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Development of New Carbonylation Reactions toward Sustainable Synthesis of Aliphatic Carboxylic Acid Derivatives

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Xingwei Gu

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1. Gutachter:

Prof. Dr. Xiao-Feng Wu

Leibniz-Institut für Katalyse e. V. Albert-Einstein-Str. 29a, 18059 Rostock, Germany

2. Gutachter:

Prof. Dr. Bartolo Gabriele

Laboratory of Industrial and Synthetic Organic Chemistry (LISOC)

Department of Chemistry and Chemical Technologies University of Calabria

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You can enjoy a grander sight, By climbing to a greater height.

欲穷千里目，更上一层楼。-- 唐·王焕之

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Abstract

Development of New Carbonylation Reactions toward Sustainable Synthesis of Aliphatic Carboxylic Acid Derivatives

Xingwei Gu

Leibniz-Institut für Katalyse e.V.

This dissertation is mainly focused on the development of new carbonylation reactions toward green synthesis of aliphatic carboxylic acid derivatives. Transition metal-catalyzed carbonylative coupling is one of the most efficient methods for accessing carboxylic acid derivatives. In recent years, as the concept of green chemistry has taken hold, utilizing abundant andinexpensive metals to replace noble metals has become a key strategy for carbonylative coupling. In addition, light, as a kind of clean energy, which activates substrates under mild conditions and forms highly reactive free radicals, is the future direction of carbonylation development. Therefore, we focus on the developing novel non-noble metal catalyzed as well as photo-promoted carbonylation coupling reactions. Specifically, an iron-catalyzed synthesis of aliphatic amides from alkylboronic esters via single electron transfer has been proposed. Subsequently, we developed the first photo-induced manganese-catalyzed synthesis of aliphatic amides at room temperature and atmospheric pressure. Last, we describe a high efficiency approach to obtain alkylphenol esters from alkyl iodides with phenol by phosphine-catalyzed photo-induction under atmospheric pressure through charge-transfer complex.

Entwicklung neuer Carbonylierungsreaktionen zur nachhaltigen Synthese von aliphatischen Carbonsäurederivaten

Xingwei Gu

Leibniz-Institut für Katalyse e.V.

Diese Dissertation befasst sich hauptsächlich mit der Entwicklung neuer Carbonylierungsreaktionen zur grünen Synthese von aliphatischen Carbonsäurederivaten. Die übergangsmetallkatalysierte carbonylative Kopplung ist einer der effizientesten Ansätze für den Zugang zu Carbonsäurederivaten. In den letzten Jahren, in denen sich das Konzept der grünen Chemie durchgesetzt hat, ist die Verwendung von reichlich vorhandenen kostengünstigen Metallen als Ersatz für Edelmetalle zu einer Schlüsselstrategie für die carbonylative Kopplung geworden. Darüber hinaus ist Licht als eine Art saubere Energie, die Substrate unter milden Bedingungen aktiviert und hochreaktive freie Radikale bildet, die zukünftige Richtung der Carbonylierungsentwicklung. Daher konzentrieren wir uns auf die Entwicklung neuartiger, nicht edelmetallkatalysierter sowie lichtgeförderter Carbonylierungskupplungsreaktionen. Insbesondere wurde eine eisenkatalysierte Synthese von aliphatischen Amiden aus Alkylboronsäureestern über einen einzelnen Elektronentransfer vorgeschlagen. Anschließend wurde die erste photoinduzierte mangankatalysierte Synthese von aliphatischen Amiden bei Raumtemperatur und Atmosphärendruck entwickelt. Schließlich beschreiben wir einen hocheffizienten Ansatz zur Gewinnung von

Alkylphenolestern aus Alkyljodiden mit Phenol durch phosphinkatalysierte Photoinduktion unter Atmosphärendruck mittels eines Ladungstransferkomplexes.

List of abbreviations

acac	*Acetylacetone*
Ac	*Acetyl*
Ar	*Aryl*
Ad	*Adamantyl*
AIBN	*2,2'-Azobis(2-Methylpropionitril)*
atm	*Atmosphere*
^{n}Bu	*n-Butyl*
Bu_4NI	*Tetrabutylammonium iodide*
bpy	*2,2'-Bipyridyl*
Cat.	*Catalyst*
Co	*Cobalt*
CO	*Carbon monoxide*
Cu	*Copper*
Cy	*Cyclohexyl*
DTBP	*Di-tert-butyl peroxide*
DPPO	*Diphenylphosphine oxide*
DCE	*1,2-Dichloroethane*
Et	*Ethyl*
etc.	*Et cetera*
equiv.	*Equivalent*
et al.	*Et alii*
Et_3N	*Triethylamine*
Fe	*Iron*
h	*hour*
H_2	*Hydrogen*
IPrCuCl	*Chloro[1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene]copper(I)*
IMesCuCl	*Chloro[1,3-Bis(2,4,6-trimethylphenyl)imidazol-2-ylidene]copper(I)*
In	*Indium*
L	*Ligand*
M	*Metal*
Me	*Methyl*
MeCN	*Acetonitrile*
MeOH	*Methanol*
Mg	*Magnesium*
Mn	*Manganese*
Ni	*Nickel*

mmol	*millimole*
mol	*mole*
NMR	*Nuclear magnetic resonance*
N_2	*Nitrogen*
OAc	*Acetoxy*
Ph	*Phenyl*
$PhCF_3$	*Benzotrifluoride*
PhMe	*Toluene*
Pd	*Palladium*
Phen	*Phenanthrolin*
PPh_3	*Triphenylphosphine*
psi	*Pound per square inch*
quant.	*Quantitative*
rt	*Room temperature*
THF	*Tetrahydrofuran*
Tc	*thiophene-2-carboxylate*
TBPA	*tert-Butyl peracetate*
TMU	*Tetramethylurea*
Xantphos	*4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene*

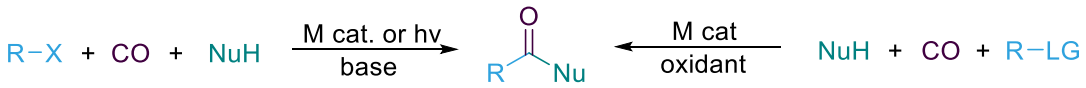
Contents

List of schemes

1. Introduction

Carbonylation reactions employing carbon monoxide (CO) as a cheap and abundant source of C1 are straightforward and atom-economical strategies for the synthesis of a variety of carbonyl-containing compounds and their derivatives.[1] After more than half a century of development, transition metal-catalyzed carbonylation reactions have become among the most effective methods for synthesizing carbonyl compounds.[2] However, carbonylation reactions commonly require high temperatures and pressures, and most carbonylation reactions have been studied based on noble metal catalysis, with established catalytic systems.[3] In recent years, driven by the principles of green chemistry, developing new carbonylation reactions is a hot research topic nowadays.[4] There are several strategies: (1) substituting precious metals with economically viable alternatives in carbonylation reactions, (2) photopromoting activated substrates to improve reaction conditions, (3) developing unactivated and cost-effective feedstocks for carbonylation reactions.

Aliphatic carboxylic acid derivatives are widely found in natural product drugs and bioactive molecules, serving as crucial intermediates for synthesizing functional materials and industrial products.[5] The carbonylation reaction of alkyl halides with different types of nucleophiles represents one of the most straightforward and efficient methods for assembling aliphatic carboxylic acid derivatives.[6] For instance, employing alcohols, amines, and water as cross-coupling nucleophiles is known as alkoxycarbonylation, aminocarbonylation, and hydroxycarbonylation, respectively. Furthermore, employing F^-, Cl^-, and carboxylic acids as nucleophiles can produce acyl fluorides, chlorides, and anhydrides, respectively. In the past, most studies on the carbonylation of alkyl halides have focused on the more reactive alkyl iodides.[7] However, in recent years, there has been a growing interest in utilizing the less reactive and more economical alkyl bromides and chlorides as carbonylation substrates.



a. Classical carbonylative coupling *b*. Oxidative carbonylative coupling

Scheme 1 Carbonylative coupling to access alkyl carboxylic acid derivatives

On the other hand, oxidative carbonylation has been equally important strategy for the synthesis of aliphatic carboxylic acid derivatives.[8] This protocol accesses the corresponding carboxylic acid derivatives such as esters, amides, and others from two nucleophiles with the assistance of an oxidant. Its unique reaction mechanism provides additional opportunities for new reactions that cannot be achieved with classical carbonylation couplings.

Above all mentioned, this dissertation is mainly focused on the development of new carbonylation reactions toward green synthesis of aliphatic carboxylic acid derivatives. These include, inexpensive metal-catalyzed carbonylation, photopromoted carbonylation, and oxidative carbonylation.

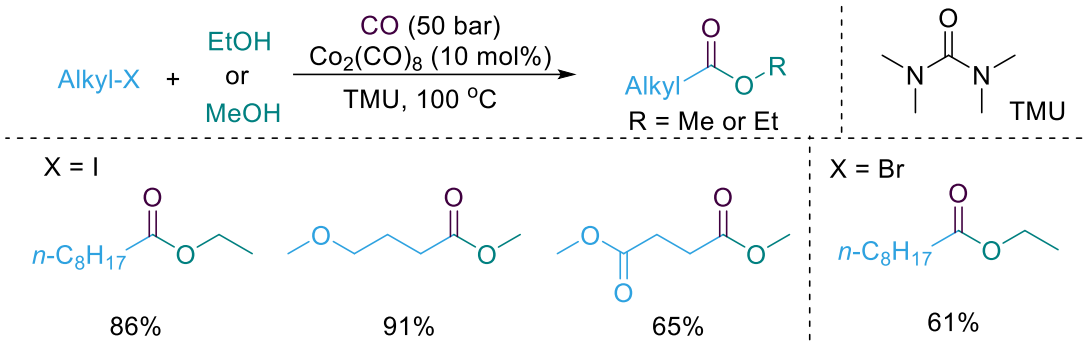
2. Carbonylative coupling reaction of alkyl halides for synthesizing aliphatic carboxylic acid derivatives

The carbonylative coupling reaction of alkyl halides with nucleophiles is among the most efficient methods for accessing aliphatic carboxylic acid derivatives.[9] However, carbonylation of C(sp^3)–X bonds, especially unactivated alkyl halides, has been highly challenging due to their oxidative addition difficulties as well as the presence of competitive *β*-elimination reactions.[10] In the past decades, most of the carbonylation of alkyl halides has been based on noble metal catalysis, therefore, the development of novel green carbonylation coupling reactions using inexpensive or metal-free metals is the current research hotspot.

2.1 Alkoxycarbonylation of alkyl halides

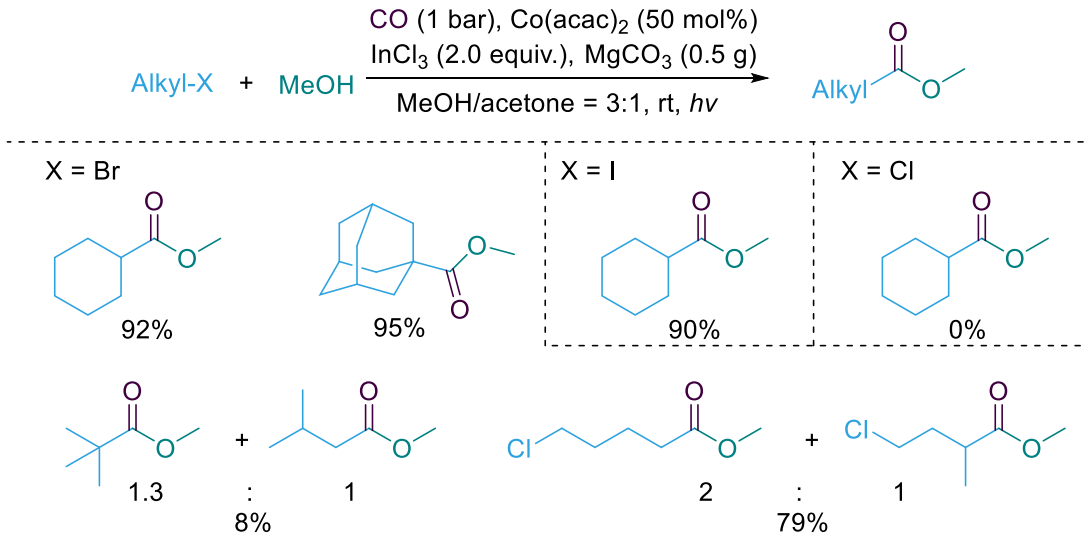
2.1.1 Co-catalyzed alkoxycarbonylation

Cobalt is a suitable alternative to noble metals in carbonylation. As early as 1963, Heck and Breslow reported the $Na[Co(CO)_4]$-catalyzed alkoxycarbonylation reaction.[11] In general, alkyl halides were catalyzed using $Na[Co(CO)_4]$ in the presence of excess dicyclohexylethylamine or sodium methanol, using methanol as solvent and at 1000 psi carbon monoxide pressure to afford alkyl carboxylic acid esters in moderate yields. In 1991, the group of Fuchikami reported the alkoxycarbonylation of unactivated alkyl iodides in good yields using $Co_2(CO)_8$ as a catalyst.[12] Soon after, the group made adjustments to the reaction regime to further broaden the substrate range of the approach, and it is worth mentioning that unactivated alkyl bromide was also suitable for the reaction conditions with good yields (Scheme 2).[13] In addition, the selection of the solvent is known to be critical through a number of experiments. TMU can effectively inhibit *β*-elimination from starting materials or M-X bonds when used as solvent.



Scheme 2 Cobalt-catalyzed alkoxycarbonylation of alkyl halides

In 2003, Dragojlovic's group reported the alkoxycarbonylation of alkyl bromides in the presence of inexpensive cobalt catalysts at room temperature and at atmospheric pressure of CO (Scheme 3).[14] The reaction was carried out under a low-pressure mercury lamp, and it was discovered that the use of Lewis acid as an additive was able to substantially increase the rate of the carbonylation reaction. Also, in this carbonylation reaction acetone was essential for the reaction and the authors suggest that acetone was a sensitizer. This protocol also has some shortcomings in that for non-cyclic substrates, the products are usually accompanied by different isomers.

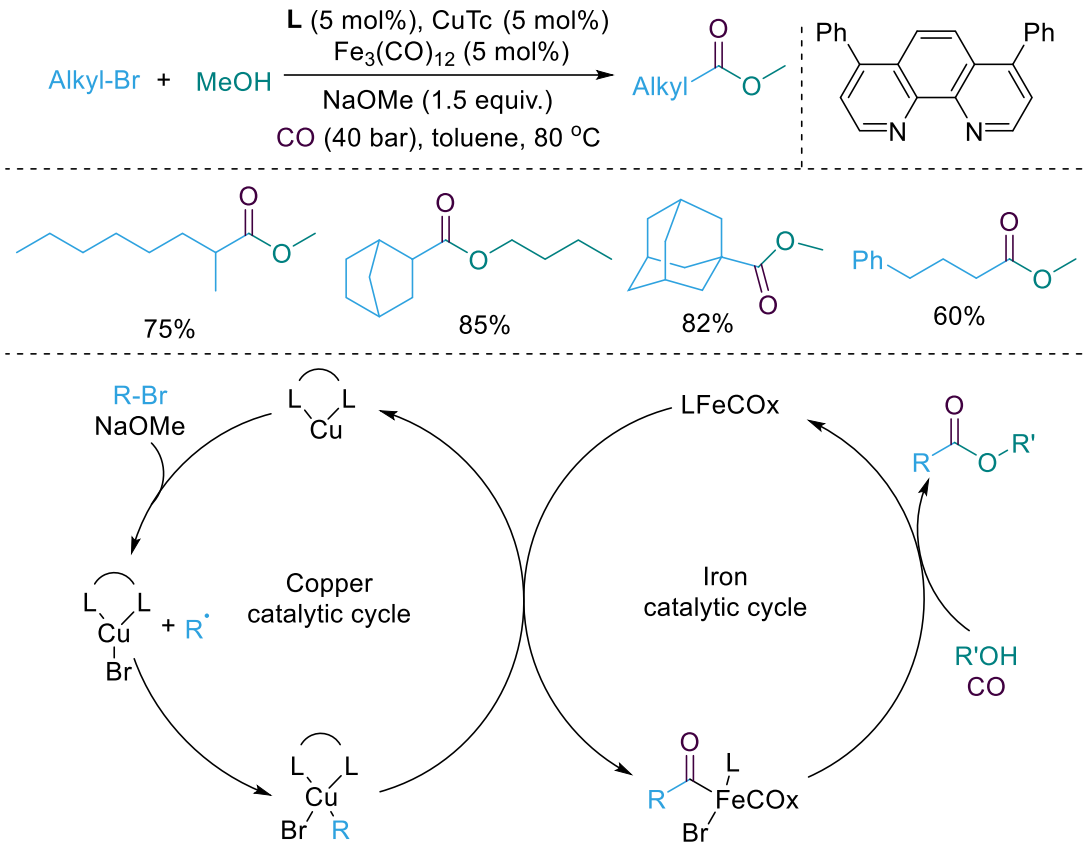


Scheme 3 Cobalt-catalyzed carbonylation of alkyl halides with methanol

2.1.2 Cu-catalyzed alkoxycarbonylation

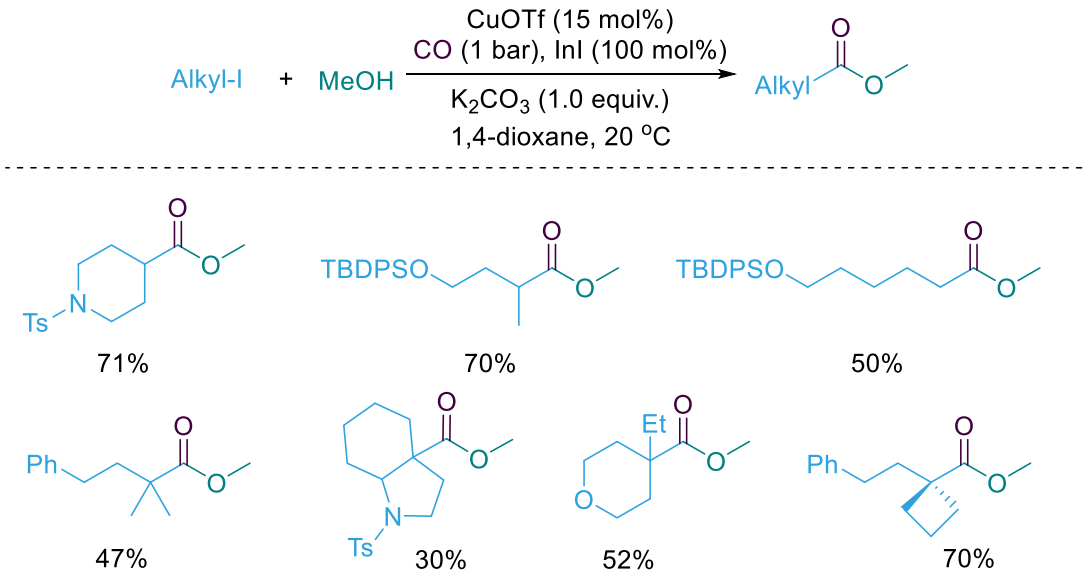
Copper salts are affordable, readily available, environmentally friendly and relatively non-toxic. However, copper-catalyzed carbonylation reactions have attracted increasing attention until recent years.[15]

In 2018, the Wu group reported an interesting example of Cu/Fe co-catalyzed alkoxycarbonylation of unactivated alkyl bromides (Scheme 4).[16] The authors used the bidentate ligand bathophenanthroline to enhance the efficiency of the copper catalysts in achieving the alkoxycarbonylation of primary, secondary and tertiary alkyl bromides and conversion to the corresponding aliphatic esters. Mechanistic studies indicated that this alkoxycarbonylation produced carbon radicals through copper abstraction of bromine atom, after which carbonyl iron activated the copper catalyst to form acylcarbonyl-iron complex. Subsequent nucleophilic attack yields the desired esters.



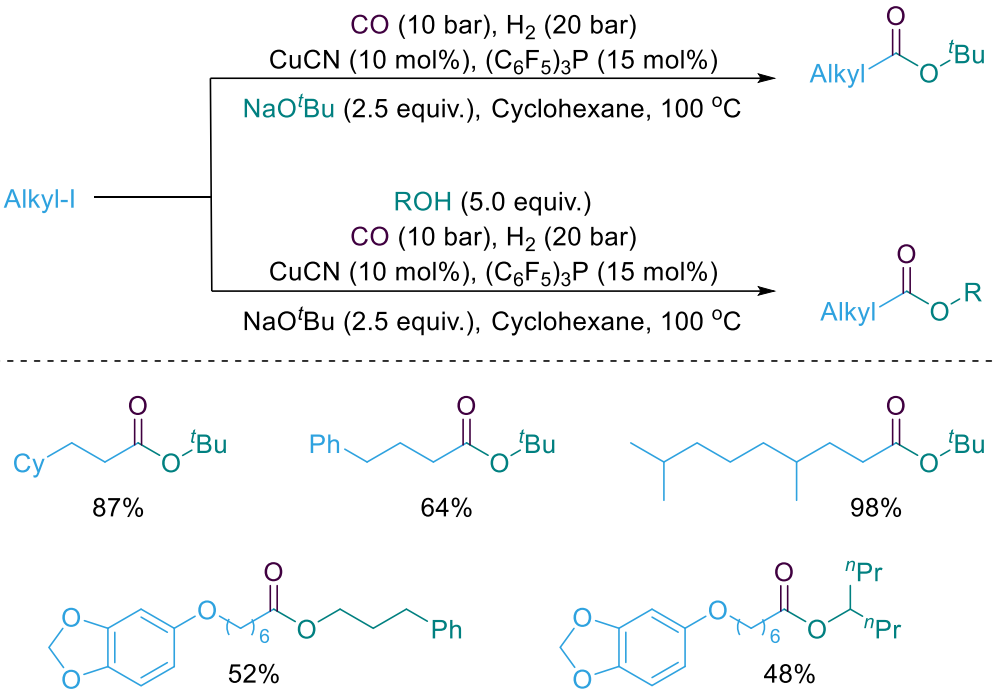
Scheme 4 Copper/iron co-catalyzed alkoxycarbonylation of alkyl bromides with methanol

In 2019, Gong's group reported the Cu-catalyzed and In-mediated alkoxycarbonylation of alkyl iodides at room temperature and atmospheric pressure (Scheme 5).[17] Indium powder or indium iodide is essential, and the authors hypothesize that it could serve as a mediator to facilitate coordination between copper and carbon monoxide, resulting in the production of active $InCu_x(CO)_y$ intermediates. It is worth mentioning that carbonylation of tertiary alkyl halides is normally difficult due to their steric hindrance. However, under this protocol, tertiary alkyl iodides are also appropriate reaction partners, yielding products in moderate to good yields.



Scheme 5 Copper-catalyzed alkoxycarbonylation of alkyl iodides with methanol

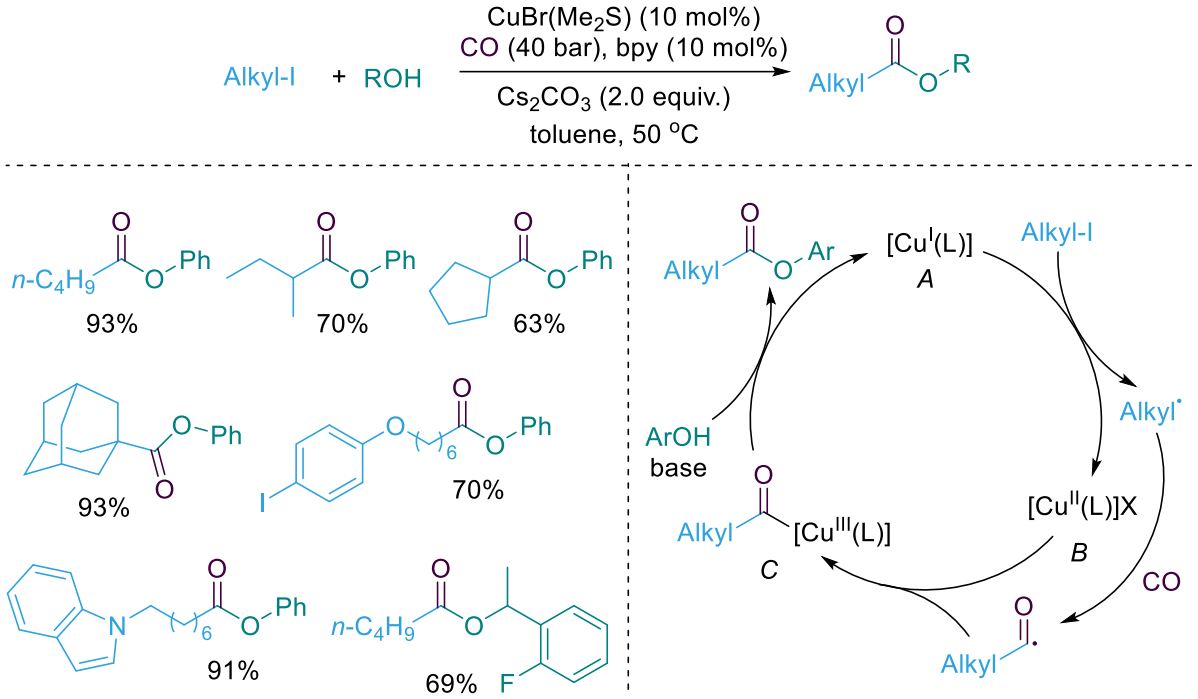
In 2021, Wu and co-workers reported a copper-catalyzed alkoxycarbonylation of unactivated alkyl iodides using NaO^{t}Bu as the nucleophilic reagent and base to afford a variety of *tert*-butyl esters in good yields (Scheme 6).[18] In addition, when additional primary and secondary alcohols are added to the catalyzed system, the corresponding aliphatic esters can also be accessed in good yields. Mechanistic studies indicate that this alkoxycarbonylation process involves radical intermediates.



