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A Mild, Selective Copper-Catalyzed Oxidative Phosphonation of α-Amino Ketones

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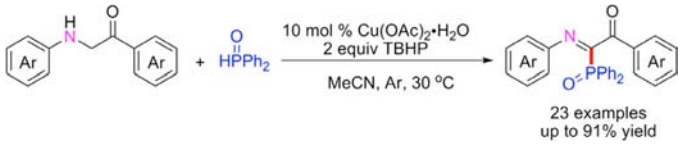
ABSTRACT



A novel and selective method of simple copper-salt catalyzed phosphonation of α-amino carbonyl compounds to afford imidoylphosphonates is reported. This reaction system has a broad reaction scope. The convenient and environmentally benign process makes this protocol very attractive.

Organic phosphorus compounds are widely present in organic synthesis blocks, pharmaceutical chemicals, and phosphine-containing ligands.[1] Therefore, the development of more concise and efficient methods to build the C−P bond is always highly desirable and presents a challenge to researchers in organic chemistry. Recently, direct C−H bond cleavage has offered one of the most straightforward and efficient pathways for C−P bond construction.[2] In particular, oxidative cross-coupling and CDC (catalytic dehydrogenative cross-coupling) reactions have attracted great attention for excellent atom economy and an environmentally friendly approach.[3] In the past decades, Li and other groups have made significant progress and developed various functionalizations of the C−H bond adjacent to nitrogen by employing different nucleophiles.[4] Several groups have also performed phosphonation of sp^3 C−H bonds of tertiary amines to afford α-aminophosphonates (**a**, Scheme 1).[5,2b] The unveiling of new organophosphorus transformations has dominated our interests.[6] Herein, we disclose a novel reaction of copper-catalyzed oxidative phosphonation of α-amino ketones for the synthesis of imidoylphosphonates by two oxidative dehydrogenation processes (**b**, Scheme 1). Compared to hexahydropyridine and pyrrolidine derivatives, α-amino ketones possess a more universal appeal given their extensive applications. Very recently, Li and co-workers reported a copper-catalyzed C−H oxidative/cross-coupling of α-amino carbonyls with

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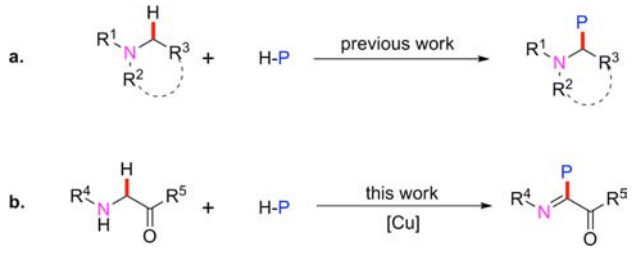
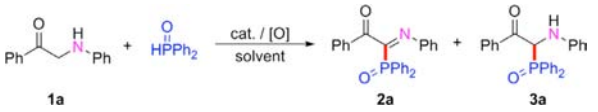
indoles to furnish 2-(1*H*-indol-3-yl)-2-iminocarbonyls and 2-(1*H*-indol-3-yl)-2-oxocarbonyls selectively.[7] To the best of our knowledge, transition-metal-catalyzed α-phosphonation of secondary amines leading to imidoylphosphonates has not been reported. Compounds containing the imidoylphosphonate structure are very important units in organic synthesis and metal−ligand design.[8]

Scheme 1. C−P Bond Formation Adjacent to a Nitrogen Atom



Our initial study began with 1-phenyl-2-(phenylamino)-ethanone (**1a**) and diphenylphosphine oxide in the presence of 10 mol % $Cu(OAc)_2 \cdot H_2O$ and 2.0 equiv of TBHP in CH_2Cl_2 under an argon atmosphere (Table 1, entry 1). To our delight, the reaction occurred, but the product was obtained with a mixture of 2-(diphenylphosphoryl)-1-phenyl-2-(phenylimino)ethanone (**2a**) and 2-(diphenylphosphoryl)-1-phenyl-2-(phenylamino)ethanone (**3a**), and the ratio of **2a/3a** was 1:1. Encouraged by this result, our further optimization of the reaction conditions focused on producing a single product. The reaction underwent various solvent screenings before a single product **2a** was acquired in DMSO or MeCN in 61% and 82% yields (entries 2−5). Furthermore, replacing the TBHP with other oxidants such as $K_2S_2O_8$ and $(t\text{-BuO})_2$ resulted in both lower yields and a lower ratio of **2a/3a** (entries 6 and 7). We also found that a reduction or an increase in the amount of TBHP resulted in a lower yield or a poor ratio of **2a**/**3a** (entries 8 and 9). Remarkably, the equivalent of diphenylphosphine oxide in the reaction is crucial to the ratio of **2a/**

