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Copper-Catalyzed Oxidative Cross-Coupling of *H*-Phosphonates and Amides to *N*-Acylphosphoramidates

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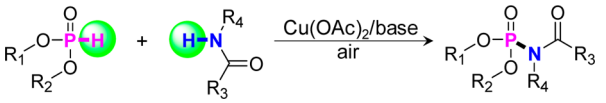
ABSTRACT



A simple combination of copper(II) acetate ($Cu(OAc)_2$) and an appropriate base could promote oxidative cross-coupling of *H*-phosphonates and amides using air as a terminal oxidant. The substrate scope was broad with respect to both dialkyl *H*-phosphonates and nitrogen nucleophiles (including oxazolidinone, lactam, pyrrolidinone, urea, indole, and sulfonamide derivatives), giving the corresponding P−N coupling products in moderate to high yields.

N-Acylphosphoramidates are very important structural key motifs in various bioactive natural products and pharmaceuticals such as Agrocin 84,[1] Microcin C7,[2] Phosmidosin,[3] and Fosaprepitant,[4] which are reported to show antifungal, antitumor, and antiemetic activities (Figure S1). In general, *N*-acylphosphoramidates have been synthesized by multistep nongreen procedures. For example, the most widely utilized procedure is nucleophilic substitution of chlorophosphonates with amides in the presence of strong bases, e.g., *n*-BuLi (Figure 1, A).[5] Another approach to *N*-acylphosphoramidates is a reaction of phosphoramides with acyl chlorides or mixed anhydrides (Figure 1, B).[6] Recently, Che and co-workers have reported a ruthenium(IV) porphyrine complex-catalyzed phosphoramidation of aldehydes with phosphoryl azides (Figure 1, C).[7] However, these reported procedures have utilized chlorophosphonates as starting materials, which are generally prepared by chlorination of *H*-phosphonates or phosphates using hazardous reagents, e.g., Cl_2, $COCl_2$, or SO_2Cl_2.[8] Thus, they have severe drawbacks, which include tedious multistep procedures, handling of toxic reagents, and production of large amounts of waste during not only phosphorylation but also chlorination steps. The development of novel green synthetic procedures for *N*-acylphosphoramidates directly using *H*-phosphonates as starting materials is very desirable, because they are more readily available and easy-to-handle in comparison with chlorophosphonates and, most importantly, no prefunctionalization step of *H*-phosphonates is required, which can greatly improve the overall synthetic efficiency of *N*-acylphosphoramidates. To date there is remarkable progress in the development of P−C[9] and P−heteroatom[10] bond forming reactions via direct activation of the P−H bond. Recently, copper-catalyzed (or mediated) oxidative cross-coupling was proven to be a highly efficient approach for the construction of C−C and

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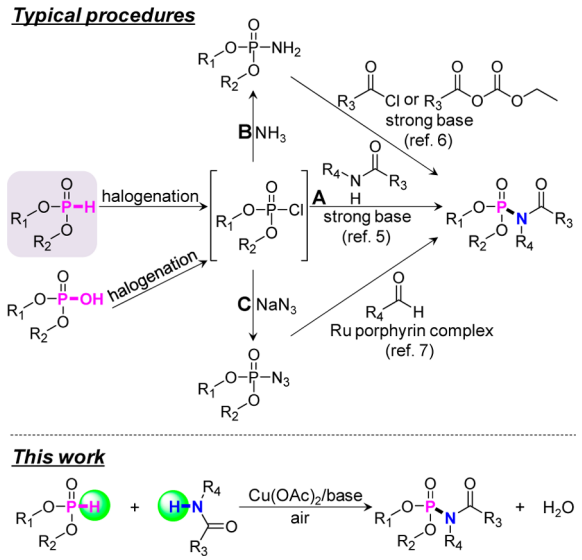

Figure 1. Synthetic procedures for *N*-acylphosphoramidates.

heteroatom−C bonds (including P−C and N−C bonds).[11] Quite recently, we have also developed the copper-catalyzed aerobic oxidative cross-coupling of terminal alkynes and amides to ynamides.[12]

Our continuing interest in copper-catalyzed aerobic oxidative cross-coupling reactions prompted us to explore novel methodology to synthesize *N*-acylphosphoramidates.

