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Nickel/photoredox-catalyzed carbonylative transformations of α-phosphorus-, α-sulfur-, and α-boron-substituted alkyl halides†

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Organophosphorus compounds are important motifs in living organisms, medicinal chemistry, agricultural chemistry, materials science, catalysts, ligands, *etc.* However, catalytic carbonylative transformation of α-phosphorus, α-sulfur or α-boron substituted alkyl halides remains a formidable challenge due to α-heteroatom effects. In this report, we describe a nickel/photoredox dual-catalytic strategy for the direct amino- and alkoxycarbonylation of α-phosphorus, α-sulfur, and α-boron substituted organohalides with an array of reaction partners under low CO gas pressure which furnished various high-value products in excellent yields. The utility of this process was also demonstrated by the development of a new α-phosphine amide ligand. Additionally, this synergistic protocol also facilitates a sequential four-component carbonylation in the presence of vinyl phosphonate.

Introduction

Phosphorus is one of the essential elements for life and is closely related to living organisms. In addition, organophosphorus compounds are not only important structural motifs of genes, but also widely used in medicinal chemistry, agricultural chemistry, materials science, organic synthesis, and other fields.[1] In particular, β-phosphonyl acids and derivatives, an indispensable class of phosphorus skeletons, are widely utilized as ligands and key intermediates in organometallic species-mediated reactions due to their unique chemical properties.[2] Thus, developing efficient strategies to access β-phosphonyl acids from readily available starting materials remains an important task. One of the most attractive approaches is the use of broadly available carbon monoxide as the C1/carbonyl source toward organophosphorus molecules.

Carbonylation reactions have become indispensable tools for constructing carbonyl-containing compounds in organic and medicinal chemistry as they enable the efficient and robust union of molecular fragments and carbon monoxide.[3] Over the last few decades, multiple generations of catalytic systems have been explored that have elevated the transition metal-catalyzed carbonylation of organohalides to an essential transformation.[4] Compared with mature noble metal catalysts, cheap metal catalysts such as nickel have also been explored successfully by taking advantage of slow CO-releasing reagents and specialized ligand complexes to minimize the generation of highly toxic and low catalytic activity $Ni(CO)_n$.[5] Concerning the substrates applied, aryl,[6] benzylic,[7] and alkyl halides[8] have been relatively well studied, even with nickel catalysts (Fig. 1(a)); however, carbonylative transformations of α-heteroatom substituted organohalides to construct high-value α-heteroatom substituted amides or esters remain less developed, with some examples of α-phosphorus- and α-sulfur-substituted alkyl halides.[9]

α-Heteroatom functionalization is a key and challenging strategy in organic synthesis.[9] However, because of the unique properties (electron cloud density, bond energy, resonance, *etc.*) of heteroatoms, the substituents containing heteroatoms could change the properties and reaction characteristics of the molecules, especially in adjacent positions.[9c,10] In addition, the coordination of π-acidic CO and heteroatoms with metal catalysts might decrease or even inhibit metal catalytic activity.[11] On the other hand, the rate of decarbonylation depends strongly on the nature of substituents, and the α-heteroatoms can effectively stabilize the adjacent carbon radicals, resulting in acyl radicals that tend to decarbonylate to form a stable radical species, especially at lower CO pressures or higher temperatures.[12,13] Additionally, owing to the relatively more polar carbon–halogen bonds, α-heteroatom

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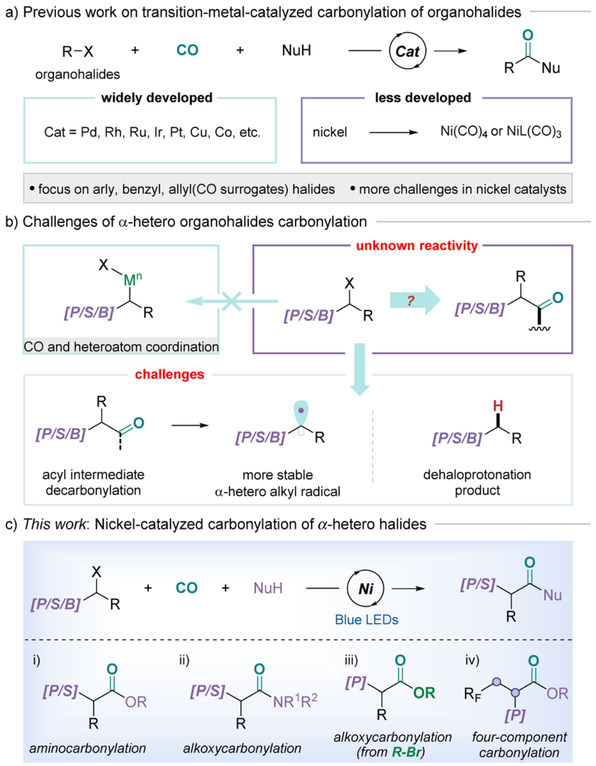
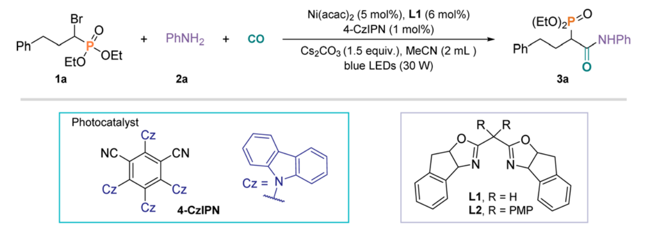


