–N bonds (Scheme 65a). The C–H bond carbonylation with carbon monoxide and then the addition to DIAD leading toward the formation of acyl hydrazines (Scheme 65b).

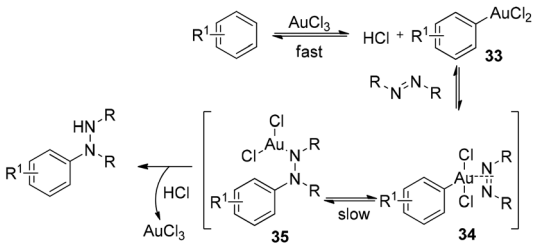
Azaarenes and pyridines are structurally important classes of organic compounds, which have widespread applications in pharmaceuticals products.[102] In 2013, Huang and co-workers developed a Cu-catalyzed C–H bond amination of azaarene by dialkyl azodicarboxylate for the synthesis of azaarene-containing hydrazines.[103] Optimization studies revealed that Lewis acid catalyst $Cu(OTf)_2$ with DPPP (diphenyl-1-pyrenylphosphine) as the ligand was suitable for this transformation (Scheme 66).

Aryl-substituted hydrazides are very useful for the synthesis of valuable heterocycles (pyarazoles or indoles). In 2011, Zhang and co-workers developed a gold(III)-catalyzed direct C–H bond amination of arenes with dialkyl azodicarboxylates (Scheme 67).[104] This reaction provides a synthetically useful



Scheme 67 Gold(III)-catalyzed direct C–H bond amination of arenes with dialkyl azodicarboxylate.

procedure for the construction of heterocyclic compounds from electron-deficient arenes. The author proposed an $AuCl_3$-catalyzed reaction mechanism (Scheme 68). The first step involves the formation of the aryl gold(III) complex **33**. Then,

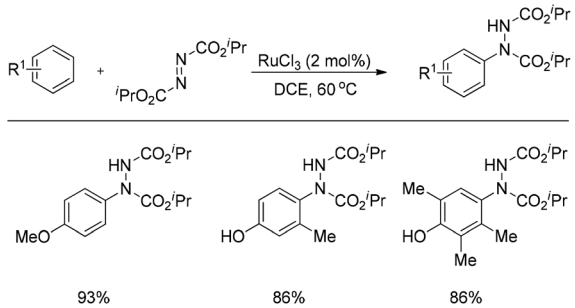


Scheme 68 Proposed mechanism.

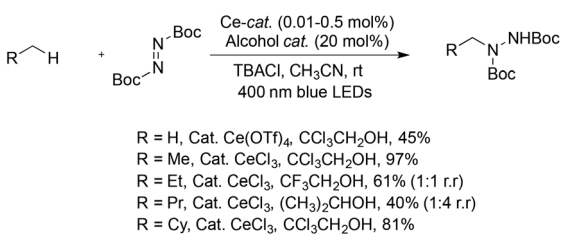
the coordination between the gold(III) complex and dialkyl azodicarboxylate delivers complex **34**. Insertion of azodicarboxylate into carbon–Au leads to the formation of complex **35**, which could be readily protonated to generate the corresponding product and recycle the gold(III) catalyst.

In 2013, Mandal and co-workers reported a ruthenium-catalyzed C–H bond amination of arenes with diisopropyl azodicarboxylate.[105] A catalytic system consisting of $RuCl_3$ in dichloroethane at 60 °C gave the optimal results for this amination reaction (Scheme 69). The amination products were obtained in moderate to high yields. Notably, the catalyst can be recovered and reused.

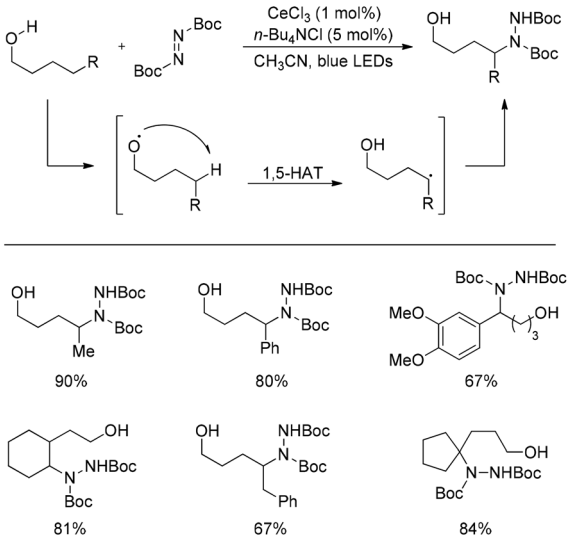
Recent studies have highlighted cerium photocatalytic amination reactions, which can give C–C bond cleavage of cycloalkanols[72] but are also involved in C–H bond amination reactions.[106,107] An outstanding report by Zuo and co-workers documented the C–H bond amination of inert alkanes, such as methane and ethane, by using visible-light irradiation under mild reaction conditions (Scheme 70).[106] High catalytic



Scheme 69 Ru-Catalyzed C–H bond amination of arenes with diisopropyl azodicarboxylate.



