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COMMUNICATION

A novel copper-catalyzed reductive coupling of *N*-tosylhydrazones with *H*-phosphorus oxides†‡

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We report here a novel $C(sp^3)$–P bonds formation *via* copper-catalyzed reductive coupling of *N*-tosylhydrazones with *H*-phosphorus oxides. A variety of aliphatic and aromatic substrates bearing electron-rich and electron-deficient substituents affords phosphine oxide derivatives with moderate to good yields. This work suggests a new transformation of aldehydes/ketones *via* *N*-tosylhydrazones to organophosphorus compounds.

Introduction

N-Tosylhydrazones, well-known as the key reagents in Shapiro reaction, have been versatile synthetic intermediates for almost 60 years from their discovery in the mid-20th century.[1] The renewed interest in *N*-tosylhydrazones has occurred since the first palladium catalyzed cross-coupling of *N*-tosylhydrazones with aromatic bromides was documented by Barluenga group in 2007.[2] Leading scientists such as Barluenga and Valdés's group, Wang's group and others have contributed various transition metal catalyzed cross-coupling reactions of *N*-tosylhydrazones with alkynes,[3] azoles,[4] amines,[5] aryl boronic acids,[6] aryl sulfonates,[7] benzylic halides,[8] isocyanides,[9] trialkylsilylethynes,[10] and in the cascade carbonylations *etc.*,[11] which have shown versatility and generality of this reagent to build useful functionalities for synthetic compounds. It is noteworthy that all of the above processes went through metal–carbenes intermediates which were generated *in situ* from *N*-tosylhydrazones while exposed to transition metals under basic and thermal conditions. For instance, Wang *et al.*[3a] proposed a copper-carbene intermediate in the copper(I)-catalyzed cross-coupling of *N*-tosylhydrazones with terminal alkynes to afford trisubstituted allenes. However, to the best of our knowledge, the *catalytic coupling reaction* of *N*-tosylhydrazones with *H*-phosphorus oxides such as diarylphosphine oxides and *H*-phosphonates has never been reported.[12]

Organophosphorus compounds play a vital role in organic synthesis, catalysis, biochemistry, and materials chemistry, which qualify the great importance to build C–P bonds.[13] Although various methods to prepare organophosphorus compounds have been developed, the traditional approaches including Michaelis–Arbuzov reaction still suffered from low efficiency, poor selectivity, and sometimes higher temperature with long time heating.[13c,14] Until recently, Han *et al.* demonstrated a serial breakthrough in the transition metal catalyzed addition of H–P(O) bonds to unsaturated carbon–carbon bonds.[15] Of particular interest among them is the palladium catalyzed hydrophosphorylation of alkenes towards the formation of $C(sp^3)$–P bond with excellent yields, albeit acyclic and six-membered cyclic *H*-phosphonates were proven to be inert[15a] [Scheme 1(a)]. Stawinski *et al.*[16] reported a palladium-catalyzed cross-coupling of *H*-phosphonate diesters with benzyl halides, however, the substrates couldn't be expanded to benzylic halides with side chains or aliphatic halides owing to β-H elimination during the palladium catalytic cycle [Scheme 1(b)]. Polozov and co-workers demonstrated a one-pot synthesis of dialkyl phosphonates from diazo compounds and dialkyl hydrogen phosphites catalyzed by Cu(acac)$_2$, to be noted, the substrate scopes were restricted with diazo compounds with electron-withdrawing substituents[17] [Scheme 1(c)]. Although some achievements have been made,[18] the catalytic approaches to build $C(sp^3)$–P bond are still very

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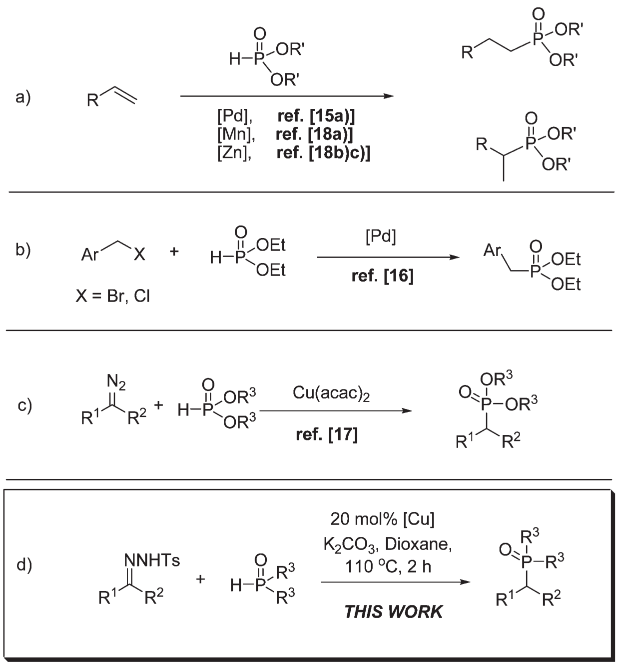
‡ Typical procedure for the copper-catalyzed reductive coupling reaction: 2 mmol diaryl phosphine oxide or *H*-phosphonate, 1 mmol *N*-tosylhydrazone and 3 mmol K_2CO_3 were charged into 25 mL oven-dried flask, and backfilled with nitrogen for three times. 5 mL fresh-distilled 1,4-dioxane or DMF was then injected into the flask, following by heating up to 110 °C for 2 h. The reaction was monitored by TLC until starting materials consumed, then removed all the volatiles for further purification on silica chromatography.

