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Phosphine oxides as efficient neutral coordinate-organocatalysts for stereoselective allylation of *N*-acylhydrazones

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Phosphine oxides were found to be efficient neutral coordinate-organocatalysts (*NCOs*) for the allylation of *N*-acylhydrazones. Among the phosphine oxides tested, a three carbon-tethered bisphosphine oxide (dppp dioxide) was found to be the most effective, and in the presence of dppp dioxide, less reactive aromatic and α,β-unsaturated *N*-acylhydrazones underwent allylation as well as diastereoselective crotylation. Furthermore, a polymer-supported phosphine oxide was also developed as an effective immobilized *NCO*.

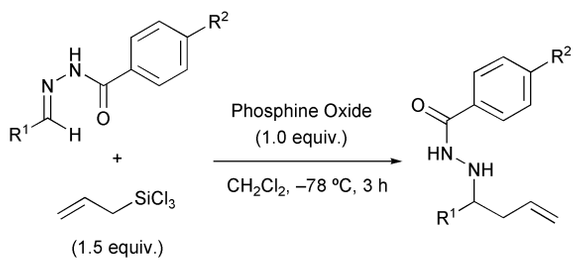
Metal-free organic molecule-catalyzed reactions have been widely focused on because of their stability and environmentally benign nature compared to metal complex-catalysts.[1] In the allylation of aldehydes using allyltrichlorosilanes, Lewis bases such as *N*,*N*-dimethylformamide (DMF),[2] ureas,[3] pyridine *N*-oxides,[4] phosphoramides,[5] phosphine oxides,[6] and sulfoxides[7] have been reported to be effective as catalysts. In these reactions, allyltrichlorosilanes form an active hypervalent silicon species by coordination of the Lewis base serving as nucleophile.[8] We previously defined these Lewis bases as neutral coordinate-organocatalysts (*NCOs*) so that they can be distinguished from anionic Lewis bases such as alkoxide and halide anions.[9]

As for the allylation of azomethine compounds such as *N*-(2-hydroxyphenyl)imines[10] and *N*-acylhydrazones, we have found several types of effective *NCOs*.[7] Among them, sulfoxides were found to be one of the most effective *NCOs*, and enantioselective allylations have been successfully achieved using chiral sulfoxides such as (+)-methyl *p*-tolyl sulfoxide, though three equivalents of sulfoxides and 2-methyl-2-butene as an acid scavenger were required in that system because of the low stability of sulfoxides under acidic conditions. Herein, we report phosphine oxides as further advanced *NCOs* in the allylation of *N*-acylhydrazones. Phosphine oxides are more stable under acidic or oxidative conditions than sulfoxides.[11]

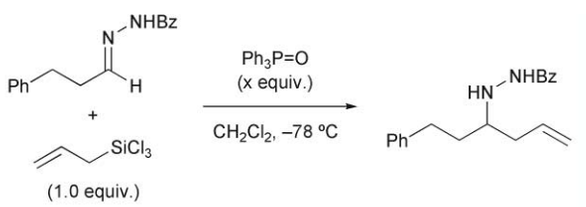
At the outset, the reactions of typical aromatic and aliphatic *N*-benzoylhydrazones with allyltrichlorosilane (1.5 equiv.) were performed in the presence of one equivalent of a phosphine oxide (Table 1). It was found that triphenylphosphine oxide was the most effective among the *NCOs* tested in the reaction with 3-phenylpropanal-derived *N*-benzoylhydrazone as a substrate (Table 1, entry 1), while benzaldehyde-derived *N*-benzoylhydrazones gave lower yields (entries 7–9).

We then conducted a kinetic study at the initial stage of allylation of an aliphatic *N*-benzoylhydrazone using different equivalents of triphenylphosphine oxide ranging from 50 mol% to 300 mol%, and the results are shown in Fig. 1. With increasing equivalents of *NCO* up to 200 mol%, the yield got significantly better. However, the use of 300 mol% phosphine oxide did not improve the yield. It was suggested that two *NCO* molecules coordinated to allyltrichlorosilane to facilitate the