Scheme 70 Functionalization of alkanes by cerium photocatalysis.



Scheme 71 Visible-light-induced δ-C–H amination of alkanols.

efficiency and selectivity were obtained by using cerium salts as photocatalysts. The mixed liquid/gas approach was adapted to a continuous flow reaction system, enabling the scalable photocatalytic reactions. A notable exception of this work was the δ-C–H amination of alkanols[107] under the utilization of ligand-to-metal charge transfer (LMCT) excitation, induced by the cerium photocatalyst to generate alkoxy radicals. Finally, δ-C–H amination was achieved by coupling of the alkyl radical with DTBAD, generated *via* 1,5-HAT. The reaction proceeded with high site-selectivity for C–H amination of primary alcohols without the need for prefunctionalization (Scheme 71).

7. Conclusions

In this review, we have summarized the synthesis of dialkyl azodicarboxylates and their applications. The past few decades have witnessed significant developments in the chemistry involving dialky azodicarboxylates. The emergence of an array of new catalytic systems enables the transformation of azodicarboxylates as versatile reagents for diverse syntheses. Beside their traditional applications in Mitsunobu reactions, as oxidants, and in electrophilic amination reactions, the use of dialkyl azodicarboxylates in carbonylation reactions, asymmetric nucleophilic aminations, and photo-induced C–H aminations has been discussed in detail.

Despite the long history of and significant developments in this field, there is still room for further development. For example, the substrate scope of the reaction in C–H bond carbonylation is very limited. The utility of dialkyl azodicarboxylates as a convenient carbon monoxide source requires the installation of an aminoquinoline-directing group on the substrates. As a readily available electrophilic nitrogen precursor, their potential for bringing new amine functionalities into

molecules with high enantio- and/or chemo-selectivity is still underdeveloped.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We gratefully acknowledge the NSFC (21602160, 21772148, 21622203), the National Program for 1000 Young Talents of China, and Wuhan University for financial support. We sincerely thank the reviewers for the remarkable level of suggestions and corrections.

Notes and references

1 (*a*) S. Fletcher, *Org. Chem. Front.*, 2015, **2**, 739–752; (*b*) D. P. Furkert, B. Breitenbach, L. Juen, I. Sroka, M. Pantin and M. A. Brimble, *Eur. J. Org. Chem.*, 2014, 7806–7809; (*c*) R. H. Beddoe, H. F. Sneddon and R. M. Denton, *Org. Biomol. Chem.*, 2018, **16**, 7774–7781.

2 (*a*) A. M. R. Smith and K. K. (Mimi) Hii, *Chem. Rev.*, 2011, **111**, 1637–1656; (*b*) X. Xu, G. Cheng and X. Li, *Chin. J. Org. Chem.*, 2012, **32**, 1024–1040; (*c*) F. Zhou, F.-N. Liao, J.-S. Yu and J. Zhou, *Synthesis*, 2014, 2983–3003.

3 (*a*) V. Nair, A. T. Biju, S. C. Mathew and B. P. Babu, *Chem. – Asian J.*, 2008, **3**, 810–820; (*b*) A. M. Zhirov and A. V. Aksenov, *Russ. Chem. Rev.*, 2014, **83**, 502–522.

4 (*a*) B. H. Lipshutz, D. W. Chung, B. Rich and R. Corral, *Org. Lett.*, 2006, **8**, 5069–5072; (*b*) B. R. Taft, E. C. Swift and B. H. Lipshutz, *Synthesis*, 2009, 0332–0334.

5 J. Yang, L. Dai, X. Wang and Y. Chen, *Tetrahedron*, 2011, **67**, 1456–1462.

6 J. H. Yang, L. Y. Dai, X. Z. Wang and Y. Q. Chen, *Chin. Chem. Lett.*, 2011, **22**, 1047–1050.

7 S. Dandapani, J. J. Newsome and D. P. Curran, *Tetrahedron Lett.*, 2004, **45**, 6653–6656.

8 O. Mitsunobu and M. Yamada, *Bull. Chem. Soc. Jpn.*, 1967, **40**, 2380–2382.

9 (*a*) O. Mitsunobu, *Synthesis*, 1981, 1–28; (*b*) K. C. K. Swamy, N. N. B. Kumar, E. Balaraman and K. V. P. Pavan Kumar, *Chem. Rev.*, 2009, **109**, 2551–2651; (*c*) A. Manvar and A. Shah, *Org. Biomol. Chem.*, 2014, **12**, 8112–8124.

