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Stereocontrolled C(sp³)-P bond formation with non-activated alkyl halides and tosylates†

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The C(sp³)-P bond is formed *via* the reaction between P-H compounds and non-activated alkyl electrophiles, especially secondary alkyl halides and tosylates. This reaction proceeds *via* an S_N2 mechanism with inversion of configuration, so it can be used to form C-P bonds with stereocontrol from chiral secondary alcohols.

Organic phosphorus compounds are a group of molecules important to a broad range of fields including synthetic chemistry, biology, materials chemistry, catalytic chemistry, coordination chemistry, agriculture, and pharmaceutical chemistry,¹ for which reason they have drawn considerable attention. In recent years, reactions catalyzed by transition metals (Pd,^{2,3} Ni,^{4,5} Cu⁶) have been developed to construct C(sp²)-P and C(sp)-P bonds. Nonetheless, longstanding methods of C(sp³)-P synthesis include (1) substitution reactions of carbon electrophiles with alkali metal phosphides or carbon nucleophiles (organolithiums or Grignard reagents) with P-Cl derivatives, which are hindered by air-unstable substrates and low functional group tolerance;⁷ (2) the Michaelis-Arbusov reaction⁸ and the base-promoted H-phosphinate alkylation,⁹ the former of which is limited to the generation of products of primary P-alkyl phosphine oxides and the latter of which is not only limited by the poor compatibility of functional groups due to the employment of strong basic condition (such as BuLi,^{9a} NaH,^{9b} Na,^{9c} LDA,^{9d} and KHMDS,^{9e}) but also not easily applied to the production of secondary alkyl halides.¹⁰ In this context, developing a new method for C(sp³)-P synthesis, especially for the secondary C(sp³)-P compounds, remains a serious challenge, particularly because of the problem of β-hydride elimination.^{11,12}

The current work reports a new method of performing the coupling reaction using non-activated primary and secondary alkyl electrophiles with P-H compounds. In this method, LiOMe served as a mild base and TMEDA served as the additive to inhibit β-hydride elimination, and no transition metal catalyst was used. The reaction can be applied to both pentavalent P(O)-H compounds (secondary phosphine oxide, and H-

phosphonate) and trivalent P-H compounds, and it provides a one-step method of producing chelating bisphosphine ligands. Moreover, because the reaction proceeds *via* the S_N2 mechanism, it can be considered a generic method for C-P bond formation with stereocontrol.

This work is encouraged by the recent advances in copper-catalyzed cross-coupling of alkyl electrophiles,¹³ especially for activation of secondary alkyl electrophiles,¹⁴ the catalyst system (CuI/TMEDA/LiOMe) developed by our group^{14c} was first used to test the reaction of bromocyclopentane (**1a**) with diphenylphosphine oxide (**2a**). The initial results showed a promising yield of 48% (Table 1, entry 1) under room temperature with THF as the solvent. Multiple reaction parameters were further optimized during the development of the method. In a test of various solvents (entries 2–6), polar reagents showed higher yield. For example, a reaction yield of 74% was obtained (entry 6) using NMP as the solvent. An increase of reaction temperature to 40 °C further improved the yield to 89% (entry 7). The reaction still generated a yield of 88% (entry 8), even when CuI was not used as the catalyst, which indicated a reaction mechanism of base-promoted alkyl substitution. The reaction efficiency was reduced by other bases (LiO^tBu, NaO^tBu, NaOMe, Cs₂CO₃, K₂CO₃, KHMDS, LiHMDS) (entries 9–15). TMEDA (*N,N,N',N'*-tetramethylethylenediamine) was proved to be critical to the reaction, which may suppress the undesirable side reactions such as the formation of olefin through elimination of hydrogen chloride, as reported previously.^{14,15} Other additives, including PBU₃, PPh₃, and DMEDA were also tested, but they were not as efficient as TMEDA (entries 16–19). Results also showed that secondary alkyl tosylate (R-OTs, entry 20) and alkyl iodide (entry 21) were also suitable substrates for this reaction, but inert alkyl chloride was notably less efficient (entry 22).

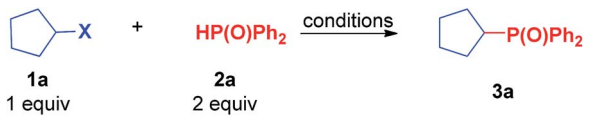
The results of the current study indicated that the reaction of LiOMe/TMEDA/NMP can be used to generate C(sp³)-P bonds efficiently using the secondary alkyl bromides (or tosylates) and that there was no need for the Cu-catalyst. The reaction was tested further with various substrates (Scheme 1), including

