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Base-Accelerated Enantioselective Substitution of Morita−Baylis−Hillman Carbonates with Dialkyl Phosphine Oxides

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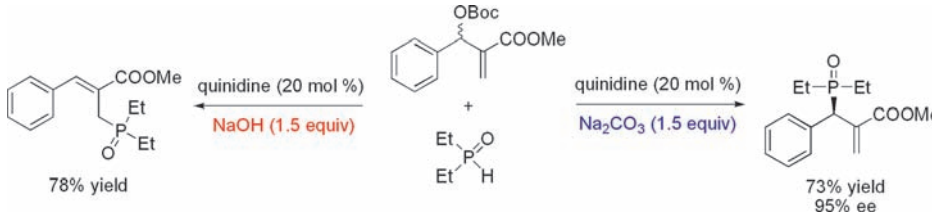
ABSTRACT



A base could accelerate the S_N2' or S_N2'−S_N2' reaction of Morita−Baylis−Hillman (MBH) carbonates with dialkyl phosphine oxides, but the judicial choice of an appropriate base would greatly depress this competitive S_N2' reaction and allow for a highly enantioselective allylic substitution reaction with satisfactory yields and excellent enantioselectivities.

Chiral phosphorus compounds have been extensively employed in asymmetric metal-catalysis or organocatalysis.[1] However, such compounds are expensive, and their preparations usually require a resolution or are limited to the use of enantiopure starting materials.[2] The synthesis of chiral phosphine oxides through asymmetric catalysis is rare. Thus, the development of more efficient catalytic methods for the synthesis of optically active phosphine oxides is currently of pressing importance.[3] Previous studies in this area mainly focused on the addition of reactive diaryl phosphine oxides to various electrophiles[4] or the use of phosphine oxide-containing substrates in asymmetric addition[5] to provide optically active phosphine oxide compounds with high enantioselectivity.

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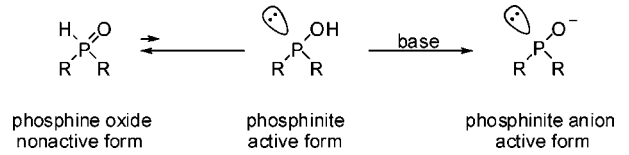
However, the use of less reactive dialkyl phosphine oxides as *P*-nucleophiles is still a challenge and has been reported less. Recently, another strategy, the substitution of Morita−Baylis−Hillman (MBH) adducts with various nucleophiles, has emerged as a very versatile approach to deliver multifunctional allylic-substituted compounds.[6] We envisaged that the asymmetric substitution of MBH carbonates with dialkyl phosphine oxides might be developed.

Phosphine oxides undergo an equilibrium in phosphine oxide−phosphinite tautomerism in solution. The phosphinite tautomer is thought to be the actual nucleophilic species in the bond-forming step. However, under neutral conditions, the equilibrium lies predominantly toward the left (Scheme 1).[7] On the other hand, the higher pK_a values of dialkyl

Scheme 1. The Strategy for the Activation of Phosphine Oxides



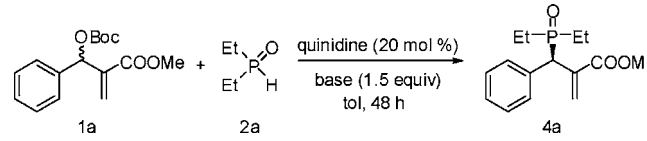
phosphine oxides relative to diaryl phosphine oxides makes them less reactive in bond-forming.[7c] Thus, the activation of dialkyl phosphine oxides is essential for achieving sufficient reactivity. A simple strategy to address these issues is the deprotonation of dialkyl phosphine oxides with an appropriate base because the equilibrium could shift toward the reactive phosphinite tautomer under basic conditions (Scheme 1).[8] However, because phosphine oxides should be deprotonated by a base, the pK_a difference between phosphine oxide and phosphinite could alter the degree of asymmetric induction. Therefore, the basicity of the base should be optimized, and the judicial choice of an appropriate base seems to be of great importance.[9]

Herein, we describe that base could significantly accelerate the organic Lewis base-catalyzed asymmetric substitution of MBH carbonates with dialkyl phosphine oxides.

As part of our continuing interest in asymmetric phosphonylation,[10] we recently reported the asymmetric allylic substitution of MBH carbonates with diaryl phosphine oxides.[10a] However, the reaction did not proceed when the less reactive dialkyl phosphine oxides were employed. We questioned whether inorganic bases, which have a relatively weak basicity, would generate an active phosphinite tautomer at an appropriate rate, thereby enhancing the substitution of MBH carbonates with dialkyl phosphine oxides.