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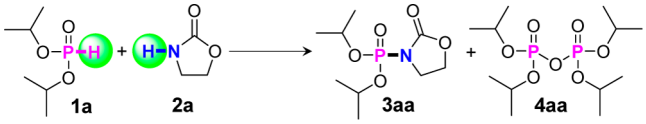
Table 1. Oxidative Cross-Coupling of **1a** and **2a** under Various Conditions[a]



				yield (%)	
entry	catalyst	**1a**/**2a**	conv of **1a** (%)	**3aa**	**4aa**
1[b]	$Cu(OAc)_2$	1/2	82	17	1
2[c]	$Cu(OAc)_2$	1/2	93	51	1
3	$Cu(OAc)_2$	1/2	99	81	1
4	$Cu(OAc)_2$	1/3	99	90	1
5[d]	$Cu(OAc)_2$	1/3	93	84	1
6	$Cu(OAc)_2$	1/5	>99	89	1
7	$Cu(OAc)_2$	1/1	93	68	6
8	$Cu(OTf)_2$	1/3	97	89	1
9	$[Cu(\mu\text{-}OH)(tmen)]_2Cl_2$	1/3	>99	62	38
10	$CuCl_2$	1/3	>99	63	37
11	$Cu(acac)_2$	1/3	2	1	nd
12	CuI	1/3	12	1	6
13	$CuSO_4 \cdot 5H_2O$	1/3	44	25	2
14	$Cu(OH)_2$	1/3	3	nd	nd
15	Cu_2O	1/3	<1	nd	nd
16	$Ni(OAc)_2 \cdot 4H_2O$	1/3	<1	nd	nd
17	$Co(OAc)_2 \cdot 4H_2O$	1/3	<1	nd	nd
18	$Fe(OAc)_2$	1/3	<1	nd	nd
19	$Mn(OAc)_2 \cdot 4H_2O$	1/3	<1	nd	nd
20	$Pd(OAc)_2$	1/3	7	nd	nd
21	none	1/3	<1	nd	nd

[a] Reaction conditions: **1a** (0.2 mmol), catalyst (10 mol %), Et_3N (0.2 mmol), MS 4 A (100 mg), toluene (2 mL), 80 °C, under air (1 atm). A toluene solution of **1a** (1 mL, 0.2 M) was added to the reaction mixture over 30 min by a syringe pump, and the reaction mixture was stirred for an additional 10 min. Conversion and yield were determined by GC analysis. nd = not detected (< 1%). [b] Mixed in a single step, without MS 4 A, 40 min. [c] Mixed in a single step, MS 4 A (100 mg), 40 min. [d] $Cu(OAc)_2$ (5 mol %).

In this paper, we demonstrate for the first time the successful application of copper-catalyzed aerobic oxidative cross-coupling to form P−N bonds, i.e., cross-coupling of *H*-phosphonates and amides to *N*-acylphosphoramidates. The present catalyst system can employ air as a terminal oxidant and produces water as a sole byproduct, providing a quite simple, efficient, and green synthetic route to highly important *N*-acylphosphoramidate functionalities (Figure 1, lower). To the best of our knowledge, there is no pre-existing example of a metal-catalyzed aerobic oxidative cross-coupling of phosphorus and nitrogen nucleophiles to form P−N bonds.

First, we optimized the reaction conditions by using $Cu(OAc)_2$ (OAc = acetate) (10 mol %) as a catalyst for the cross-coupling of diisopropylphosphonate (**1a**) and 2-oxazolidinone (**2a**) to diisopropyl(2-oxooxazolidin-3-yl)-phosphonate (**3aa**). In the presence of $Cu(OAc)_2$ and triethylamine (Et_3N) under 1 atm of air, the reaction of **1a** and **2a** (1:2, mixed in a single step) gave the desired cross-coupling product **3aa** in 17% yield (Table 1, entry 1).