Scheme 6 Copper-catalyzed alkoxycarbonylation of alkyl iodides using NaO^{t}Bu as the nucleophilic

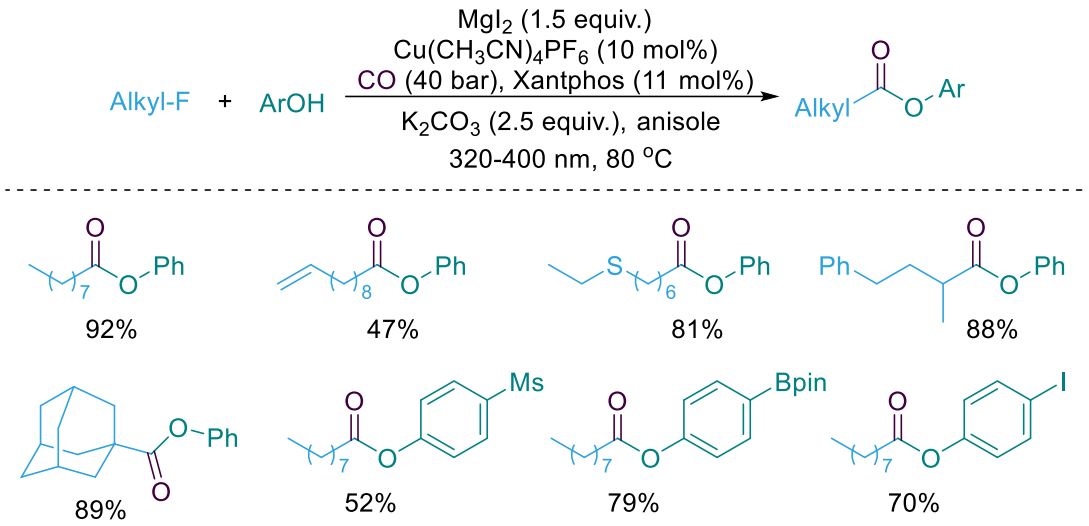
In contrast to alkyl alcohols, which are effective coupling partners in carbonylation coupling reactions, the use of phenols as nucleophilic reagents in alkoxycarbonylation is often limited. In 2022, the group of Wu reported

accomplishment of the alkoxycarbonylation of phenol compounds with alkyl iodides using low-cost and abundant copper metal as catalyst (Scheme 7).[19] In addition, the method is perfectly suitable for the carbonylation coupling of aliphatic alcohols. Mechanistic studies have shown that the reaction undergoes a radical process. Alkyl iodides are first activated by copper to produce alkyl radicals. The alkyl radical is then captured by carbon monoxide to form an acyl radical, which further combines with copper to form an acyl copper intermediate. Finally, anion exchange with phenol is followed by reductive elimination to afford the desired ester and regeneration of the copper catalyst. Shortly thereafter, the Evano group reported a similar copper-catalyzed alkoxycarbonylation of alkyl iodides, which also possessed good performance.[20]



Scheme 7 Copper-catalyzed alkoxycarbonylation of alkyl iodides

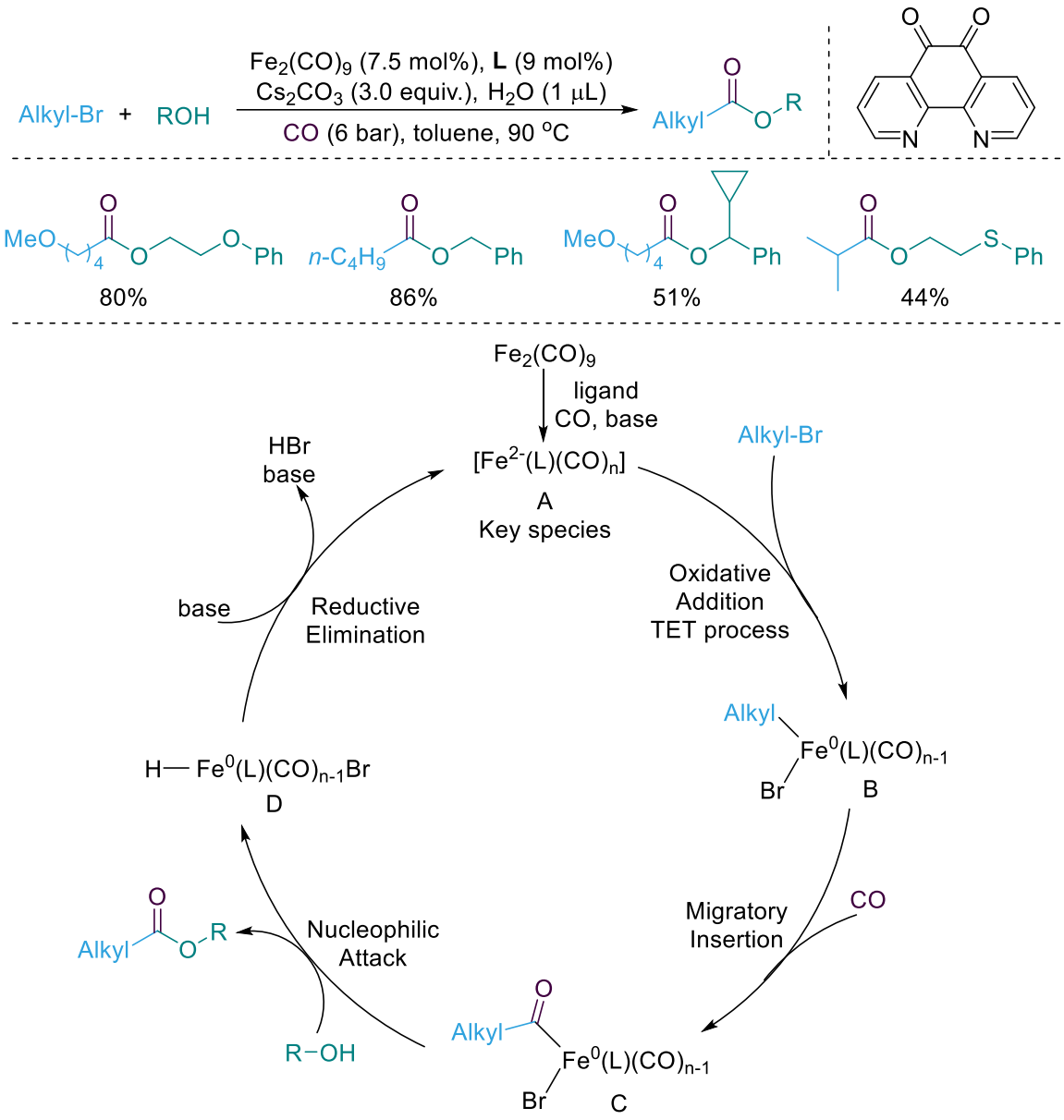
Carbon-fluorine bond (BDE = 485 kJ mol^{-1}) is the strongest σ-bond in organic chemistry whose functionalization has been a substantial challenge. Recently, Wu's group reported the alkoxycarbonylation of alkyl fluorines with phenols under light irradiation (Scheme 8).[21] The authors found that the addition of magnesium iodide not only produces more reactive species by *in situ* halogen exchange, but also avoids the influence of fluoride ions in the reaction solution on the subsequent radical process.



Scheme 8 Copper-catalyzed alkoxycarbonylation of alkyl fluorines with phenols

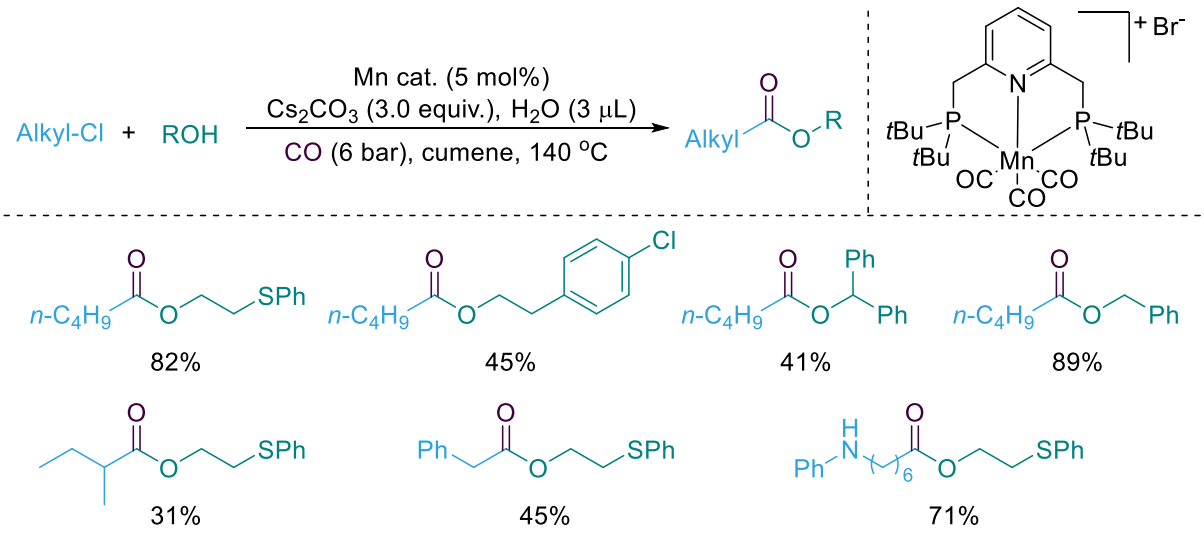
2.1.3 Other metal-catalyzed alkoxycarbonylation

Carbonyl iron complexes are widely used in carbonylation reactions. In 2022, the first low-valent iron-catalyzed alkoxycarbonylation of alkyl bromines was reported by the Wu group (Scheme 9).[22] Mechanistic studies showed that the reaction activates alkyl bromides *via* a two-electron transfer process (TET) and that only Fe^0 and Fe^{2-} sources could initiate alkoxycarbonylation, while the reaction could not proceed using Fe^{2+} or Fe^{3+} salts as catalysts. In addition, adding a minor amount of water to the reaction system was effective in enhancing the reactivity of alkoxycarbonylation. The authors concluded that the water increased the solubility of the base and promoted the nucleophilic attack and reductive elimination processes. In addition, the protocol is equally applicable to alkyl iodide, tosylate, and mesylate, yielding the corresponding esters.



Scheme 9 Iron-catalyzed alkoxycarbonylation of alkyl bromines

Alkyl chlorines are an inexpensive class of chemicals. The development of carbonylation reactions suitable for unactivated alkyl chlorines has been a long-standing target in the field. However, due the high dissociation energy of the carbon-chlorine bond, oxidative addition is particularly difficult, especially in the CO atmosphere where the metal catalysts tend to deactivate. In 2023, the Wu group reported an example of the activation of the carbon-chlorine bond using a pincer manganese catalyst to accomplish the alkoxycarbonylation of alkyl chlorides and gain the desired ester in moderate to excellent yields (Scheme 10).[23] Furthermore, the authors additionally added sodium or lithium bromide to the reaction system, the yield of the ester did not increase, and the yield of alkyl bromide decreased instead under this method. This demonstrated that the alkyl chlorides did not undergo an in situ Finklestein reaction, but rather a direct oxidative addition.



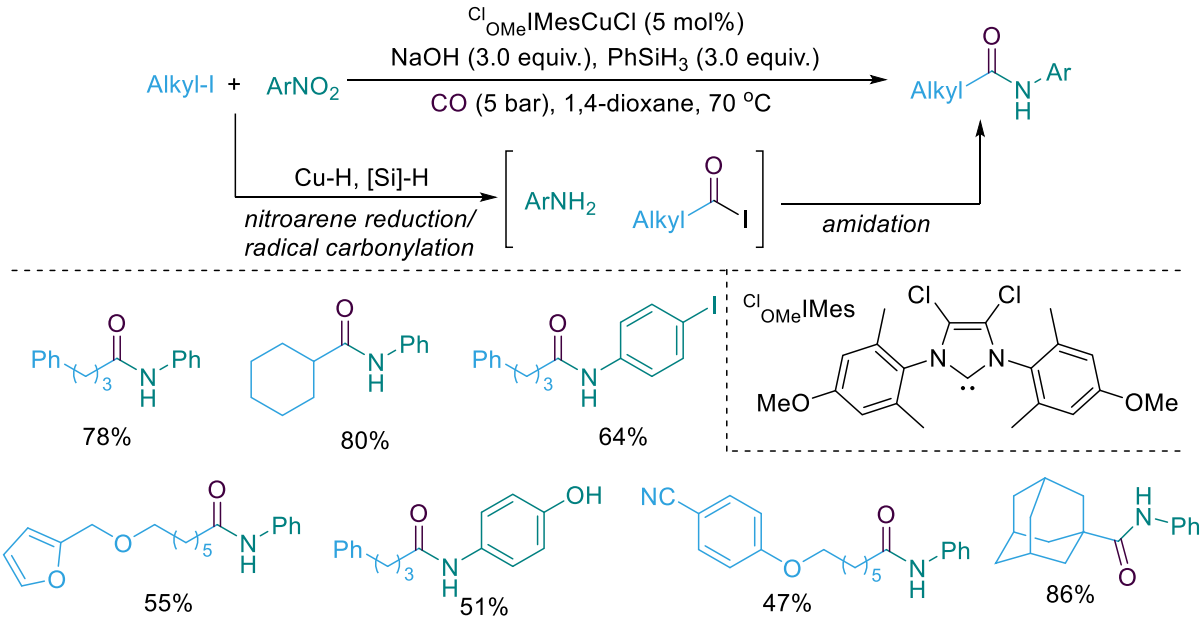
Scheme 10 Manganese-catalyzed alkoxycarbonylation of alkyl chlorides

2.2 Aminocarbonylation of alkyl halides

Amides are among the most important structural motifs in various natural products and biologically active molecules, which are widely used in the synthesis of polymeric materials, agrochemicals or active pharmaceutical ingredients.[24] Therefore, the effective construction of amide bonds has aroused great interest in the synthetic community. Among the numerous methods for the preparation of aliphatic amides, the aminocarbonylation of alkyl halides is a straightforward strategy for the synthesis of amides.

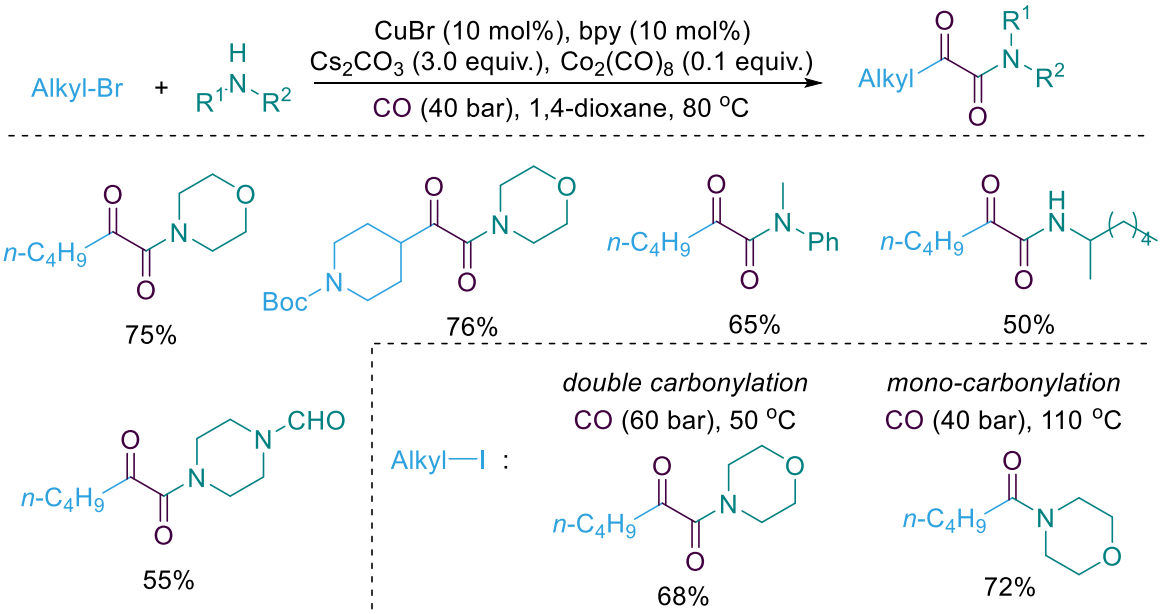
2.2.1 Cu-catalyzed aminocarbonylation

Nitroarenes are an economical chemical that can be used as a substitute for aniline under reducing conditions. In 2019, Mankad's group reported a copper-catalyzed reductive aminocarbonylation of alkyl iodides using nitroarenes as a nitrogen source (Scheme 11).[25] The authors performed controlled experiments and discovered that (NHC)CuH is a key intermediate in the reduction of nitroarenes. Thus, the copper catalyst plays a dual role of synergistically mediating the carbonylation of alkyl iodides as well as the reduction of nitroarenes.



Scheme 11 Copper-catalyzed reductive aminocarbonylation of alkyl iodides

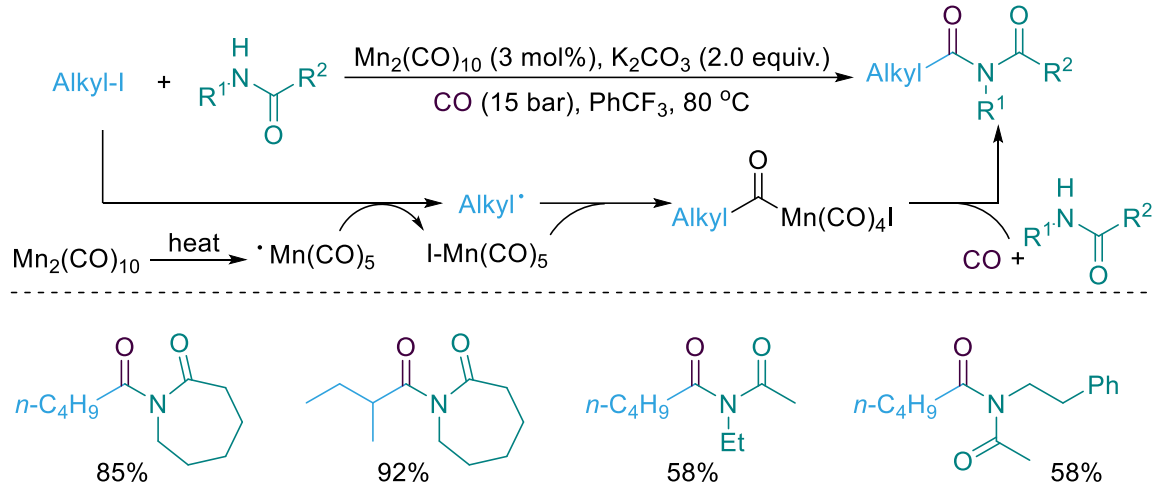
α-keto amides are common structural backbones for natural products as well as for several common inhibitors. Due to the multiple reaction sites in the structure, they are also important synthetic units in various organic transformations. In 2022, the group of Wu reported a copper-catalyzed double carbonylation of alkyl bromides with amines to provide a series of useful *α*-keto amides (Scheme 12).[26] The reaction has excellent functional group tolerance. For instance, primary amines are usually difficult to double carbonylation because of α-keto amides' tendency to form Schiff bases *in situ*, however, they are tolerant in this system as well. Furthermore, alkyl iodides can be selectively double or mono-carbonylated with amines under temperature and carbon monoxide pressure regulation. A similar aminocarbonylation of alkyl iodides was reported shortly thereafter by Evano's group, with the advantage that the reaction afforded a range of aliphatic amides at 5 bar of carbon monoxide.[27]



Scheme 12 Copper-catalyzed double carbonylation of alkyl bromides with amines

2.2.2 Other metal-catalyzed aminocarbonylation

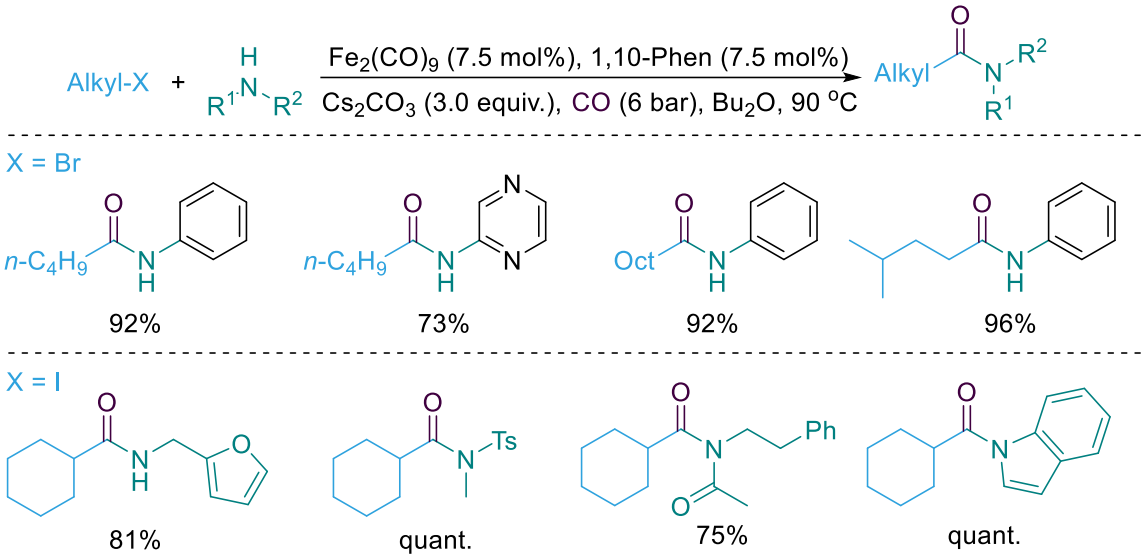
Imides are important intermediates in the fine chemical industry, widely used in detergents, agrochemicals and pharmaceutical intermediates. In 2017, Wu's group described the manganese-catalyzed carbonylative coupling reaction of alkyl iodides with amides to afford the corresponding imides in moderate to good yields (Scheme 13).[28] Mechanistic studies have shown that the reaction undergoes a radical process, where initially, $Mn_2(CO)_{10}$ is thermally induced to decompose into $Mn(CO)_5$ radical. Then the $Mn(CO)_5$ radical extracts the iodine atom from the alkyl iodine to form an alkyl radical and $IMn(CO)_5$, which combine to form an acyl manganese intermediate. Final amide nucleophilic attack afforded the product.



Scheme 13 Manganese-catalyzed carbonylative coupling reaction of alkyl iodides with amides

In 2023, the Wu group reported an iron-catalyzed aminocarbonylation of unactivated alkyl halides (Scheme 14).[29] The reaction has excellent functional group compatibility, in addition to amines, amides and indoles are

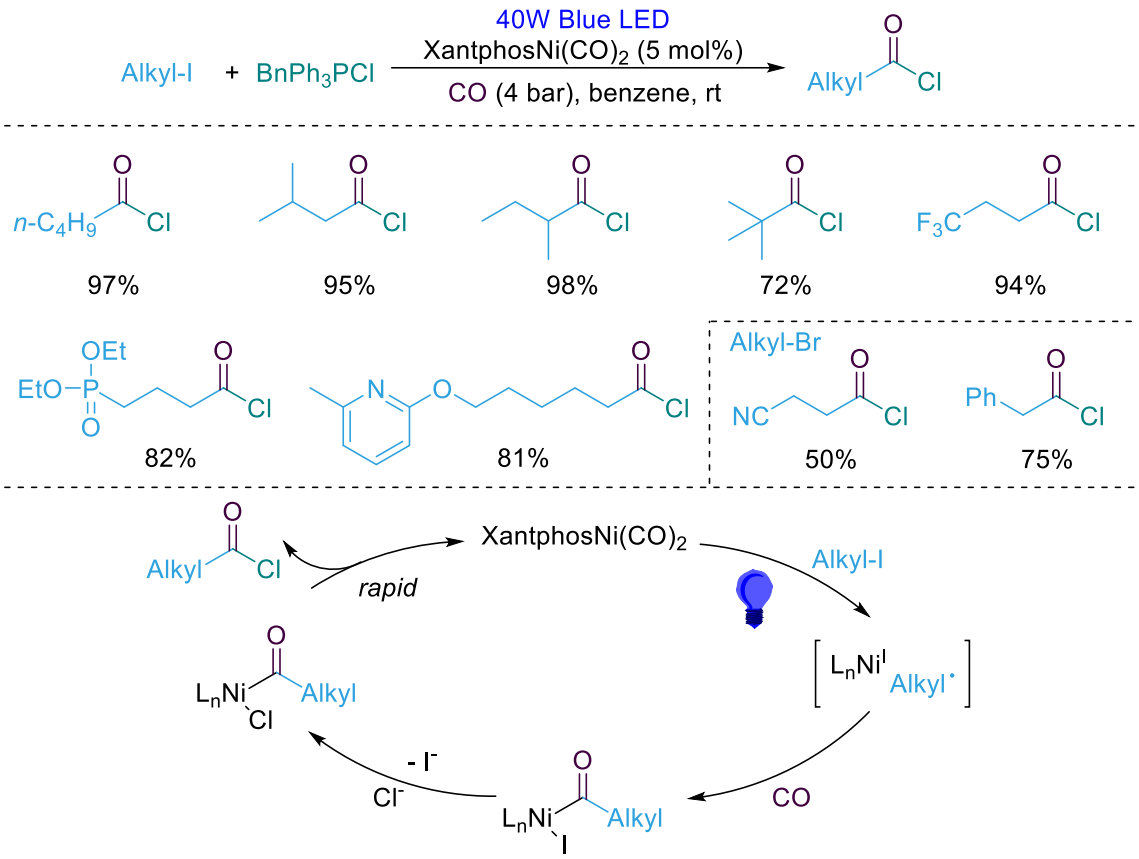
also suitable reaction partners. It is should be noted that when alkyl iodides are used as electrophiles, carbonylation proceeds *via* the radical pathway, whereas alkyl bromides proceed through a two-electron transfer process (TET).



Scheme 14 Iron-catalyzed aminocarbonylation of unactivated alkyl halides

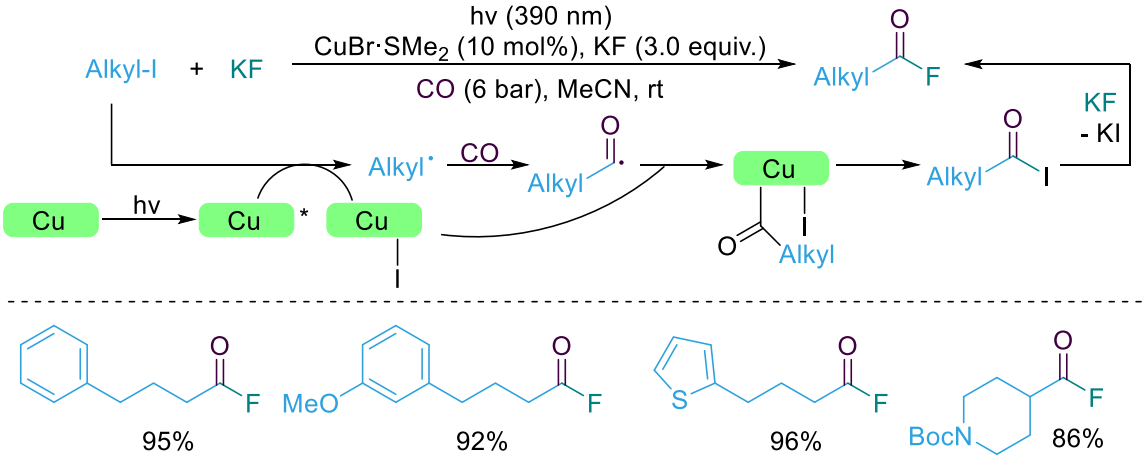
2.3 Synthesis of acyl fluorides, chlorides and anhydrides

Acyl fluorides, acyl chlorides and anhydrides are highly reactive carboxylic acid derivatives and are important acylation reagents in chemical synthesis and have a wide variety of applications. In 2022, Arndtsen's group developed a visible light-driven nickel-catalyzed carbonyl coupling reaction (Scheme 15).[30] This protocol enables the conversion of alkyl halides into versatile acid chlorides and the formation of useful esters, amides, and thioesters by coupling with nucleophilic reagents at ambient temperature. In addition, carbon monoxide had no inhibitory effect in the system, and mechanistic studies indicated that carbon monoxide-ligated Ni^0 was an effective catalyst for the reaction.



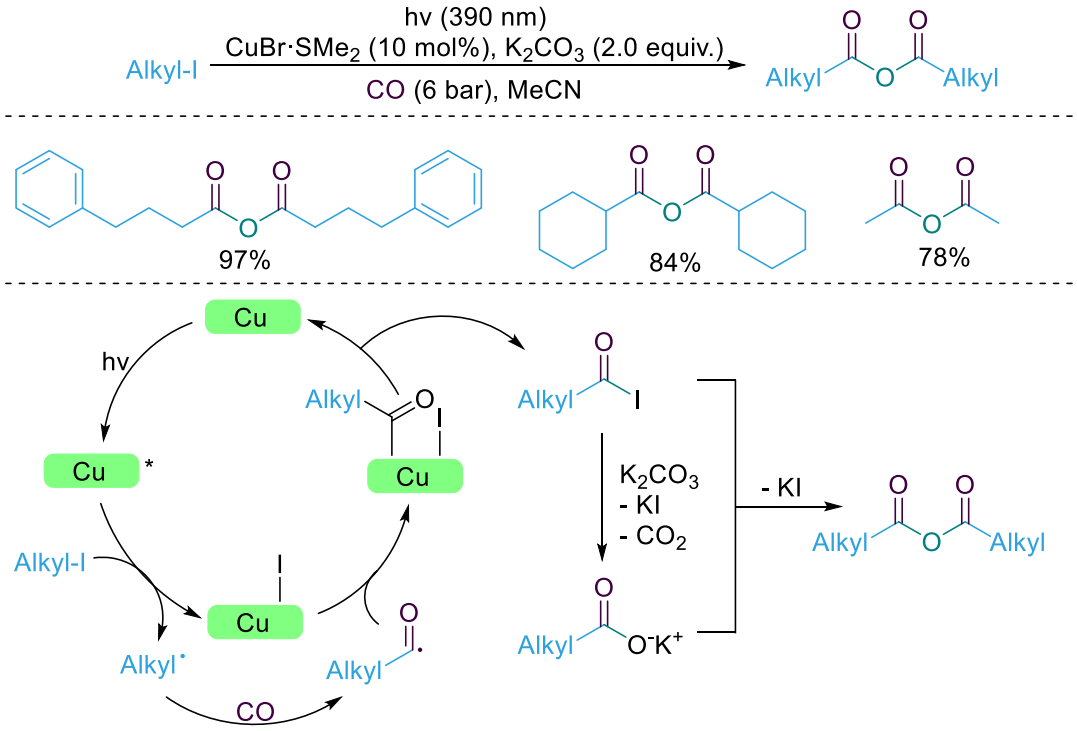
Scheme 15 Visible light-driven nickel-catalyzed carbonyl coupling reaction

In recent years, the synthesis and transformation of acyl fluorides has attracted interest. Due to their distinctive stability and high electrophilic reactivity, acyl fluorides are easier to handle compared to other acyl halides. Traditionally, acyl fluorides are usually available from the reaction of carboxylic acids preincorporated with carbonyl group and stoichiometric fluorinating reagents. Mankad's group reported the copper-catalyzed fluorocarbonylation of alkyl halides in 2024 (Scheme 16).[31] The reaction used inexpensive KF as the fluorine source and the corresponding acyl fluorides were obtained in good yields under blue light conditions. Several controlled experiments were performed, and the authors concluded that the alkyl iodide first undergoes a radical process to obtain the acyl iodide. Afterwards salt metathesis of acyl iodide with KF yields acyl fluoride.



