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Copper-catalyzed P–H insertion reactions of sulfoxonium ylides†

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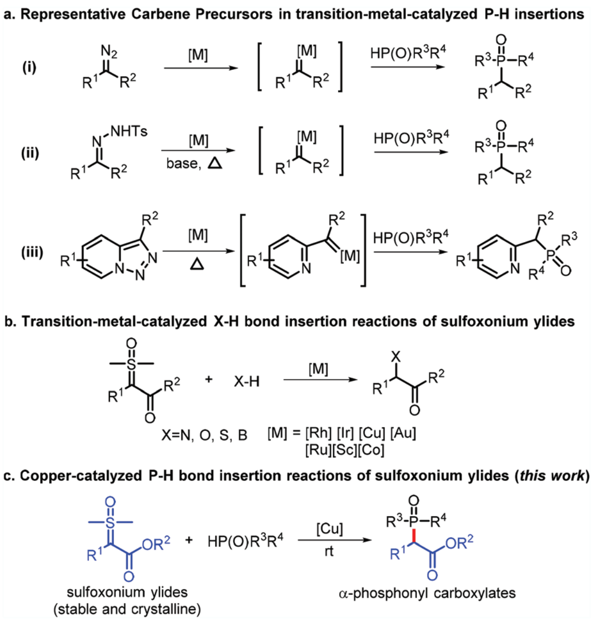
A copper-catalyzed P–H insertion reaction between sulfoxonium ylides and H-phosphorus oxides has been demonstrated, furnishing α-phosphonyl carboxylate derivatives in 41–93% yields. This methodology utilizing bench-stable and thermodynamically stable sulfoxonium ylides as carbene precursors in the presence of the inexpensive and readily available copper catalyst shows advantages such as mild reaction conditions, good functional group compatibility, and easy scale-up, which make this protocol attractive for large-scale chemical processing and processing at the industrial scale.

Organophosphorus compounds play key roles in various fields, such as in agrochemistry,[1] pharmacy,[2] materials science,[3] and catalysis chemistry.[4] The transition-metal-catalyzed heteroatom–hydrogen bond (X–H) insertion of carbene represents a straightforward and atom-economical method for the construction of C-heteroatom bonds.[5] Much effort has been made to develop P–H insertion reactions of H-phosphorus oxides with various diazo compounds,[6] among which the α-diazo carbonyl compound is a reactive metal–carbene precursor for the construction of α-phosphonyl carboxylate derivatives (Scheme 1a-i).[6a–c] Large-scale reactions using diazo compounds are challenging due to their thermal instability and the release of nitrogen gas. Besides diazo compounds, hydrazones[7] and triazo compounds[8] have already been used as alternative carbene precursors in P–H insertions (Scheme 1a-ii and iii). However, the generation of metal carbenes from hydrazones and triazo compounds generally suffers from the the use of excess amounts of a base or high temperature. Therefore, the development of catalytic P–H insertion with stable carbene precursors under mild reaction conditions to obtain various α-phosphonyl carboxylate derivatives is highly valuable.

Sulfoxonium ylides have emerged as increasingly valuable carbene precursors with numerous advantages such as their thermally stable and crystalline nature, and nonvolatile dimethyl sulfoxide (DMSO) as the byproduct.[9] Remarkable achievements have been made in X–H (X = N, O, S, B) insertion reactions with sulfoxonium ylides as surrogates of diazo compounds (Scheme 1b).[10–13] To the best of our knowledge, the P–H insertion reaction with sulfoxonium ylides for the construction of C–P bonds has not been reported previously. In continuation of our research on metal carbene chemistry and considering the importance of organophosphorus compounds, we describe herein the P–H insertion reactions with sulfoxonium ylides catalyzed by the inexpensive and readily available



Scheme 1 Metal–carbene insertions for C–X bond formation.

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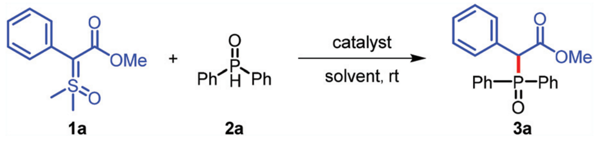
copper catalyst under mild reaction conditions for the synthesis of α-phosphonyl carboxylates (Scheme 1c).

Initially, sulfoxonium ylide **1a** and diphenylphosphine oxide **2a** were studied as substrates for P–H insertions in DCM at room temperature (Table 1). First, we tested metal catalysts. Unfortunately, no reaction occurred under the catalytic conditions with the typically used Rh, Ir, Ru, or Au catalyst (entries 1–4). The reaction in the presence of 10 mol% CuCl generated the desired insertion product **3a** in 29% yield (entry 5). Encouraged by this result, we next explored other copper catalysts (entries 6–13), among which inexpensive and readily available Cu(OAc)$_2$ proved superior, affording **3a** in 63% yield (entry 13). The solvents DMSO and DMF were found to be essentially ineffective in the reaction (entries 14 and 15). CHCl$_3$ was a suitable solvent for this reaction, affording **3a** in 40% yield (entry 16). The reaction was not subjected to notable temperature effects (see the ESI†). When the reaction was conducted in the absence of a metal catalyst, no product was obtained, indicating the important role of the copper catalyst in the decomposition of sulfoxonium ylides (entry 13 *vs.* 17).