In this case, most of **1a** decomposed to unidentified by-products possibly due to hydrolytic decomposition, resulting in a low yield of **3aa**. When molecular sieves 4 A (MS 4 A) was added to the reaction mixture, the yield of **3aa** increased up to 51% along with a trace amount of a pyrophosphate (**4aa**) derived from the homocoupling of **1a** (Table 1, entry 2). Further improvement of the yield of **3aa** up to 81% was achieved by slow addition of **1a** to the reaction mixture containing $Cu(OAc)_2$, Et_3N, and MS 4 A under open air conditions (Table 1, entry 3). These results could be attributed to the successful suppression of the hydrolytic decomposition of **1a** by the use of MS 4 A and the slow addition of **1a**. Upon changing the molar ratio of **1a** to **2a** from 1:2 to 1:3, a 90% yield of **3aa** was obtained (Table 1, entry 4). The use of the reduced amount of $Cu(OAc)_2$ (5 mol %) resulted in only a slight decrease in the yield of **3aa** (Table 1, entry 5). No further increase in the yield of **3aa** was observed when using 5 equiv of **2a** (Table 1, entry 6). The cross-coupling proceeded even with 1 equiv of **2a** with respect to **1a** albeit in a moderate yield of **3aa** (Table 1, entry 7).

Among the various copper catalysts examined, $Cu(OAc)_2$ showed the highest activity and selectivity for the cross-coupling of **1a** and **2a** (Table 1, entry 4). $Cu(OTf)_2$ (OTf = triflate) showed almost the same activity and selectivity as those of $Cu(OAc)_2$ (Table 1, entry 8). Other copper catalysts such as $[Cu(\mu\text{-OH})(tmen)]_2Cl_2$ (tmen = *N,N,N′,N′*-tetramethylethylendiamine), $CuCl_2$, $Cu(acac)_2$ (acac = acetylacetonate), CuI, and $CuSO_4 \cdot 5H_2O$ showed lower activities and/or selectivities than those of $Cu(OAc)_2$ (Table 1, entries 9–13). $Cu(OH)_2$ and Cu_2O, which were reported to be highly efficient catalysts for the cross-coupling of terminal alkynes and amides,[12] showed no activity for the present cross-coupling (Table 1, entries 14 and 15). Other commonly utilized metal acetates such as $Ni(OAc)_2 \cdot 4H_2O$, $Co(OAc)_2 \cdot 4H_2O$, $Fe(OAc)_2$, $Mn(OAc)_2 \cdot 4H_2O$, and $Pd(OAc)_2$ were not effective for the present cross-coupling (Table 1, entries 16–20).

In the present $Cu(OAc)_2$-catalyzed cross-coupling, various inorganic and organic bases could effectively promote the reaction, affording **3aa** in high yields (Table S1). For the cross-coupling of **1a** and **2a**, K_2CO_3 was the best base, giving **3aa** in an almost quantitative yield (Table S1, entry 4). Although the cross-coupling proceeded to some extent in the absence of bases, the yield of **3aa** was significantly decreased (Table S1, entry 12). The best solvent was toluene, and other solvents such as 1,2-dichloroethane, 1,4-dioxane, 2- propanol, acetonitrile, DMF, and DMSO were not effective (Table S2). When the reaction of **1a** and **2a** was carried out under an Ar atmosphere, only a "stoichiometric" amount of **3aa** with respect to $Cu(OAc)_2$ was obtained (Table S2, entry 2). This result suggests that reductive elimination of the P–N bonds takes place, and then the reduced copper species can be reoxidized by O_2 (air) during the present cross-coupling (Scheme S1).