10 D. Camp, M. V. Itzstein and I. D. Jenkins, *Tetrahedron*, 2015, **71**, 4946–4948.

11 W.-Y. Yu, W. N. Sit, K.-M. Lai, Z. Zhou and A. S. C. Chan, *J. Am. Chem. Soc.*, 2008, **130**, 3304–3306.

12 Y. Huang, G. Li, J. Huang and J. You, *Org. Chem. Front.*, 2014, **1**, 347–350 and reference cited therein.

13 N. Xu, D. Li, Y. Zhanga and L. Wang, *Org. Biomol. Chem.*, 2015, **13**, 9083–9092.

14 R. Sang, Y. Zheng, H. Zhang, X. Wu, Q. Wang, L. Hai and Y. Wu, *Org. Chem. Front.*, 2018, **5**, 648–652.

15 (*a*) J. Ni, J. Li, Z. Fan and A. Zhang, *Org. Lett.*, 2016, **18**, 5960–5963; (*b*) T. T. Nguyen, L. Grigorjeva and O. Daugulis, *Chem. Commun.*, 2017, **53**, 5136–5138.

16 F. Ling, C. Ai, Y. Lv and W. Zhong, *Adv. Synth. Catal.*, 2017, **359**, 3707–3712.

17 J.-B. Peng, B. Chen, X. Qi, J. Yinga and X.-F. Wu, *Org. Biomol. Chem.*, 2018, **16**, 1632–1635.

18 S. Ramesh, P. N. Arunachalam and A. Lalitha, *RSC Adv.*, 2013, **3**, 8666–8669.

19 M. Usman, Z.-H. Ren, Y.-Y. Wang and Z.-H. Guan, *RSC Adv.*, 2016, **6**, 107542–107546.

20 M. Usman, Z.-H. Ren, Y.-Y. Wang and Z.-H. Guan, *Org. Biomol. Chem.*, 2017, **15**, 1091–1095.

21 H. T. Cao and R. Grée, *Tetrahedron Lett.*, 2009, **50**, 1493–1494 and reference cited therein.

22 (*a*) K. Kato and O. Mitsunobu, *J. Org. Chem.*, 1970, **35**, 4227–4229; (*b*) T. Mukaiyama and K. A. Takahashi, *Tetrahedron Lett.*, 1968, **9**, 5907–5908; (*c*) G. R. Morais and R. A. Falconer, *Tetrahedron Lett.*, 2007, **48**, 7637–7641; (*d*) R. Axen, M. Chaykovsky and B. Witkop, *J. Org. Chem.*, 1967, **32**, 4117–4118.

23 W. Y. Chan and C. Berthelette, *Tetrahedron Lett.*, 2002, **43**, 4537–4540.

24 L.-X. Shao and M. Shi, *Eur. J. Org. Chem.*, 2004, 426–430.

25 N. Iranpoor, H. Firouzabadi, D. Khalili and R. Shahin, *Tetrahedron Lett.*, 2010, **51**, 3508–3510.

26 (*a*) Z. Ding and N. Yoshikai, *Angew. Chem., Int. Ed.*, 2013, **52**, 8574–8578; (*b*) M. T. Stone, *Org. Lett.*, 2011, **13**, 2326–2329, and reference cited therein.

27 (*a*) L. Chu and F.-L. Qing, *Chem. Commun.*, 2010, **46**, 6285–6287; (*b*) J. C. A. Flanagan, L. M. Dornan, M. G. McLaughlin, N. G. McCreanor, M. J. Cook and M. J. Muldoon, *Green Chem.*, 2012, **14**, 1281–1283.

28 (*a*) H. S. Kim, G. Jeong, H. C. Lee, J. H. Kim and Y. T. Park, *J. Heterocycl. Chem.*, 2000, **37**, 1277–1280; (*b*) T. Takahashi, Y. Li, T. Ito, F. Xu, K. Nakajima and Y. Liu, *J. Am. Chem. Soc.*, 2002, **124**, 1144–1145; (*c*) R. Lü, X. Cheng, X. Zheng and S. Ma, *Chem. Commun.*, 2014, **50**, 1537–1539; (*d*) D. Hong, Y. Zhu, X. Lin and Y. Wang, *Tetrahedron*, 2011, **67**, 650–654; (*e*) K. Fourmy and A. Voituriez, *Org. Lett.*, 2015, **17**, 1537–1540; (*f*) B. S. Gerstenberger, M. R. Rauckhorst and J. T. Starr, *Org. Lett.*, 2009, **11**, 2097–2100.

