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Advanced Synthesis & Catalysis

Phosphorylation of Glycine Derivatives *via* Copper(I)-Catalyzed C*sp*^{3}–H Bond Functionalization

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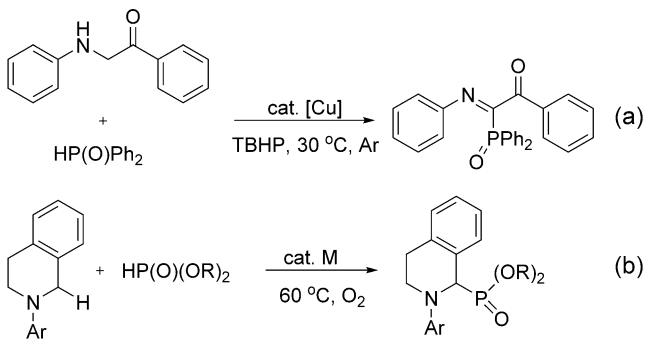
Abstract: A simple and efficient one-pot approach has been developed for a copper-catalyzed phosphorylation of glycine derivatives under air and at room temperature. The present cross-dehydrogenative coupling allows various methoxyphenyl-protected glycine derivatives to be phosphorylated using diverse alkyl and aryl phosphites through an oxidative coupling between C*sp*^{3}–H and P–H bonds catalyzed by copper iodide. This method provides a new synthetic tool to obtain biologically active α-aminophosphonates.

Keywords: aminophosphonates; copper; glycine derivatives; organophosphorus compounds; phosphorylation

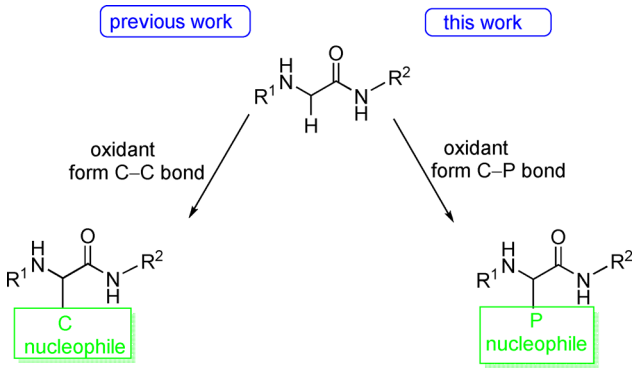
Organophosphorus compounds have received much interest because of their broad applications in the fields of pharmaceuticals[1] and agrochemicals.[2] They effectively show antibacterial,[3] antifungal,[4] enzyme inhibitory[5] and catalytic antibody activities.[6] They are also widely used for organic synthesis,[7] most notably in Horner–Wadsworth–Emmons and Wittig-type reactions,[8] and also exhibit high triplet energy characteristics making them suitable host materials for phosphorescent organic light-emitting diodes.[9] Because of the importance of organophosphorus compounds, there is a continuing demand for the development of new synthetic tools forming C*sp*–P,[10] C*sp*^{2}–P[11] and C*sp*^{3}–P[12] bonds. Among these, the selective phosphorylation of the relatively unreactive C*sp*^{3}–H bond is an attractive pathway to explore in order to introduce a phosphorus moiety in saturated organic compounds. Yang[13] previously reported a copper-catalyzed phosphinylation of α-amino carbonyl compounds to afford imidoylphosphonates in nitromethane [Scheme 1, Eq. (a)]. On the other hand, the Li group[14] also reported the C–H/P–H oxidative coupling between *N*-phenyltetrahydroisoquinoline compounds and dialkyl phosphites [Scheme 1, Eq. (b)].

Recently, development of the cross-dehydrogenative coupling (CDC) reaction[15] has allowed the C–H functionalization of amino acids and short-chain peptides at the N-terminus effectively (Scheme 2).[16] Direct phosphorylation of glycine derivatives *via* C–H/P–H cross-dehydrogenative coupling with phosphine will potentially provide a convenient method to generate diverse organophosphorus compounds for biomedical applications. However, to the best of our knowledge, no example of phosphorylation of glycine derivatives has ever been reported. Herein, we report a novel *phosphorylation of glycine derivatives via copper(I)-catalyzed C*sp^3*–H bond functionalization* (Scheme 2).

To optimize the experimental conditions, we chose a model coupling reaction between *N*-PMP (*p*-me-



Scheme 1. Methods for phosphorylation of the C*sp*^{3}–H bond.