Fig. 1 The background of α-heteroatom halide carbonylation.

Table 1 Investigation of reaction conditions[a]



Entry	Variation from standard conditions	**3a** (%)
1	None	68
2	$NiBr_2$(DME) instead of $Ni(acac)_2$	17
3	$Ni(TMHD)_2$ instead of $Ni(acac)_2$	36
4	**L2** instead of **L1**	20
5	Acr-Mes$^+ClO_4^-$ instead of 4-CzIPN	2
6	*fac*-Ir$(ppy)_3$ instead of 4-CzIPN	59
7	$PhCF_3$ as solvent	62
8	THF, DMAc, DCE as solvent	0–10
9	DiPEA instead of Cs_2CO_3	0
10	1 bar CO instead of 10 bar CO	60
11	1.5 equiv. of **1a** was used	75
12	With 10 mol% KI	93
13	1 bar CO, 1.5 equiv. of **1a**, and 10 mol% KI	82
14[b]	w/o Ni and PC	0
15	w/o PC or Ni or **L1** or Cs_2CO_3 or light	0

[a] Reaction conditions: **1a** (1.2 equiv.), **2a** (0.2 mmol), $Ni(acac)_2$ (5 mol%), **L1** (6 mol%), 4-CzIPN (1 mol%), Cs_2CO_3 (1.5 equiv.), CO (10 bar), MeCN (2 mL), 30 W blue LEDs, 18–25 °C, 24 h, isolated yields. acac = acetylacetone; TMHD = 2,2,6,6-tetramethyl-3,5-heptanedione. [b] 60 bar CO.

substituted alkyl halides can readily undergo dehaloprotonation (Fig. 1(b)). To overcome these challenges, the development of novel and efficient strategies is highly in demand.

Considering the challenges discussed above, we questioned if photoredox catalysis may offer a unique pathway for the carbonylation of α-heteroatom substituted alkyl halides. Synergistic photoredox catalysis and metal catalysis offer a powerful catalytic platform for many challenging organic transformations. Several outstanding studies have shown that pairing a visible-light photocatalyst with a conventional nickel or palladium catalyst can accelerate challenging steps in reactions.[14] Herein, we report the first example of nickel/photoredox dual-catalyzed carbonylation of α-heteroatom substituted alkyl halides with various nucleophiles under low CO pressure, furnishing a series of high-value compounds (Fig. 1(c)). Notably, this catalytic strategy also enables the multicomponent carbonylation of vinyl phosphonate and affords the target compounds in moderate yields and with high selectivity.

