Communication

Visible-light-Driven External-Reductant-Free Cross-Electrophile Couplings of Tetraalkyl Ammonium Salts

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Supporting Information Placeholder

ABSTRACT: Cross-electrophile couplings between two electrophiles are powerful and economic methods to generate C—C bonds in the presence of stoichiometric external reductants. Herein, we report a novel strategy to realize the first external-reductant-free cross-electrophile coupling via visible-light photoredox catalysis. A variety of tetraalkyl ammonium salts, bearing primary, secondary, and tertiary C—N bonds, undergo selective couplings with aldehydes/ketone and CO_2. Notably, the in situ generated byproduct, trimethylamine, is efficiently utilized as the electron donor. Moreover, this protocol exhibits mild reaction conditions, low catalyst loading, broad substrate scope, good functional group tolerance, and facile scalability. Mechanistic studies indicate that benzyl radicals and anions might be generated as the key intermediates via photocatalysis, providing a new direction for cross-electrophile couplings.

Carbon-carbon bonds formation plays a vital role in producing organic compounds with structural complexity and diversity. Transition metal-catalyzed cross coupling reactions have become one of the most useful and important methods to generate C—C bonds.[1] In order to avoid pre-generation and handling of organometallic reagents, cross-electrophile couplings have been recently well developed through directly using abundant and stable electrophiles, therefore featuring easy operation and high step-economy.[2] However, stoichiometric external reductants are required in such reactions (Figure 1A). Moreover, compared with organohalides, readily available organo pseudohalides are less investigated. Herein, we report the first external reductant-free cross-electrophile couplings of tetraalkyl ammonium salts with aldehydes/ketone and CO_2 via visible-light photoredox catalysis (Figure 1B). Notably, the trimethylamine, in situ generated as the byproduct, is utilized as the electron donor.

The C—N bonds are prevalent in natural products, materials and bioactive molecules. The selective cleavage and functionalization of C—N bonds is highly important but challenging due to the low reactivity and selectivity.[3,4] Stable and highly crystalline organoammonium salts are important substances containing C—N bonds and have been utilized as electrophiles in transition-metal-catalyzed coupling reactions via C—N bond cleavage.[4] In these
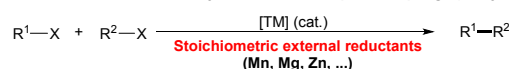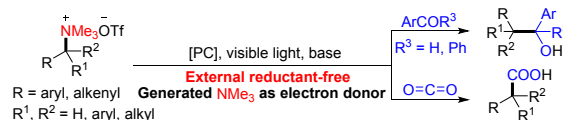
Figure 1. Cross-electrophile couplings. TM = transition metal. PC = photocatalyst.

Figure 2. Catalytic cleavage of C—N bonds in ammonium triflates.

reactions amines are released as byproducts, which have never been reutilized to our knowledge (Figure 2A). Although great progresses have been achieved in C—halogen bond cleavage via visible-light photoredox catalysis[5] with amines as electron donors, there is only one example on visible-light photocatalyzed reductive cleavage of C—N bonds in organoammonium salts.[6a] In principle, we could consider *tetraalkyl ammonium salts as the electrophiles bearing a built-in reductant (amine)*. We hypothesized that the photocatalyzed single electron reduction of tetraalkyl ammonium salts might afford alkyl radicals and release amines, which could act as electron donors to reduce the oxidized or excited photocatalyst (Figure 2B). The generated amine radical cations could be deprotonated by base to give α-amino radicals, which might also act as electron donors. Moreover, the alkyl radicals, such as benzyl radicals, might be further reduced by photocatalyst to give carbon anions, which underwent facile nucleophilic attack to other electrophiles to give the desired cross-electrophile coupling products. If the proof-of-concept is successful, it would provide a mild and economic method to

resolve the long-standing metal hazard issue. However, it is highly challenging to efficiently use the catalytically generated amines in low concentration as the reductants. Moreover, the visible-light photoredox catalysis has rarely been investigated in C—N cleavage.[6]