Table 1. Screening for Optimal Reaction Conditions[a,b]



entry	cat. (mol %)	oxidant (equiv)	solvent	product (%)	**2a**:**3a**[c]
1	$Cu(OAc)_2 \cdot H_2O$ (10)	TBHP (2.0)	CH_2Cl_2	58	1:1
2	$Cu(OAc)_2 \cdot H_2O$ (10)	TBHP (2.0)	toluene	trace	
3	$Cu(OAc)_2 \cdot H_2O$ (10)	TBHP (2.0)	$ClCH_2CH_2Cl$	30	10:1
4	$Cu(OAc)_2 \cdot H_2O$ (10)	TBHP (2.0)	DMSO	61	>99:1[d]
5	$Cu(OAc)_2 \cdot H_2O$ (10)	TBHP (2.0)	MeCN	82	>99:1
6	$Cu(OAc)_2 \cdot H_2O$ (10)	$K_2S_2O_8$ (2.0)	MeCN	39	1:1
7	$Cu(OAc)_2 \cdot H_2O$ (10)	$(t\text{-BuO})_2$ (2.0)	MeCN	trace	
8	$Cu(OAc)_2 \cdot H_2O$ (10)	TBHP (1.5)	MeCN	55	6:1
9	$Cu(OAc)_2 \cdot H_2O$ (10)	TBHP (2.5)	MeCN	79	>99:1
10[e]	$Cu(OAc)_2 \cdot H_2O$ (10)	TBHP (2.0)	MeCN	71	>99:1
11[f]	$Cu(OAc)_2 \cdot H_2O$ (10)	TBHP (2.0)	MeCN	83	1:1
12	$Cu(OAc)_2 \cdot H_2O$ (15)	TBHP (2.0)	MeCN	82	35:1
13	$Cu(OAc)_2 \cdot H_2O$ (5)	TBHP (2.0)	MeCN	83	50:1
14[g]	$Cu(OAc)_2 \cdot H_2O$ (10)	TBHP (2.0)	MeCN	85	>99:1
15[h]	$Cu(OAc)_2 \cdot H_2O$ (10)	TBHP (2.0)	MeCN	84	>99:1
16	CuCl (10)	TBHP (2.0)	MeCN	34	6:1
17	$Cu(OAc)_2$ (10)	TBHP (2.0)	MeCN	78	17:1
18	CuI (10)	TBHP (2.0)	MeCN	49	>99:1
19	$Cu(OTf)_2$ (10)	TBHP (2.0)	MeCN	43	>99:1

[a] Reaction conditions: **1a** (0.2 mmol), $H(O)PPh_2$ (0.3 mmol), catalyst (10 mol %) TBHP (5−6 M in decane), and solvent (2.0 mL) under Ar for 16 h at 30 °C. [b] Isolated yields. [c] Determined by ^{31}P NMR. [d] **3a** was not detectable by ^{31}P NMR. [e] 1.2 equiv of $H(O)PPh_2$. [f] 2.0 equiv of $H(O)PPh_2$. [g] MeCN (3 mL). [h] MeCN (4 mL).

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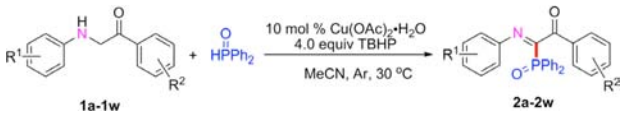
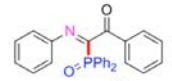
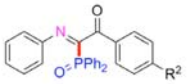
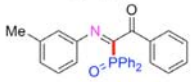
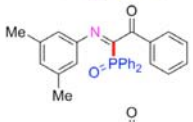
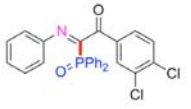
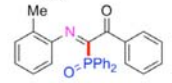
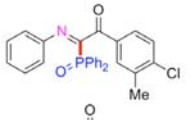
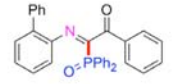
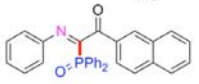
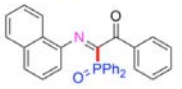
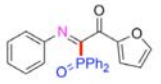
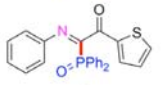
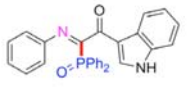
Table 2. Scope of Copper-Catalyzed Synthesis of 2-(Diphenylphosphoryl)-2-iminocarbonyls[a]