Results and discussion

To establish this transformation and explore the optimal conditions, bromophosphate **1a** and aniline **2a** were selected as the model substrates. After a systematic evaluation of all the reaction parameters, the optimized reaction conditions were determined, as summarized in Table 1 (for more details, see the ESI†). Lower yields were obtained with other nickel catalysts than those with $Ni(acac)_2$ (Table 1, entries 2 and 3). The nature of the ligand played an essential role in improving the yield of this reaction, and the bidentate nitrogen ligand **L2** resulted in decreased yield (Table 1, entry 4). Next, Acr-Mes + ClO_4^- made the reaction almost impossible to occur (Table 1, entry 5). When *fac*-Ir$(ppy)_3$ instead of 4-CzIPN was tested, a similar yet slightly diminished reactivity was observed (Table 1, entry 6). Diminished yield or no product was detected when using THF, DMAc, and DCE (the dehaloprotonation product was the main by-product), but $PhCF_3$ could give a good yield (Table 1, entries 7 and 8). Screening of the bases highlighted the significant promotion of this carbonylation by Cs_2CO_3 (Table 1, entry 9). Notably, a good yield was also obtained with only 1 bar CO (Table 1, entries 10 and 14). Further assessment on the amount of bromophosphate indicated that 1.5 equivalents performed the best (Table 1, entry 11). In addition, the best yield of the desired product was observed in the presence of 10 mol% KI (Table 1, entry 12). We hypothesize that the reaction begins with the nucleophilic substitution of bromophosphate **1a** with KI to form the corresponding iodophosphate. The desired product could not be detected under 60 bar CO in the presence of nickel or a photocatalyst (Table 1, entry 14). Experiments without a photocatalyst, nickel catalyst, ligand, Cs_2CO_3, or light failed to produce the desired carbonylated product, implying that all these components are necessary for the reaction to proceed (Table 1, entry 15). It is worthy of mention that easily accessible chiral dioxazole ligands were tested with the idea of introducing a chiral center, but low or no yield of the desired product was obtained without enantioselectivity.

Encouraged by these results, we first investigated the scope of various nucleophiles under the optimized conditions (Fig. 2). Various aromatic amines substituted with an electron-donating group or an electron-withdrawing group were all suitable coupling partners. A variety of substituents including –F (**3d**), –Cl (**3e**), –Br (**3f**), and –CF_3 (**3g**) survived, providing possibilities for further derivatization. The sterically bulky amine **3h** also reacted equally well. In addition, a wide range of strongly nucleophilic alkylamines could be used, including benzylamine (**3m**), butylamine (**3n**), and amantadine (**3o**). Gratifyingly, heterocycle-containing substrates that readily coordinate with metals could successfully participate in this transformation to deliver the corresponding products in good yields (**3p**, **3q**, **3r**, and **3s**). Next, some alcohols were also tested, such as long chain alcohols (**4a**, **4b**, and **4c**), cycloalcohols (**4d** and **4e**), 3-methoxy-1-propanol (**4f**), chiral alcohol (**4g**) and benzyl alcohol (**4h**), giving the target products in moderate to excellent yields. Only a trace amount of the carbonylated product was detected when using sterically bulky *tert*-butanol as the substrate. In addition, phenols, which readily quench radicals, were also suitable substrates for this transformation (**4j**, **4k**, **4l**, and **4m**). However, *tert*-butanol led to only a trace amount of the desired product (**4i**). Subsequently, we turned our attention to challenging nucleophiles. Several alcohols with various sensitive functional groups including trimethylsilyl (–TMS) and halogen atoms (–Cl and –I) were converted into the corresponding products in moderate to good yields (**4n**, **4o**, and **4p**). CD_3OD was successfully converted into the corresponding D-containing product (**4q**) in 69% yield. Notably, the catalytic efficiency was unaffected when substrates with a carbon–carbon double bond (**4r**, **4s**, **4t**, and **4u**) were