Compound (3a) White solids. **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 1.56 (dd, J = 16, 7.6 Hz, 3H), 3.59 (qu, J = 14.8, 7.6 Hz, 1H), 3.76 (s, 3H), 6.75 (d, J = 8.8 Hz, 2H), 7.16 (dd, J = 8.4, 2.4 Hz, 2H), 7.27–7.40 (m, 3H), 7.47–7.58 (m, 5H), 7.88–7.93 (m, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 15.60 (d, $J_{C,P}$ = 2.0 Hz), 39.97 (d, $J_{C,P}$ = 67.4 Hz), 55.20, 113.70 (d, $J_{C,P}$ = 1.20 Hz), 127.99, 128.11, 128.58, 128.69, 129.77 (d, $J_{C,P}$ = 5.60 Hz), 130.14, 130.20, 131.13, 131.22, 131.24, 131.27, 131.35, 131.43, 131.63, 131.66, 131.69, 132.60 (d, $J_{C,P}$ = 13.5 Hz), 158.51 (d, $J_{C,P}$ = 2.2 Hz). **^{31}P NMR** δ: 33.48. **HR-MS:** calcd for $C_{21}H_{22}O_2P$ 337.1357 ([M + H$^+$]), found 337.1355.

§ These two authors contributed equally to this paper.

limited as aforementioned, thus, it is highly desirable to develop a transition metal catalyzed method for this kind of transformations with broad substrate scopes, higher selectivity/efficiency, and lower cost. We conceived that *H*-phosphorus compounds such as diaryl phosphine oxides and *H*-phosphonates, with labile H–P(O) bonds, might react efficiently with [M]-carbenes *in situ* generated from *N*-tosylhydrazones then undergo rearrangement to form organophosphorus compounds. As our continuing interest in the synthesis and application of organophosphorus compounds,[19] herein we would like to report, for the first time, the copper-catalyzed reductive coupling of *N*-tosylhydrazones with *H*-phosphorus oxides.



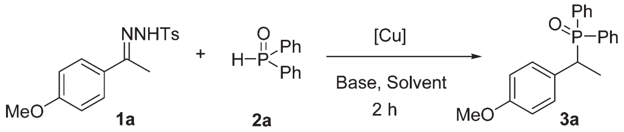
Scheme 1 Catalytic approaches to build C(sp^3)–P bonds.

Results and discussion

The investigation was initiated by exploring the reaction of 1-(1-(4-methoxyphenyl)ethylidene)-2-tosylhydrazine (**1a**) with diphenylphosphine oxide (**2a**) under basic conditions. Although no product was detected under metal-free conditions within short reaction time,[20] the cross-coupling proceeded smoothly in the presence of 20 mol% CuI/1,10-phenanthroline to afford product **3a** with 64% yield in two hours[21] (Table 1, entries 1, 2). To our delight, the reaction still proceeded with comparable efficiency without adding any ligands. Excess diphenylphosphine oxide, which might suppress the decomposition of *N*-tosylhydrazones, improved the yield up to 71% (entries 5, 6). Various combinations of bases and solvents were then screened to get the optimal conditions, eventually, K_2CO_3/Dioxane was found to be the best combinations (entries 7–9). A number of Cu(I) and Cu(II) salts were applied in this reductive coupling reaction, other Cu(I) salts such as CuCl, CuBr, Cu_2O showed worse results than CuI (entries 10–12). Notably, $CuCl_2$ as the catalyst afforded superior result to CuI and $Cu(CN)_4PF_6$, with 80% isolated yield, albeit increasing the temperature and reaction time did not augment the yield (entry 15).