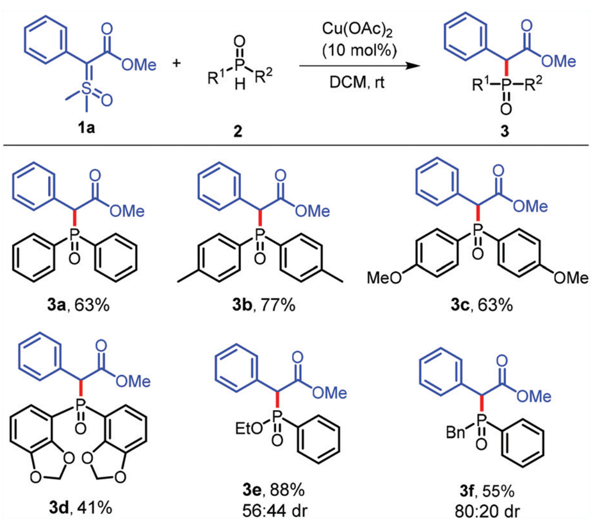
Table 1 Optimization of reaction conditions[a]



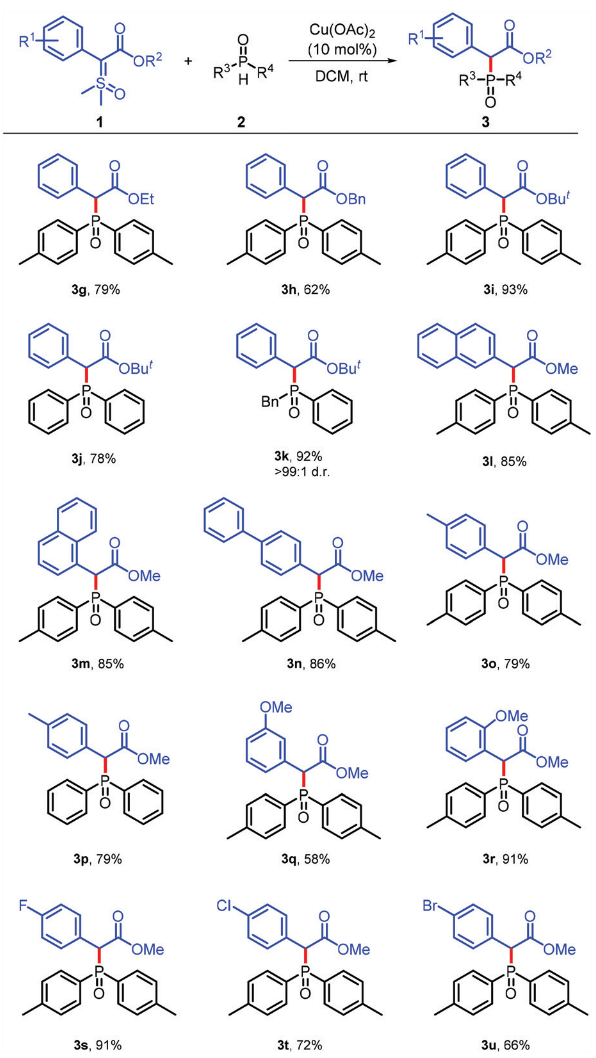
Entry	Catalyst	Solvent	Yield[b] (%)
1	RhCp*Cl$_2$	DCM	N.R.
2	[Ir(COD)Cl]$_2$	DCM	N.R.
3	[Ru(*p*-cymene)]Cl$_2$	DCM	N.R.
4	AuCl	DCM	N.R.
5	CuCl	DCM	29
6	Cu(acac)$_2$	DCM	43
7	CuCN	DCM	29
8	CuI	DCM	37
9	CuBr$_2$	DCM	40
10	CuTc	DCM	29
11	Cu(OTf)$_2$	DCM	43
12	[(CH$_3$CN)$_4$Cu]PF$_6$	DCM	46
13	**Cu(OAc)$_2$**	**DCM**	**63**
14	Cu(OAc)$_2$	DMSO	N.R.
15	Cu(OAc)$_2$	DMF	N.R.
16	Cu(OAc)$_2$	CHCl$_3$	40
17	—	DCM	N.R.

[a] Reaction conditions: the reactions were performed with **1a** (0.1 mmol) and **2a** (0.2 mmol) in the presence of 10 mol% catalyst in 2.0 mL of solvent at room temperature for 18–36 h. [b] Isolated yield. N.R. = no reaction.