Scheme 2. Functionalization of glycine derivatives.

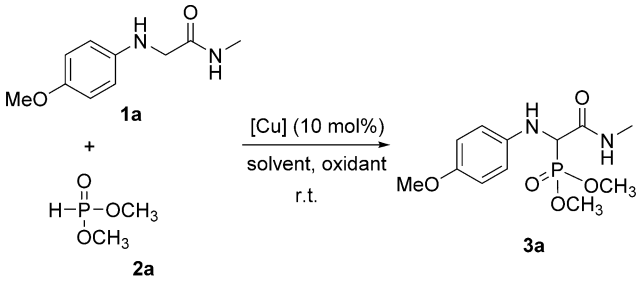
thoxyphenyl)glycine amide derivatives **1a** (as amine substrates) and dimethyl phosphonate **2a** (as pro-nucleophile). Interestingly, most of the oxidants (Table 1, entries 1–7) and copper salts (Table 1, entries 8–16) investigated were not effective for this reaction. The combination of CuI as catalyst and TBHP as oxidant provided the desired product in high (92%) yield (Table 1, entries 17–19). Water could also be used as solvent for the reaction, albeit resulting in a 34% yield (Table 1, entry 20). Examination of solvent effects showed that DCE was the best solvent and gave a 98% yield of the corresponding product (Table 1, entry 21). Notably, the reaction could also proceed at room temperature under air atmosphere with CuI as catalyst and TBHP as oxidant (Table 1, entries 22–28).

Under the optimized conditions, the new method to generate C*sp*^{3}–P bonds was found to be effective for a number of different phosphonates. Excellent yields were achieved using diethyl phosphite (**2b**) (Table 2, entry 2), diisopropyl phosphite (**2c**) (Table 2, entry 3) and dibenzyl phosphite (**2e**) (Table 2, entry 5) respectively. However, only a moderate 51% yield was obtained when diphenyl phosphite (**2d**) (Table 2, entry 4) was applied (Table 2, entries 8, 10, 18, and 20), which we attributed to steric effects.

Then, various glycine derivatives were coupled with dialkyl phosphites under the optimized conditions (Table 2). Secondary amides all afforded the corresponding products effectively. For example, methyl-substituted (**1a**, **1b**, Table 2, entries 1–6), phenyl-*n*-propyl-substituted (**1c**, Table 2, entrie 7–9) *n*-butyl-substituted (**1d**, Table 2, entries 10–14), phenyl-*n*-butyl-substituted (**1e**, Table 2, entries 15–19) and *n*-octyl-substituted (**1f**, Table 2, entries 20–22) all reacted well to give the corresponding phosphorylated products. When a tertiary amide **1h** or an ethyl ester **1i** (Table 2, entries 23 and 24) was used, the reaction did not proceed at all under the current conditions. The reaction of **1j** (Table 2, entry 25) gave a mixture of unidentified compounds. These results show that the substituents on the amine play a significant role in the success of the reaction. We hypothesize that R^1 plays a dual role in the reaction, possibly both by decreasing the oxidation potential of the substrate and by stabilizing the generated reaction intermediate.

The aryl protecting group on the amine of the glycine derivatives also plays an important role in both the phosphorylation reaction as well as in the poten-

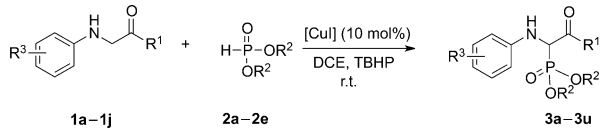
Table 1. Copper-catalyzed phosphorylation of N-PMP (*p*-methoxyphenyl) glycine amide derivative.[a]