29 For recent reviews, see: (*a*) R. Ciriminna and M. Pagliaro, *Org. Process Res. Dev.*, 2010, **14**, 245–251; (*b*) J. Piera and J.-E. Bäckvall, *Angew. Chem., Int. Ed.*, 2008, **47**, 3506–3523; (*c*) R. A. Sheldon and I. W. C. E. Arends, *Adv. Synth. Catal.*, 2004, **346**, 1051–1071; (*d*) T. Vogler and A. Studer, *Synthesis*, 2008, 1979–1993; (*e*) A. E. J. de Nooy, A. C. Besemer and H. van Bekkum, *Synthesis*, 1996, 1153–1174.

30 For reviews on using TEMPO, see: (*a*) X. He, Z. Shen, W. Mo, N. Sun, B. Hu and X. Hu, *Adv. Synth. Catal.*, 2009, **351**, 89–92; (*b*) R. Liu, X. Liang, C. Dong and X. Hu, *J. Am.*

Chem. Soc., 2004, **126**, 4112–4113; (*c*) L. D. Luca, G. Giacomelli, S. Masala and A. Porcheddu, *J. Org. Chem.*, 2003, **68**, 4999–5001; (*d*) R. A. Miller and R. S. Hoerrner, *Org. Lett.*, 2003, **5**, 285–287; (*e*) L. D. Luca, G. Giacomelli and A. Porcheddu, *Org. Lett.*, 2001, **3**, 3041–3043; (*f*) C. Bolm, A. S. Magnus and J. P. Hildebrand, *Org. Lett.*, 2000, **2**, 1173–1175; (*g*) X. Wang, R. Liu, Y. Jin and X. Liang, *Chem. – Eur. J.*, 2008, **14**, 2679–2685; (*h*) M. Lei, R.-J. Hu and Y.-G. Wang, *Tetrahedron*, 2006, **62**, 8928–8932; (*i*) G. Yang, W. Wang, W. Zhu, C. An, X. Gao and M. Song, *Synlett*, 2010, 437–440.

31 (*a*) F. Yoneda, K. Suzuki and Y. Nitta, *J. Am. Chem. Soc.*, 1966, **88**, 2328–2329; (*b*) F. Yoneda, K. Suzuki and Y. Nitta, *J. Org. Chem.*, 1967, **32**, 727–729.

32 R. M. Moriarty, I. Prakash and R. Penrnasta, *Synth. Commun.*, 1987, **17**, 409–413.

33 E. C. Taylor and F. Yoneda, *Chem. Commun.*, 1967, 199–200.

34 M. Hayashi, M. Shibuya and Y. Iwabuchi, *J. Org. Chem.*, 2012, **77**, 3005–3009.

35 (*a*) M. Shibuya, Y. Sasano, M. Tomizawa, T. Hamada, M. Kozawa, N. Nagahama and Y. Iwabuchi, *Synthesis*, 2011, 3418–3425; (*b*) M. Shibuya, Y. Osada, Y. Sasano, M. Tomizawa and Y. Iwabuchi, *J. Am. Chem. Soc.*, 2011, **133**, 6497–6500; (*c*) M. Hayashi, Y. Sasano, S. Nagasawa, M. Shibuya and Y. Iwabuchi, *Chem. Pharm. Bull.*, 2011, **59**, 1570–1573; (*d*) M. Shibuya, M. Tomizawa, Y. Sasano and Y. Iwabuchi, *J. Org. Chem.*, 2009, **74**, 4619–4622; (*e*) M. Shibuya, T. Sato, M. Tomizawa and Y. Iwabuchi, *Chem. Commun.*, 2009, 1739–1741; (*f*) M. Shibuya, M. Tomizawa, I. Suzuki and Y. Iwabuchi, *J. Am. Chem. Soc.*, 2006, **128**, 8412–8413.

36 (*a*) R. A. Sheldon, I. W. C. E. Arends, G.-J. T. Brink and A. Dijksman, *Acc. Chem. Res.*, 2002, **35**, 774–781; (*b*) B.-Z. Zhan and A. Thompson, *Tetrahedron*, 2004, **60**, 2917–2935; (*c*) T. Mallat and A. Baiker, *Chem. Rev.*, 2004, **104**, 3037–3058; (*d*) M. J. Schultz and M. S. Sigman, *Tetrahedron*, 2006, **62**, 8227–8241.

37 (*a*) J. Yamaguchi, A. D. Yamaguchi and K. Itami, *Angew. Chem., Int. Ed.*, 2012, **51**, 2–52; (*b*) L. Ackermann, *Org. Process Res. Dev.*, 2015, **19**, 260–269; (*c*) L. G. Mercier and M. Leclerc, *Acc. Chem. Res.*, 2013, **46**, 1597–1605.