Scheme 16 Copper-catalyzed fluorocarbonylation of alkyl halides

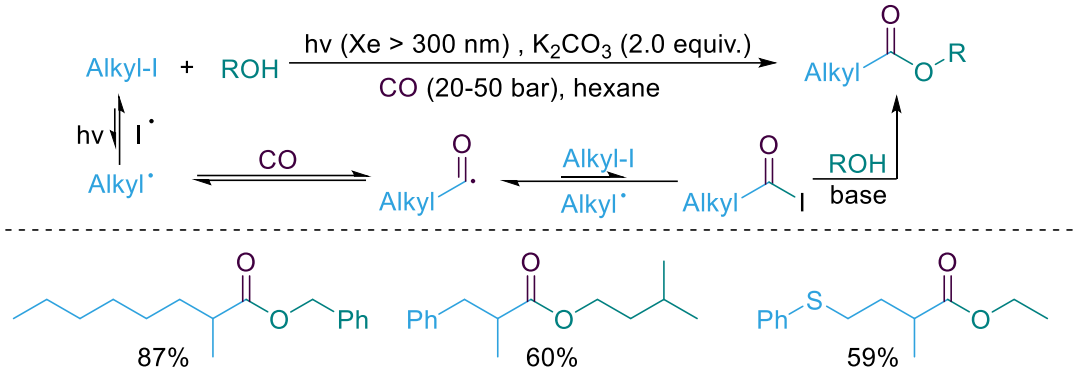
Acid anhydride is the dehydrated form of carboxylic acid which is valuable in the chemical industry. However, currently anhydrides are mainly produced by two Rh-catalyzed carbonylation reactions. In 2023, Mankad's group used an inexpensive copper catalyst to produce aliphatic symmetrical anhydrides directly from the carbonylation of alkyl halides in one step under light irradiation (Scheme 17).[32] The reaction has a good scope of substrates. Mechanistic studies have shown that the anhydride is obtained by condensation of acyl iodides with carboxylates.



Scheme 17 Copper-catalyzed carbonylation of alkyl iodides to synthesize anhydrides

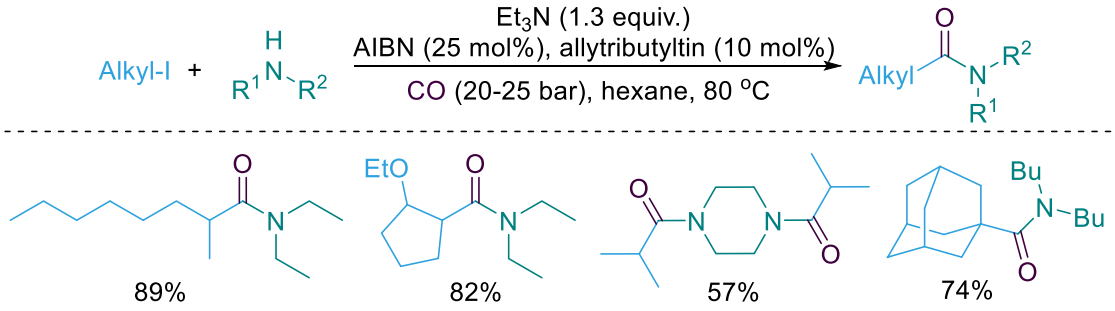
2.4 Metal-free carbonylation of alkyl halides

Metal-free carbonylation of alkyl halides commonly requires high-energy photocatalysis (Xe or Hg lamps). The radical carbonylation reaction is typically accompanied by high pressures of carbon monoxide, thus requiring complex equipment limiting the industrialization of photocarbonylation. In 1997, Sonoda's group reported the metal-free radical alkoxycarbonylation of alkyl iodides under irradiation conditions (Scheme 18).[33] The reaction has good chemoselectivity and *β*-hydrogen-eliminated olefins are the major by-products.



Scheme 18 Metal-free radical alkoxycarbonylation of alkyl iodides

In addition to photoinitiation, AIBN-allyltributyltin can also act as a thermal initiator to promote the formation of alkyl radicals from alkyl iodides. In 1998, Ryu's group realized the aminocarbonylation of alkyl iodides using AIBN-allytin to afford the desired amides in good yields (Scheme 19).[34] The reaction shows excellent chemoselectivity and the amide is the only product of the carbonylation even when MeOH is used as solvent. In 2001, the group conducted more intensive research on the application of chemoselectivity.[35] The strategy is based on atom transfer carbonylation/ionic dehydration sequences, which provide a useful pathway for the generation of azaheterocyclic compounds.



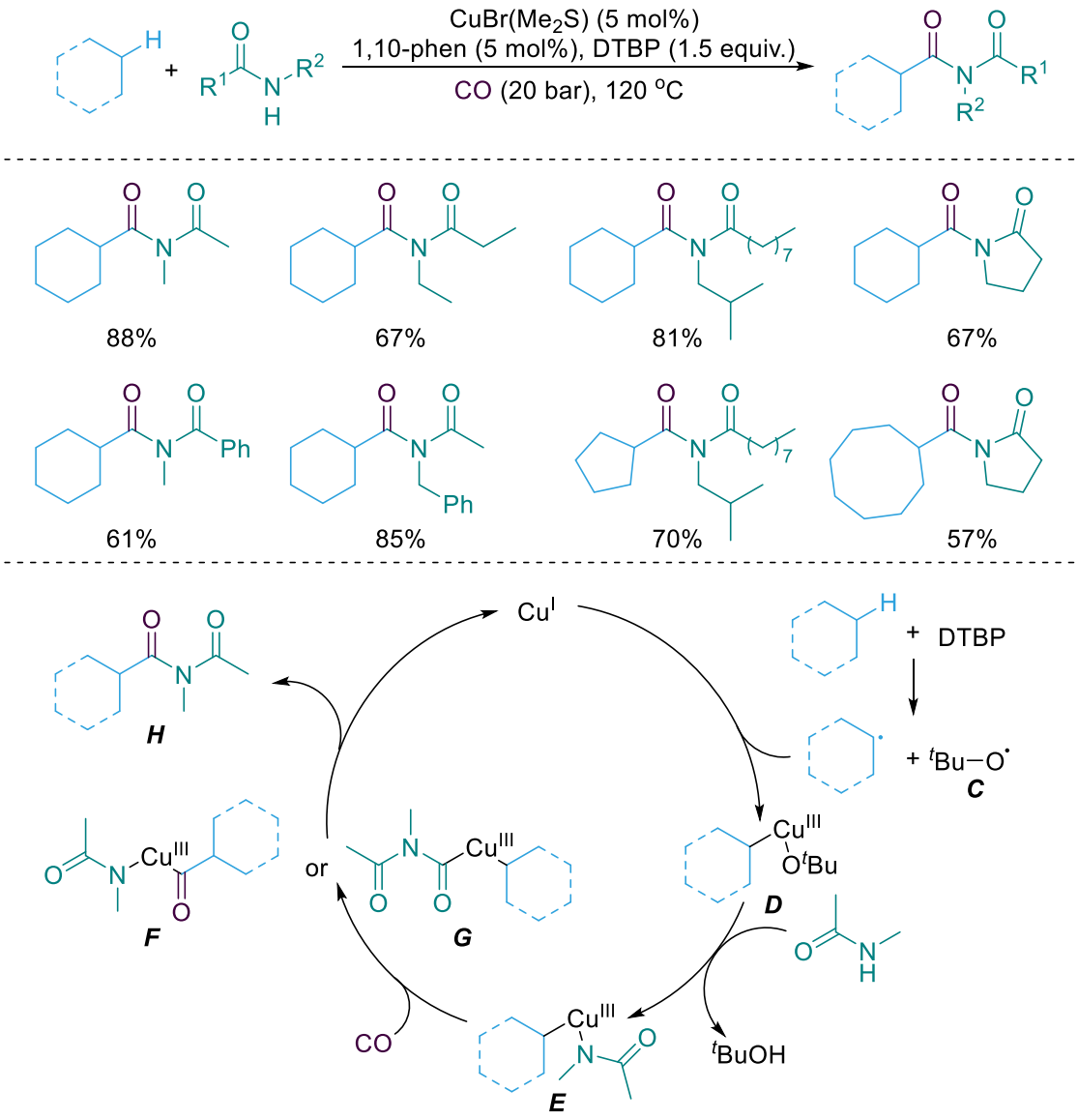
Scheme 19 Aminocarbonylation of alkyl iodides using AIBN-allytin

3. Oxidative carbonylative coupling reaction for synthesizing aliphatic carboxylic acid derivatives

Carbonylation coupling of nucleophiles and electrophiles with carbon monoxide is a powerful tool for the synthesis of carbonyl derivatives. In comparison, oxidative carbonylation reaction, a method for the synthesis of carbonylated derivatives using two nucleophiles with the assistance of an oxidant, has attracted a great deal of attention, and has also created new opportunities for carbonylation reactions.

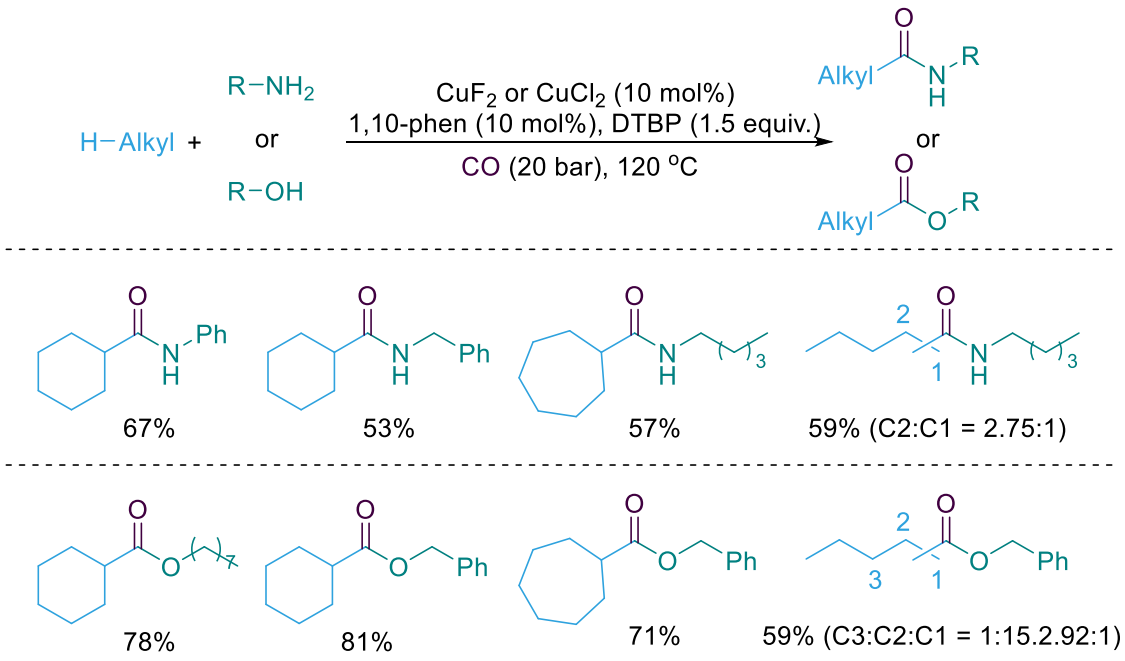
3.1 Cu-catalyzed oxidative carbonylation reactions

Amides are important intermediates and components in organic synthesis. However, the low nucleophilicity of amides limits their applications in carbonyl coupling reactions compared to alcohols and amines. In 2016, Wu's group pioneered the reported copper-catalyzed carbonylation coupling reaction of cycloalkanes with amides. In the presence of a suitable oxidant, the desired imide is afforded in moderate to excellent yields (Scheme 20).[36] The yield decreased when TEMPO was added to the standard reaction, and the authors concluded that the reaction proceeded via a radical process. First the peroxide undergoes copper-catalyzed or thermal homolysis to form tert-butoxy radical which reacts with the cycloalkane to form alkyl radical. The Cu^{I} species is then oxidized to form a Cu^{III} intermediate **D**, which reacts with the amide to yield intermediate **E**. Finally, carbon monoxide is inserted to form intermediates **F** or **G**, and the desired product is obtained after reductive elimination.



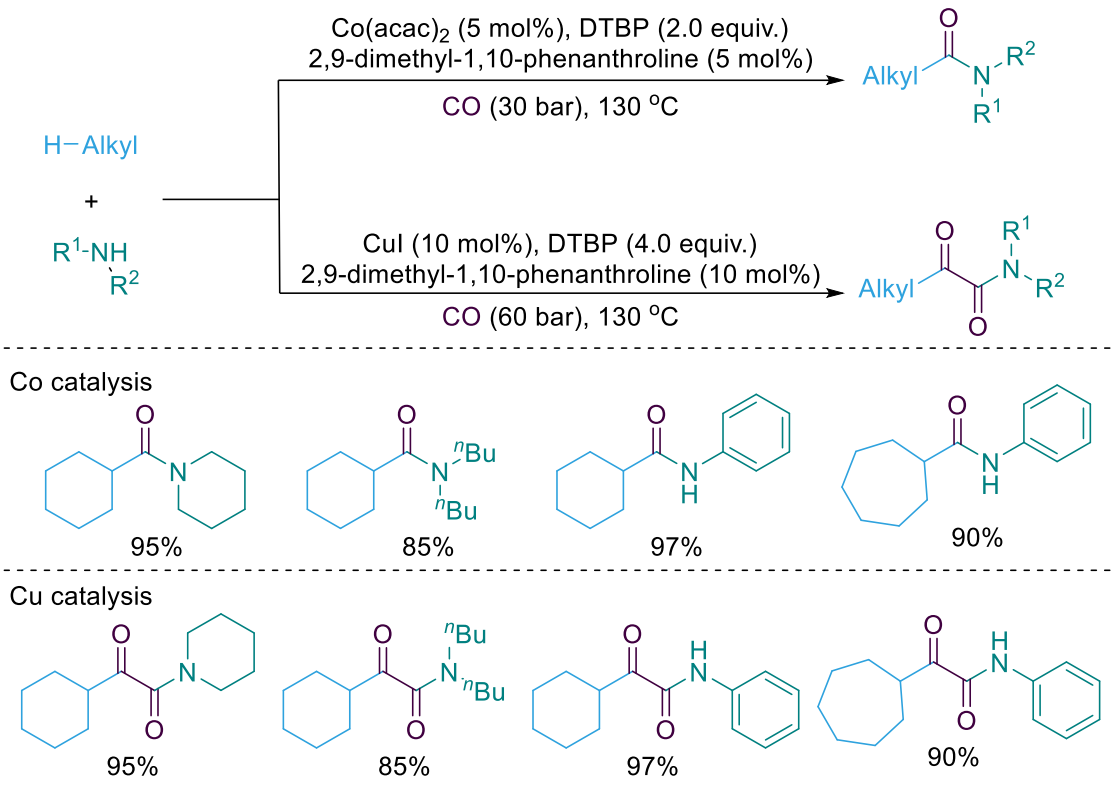
Scheme 20 Copper-catalyzed carbonylation coupling reaction of cycloalkanes with amides

Soon after, Wu's group sequentially achieved oxidative carbonylation of amines and alcohols under similar conditions (Scheme 21),[37, 38] further broadening the scope of substrates as well as demonstrating the powerful applicability of the protocol. And the reaction mechanism is comparable to that previously reported.



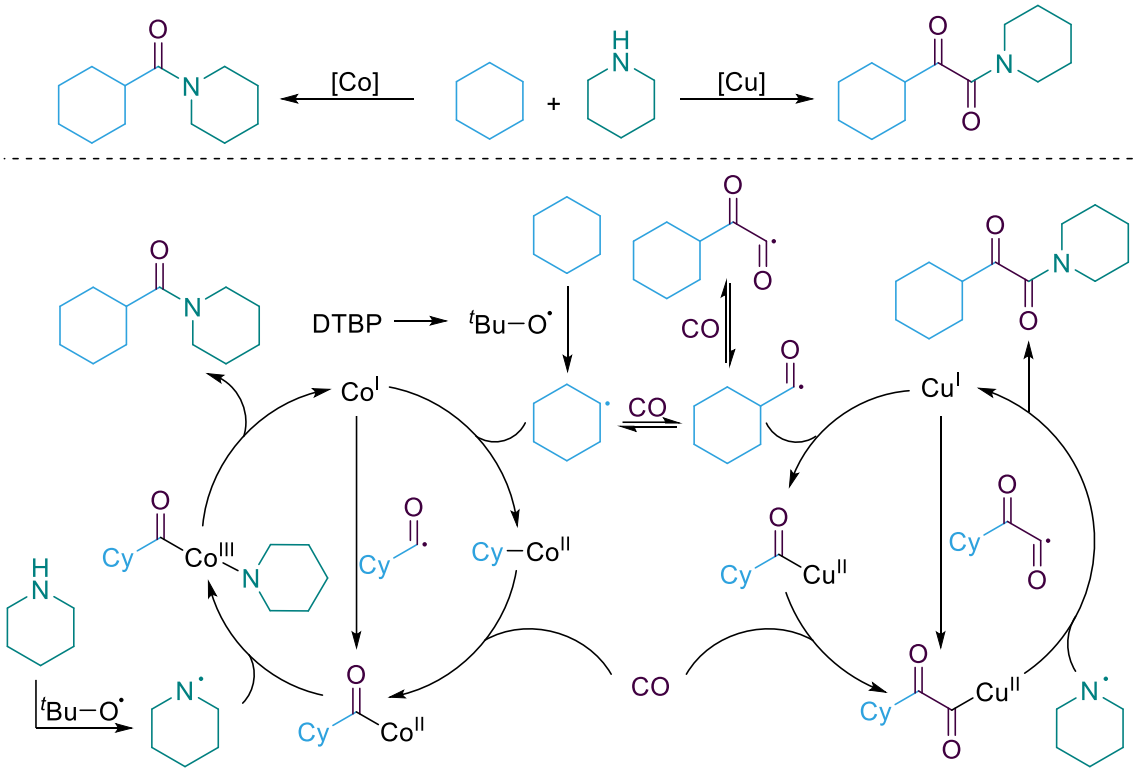
Scheme 21 Copper-catalyzed oxidative carbonylation of amines and alcohols

Achieving regioselective control to acquire different products from the same substrate is fascinating. In 2022, the group of Lei accomplished cobalt-catalyzed oxidative monocarbonylation and copper-catalyzed oxidative double carbonylation of alkanes by varying the collocation of metal complexes (Scheme 22),[39] In these two systems, various amines, such as aliphatic, aryl, primary and secondary amines, are tolerated and provided with the corresponding alkyl amides and alkyl α-keto amides.



Scheme 22 copper-catalyzed oxidative double carbonylation of alkanes

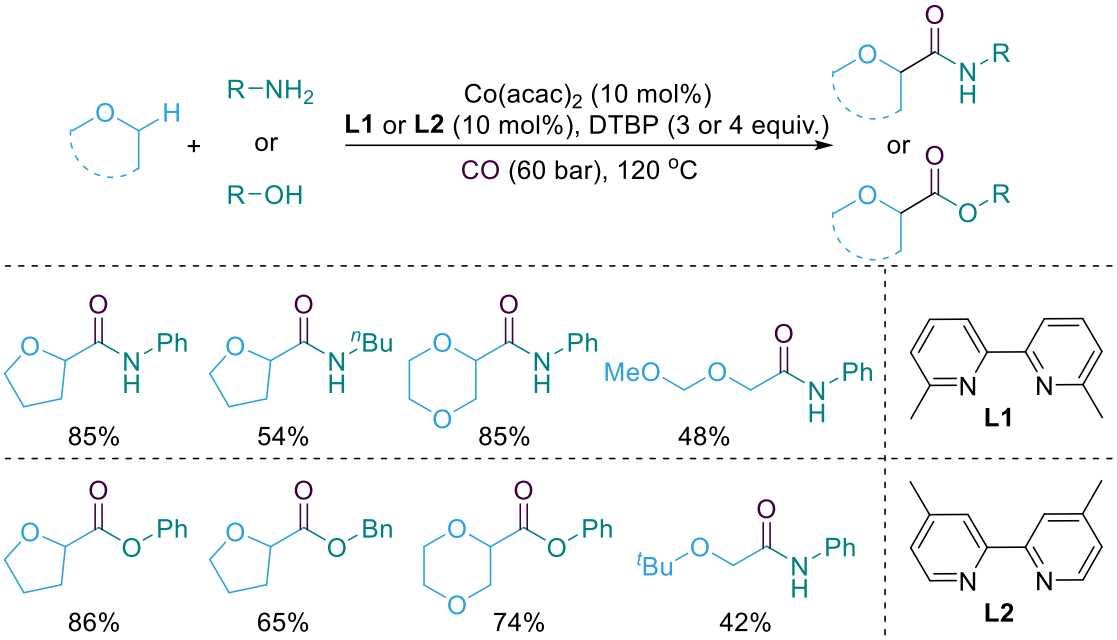
The authors propose plausible reaction mechanisms for monocarbonylation and double carbonylation (Scheme 23). It is worth noting that the authors consider the combination of Cu^{I} and 2,9-dimethyl-1,10-phenanthroline as somewhat inert and very special. Thus, the combination of Cu^{I} with 2,9-dimethyl-1,10-phenanthroline has a different reaction route than most metal and ligand combinations. Cu^{I} and 2,9-dimethyl-1,10-phenanthroline preferentially form cyclohexyl α-ketoacyl Cu^{II} intermediates, which stabilize the cyclohexyl α-ketoacyl radical and afford double carbonylation products.



Scheme 23 Plausible reaction mechanisms for monocarbonylation and double carbonylation

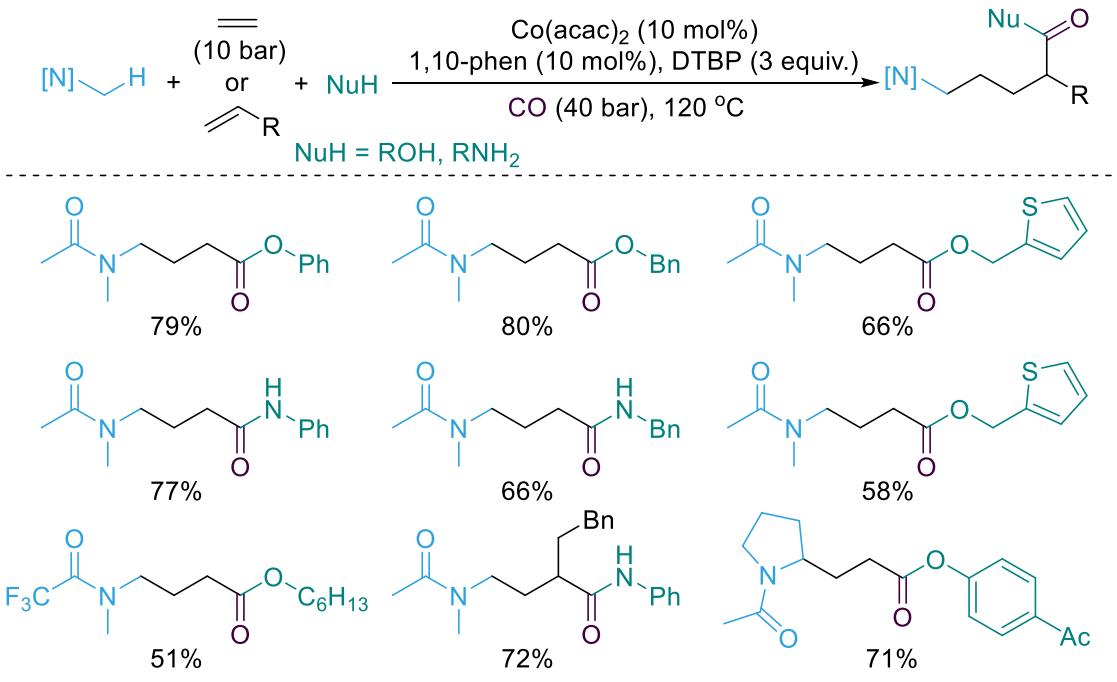
3.2 Co-catalyzed oxidative carbonylation reactions

α-Acylated ethers assume an essential role in a wide variety of biologically active pharmaceuticals. It has been reported that more than two-thirds of FDA-approved drugs contain the ether moiety. Thus, the functionalization of ethers as starting materials is promising. In 2022, Wu's group reported a cobalt-catalyzed oxidative carbonylation of ethers with amines to access *α*-amide-substituted ethers (Scheme 24).[40] Oxidative carbonylation is usually performed using one of the substrates as a solvent to provide the product in satisfactory yield. Therefore, certain solid or high boiling point raw materials are limited when used as substrates. Here, the authors were able to address the issue well using chlorobenzene as a solvent in this carbonylation process and exhibited moderate yields. In the same year, the group also reported the cobalt-catalyzed alkoxycarbonylation of ethers. [41] Mechanistic studies have shown that the reaction proceeds through a radical process.



Scheme 24 Cobalt-catalyzed oxidative carbonylation of ethers with amines

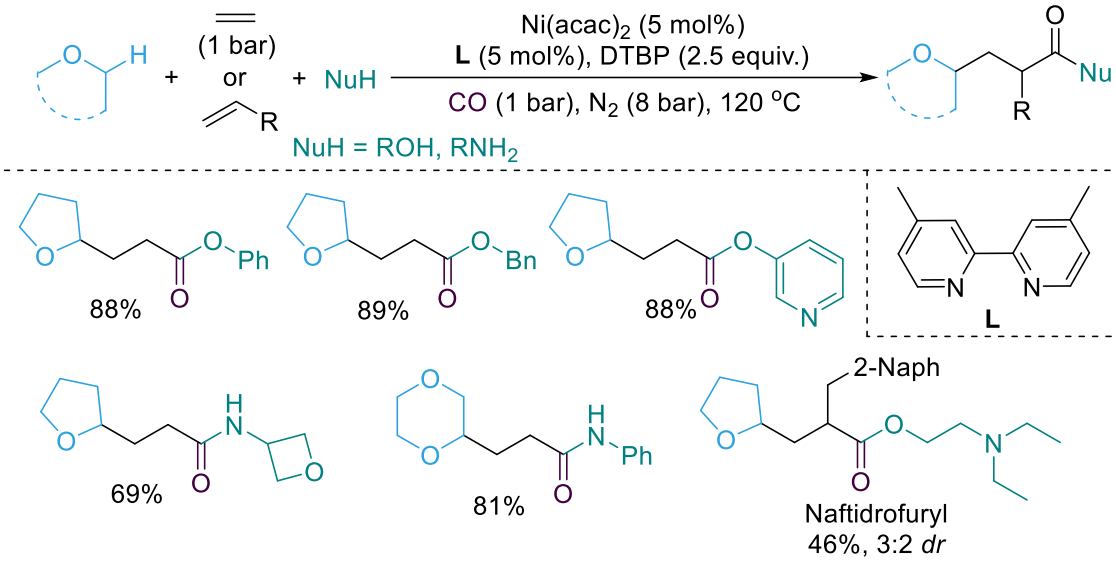
In comparison to the synthesis of α-amino acids and β-amino acids, which have well-established preparation methods, γ-amino acids tend to require multi-step preparation, limiting their development. In 2023, Wu's group reported cobalt-catalyzed oxidative aminocarbonylation of olefins for the synthesis of γ-amino acid derivatives and peptides (Scheme 25).[42] This four-component reaction exhibited excellent chemoselectivity, yielding the corresponding γ-amino acid derivatives in moderate to excellent yields. In addition to amines, alcohols are also suitable carbonylation partners.