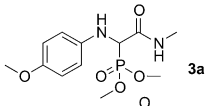
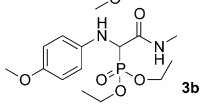
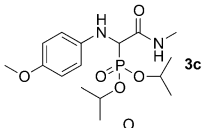
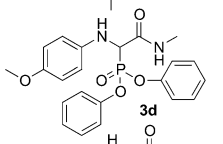
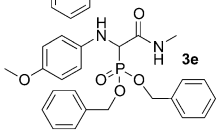
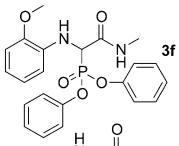
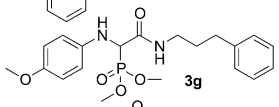
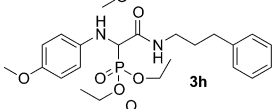
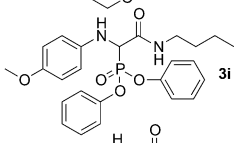
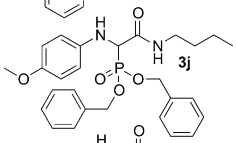
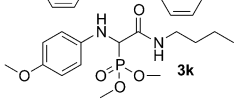
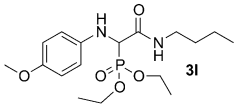
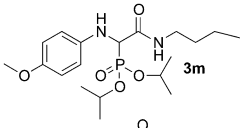
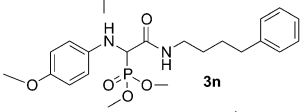
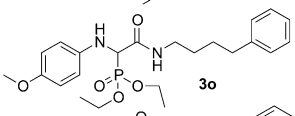
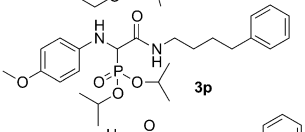
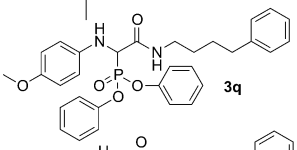
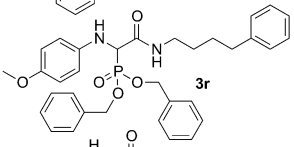
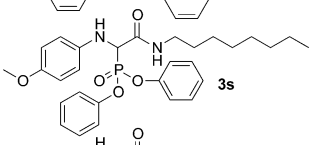
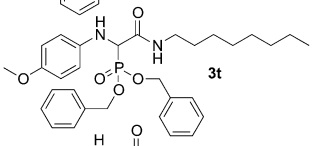
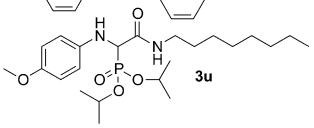
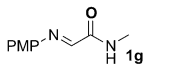
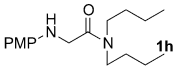
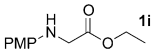
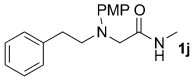
Entry	Catalyst	Oxidant	Solvent	Yield [%][b]
1	CuBr	TBHP in water	DCM	12[c,e]
2	CuBr	TBHP in decane	DCM	48[c,e]
3	CuBr	*tert*-butyl peroxide	DCM	15[c,e]
4	CuBr	dicumyl peroxide	DCM	6[c,e]
5	CuBr	MCPBA	DCM	0[c,e]
6	CuBr	benzoyl peroxide	DCM	0[c,e]
7	CuBr	TBHP	DCM	46[c,e]
8	CuBr	TBHP	DCM	48[d,e]
9	$CuBr_2$	TBHP	DCM	44[c,e]
10	$CuBr_2$	TBHP	DCM	50[d,e]
11	CuCl	TBHP	DCM	6[d,e]
12	$CuCl_2$	TBHP	DCM	0[d,e]
13	$Cu(Ac)_2$	TBHP	DCM	3[d,e]
14	CuO	TBHP	DCM	7[d,e]
15	Cu_2O	TBHP	DCM	5[d,e]
16	CuF_2	TBHP	DCM	1[d,e]
17	CuI	TBHP	DCM	74[c,f]
18	CuI	TBHP	DCM	76[d,f]
19	CuI	TBHP	DCM	92[d,e]
20	CuI	TBHP	H_2O	34[d,e]
21	CuI	TBHP	DCE	98[d,e]
22	CuI	TBHP	MeOH	0[d,e]
23	CuI	TBHP	CH_3CN	45[d,e]
24	CuI	TBHP	THF	23[d,e]
25	CuI	TBHP	EtOAc	20[d,e]
26	CuI	TBHP	dioxane	45[d,e]
27	CuI	TBHP	hexane	4[d,e]
28	CuI	TBHP	toluene	23[d,e]

[a] *Reaction conditions:* glycine derivative (0.30 mmol), dialkyl phosphite (0.90 mmol), TBHP (54 μL, 5–6 M in nonane otherwise mentioned), catalyst (0.03 mmol), solvent (0.5 mL).
[b] NMR yields using an internal standard.
[c] Under N_2.
[d] Under air.
[e] For 19 h.
[f] For 12 h.