Table 1 Effect of the structure of phosphine oxide



Entry	R^1	R^2	Phosphine oxide	Yield/%
1	$PhCH_2CH_2$	H	$Ph_3P{=}O$	72
2		H	$^nBu_3P{=}O$	57
3		H	$^cHex_3P{=}O$	4
4		H	$(o\text{-Tol})_3P{=}O$	5
5		Cl	$Ph_3P{=}O$	79
6		CF_3	$Ph_3P{=}O$	67
7	Ph	Ph	$Ph_3P{=}O$	3
8		Ph	$^nBu_3P{=}O$	12
9		OMe	$Ph_3P{=}O$	24



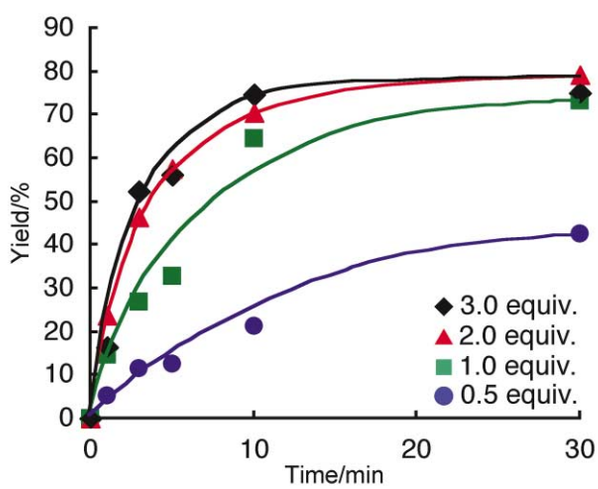


Fig. 1 Effect of the amount of $Ph_3P{=}O$.

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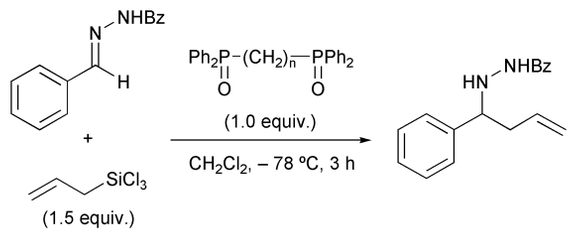
Table 2 Effect of methylene-tethered bisphosphine oxides

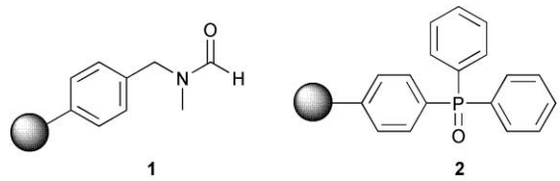


n	1	2	3	4	5	6	3[a]
Yield/%	6	15	71	3	23	24	45

[a] 50 mol% of phosphine oxide was used.

reaction. Meanwhile, Denmark and his co-workers investigated the mechanism of allylation of aldehydes with allyltrichlorosilanes using phosphoramides as *NCOs*. They concluded that the allylation was promoted *via* activation of the silane by two phosphoramide molecules.[12] Based on these results, we next decided to examine the effect of methylene-tethered bisphosphine oxides on the selectivity and reactivity of the reactions (Table 2). It was found that by changing the length of the tether, the yield was dramatically changed. When one equivalent of 1,3-bis(diphenylphosphino)propane dioxide (n = 3, dppp dioxide) was used, the best yield was obtained, while in the case of n = 4, the reaction scarcely proceeded possibly because of poor solubility of the *NCO*.

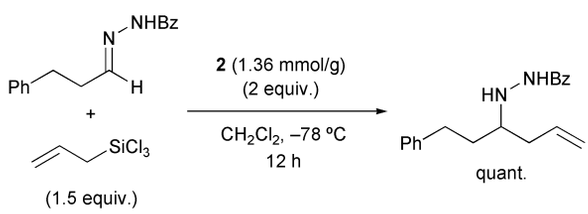
We then examined substrate generality using dppp dioxide as an *NCO* (Table 3).† Aliphatic, aromatic, and α,β-unsaturated *N*-acylhydrazones underwent allylation and stereospecific crotylation in the presence of dppp dioxide. While *syn*-adducts were obtained stereoselectively from (*E*)-crotyltrichlorosilane, *anti*-adducts were found preferentially from (*Z*)-crotyltrichlorosilane. A higher concentration (0.3 M relative to a hydrazone) improved the yield significantly (entry 1 *vs.* 2). Although the yields were still unsatisfactory in some cases



Scheme 1 Polymer-supported *NCOs*.