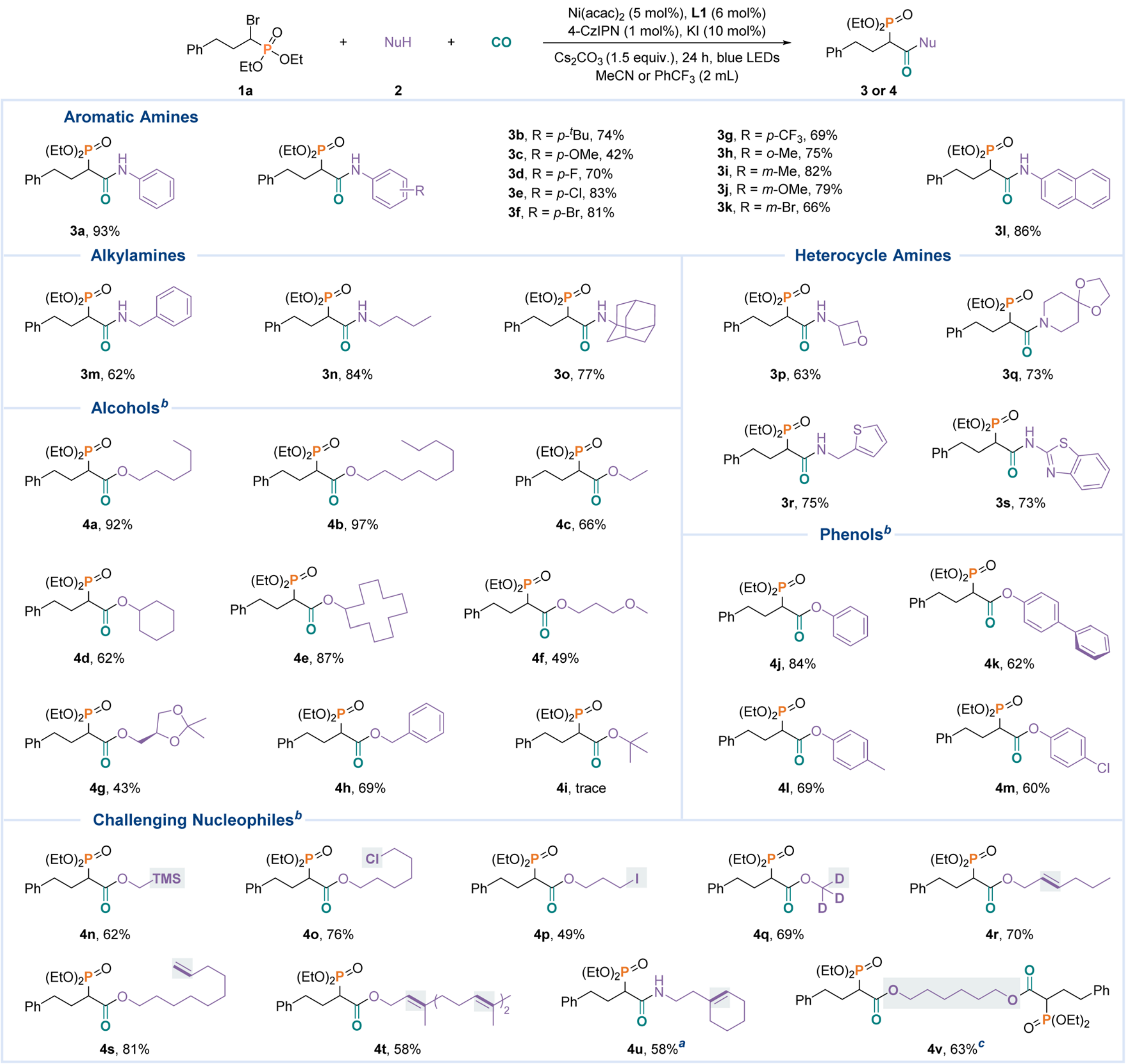


Fig. 2 Substrate scope. [a] Reaction conditions: **1a** (1.2 equiv.), **2** (0.2 mmol), $Ni(acac)_2$ (5 mol%), **L1** (6 mol%), 4-CzIPN (1 mol%), Cs_2CO_3 (1.5 equiv.), KI (10 mol%), CO (10 bar), MeCN (2 mL), 30 W blue LEDs, 18–25 °C, 24 h, isolated yields. [b] $PhCF_3$ (2 mL). [c] **1a** (2.4 equiv.), 1,6-hexanediol (0.2 mmol), $Ni(acac)_2$ (10 mol%), **L1** (12 mol%), 4-CzIPN (2 mol%), Cs_2CO_3 (3 equiv.), KI (20 mol%), CO (10 bar), $PhCF_3$ (3 mL).

used. Finally, we explored the reactivity of diols, and 1,6-hexanediol successfully delivered the diester product in good yield (**4v**). However, no target product could be obtained when thiophenol was used as the nucleophile.

The conditions shown in Table 1 were then used for the transformation of various α-heteroatom substituted halides (Fig. 3). A series of phosphates with different steric hindrance, including diethyl, diisopropyl (**5a**), and dibutyl (**5b**) phosphonates, could be tolerated in this reaction. Other α-alkyl substituents of bromophosphates, such as long chain alkanes (**5d**, **5e**, **5g**, and **5j**), cycloalkane (**5f**), heteroatom substituted alkane (**6h**), and halogen atom substituted alkane (**5i**), could be used in this reaction. However, both internal alkene (**5k**) and terminal alkene (**5l**) were all well tolerated in the transformation. Subsequently, α-bromoalkyldiarylphosphine oxides were successfully employed in this reaction, affording the target products in good to excellent yields (**5m**, **5n**, **5o**, **5p**, **5q**, and **5r**). To demonstrate the practicality of this transformation, several natural products and bioactive molecules were also tested (Fig. 3). Aminoglutethimide (**6a**), sulfalen (**6b**), and amino acid derivatives (**6c** and **6d**) were all suitable substrates. Likewise, geraniol (**6e**), phytol (**6f**), cholesterol (**6g**), menthol (**6h**) diacetonefructose (**6i**), lanosterol (**6j**), and epiandrosterone (**6k**) also reacted smoothly.