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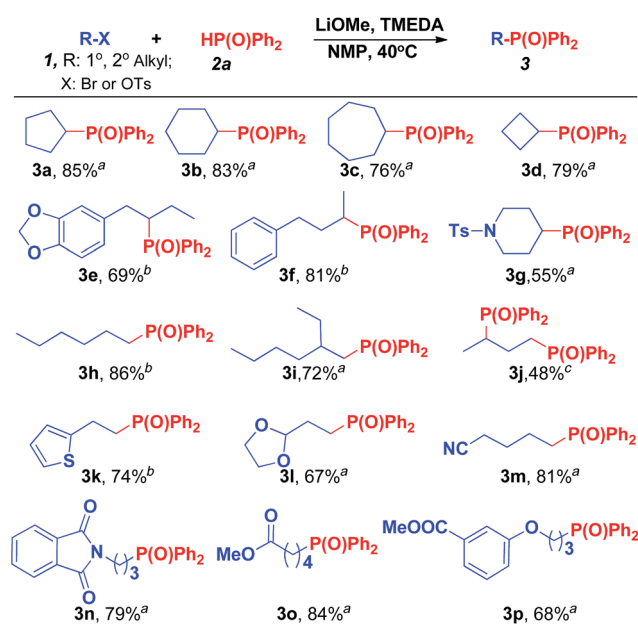


Table 1 Reaction between 1a and 2a under various conditions



Entry	X	Catalyst (10 mol%)	Additive (20 mol%)	Base (2 equiv.)	Solvent (0.5 mL)	Temp. (°C)	Yield ^a (%)
1	Br	CuI	TMEDA	LiOMe	THF	25	48
2	Br	CuI	TMEDA	LiOMe	Toluene	25	12
3	Br	CuI	TMEDA	LiOMe	Dioxane	25	21
4	Br	CuI	TMEDA	LiOMe	DMF	25	68
5	Br	CuI	TMEDA	LiOMe	DMSO	25	65
6	Br	CuI	TMEDA	LiOMe	NMP	25	74
7	Br	CuI	TMEDA	LiOMe	NMP	40	89
8	Br	—	TMEDA	LiOMe	NMP	40	88(85 ^b)
9	Br	—	TMEDA	LiO ^t Bu	NMP	40	78
10	Br	—	TMEDA	NaO ^t Bu	NMP	40	69
11	Br	—	TMEDA	NaOMe	NMP	40	71
12	Br	—	TMEDA	Cs ₂ CO ₃	NMP	40	58
13	Br	—	TMEDA	K ₂ CO ₃	NMP	40	16
14	Br	—	TMEDA	LiHMDS	NMP	40	42
15	Br	—	TMEDA	KHMDS	NMP	40	54
16	Br	—	P ⁿ Bu ₃	LiOMe	NMP	40	73
17	Br	—	PPh ₃	LiOMe	NMP	40	63
18	Br	—	DMEDA	LiOMe	NMP	40	72
19	Br	—	—	LiOMe	NMP	40	55
20	OTs	—	TMEDA	LiOMe	NMP	40	85(81 ^b)
21	I	—	TMEDA	LiOMe	NMP	40	76
22	Cl	—	TMEDA	LiOMe	NMP	40	21

^a Reaction conditions: R-X (0.25 mmol), HP(O)Ph₂ (0.5 mmol), CuI (10 mol%), additive (20 mol%), base (0.5 mmol), GC yields after 24 hours (average of two runs). ^b Isolated yields.



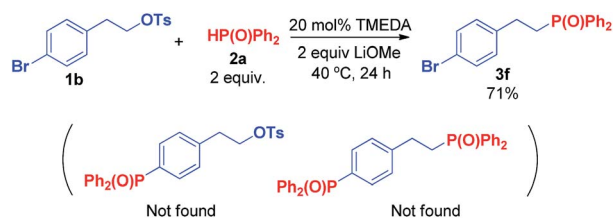
Scheme 1 Electrophiles scope of the coupling reaction. ^aReactions were carried out at 40 °C for 24 h on a 0.25 mmol scale using R-Br. For details about each substrate please see ESI.† Yields were determined through the isolation of the desired products. ^b1 equiv. of R-OTs was used. ^c4 equiv. of **2a** and LiOMe were used.

cyclic and acyclic secondary alkyl bromides (**3a–3d**, **3g**, **3j**) and tosylates (**3e**, **3f**). All of those substrates showed positive reactions regardless of different chain lengths and branching. Primary alkyl electrophiles also gave good to excellent yields under the same reaction conditions (**3h–3m**), but tertiary alkyl electrophilic reagents did not succeed. Some functional groups were also compatible with the reaction, including dioxolane (**3e**, **3l**), N-Ts (**3g**), cyano group (**3m**), amide (**3n**), ester (**3o**, **3p**) and heterocyclic groups (**3k**).

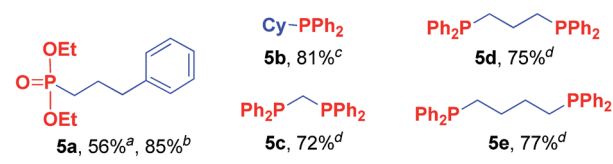
Regarding chemoselectivity, results showed the alkyl-OTs site to be more active than the aryl-Br site when both were present in the same substrate. In the reaction of **1b** and **2a**, the compound with C(sp³)-P bond was the only product, but aryl-bromide remained intact and capable of undergoing further functionalization (Scheme 2) *via* a coupling reaction. The high selectivity to the groups of sp²-C and sp³-C in the reaction will be useful for the synthesis of complicated compounds.