Scheme 25 Cobalt-catalyzed oxidative aminocarbonylation for the synthesis of γ-amino acid derivatives

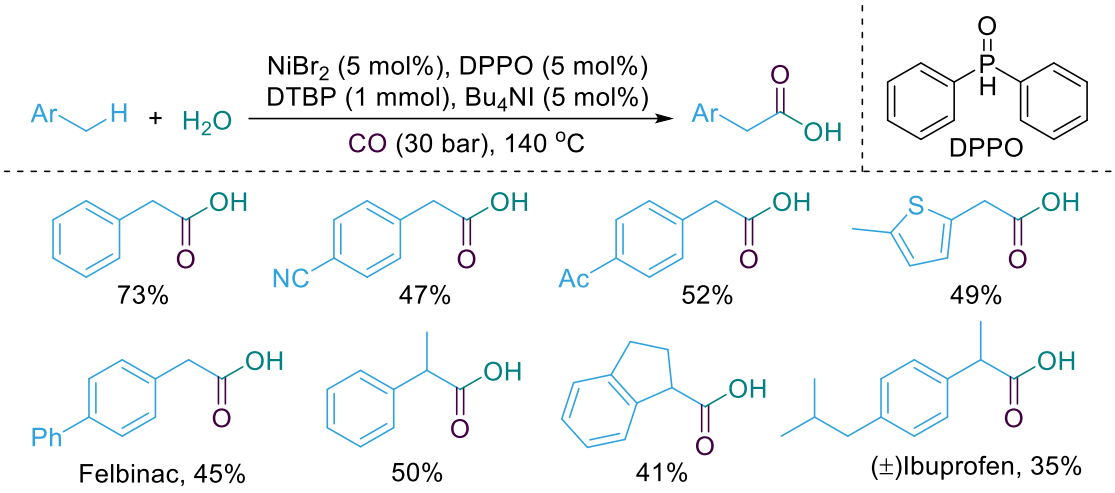
3.3 Ni-catalyzed oxidative carbonylation reactions

Carbonylation reactions involving nickel usually produce highly toxic $Ni(CO)_4$ and $Ni(CO)_3L$, which results in the loss of catalytic activity of the nickel catalyst. However, nickel is currently a popular metal catalyst for carbonylation due to its unique catalytic activity, low cost, and high abundance. In 2022, Wu's group reported the nickel-catalyzed four-component carbonylation of ethers and olefins, where the reaction could be carried out at low CO pressure and showed good functional group tolerance (Scheme 26).[43] It is worth noting that the medicine Naftidrofuryl for the treatment of cerebrovascular disease (CVD) is available under this protocol in only one step.



Scheme 26 Nickel-catalyzed four-component carbonylation of ethers and olefins

Synthesis of arylacetic acid is commonly obtained by nucleophilic substitution of sodium cyanide and benzyl halide followed by strong acid hydrolysis. The use of excessive sodium cyanide creates inconvenience for industrial production, thus, the development of green and efficient synthesis of arylacetic acids has received great attention. In 2022, Huang's group reported the nickel-catalyzed oxidative carbonylation of alkylbenzenes to obtain a series of useful arylacetic acids (Scheme 27).[44] The program uses inexpensive alkylaromatics to gain the corresponding products in medium yields with high chemoselectivity. Meanwhile, this protocol's synthetic easiness and utility in medicinal chemistry was demonstrated by the synthesis of the marketed drugs ibuprofen and diclofenac.



Scheme 27 Nickel-catalyzed oxidative carbonylation of alkylbenzenes for the preparation of arylacetic acids

4. Objectives of this work

Carbonylation reaction involving carbon monoxide is a powerful tool for the construction of carbonyl-containing molecules. Over half a century of development, most carbonylation reactions depend on noble metal catalysis such as palladium, rhodium, and iridium, while the reactions are commonly accompanied by high temperatures and pressures. In recent years, with the development of green chemistry, utilizing inexpensive metals as economic alternatives to noble metals is a promising strategy. In addition, enabling the carbonylation reaction to proceed under moderate conditions by photo-promotion has been a current research hotspot. The main purpose of this work is to develop novel carbonylation reactions for the synthesis of a range on useful aliphatic carboxylic acid derivatives by carbonylation using inexpensive metals or without metal.

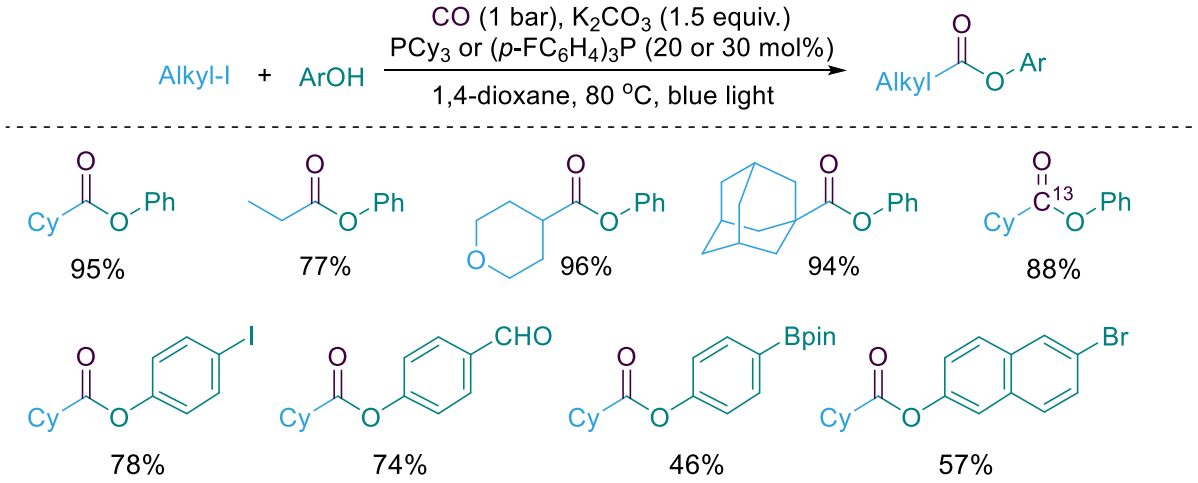
Compared to aryl halides, carbonylation reactions of alkyl halides, especially unactivated alkyl halides, are relatively challenging due to their difficult oxidative addition and the existence of competing *β*-elimination reactions. Building on the continuous efforts of organic chemists, the carbonylation of alkyl halides with noble metal-catalyzed or high energy photo-induced single-electron transfer processes has been successfully established, however, the reaction conditions are typically harsh. Hence, there is a need to develop novel efficient and mild method for the synthesis of aliphatic carboxylic acid derivatives using alkyl halides based on non-precious metal-catalyzed carbonylation reactions.

On the other hand, oxidative carbonylation reactions, utilizing two nucleophilic reagents and an oxidant to synthesize carbonyl derivatives, offer a distinctive reaction mechanism that opens up new opportunities for carbonylation reaction.

The benzotriazoles are important structural motifs in biologically active medicines. However, the industrial access to benzotriazoles produces nitrous acid and releases several toxic nitrogen oxides such as N_2O_3, NO_2, and NO. Therefore, the last part describes a new approach for the green synthesis of benzotriazoles.

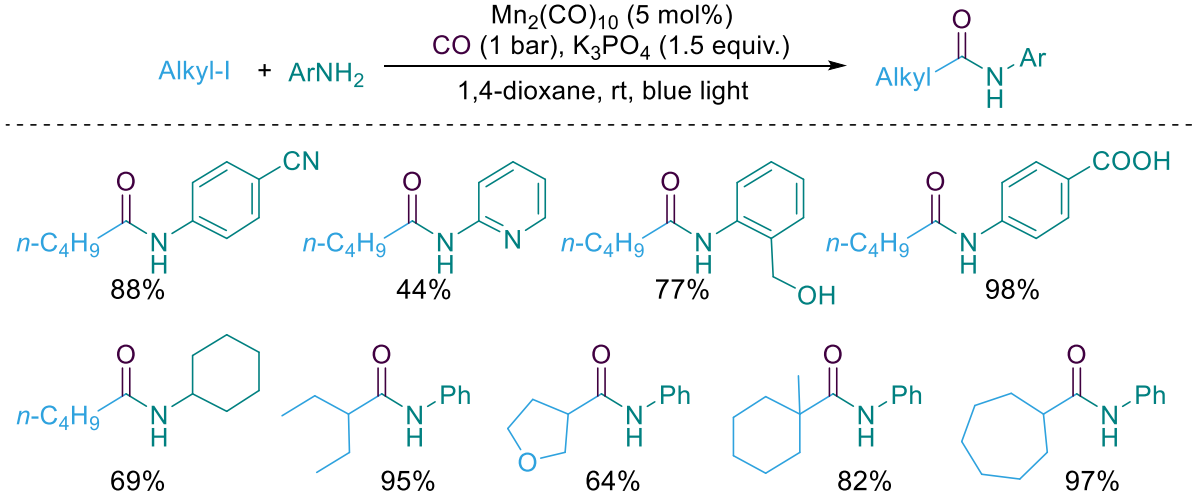
5. Summary of works

Phosphine-catalyzed photo-induced alkoxycarbonylation of alkyl iodides with phenols and 1,4-dioxane through charge-transfer complex (*Chin. J. Catal.* **2023**, 48, 214-223). In this paper, we developed a phosphine-catalyzed carbonylation of phenols and alkyl iodides *via* EDA photoactivation without the involvement of transition metals. The method provides a general approach for the efficient synthesis of useful alkylphenol esters with high functional group tolerance and excellent chemoselectivity.



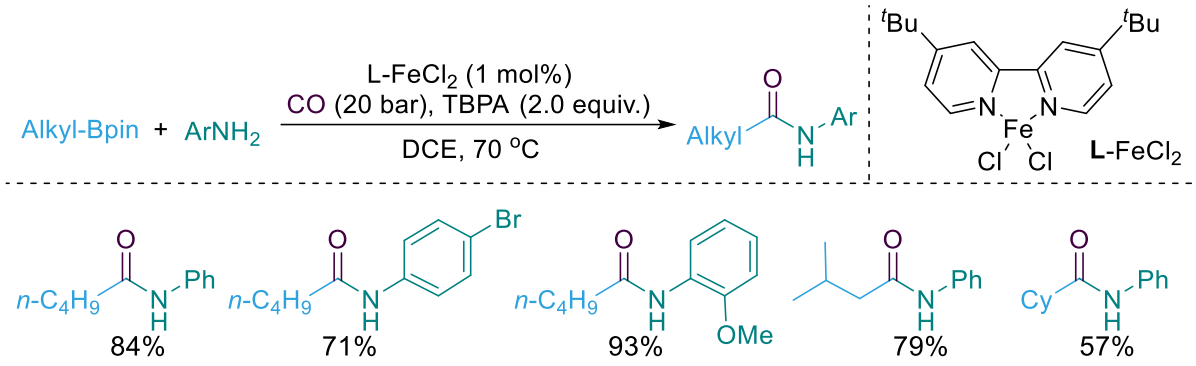
Scheme 28 Phosphine-catalyzed photo-induced alkoxycarbonylation of alkyl iodides

Visible light-induced manganese-catalyzed aminocarbonylation of alkyl iodides under atmospheric pressure at room temperature (*Org. Chem. Front.* **2024**,11, 442-447). In this paper we demonstrate a protocol for the manganese-catalyzed aminocarbonylation of alkyl iodides for the efficient synthesis of aliphatic amides. Through photoinduction, the reaction can be carried out at room temperature and atmospheric pressure without the necessity of complex equipment.



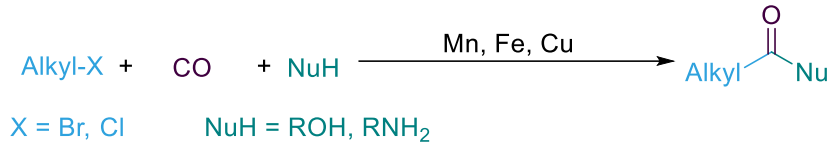
Scheme 29 Visible light-induced manganese-catalyzed aminocarbonylation of alkyl iodides

Iron-catalyzed carbonylative synthesis of amides from alkyl-boronic pinacol ester via a single electron transfer process (*J. Catal.* **2024**, 429, 115273). In this paper, we developed an iron-catalyzed oxidative aminocarbonylation of alkylboronic pinacol esters. Due to the importance of organoboron as a chemical intermediate, this method provides efficient conversion of alkylboronic pinacol esters to synthesize useful aliphatic amides, which provides a new strategy for the generation of radicals from alkylboronic acid pinacol esters.



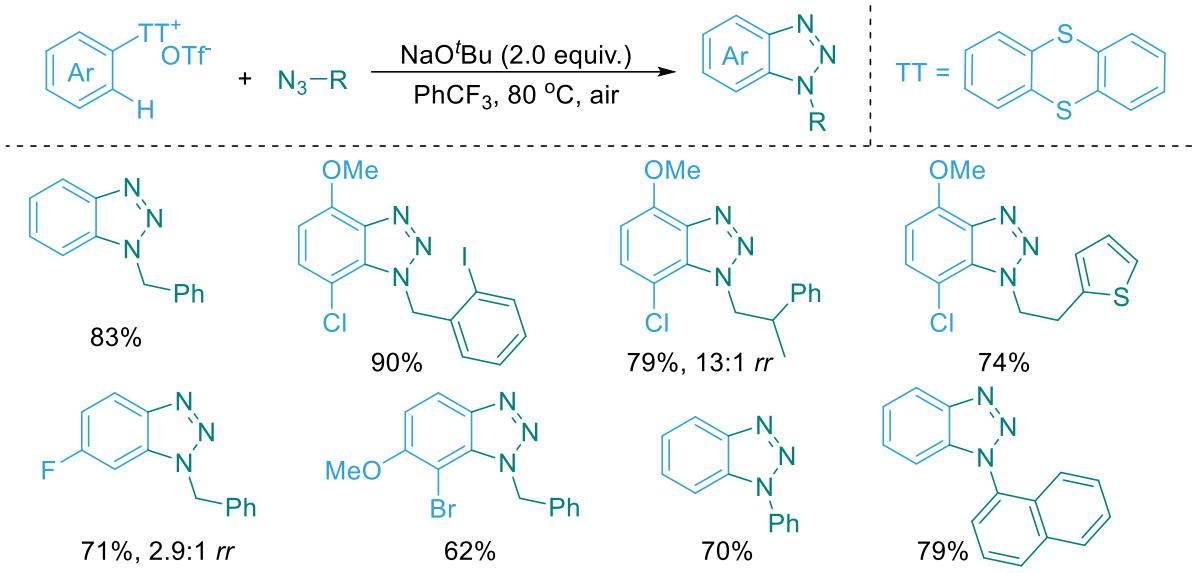
Scheme 30 Iron-catalyzed aminocarbonylation of alkyl-boronic pinacol esters

Abundant metal-catalyzed carbonylation of alkyl bromides and alkyl chlorides (*Org. Chem. Front.* **2023**,10, 1587-1591). In this paper, we summarize and discussed the non-noble metal-catalyzed carbonylation of unactivated alkyl halides. These alkyl halides form a variety of carbonyl compounds by carbonylation, including ketones, amides, ketoamides, and esters.



Scheme 31 Abundant metal-catalyzed carbonylation of alkyl bromides and alkyl chlorides

[3 + 2] Cycloaddition of azides with arynes formed *via* C–H deprotonation of aryl sulfonium salts (*Green Chem.* **2023**, 25, 6282-6286). In this paper, we reported a novel approach to [3 + 2] cycloaddition reactions with azides using aryl sulfonium salts as aryne precursors to provide benzotriazoles. The reaction utilizes readily available aromatics as feedstock and offers excellent atom economy, environmental friendliness, and high functional group tolerance. In addition, the excellent performance of gram-scale and derivatization reactions provides potential opportunities for large-scale production and other applications.



Scheme 32 [3 + 2] Cycloaddition of azides with arynes

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7. Publications

7.1 Phosphine-catalyzed photo-induced alkoxycarbonylation of alkyl iodides with phenols and 1,4-dioxane through charge-transfer complex

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In this paper, I finished the optimization of reaction conditions, investigation of substrate scope and writing the manuscript. My contribution as the co-first author of this paper is approximately 70%.

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Article

Phosphine-catalyzed photo-induced alkoxycarbonylation of alkyl iodides with phenols and 1,4-dioxane through charge-transfer complex

Xing-Wei Gu [a,1], Youcan Zhang [b,1], Fengqian Zhao [a], Han-Jun Ai [a], Xiao-Feng Wu [a,b,*]

[a] *Leibniz-Institut für Katalyse e.V., 18059 Rostock, Germany*

[b] *Dalian National Laboratory for Clean Energy, Dalian Institute of Chemical Physics, Chinese Academy of Sciences, Dalian 116023, Liaoning, China*

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ABSTRACT

The combining of charge-transfer complex and light irradiation offers a promising solution for the requests of sustainable chemistry. Herein, we developed a phosphine-catalyzed visible light-induced alkoxycarbonylation of alkyl iodides with phenols and ethers. Based on the electron donor-acceptor photoactivation strategy, the reaction can be realized at atmospheric pressure of CO under transition metal-free conditions. This promising approach demonstrates high functional group tolerance and excellent chemoselectivity. Additionally, five-component perfluoroalkylative carbonylation for the synthesis of β-perfluoroalkyl acyloxy esters from unactivated olefins and perfluoroalkyl iodides can be realized as well. Moreover, due to the excellent performance of the gram-scale reaction and ^{13}CO results, it provides potential opportunities for large-scale production and other applications.

1. Introduction

As a cheap and readily available C1 source, CO gas has been widely used in carbonylation reactions to produce a range of promising carbonylated compounds with high efficiency, atomic economy and excellent selectivity [1–6]. Among the numerous transformations, photocarbonylation has become a topic with increasing attention in the field of organic synthesis [7–11]. In recent years, with the rapid development of photocatalysis, photocarbonylation has evolved from high-energy photocatalysis (Xe or Hg lamps) with demanding conditions to mild systems with photoredox catalysis [12–17]. During this period, electron donor-acceptor (EDA) photoactivation has received increasing attention from the scientific community [18–26]. This strategy exploits the combination of an electron acceptor molecule **A** and a donor molecule **D** to form a new molecular aggregate in the ground state, which is then photo-excited and undergoes an intramolecular single electron transfer (SET) process and generates radical intermediates under mild conditions (Scheme 1(a)) [27–31]. As an attractive approach, EDA photoactivation not only allows the production of free radicals by light alone without the involvement of an exogenous photocatalyst, but also simple to operate and avoids the use of expensive transition metals. However, no successful report has been published on the carbonylation *via* EDA photoactivation, to the best of our knowledge.

Esters are an important class of functional groups common-

* Corresponding author. E-mail: Xiao-Feng.Wu@catalysis.de, xwu2020@dicp.ac.cn (X.-F. Wu).
[1] Contributed equally to this work.
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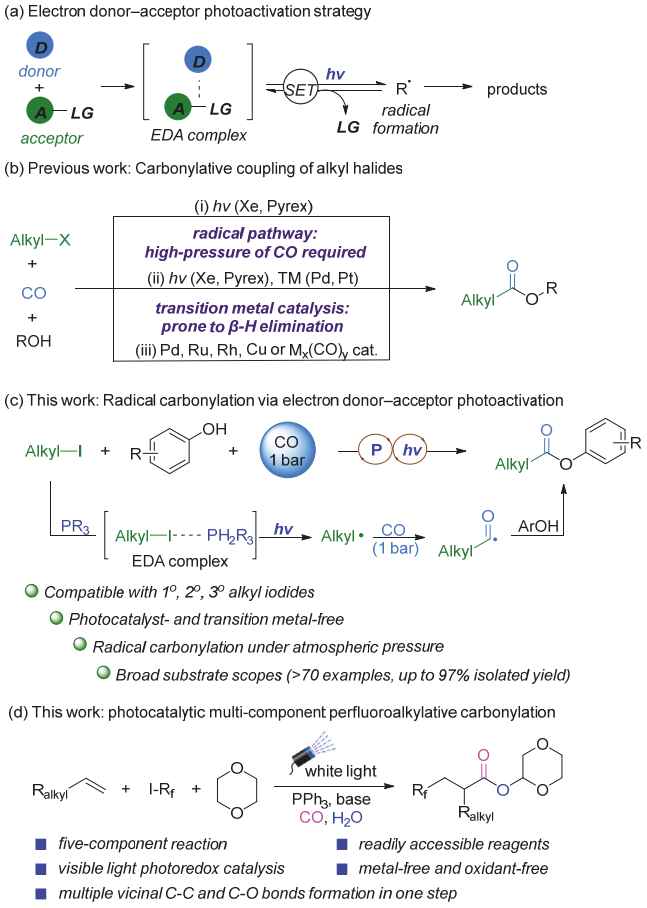


Scheme 1. Strategies for alkyl halide carbonylation.

ly found in natural products, pharmaceuticals, functional materials, polymers, and biologically active scaffolds [32,33]. To date, scientists have been fascinated by the search for an efficient and simple method for synthesizing esters. Among the possible procedures, the carbonylation of alkyl halides have received considerable attention since the seminal work on the catalytic alkoxycarbonylation of unactivated alkyl halides reported by Heck *et al*. [34] in 1963. However, the carbonylation of alkyl halides is one of the long-standing challenges in organic synthesis compared with aryl halides [35–38].

The fundamental reason is that the current activation of alkyl halides mainly relies on the participation of metals, and the generated metal alkyl intermediates are prone to the rapid elimination of β-hydrides [39]. Based on the continues efforts from organic chemists, these current carbonylation of alkyl halides strategies are comprised of three approaches: (1) high energy photocatalysis (Xe lamp) [40], (2) light-assisted (high energy or visible light induced) metal-catalyzed carbonylation reactions [41–44] and (3) transition metal catalysis, such as Pd, Ru, Rh, Cu and other metal carbonyl complexes (Scheme 1(b)) [45–50]. Although the above strategies have made significant progresses in the carbonylation field, these approaches still suffer from disadvantages such as the requirement of high CO pressure, the use of noble metal catalysts, and complex high pressure equipment.

It is also worth mentioning that compared with using aliphatic alcohols as the reaction partners, only one procedure on carbonylation of alkyl halides with phenols have been reported which was based on expensive rhodium catalyst through oxidative addition [51]. The main reason is the facile nucleophilic substitution reaction between alkyl halides and phenols in the presence of base and should also include the outstanding radical capture ability of phenols. Hence, the efficient and selective carbonylation of alkyl halides with phenols remains a challenge, especially in the absence of transition metal catalysts. Additionally, attracted by the distinctive properties of fluoroalkyl groups which can dramatically alter the lipid solubility, stability, and other physicochemical properties of the compounds, the fluoroalkylative carbonylation of alkenes can simultaneously introduce carbonyl and fluoroalkyl units into the parent moiety to form fluoroalkyl-functionalized carbonylated compounds become more interesting.

Herein, we report an interesting carbonylation procedure *via* EDA photoactivation, without the involvement of transition metals, phosphine-catalyzed the carbonylation of phenols and alkyl iodides with high functional group tolerance and good chemoselectivity under the irradiation of visible light. Meanwhile, excitingly this approach can be achieved at atmospheric pressure of CO, which is unprecedented in the radical carbonylation reactions (Scheme 1(c)). Then, a photocatalytic five-component perfluoroalkylative carbonylation for the synthesis of β-perfluoroalkyl acyloxy esters under transition met-

al-free and oxidant-free conditions was realized as well (Scheme 1(d)). This transformation represents an atomic and stepwise economical and environmentally friendly free radical relay process, which involves radical addition, C(sp^3)–H bond activation of dioxane, and esterification steps.

2. Experimental

2.1. Reagents and solvents

Unless otherwise noted, the chemicals were commercially available from Sigma-Aldrich, TCI or Alfa Aesar and were used without further purification. Dioxane bought from Alfa Aesar, HPLC grade, 99% min, packaged under argon in resealable ChemSeal bottles. The reaction does not require the glovebox.

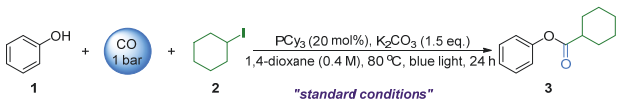
2.2. Purification

The products were isolated from the reaction mixture by column chromatography on silica gel 60, 0.063–0.2 mm, 70–230 mesh (Merck). Gradient flash chromatography was conducted eluting with PE/EA, PE refers to pentane and EA refers to ethyl acetate, they were listed as volume/volume ratios.

2.3. Irradiation

The light source was placed ca. 23 cm from the reaction vial on top of a manufactured autoclave (see Fig. S1). In every reaction the strong light source Portable Lumatec SUPERLITE S 04 was used with different set filters: blue (λ_{max} = 400–500 nm) at maximum intensity (100% power). Figs. S2 and S3 illustrate relevant photophysical properties of the lamps.

Table 1
Optimization of the reaction conditions.[a]



Entry	Variation from the "Standard conditions"	Yield (%)[b]
1	none	>96 (95)
2	10 mol% PCy_3	91
3	0.2 mol L^{-1} dioxane	95
4[c]	$^nBu_3P$ instead of PCy_3	90
5[c]	PPh_3 instead of PCy_3	n.d.
6[c]	(p-$FC_6H_4)_3P$ instead of PCy_3	n.d.
7[c]	Na_2CO_3 instead of K_2CO_3	46
8[c]	Cs_2CO_3 instead of K_2CO_3	9
9[c]	Et_3N instead of K_2CO_3	24
10[c]	18 h instead of 24 h	85
11	50 °C instead of 80 °C	68
12	No PCy_3	n.d.
13	No light	n.d.

[a] The reaction was conducted using **1** (0.2 mmol), **2** (0.3 mmol) with blue light (400–500 nm) under indicated conditions. [b] Determined by GC with hexadecane as internal standard. [c] The reaction solvent is 1,4-dioxane (0.2 mol L^{-1}). Isolated yield is shown in parentheses.

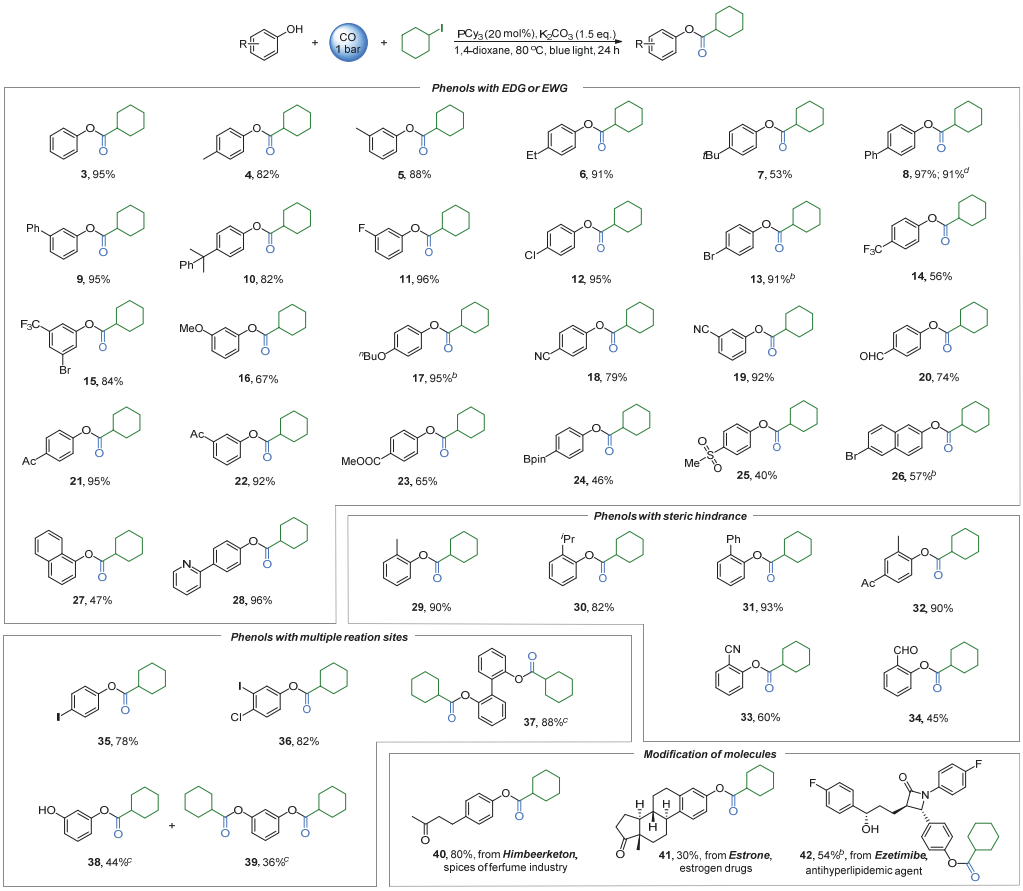
2.4. Data collection

GC-yields were calculated using hexadecane as internal standard. GC analysis was performed on an Agilent HP-7890A instrument with FID detector and HP-5 capillary column (polydimethylsiloxane with 5% phenyl groups, 30 m, 0.32 mm i.d., 0.25 μm film thickness) using argon as carrier gas. High resolution mass spectra (HRMS) were recorded on Agilent 6210. NMR spectra were recorded on Bruker Avance 300 and Bruker ARX 400 spectrometers. Chemical shifts (ppm) are given relative to solvent: references for CDCl3 were 7.26 ppm (^{1}H NMR) and 77.00 ppm (^{13}C NMR). All measurements were carried out at room temperature unless otherwise stated.