With the optimized conditions in hand,[22] studies on the expansion of substrate scopes were then carried out. Various

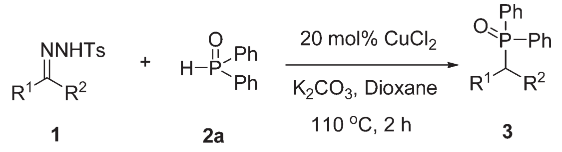
Table 1 Screening conditions for copper-catalyzed reductive coupling of *N*-tosylhydrazones with diphenylphosphine oxide[a]



Entry	Catalyst loading/ligand	Solvent/base	Yield[b] (%)
1	0	K_2CO_3/Dioxane	0[c]
2	20 mol% CuI/1,10-phenanthroline	K_2CO_3/Dioxane	64[d]
3	20 mol% CuI/1,10-phenanthroline	K_2CO_3/Dioxane	70
4	10 mol% CuI	K_2CO_3/Dioxane	66
5	20 mol% CuI	K_2CO_3/Dioxane	71
6	20 mol% CuI	K_2CO_3/Dioxane	69[c]
7	20 mol% CuI	DIPEA/THF	60
8	20 mol% CuI	DBU/Dioxane	65
9	20 mol% CuI	Cs_2CO_3/DMF	70
10	20 mol% CuCl	K_2CO_3/Dioxane	52
11	20 mol% CuBr	K_2CO_3/Dioxane	66
12	20 mol% Cu_2O(nano)	K_2CO_3/Dioxane	Trace
13	20 mol% $Cu(OAc)_2$	K_2CO_3/Dioxane	47
14	20 mol% $Cu(acac)_2$	K_2CO_3/Dioxane	61
15	20 mol% $CuCl_2$	K_2CO_3/Dioxane	80
16	20 mol% $CuSO_4$	K_2CO_3/Dioxane	Trace
17	20 mol% $Cu(OTf)_2$	K_2CO_3/Dioxane	43
18	20 mol% $Cu(CN)_4PF_6$	K_2CO_3/Dioxane	71

[a] 1 mmol *N*-tosylhydrazone (**1a**), 2 mmol diphenylphosphine oxide (**2a**), 3 mmol base, 5 mL solvent, reflux temperature or 110 °C, 2 h. [b] Isolated yield based on *N*-tosylhydrazones. [c] **1a**/**2a** = 1 : 1. [d] **1a**/**2a** = 2 : 1.

Table 2 Substrate scopes of the cross-coupling of *N*-tosylhydrazones with diphenylphosphine oxide catalyzed by 20 mol% $CuCl_2$ [a]



Entry	R_1	R_2	Product	Yield[b] (%)
1	p-$MeOC_6H_4$	Me	**3a**	80
2	p-MeC_6H_4	Me	**3b**	70
3	C_6H_5	Me	**3c**	66
4	C_6H_5	Et	**3d**	60
5	p-ClC_6H_4	Me	**3e**	55
6	p-$CF_3C_6H_4$	Me	**3f**	63
7	2,4-Dimethyl-C_6H_3	Me	**3g**	56
8	Naphthyl	Me	**3h**	65
9	Cyclohexyl		**3i**	79[c]
10	n-C_3H_7	Me	**3j**	67[c]
11	p-$MeOC_6H_4$	H	**3k**	82
12	C_6H_5	H	**3l**	80
13	p-FC_6H_4	H	**3m**	51
14	i-C_3H_7	H	**3n**	50

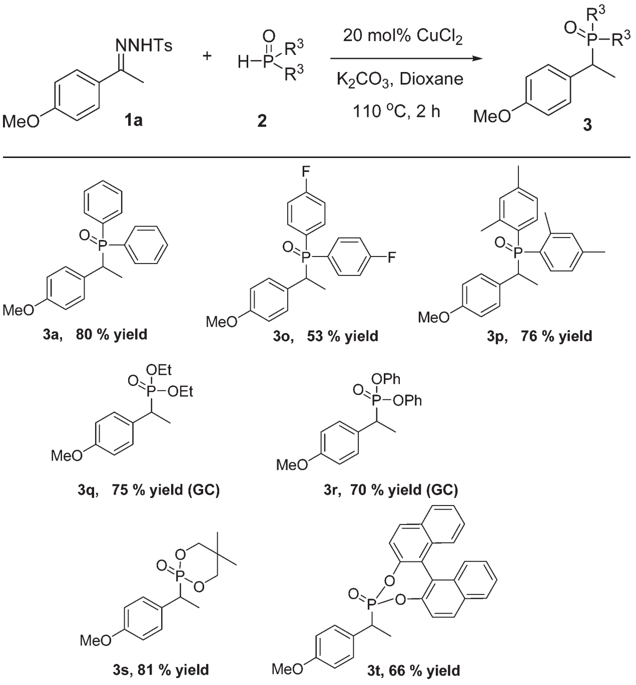
[a] 1 mmol *N*-tosylhydrazone (**1**), 2 mmol diphenylphosphine oxide (**2a**), 3 mmol K_2CO_3, 5 mL dioxane, 110 °C, 2 h. [b] Isolated yield based on *N*-tosylhydrazones. [c] DMF as solvent.