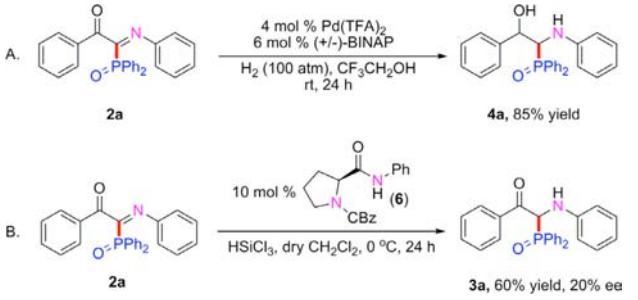


entry	product	yield (%)[b]	entry	product	yield (%)[b]
2a		85[c]			
2b	R^1 = Me	85	2l	R^2 = F	80
2c	R^1 = F	88[c]	2m	R^2 = Br	82
2d	R^1 = Cl	63[c]	2n	R^2 = Cl	82[c]
2e	R^1 = Br	70	2o	R^2 = Me	83
2f		91	2p	R^2 = MeO	75
2g		90	2q	R^2 = Ph	74[c]
2h		91	2r		76
2i		47	2s		80
2j		20	2t		72
2k		41	2u		42
			2v		43
			2w		42

[a] Reaction conditions: **1** (0.2 mmol), **2** (0.3 mmol), $Cu(OAc)_2 \cdot H_2O$ (10 mol %), TBHP (4.0 equiv, 5−6 M in decane), and MeCN (3.0 mL) at 30 °C under Ar. [b] Isolated yields. [c] 2.0 equiv of TBHP was used.

3a: indeed, an increase in the amount of diphenylphosphine oxide from 1.2 to 2.0 equiv caused a reduction in the ratio of **2a/3a** to 1:1 (entries 10 and 11). On the other hand, the loading of $Cu(OAc)_2 \cdot H_2O$ also proved very important to the ratio of **2a/3a**. The use of 5 mol % or 15 mol % $Cu(OAc)_2 \cdot H_2O$ made no difference; the lower ratio of **2a/3a** was achieved with higher yields (entries 12−13).

Scheme 2. Two Methods of Hydrogenation of **2a**



Subsequently, we investigated the reaction concentration. When the amount of the MeCN was increased from 2 to 3 mL for 0.2 mmol of **1a**, the best yield of **2a** was afforded in 85% as a single product (entries 14 and 15). Finally, screenings of copper salts showed that the $Cu(OAc)_2 \cdot H_2O$ is still the optimal choice (entries 16−19).

With optimized reaction conditions in hand (Table 1, entry 14), we examined various α-amino carbonyls so as to gauge the scope of the reaction (Table 2). Various substituted *N*-aryl groups were investigated first. When substituent groups were located on the para-position of the amido unit, we obtained higher yields with electron-donating than with electron-withdrawing groups (**2b**−**e**). Remarkably, with the methyl group on the meta-position of the amido unit or 3,4-dimethyl and 3,5-dimethyl groups on the *N*-phenyl ring, the corresponding products were obtained in excellent yields (**2f**−**h**). To our surprise, the steric hindrance was very distinct: when the methyl and phenyl group on the ortho-position of amido or the benzene ring was changed into naphthalene, the lowest yields were observed under optimal reaction conditions (**2i**−**k**). On the other hand, we also evaluated aryl groups linked with a carbonyl. Different functional groups, including multi substituted aryl and naphthyl, underwent the reaction smoothly and converted into the corresponding products with good yields regardless of electron donating or electron withdrawing groups (**2l**−**t**). In particular, several heterocyclic substrates that possess 2-furyl, 2-thienyl, and 3-indolyl groups were also found suitable for the reaction with moderate yields (**2u**−**w**).

α-Phosphorylated amino alcohols are used extensively in life science as well as pharmaceuticals.[9] To demonstrate the utility of our chemistry, we tried two methods of hydrogenation of **2a**, which are listed in Scheme 2. In the presence of $Pd(TFA)_2$ and (±)-BINAP under H_2 atmosphere, the α-phosphorylated amino alcohol **4a** was obtained in 85% yield.[10] If the organic small molecule **6** was