3. Results and discussion

We initially explored the carbonylation reaction with phenol **1** and iodocyclohexane **2** as the model substrates. After a systematic survey of reaction parameters, the following optimum conditions were identified: PCy_3 (20 mol%), K_2CO_3 (1.5 equiv.), 1,4-dioxane (0.4 mol L^{-1}), irradiation with blue light (400–500 nm) at 80 °C for 24 h, affording the desired alkylphenol ester **3** in 95% isolated yield (Table 1, entry 1). Reducing the amount of PCy_3 from 20% to 10% decreased the yield to 91% (Table 1, entry 2). A decrease in reaction concentration resulted in a slight decrease in the yield (Table 1, entry 3). When using n-Bu_3P as a cheaper catalyst, the yield can still reach 90%. However, aryl substituted phosphines worked poorly as catalysts (Table 1, entries 4–6). Other bases, such as Na_2CO_3, Cs_2CO_3 or Et_3N, could also afford the desired ester **3** but in a lower yield (Table 1, entries 7–9). Experiments show that prolonging the time can make the reaction fully converted (Table 1, entry 10). After lowering the temperature, the carbonylation reaction could proceed but with decreased efficiency (Table 1, entry 11). Control experiments revealed that both the phosphine catalyst and visible light irradiation were essential for the desired reaction (Table 1, entries 12 and 13).

With the optimal reaction conditions in hand, we next investigated the substrate scope of this phosphine-catalyzed carbonylation. As shown in Scheme 2, a broad array of phenols could be served as effective reaction partners, providing the desired phenol esters in good to excellent yields. Phenols bearing both electron-donating and electron-withdrawing groups (**3**–**28**) efficiently participated in the reaction to provide the desired products. Functional groups including halogens (F, Cl, Br, **11**–**14**), trifluoromethyl (**15**), alkoxy (**16**,**17**), –CN (**18**,**19**), –CHO (**20**), –Ac (**21**,**22**), –COOMe (**23**), –Bpin (**24**) and –Ms (**25**), survived in this radical cascade intact, giving the corresponding esters in high yields. Naphthalene was also easily introduced into the product (**26**,**27**). Heterocycles such as pyridyl-substituted phenols participated in the reaction to afford ester **28** in 96% yield. Subsequently, to test the effect of steric hindrance on the reaction, phenols with different groups substituted at the *ortho* position were used. Fortunately, no detrimental effects to the reactivity of this process were observed when *ortho*-substituted phenol were tested, and the desired *ortho*-substituted phenol esters (**29**–**34**) were obtained



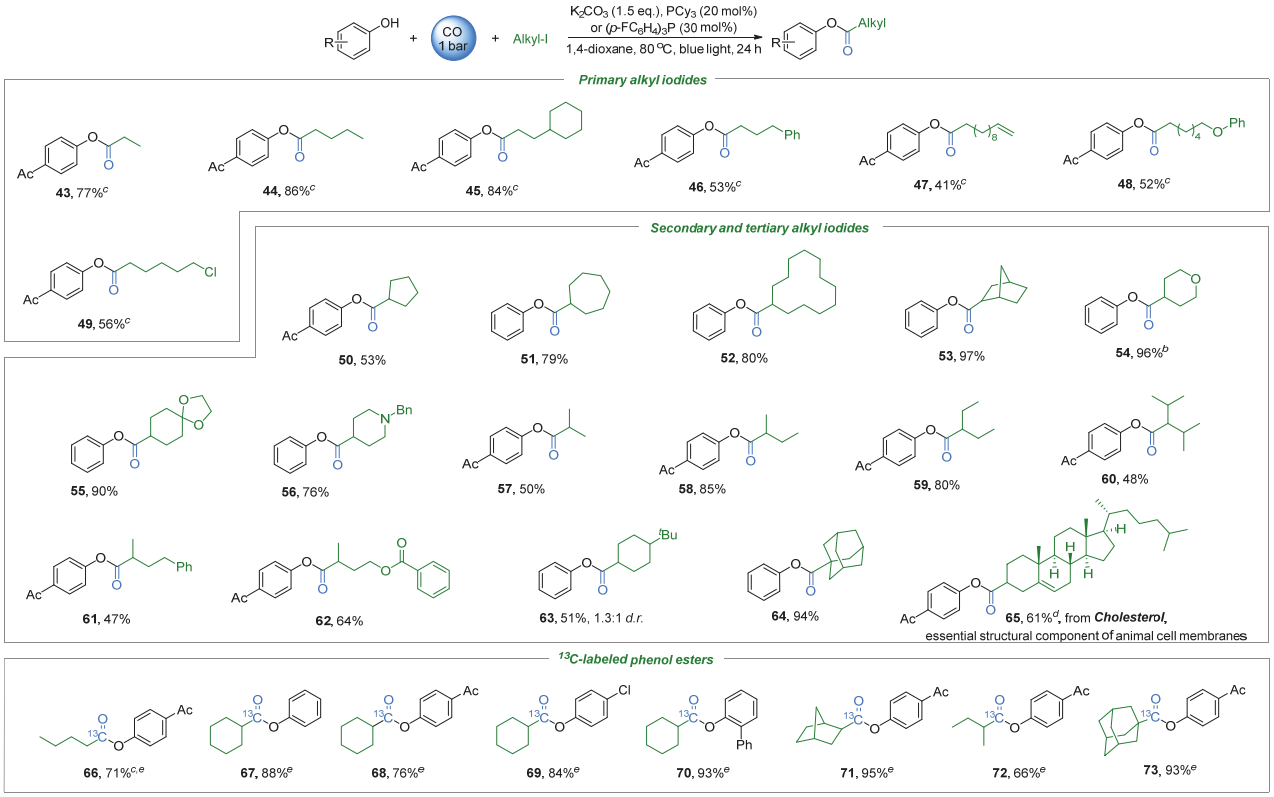
Scheme 2. Scope of phenols. [a] Reaction conditions: phenols (0.2 mmol), alkyl iodide (0.3 mmol), K_2CO_3 (0.3 mmol), PCy_3 (20 mol%), 1,4-dioxane (0.5 mL), CO (1 bar), irradiation with blue light (400–500 nm) at 80 °C for 24 h. [b] PCy_3 (50 mol%). [c] phenols (0.2 mmol), alkyl iodide (0.6 mmol), K_2CO_3 (0.6 mmol), PCy_3 (40 mol%), 1,4-dioxane (1 mL). [d] The reaction was performed on a 5 mmol scale (1.27 g).

in moderate to high yields. Remarkably, phenols which have a strong coordination group in the *ortho* position, such as –CN and –CHO, were also successfully delivered the desired products **33**,**34** in 60% and 45% yields, respectively. Next, we investigated the selectivity of the reaction by using phenols with multiple reaction sites. For example, iodide-substituted phenols, were successfully converted to iodide-substituted phenol esters (**35**,**36**) in good yields, offering opportunities for further structure modification. 2,2'-Biphenol was also smoothly converted to the corresponding diester formation product **37** in excellent result. Remarkably resorcinol was not completely converted to the corresponding diester under the same procedure, and this is probably attributable to the unexpected electronic property of phenol with –OCOR group that impedes further carbonylation (**38**,**39**). Aliphatic alcohols were also tested but proven to be not suitable reaction partner here.

Subsequently, we applied our phosphine-catalyzed carbonylation method in the late-stage functionalization of complex molecules such as Himbeerketon, Estrone and Ezetimbe, and the corresponding phenol esters (**40**–**42**) were obtained in moderate to high yields. It is interesting to mention that the current carbonylation reaction has good selectivity toward phenolic hydroxyl (such as **42**), that is, the carbonylation occurs predominantly on the phenolic hydroxyl group rather than the alcoholic hydroxyl group. This provides a convenient synthetic method for site-directed modification of bioactive molecules without the need for protection-deprotection procedures. To demonstrate the practicability of our protocol, a gram-scale experiment (5 mmol) was conducted and ester **8** was obtained in excellent yield (1.27 g, 91%), thus providing potential opportunity for applications in large-scale production.

Next, we also investigated the scope of alkyl iodides in this phosphine-catalyzed carbonylation (Scheme 3). Unfortunately, the previous method of carbonylation is not applicable to primary alkyl iodides. This is probably due to the inability of the PCy_3 to form a stable EDA complex with primary alkyl iodides. However, further optimization of the conditions showed that by simply replacing PCy_3 with tris(4-fluorophenyl)phosphine and reducing the concentration of the reaction, the corresponding phenol esters (**43**–**49**) can be obtained in moderate to excellent yields (For detailed screening of primary alkyl iodide reaction conditions, see Table S2 in the Supporting Information). Using the 4′-hydroxyacetophenone as the alkyl iodides partner, a variety of readily available phenol esters were obtained under a slightly modified reaction condition.

In addition to alkyl groups (**43**–**46**), functional groups such as alkenyl (**47**), ether (**48**), chloride (**49**) were all compatible. It is noteworthy that the method of PCy_3 as a phosphine catalyst was also applicable to the carbonylation of secondary alkyl iodides, including both acyclic and cyclic substrates, delivering

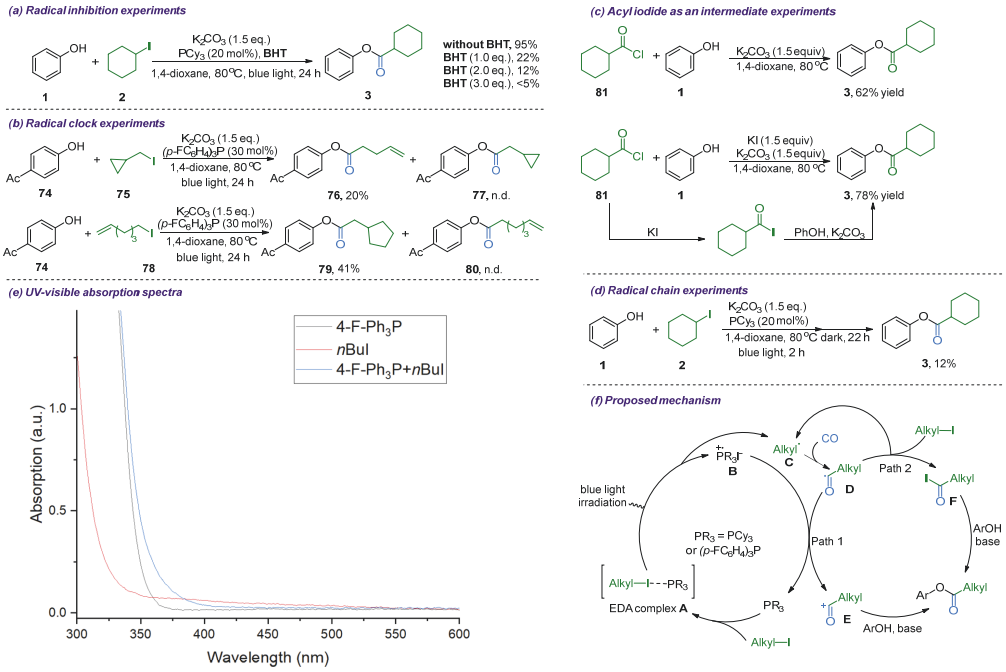


Scheme 3. Scope of Alkyl iodides. [a] Reaction conditions: phenols (0.2 mmol), alkyl iodides (0.3 mmol), K_2CO_3 (0.3 mmol), PCy_3 (20 mol%), 1,4-dioxane (0.5 mL), CO (1 bar), irradiation with blue light (400–500 nm) at 80 °C for 24 h. [b] PCy_3 (50 mol%). [c] $(p\text{-}FC_6H_4)_3P$ (30 mol%), 1,4-dioxane (2 mL). [d] The reaction was performed on a 0.1 mmol scale. [e] The reaction was performed under 1 atm of ^{13}CO pressure.

the corresponding phenol esters with good yields (**50**–**63**). Cyclic substrates, such as 5- through 12-membered cyclic alkyl iodides, all generally performed well (**50**–**53**). Cyclic groups relevant to medicinal chemistry such as 2*H*-pyran (**54**), acetal (**55**) and piperidine (**56**) were well tolerated. Chain alkyl iodides were also smoothly converted into the corresponding esters (**57**–**62**) in good results. However, when the steric hindrance of the secondary alkyl iodide increases, the yield decreased significantly. Notably, only a 1.3:1 diastereoselective phenol ester was obtained when using an alkyl iodide with a diastereoselective ratio of 9:1, this basically indicates that the reaction may undergoes a free radical process. The carbonylation of tertiary alkyl iodide such as 1-iodoadamentane was also successfully delivered the desired product **64** in 94% yield. The cholesterol derivative was also efficiently carbonylated to give product **65** in 61% yield. However, no reaction occurred when alkyl bromide or alkyl chloride was tested as the substrate, even in the presence of NaI for *in-situ* alkyl iodide formation. Potential toxicity studies are an essential part of the drug discovery and clinical process, and the use of stable isotope labeled compounds allows the metabolic processes of drugs to be traced and the causes of toxicity to be identified [52–56]. ^{13}CO gas is commonly used as a base material for the preparation of a range of stable isotope labeled drugs, however, the preparation process often requires high ^{13}CO pressures and some noble metals. Thus, to highlight the efficacy of this methodology, a series of carbon-13 labeled phenol esters was obtained in good to excellent yields, which provides potential opportunities for isotopically labeled drug production applications.

To gain some insight into the mechanism of this reaction, we set up control experiments to shed light on the reaction mechanism. When BHT (2,6-di-*tert*-butyl-4-methylphenol, a radical scavenger, 1–3 equiv) was added to the reaction under the standard conditions, the target reaction was gradually inhibited (Scheme 4(a)). Furthermore, in the radical clock experiments, (iodomethyl)cyclopropane and 6-iodohex-1-ene provided the corresponding ring-opening expansion product **76** and the cyclization product **79** with high selectivity, respectively (Scheme 4(b)). These experiments indicate that the reaction undergoes a free radical process. Subsequently, when we utilized acyl chloride as the substrate to react with phenol, product **3** was obtained in 62% yield. Moreover, the yield was increased to 78% by adding KI to the reaction for in situ formation of acyl iodide (Scheme 4(c)). Therefore, the reaction mechanism may involve the *in-situ* generation of acyl iodide. To figure out if it is a radical chain reaction, we turned off the light after 2 h and then performed the reaction in the dark for 22 h. However, the conversion of the reaction was very low and only 12% yield of **3** was obtained (Scheme 4(d)), thus, we can rule out the possibility of the radical chain reaction. Finally, in the UV/visible absorption study, the combination of phosphine catalyst and alkyl halide resulted in a red-shifted spectrum, verifying the envisioned EDA complex (Scheme 4(e)).

Based on the above results and previous reports [57–60], a possible mechanism is proposed. Initially, an EDA complex **A** is formed from the alkyl iodide and the PCy_3, which will be acti-



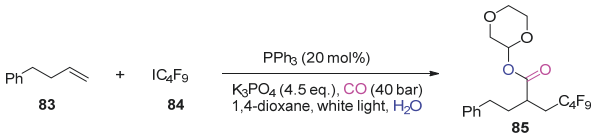
Scheme 4. Mechanistic experiments and proposed mechanism.

vated by blue light and fragment into the phosphinium radical ion pair **B** and the alkyl radical **C.** Then, CO will be trapped by the alkyl radical **C** to form the acyl radical **D**. Two reaction pathways may be followed, the acyl radical **D** is can be oxidized by intermediate **B** into acyl cation **E**, after which it reacts with phenol in the presence of a base to generate the alkylphenol ester (Path 1); the acyl radical **D** may also undergo iodine migration with alkyl iodide to form alkyl radicals **C** and acyl iodide **F** which then provides the desired alkylphenol ester (Path 2).

Inspired by those results, we become interested to develop a multi-component radical relay procedure with similar concept. To establish this visible light-mediated perfluoroalkylative carbonylation of unactivated alkenes, we began a systematic investigation of this reaction system by selecting 4-phenyl-1-butene **83** and perfluorobutyl iodide **84** as the parent frame and the fluoroalkyl source, respectively. Among the selected results summarized in Table 2, this five-component radical relay reaction successfully delivered the carbonylation product **85** in 53% isolated yield in the presence of PPh_3, K_3PO_4, and H_2O in 1,4-dioxane at room temperature under 40 bar of CO atmosphere and visible light irradiation (Table 2, entry 1). Other phosphines, whether monophosphines X-Phos and PCy_3 or diphosphines DPPP and Xantphos were able to facilitate the reaction successfully, affording the desired product **85** in 38%–56% yields (Table 2, entries 2 and 3). Decreasing the amount of K_3PO_4 resulted in a slightly lower yield of the target product (Table 2, entry 4). In addition, K_3PO_4 was found to be the optimal base according to base screening (Table 2, entries 5–7). To our delight, the desired product yield was not affected even with adding a halving amount of water (Table 2, entry 8). However, when the amount of PPh_3 was halved or without PPh_3, the yields of the target product **85** were reduced to 48% and 31%, respectively (Table 2, entries 9 and 10). When performing the reaction without base or in the absence of irradiation neither the desired product was obtained, indicating that the base and visible light irradiation are essential elements for the multi-component perfluoroalkylative carbonylation smoothly (Table 2, entries 11 and 12).

After determining the optimal reaction conditions, we then investigated the scope of substrates for the perfluoroalkylative carbonylation of unactivated alkenes and perfluoroalkyl iodides, as shown in Scheme 5. Firstly, the effect of chain length of alkyl olefins with terminal functional groups to the yield of

Table 2
Optimization of reaction conditions [a].



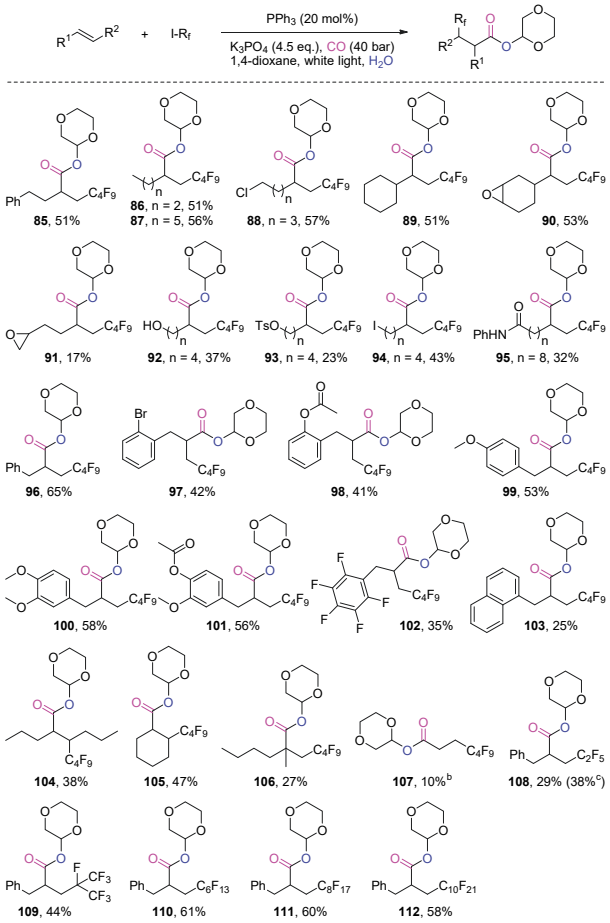
Entry	Variations from the standard conditions	Yield [b] (%)
1	none	56 (53) [c]
2	X-Phos or PCy_3 instead of PPh_3	43, 38
3 [d]	DPPP or Xantphos instead of PPh_3	50, 56
4	adding 3 eq. K_3PO_4	51
5 [e]	K_2CO_3 instead of K_3PO_4	50
6 [e]	Na_3PO_4 instead of K_3PO_4	43
7 [e]	DIPEA instead of K_3PO_4	trace
8	adding 50 uL H_2O	56
9	adding 10 mol% PPh_3	48
10	without PPh_3	31
11	without K_3PO_4	n.d.
12	no light	n.d.

[a] Reaction conditions: **83** (0.1 mmol), **84** (0.15 mmol), PPh_3 (20 mol %), K_3PO_4 (4.5 eq.), and H_2O (0.1 mL) in 1,4-dioxane (1 mL) at r.t. for 24 h. [b] Yields were determined by GC-FID analysis using *n*-hexadecane as internal standard. [c] Isolated yield. [d] DPPP or XantPhos (10 mol%). [e] Base (3 equiv.).

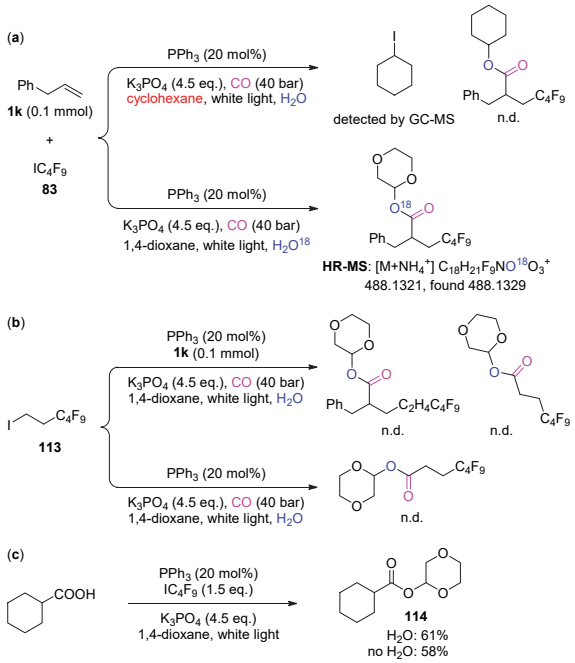
the corresponding products was evaluated. The model substrate 4-phenyl-1-butene provided 51% yield of the desired product. Alkyl olefins with different chain lengths gave the corresponding products **86** and **87** in 51% and 56% yields, respectively. Alkenes containing remote chlorine, cyclohexyl, and oxabicycloheptyl were successfully undergo perfluoroalkylation/carbonylation and provided 51%–57% yields of the targeted compounds. Notably, oxirane and unprotected hydroxyl groups were tolerated under the reaction conditions, albeit the desired products **91** and **92** were derived in lower yields. Surprisingly, the *O*-tosyl-protected homoallyl alcohol gave the corresponding carbonylated product **93** in 23% yield, while also receiving a 43% yield of the iodine-substituted carbonylated product **94**. Additionally, an amide group was smoothly reformed into the corresponding product **95**. Furthermore, allylbenzene could produce the desired product **96** in good yield. Monosubstituted allylbenzenes were converted gently to the corresponding products with bromine, ester, and methoxy functional groups in moderate yields. For disubstituted allylbenzenes, the desired product was obtained in 58% **100** and 56% **101** yields, respectively. Alkenes, such as 1-allylpentafluorobenzene and 1-allylnaphthalene, produced the desired products in lower yields than mono- and di-substituted allylbenzenes due to steric hindrance. Both chain and cyclic internal alkenes could be employed well, leading to the corresponding products **104** and **105** in 38% and 47% yields, respectively. Olefin with a tertiary carbonylation site and ethylene were also examined and been able to obtain the target products **106** and **107** successively. Finally, we also explored various perfluoroalkyl iodide substrates, and the corresponding products **108**–**112** were derived in 29%–61% yields. It is important to mention that other ethers, such as THF, anisole, and diethyl ether were also tested but only traces amount of the desired product could be detected.

To gain more insight into this radical relay reaction, several control experiments were performed, as summarized in Scheme 6. Under the standard reaction conditions, when cyclohexane was used instead of 1,4-dioxane, no corresponding carbonylative esterification product was afforded and only cyclohexyl iodide was detected by GC-MS; the ^{18}O-labeled carbonylation product could be detected by HR-MS when using $H_2{}^{18}O$ instead of H_2O (Scheme 6(a)). These results indicated that this visible-light-induced multicomponent perfluoroalkylative carbonylation system promotes the cleavage of C(sp^3)-H, and the oxygen of ester moiety adjacent to the dioxane ring is derived from water. No carbonylation products were detected when alkyl iodide **113** was employed instead of perfluoroalkyl iodide, which revealed that the β-perfluoroalkyl-substituted alkyl iodide, a by-product generated during the reaction, could not undergo the radical relay process under the standard conditions (Scheme 6(b)). In addition, the target esterification product **114** can be obtained in 61% yield when cyclohexane carboxylic acid was utilized in the absence of alkene and CO, and a similar yield was observed when H_2O was also removed in the above conditions (Scheme 6(c)), which suggested that

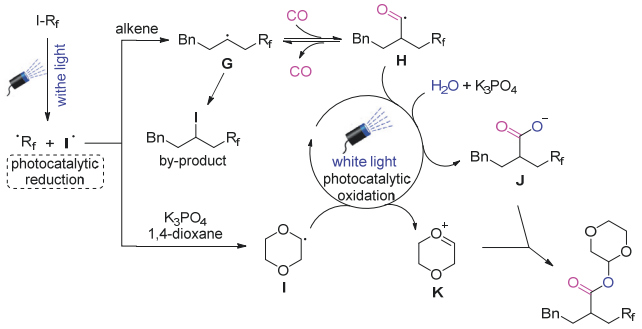
Scheme 5
Substrate scope of alkenes and perfluoroalkyl iodides [a–c].



[a] Reaction conditions: alkene (0.2 mmol), alkyl iodide (0.3 mmol), PPh_3 (20 mol %), K_3PO_4 (10 mol %), and H_2O (0.1 mL) in 1,4-dioxane (1 mL) at rt for 24 h under CO (40 bar), isolated yield. [b] ethylene (2 bar), alkyl iodide (0.3 mmol), the isolated yield is calculated based on the perfluorobutyl iodide used. [c] pentafluoroiodoethane (0.6 mmol).



Scheme 6. Control experiments. (a) Reaction in different solvent; (b) Reactions with alkyl iodide; (c) Reaction with acid.



Scheme 7. Possible mechanism.

H_2O could facilitate generating the corresponding β-perfluoroalkyl-substituted carboxylic acid intermediate.

Based on the above experimental results and literature [61], we proposed a possible mechanism to explain this visible-light-induced radical cascade process, as shown in Scheme 7. The photoredox catalysis initiated with the homogeneous cleavage of the perfluoroalkyl iodide C–I bond to give perfluorinated alkyl radical and iodine radical. Then, the addition of perfluoroalkyl radical to alkene generated a new carbon radical **G**, which would be captured by CO to give an acyl radical **H** or converted to a by-product perfluoroalkyl-substituted alkyl iodide which could not undergo further radical relay reaction; meanwhile, the C(sp^3)–H cleavage of 1,4-dioxane produced the corresponding carbon radical **I**. Subsequently, in the presence of water and base, acyl radical **H** and intermediate **I** underwent a photocatalytic oxidation process to form carboxylic acid negative ion **J** and dioxane positive ion **K**, respectively. Finally, an addition process occurred between intermediate **J** and intermediate **K** to afford the desired perfluoroalkylative carbonylation product.

In conclusion, we have developed a phosphine-catalyzed radical carbonylation of alkyl iodides *via* EDA photoactivation under atmospheric pressure. Under mild conditions, various alkylphenol esters were efficiently prepared without transition metal catalysts. Additionally, five-component perfluoroalkylative carbonylation for the synthesis of β-perfluoroalkyl acyloxy esters from unactivated olefins and perfluoroalkyl iodides can be realized as well. With the excellent performance of the gram-scale reaction and carbon-13 labeling experiments, it provides potential opportunities for large-scale production and many other applications.

Electronic supporting information

General comments, general procedure, analytic data, and NMR spectra (PDF) are available in the online version of this article.

The authors declare no competing financial interest.

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Graphical Abstract

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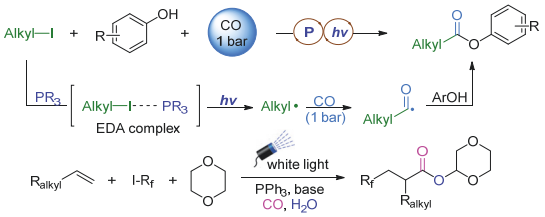
Phosphine-catalyzed photo-induced alkoxycarbonylation of alkyl iodides with phenols and 1,4-dioxane through charge-transfer complex

Xing-Wei Gu, Youcan Zhang, Fengqian Zhao, Han-Jun Ai, Xiao-Feng Wu *
Leibniz-Institut für Katalyse, Germany;
Dalian Institute of Chemical Physics, Chinese Academy of Sciences, China



We have developed an interesting phosphine-catalyzed carbonylation by charge-transfer complex through photoactivation under atmospheric pressure of CO. Five-component perfluoroalkylative carbonylation for the synthesis of β-perfluoroalkyl acyloxy esters from unactivated olefins and perfluoroalkyl iodides can be realized as well. Notably, a series of carbon-13 labeled products were also obtained in good to excellent yields by using 1 bar of ^{13}CO.