Next, we found that various sulfur-containing compounds were also suitable carbonylated substrates (Fig. 4). Good yields were obtained with different functionalized α-bromo sulfone compounds (**7a**, **7b**, **7c**, **7d**, and **7e**). Finally, a carbonylative homologation of halomethylorganoborons, which are also important C1 reagents,[15] was tested in this transformation. However, only acetylation products (**7f** and **7g**) were obtained in good yields, which formed through a base-promoted proto-

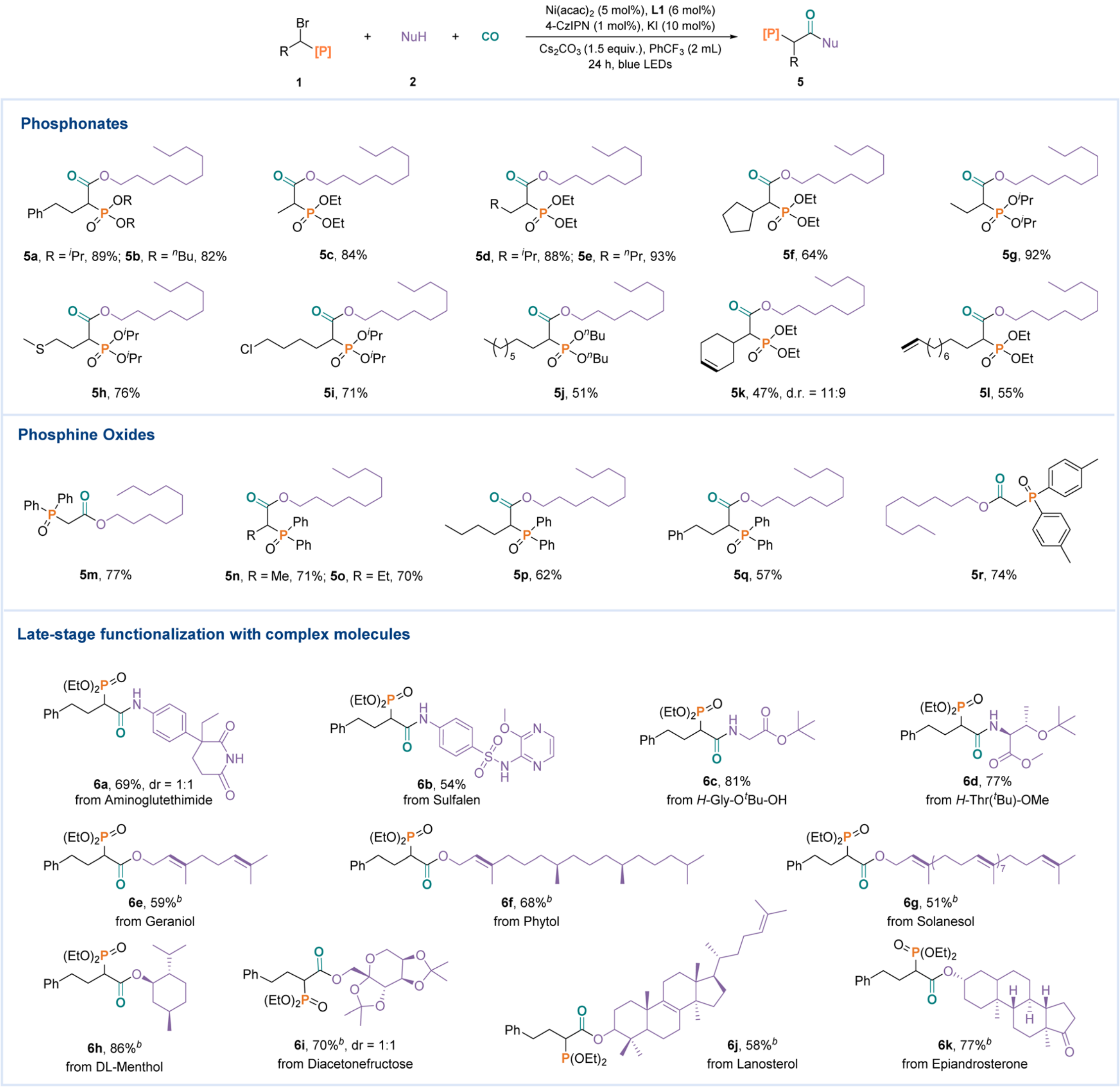


Fig. 3 Substrate scope of α-phosphonates and complex molecules. Reaction conditions: **1a** (1.2 equiv.), **2** (0.2 mmol), Ni(acac)$_2$ (5 mol%), **L1** (6 mol%), 4-CzIPN (1 mol%), Cs$_2$CO$_3$ (1.5 equiv.), KI (10 mol%), CO (10 bar), MeCN (2 mL), 30 W blue LEDs, 18–25 °C, 24 h, isolated yields. ^{a} PhCF$_3$ (2 mL).