Table 2. Scope of glycine amide derivatives.[a]



1a–1j 2a–2e 3a–3u

Entry	1	2	Product	Yield [%][b]
1	1a	2a	 3a	94 (98)
2	1a	2b	 3b	84 (89)
3	1a	2c	 3c	78 (82)
4	1a	2d	 3d	45 (51)
5	1a	2e	 3e	77 (85)
6	1b	2d	 3f	84 (92)
7	1c	2a	 3g	84 (87)
8	1c	2b	 3h	74 (79)
9	1d	2d	 3i	44 (56)
10	1d	2e	 3j	84 (88)
11	1d	2a	 3k	80 (88)
12	1d	2b	 3l	70 (78)
13	1d	2c	 3m	50(60)
14	1e	2a	 3n	84 (89)
15	1e	2b	 3o	74 (79)
16	1e	2c	 3p	44 (59)
17	1e	2d	 3q	45 (56)
18	1e	2e	 3r	82 (87)
19	1f	2d	 3s	54 (58)
20	1f	2e	 3t	74 (80)
21	1f	2c	 3u	54 (61)
22	 1g	2a	3a	98 (94)
23	 1h	2a	NR	
24	 1i	2a	NR	
25	 1j	2a	NR	

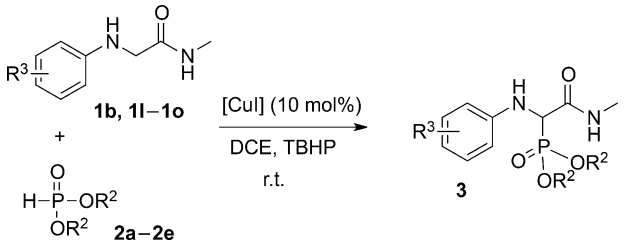
[a] *Reaction conditions:* glycine derivative (0.30 mmol), dialkyl phosphite (0.90 mmol), TBHP (54 μL, 5–6 M in nonane), catalyst (0.03 mmol), solvent (0.5 mL), under air for 19 h.

[b] Isolated yields are based on amines, and NMR yields using an internal standard are given in parentheses.

tial further structural modifications performed for biological applications. An easily removable aryl group will offer a ready access to the free amine. There is a wide variety of aryl-based amine protecting groups, such as the alkylphenyl, the halophenyl, and the phenyl groups. Therefore in order to investigate the influence of the amine protecting group on the reaction, various protected glycine amide derivatives were synthesized and examined under the optimized reaction conditions with dimethyl phosphonate or diphenyl phosphite (Table 3, entries 8–10). However, no desired coupling product was found with those substrates, illustrating the decisive effect of the N-PMP group on the phosphorylation reaction.

Nevertheless, the desired product was also obtained in good yield (92%) when (*o*-methoxyphenyl) glycine amide derivative **1b** was employed in place of (*p*-methoxyphenyl) glycine amide derivative to react with **2d** (Table 2, entry 6) under the same conditions. Surprisingly, the conditions were not applicable to phosphonites **2a**, **2b**, **2c** and **2e**. We postulated that **1b** could easily form a stable five-membered ring *via* the coordination with the Cu catalyst, thus slowing down the reaction rate (Figure 1). To overcome this issue, we decided to perform the reaction with a preformed chelated Cu-complex. Di(2-pyridyl) ketone was our first choice of ligand as it was previously shown to be efficient for a number of oxidative couplings;[17] unfortunately, no desired product was observed under these conditions for the present reaction (Table 3, entries 1–5). The results illustrated that diphenyl phosphite endows better nucleophilic ability than dialkyl phosphites, thus allowing a more effective coupling reaction. Finally, (*m*-methoxyphenyl) glycine amide and other glycine derivatives **1l–1o** could not react with **2a–2e** at all (Table 3, entries 6 and 7).