To test our hypothesis, our experiments began with the addition of some inorganic bases to the catalytic system we previously reported. In the control experiment, the reaction did not occur without the addition of a base (Table 1, entry

Table 1. Optimization of the Reaction[a]

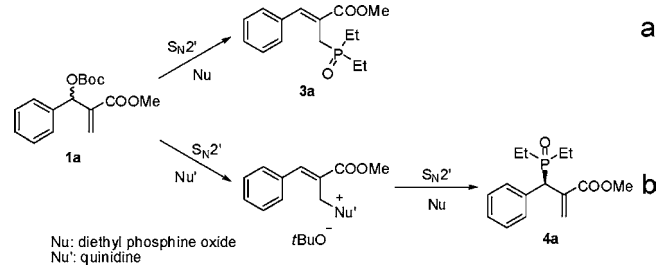


entry	Na_2CO_3	product	yield[b] (%)	ee[c] (%)
1	none			
2	NaOH	**3a**	78	
3	Na_2CO_3	**4a**	81	92
4	Li_2CO_3	**4a**	73	88
5	K_2CO_3	**4a**	77	87
6	Cs_2CO_3	**4a**	<10	nd[d]
7	$NaHCO_3$	**4a**	63	86
8[e]	Na_2CO_3	**4a**	73	95

[a] Unless noted otherwise, all reactions were performed with 0.20 mmol of **1a**, 0.50 mmol of **2a**, 0.30 mmol of base, and 0.04 mmol of quinidine in 1.0 mL of toluene at room temperature for 48 h. [b] Isolated yield. [c] Determined by chiral HPLC on a Chiralpak AD column. [d] Not determined. [e] The reaction was performed at 0 °C for 72 h.

1). The addition of sodium hydroxide led to the S_N2' product **3a** as the main product (**3a**:**4a** = 9:1) (Table 1, entry 2). This was probably because the basicity is too strong, and a direct S_N2' reaction occurred without the assistance of the nucleophilic catalyst (Table 1, entry 2 and Scheme 2a).[11]

Scheme 2. S_N2' Reaction (path a) vs S_N2'−S_N2' Reaction (path b) of MBH Carbonate **1a** with Diethyl Phosphine Oxide **2a**



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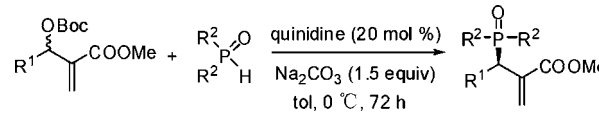
Although the result was less than satisfactory, an interesting finding was that diethyl phosphine oxide could be activated by a base. At this stage, it was thought that an appropriate base which could activate the dialkyl phosphine oxides, and depress the S_N2' reaction would facilitate the substitution reaction. We next tested some alkaline metal carbonates. It was found that the addition of 1.5 equiv of sodium carbonate significantly accelerated the asymmetric substitution in moderate yield and good enantioselectivity (Table 1, entry 3). Lithium carbonate and potassium carbonate each increased the reaction, but showed lower enantioselectivities (Table 1, entries 4 and 5). The addition of cesium carbonate resulted in significantly diminished yield due to the background reaction (Table 1, entry 6). Of the base tested, sodium carbonate showed the most promising result. Compared with our previous protocols, the addition of 4 Å MS and the use of xylenes as the solvent had no positive effect. By lowering the reaction temperature to 0 °C, the ee was improved to 95% (Table 1, entry 8).

Having established that the system quinidine[12]/Na_2CO_3 can accelerate the substitution reaction, we next examined the scope and limitation of the reaction (Table 2). Generally, a wide range of MBH carbonates **1** and dialkylphosphine oxides **2** were suitable for the reaction, affording allylic phosphine oxides **4** in moderate yields and excellent enantioselectivities. It appears that the position and electronic properties of substituents on aromatic rings have a limited effect on the efficiency of this process (Table 2, entries 1−10). Unfortunately, when 2-furyl-substituted MBH carbonate was used, only moderate ee was obtained (Table 2, entry 11). For less reactive alkyl-substituted MBH carbonates, the reaction showed much lower reactivity.[13] Moreover, the scope of the reaction can be successfully extended utilizing other dialkyl phosphine oxides **2b**−**d**, and high enantioselectivities were generally achieved (Table 2, entries 12−14).