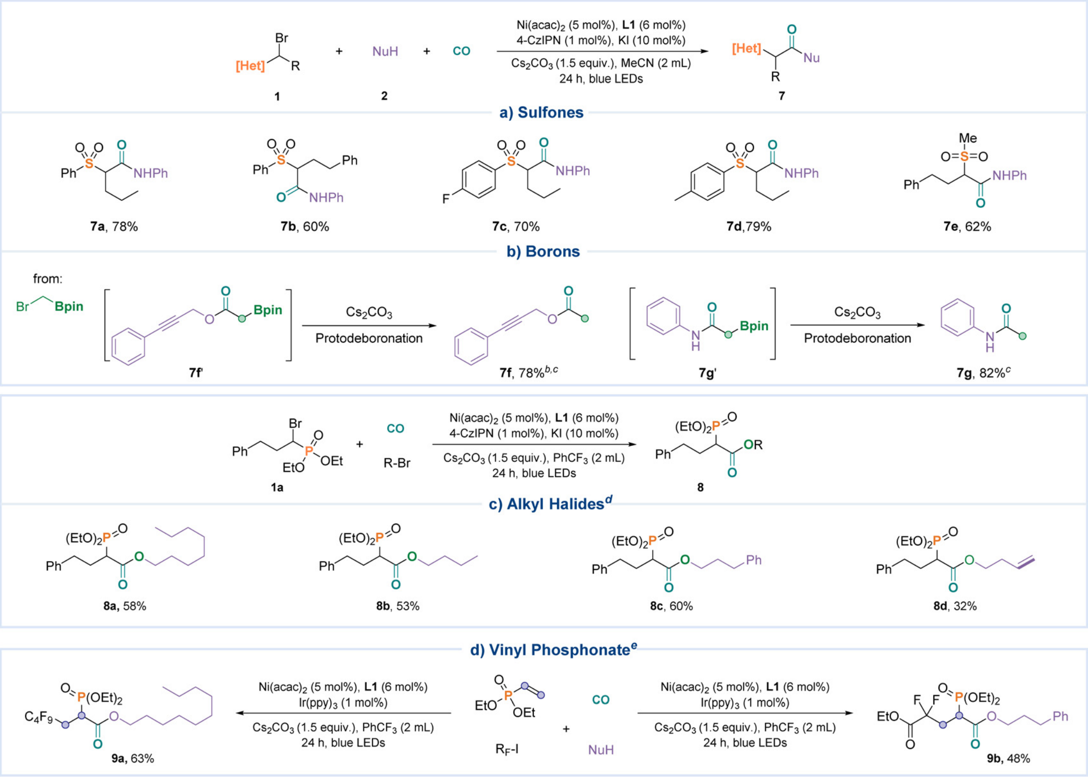


Fig. 4 Testing of reaction diversity. Reaction conditions: **1a** (1.2 equiv.), **2** (0.2 mmol), Ni(acac)$_2$ (5 mol%), **L1** (6 mol%), 4-CzIPN (1 mol%), Cs$_2$CO$_3$ (1.5 equiv.), KI (10 mol%), CO (10 bar), MeCN (2 mL), 30 W blue LEDs, 18–25 °C, 24 h. ^{a} PhCF$_3$ (2 mL). ^{b} Yield reported post-deboronation. ^{c} R-Br (0.2 mmol), Cs$_2$CO$_3$ (3.5 equiv.), PhCF$_3$ (2 mL). ^{d} Vinyl phosphonate (1.5 equiv.), RF-I (2.5 equiv.), PhCF$_3$ (2 mL).

deboronation of the originally produced carbonylative α-acylboron products.[16]

According to the literature, alkyl halides can be converted to the corresponding alcohols *via* oxyanions in the presence of bases.[17] To our delight, we attempted to use alkyl halides instead of alcohols and the corresponding products were delivered in moderate yields (Fig. 4(c); **8a**, **8b**, **8c**, and **8d**). Catalytic carbonylative multicomponent reactions (CMCRs) represent a powerful and efficient strategy for the rapid construction of carbonyl-containing products in a single operation.[18] Notably, a nickel/photoredox dual-catalyzed four-component α-heteroatom carbonylation reaction was also successfully achieved, and the target products were obtained in moderate yields (Fig. 4(d); **9a** and **9b**). In this way, the introduction of three useful fragments of phosphine, carbonyl, and fluorine into one molecule can be achieved.