With these challenges in minds, we started to investigate the cross-electrophile couplings with the air and thermally stable benzyltrimethyl ammonium triflate **1a** as the substrate, which can be easily synthesized in one-step from readily available benzylic amines. As well known, the Barbier-type reaction is one of the most efficient methods to generate alcohols from alkyl halides with carbonyl-containing compounds in the presence of stoichiometric metallic reductants, such as Mg, Sn, In, etc.[7] We wondered whether we could realize visible-light-driven Barbier-type reactions[8] in the absence of external reductants. After systematic screening of the reaction of **1a** with benzaldehyde **2a** (see the Supporting Information (SI) for details), we were delighted to get the desired product **3a** in 70% yield in the absence of external reductant. Control experiments demonstrated that the photocatalyst, base and visible light were indispensable (Table S3). Interestingly, in this reaction we did not detect pinacol-type byproducts through homocoupling of ketyl radical.[9] With the optimized conditions in hand, we investigated the generality of the reaction. As shown in Table 1, aldehydes with either electron-neutral groups (**3b**), electron-donating group (EDG, **3d**), or electron-withdrawing groups (EWGs, **3c**) reacted smoothly to give the desired alcohols in good yields. This cross-electrophile coupling was not sensitive to steric hindrance, as 2-methylbenzaldehyde **2f** reacted smoothly. Besides aldehydes, we were delighted to find benzophenone **2h**, which underwent facile reduction and homocoupling via photocatalysis,[9b,10] was also suitable for this reaction.

Table 1. Visible-light-driven cross-electrophile couplings between 1a and aldehydes/ketone[a]
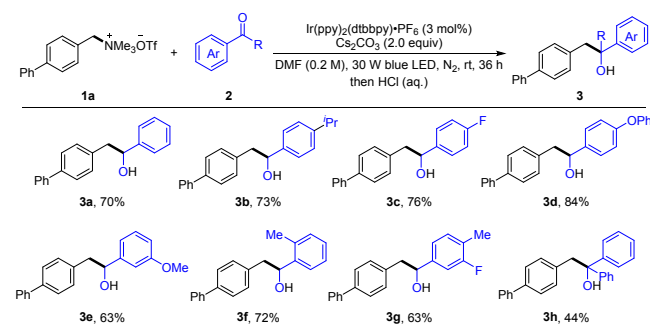

[a]**1a** (0.4 mmol), **2** (0.2 mmol).

Moreover, various ammonium salts were also investigated with 4-fluorobenzaldehyde **2c** due to the importance of fluorine-containing compounds. Gratifyingly, many kinds of functional groups were well tolerated, including CF$_3$ (**3j**, **3o**, **3q**), ester (**3k**, **3p**), OCF$_3$ (**3l**), and thiophene (**3m**). The electron-poor substrates showed better reactivity than those electron-neutral and electron-rich ones, which might arise from the easier single electron reduction of ammonium salts and higher stability of the benzylic anions. Notably, besides primary benzylic C — N bonds, the secondary ones in ammonium salts could also be selectively cleaved to afford alcohols (**3r-3w**) in high yields.

Based on this success, we further considered whether other electrophiles, especially more inert ones, could be applied in such catalytic system. As well-known, CO$_2$ is much less reactive than

