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Oxidative C(sp^2)−H Phosphonation of Aldehyde Hydrazones

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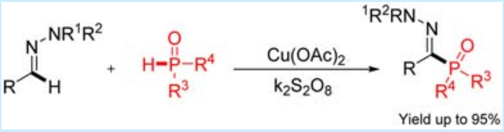
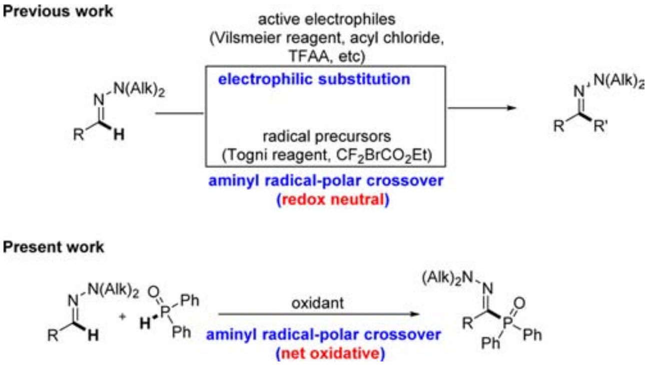
Supporting Information

ABSTRACT: A $K_2S_2O_8$/Cu(OAc)$_2$-mediated oxidative C−H/P−H cross-coupling of aldehyde hydrazones with diphenylphosphine oxide for the direct preparation of functionalized α-iminophosphine oxides is reported. The reaction shows good functional group tolerance and proceeds smoothly under mild conditions. This strategic protocol for C−P bond formation is facilitated by a net oxidative aminyl radical−polar crossover process.



N,N-Dialkylhydrazones belong to a significant class of chemicals because of their many applications in synthetic organic chemistry.[1] The most impressive property of *N,N*-dialkylhydrazones is the umpolung of the imine reactivity, which is attributed to the conjugative interaction between the C═N bond and the lone pair of the terminal nitrogen atom.[2] Hence, the common methods for the preparation of functionalized *N,N*-dialkylhydrazones rely on electrophilic substitution at the azomethine carbon atom.[2,3] However, these protocols suffer from limited active electrophiles such as Vilsmeier reagent,[3a] acyl chloride,[3b] trifluoroacetic anhydride (TFAA),[3c] and so on (Scheme 1). Thus, recent attention has been paid to the development of novel and effective methodologies for the functionalization of aldehyde hydrazones (Scheme 1).[4] Along this line, group of Bouyssi and Baudoin realized the copper-catalyzed trifluoromethylation of *N,N*-dialkylhydrazones using Togni reagent.[4a] Our group reported a photoredox method for the C−H difluoroalkylation of *N,N*-dialkylhydrazones with halodifluoromethylated compounds.[4b] Very recently, the Hashmi group[4d] and Bouyssi group[4c] independently realized the similar fluoroalkylation reaction by gold catalysis and palladium catalysis. From a general view, these strategic achievements all utilized the hydrazone as a radical acceptor, and the dialkyl group was found to be a key activating unit.

Scheme 1. C−H Functionalization of Aldehyde Hydrazones



Phosphorus-containing compounds widely appear in organic ligands,[5] functional materials,[6] and pharmaceutical chemicals.[7] In addition, compounds containing a P−C−N unit often show important biological activity.[8] Encouraged by our previous result on the photoredox neutral difluoroalkylation of aldehyde *N,N*-dialkylhydrazones,[4b] we wondered whether a oxidative radical C−H/P−H cross-coupling based on the aminyl radical−polar crossover (ARPC) process could be developed for the synthesis of α-iminophosphine oxides (Scheme 1).[9] To the best of our knowledge, only a few cases for the synthesis of α-iminophosphine oxides were reported.[9e,10] In addition, the success of net oxidative reaction based on the ARPC process would represent an alternative and complementary method for the functionalization of aldehyde hydrazones.

For the past several years, the generation of a P-centered radical from diphenylphosphine oxide has been widely studied.[9c,g,h] Based on these previous reports, we initiated our studies by choosing aldehyde hydrazone **1a** and diphenylphosphine oxide **2a** as the model substrates and used $AgNO_3$ (0.5 equiv)/$K_2S_2O_8$ (2 equiv) as oxidant in CH_3CN at 60 °C for 20 h. To our delight, the desired product **3a** was obtained in 46% yield (Table 1, entry 1). Encouraged by this preliminary result, we further optimized the reaction conditions. To our surprise, the reaction could also proceed smoothly without any Ag salts (Table 1, entry 2). This result suggested that $K_2S_2O_8$ could act as both oxidant and radical initiator in the net oxidative ARPC process, albeit with a moderate efficiency.[11] Other different oxidants such as *tert*-butyl hydroperoxide (TBHP) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) were also investigated but did not facilitate the reaction well under these conditions (Table 1, entry 3 and 4). To further improve the reaction conditions, various silver salts and copper salts, temperature, and the loading of diphenylphosphine oxide **2a** were respectively investigated (Table 1, entries 5−15). It was