To demonstrate the practicality and synthetic utility of this methodology, the carbonylation was performed on the 1 mmol scale and the target product **3a** was delivered in 73% yield (Fig. 5(a)). Subsequently, we synthesized the Wittig–Horner reagent *via* a one-step reaction (Fig. 5(b)). Next, we successfully obtained the phosphine ligand **11** in 63% yield through the reduction reaction (Fig. 5(c)). The obtained phosphine ligand is a valuable and potential ligand in organic synthetic chemistry.[19]

Subsequently, to better understand the pathway of this transformation, several control experiments were performed, as presented in Fig. 6. First, radical inhibition experiments were carried out by adding radical scavengers, and the results indicated that the reaction possibly proceeded *via* a radical pathway (Fig. 6(a)). The captured radical intermediate was detected by GC-MS and HRMS. Next, competition experiments between primary and secondary alkyl bromides with aniline were performed, and the primary substrate gave a slightly

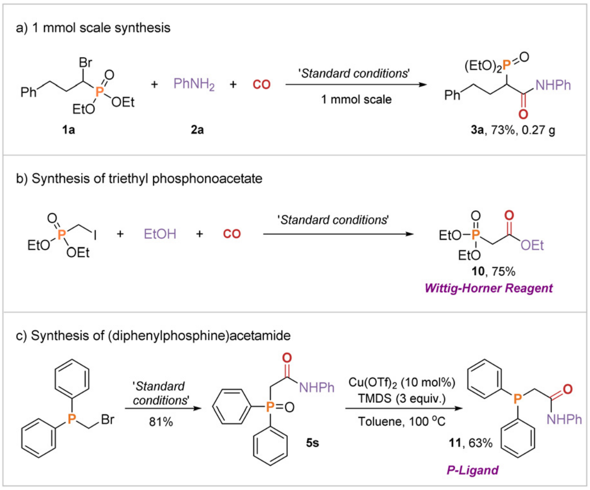
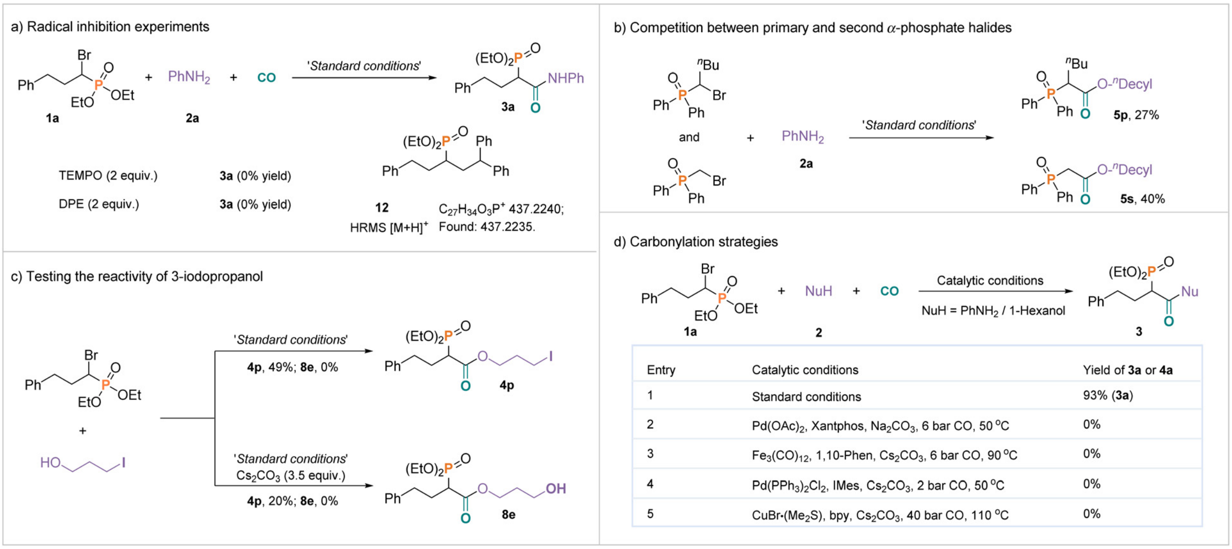


Fig. 5 Synthetic applications.