To provide more insight into the mechanism, control experiments were performed. As shown in Table 3, neither quinidine nor Na_2CO_3 on its own was effective enough to accelerate the substitution of MBH carbonate with diethyl phosphine oxide (Table 3, entries 1 and 2). Only when these two were used synergistically in a double-activation way could this transformation perform excellently (Table 3, entry 3). These results showed that both the activation of diethyl phosphine oxide and the assistance of the nucleophilic catalyst were essential for the substitution reaction.[14] Next, we investigated the role of the C-6-OMe of quinidine, which showed little effect on the reaction. When cinchonine was used as the catalyst, similar result was observed (Table 3, entry 3 vs 4). Furthermore, protection of C-9-OH of quinidine gave a poor result (Table 3, entry 5). This result showed that hydrogen bonding between the hydroxyl group and sodium phosphinite plays a key role in the reaction.[15] On

Table 2. Scope of the Reaction[a]



1 **2** **4**

entry	**1**, R^1	**2**, R^2	product	yield[b] (%)	ee[c] (%)
1	**1a**, Ph	**2a**, Et	**4a**	73	95
2	**1b**, 2-FPh	**2a**, Et	**4b**	66	91
3	**1c**, 2-ClPh	**2a**, Et	**4c**	63	95
4	**1d**, 2-MeOPh	**2a**, Et	**4d**	61	90
5	**1e**, 3-ClPh	**2a**, Et	**4e**	80	94
6	**1f**, 3-MeOPh	**2a**, Et	**4f**	87	95
7	**1g**, 4-FPh	**2a**, Et	**4g**	75	92
8	**1h**, 4-ClPh	**2a**, Et	**4h**	78	96
9	**1i**, 4-BrPh	**2a**, Et	**4i**	76	95
10	**1j**, 4-MeOPh	**2a**, Et	**4j**	83	96
11	**1k**, 2-furyl	**2a**, Et	**4k**	48	71
12	**1a**, Ph	**2b**, n-Pr	***4l***	81	90
13	**1a**, Ph	**2c**, n-Bu	**4m**	63	98
14	**1a**, Ph	**2d**, allylic	**4n**	92	90

[a] All reactions were performed with 0.20 mmol of **1**, 0.50 mmol of **2**, 0.30 mmol of Na_2CO_3, and 0.04 mmol of quinidine in 1.0 mL of toluene at 0 °C for 72 h. [b] Isolated yield. [c] For analysis of the ee values of the products, see the Supporting Information.

Table 3. Control Experiments[a]

entry	catalyst	base	yield[b] (%)	ee[c] (%)
1	none	Na_2CO_3		
2	quinidine	none		
3	quinidine	Na_2CO_3	81	92
4	cinchonine	Na_2CO_3	78	88
5	QD-TMS[d]	Na_2CO_3	21	nd[e]

[a] All reactions were performed with 0.20 mmol of **1a**, 0.50 mmol of **2a**, 0.30 mmol of base, and 0.04 mmol of catalyst in 1.0 mL of toluene at room temperature for 48 h. [b] Isolated yield. [c] Determined by chiral HPLC on a Chiralpak AD column. [d] The hydroxyl group of quinidine was protected by TMSCl. [e] Not determined.

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(12) For a review on modified Cinchona alkaloids, see: Tian, S.-K.; Chen, Y.; Hang, J.; Tang, L.; McDaid, P.; Deng, L. *Acc. Chem. Res.* **2004**, *37*, 621.

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the basis of all these observations, we proposed a tentative transition state for the substitution of MBH carbonate with diethyl phosphine oxide using the system quinidine/Na_2CO_3 (Figure 1).

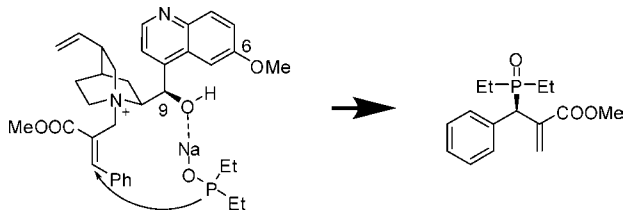

Figure 1. Proposed transition state.

In summary, we have found that a base could significantly accelerate the enantioselective allylic substitution of MBH carbonates with dialkylphosphine oxides, which provides direct access to optically allylic phosphine oxides with satisfactory yields and excellent enantioselectivities. Although the competitive S_N2' reaction would occur under basic conditions, the judicial choice of an appropriate base would greatly depress this competitive reaction and allow for a highly enantioselective allylic substitution reaction. In this catalytic system, the less reactive dialkyl phosphine oxides can be activated by Na_2CO_3 because the equilibrium could shift toward the reactive phosphinite tautomer under such conditions. Further applications of the current methodology are ongoing in our laboratory.

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Supporting Information Available: Experimental details and characterization data for the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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