Results also showed that other nucleophiles can also be used in this reaction (Scheme 3). The pentavalent P(O)-H compound (H-phosphonate) can generate a medium yield under standard reaction conditions, but it produces an excellent yield if Cs₂CO₃ serves as the base instead of LiOMe (**5a**). More importantly, trivalent P-H compounds can react easily with both primary and secondary alkyl electrophiles (**5b–5e**), which provided a one-step method for chelating bisphosphine ligands such as dppm (**5c**), dppp (**5d**), and dppb (**5e**).^{9f,16}





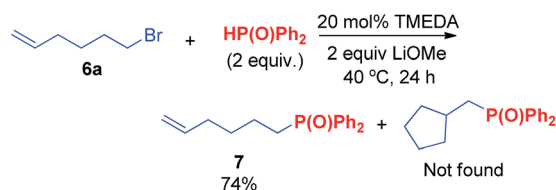
Scheme 2 Selectivity between alkyl and aryl sites.



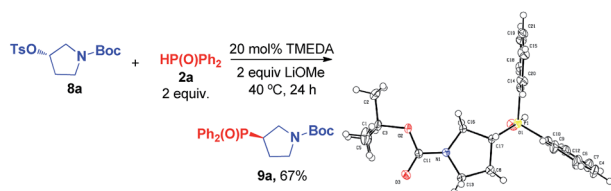
Scheme 3 Nucleophiles scope of the coupling reaction. ^aReactions were carried out at 40 °C for 24 h on a 0.25 mmol scale using diethyl phosphite and LiOMe. For details about each substrate please see ESI.† Yields were determined through the isolation of the desired products. ^b2 equiv. of Cs₂CO₃ was used. ^c2 equiv. of diphenylphosphine was used. ^d4 equiv. of diphenylphosphine and LiOMe were used.

To understand the reaction mechanism, 6-bromohex-1-ene (**6a**) first served as the substrate in the reaction, which only generated product **7**, with no cyclization product produced (Scheme 4). The results indicated a base-promoting S_N2 substitution mechanism rather than radical mechanism.

Secondary alkyl tosylates can be used in this reaction, which allows the use of chiral substrates to examine the stereochemistry of the reaction. As shown in Scheme 5, chiral tosylate (**8a**) can be produced through the reaction of chiral alcohols in only one step. **8a** and **2a** can react to generate product **9a** with a good yield. The X-ray crystal analysis of **9a** indicated an inversion of configuration, which confirmed the hypothetical S_N2 mechanism of the reaction.^{7d,e}



Scheme 4 Radical trapping experiment.



Scheme 5 Inversion of configuration.

Table 2 Construction of C–P bonds with stereocontrol from chiral secondary alcohols^a

Entry	Alkyl-OTs	Product	Yield (%)	ee (%)
1			67	99
2			70	95
3			71	98
4			80	96
5			79	97
6			75	98

^a Reactions were carried out at 40 °C for 24 h on a 0.5 mmol scale using 20 mol% TMEDA, 2 equiv. LiOMe, R-OTs (0.5 mmol), NMP(0.5 mL), and HP(O)Ph₂ (1.0 mmol). For details about each substrate please see ESI.† Yields were determined through the isolation of the desired products. The ee% values were determined by chiral HPLC analysis.

It is highly important that the reaction can be used to generate C–P bonds with stereocontrol when chiral secondary alcohols are the starting material. As shown in Table 2, cyclic and acyclic chiral alcohols were converted to the corresponding tosylates quantitatively. Through this reaction, diphenylphosphine oxide (**2a**) reacted with chiral tosylates with good yields, which, after two-step conversions, still remained as high as 95–99% ee%. Because many methods can be used for chiral alcohol synthesis,¹⁷ this new method expanded the C–P bond synthesis with stereocontrol.

Conclusions

The current study developed a new method of synthesizing C(sp³)-P compounds through non-activated alkyl halides (or tosylates) with P–H compounds. The reaction is a rare example of phosphorylation with secondary alkyl electrophiles. Both TMEDA and LiOMe have been proven to be important to the efficiency of the reaction. In addition to pentavalent P(O)–H compounds and trivalent P–H compounds have also been found to participate in this process, which provides a convenient, one-



step means of synthesizing chelating bisphosphine ligands. The reaction is actually highly selective for alkyl halides, and aryl halides are inert. The X-ray crystal analysis of the reaction products indicated a S_N2 reaction mechanism with configuration inversion. In this way, the reaction provides a generic method for using chiral secondary alcohols to produce C–P bond with stereocontrol. Further investigation will be carried out on using tertiary alkyl electrophiles as the reaction substrates with more P–H compounds.

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