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膦催化光促进的烷基碘和苯酚及1,4-二氧六环的以电子转移化合物为媒介的羰基化酯化反应

顾幸威[a,1], 张有灿[b,1], 赵丰乾[a], 艾汉均[a], 吴小锋[a,b,*]
[a]莱布尼茨催化研究所, 德国
[b]中国科学院大连化学物理研究所, 大连洁净能源国家实验室, 辽宁大连116023, 中国

摘要: 在可持续发展化学的框架内, 有机结合电子转移化合物和可见光无疑提供了一条非常理想的选择. 电子转移化合物可以在可见光的照射下被激活, 然后向目标反应进发, 在不需要金属催化剂的情况下实现目标转化. 在各类化合物中, 酯类化合物在各个领域都占据着非常重要的地位. 羰基化酯化反应可以把廉价的一氧化碳分子引入到母体分子中, 如果以醇或者酚作为亲核试剂, 其中酯类化合物可以被直接制得.

本文发展了一种膦催化的光促进烷基碘和苯酚的羰基化酯化反应. 电子转移化合物在可见光照射下得以活化, 在不需要过渡金属催化剂的情况下, 该反应可以在标准大气压的一氧化碳气体氛围下实现. 该反应体系展现出较好的官能团兼容性和较好的化学选择性, 酯基、氟、氯、氰基、酰基、醚、砜等官能团都能够被很好地兼容. 也可以采用天然产物大分子化合物作为原料, 并得到中等收率的目标产物. ^{13}碳标记的一氧化碳实验结果表明, 产物中的羰基来源于一氧化碳且能得到中等偏高收率的产物. 机理研究结果验证了反应的自由基属性, 且该反应能够放大到克级. 同时, 利用自由基参与的多米诺反应, 该策略也能被用于多组分的多氟烷基化羰基化反应. 综上, 本文结果也为该策略应用于批量生产及其他领域提供了参考和借鉴.

关键词: 羰基化反应; 电子转移化合物; 酯; 烷基碘; 可见光

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*通讯联系人.电子信箱: xwu2020@dicp.ac.cn, xiao-feng.wu@catalysis.de (吴小锋).

[1]共同第一作者.

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7.2 Visible light-induced manganese-catalyzed aminocarbonylation of alkyl iodides under atmospheric pressure at room temperature

Yan-Hua Zhao, Xing-Wei Gu and Xiao-Feng Wu

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Author contributions:

In this paper, I finished the optimization of reaction conditions, investigation of substrate scope. My contribution as the co-author of this paper is approximately 45%.

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Visible light-induced manganese-catalyzed aminocarbonylation of alkyl iodides under atmospheric pressure at room temperature†

Yan-Hua Zhao,‡[a] Xing-Wei Gu‡[a] and Xiao-Feng Wu *[a,b]

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Manganese catalysts, with advantages including low cost and relatively low toxicity, are attractive for application in carbonylation reactions. Herein, we report the synthesis of a series of amides *via* visible-light-induced manganese-catalyzed carbonylation of alkyl iodides using carbon monoxide as the C1 source. The reaction proceeds effectively at ambient temperature and pressure in the absence of ligands with a variety of alkyl iodides and aryl amines.

Introduction

Amides are some of the most important structural units in medicinal chemistry and biochemistry and are widely found in naturally occurring products and synthetic compounds.[1] Selected examples of valuable amide compounds are shown (Scheme 1), such as valsartan (Diovan), which is used to treat high blood pressure, heart failure, and diabetic kidney disease;[2a] lacosamide (Vimpat), which is used for the treatment of partial-onset seizures and primary generalized tonic-clonic seizures;[2b] lidocaine (Lidoderm), which is a local anesthetic of the amino amide type;[2c] fentanyl (fentanyl), which is a highly potent synthetic piperidine opioid drug primarily used as an analgesic.[2d] Therefore, it is of great significance to develop alternative methods for the synthesis of various amide compounds, especially the synthesis of amides from cheap and easily available raw materials. Carbon monoxide, as a cheap and abundant C1 source, is an important synthon in the carbonylation reaction which represents a straightforward method for the synthesis of amides.[3]

During the past few decades, the aminocarbonylation of aryl and benzyl electrophilic reagents has been successfully established and even applied in industrial production.[4] However, the aminocarbonylation of alkyl halides has been developed relatively slowly and usually requires harsh conditions to achieve the target reaction.[5] Among them, noble metal-catalyzed (Pd, Rh, Ru, Ir) carbonylation reactions are outstandingly effective (Scheme 2a).[6] Nevertheless, for sustainable development, economically improved and environmentally friendly alternative catalytic solutions are highly recommended.

In recent years, visible light photocatalysis has attracted attention from the synthetic chemistry community. This is because, unlike traditional thermal and catalytic reactions, it has high selectivity, unique reaction pathways, and mild reaction conditions.[7] The combination of carbonylation strategies with the advantages of photocatalytic applications can produce highly sustainable processes.[8] In 2016, Odell's group presented the synthesis of aliphatic amides from unactivated alkyl iodides *via* aminocarbonylation using photoredox catalysis (Scheme 2b).[9] In 2019, Elmore and co-workers reported the use of visible-light-induced Pd-catalyzed aminocarbonylation of alkyl iodides to obtain [^{14}C] alkyl amides (Scheme 2c).[10] In 2020, Polyzos' group reported an Ir-photosensor-based visible light-induced aminocarbonylation of amines with alkyl halides under continuous flow conditions (Scheme 2d).[11] In previous works, strategies combining a metal catalyst and visible light for the aminocarbonylation of alkyl halides at room temperature and ambient pressure of CO have been rarely reported. Inspired by the work reported by Wang's group on the Giese

[a]*Leibniz-Institut für Katalyse e.V., 18059 Rostock, Germany.*
E-mail: Xiao-Feng.Wu@catalysis.de
[b]*Dalian National Laboratory for Clean Energy, Dalian Institute of Chemical Physics, Chinese Academy of Sciences, 116023 Dalian, Liaoning, China.*
E-mail: xwu2020@dicp.ac.cn

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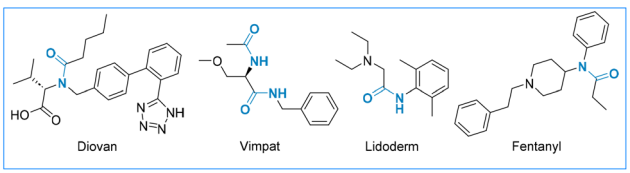
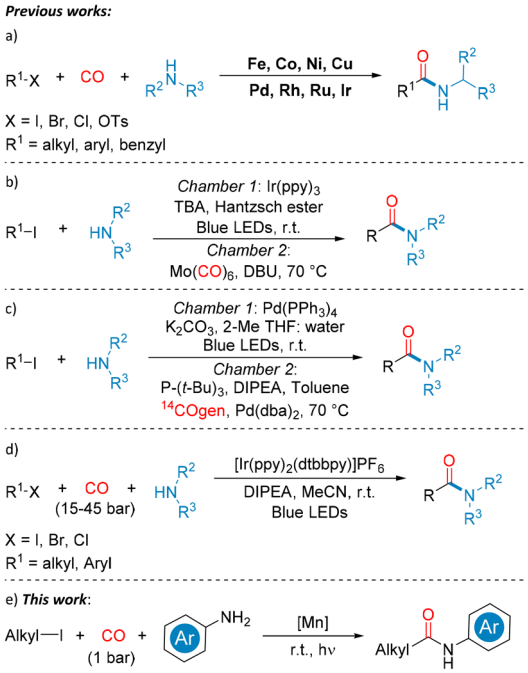
‡These authors contributed equally.



Scheme 1 Representative bioactive imide derivatives.



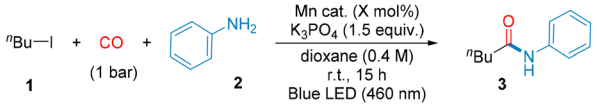
Scheme 2 Transition metal-catalyzed carbonylation of alkyl halides.

addition of unactivated alkyl iodides to electron-poor olefins (Michael acceptors) by combining inexpensive Mn metal catalysis and visible light induction,[12] herein we report a mild, visible-light-induced manganese-catalyzed aminocarbonylation of alkyl iodides with aryl amines (Scheme 2e). The method is characterized by high yields and good functional group tolerance. Excitingly, the protocol can be implemented under ambient carbon monoxide pressure at room temperature, providing a new alternative approach for amide production.

Results and discussion

We started this study with aniline **1** and *n*-butyl iodide **2** as the model substrates to produce compound **3** as the target amide (Table 1). When $Mn_2(CO)_{10}$ (5 mol%) or $Mn(CO)_5Br$ (10 mol%) was applied as the catalyst, the reaction proceeded smoothly and gave the desired amidated product **3** in good yields (Table 1, entries 1 and 2). Reducing the manganese catalyst loading decreased the yields of both reactions, but $Mn_2(CO)_{10}$ (2 mol%) gives better results than $Mn(CO)_5Br$ (5 mol%) (Table 1, entries 3 and 4). However, changing the solvent to THF, DMAc, or DCE decreased the yield of **3** substantially (Table 1, entries 5–7). Other bases (*e.g.*, Na_2CO_3 or Cs_2CO_3) could also provide the desired amide **3**, though in lower yields (Table 1, entries 8 and 9). Then, the wavelength of the light source was changed, and the yield dropped to 71% (Table 1, entry 10). Upon elevating the temperature, the carbonylation reaction could continue without a significant change in the efficiency (Table 1, entry 11). Decreasing or increasing the concentration of the reaction resulted in a slight decrease in yield

Table 1 Optimization of the reaction conditions[a]

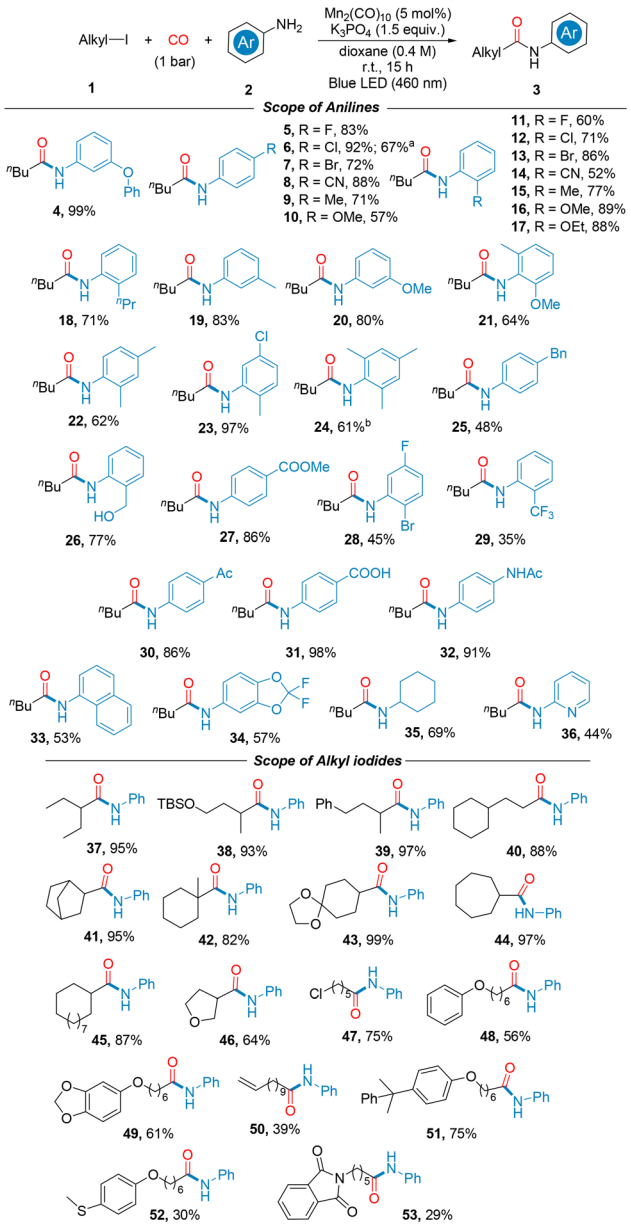


Entry	Variation from the standard conditions	Yield[b] (%)
1	5 mol% $Mn_2(CO)_{10}$	80 (83)
2	10 mol% $Mn(CO)_5Br$	81
3	2 mol% $Mn_2(CO)_{10}$	66
4	5 mol% $Mn(CO)_5Br$	31
5	THF as solvent	53
6	DMAc as solvent	22
7	DCE as solvent	29
8	Na_2CO_3 instead of K_3PO_4	62
9	Cs_2CO_3 instead of K_3PO_4	64
10	415 (nm) instead of 460 (nm)	74
11	50 °C instead of 25 °C	81
12	0.2 mol L^{-1} dioxane	71
13	0.4 mol L^{-1} dioxane	60
14	24 h instead of 15 h	79
15	No $Mn_2(CO)_{10}$	0
16	No light	0
17	No CO	<5

[a] The reaction was conducted using **1** (0.3 mmol), **2** (0.2 mmol), K_3PO_4 (1.5 equiv.) and dioxane (0.4 M) in blue light (460 nm) under indicated conditions. [b] Determined by GC with hexadecane as the internal standard. The isolated yield is shown in parentheses.

(Table 1, entries 12 and 13). Experiments showed that extending the time had no effect on the reaction efficiency (Table 1, entry 14). Control experiments showed that both the manganese catalyst and visible light irradiation were essential for the desired reaction (Table 1, entries 15 and 16). Only a trace amount of the desired product could be detected in the absence of CO gas (Table 1, entry 17). A systematic investigation of the reaction parameters led to the determination of the optimal reaction conditions: $Mn_2(CO)_{10}$ (5 mol%), K_3PO_4 (1.5 equiv.), 1,4-dioxane (0.4 mol L^{-1}), and blue-light irradiation (460 nm) for 15 h at room temperature, which afforded the desired amide compound **3** in 83% isolated yield (Table 1, entry 1).

After determining the optimal conditions, we first examined the substrate scope with a range of amines (Scheme 3). Delightfully, a variety of aromatic amines with different substituents were able to react successfully under the standard conditions and the corresponding amide products were obtained in moderate to excellent yields (**3–36**). In order to explore the chemoselectivity of the reaction, we investigated anilines containing $C(sp^2)$–X bonds (X = F, Cl, and Br) as substrates and obtained the desired amide products in moderate to excellent yields (**5–7**, **11–13**, **28**), thus demonstrating the good chemoselectivity of the catalytic system and providing opportunities for further structural modifications. However, only a trace amount of the desired product was detected in the case of 2-iodoaniline. Furthermore, *ortho*-, *meta*-, and *para*-substituted anilines could be transformed in good to excellent yields as well (**4–32**). It is noteworthy that our protocol has good functional group compatibility and that the electronic effects of



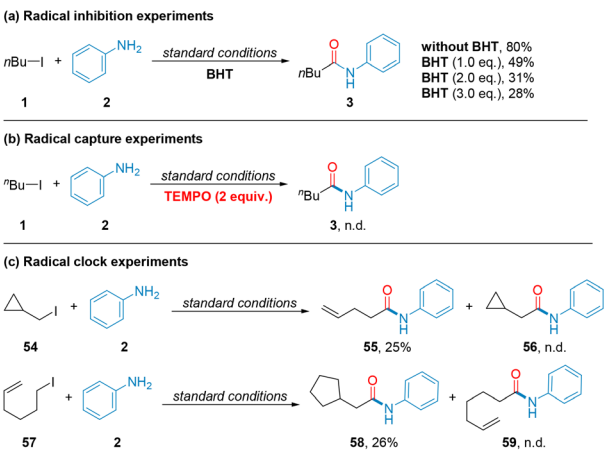
Scheme 3 Scope of anilines and alkyl iodides. Reaction conditions: **1** (0.3 mmol), **2** (0.2 mmol), $Mn_2(CO)_{10}$ (5 mol%), K_3PO_4 (1.5 equiv.), CO (1 bar), dioxane (0.4 M), irradiation with blue light (460 nm) at r.t. for 15 h. Yields of isolated products are shown. [a]1 mmol scale. [b]With 90% purity.

cycloaromatics appear to have a negligible impact on the reaction, with cyano (**8**, **14**), ether (**4**, **10**, **16**, **17**, **20**), alkyl (**9**, **15**, **18**, **19**), benzyl (**25**), alcoholic hydroxyl (**26**), ester (**27**), trifluoromethyl (**29**), ketone (**30**), amide (**32**), and even carboxyl (**31**) groups being tolerated, as well as polysubstituted anilines being equally well suited to the reaction conditions (**21**–**24**). Other aromatic framework amines (**33**), heterocycle-containing anilines (**34**), heteroaryl amines (**36**), and alkyl amines (**35**) also underwent aminocarbonylation without difficulty, reflecting the broad synthetic applicability of the reaction. In the cases of 2-iodoaniline, diphenylamine and piperidine, only a trace amount of the corresponding product was detected.

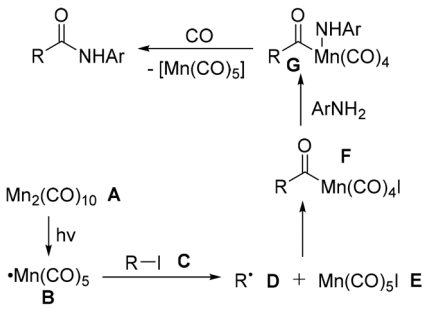
Subsequently, a variety of alkyl iodides containing different functional groups and structural blocks were tested (Scheme 3). The methodology showed overall good versatility and good tolerance of the various functional groups. Alkyl iodides with different carbon chain lengths were successfully converted to the corresponding amides (**37**–**40**) in excellent yields (88–97%). In addition, cycloalkane iodides and heterocycloalkane iodides underwent this transformation successfully to the desired products in high yields (**41**–**46**). In addition to this, ether (**48**–**49**, **51**–**52**), chlorine (**47**), terminal olefin (**50**), and phthalimide (**53**) groups were also tolerated. Additionally, this reaction can be easily extended to a 1 mmol scale as well. With 4-chloroaniline as the reaction partner, 67% yield of the desired product **6** was obtained. No desired product was formed when using 1-bromo-6-iodohexane as the substrate.

Next, a series of mechanistic experiments were performed to gain insight into the mechanism of the reaction (Scheme 4). The reaction was partly inhibited when BHT (2,6-di-*tert*-butyl-4-methylphenol, a free radical scavenger, 1–3 equiv.) was added to the reaction under standard conditions (Scheme 4a). At the same time, when 2 equivalents of 2,2,6,6-tetramethylpiperidin-1-yloxy (TEMPO) were added to the standard reaction, the desired product could not be detected (Scheme 4b). Subsequently, we performed free radical clock experiments with (iodomethyl)cyclopropane and 6-iodohex-1-ene, which provided the corresponding ring-opening product **55** and cyclization product **56**, respectively, with high selectivity (Scheme 4c). These experimental results indicate that this carbonylation reaction proceeds *via* a free radical process. In addition, to figure out whether the process is a free radical chain reaction, we turned off the light after 2 hours and then continued the reaction in the dark for another 13 hours. The reaction was carried out in a dark environment. However, the conversion of the reaction was obviously reduced and only 57% yield of **3** was obtained. Therefore, we exclude the possibility of a free radical chain reaction.

Based on the above observations and previous related reports, a possible reaction mechanism is proposed



Scheme 4 Mechanistic studies.



Scheme 5 Proposed mechanism.

(Scheme 5). First, under blue light irradiation, the Mn–Mn bond in $Mn_2(CO)_{10}$ (**A**) undergoes homopolymerization to generate $^{\bullet}[Mn(CO)_5]$ (**B**) radicals.[13] Subsequent extraction of the iodine atom from the alkyl iodide (**C**) by radical **B** generates $Mn(CO)_5I$ (**E**) and gives the alkyl radical (**D**). Then the alkyl radical **D** undergoes carbonylation with **E** to give the acyl manganese $RCOMn(CO)_4I$ intermediate **F**.[14] Intermediate **F** then reacts with an arylamine to form the final alkyl amide product and release the catalyst for the next catalytic cycle after the reductive elimination step.

Conclusions

In conclusion, we have developed an alternative method for the synthesis of amides by visible-light-induced manganese-catalyzed aminocarbonylation of alkyl iodides at room temperature and under ambient pressure of carbon monoxide. The method is characterized by mild conditions and efficient preparation of various alkylamides from aryl amines without ligands. All these characteristics offer potential opportunities for many other applications of this procedure.

Procedure and characterization

$Mn_2(CO)_{10}$ (0.01 mmol, 5 mol%), K_3PO_4 (0.3 mmol, 1.5 eq.), degassed dioxane (0.5 mL), 1 (0.3 mmol, 1.5 eq.), and 2 (0.2 mmol, 1 eq.) were added sequentially to a 4 mL snap vial under an Ar atmosphere. The vials were cannulated, transferred to a photoautoclave and closed. The photoautoclave was then flushed three times each with nitrogen and CO and filled with 1 bar of carbon monoxide. After stirring at 25 °C for 15 h in blue light (460 nm) under indicated conditions, the yield was determined by GC with hexadecane as the internal standard. The isolated yield is shown in parentheses. The resulting crude mixture was purified by silica gel column chromatography (*n*-hexane/ethyl acetate, v/v = 15/1) to give *N*-phenylpentanamide **3** (29.5 mg, 83% yield) as a white solid. The product **3** is known, and the following data are identical to those given in the corresponding literature;[15] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (d, J = 7.6 Hz, 2H), 7.31 (t, J = 7.8 Hz, 2H), 7.09 (t, J = 7.4 Hz, 1H), 2.36 (t, J = 7.6 Hz, 2H), 1.71 (p, J = 7.5 Hz, 2H), 1.40 (h, J = 7.6 Hz, 2H), 0.94 (t, J = 7.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.6, 137.9, 128.9, 124.1, 119.9, 37.5, 27.7, 22.3, 13.8.

Conflicts of interest

There are no conflicts to declare.

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7.3 Iron-catalyzed carbonylative synthesis of amides from alkyl-boronic pinacol ester via a single electron transfer process

Xing-Wei Gu, Alex De Salvo, Raffaella Mancuso and Xiao-Feng Wu

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Author contributions:

In this paper, I finished the optimization of reaction conditions, investigation of substrate scope and writing the manuscript. My contribution as the co-first author of this paper is approximately 70%.

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Iron-Catalyzed carbonylative synthesis of amides from Alkyl-Boronic pinacol ester *via* a single electron transfer process

Xing-Wei Gu [a,1], Alex De Salvo [b,1], Raffaella Mancuso [b,*], Xiao-Feng Wu [a,c,d,*]

[a] Leibniz-Institut für Katalyse e.V., Albert-Einstein-Str. 29a, 18059 Rostock, Germany
[b] Laboratory of Industrial and Synthetic Organic Chemistry (LISOC), Department of Chemistry and Chemical Technologies, University of Calabria, Via Pietro Bucci 12/C, 87036 Arcavacata di Rende, (CS), Italy
[c] Dalian National Laboratory for Clean Energy, Dalian Institute of Chemical Physics, Chinese Academy of Sciences, 116023 Liaoning, China
[d] College of Material Chemistry and Chemical Engineering, Key Laboratory of Organosilicon Chemistry and Material Technology, Ministry of Education, Hangzhou Normal University, Hangzhou 311121, Zhejiang, China

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ABSTRACT

An iron-catalyzed oxidative aminocarbonylation of alkyl boronic pinacol esters via alkyl radical intermediate has been developed. Various aliphatic amides were produced in good yields from the corresponding alkyl boronic esters and anilines in the presence of oxidant under carbon monoxide pressure.

In synthetic chemistry, boronic acids and their derivatives are versatile intermediates used in the synthesis of complex molecules. Indeed, they are involved in various chemical reactions such as Suzuki-Miyaura coupling [1] which has been widely used to construct C–C bonds from C-B bonds.[2–6] In addition, C-B bonds can also be converted into carbon-heteroatom bonds and carbon-halogen bonds easily and efficiently.[7,8] On the other hand, there are few examples of aminocarbonylation of boronic acids in the literature. In 2016, the research group of Jiao reported a palladium-catalyzed aminocarbonylation of organoboronic acids with amines toward amides (Scheme 1a)[9] Unfortunately, only 31 % yield of the desired product was obtained when alkylboronic acid was used as substrate while arylboronic acid worked well. We also developed a new palladium-catalyzed aminocarbonylation of aryl boronic acids with nitroarenes as the aniline sources and oxidant for the synthesis of amides.[10] Alkylboronic acids were also failed under that conditons.

Alkylboronic acid pinacol esters have attracted much attention due to their high stability, wide applicability, low toxicity and simplicity of preparation. The corresponding alkyl radicals can be generated from alkyl boranes,[11] alkyl-trifluoroborate salts,[12,13] and boronates.[14] In more detail, Ley et al. developed a method to generate carbon radicals from alkylboronic pinacol esters using pyridine derivatives as a Lewis base activator.[15–17] Phenyllithium was used by Aggarwal's group to prepare alkylarylboronate complexes, which act as alkyl radical precursors through single-electron oxidation.[18–20] Another example has been reported by Renaud group; they reported a transesterification strategy for the in situ-conversion of alkyl-boronic pinacol esters into alkylboronic catechol esters. These ones undergo nucleohomolytic substitution by reaction with sulfonyl radicals, aryloxy radicals or TEMPO to generate the corresponding alkyl radicals.[21,22] Instead, Studer and his colleagues used the *N*-nitrosamines as radical initiator for the radical generation.[23] Moreover, the Chen's group reported a Minisci C–H alkylation of N-heteroarenes using boronic acids and a peroxide as radical generator.[24].

The amide bond is an essential linkage in organic chemistry and, represent the key functional group in peptides, polymers and many natural products and pharmaceuticals.[25–28] As a matter of fact, the research for new synthetic methods to obtain amides has become increasingly important, for this reason the amide synthesis via metal-catalyzed aminocarbonylation has been widely reported.[29–32] Inspired by the above backgrounds and fill the limitation existing, we developed a new aminocarbonylation for amides synthesis from

* Corresponding authors.
E-mail addresses: raffaella.mancuso@unical.it (R. Mancuso), Xiao-Feng.Wu@catalysis.de, xwu2020@dicp.ac.cn (X.-F. Wu).
[1] X.-W. Gu and A. De Salvo contributed equally.

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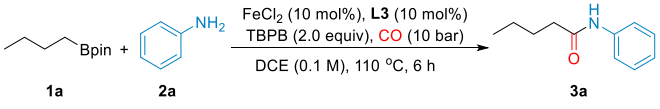
alkylboronic pinacol esters via radical intermediate (Scheme 1b).

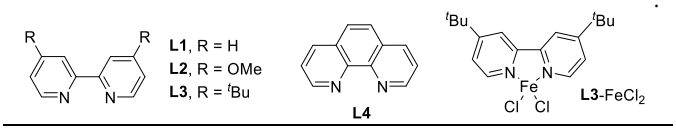
We initially explored the aminocarbonylation with alkylbuthylboronic pinacol ester (alkyl-Bpin) **1a** and aniline **2a** as the model substrates. As shown in Table 1, by using $FeCl_2$ as the catalyst, dtbbpy **L3** as the ligand, and TBPB (*tert*-butyl peroxybenzoate) as the oxidant under 10 bar CO pressure at 110 °C for 6 h, amide **3a** were successfully obtained in 59 % yield (Table 1, entry 1). Other bidentate nitrogen ligands (**L1**, **L2**, **L4**) were tested and found to have no significant effect on the reaction outcome, and **L3** remaining the best ligand for this process (Table 1, entries 2–4). Importantly, without ligand, the aminocarbonylation could also proceed, but resulted in decreased yield (Table1, entry 5). In the absence of $FeCl_2$, the reaction cannot proceed (Table1, entry 6). Then, the yield can be improved to 72 % by increasing reaction concentration and decreasing the temperature to 70 °C (Table1, entry 7). Increasing the pressure of CO significantly improves the yield (Table1, entry 8). It is noteworthy that satisfactory yield was also obtained with only 1 mol% $FeCl_2$ and 1.2 mol% **L3** (Table1, entry 9). To make the operation more convenient, we used $FeCl_2$ with dtbbpy **L3** to prepare the complex **L3**-$FeCl_2$ as a catalyst, which afforded 84 % isolated yield when TBPA (*tert*-butyl peracetate) was used as the oxidant (Table1, entry 10).