Table 3. Examination of various protecting groups.[a]



Entry	**1**/R_3	**2**	Di(2-pyridyl) ketone	**3**/Yield [%][b]
1	**1b**/*o*-OCH_3	**2d**	–	**3f**/84 (92)
2	**1b**/*o*-OCH_3	**2a**	0.2 mmol	NR
3	**1b**/*o*-OCH_3	**2b**	0.2 mmol	NR
4	**1b**/*o*-OCH_3	**2c**	0.2 mmol	NR
5	**1b**/*o*-OCH_3	**2e**	0.2 mmol	NR
6	**1l**/*m*-OCH_3	**2d**	–	NR
7	**1l**/*m*-OCH_3	**2a**	–	NR
8	**1m**/*p*-CH_3	**2a**	–	NR
9	**1n**/*p*-Br	**2a**	–	NR
10	**1o**/H	**2a**	–	NR

[a] *Reaction conditions:* glycine derivative (0.30 mmol), dialkyl phosphite (0.90 mmol), TBHP (54 μL, 5–6 M in nonane), CuI (0.03 mmol), DCE (0.5 mL).

[b] Isolated yields are based on amines, and ^{1}H NMR yields using an internal standard are given in parentheses. NR = no reaction.

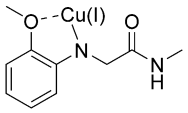
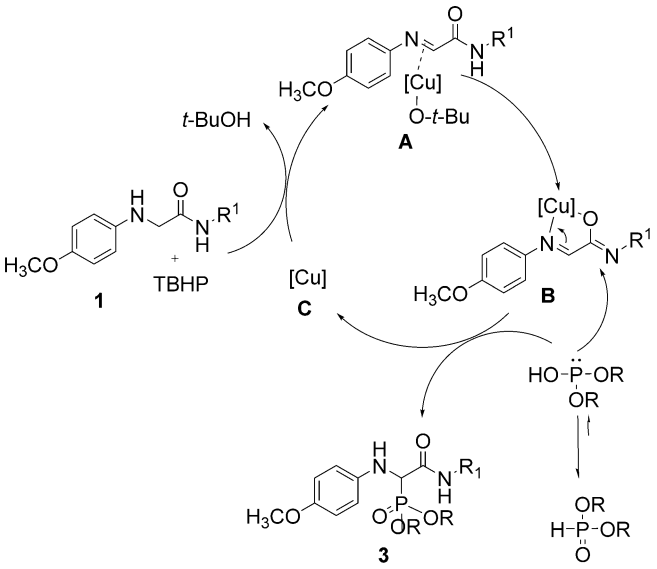


Figure 1. Chelation and deactivation of the glycine amide derivative **1b** with copper.

A tentative mechanism for this phosphorylation reaction is proposed with the generation of an iminol intermediate (Scheme 3). First of all, the imino amide intermediate **A** was produced *via* the reaction of starting material **1** with TBHP catalyzed by CuI. Then, isomerization and chelation generated intermediate **B**. The more nucleophilic phosphite form, in equilibrium with the phosphonate reagent, will finally attack intermediate **B** to provide the product **3** and regenerate the active copper catalyst.

In summary, an efficient formal C–H phosphorylation of glycine derivatives *via* a copper-catalyzed CDC with various phosphonates has been developed. This new method provides a simple approach to synthesize biologically important α-aminophosphonates from readily available glycine derivatives. The scope, mechanism and application of this phosphorylation are currently under investigation.



Scheme 3. Proposed mechanism for the phosphorylation of glycine derivatives.

Experimental Section

Typical Procedure

Dimethyl phosphite **2a** (0.9 mmol), glycine amide **1a** (58.2 mg, 0.3 mmol) and CuI (5.7 mg, 0.03 mmol) were mixed in DCE (0.5 mL). The solution was stirred at room temperature for 1 min, followed by the addition of TBHP (54 μL, 5–6 M in decane). The test tube was capped and the mixture was stirred at room temperature for 19 h. Then the reaction mixture was filtered through a small pad of silica gel and concentrated under vacuum. Flash column chromatography on silica gel using ethyl acetate/hexanes (1:3) furnished the final coupling product **3a** as a white solid; yield: 85.2 mg (94%).

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6 Phosphorylation of Glycine Derivatives *via* Copper(I)-Catalyzed Csp^3–H Bond Functionalization

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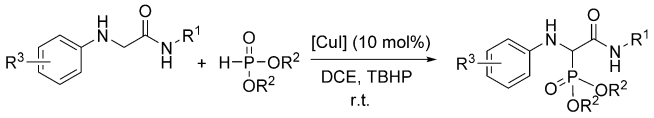

R^1 = Me, Bu, $(CH_2)_3Ph$, $(CH_2)_4Ph$, *n*-octyl
R^2 = Me, Et, *i*-Pr, Ph, Bn
R^3 = *o*-OMe, *p*-OMe

21 examples; 51–98% yields