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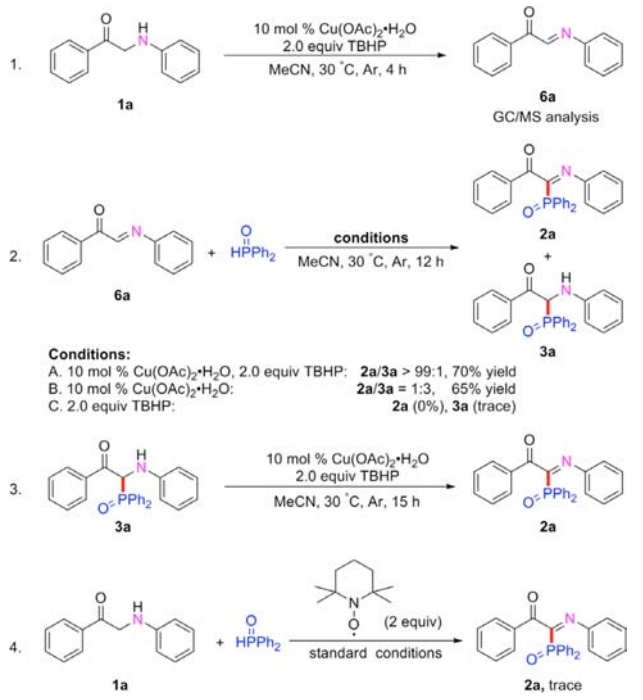
Scheme 3. Different Control Experiments and Radical Trapping



used as catalyst and $HSiCl_3$ was used as the reducing agent, **2a** was selectively reduced and converted to **3a** in 60% yield.[11]

To shed light on the possible mechanism of the reaction, we carried out several control experiments. According to the results of this transformations, we predicted that the imine **6a** may in fact be a key intermediate in the reaction. Therefore, we conducted the first control experiment involving oxidation of **1a** in the absence of diphenylphosphine oxide under standard conditions. The GC−MS trace analysis showed that **1a** converted almost completely into **6a** within 4 h (Scheme 3, step 1). Subsequently, the reaction of the intermediate of **6a** and diphenylphosphine oxide proceeded under standard conditions (Scheme 3, step 2), successfully affording the phosphonated product of **2a** in 70% yield. Without the aid of TBHP, however, the mixture of **2a** and **3a** was obtained in 65% yield with a ratio of 1:3. Furthermore, using only TBHP failed to prompt the reaction. The formation of imidoylphosphonates **2a** was also considered through the second oxidative dehydrogenation. The key intermediate is the byproduct of **3a**. To verify this hypothesis, we used **3a** as the substrate to conduct the oxidative dehydrogenation under standard conditions. As we expected, **3a** was converted into imidoylphosphonates **2a** with an 80% yield (Scheme 3, step 3). The radical trapping experiment was also performed in the presence of 2,2,6,6-tetramethylpiperidine oxide (TEMPO). Indeed, the addition of 2.0 equiv of TEMPO that led to the oxidative phosphonation process was remarkably suppressed. This result suggests that the transformation reaction might involve a radical process (Scheme 3, step 4).

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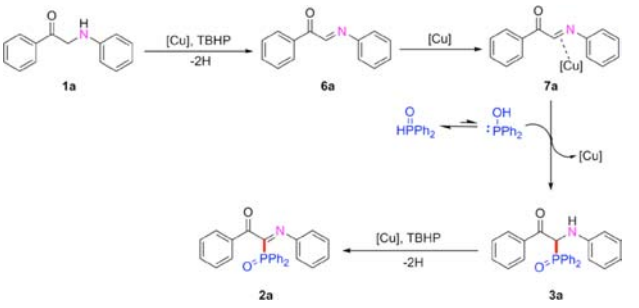
Scheme 4. Plausible mechanism of Copper-Catalyzed Oxidative Phosphonation of α-Amino Ketones



On the basis of these experimental results and previous reports, we propose a possible mechanism of this reaction illustrated in Scheme 4.[3−5,7] Initially, **1a** is oxidized by $Cu(OAc)_2 \cdot H_2O$ and TBHP to generate the intermediate of imine **6a**,[7] but only after the copper salt coordinated with **6a** to form the activated copper complex **7a**.[4m] Subsequently, the diphenylphosphine oxide undergoes nucleophilic attack as well as addition to **7a** to produce the intermediate **3a**.[5] Finally, as in the first step, oxidative deprotonation takes place, thus producing the product **2a**.

In summary, we have developed a novel protocol of copper-catalyzed oxidative phosphonation of α-amino carbonyls with diphenylphosphine with high chemoselectivity. This reaction exhibits excellent atom economy and is environmentally friendly. Additional studies on the application of asymmetric hydrogenation of 2-(diphenylphosphoryl)-2-iminocarbonyls are underway.

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Supporting Information Available. Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.