With the optimized reaction conditions established, we first evaluated the substrate scope of H–phosphine oxides **2** (Scheme 2). Sulfoxonium ylide **1a** and various H–phosphine



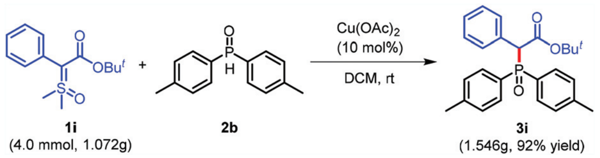
Scheme 2 Scope of H–phosphine oxides. Reaction conditions: the reactions were carried out with Cu(OAc)$_2$ (0.01 mmol), **1a** (0.10 mmol), and **2** (0.20 mmol) in CH$_2$Cl$_2$ (2.0 mL) at room temperature for 18–36 h. Isolated yield.



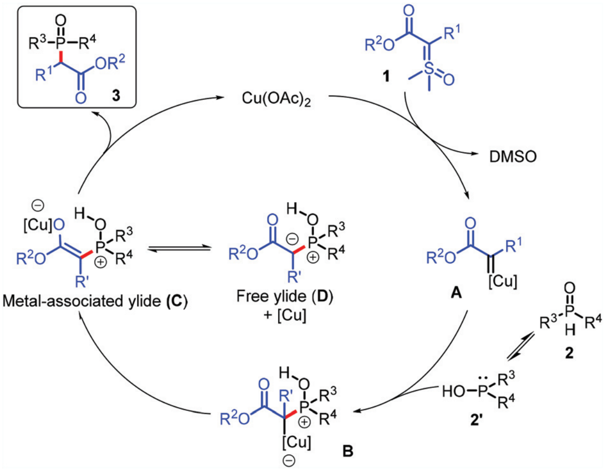
Scheme 3 Scope of sulfoxonium ylides. Reaction conditions: the reactions were carried out with Cu(OAc)$_2$ (0.01 mmol), **1** (0.10 mmol), and **2** (0.20 mmol) in CH$_2$Cl$_2$ (2.0 mL) at room temperature for 18–36 h. Isolated yield.

oxides **2** reacted smoothly in the presence of $Cu(OAc)_2$ to afford products **3a–f** in moderate to high yields. H–phosphine oxides with electron-rich substituted groups such as Me and OMe were tolerated and gave **3b** and **3c** in 77% and 63% yield, respectively. Moreover, bis(benzo[*d*][1,3]dioxol-4-yl)phosphine oxide could take part in the transformation to deliver the corresponding product **3d** in moderate yield. Notably, when ethyl phenylphosphinate was chosen as the substrate, the expected product **3e** was obtained in 88% yield with 56 : 44 dr. Furthermore, the use of benzyl (phenyl)phosphine oxide was also feasible for this reaction, producing **3f** in 55% yield with 80 : 20 dr.

Next, a series of sulfoxonium ylides was investigated as carbene precursors (Scheme 3). Sulfoxonium ylides bearing different ester moieties all afforded the expected products **3** in high yields. Sulfoxonium ylides with a *tert*-butyl ester group furnished the P–H insertion products **3i**, **3j**, and **3k** in 93%, 78%, and 92% yields, respectively. 1-Naphthyl and 2-naphthyl substituted groups were all tolerated, providing the corresponding products **3l** and **3m** in good yields (85% and 85%, respectively). Furthermore, electron-rich motifs (R^1 = 4-$C_6H_5C_6H_4$, 4-MeC_6H_4, 3-$MeOC_6H_4$, 2-$MeOC_6H_4$) were tolerant and gave the desired products **3n–r** with good chemoselectivities (58–91% yields). Various halogen substituents such as F, Cl, and Br at the *para* positions of the phenyl ring generated products **3s–u** in 66–91% yields. Aliphatic sulfoxonium ylides were not investigated.



Scheme 4 Scaled-up reaction.



Scheme 5 Proposed mechanism.

To demonstrate the synthetic utility of the catalytic reaction, a gram-scale experiment was performed. The reaction was conducted at a 4.0 mmol scale under the standard reaction conditions, affording **3i** in 92% yield (Scheme 4).

On the basis of the above experimental results and precedent literature,[5a,10c,14] we propose a possible mechanism for this P–H insertion reaction (Scheme 5). At the beginning of the catalytic cycle, the Cu–carbene complex **A** is the sulfoxonium ylide with the release of DMSO. The subsequent nucleophilic attack on the Cu–carbene complex **A** by phosphinous acid 2′, tautomerized from 2, generates the zwitterionic intermediate **B**, which forms the metal-associated ylide (**C**) that is in equilibrium with the free ylide (**D**). Both **C** and **D** afford the final product **3** *via* a proton transfer.

Conclusions

In summary, we have accomplished a catalytic P–H insertion reaction by using sulfoxonium ylides as carbene precursors. This scalable protocol provides a straightforward approach for synthesizing α-phosphonyl carboxylate derivatives in moderate to high yields. The great stability of sulfoxonium ylides, mild reaction conditions, easy scale up, as well as the use of the inexpensive and readily available copper catalyst make this catalytic reaction attractive for large-scale chemical processing and processing at the industrial scale.

Conflicts of interest

There are no conflicts to declare.

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