With the optimal reaction conditions in hand, we immediately investigated the substrate scope of this iron-catalyzed aminocarbonylation. As shown in Scheme 2, a broad array of arylamines could be served as effective reaction partners, provided the desired amides in good to excellent yields. Arylamines bearing both electron-donating and electron-withdrawing groups (**3a**-**3q**) efficiently participated in the reaction to provide the desired products. The aryl amines with different positions of alkyl substitution slightly affected the yields and the results showed that the *meta* position was better than the *para* position than the *ortho* position (**3a**-**3f**). Functional groups including halogens (F, Cl, Br, **3 g**-**3j**), alkoxy (**3 k**-**3 m**), -Ph (**3n**), -Bn (**3o**), -Ac (**3p**), survived in this reaction conditions, gave the corresponding amides in good to high yields. Among them, methoxy-substituted aniline exhibited excellent reactivity, provided the desired amides **3 k**, **3 l**, **3 m** in 83 % to 93 % isolated yields. Finally, substrate bearing natural product such as *DL-Menthol* also worked well under this aminocarbonylation conditions to afford corresponding amide **3q** in 59 % isolated yield. It is worth noting that our model system can also be performed on 6.44 mmol scale without loss of efficiency and provided **3a** in 81 % isolated yield. Its worthy to mention that aliphatic amine was also tested, but no desired product could be detected. This might due to the high basicity of alkylamine which make it easier to be oxidized.

Next, we also investigated the scope of alkyl-Bpin in this iron-catalyzed aminocarbonylation. As shown in Scheme 2, unactivated primary alkyl-Bpin were available as the coupling partners. The length of the carbon chain did not affect the reaction outcome much and the desired products (**3r**-**3s x**) could be obtained in good to excellent yields. Furthermore, the substrate containing ester group was also tolerated and the desired amide **3y** was produced in 70 % isolated yield. To our

Table 1
Optimization of the reaction conditions.[a]





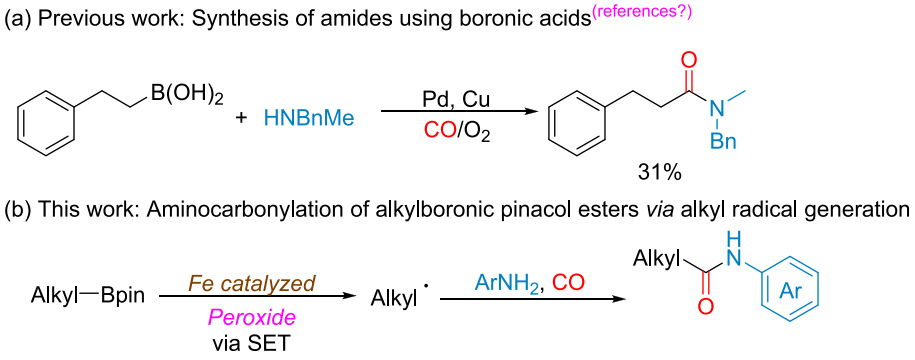
Entry	Variations as shown	Yield **3a** (%)[b]
1	None	59
2	**L1** instead of **L3**	54
3	**L2** instead of **L3**	51
4	**L4** instead of **L3**	49
5	Without ligand	43
6	Without $FeCl_2$	nr
7[c]	70 °C as reaction temperature	72
8[d]	CO (20 bar), CO (30 bar)	83, 86
9[e]	$FeCl_2$ (1 mol%) and **L3** (1.2 mol%)	83
10[f]	TBPA instead of TBPB	85 (84)

[a] The reaction was conducted using **1a** (0.3 mmol) and **2a** (0.2 mmol) under indicated conditions. [b]Determined by GC with hexadecane as internal standard. [c]DCE (0.2 M). [d]DCE (0.2 M), 70 °C. [e]DCE (0.2 M), 70 °C, CO (20 bar). [f]DCE (0.2 M), 70 °C, CO (20 bar), **L3**-$FeCl_2$ (1 mol%). Isolated yield is shown in parentheses.

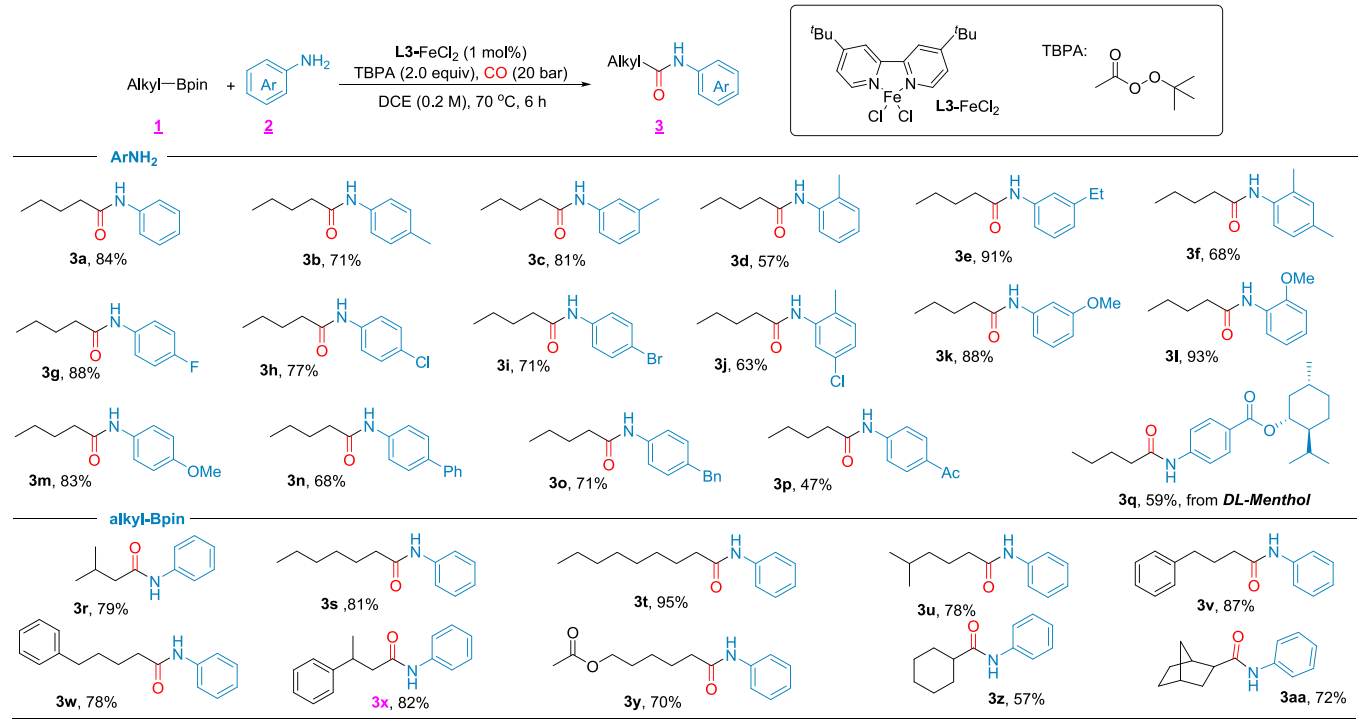
delight, secondary alkyl-Bpin (**3z**, **3aa**) can furnished the target products in good yields under this reaction conditions as well. However, no desired product could be detected when arylboronic acids were tested.

To gain more insight into the mechanism of this iron-catalyzed aminocarbonylation, we set up several experiments to shed light on the reaction mechanism (Scheme 3). When 1,1-diphenylethylene was used as the radical trapping agent, the expected product **3a** was not obtained, however products **4** and **5** could be detected from GC–MS, indicating that alkyl radicals and acyl radicals were formed during the reaction (Scheme 3, eq. a). The TEMPO captured alkyl radical reconfirming that the reaction undergoes a radical process (Scheme 3, eq. b). Meanwhile, the desired product was not obtained regardless of the amount of BHT added, and we thought that the resulting *tert*-butoxyl radicals might have been quenched directly by BHT (2,6-di-*tert*-butyl-4-methylphenol, a radical scavenger, 1–3 (equiv), which prevented the subsequent process from proceeding (Scheme 3, eq. c).

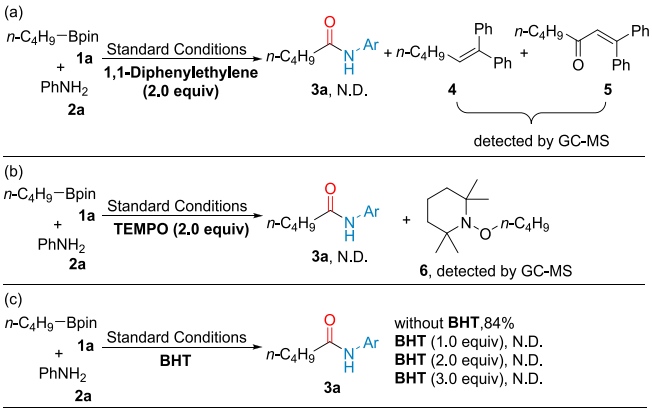
On the basis of above results and previous reports, [33–37] a possible mechanism for the iron-catalyzed aminocarbonylation reaction was proposed (Scheme 4). Initially, TBPA was activated in the presence of **L3**-$Fe^{II}X_2$ to form *tert*-butoxy radical **A** and **L3**-$Fe^{III}X_2OAc$ specie. Subsequently, the *tert*-butoxy radical **A** abstract the -Bpin group from alkyl-Bpin to form an alkyl radical **B**. The acyl radical **C** is generated from alkyl radical **B** by capture of CO in a carbon monoxide atmosphere, followed with oxidation by **L3**-$Fe^{III}X_2OAc$ to form acyl cation



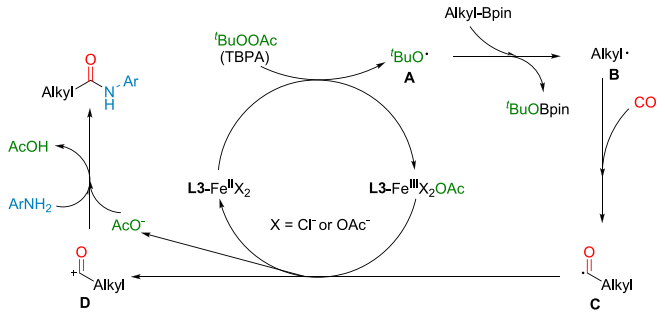
Scheme 1. Previous work and Our Design.



Scheme 2. Scope of $ArNH_2$ and alkyl-Bpin.[a]



Scheme 3. Radical capture experiments.



Scheme 4. Proposed mechanism.

intermediate **D**. Finally, the arylamine reacts with the acyl cation **D** to provide the desired amide.

In conclusion, we have developed an iron-catalyzed aminocarbonylation of alkylboronic esters to synthesize a series of amides from alkylboronic pinacol esters (alkyl-Bpin) and anilines. Good yields of the desired amides can be obtained in general.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

Acknowledgment

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcat.2023.115273.

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7.4 Abundant metal-catalyzed carbonylation of alkyl bromides and alkyl chlorides

Xing-Wei Gu and Xiao-Feng Wu

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Author contributions:

In this paper, I wrote this review paper. My contribution as the first author of this paper is approximately 90%.

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Abundant metal-catalyzed carbonylation of alkyl bromides and alkyl chlorides

Xing-Wei Gu[a,b] and Xiao-Feng Wu *[a,b]

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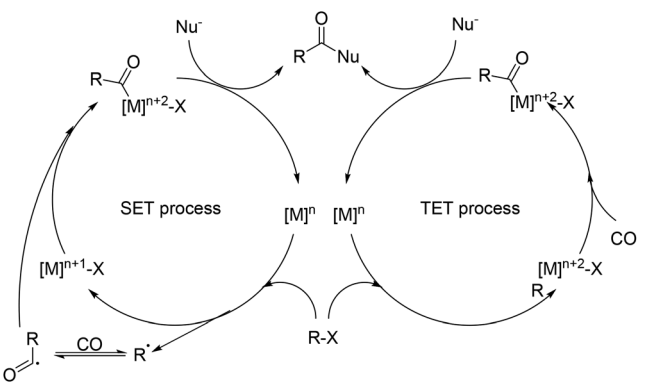
Transition metal-catalyzed carbonylation of alkyl halides is one of the most efficient methods for the assembly of aliphatic carbonyl-containing compounds. Despite the long history of carbonylation chemistry, core breakthroughs are still rare. For example, (1) the extensive use of noble metals makes it urgent to find suitable inexpensive metals as substitute catalysts, and (2) the substrates applied are still dominated by expensive alkyl iodides. In this paper, we discuss the carbonylation reactions of alkyl bromides and chlorides catalyzed by abundant metals developed by our group recently.

Introduction

As a cheap and abundant source of C1, carbon monoxide (CO) is an important synthon in carbonylation reactions to produce a range of promising carbonylated compounds, such as esters, amides, ketones and so on.[1] Over half a century of development, transition metal-catalyzed carbonylation of alkyl halides has now emerged as one of the most powerful methods for the assembly of aliphatic carbonyl-containing compounds.[2] Among them, noble metal-catalyzed (Pd, Rh, Ru and Ir) carbonylation reactions are outstanding and suitable catalytic systems have been established, such as carbonylated C–C coupling reactions, carbonylated Heck, Sonogashira, and Suzuki reactions, and carbonylation of alkyl halides with nucleophilic reagents such as alcohols and amines.[3] In contrast, the carbonylation reactions catalyzed by abundant metals (Mn, Fe, Co, Ni, and Cu) are progressing relatively slow.[4] One of the most important features of abundant metals is that they can participate in one- and two-electron elemental reactions, while reactions catalyzed by noble metals usually proceed *via* a two-electron process (Scheme 1). Thus, abundant metal catalysis can be an economical alternative to noble metals in carbonylation reactions, and their unique properties also provide additional opportunities for new reactions that cannot be achieved with noble metal catalysis.

Carbonylation of alkyl halides has long been a hot topic of research. However, the carbonylation of C(sp^3)–X bonds, particularly those of unactivated alkyl halides, is relatively challenging compared to that of aryl halides due to the difficulty of oxidative addition and competing β-elimination reactions.[5] Based on the continuous efforts of organic chemists, particularly the pioneering studies of Heck, Alper, Ryu and others,[6] and the intensive research of Arndtsen,[7] Mankad[8] and our group[9] in recent years, many carbonylation proposals for alkyl halides based on transition metal-catalyzed or photoinduced single-electron transfer (SET) processes have been successfully established. However, most of the research studies on the carbonylation of alkyl halides have focused on more active alkyl iodides, while the carbonylation reactions of less active and inexpensive alkyl bromides and alkyl chlorides have been rarely reported.[10] Therefore, there is still a pressing demand for the development of carbonylation reactions applicable to alkyl bromides and alkyl chlorides.

In this article, we summarize our recent studies on base metal catalyzed carbonylation reactions of unactivated alkyl halides, which are capable of forming a wide variety of carbonyl compounds or their derivatives, including ketones, amides, ketoamides, and esters.



Scheme 1 General mechanism for metal-catalysed SET or TET carbonylation.

[a]*Dalian National Laboratory for Clean Energy, Dalian Institute of Chemical Physics, Chinese Academy of Sciences, 116023 Dalian, Liaoning, China.*
E-mail: xwu2020@dicp.ac.cn
[b]*Leibniz-Institut für Katalyse e.V., 18059 Rostock, Germany.*
E-mail: Xiao-Feng.Wu@catalysis.de

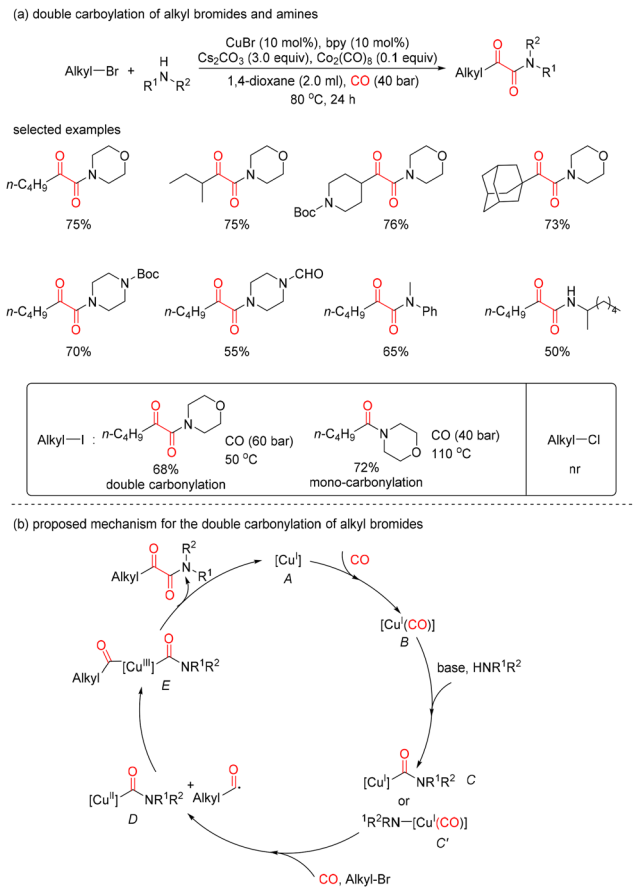
Carbonylation reaction of alkyl bromides

In recent years, with the continuous exploration and research on the copper-catalyzed carbonylation of alkyl halides by Mankad's group, and the brilliant performance achieved, it has now become one of the research hotspots.[11] In 2022, our group developed a copper-catalyzed double carbonylation of alkyl bromides using amines as nucleophilic reagents to give a series of α-ketoamides with high chemoselectivity (Scheme 2a).[12] The reaction system is extremely tolerant towards functional groups such as halogens, Boc-protected amides, ethers, acetoxides, esters and indoles, and is suitable for aliphatic and aryl amines. Surprisingly, primary amines are not normally used in double carbonylation reactions due to the tendency of α-ketoamides to form Schiff bases *in situ*; however, primary amines are also tolerated in this system.[13] It is worth mentioning that alkyl iodides are selectively double and mono-carbocarbonylated under the modulation of metal, ligand, and CO pressure. Unfortunately, alkyl chloride is not suitable for this reaction system.

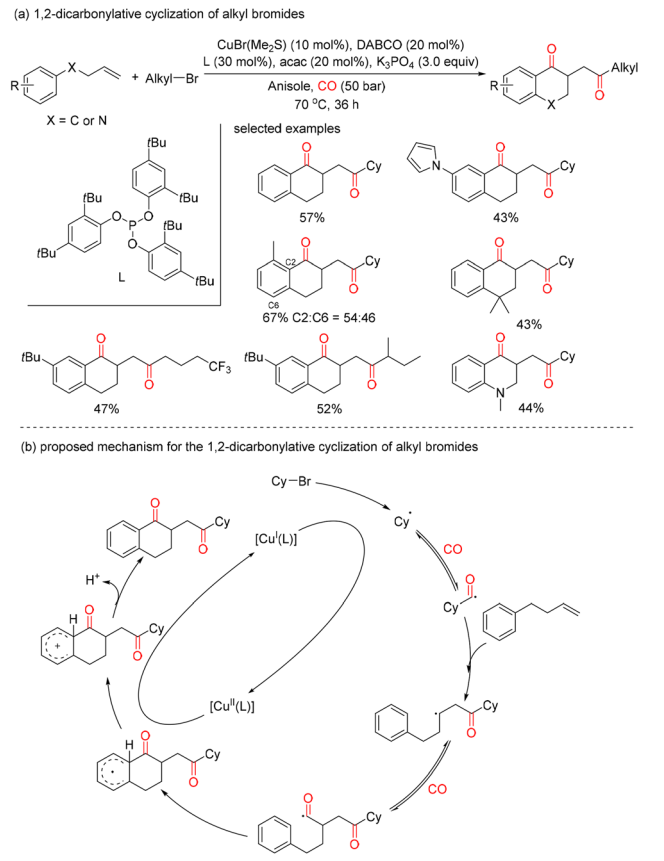
We proposed that the reaction proceeds through a radical process (Scheme 2b), with CO first coordinated to the copper salt to form the (carbonyl) copper species **B**. This is followed by nucleophilic attack by the amine on the coordinated CO to form complex **C** or an anionic ligand exchange with complex **B** to form complex **C′**. The alkyl bromide then undergoes a SET process with either **C** or **C′** to form complex **D** and an alkyl radical, which captures CO to afford an acyl radical, which subsequently combines with **D** to produce the key intermediate **E**. Finally, the reductive elimination of **E** gives α-ketoamide and regenerates the catalyst.

Soon after, our group reported a second case of copper-catalyzed carbonylation of alkyl bromides.[14] In this copper-catalyzed 1,2-dicarbonyaltive cyclization system (Scheme 3a), 4-aryl-1-butenes and alkyl bromides constructed a series of α-tetralone and 2,3-dihydroquinolin-4-one through a radical cascade process, constructing four new C–C bonds, and introducing two carbonyl groups and a ring. This reaction has a wide substrate scope and yields the product in moderate to good yields. Also, through the derivatization reaction, the product can be converted into three consecutive cyclic structures.

In the mechanistic study, we proposed that the reaction may undergo a free radical cascade process (Scheme 3b). First, the alkyl bromide undergoes a copper-catalyzed SET process to produce an alkyl radical, which then traps CO to form an acyl radical. Subsequently, the acyl radical combines with an olefin



Scheme 2 Cu-catalyzed double carbonylation of alkyl bromides.

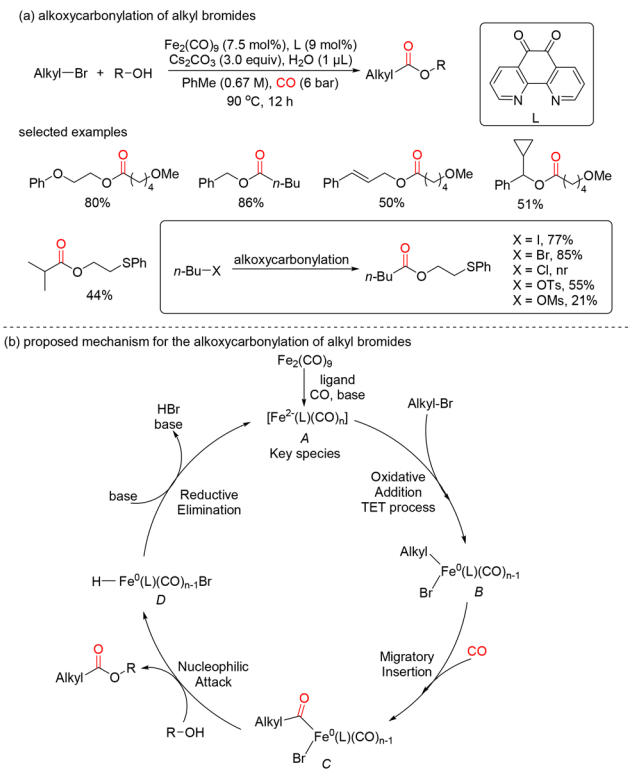


Scheme 3 Cu-catalyzed 1,2-dicarbonylation cyclization of alkyl bromides.

to form a new alkyl radical that again traps a molecule of CO. Finally, it reacts with an aromatic hydrocarbon and undergoes a deprotonation process to obtain the product.

Esters are an important class of functional groups commonly found in natural products, pharmaceuticals, agrochemicals, functional materials, and bioactive scaffolds.[15] The catalytic alkoxycarbonylation of alkyl halides has long been a hot topic in carbonylation reactions due to its direct and efficient use of carbon monoxide (CO) as a cheap and abundant source of C1. Recently, our group has reported a novel alkoxycarbonylation system *via* an *in situ* generated Fe^{2-} catalyst which was produced from Fe^0 with CO and/or a base as the reductant (Scheme 4a).[16] Among them, the chemical valence of the iron source is crucial for the reaction to proceed and only Fe^0 and Fe^{2-} can initiate alkoxycarbonylation, while the reaction cannot proceed when Fe^{2+} or Fe^{3+} catalysts are used. In addition, the authors found that the addition of additional small amounts of water to the system to increase the solubility of the base facilitated the nucleophilic attack and the reductive elimination step, thereby increasing the alkoxycarbonylation reactivity. Under optimal conditions, the method exhibited excellent reaction generality, with only tertiary alcohols and phenols being limited in this system, while the remaining alcohols such as primary alcohols, secondary alcohols, allyl alcohols and benzyl alcohols all produced the target products in good to excellent yields. Also, in this system, some other alkyl electrophilic reagents such as secondary alkyl bromides, alkyl iodide, tosylate, and mesylate could be used to provide the desired ester; however, alkyl chloride is not applicable to this strategy.

Unlike the previously reported alkyl halides that undergo a single electron transfer process (Scheme 4b), the low-valence iron catalyst in this system activates the alkyl bromide through a two-electron transfer process to achieve the alkoxycarbonylation reaction. Based on the comparison of pure compound spectra and DFT calculations, as well as stepwise *in situ* IR experiments, the authors propose that the active catalyst for the reaction is an $[Fe(CO)n(L)]^{2-}$ type complex. The complex first forms the alkyl iron complex **B** with alkyl bromide by a two-electron transfer (TET) process, followed by the migration insertion of CO and nucleophilic attack of alcohols to afford the ester compound. Finally, complex **D** is eliminated by reduction in the presence of a base to complete the catalytic cycle. It is worth mentioning that alkyl iodides undergo alkoxycarbonylation by a single-electron transfer (SET) process in the same system.

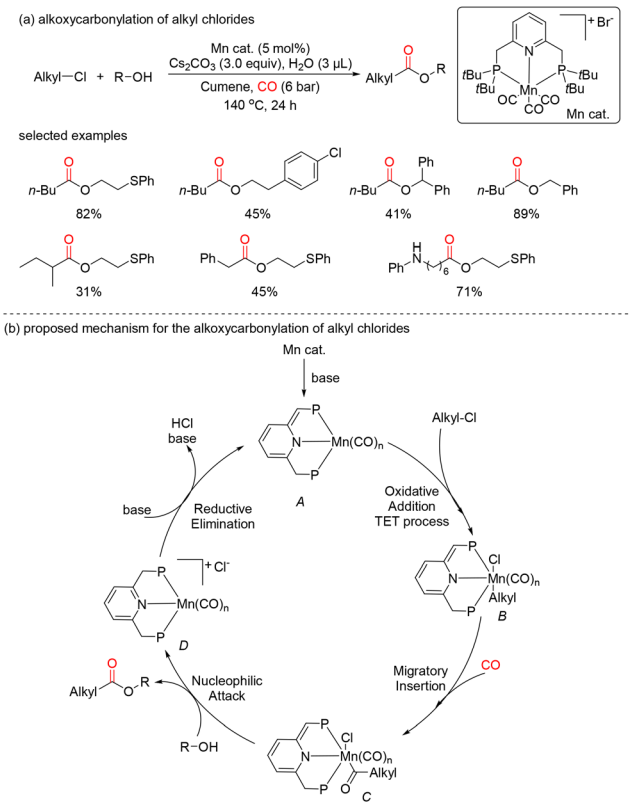


Scheme 4 Fe-catalyzed alkoxycarbonylation of alkyl bromides.

Carbonylation reaction of alkyl chlorine

Soon after, our group focused on the carbonylation reaction of cheaper alkyl chlorine. However, $C(sp^3)$–Cl has a high dissociation energy,[17] and oxidative addition is particularly difficult, particularly when the metal catalyst is easily deactivated under a CO atmosphere, which makes the carbonylation of alkyl chlorides more difficult.[18] To overcome the difficulties, we used pincer complexes as efficient inert chemical bond activation catalysts and "harder" manganese metal to improve the oxidative addition capacity of manganese metal, thus successfully achieving the alkoxycarbonylation of abundant, cheap, and less toxic alkyl chlorides (Scheme 5a).[19] This pincer manganese catalyzed alkoxycarbonylation system of alkyl chlorides is applicable to primary alcohols, secondary alcohols, and benzyl alcohols, all showing excellent performance in obtaining esters in good to excellent yields. Unfortunately, tertiary alcohols were used as substrates in low yields, and phenol and allyl alcohol could not even participate in the reaction. Under standard conditions, the yields of the target products afforded by the primary alkyl chloride ranged from good to excellent. However, the reactivity of secondary alkyl chloride and benzyl chloride decreased due to the increased steric hindrance.