Finally, we investigated the scope of the present $Cu(OAc)_2$-catalyzed oxidative cross-coupling of *H*-phosphonates and amides using air as a terminal oxidant. The suitable reaction conditions, especially the best bases

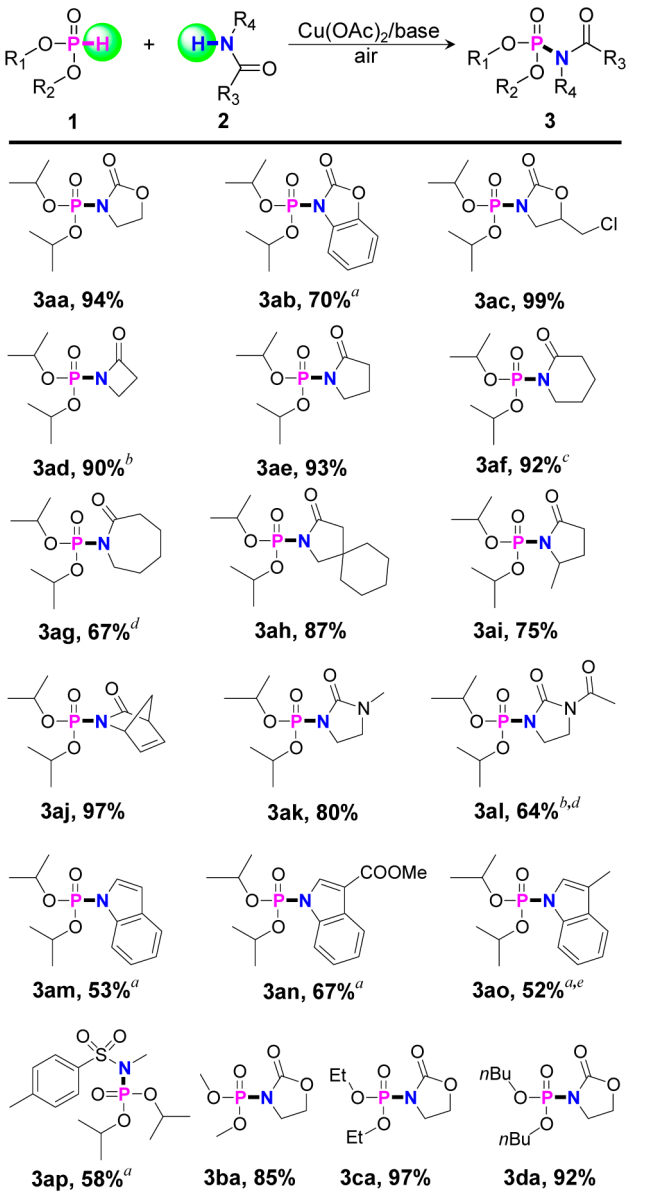


Figure 2. Aerobic oxidative cross-coupling of various *H*-phosphonates and nitrogen nucleophiles. Reaction conditions: **1** (0.2 mmol), **2** (0.6 mmol), $Cu(OAc)_2$ (10 mol %), K_2CO_3 (0.2 mmol), MS 4 A (100 mg), toluene (2 mL), 80 °C, under air (1 atm). A toluene solution of **1** (1 mL, 0.2 M) was added to the reaction mixture over 30 min by a syringe pump, and the reaction mixture was stirred for an additional 10 min (unless otherwise noted). The isolated yields (based on **1**) are reported. [a] 4-Methylpyridine (0.8 mmol) instead of K_2CO_3. [b] 1.5 h. [c] 2,2′-Bipyridyl (20 mol %). [d] 6,6′-Dimethylbipyridyl (20 mol %). [e] 1 h.

(Table S3), were dependent on the types of substrates. Under the optimized reaction conditions, various kinds of structurally diverse *N*-acylphosphoramidates could be synthesized from *H*-phosphonates and amides (Figure S2). The isolation of the *N*-acylphosphoramidate products obtained from the present oxidative cross-coupling of *H*-phosphonates and amides was very easy.[13] The isolated yields of products are summarized in Figure 2. For the cross-coupling of benzooxazolidinone (**2b**) and **1a**, a good