Table 2. Visible-light-driven reductive cross-electrophile couplings between ammonium salts and 2c[a]
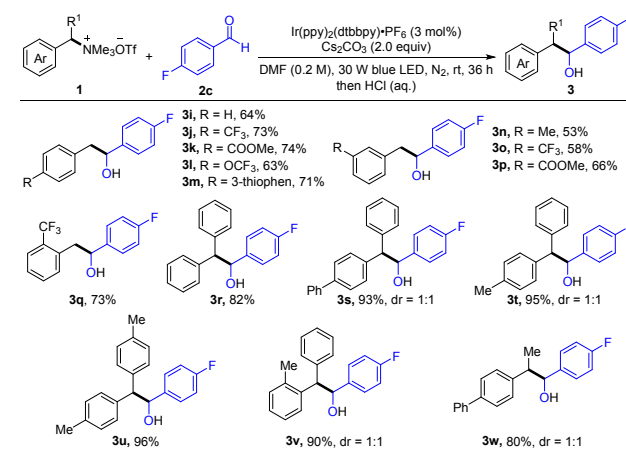

[a]The standard reaction conditions as Table 1.

aldehydes due to its thermodynamic stability and kinetic inertness. However, due to its abundance, nontoxicity and easy availability, CO$_2$ has been utilized as an appealing C1 source to synthesize diverse value-added molecules,[11] including important carboxylic acids.[12] Notably, the catalytic reductive carboxylation of organic (pseudo)halides with CO$_2$ have been developed significantly by many groups[2h,4j,12,13] with the use of external stoichiometric metallic (ZnEt$_2$, Mn, etc.) or organic reductants (amine, Hantzsch ester).

With a slight modification of the reaction conditions, we were delighted to realize the first external reductant-free carboxylations of organic pseudohalides with CO$_2$. Besides **1a**, benzyltriethyl and benzyldimethylisopropyl ammonium triflates also worked well (See Table S8 in SI for details). As shown in Table 3, a variety of ammonium salts with different substituents on the aromatic ring underwent the carboxylation smoothly. Besides the substrates with EWGs (**4d-4h**), those substrates bearing EDGs (**4i**, **4l**, **4r**) also afforded the desired acids in moderate yields. Remarkably, a wide range of functional groups, such as C—F bond (**4d**), CF$_3$ (**4e**, **4p**, **4t**), nitrile (**4f**), ester (**4g**, **4q**) and methoxyl (**4l**, **4r**), were all tolerated well. Moreover, heterocycles, including furan (**4j**), benzofuran (**4v**), benzothiophene (**4w**), and thiophene (**4k**, **4x**), also did not deter the carboxylation. Notably, product **4v** could undergo dearomatization to give 2,3-dihydrobenzofuran, which is an important motif in many bioactive compounds.[14] Importantly, this reaction could be easily scalable, as demonstrated by the gram scale synthesis of **4a** in 68% yield with lower catalyst loading.

**Table 3. Visible-light-driven carboxylation of primary C—N bonds[a]**
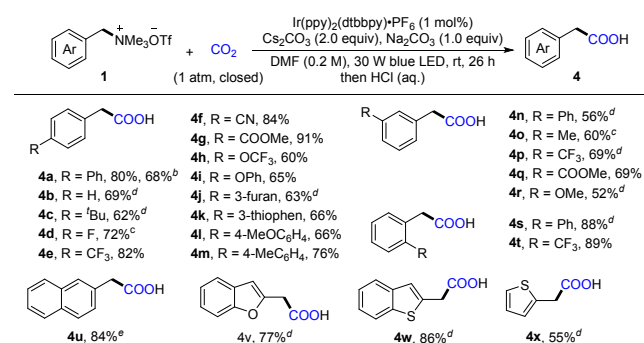
[a]0.2 mmol scale. [b]Gram scale: **1a** (8 mmol), [Ir]-catalyst

(0.5 mol%), Cs_2CO_3 (1.5 equiv), Na_2CO_3 (1.0 equiv), DMF (0.4 M). [c][Ir]-catalyst (3 mol%), Na_2HPO_4 instead of Na_2CO_3, 36 h. [d][Ir]-catalyst (3 mol%), 36 h. [e]12 h, without Na_2CO_3.

