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Copper-catalyzed aerobic oxidative cross-coupling of arylamines and dialkylphosphites leading to N-arylphosphoramidates

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ABSTRACT

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Phosphoramidates have found wide applications as structure motifs in bioactive compounds such as phosphoramidatesubstituted nucleosides, N-phosphoryl amino acids, and *N*-phosphoryl peptides.¹ Phosphoramidates also play a significant role in organic synthesis. For example, N-arylphosphoramidates have been used for the preparation of imines² and various heterocycles such as quinazolinediones³, aziridines⁴, and azetidines.⁵ Despite the increasing importance of phosphoramidates, only two standard procedures have been widely used in the laboratory. One route that forms phosphoramidates via the nucleophilic substitution of phosphorochloridates or phosphorodichloridates with amines in the presence of a base (Scheme 1).^{6,1g} Another involves reactions of dialkyl or dibenzyl phosphites with amines using a halogen source like CCl₄ or other improved alternatives as activate agents (Scheme 1).⁷ Other methods for the synthesis of phosphoramidates include the oxidation of phosphate trimesters with I₂ in the presence of alkylamines and the reduction of nitroarenes with triethyl phophite followed by phosphorylation with triethyl phosphate.⁸ These procedures have in common that they are based on the prefunctionalization-defunctionalization strategy. As results, these procedures use additional active agents or produce undesired by-products.

Recently, there has been increasing emphasis on reducing the amount of toxic waste and byproducts arising from a chemical process. As an effort to develop green chemistry for chemical synthesis, a new concept of cross-dehydrogenative coupling was established.⁹ To date, there is remarkable progress in the develop-



An efficient method to generate N-P bonds directly from N-H and P-H bonds is described. Various arvl-

amines and dialkylphosphites were directly oxidized to the corresponding N-arylphosphoramidates at

room temperature in moderate to good yields by using an inexpensive catalyst-oxidant (CuBr/air)

Scheme 1. The standard methods for the synthesis of phosphoramidates.

ment of C–C,¹⁰ N–N¹¹, and P–P¹² bond forming reactions via dehydrogenative coupling. We envision that N–P bond may be formed via cross-dehydrogenative coupling.¹³

We commenced our studies by examining the cross-coupling of diisopropyl phosphite with excess p-methylaniline at room temperature under air. In the absence of a catalyst, no desired product was observed. Using 10 mol % of CuBr₂ as the catalyst, 48% of desired product was obtained. After screening different copper salts, we found that CuBr performed the best (Table 1, entries 2–8). CuCl also facilitated the reaction, but was less efficient than CuBr (entry 4 vs entry 3). Other catalysts including Cu(OAc)₂·H₂O, Cul, Cu(OTf)₂, and Cu₂O were inefficient or inactive. Attempts to use other transition-metal catalysts such as FeBr₃ and CoBr₂ were unsuccessful. Impressively, no desired product was observed under nitrogen (entry 9), indicating that oxygen is essential to this reaction. We then surveyed the effect of different solvents (entries 10-14). When toluene was replaced with ethyl acetate as the solvent, we were pleased to find that the product could be obtained in 80% yield. The reaction gave low yields in EtOH, THF, and H₂O. In the absence of a solvent, the reaction also performed, albeit with a





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Table 1

Copper-catalyzed cross-dehydrogenative coupling of p -methylaniline and diisopropyl phosphate^{\rm a}



Entry	Catalyst (mol %)	Solvent	Yield ^b (%)
1	_	Toluene	N.D.
2	CuBr ₂ (10)	Toluene	N.D.
3	CuBr (10)	Toluene	54
4	CuCl (10)	Toluene	45
5	$Cu(OAc)_2 \cdot H_2O(10)$	Toluene	17
6	CuI (10)	Toluene	6
7	$Cu(OTf)_2$ (10)	Toluene	N.D.
8	Cu ₂ O (10)	Toluene	N.D.
9 ^b	CuBr (10)	Toluene	N.D.
10	CuBr (10)	Ethyl acetate	80
11	CuBr (10)	EtOH	52
12	CuBr (10)	THF	60
13	CuBr (10)	H ₂ O	39
14 ^c	CuBr (10)	-	49
15	CuBr (2.5)	Ethyl acetate	54
16	CuBr (5)	Ethyl acetate	80
17	CuBr (20)	Ethyl acetate	32
18 ^d	CuBr (5)	Ethyl acetate	78

^a *p*-Methylaniline, 1.5 mmol; diisopropyl phosphite, 1 mmol; solvent, 1 mL; under air; at room temperature; 22 h; isolated yields.

^b Under nitrogen.

^C No solvent.

^d 50 °C; 8 h.

moderate yield (entry 14). Further, the catalyst loading was screened, and it was found that 5 mol % of CuBr was efficient to obtain a reasonable yield (entries 15–17 and entry 10). When the reaction was carried out at 50 °C, the yield decreased slightly (entry 18). In summary, 5 mol % of CuBr in ethyl acetate, at room temperature, under air atmosphere were the optimized reaction conditions.

With optimized conditions in hand, we investigated the scope of this transformation (Table 2). Various phosphoramidates were produced from arylamines and diisopropyl phosphite in moderate to good yields (3a-j). This reaction was tolerant of several functional groups. Both electron-rich and electron-deficient substrates (para or meta substituted) were well-tolerated. Arylamines bearing fluoro (3d), chloro (3e and 3f), or bromo (3g) groups were good substrates, providing convenient handles for subsequent functionalization processes. Arylamines bearing an ortho substituent or a strong electron-withdraw substituent could not smoothly afford the desired product (**3i-k**). The cross-coupling of α -naphthylamine with diisopropyl phosphite produced 31 in 49% yield. Although alkylamines were not compatible with this method, benzylamine is an acceptable substrate (3m). Secondary arylamines were not good substrates for this transformation. But increasing the loading of N-methylaniline to 5:1 (amine/phosphate ratio), the corresponding product was obtained in an acceptable yield (3n). In addition to diisopropyl phosphite, other dialkyl phosphites including diethyl phosphite and di-n-butyl phosphite were also good substrates for this cross-coupling reaction (**30-r**). Interestingly, di-n-butyl phosphite performed more effectively and afforded the desired product in higher yield than other dialkyl phosphites. For example, the reaction of *p*-methylanilide with di-*n*-butyl phosphite, diisopropyl phosphite, and diethyl phosphite afforded the corresponding phosphoramidates in 94%, 80%, and 64% yields, respectively (**3p**, **3b** and **3o**).

Table 2

Copper catalyzed cross-dehydrogenative coupling of arylamines and dialkylphosphites $^{\rm a}$





^a 1, 1.5 mmol; 2, 1 mmol; ethyl acetate, 1 mL; CuBr, 5 mol %; under air; at room temperature; 22 h.

^b Isolated yields.

^c N-methylaniline 5 mmol.

In conclusion, we have developed an efficient and green method to prepare *N*-aryl-phosphoramidates via Cu-catalyzed cross-dehydrogenative coupling.

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Supplementary data

Supplementary data (the detailed experimental procedures and compounds characterization) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/ j.tetlet.2013.09.006.

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