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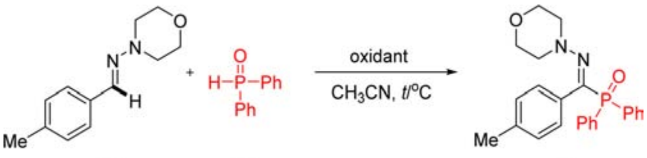
Table 1. Phosphorylation of Aldehyde Hydrazone 1a with Diphenylphosphine Oxide under Various Conditions[a]



1a **2a** **3a**

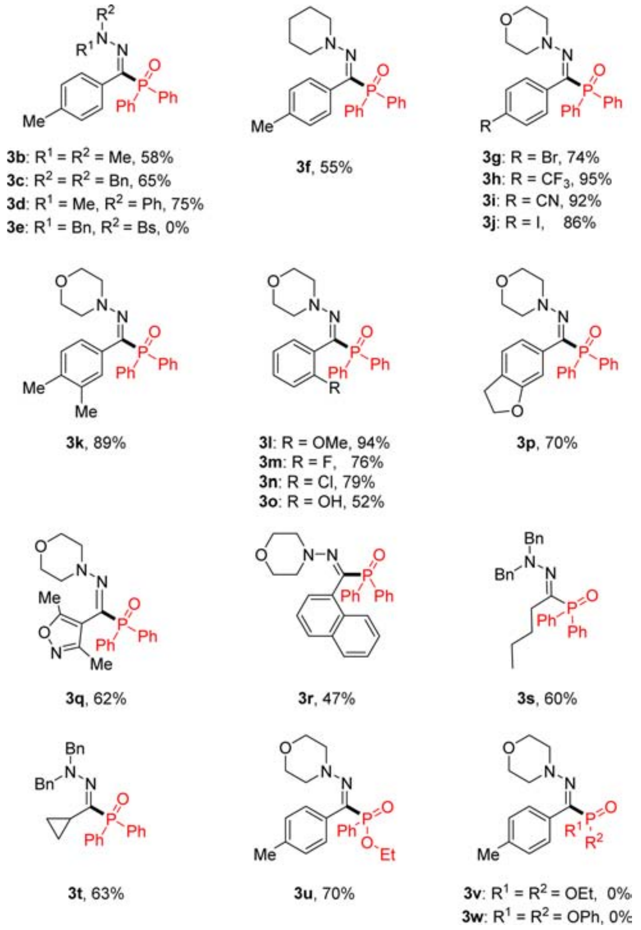
entry	oxidant (equiv)	temp (°C)	yield[b] (%)
1	$AgNO_3$ (0.5) + $K_2S_2O_8$ (2)	60	46
2	$K_2S_2O_8$ (2)	60	45
3	TBHP (2)	60	trace
4	DDQ(2)	60	0
5	AgOTf (0.5) + $K_2S_2O_8$ (2)	60	40
6	AgOAc (0.5) + $K_2S_2O_8$ (2)	60	35
7	$Cu(OAc)_2$ (0.5) + $K_2S_2O_8$ (2)	60	89
8	$Cu(OAc)_2$ (0.5) + $K_2S_2O_8$ (2)	25	51
9	$Cu(OAc)_2$ (0.5) + $K_2S_2O_8$ (2)	80	86
10	$Cu(OAc)_2$ (0.25) + $K_2S_2O_8$ (2)	60	85
11	$Cu(OAc)_2$ (0.10) + $K_2S_2O_8$ (2)	60	76
12	$CuBr_2$ (0.10) + $K_2S_2O_8$ (2)	60	40
13	$Cu(OTf)_2$ (0.10) + $K_2S_2O_8$ (2)	60	25
14	$CuCl_2$ (0.10) + $K_2S_2O_8$ (2)	60	43
15	$CuSO_4$ (0.10) + $K_2S_2O_8$ (2)	60	56
16[c]	$Cu(OAc)_2$ (0.25) + $K_2S_2O_8$ (2)	60	90
17	$Cu(OAc)_2$ (0.25)	60	trace

[a]Reactions were carried out with **1a** (0.1 mmol), **2a** (0.3 mmol), and oxidant in CH_3CN (2 mL) under N_2 for 20 h. [b]Isolated yields. [c]Using 2 equiv of **2a**.

shown that only $Cu(OAc)_2$ promoted the reaction well with a good yield of 89% (Table 1, entry 7). The yield was decreased when the reaction temperature was changed to 25 or 80 °C (Table 1, entry 8 and 9). Later, we found that a decrease in the amount of $Cu(OAc)_2$ would lead slightly lower yields (Table 1, entries 10 and 11), whereas only 2 equiv of diphenylphosphine oxide **2a** was required for the phosphorylation reaction with the highest yield of 90% (Table 1, entry 16). Finally, the oxidant $K_2S_2O_8$ was found to be essential for the reaction, as only traces of the desired product were obtained in its absence (Table 1, entry 17). It is worth mentioning that product **3a** was determined to be exclusively *E* configured by $^1H-^1H$ NOESY NMR experiments.