Afterwards, to explain the effect of bromine ions in the pincer manganese catalyst on the experiment, the authors added additional sodium bromide or lithium bromide to the reaction system, and the yield of the ester did not increase. Also, when the alkyl chloride was replaced with alkyl bromide, the yield of the ester decreased instead. This indicates that the alkyl chloride did not undergo the *in situ* Finklestein reaction, but the reaction was achieved by direct oxidative addition. Therefore, the authors explained the mechanism of this alkoxycarbonylation reaction as follows (Scheme 5b). First, the pincer manganese catalyst forms active manganese complex **A** in the presence of a base, followed by oxidative addition with



Scheme 5 Mn-catalyzed alkoxycarbonylation of alkyl chlorides.

alkyl chloride and the migration insertion of CO to form acyl manganese complex **C**. Finally, the ester is afforded by nucleophilic addition of alcohols, and intermediate **D** completes the entire catalytic cycle by reductive elimination in the presence of a base.

Summary and outlook

Throughout the history of carbonylation, many carbonylation schemes based on metal-mediated or photoinduced alkyl halides have been successfully established. Despite the significant progress made by various groups in this field, core breakthroughs are still needed. For example, (1) the vast majority of reported systems are still dominated by the highly active but expensive alkyl iodides, with relatively few carbonylation reactions of relatively inexpensive alkyl bromides and alkyl chlorides, which thus urgently need attention, and (2) precious metals are used too frequently in the field of carbonylation, so the use of inexpensive metals with low cost and abundant reserves will be an important development direction for future carbonylation reactions.

We hope that our recent studies on the abundant-metal (Fe, Cu, Mn) catalyzed carbonylative transformation of alkyl bromides and alkyl chlorides can attract more chemists to work on this topic and overcome the discussed challenges in the near future!

Finally, we would like to mention that "Abundant metal catalysts are not just replacement of noble metals, their characteristic activities are even more attractive"!

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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7.5 [3 + 2] Cycloaddition of azides with arynes formed *via* C–H deprotonation of aryl sulfonium salts

Xing-Wei Gu, Yan-Hua Zhao and Xiao-Feng Wu

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Author contributions:

In this paper, I finished the optimization of reaction conditions, investigation of substrate scope and writing the manuscript. My contribution as the co-first author of this paper is approximately 70%.

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[3 + 2] Cycloaddition of azides with arynes formed *via* C–H deprotonation of aryl sulfonium salts†

Xing-Wei Gu,‡[a] Yan-Hua Zhao‡[a] and Xiao-Feng Wu *[a,b]

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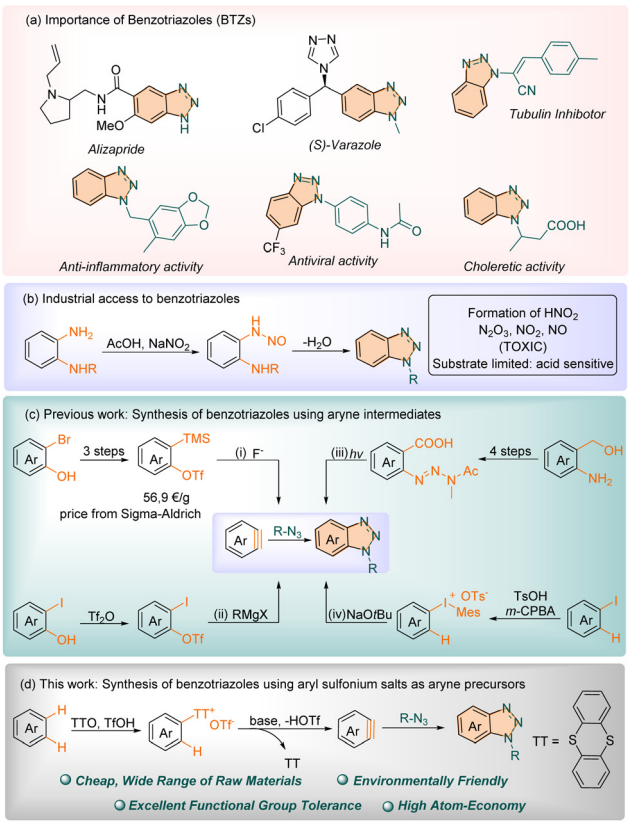
Herein, we developed a new methodology of using aryl sulfonium salts as the aryne precursor for [3 + 2] cycloaddition reactions with azides. The reaction using readily available arenes as the feedstock features excellent atom economy, environmental friendliness and high functional group tolerance. Moreover, due to the excellent performance of the gram-scale reaction, deuterium labeling result and derivatization reactions, there are potential opportunities for large-scale production and other applications.

Introduction

Benzotriazoles are common structural motifs in pharmaceuticals, corrosion inhibitors, and supramolecular ligands and materials.[1] Because of the stronger π–π stacking interactions of benzotriazoles than those of triazoles, the three nitrogen atoms more readily form hydrogen and coordination bonds, causing benzotriazole derivatives to bind more readily to enzymes and receptors in biological systems and produce a wide range of biological activities.[2] Currently, benzotriazole derivatives are broadly used in pharmaceuticals, including alizapride, (*S*)-varazole and tubulin inhibitors,[3] and they exhibit promising biological activities such as anti-inflammatory activity, antiviral activity and choleretic activity (Scheme 1a).[4] The main method of accessing benzotriazole industrially is the nitrosation of *o*-phenylenediamine with sodium nitrite and its preparation after dehydration (Scheme 1b).[5] However, the method requires an acidic environment, thus limiting the range of substrates containing acid-sensitive functional groups. Additionally, this method produces nitrous acid which is prone to produce some toxic nitrogen oxides such as N_2O_3, NO_2, and NO. Therefore, the development of alternative environmentally friendly methods for the synthesis of benzotriazoles is still in demand.

Arynes are transient species and a class of extremely active organic intermediates.[6] The [3 + 2] type cycloaddition reaction of benzynes with azides provides a convenient and moderate approach for the synthesis of *N*-substituted benzotriazoles (Scheme 1c).[7] Although many aryne precursors have been developed and used to accomplish the synthesis of benzotriazoles, there are still challenges that need to be overcome.



Scheme 1 (a) Representative examples of benzotriazole-containing active compounds. (b and c) Current methods for synthesizing benzotriazoles. (d) This work.

[a]*Leibniz-Institut für Katalyse e.V., 18059 Rostock, Germany.*
E-mail: Xiao-Feng.Wu@catalysis.de
[b]*Dalian National Laboratory for Clean Energy, Dalian Institute of Chemical Physics, Chinese Academy of Sciences, 116023 Dalian, Liaoning, China.*
E-mail: xwu2020@dicp.ac.cn

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‡These authors contributed equally.

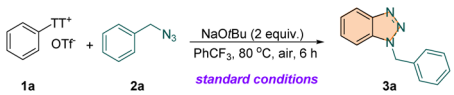
O-Silylaryl triflates are the most commonly used aryne precursors under the promotion of fluoride (i, Scheme 1c).[8] However, its preparation is lengthy (3 steps, starting from *o*-bromophenol) and expensive, thus limiting its industrial production. Meanwhile, the requirement of fluoride to activate the reaction precursor makes some fluoride-sensitive groups intolerable.[9] Similarly, the aryne precursor *o*-iodo triflates are synthesized in one step from *o*-iodophenols; however, highly reactive Grignard reagents are required as activators which greatly restricts the adaptability of the substrates (ii, Scheme 1c).[10] In 2014, the group of Schnarr reported a photoinduced [3 + 2] cycloaddition reaction of arynes with azides (iii, Scheme 1c).[11] This reaction system enables the synthesis of benzotriazoles under light conditions only, further broadening the range of substrates, but unfortunately, the preparation of aryne precursors is too lengthy (4 steps, starting from 2-aminobenzyl alcohol). In 2016, Stuart and co-authors reported an example in which aryl(mesityl)iodonium salts were used as aryne precursors and applied to the synthesis of benzotriazoles with azides as the reaction partner (iv, Scheme 1c).[12] In this procedure, aryl iodides were used as the substrate precursors in the presence of the strong oxidizer *m*-CPBA. Recently, Stuart's group have reported their pioneering discovery of using aryl sulfonium salts as aryne precursors, in which aryl sulfonium salts could be easily synthesized from inexpensive and readily available arenes.[13,14] Inspired by those results, we considered whether the synthesis of benzotriazoles could be achieved by using aryl sulfonium salts as aryne precursors. In this manner, the newly developed procedure can have improved functional group tolerance and also synthetic efficiency.

Herein, we report a convenient and atom-economical (-TfOH) approach using aryl sulfonium salts (which can be produced from a wide range of arenes selectively) as the starting material for the synthesis of benzotriazoles *via* C–H deprotonation to form arynes and then react with azides. This strategy has high functional group tolerance and good regioselectivity. More importantly, the thianthrene released can be recovered and reused (Scheme 1d).

Results and discussion

We initially explored the [3 + 2] cycloaddition with phenyl sulfonium salt **1a** and benzyl azide **2a** as the model substrates (Table 1). After a systematic investigation of the reaction parameters such as temperature, solvent, and base, the following optimum conditions were identified: aryl sulfonium salt **1a** (1.5 equiv.), benzyl azide **2a** (1.0 equiv.), NaO*t*Bu (2.0 equiv.), $PhCF_3$ (0.1 M), reaction at 80 °C under an air atmosphere for 6 h, affording the desired benzotriazole **3a** in 96% GC yield (83% isolated yield) (Table 1, entry 1). Increasing the concentration of the reaction from 0.1 M to 0.2 M decreased the yield to 93% (Table 1, entry 2). As the temperature decreases, the cycloaddition reaction can still proceed, but the efficiency decreases gradually and only trace amounts of the product can be detected at room temperature (Table 1, entry 3).

Table 1 Optimization of the reaction conditions[a]

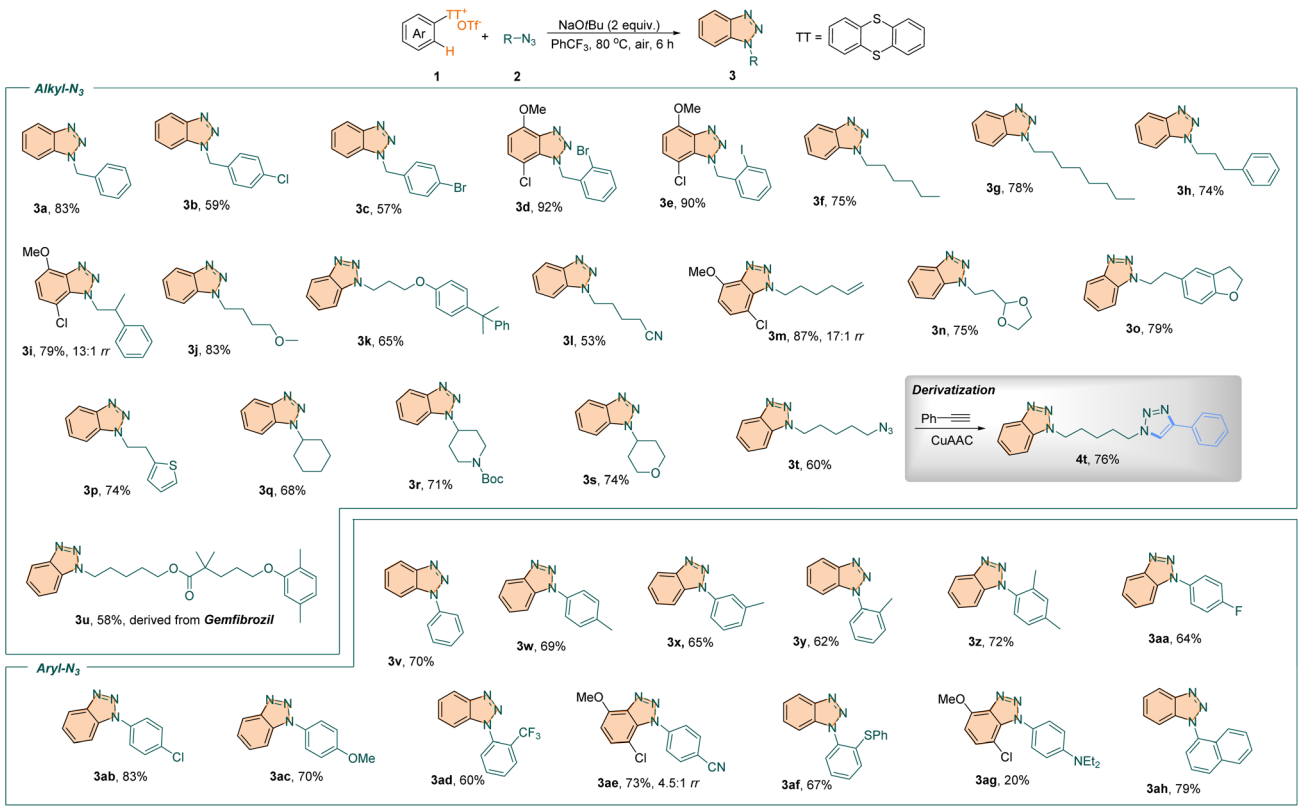


Entry	Variation from the "standard conditions"	Yield[b] (%)
1	None	96 (83)
2	0.2 M $PhCF_3$	93
3	60 °C, 40 °C, rt instead of 80 °C	85, 24, trace
4	1.5 equiv. NaO*t*Bu	71
5	1.0 equiv. NaO*t*Bu	29
6	Toluene instead of $PhCF_3$	48
7	1,4-dioxane instead of $PhCF_3$	50
8	MeCN, DCE, acetone instead of $PhCF_3$	n.d.
9[c]	KO*t*Bu instead of NaO*t*Bu	15
10[c]	LiO*t*Bu, NaOMe, NaOH instead of NaO*t*Bu	n.d.

[a] The reaction was conducted using **1a** (0.3 mmol) and **2a** (0.2 mmol) under indicated conditions. [b] Determined by GC with hexadecane as the internal standard. [c] The reaction solvent is toluene. Isolated yield is shown in parentheses.

Experiments showed that when the amount of NaO*t*Bu was reduced, the yield of the desired product also decreased (Table 1, entries 4 and 5). In the solvents tested, the target product **3a** was obtained in moderate yields with toluene or 1,4-dioxane as the reaction medium (Table 1, entries 6 and 7). However, when MeCN, DCE and acetone were used as the solvents, the desired benzotriazole **3a** could not be detected (Table 1, entry 8). The desired benzotriazole **3a** product could also be detected with KO*t*Bu as the base, but in a lower yield (Table 1, entry 9). Other bases, such as LiO*t*Bu, NaOMe or NaOH could not promote the reaction to give the target product **3a** (Table 1, entry 10).

With the optimal reaction conditions in hand, we next investigated the substrate scope of this [3 + 2] cycloaddition. As shown in Scheme 2, a wide range of azides were first tested as reaction partners. In general, the corresponding benzotriazoles were obtained in good to excellent yields. Benzyl azides as templates could easily provide the corresponding benzotriazoles (**3a–3e**), although the halogen-substituted benzyl azides decreased the yields to some extent. The growth of the alkyl chain did not affect the reaction much and the corresponding products (**3f–3i**) could be obtained in good yields. In addition to alkyl groups, functional groups such as ether (**3j** and **3k**), cyano (**3l**), and alkenyl (**3m**) were all compatible. Heterocyclic groups relevant to medicinal molecules such as acetal (**3n**), benzofuran (**3o**), and thiophene (**3p**) showed good tolerability. Secondary cyclic azides were also suitable under these reaction conditions and provided the corresponding benzotriazoles (**3q–3s**) in good yields. It is worth mentioning that substrates with multiple reaction sites (**3t**) could selectively react with only one azide group without changing the reaction conditions. Under copper catalysis, the other azide groups can react with phenylacetylene to provide the desired product (**4t**) with two triazole-containing fragments in 76% yield. Subsequently, we applied our cycloaddition method for the

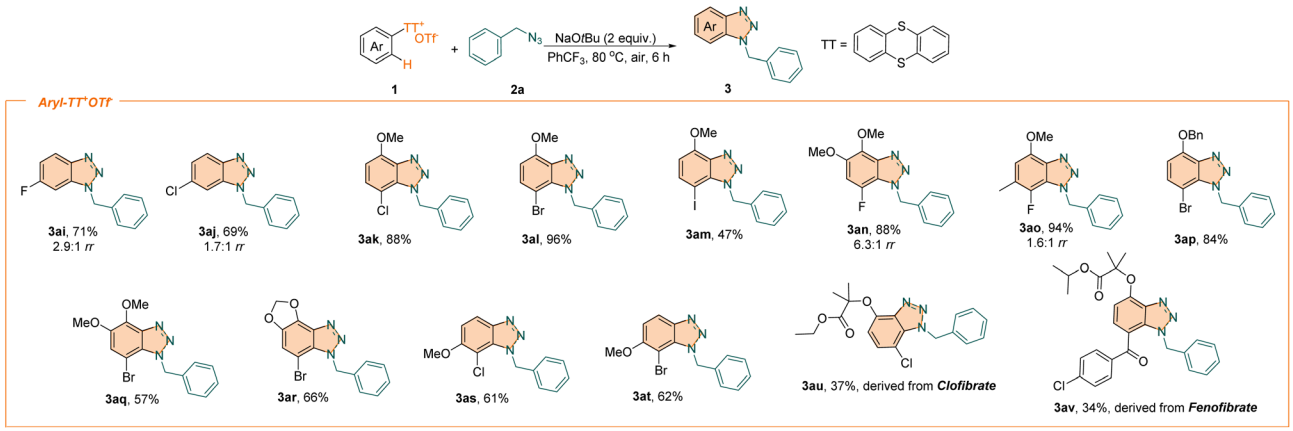


Scheme 2 Scope of azides. Reaction conditions: azides (0.2 mmol), aryl sulfonium salts (0.3 mmol), NaO*t*Bu (0.4 mmol), $PhCF_3$ (2 mL), under air at 80 °C for 6 h. The regioselectivity was determined by ^1H NMR spectroscopy of the isolated product.

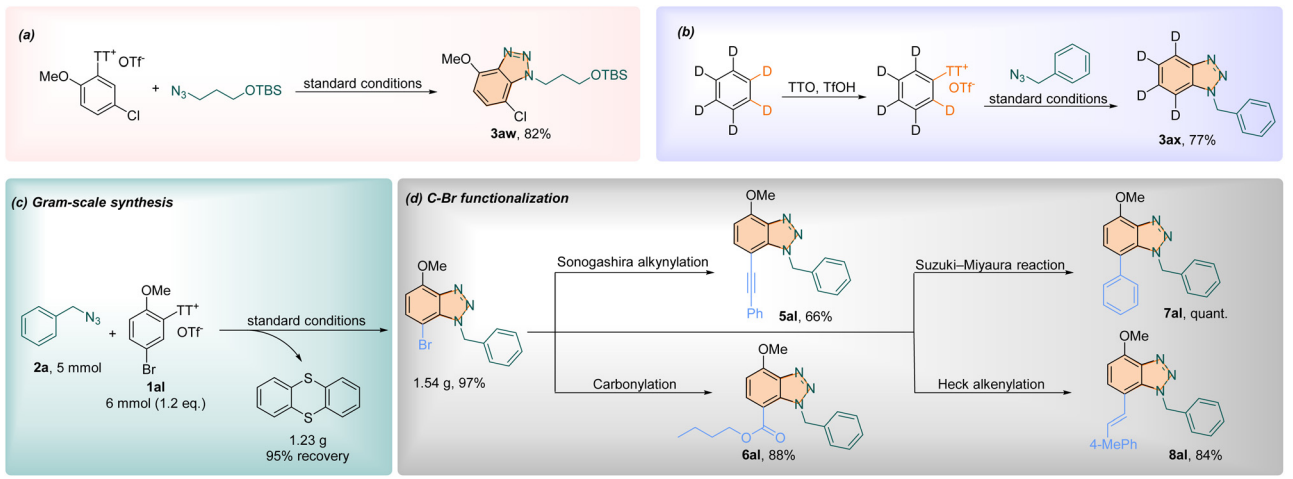
late-stage functionalization of gemfibrozil, a medicine for the treatment of high cholesterol, and the corresponding benzotriazole (**3u**) was obtained in 58% yield. Notably, the method was also applied to the cycloaddition reaction of aryl azides with aryl sulfonium salts which provided the corresponding benzotriazoles in good yields. Aryl azides bearing both electron-donating and electron-withdrawing groups (**3v–3ah**) efficiently participated in the reaction to provide the desired products. Functional groups including halogens (F, Cl, **3aa**, and **3ab**), alkoxy (**3ac**), trifluoromethyl (**3ad**), cyano (**3ae**), and thioether (**3af**) survived this reaction system, and the corresponding benzotriazoles were obtained in high yields. It is noteworthy that perhaps due to the influence of cyanoelectronegativity, benzotriazole **3ae** was obtained with a 4.5 : 1 regioselectivity. Naphthalene was also easily introduced into the product (**3ah**). The effect of steric hindrance on the reaction was not significant, and no detrimental effects on the reactivity of this process were observed when *ortho*-substituted aryl azides (**3y**, **3z**, **3ad**, and **3af**) were tested. It is also worth mentioning that no desired product was detected when benzoyl azide was tested under our standard conditions.

Next, we also investigated the scope of aryl sulfonium salts in this [3 + 2] cycloaddition (Scheme 3). Both mono- and polysubstituted arylsulfonium salts could participate effectively in the reaction and provide the desired products in moderate to excellent yields. It is worth noting that a regioselectivity problem can occur when there is only a single substituent on the aromatic ring; however, this phenomenon is weakened for products with OMe substitution on the aromatic ring. The main reason is that due to the presence of OMe, the *meta*-transition state has the lowest distortion energy and is most easily attacked, thus enabling the formation of a single isomer. Since fluorine and methoxy have similar transition state distortion energies, the products **3an** and **3ao** produced a certain proportion of isomers.[15] The clofibrate and fenofibrate derivatives also efficiently underwent cycloaddition to afford the products **3au** and **3av** in 37% and 34% yields, respectively.

Then, to demonstrate the practicality of our method, the following experiments were performed. *O*-Silylaryl triflates are the most commonly employed aryne precursors and usually require an external fluorine source to activate the substrate, which limits the use of some fluorine-sensitive functional groups. In this reaction, the use of sodium *tert*-butoxide as an activator enabled the fluorine-sensitive silyl group to remain intact and afforded the desired silyl-containing benzotriazole (**3aw**) in good yield. Isotopically labeled molecules are widely used in medicinal chemistry, mainly because isotopically labeled compounds could be used to trace the metabolic process of drugs and to determine the cause of toxicity.[16] This approach allows the formation of deuterated aryl sulfonium salts from simple and readily available benzene-d6, and deuterated benzotriazole was formed under the standard conditions,



Scheme 3 Scope of aryl sulfonium salts. Reaction conditions: azides (0.2 mmol), aryl sulfonium salts (0.3 mmol), NaO*t*Bu (0.4 mmol), $PhCF_3$ (2 mL), under air at 80 °C for 6 h. The regioselectivity was determined by ^1H NMR spectroscopy of the isolated product.



Scheme 4 Synthetic applications.

which has good application prospects. Subsequently, we performed a gram-scale reaction for [3 + 2] cycloaddition, which provided excellent yield and 95% of the thianthrene was recovered even after reducing the amount of aryl sulfonium salt to 1.2 equivalents compared with that of the small-scale process, showing increased potential for large-scale applications. To further expand the product range of benzotriazoles, further functionalization of the obtained product was carried out. Notably, palladium-catalyzed coupling reactions were perfectly applicable to these molecules, and Sonogashira alkynylation, Suzuki–Miyaura coupling, carbonylation, and Heck alkenylation were readily performed (Scheme 4).

Conclusions

In conclusion, we have developed an approach for the [3 + 2] cycloaddition of azides with arynes produced from aryl sulfonium salts *via* C–H deprotonation to provide benzotriazoles. Under mild conditions, a variety of benzotriazoles can be efficiently prepared with outstanding atom economy. Remarkably, this reaction also shows excellent performance in gram-scale reactions and deuterium labeling experiments, which provide potential opportunities for large-scale production, synthesis of biopharmaceuticals and also many other applications.

Author contributions

X.-F. W. conceived and directed the project. X.-W. G. and Y.-H. Z. performed all the experiments. X.-W. G. and X.-F. W. wrote the manuscript and ESI.

Conflicts of interest

There are no conflicts to declare.

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8. Curriculum Vitae

Xing-Wei Gu

Leibniz Institute for Catalysis (LIKAT)

Room 2.204, Albert-Einstein-Str. 29a, 18059 Rostock, Germany

Phone: +49(381)1281-173

Email: Xing-Wei.Gu@catalysis.de

Personals:

Date of birth: 17th February, 1995

Place of birth: Zhejiang, China

Nationality: Chinese

Education:

- ♦ 10/2021 – current Ph.D. candidate, Leibniz Institute for Catalysis, Germany
- ♦ 09/2018 – 06/2021 M.Sc., Hangzhou Normal University, China
- ♦ 09/2014 – 06/2018 B.Sc., Hangzhou Normal University Qianjiang College, China

Awards:

- ♦ Scholarship from China Scholarship Council (2021)
- ♦ National scholarship, Ministry of Education of People's Republic of China (2020)
- ♦ The First Prize Scholarship from Hangzhou Normal University (2019)

Relevant Skills:

- ♦ Organic synthesis, Asymmetric catalysis.
- ♦ Skilled in operation of analytical instruments: GC, GC-MS, HPLC, IR, NMR.
- ♦ Proficient with high-pressure equipment.
- ♦ Skills with MS Office, ChemOffice, SciFinder, Reaxys.

Language Skills:

Mandarin (native), English (fluent), German (basic)

Selected Publications:

1. **X. W. Gu**,[+] Y. Zhang,[+] F. Zhao, H. J. Ai, X. F. Wu. *Chin. J. Catal.* **2023**, 48, 214-223.
2. **X. W. Gu**,[+] A. D. Salvo,[+] R. Mancuso, X. F. Wu. *J. Catal.* **2024**, 429, 115273.
3. **X. W. Gu**,[+] Y. H. Zhao,[+] X. F. Wu. *Green Chem.* **2023**, 25, 6282-6286.
4. **X. W. Gu**, X. F. Wu. *Org. Chem. Front.* **2023**, 10, 1587-1591.
5. Y. H. Zhao,[+] **X. W. Gu**,[+] X. F. Wu. *Org. Chem. Front.* **2024**, 11, 442-447.
6. F. Zhao, **X. W. Gu**, X. F. Wu. *Angew. Chem. Int. Ed.* **2022**, 61, e202214812.
7. F. P. Wu, **X. W. Gu**, H. Q. Geng, X. F. Wu, *Chem. Sci.* **2023**, 14, 2342-2347.

8. H. J. Ai, H. Q. Geng, **X. W. Gu**, X. F. Wu. *ACS Catal.* **2023**, 13, 1310–1315. ([†]equal first author)

9. Selbstständigkeitserklärung

Universität Rostock
Dezernat 1
Referat 1.2

Doktorandinnen/Doktoranden-Erklärung gemäß § 4 Absatz 1 Buchstaben g und h der Promotionsordnung der Mathematisch-Naturwissenschaftlichen Fakultät der Universität Rostock

Name Gu, Xing-Wei .....
(Name, Vorname)

Anschrift Albert-Einstein Str. 29a, 18059, Rostock
.....
(Straße, PLZ, Wohnort)

Ich habe eine Dissertation zum Thema

Development of New Carbonylation Reactions toward Sustainable Synthesis of Aliphatic Carboxylic Acid Derivatives.....

.....

an der Mathematisch-Naturwissenschaftlichen Fakultät der Universität Rostock angefertigt. Dabei wurde ich von Frau/Herrn

Prof. Dr. Xiao-Feng Wu
.....
betreut.

Ich gebe folgende Erklärung ab:

1. Die Gelegenheit zum vorliegenden Promotionsvorhaben ist mir nicht kommerziell vermittelt worden. Insbesondere habe ich keine Organisation eingeschaltet, die gegen Entgelt Betreuerinnen/Betreuer für die Anfertigung von Dissertationen sucht oder die mir obliegenden Pflichten hinsichtlich der Prüfungsleistungen für mich ganz oder teilweise erledigt.

2. Ich versichere hiermit an Eides statt, dass ich die vorliegende Arbeit selbstständig angefertigt und ohne fremde Hilfe verfasst habe. Dazu habe ich keine außer den von mir angegebenen Hilfsmitteln und Quellen verwendet und die den benutzten Werken inhaltlich und wörtlich entnommenen Stellen habe ich als solche kenntlich gemacht.

Rostock, den ....
(Unterschrift)