38 (*a*) L. Ackermann, *Chem. Rev.*, 2011, **111**, 1315–1345; (*b*) M. C. Willis, *Chem. Rev.*, 2010, **110**, 725–748; (*c*) G. E. Dobereiner and R. H. Crabtree, *Chem. Rev.*, 2010, **110**, 681–703; (*d*) F. Kakiuchi and T. Kochi, *Synthesis*, 2008, 3013–3039; (*e*) Priyanka, R. K. Sharma and D. Katiyar, *Synthesis*, 2016, 2303–2322; (*f*) M. Usman, Z.-H. Ren, Y.-Y. Wang and Z.-H. Guan, *Synthesis*, 2017, 1419–1443.

39 (*a*) P. B. Arockiam, C. Bruneau and P. H. Dixneuf, *Chem. Rev.*, 2012, **112**, 5879–5918; (*b*) T. W. Lyons and M. S. Sanford, *Chem. Rev.*, 2010, **110**, 1147–1169; (*c*) P. Sehnal, R. J. K. Taylor and I. J. S. Fairlamb, *Chem. Rev.*, 2010, **110**, 824–889; (*d*) M. Usman, X.-W. Zhang and W.-B. Liu, *Synthesis*, 2019, 1529–1544.

40 (*a*) C. Zhang, C. Tang and N. Jiao, *Chem. Soc. Rev.*, 2012, **41**, 3464–3484; (*b*) M. Meldal and C. W. Tornøe, *Chem. Rev.*, 2008, **108**, 2952–3015; (*c*) X. Zhao, Y. Zhang and J. Wang, *Chem. Commun.*, 2012, **48**, 10162–10173.

41 (*a*) I. E. Markó, A. Gautier, R. Dumeunier, K. Doda, F. Philippart, S. M. Brown and C. J. Urch, *Angew. Chem., Int. Ed.*, 2004, **43**, 1588–1591; (*b*) A. Dijksman, I. W. C. E. Arends and R. A. Sheldon, *Org. Biomol. Chem.*, 2003, **1**, 3232–3237; (*c*) I. A. Ansari and R. Gree, *Org. Lett.*, 2002, **4**, 1507–1509; (*d*) P. Gamez, I. W. C. E. Arends, J. Reedijk and R. A. Sheldon, *Chem. Commun.*, 2003, 2414–2415; (*e*) J. M. Hoover and S. S. Stahl, *J. Am. Chem. Soc.*, 2011, **133**, 16901–16910.

42 For reviews on aerobic oxidation of alcohols, see ref. 29 and the following: (*a*) K. M. Gligorich and M. S. Sigman, *Chem. Commun.*, 2009, 3854–3867; (*b*) S. S. Stahl, *Angew. Chem., Int. Ed.*, 2004, **43**, 3400–3420.

43 For leading references, see: (*a*) T. Nishimura, T. Onoue, K. Ohe and S. Uemura, *J. Org. Chem.*, 1999, **64**, 6750–6755; (*b*) M. J. Schultz, C. C. Park and M. S. Sigman, *Chem. Commun.*, 2002, 3034–3035; (*c*) G.-J. ten Brink, I. W. C. E. Arends, M. Hoogenraad, G. Verspui and R. A. Sheldon, *Adv. Synth. Catal.*, 2003, **345**, 1341–1352; (*d*) J. A. Mueller, C. P. Goller and M. S. Sigman, *J. Am. Chem. Soc.*, 2004, **126**, 9724–9734; (*e*) M. J. Schultz, S. S. Hamilton, D. R. Jensen and M. S. Sigman, *J. Org. Chem.*, 2005, **70**, 3343–3352; (*f*) D. S. Bailie, G. M. A. Clendenning, L. McNamee and M. J. Muldoon, *Chem. Commun.*, 2010, **46**, 7238–7240.

44 (*a*) A. Dijksman, A. Marino-González, A. M. I. Payeras, I. W. C. E. Arends and R. A. Sheldon, *J. Am. Chem. Soc.*, 2001, **123**, 6826–6833; (*b*) R. Lenz and S. V. Ley, *J. Chem. Soc., Perkin Trans. 1*, 1997, 3291–3292; (*c*) M. Hasan, M. Musawir, P. N. Davey and I. V. Kozhevnikov, *J. Mol. Catal. A: Chem.*, 2002, **180**, 77–84; (*d*) N. Mizuno and K. Yamaguchi, *Catal. Today*, 2008, **132**, 18–26.