With the optimized reaction conditions in hand, the scope of this reaction was examined, and the results are summarized in Scheme 2. We first turned our attention to investigation of the *N*-substituent group effect with various *p*-tolualdehyde-derived hydrazones. The other *N*,*N*-dialkylhydrazones with acyclic amino groups such as dimethylhydrazone and dibenzylhydrazone also furnished the desired products **3b** and **3c** with moderate yields. Though the α-iminophosphonates **3d** could be obtained in a moderate yield, the electron-withdrawing *N*-Bs group-substituted hydrazone failed to give the desired product, which is in accordance with our previous study. In addition, the hydrazone-bearing 1-piperidinyl group could also react smoothly with diphenylphosphine oxide to give the product **3f** in 55% yield. We then investigated the substituent effect of the aryl moiety. In general, this reaction enjoys a broad substrate scope and excellent chemoselectivity. Aldehyde hydrazones bearing electron-withdrawing (cyano, trifluoromethyl, fluoro) or electron-donating substituents (methoxy, methyl) all provided the desired products in moderate to good yields (47–95%), and no aromatic C(sp^2)−H or C(sp^3)−H phosphonation products were detected. Additionally, versatile functional groups such as hydroxyl and halogens (Cl, Br, I) underline the practicability of this reaction. Remarkably, the C−H phosphonation of heterocyclic and naphthalene substrates could also proceed smoothly to give the target products **3q** and **3r**, albeit with low yields. To further extend the scope of this protocol, we turned our attention to the aliphatic aldehyde-derived hydrazones, and these aliphatic aldehyde-derived hydrazones proved to be suitable substrates for the reaction. Importantly, another coupling partner was not restricted to diphenylphosphine oxide. Ethyl phenylphosphinate was also used as an effective phosphonation reagent. Unfortunately, phosphonation reagents like diethyl phosphonate and diphenyl phosphonate did not work under the standard reaction conditions.

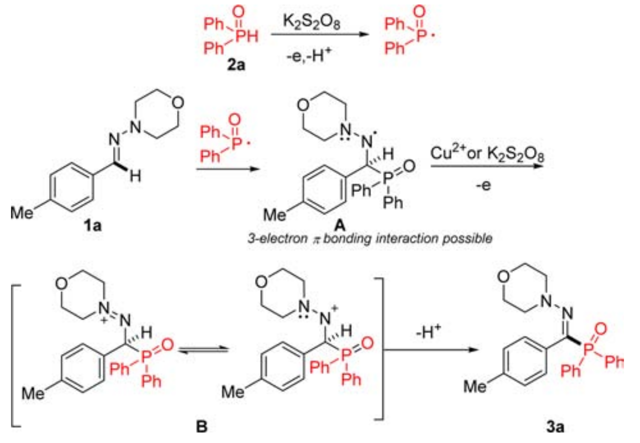
Scheme 2. Substrate Scope[a]



[a]Conditions: reactions were carried with **1a** (0.1 mmol), **2a** (0.2 mmol), $K_2S_2O_8$ (0.2 mmol), and $Cu(OAc)_2$ (0.025 mmol) in CH_3CN (2 mL) under N_2 for 20 h. Bs = benzenesulfonyl.

A plausible reaction mechanism was proposed for this C−H/P−H cross-coupling reaction (Scheme 3). First, a P-centered radical was generated from the diphenylphosphine oxide **2a** with $K_2S_2O_8$.[11] Only a trace amount of the desired product was observed when radical inhibitor 1-oxy-2,2,6,6-tetramethylpiperidine (TEMPO) was added to the reaction, which further confirmed a radical reaction. Subsequent addition of the P-centered radical to the C═N bond would produce a crucial three-electron-bonding aminyl radical intermediate **A**, which

Scheme 3. Proposed Reaction Mechanism



would be oxidized by copper(II) or $K_2S_2O_8$ to the corresponding aminyl cation **B**. Finally, deprotonation of the aminyl cation **B** would afford the **3a**.

In conclusion, we have demonstrated a practical procedure for the C−H bond phosphonation of aldehyde *N,N*-dialkylhydrazones with the commercially available diphenylphosphine oxide. It provides a novel approach to the synthesis of functionalized *α*-iminophosphine oxides. In addition, this reaction offers a new protocol for C−P bond formation which is based on the aminyl radical−polar crossover process. We anticipate the present strategy could be used for more useful transformation of the carbon−nitrogen *π* bond.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00257.

Experimental procedures and characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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