Entry	Catalytic conditions	Yield of 3a or 4a
1	Standard conditions	93% (3a)
2	$Pd(OAc)_2$, Xantphos, Na_2CO_3, 6 bar CO, 50 °C	0%
3	$Fe_3(CO)_{12}$, 1,10-Phen, Cs_2CO_3, 6 bar CO, 90 °C	0%
4	$Pd(PPh_3)_2Cl_2$, IMes, Cs_2CO_3, 2 bar CO, 50 °C	0%
5	CuBr·(Me_2S), bpy, Cs_2CO_3, 40 bar CO, 110 °C	0%

Fig. 6 Control experiments.

better yield (Fig. 6(b)). In order to test the reactivity of 3-iodopropanol, we carried out the reaction in the presence of 1.5 equivalents and 3.5 equivalents of Cs_2CO_3, respectively, and the corresponding product **8e** was not detected in both cases (Fig. 6(c)). Finally, control experiments were performed to compare the current catalytic conditions with the several previously reported reactions. The developed strategy (Fig. 6(d); entry 1) afforded the desired product in high yields, whereas the previously reported carbonylation protocols (Fig. 6(d); entries 2–5) could not yield the target product (for more details, see the ESI†).

Although elucidation of the detailed mechanism requires further studies, we proposed a possible catalytic pathway for this carbonylation reaction (Fig. 7), based on the above mechanistic studies and related literature.[20] First, blue light irradiation of the photoredox catalyst would generate the excited-state PC*, which will oxidize the NiI species *via* a SET process to generate Ni^{II} species. Subsequently, the α-phosphonate alkyl radical **A** was delivered from α-bromophosphate through a SET reduction process. Then, the α-phosphonate alkyl radical **A** was trapped by CO to give the carbamoyl radical **B**, which was then quickly intercepted by the Ni^{II} species generated above to generate intermediate **D**. Alternatively, the α-phosphonate alkyl radical **A** was intercepted by the Ni^{II} species to afford the alkyl Ni^{III} intermediate **C**, followed by migratory insertion with CO to deliver the same acyl species **D**. Next, the acyl complex **D** reacted with nucleophiles to afford the complex **E**. Finally, reductive elimination of the Ni^{III} complex **E** provided the corresponding product and regenerated the nickel(I) complex for the next catalytic cycle.

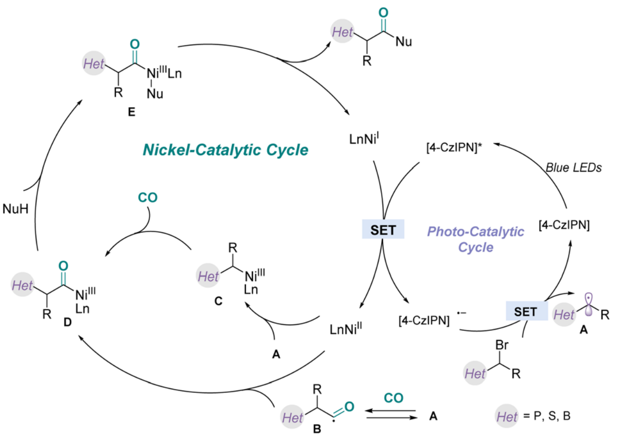


Fig. 7 Proposed mechanism.

Conclusions

In summary, we have identified a novel dual nickel/photoredox catalyzed direct amino- and alkoxycarbonylation of α-heteroatom substituted organohalides. The fundamental challenges posed by α-heteroatom effects, including decarbonylation, difficult oxidative addition, nucleophilic substitution, and reduction, can be circumvented by using the current nickel/photoredox catalyzed radical pathway. A variety of α-heteroatom substituted organohalides, including α-phosphorus, α-sulfur, and α-boron, reacted with amines, alcohols, phenols, and alkyl halides to deliver various α-heteroatom substituted amides and esters in excellent yields under mild conditions. In addition, a four-component carbonylation of vinyl phosphonate was also developed.

Author contributions

X.-F. W. conceived and directed the project. L.-C. W. performed all the experiments. L.-C. W. and X.-F. W. wrote and revised the manuscript and the ESI.†

Conflicts of interest

There are no conflicts to declare.

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