The successful carboxylation of primary C—N bonds prompted us to investigate the reactions of secondary and tertiary ones to synthesize α-substituted aryl acetic acids (Table 4). We were pleased to find many α-aryl benzyl ammonium salts reacted well. For example, products **4ac** and **4ad** were obtained in good yields, both of which could further undergo facile amidation to synthesize the antiproliferative and the inhibitors of histone deacetylase.[15] Besides those with α-aryl groups, the substrates with α-alkyl groups (**4ah-4an**) were also successfully subjected to this reaction. Notably, the utility of this method was further demonstrated by generation of important drugs ibuprofen **4ak** and naproxen **4an** in synthetically useful yields. Moreover, starting from the commercially available chiral benzylic amine (>99% ee), we prepared the ammonium salt **1am**, applied it in the standard reaction conditions and obtained racemic product **4am** in 60% yield, which suggested the formation of an achiral intermediate. To our delight, the highly challenging carboxylation of tertiary C—N bonds also worked to give **4ao** in a synthetically useful yield, which represented the first example of carboxylation of tertiary C—N bond. Besides benzyl ammonium triflates, to our delight, this strategy was also amenable to the carboxylation of allylic C—N bond to provide **4ap** in total 71% yield, albeit with low regioselectivity (eq. 1).

**Table 4. Visible-light-driven carboxylation of secondary and tertiary C—N bonds[a]**
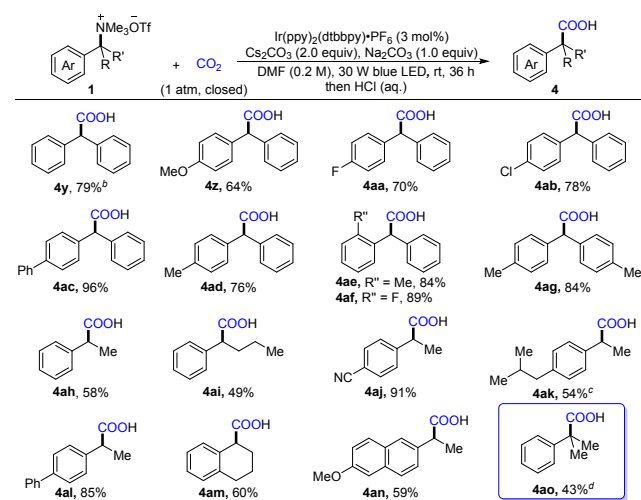
[a]The standard reaction conditions as Table 3 except [Ir]-catalyst (3 mol%), 36 h. [b][Ir]-catalyst (1 mol%), 26 h. [c][Ir]-catalyst (4 mol%). [d]K_2CO_3 instead of Na_2CO_3.
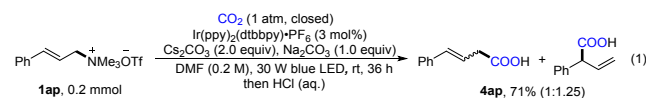
To avoid the isolation of **1a**, we further tested a convenient one-pot reaction of amine **5** with CO_2 in the presence of MeOTf to give **4a** in 63% yield (eq. 2). Notably, the absence of MeOTf led to no conversion.
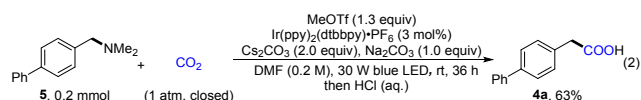
To gain more insight into these cross-electrophile couplings, we did a variety of mechanistic studies (Figure 3). As we detected trace amount of homocoupling byproducts of **1** in some cases, we first tested the effect of 2,2,6,6-tetramethyl-1-piperdinyloxy (TEMPO) to the reactions with benzaldehyde and CO_2, both of which were significantly inhibited (Figure 3A). These results were consistent with above mentioned racemization in the reaction of **1am**, indicating that radicals might be involved. Second, isotope-labeling studies were conducted. No deuterium incorporation was observed when d_7-DMF was used as the solvent. When D_2O was added, up to 97% deuterium incorporation was observed (Figure 3B). These results precluded the hydrogen atom transfer (HAT) with DMF and indicated the formation of benzylic anion intermediate. Furthermore, the reaction of deuterated substrate **1a'** afforded **6a** in 63% yield with 47% deuterium incorporation (Figure 3C). This result is in accordance with the hypothesis (Figure 2B) and indicates that both the deprotonation of amine radical cations by base and protonation of a benzylic anion might happen in the reaction mixture.
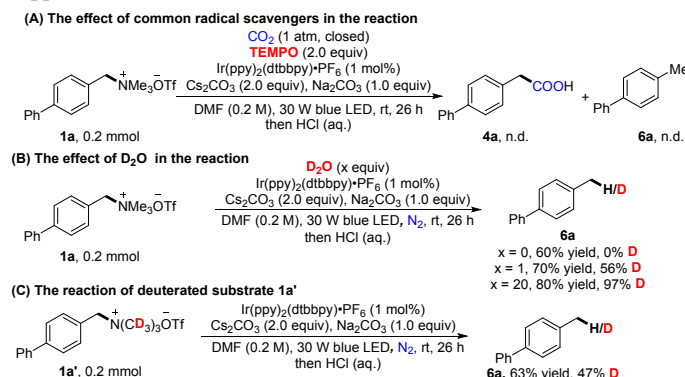
Figure 3. Mechanistic studies.