45 For Cu/TEMPO catalytic systems, see ref. 41*b–e* and the following references: (*a*) D. Geißlmeir, W. G. Jary and H. Falk, *Monatsh. Chem.*, 2005, **136**, 1591–1599; (*b*) N. Jiang and A. J. Ragauskas, *J. Org. Chem.*, 2006, **71**, 7087–7090; (*c*) S. Mannam, S. K. Alamsetti and G. Sekar, *Adv. Synth. Catal.*, 2007, **349**, 2253–2258; (*d*) P. J. Figiel, A. Sibaouih, J. U. Ahmad, M. Nieger, M. T. Räisänen, M. Leskelä and T. Repo, *Adv. Synth. Catal.*, 2009, **351**, 2625–2632.

46 For copper/dialkyl azodicarboxylate catalytict systems, see ref. 41*a* and the following references: (*a*) I. E. Markó, P. R. Giles, M. Tsukazaki, I. Chelle-Regnaut, A. Gautier, R. Dumeunier, F. Philippart, K. Doda, J.-L. Mutonkole, S. M. Brown and C. J. Urch, *Adv. Inorg. Chem.*, 2004, **56**, 211–240; (*b*) I. E. Markó, M. Tsukazaki, P. R. Giles, S. M. Brown and C. J. Urch, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 2208–2210; (*c*) I. E. Markó, A. Gautier, I. Chellé-Regnaut, P. R. Giles, M. Tsukazaki, C. J. Urch and S. M. Brown, *J. Org. Chem.*, 1998, **63**, 7576–7577.