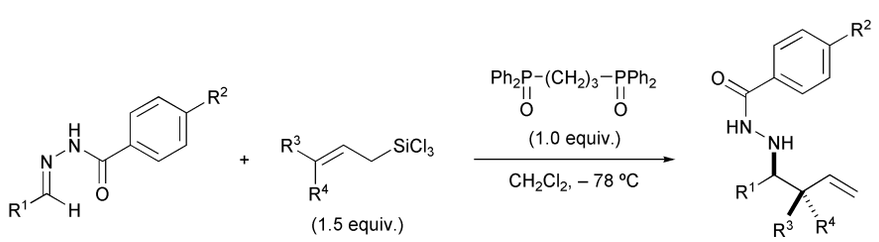
(entries 6, 7, 10, and 13), it should be noted that yields were rather improved by using dppp dioxide instead of dimethyl sulfoxide which we previously utilized as an *NCO*.[7,13]

Finally, we investigated immobilization of a phosphine oxide on a polymer-support. We have already reported polymer-supported (PS)-formamide **1** (Scheme 1) as a recoverable and reusable *NCO*, which worked well in the allylation of aldehydes with allyltrichlorosilane.[14] Although PS-formamide was the first example of an immobilized *NCO*, it showed lower activity in the allylation of *N*-acylhydrazones. Therefore, we tried to develop PS-phosphine oxides as more effective immobilized *NCOs*. PS-phosphine oxide **2** (Scheme 1) was readily prepared from oxidation of commercially available PS-phosphine using hydrogen peroxide in acetone.[15] The completion of the oxidation was confirmed by the ^{31}P swollen resin magic angle spinning NMR (SR-MAS NMR).[16] The loading level of the phosphine oxide was determined by elemental analysis.[17] Allylation of 3-phenylpropanal-derived benzoylhydrazone using **2** (2.0 equiv.) afforded the desired product quantitatively (Scheme 2).[18]



Scheme 2 Allylation of a *N*-acylhydrazone using PS-phosphine oxide **2**.

Table 3 Allylation and crotylation of *N*-acylhydrazones using dppp dioxide



Entry	R^1	R^2	R^3	R^4	Conc./M	Time/h	*syn*/*anti*	Yield/%
1	$PhCH_2CH_2$	H	H	H	0.15	1	—	46
2		H	H	H	0.3	1	—	quant.
3		H	Me	H	0.3	6	98/2	88
4		H	H	Me	0.3	6	<1/>99	quant.
5	Ph	OMe	H	H	0.3	6	—	87
6		OMe	Me	H	0.3	6	80/20	16
7		OMe	H	Me	0.3	6	<1/>99	60
8	PhCH=CH	H	H	H	0.3	6	—	90
9		H	Me	H	0.3	6	99/1	85
10		H	H	Me	0.3	6	15/85	23
11	PhC≡C	H	H	H	0.3	6	—	92
12		H	Me	H	0.3	6	99/1	83
13		H	H	Me	0.3	6	<1/>99	55

In conclusion, we have introduced phosphine oxides as novel *NCOs* in the allylation of *N*-acylhydrazones. Phosphine oxides are more stable and active than sulfoxides, and several problems observed in the allylation using sulfoxide have been overcome. Furthermore, a polymer-supported phosphine oxide has been developed as a more effective immobilized *NCO*. A mechanistic study and asymmetric reactions using the novel *NCOs* are now in progress.

Acknowledgements

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Notes and references

† *General procedure*. To a mixture of *N*-acylhydrazone (0.3 mmol) and phosphine oxide (1.0 equiv.) in dichloromethane (0.8 mL) was added allyltrichlorosilane (1.5 equiv.) in dichloromethane (0.2 mL) at −78 °C, and the mixture was stirred for 1–6 h. Then, triethylamine (0.2 mL) in methanol (1.0 mL) was added to quench the reaction. After addition of water, the mixture was extracted with dichloromethane. The organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under vacuum. The product was isolated by silica gel chromatography.

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17 The elemental analysis showed that PS-phosphine oxide **2** contained 4.2% phosphorous atoms.
18 PS-phosphine oxide **2** is not soluble but swollen in dichloromethane. After the reaction, **2** was recovered quantitatively by simple filtration and washing (water, methanol, diethyl ether, tetrahydrofuran, and dichloromethane). It might be possible that one or two phosphine oxide components in **2** activate allyltrichlorosilane in the transition state, though the latter might be less prominent in the polymer matrix.