To illustrate the possibility of NMe_3 as the electron donor, we further did Stern-Volmer luminescence studies and electrochemistry investigation (see the SI for details). The luminescence of $Ir(ppy)_2(dtbbpy) \cdot PF_6$ ($E_P{}^{Red}[Ir^{III}/Ir^{II}] = -1.80$ V vs Ag/Ag^+ in DMF) at $\lambda_{max} = 570$ nm was readily quenched by NEt_3 ($E_P{}^{Ox} = +0.63$ V vs Ag/Ag^+ in DMF) with a slope of 223.5, which was much more significant than ammonium salt **1a** (2.80) and benzaldehyde (1.07). These results suggested that it might also be readily quenched by in situ generated NMe_3 ($E_P{}^{Ox} = +0.65$ V vs Ag/Ag^+ in DMF) from **1a**[16] or α-amino radical ($E_{1/2}{}^{Red} = -1.03$ V vs SCE).[17] Moreover, the benzyl radical ($E_{1/2}{}^{Red} = -1.43$ V vs SCE)[18] might be further reduced by Ir^{II}-catalyst ($E_{1/2}{}^{Red}[Ir^{III}/Ir^{II}] = -1.51$ V vs SCE)[19] to give benzylic carbon anion, which underwent facile nucleophilic attack to aldehydes/ketone or CO_2 to give the corresponding products.[20] At this stage, we preferred such nucleophilic attack process based on the control experiments (See also Table S9 in SI for more details), although we could not exclude other alternative pathways,[21] such as coupling between benzyl radicals and ketyl radicals.[9]

In summary, we have developed the first visible-light-driven external-reductant-free cross-electrophile couplings of tetraalkyl ammonium salts with aldehydes/ketone and CO_2. Importantly, the in situ generated byproduct, NMe_3, might act as the electron donor. A wide range of benzylic C—N bonds, including primary, secondary, and tertiary ones, undergo the reactions smoothly.

These reactions feature mild conditions, low catalyst loading, high selectivity, broad substrate scope, good functional group tolerance and facile generation of important products, including ibuprofen and naproxen. Moreover, one-pot protocol is also realized with high step economy. Mechanistic studies indicate that the alkyl radical and anion might act as the key intermediates in such reactions. Further application of this novel strategy in other external reductant-free cross-electrophile couplings is underway.

ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures, spectral data, and analytical data are available free of charge via the Internet at http://pubs.acs.org.

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Notes
The authors declare no competing financial interests.

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