47 T. Iwahama, Y. Yoshino, T. Keitoku, S. Sakaguchi and Y. Ishii, *J. Org. Chem.*, 2000, **65**, 6502–6507.
48 (*a*) S. E. Martín and D. F. Suárez, *Tetrahedron Lett.*, 2002, **43**, 4475–4479; (*b*) W. Yin, C. Chu, Q. Lu, J. Tao, X. Liang and R. Liu, *Adv. Synth. Catal.*, 2010, **352**, 113–118; (*c*) N. Wang, R. Liu, J. Chen and X. Liang, *Chem. Commun.*, 2005, 5322–5324.
49 Y. Maeda, N. Kakiuchi, S. Matsumura, T. Nishimura, T. Kawamura and S. Uemura, *J. Org. Chem.*, 2002, **67**, 6718–6724.
50 (*a*) I. E. Markó, P. R. Giles, M. Tsukazaki, I. Chellé-Regnaut, C. J. Urch and S. M. Brown, *J. Am. Chem. Soc.*, 1997, **119**, 12661–12662; (*b*) I. E. Markó, P. R. Giles, M. Tsukazaki, S. M. Brown and C. J. Urch, *Science*, 1996, **274**, 2044–2046.
51 I. E. Markó, A. Gautier, J.-L. Mutonkole, R. Dumeunier, A. Ates, C. J. Urch and S. M. Brown, *J. Organomet. Chem.*, 2001, **624**, 344–347.
52 T. Nishii, T. Ouchi, A. Matsuda, Y. Matsubara, Y. Haraguchi, T. Kawano, H. Kaku, M. Horikawa and T. Tsunoda, *Tetrahedron Lett.*, 2012, **53**, 5880–5882.
53 E. Zaballos-García, M. E. González-Rosende, J. M. Jorda-Gregori, J. Sepúlveda-Arques, W. B. Jennings, D. O'Leary and S. Twomey, *Tetrahedron*, 1997, **53**, 9313–9322.
54 D. Lee and R. D. Otte, *J. Org. Chem.*, 2004, **69**, 3569–3571.
55 For references on ene-type reaction and α-amination of ether and amine functionality with dialkyl azodicarboxylate see: Q. Zhang, E. Parker, A. D. Headley and B. Ni, *Synlett*, 2010, 2453–2456 and references cited therein.
56 V. Chudasama, J. M. Ahern, D. V. Dhokia, R. J. Fitzmaurice and S. Caddick, *Chem. Commun.*, 2011, **47**, 3269–3271.
57 Y. Qin, Q. Q. Peng, J. Song and D. Zhou, *Tetrahedron Lett.*, 2011, **52**, 5880–5883.
58 H.-B. Zhang, Y. Wang, Y. Gu and P.-F. Xu, *RSC Adv.*, 2014, **4**, 27796–27799.
59 A. Mariappan, K. Rajaguru, S. Muthusubramanian and N. Bhuvanesh, *Tetrahedron Lett.*, 2015, **56**, 338–341.
60 J. Kroutil, T. Tomas and M. Černý, *Synthesis*, 2004, 446–450.
61 P. W. Jeffs, H. F. Campbell and R. L. Hawks, *J. Chem. Soc. D*, 1971, 1338b–1339.
62 J. Kroutil, T. Trnka and M. Cerny, *Org. Lett.*, 2000, **2**, 1681–1683.
63 X. Xu and X. Li, *Org. Lett.*, 2009, **11**, 1027–1029.
64 X. Xu, P. Du, D. Cheng, H. Wang and X. Li, *Chem. Commun.*, 2012, **48**, 1811–1813.
65 W. Huang, C. Ni, Y. Zhao and J. Hu, *New J. Chem.*, 2013, **37**, 1684–1687.
66 X. Xu, X. Li, L. Ma, N. Ye and B. Weng, *J. Am. Chem. Soc.*, 2008, **130**, 14048–14049.
67 B. Han, X.-L. Yang, R. Fang, W. Yu, C. Wang, X.-Y. Duan and S. Liu, *Angew. Chem., Int. Ed.*, 2012, **51**, 8816–8820.
68 X.-Y. Duan, X.-L. Yang, R. Fang, X.-X. Peng, W. Yu and B. Han, *J. Org. Chem.*, 2013, **78**, 10692–10704.
69 J. Nan, J. Liu, H. Zheng, Z. Zuo, L. Hou, H. Hu, Y. Wang and X. Luan, *Angew. Chem., Int. Ed.*, 2015, **54**, 2356–2360.
70 R. Guo, K.-N. Li, B. Liu, H.-J. Zhu, Y.-M. Fan and L.-Z. Gong, *Chem. Commun.*, 2014, **50**, 5451–5454.
71 X.-L. Min, C. Sun and Y. He, *Org. Lett.*, 2019, **21**, 724–728.
72 J.-J. Guo, A. Hu, Y. Chen, J. Sun, H. Tang and Z. Zuo, *Angew. Chem., Int. Ed.*, 2016, **55**, 15319–15322.
73 D. Wang, R. Ren and C. Zhu, *J. Org. Chem.*, 2016, **81**, 8043–8049.
74 A. Vallribera, R. M. Sebastián and A. Shafir, *Curr. Org. Chem.*, 2011, **15**, 1539–1577.
75 R. Huisgen and F. Jakob, *Liebigs Ann. Chem.*, 1954, **590**, 37–54.
76 (*a*) D. A. Evans and S. G. Nelson, *J. Am. Chem. Soc.*, 1997, **119**, 6452–6453; (*b*) D. A. Evans and D. S. Johnson, *Org. Lett.*, 1999, **1**, 595–598.
77 K. Juhl and K. A. Jørgensen, *J. Am. Chem. Soc.*, 2002, **124**, 2420–2421.
78 (*a*) M. Marigo, K. Juhl and K. A. Jørgensen, *Angew. Chem., Int. Ed.*, 2003, **42**, 1367–1369; (*b*) D. P. Huber, K. Stanek and A. Togni, *Tetrahedron: Asymmetry*, 2006, **17**, 658–664.
79 L. Bernardi, W. Zhuang and K. A. Jørgensen, *J. Am. Chem. Soc.*, 2005, **127**, 5772–57773.
80 S. Ma, N. Jiao, Z. Zheng, Z. Ma, Z. Lu, L. Ye, Y. Deng and G. Chen, *Org. Lett.*, 2004, **6**, 2193–2196.
81 (*a*) B. List, *J. Am. Chem. Soc.*, 2002, **124**, 5656–5657; (*b*) A. Bøgevig, K. Juhl, N. Kumaragurubaran, W. Zhuang and K. A. Jørgensen, *Angew. Chem., Int. Ed.*, 2002, **41**, 1790–1793.
82 J.-Y. Fu, Q.-C. Yang, Q.-L. Wang, J.-N. Ming, F.-Y. Wang, X.-Y. Xu and L.-X. Wang, *J. Org. Chem.*, 2011, **76**, 4661–4664.
83 α-Hydrazino acid derivatives are biologically and structurally important compounds. See references: (*a*) L. K. P. Lam, L. D. Arnold, T. H. Kalantar, J. G. Kelland, P. M. Lane-Bell, M. M. Palcic, M. A. Pickard and J. C. Vederas, *J. Biol. Chem.*, 1988, **263**, 11814–11819; (*b*) J. S. Morley, J. W. Payne and T. D. Hennessey, *J. Gen. Microbiol.*, 1983, **129**, 3701–3708; (*c*) S. Chen, R. A. Chrusciel, H. Nakanishi, A. Raktabutr, M. E. Johnson, A. Sato, D. Weiner, J. Hoxie, H. U. Saragovi, M. I. Greene and M. Kahn, *Proc. Natl. Acad. Sci. U. S. A.*, 1992, **89**, 5872–5876.
84 C. Thomassigny, D. Prim and C. Greck, *Tetrahedron Lett.*, 2006, **47**, 1117–1119.
85 O. Poupardin, C. Greck and J.-P. Genêt, *Synlett*, 1998, 1279–1281.
86 R. Saini, S. L. Badole and A. A. Zanwar, in *Bioactive Dietary Factors and Plant Extracts in Dermatology, Nutrition and Health*, ed. R. R. Watson and S. Zibadi, Humana Press, Totowa, NJ, 2013, ch. 8, vol. 1, pp. 73–82.
87 M. Terada, M. Nakano and H. Ube, *J. Am. Chem. Soc.*, 2006, **128**, 16044–16045.
88 M. Terada, H. Ube and Y. Yaguchi, *J. Am. Chem. Soc.*, 2006, **128**, 1454–1455.