yield was achieved by using 4-methylpyridine as a base instead of K_2CO_3 (Table S3). A 5-substituted oxazolidinone (**2c**) smoothly reacted with **1a** to give the cross-coupling product in an almost quantitative yield. The coupling of 4-, 5-, 6-, and 7-membered aliphatic cyclic amides (**2d**−**2g**) with **1a** afforded the corresponding *N*-acylphosphoramidates in high to excellent yields. Pyrrolidinone derivatives (**2h** and **2i**) were also good substrates. A bicyclic lactam, 2-azabicyclo[2.2.1]hept-5-en-3-one (**2j**), was also a suitable nitrogen nucleophile to provide the corresponding *N*-phosphoroamidate in an excellent yield. Cyclic urea derivatives (**2k** and **2l**) also worked well as coupling partners for **1a**. Notably, indole (**2m**−**2o**) and sulfonamide (**2p**) derivatives could be utilized as nitrogen nucleophiles. With regard to *H*-phosphonates, various dialkyl phosphonates (**1a**−**1d**) could be utilized as coupling partners, affording the corresponding *N*-acylphosphoramidates in high yields.

(13) The cross-coupling was carried out via the following procedure. Into a Pyrex glass test tube (volume: ca. 20 mL) were successively placed $Cu(OAc)_2$ (10 mol % with respect to a *H*-phosphonate (**1**)), a base (1−4 equiv with respect to **1**), an amide (**2**, 3 equiv with respect to **1**), MS 4 A (100 mg), toluene (1 mL), and a Teflon-coated magnetic stir bar. After the reaction mixture was stirred for 5 min, a toluene solution of **1** (0.2 M, 1 mL) was added to the reaction mixture over 30 min by a syringe pump at 80 °C, and the reaction mixture was stirred for an additional 10−60 min at 80 °C under open air conditions. After the reaction was completed, an internal standard (naphthalene) was added to the reaction mixture, and the conversion of **1** and the product yield were determined by GC analysis. As for the isolation of products (*N*-acylphosphoramidates), an internal standard was not added. After the reaction, the base and MS 4 A were filtered off, and then the filtrate was concentrated by evaporation of toluene. The crude product was subjected to column chromatography on silica gel (Silica Gel 60N (63-210 μm), Kanto Chemical, 2.5 cm ID × 15 cm length, typically chloroform/acetone = 5:1 (v/v); diethylether/*n*-hexane = 2:1 (v/v) for **3ab**, **3am**, and **3ao**; chloroform/acetone = 10:1 (v/v) for **3an** and **3ap**), giving the pure *N*-acylphosphoramidate. The products were identified by GC-MS and NMR (^{1}H, ^{13}C, and ^{31}P) analyses (see the Supporting Information).

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In summary, we have successfully developed the copper-catalyzed aerobic oxidative cross-coupling of *H*-phosphonates and amides to *N*-acylphosphoramidates. Various kinds of dialkyl *H*-phosphonates and nitrogen nucleophiles (including oxazolidinone, lactam, pyrrolidinone, urea, indole, and sulfonamide derivatives) could be utilized as coupling partners, affording the corresponding P−N coupling products. The oxidative cross-coupling demonstrated herein will provide a new green, practical synthetic route to *N*-acylphosphoramidates, which completely avoids utilization of (hazardous) stoichiometric reagents (e.g., chlorophosphonates, Cl_2, $COCl_2$, SO_2Cl_2, *n*-BuLi, and/or NaN_3 in conventional procedures, Figure 1) and the formation of vast amounts of byproducts, and will be one of the reliable choices for synthesis of these types of P−N functionalities. By referring to the literature on copper-mediated aerobic oxidative cross-coupling reactions,[12,14] the present reaction possibly proceeds according to Scheme S1.[15] Detailed mechanistic studies are now in progress.

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Supporting Information Available. Full experimental details, Tables S1−S3, Figures S1 and S2, Scheme S1, and spectral data of *N*-acylphosphoramidates. This material is available free of charge via the Internet at http://pubs.acs.org.

(15) The present reaction possibly proceeds through the following three steps: (i) coordination of amidate and phosphite species to the copper center to form a Cu(phosphite)(amidate) intermediate (**5**), (ii) reductive elimination to form the corresponding *N*-acylphosphoramidates, and (iii) reoxidation of the reduced copper species by O_2 (air) to regenerate active copper species (Scheme S1). Bases likely play two important roles: (i) abstract N−H protons from amides and (ii) increase concentration of phosphite forms (**1′**).

The authors declare no competing financial interest.