substituted *N*-tosylhydrazones were synthesized as substrates, as shown in Table 2, *N*-tosylhydrazones derived from both electron-rich (MeO–, Me–, Dimethyl–) or electron-deficient (Cl–, CF_3–, F–) aryl ketones or aldehydes could afford the corresponding organophosphorus compound (**3**) in medium to good yields (entries 1–8, 11–13). Electron-withdrawing groups on aromatic rings impaired the reaction efficiency to some extent (entries 5, 6, 13), this could be attributed to the stabilization of electron-withdrawing groups to carbene intermediates, which in turn decreased the reaction rate. It is worth to mention that alkyl derivative *N*-tosylhydrazones were also shown to be viable substrates with moderate to good yields (entries 9, 10, 14). For some cases with unsatisfied yields, DMF was found to be better solvent (entries 9, 10), however, this is not general for all substrates.

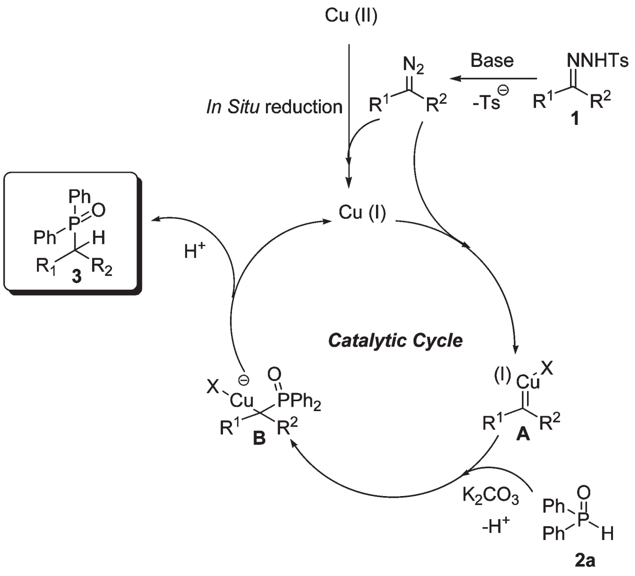
To further demonstrate the general effectiveness of this copper-catalyzed reductive coupling, various *H*-phosphorus oxides including diarylphosphine oxides and *H*-phosphonates were also investigated. As shown in Table 3, diarylphosphine oxides bearing electron-deficient group (**2o**) and steric *ortho*-substituents (**2p**) were applicable with 53% and 76% yields, respectively. Delightfully, the substrate scopes could be extended to *H*-phosphonates with cyclic or acyclic moieties, affording the corresponding phosphine oxide products (**3q–3t**) in moderate to good yields.

A plausible mechanism was proposed and shown in Scheme 2. Firstly, Cu(II) species are *in situ* reduced to Cu(I) species by the diazo compound generated from *N*-tosylhydrazones (**1**) under basic and thermal conditions.[5,23] Decomposition of diazo compound by Cu(I) species leads to the formation of the copper(I)–carbene complex (**A**). Then, nucleophilic attack of the $Ph_2P(O)^-$ on the carbene center would generate copper species (**B**), the latter is protonated to produce the final coupling product **3**.

Table 3 Substrate scopes of the cross-coupling of *N*-tosylhydrazones with various *H*-phosphorus oxides catalyzed by 20 mol% $CuCl_2$ [a]



[a] 1 mmol *N*-tosylhydrazone (**1a**), 2 mmol *H*-phosphorus oxides (**2**), 3 mmol K_2CO_3, 5 mL dioxane, 110 °C, 2 h.



Scheme 2 Plausible catalytic mechanism.

Conclusions

In summary, a novel C(sp^3)–P bonds formation *via* copper-catalyzed reductive coupling of *N*-tosylhydrazones with *H*-phosphorus oxides has been developed. The reaction proceeded smoothly with a wide range of substrate scopes to afford phosphine oxide derivatives with moderate to good yields. This work suggests a new transformation of aldehydes/ketones *via* *N*-tosylhydrazones to organophosphorus compounds. Further application of this approach to asymmetric C(sp^3)–P bonds formation is under way.

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