89 S. Saaby, M. Bella and K. A. Jørgensen, *J. Am. Chem. Soc.*, 2004, **126**, 8120–8121.
90 X. Liu, H. Li and L. Deng, *Org. Lett.*, 2005, **7**, 167–169.
91 Y. Hasegawa, M. Watanabe, I. D. Gridnev and T. Ikariya, *J. Am. Chem. Soc.*, 2008, **130**, 2158–2159.
92 T. Mashiko, K. Hara, D. Tanaka, Y. Fujiwara, N. Kumagai and M. Shibasaki, *J. Am. Chem. Soc.*, 2007, **129**, 11342–11343.
93 (*a*) Z.-Q. Qian, F. Zhou, T.-P. Du, B.-L. Wang, M. Zhao and J. Zhou, *Chem. Commun.*, 2009, 6753–6755; (*b*) L. Cheng, L. Li, D. Wang and Y.-J. Chen, *Org. Lett.*, 2009, **11**, 3874–3877; (*c*) T. Bui, M. Borregan and C. F. Barbas III, *J. Org. Chem.*, 2009, **74**, 8935–8938.
94 S. Mouri, Z. Chen, H. Mitsunuma, M. Furutachi, S. Matsunaga and M. Shibasaki, *J. Am. Chem. Soc.*, 2010, **132**, 1255–1257.
95 Z. Yang, Z. Wang, S. Bai, K. Shen, D. Chen, X. Liu, L. Lin and X. Feng, *Chem. – Eur. J.*, 2010, **16**, 6632–6637.
96 F. Zhou, X.-P. Zeng, C. Wang, X.-L. Zhao and J. Zhou, *Chem. Commun.*, 2013, **49**, 2022–2024.
97 C.-L. Zhu, F.-G. Zhang, W. Meng, J. Nie, D. Cahard and J.-A. Ma, *Angew. Chem., Int. Ed.*, 2011, **50**, 5869–5872.
98 Z. Yang, Z. Wang, S. Bai, X. Liu, L. Lin and X. Feng, *Org. Lett.*, 2011, **13**, 596–599.
99 Y. Amaoka, S. Kamijo, T. Hoshikawa and M. Inoue, *J. Org. Chem.*, 2012, **77**, 9959–9969.
100 Y. Miyake, K. Nakajima and Y. Nishibayashi, *Chem. – Eur. J.*, 2012, **18**, 16473–16477.
101 I. Ryu, A. Tani, T. Fukuyama, D. Ravelli, S. Montanaro and M. Fagnoni, *Org. Lett.*, 2013, **15**, 2554–2557.
102 (*a*) I. Nakamura and Y. Yamamoto, *Chem. Rev.*, 2004, **104**, 2127–2198; (*b*) G. Zeni and R. C. Larock, *Chem. Rev.*, 2006, **106**, 4644–4680; (*c*) G. D. Henery, *Tetrahedron*, 2004, **60**, 6043–6061; (*d*) M. C. Bagley, C. Glover and E. A. Merritt, *Synlett*, 2007, 2459–2482.
103 B. Qian, L. Yang and H. Huang, *Tetrahedron Lett.*, 2013, **54**, 711–714.
104 L. Gu, B. S. Neo and Y. Zhang, *Org. Lett.*, 2011, **13**, 1872–1874.
105 S. M. Inamdar, V. K. More and S. K. Mandal, *Tetrahedron Lett.*, 2013, **54**, 530–532.
106 A. Hu, J.-J. Guo, H. Pan and Z. Zuo, *Science*, 2018, **361**, 668–672.
107 A. Hu, J.-J. Guo, H. Pan, H. Tang, Z. Gao and Z. Zuo, *J. Am. Chem. Soc.*, 2018, **140**, 1612–1616.