Organocatalysis

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Enantioselective Activation of Aldehydes by Chiral Phosphoric Acid Catalysts in an Aza-ene-type Reaction between Glyoxylate and Enecarbamate**

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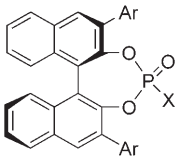
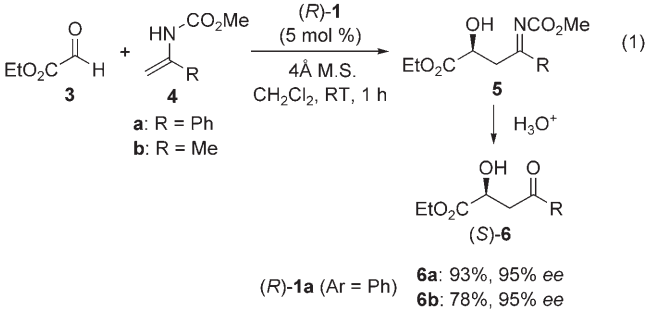
Carbonyl compounds play a central role in a diverse array of organic reactions. In particular, the activation of aldehydes for reaction represents the most fundamental transformation available to synthetic chemists, and has developed into a broad reaction class that occupies a privileged place in synthetic organic chemistry.[1] In recent years, chiral Brønsted acids have emerged as efficient enantioselective catalysts,[2] and as an attractive class of organocatalysts.[3] The activation of aldehydes by using a chiral Brønsted acid was first reported by Rawal and co-workers, who performed a hetero Diels–Alder reaction in the presence of a catalytic amount of taddol (taddol = tetraaryl-1,3-dioxolane-4,5-dimethanol).[4a] Since this milestone achievement, chiral Brønsted acid catalysis through the activation of carbonyl compounds has attracted considerable attention in organic chemistry.[4,5] Binol-derived (binol = 1,1′-bi-2-naphthol) phosphoric acid **1** is an extensively studied chiral Brønsted acid, which has been shown to be a versatile catalyst in enantioselective transformations.[2,6,7] Most of these transformations include imines as the electrophilic component; in contrast, activation of carbonyl compounds has been scarcely explored despite their synthetic utility. Recently, Yamamoto and co-workers reported the enantioselective Diels–Alder reaction of α,β-unsaturated ketones with silyloxy dienes by using binol-derived *N*-triflyl phosphoramide **2** as the acid catalyst.[8] The activation of carbonyl compounds was subsequently accomplished by Rueping et al.[9] in which they reported that **2** functioned as an efficient enantioselective catalyst for the Nazarov cyclization and the Friedel–Crafts reaction by activating ketones. These reports are the only publications that demonstrate the activation of carbonyl compounds by chiral phosphoric acid derivatives. In our continuous efforts to extend the synthetic applicability of chiral phosphoric acid catalysts,[6,7] we describe herein the first example of the activation of aldehydes by using chiral phosphoric acid **1** to efficiently accelerate an aza-ene-type reaction[6d,i,10] of glyoxylate **3**, as a reactive aldehyde, with enecarbamate **4** in a highly enantioselective manner [Eq. (1)]. We also disclose some mechanistic aspects



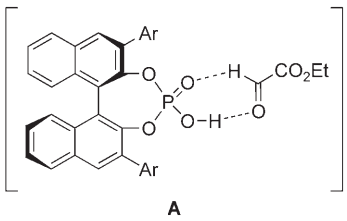
(*R*)-**1**: X = OH
(*R*)-**2**: X = $NHSO_2CF_3$



(1)

(*R*)-**1a** (Ar = Ph) **6a**: 93%, 95% *ee*; **6b**: 78%, 95% *ee*

of the enantiofacial selectivity based on DFT computational analysis of the hydrogen-bonded pair formed between glyoxylate **3** and phosphoric acid **1**. The two hydrogen-bonding interactions (**A**) are shown to be crucial to achieve high enantioselectivity.[11]



A

Our study commenced with the reaction of glyoxylate **3** and enecarbamates **4a** and **4b**, respectvely, in the presence of 4 Å molecular sieves [12] and 5 mol % phosphoric acid catalyst **1a**, which contains phenyl substituents (Ar = Ph) at the 3,3′-positions of the binaphthyl group. As shown in Equation (1), the reaction proceeded smoothly to provide the corresponding aza-ene-type products (**5a** and **b**) in high yields within 1 hour. The enantioselectivity was determined after the hydrolysis of **5** to give the β-hydroxy ketone (**6a** and **b**). Excellent enantioselectivities were observed with catalyst **1a**, which bears unmodified phenyl groups (Ar = Ph). The fact

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that the simple, phenyl-substituted catalyst provides excellent enantioselectivity is noteworthy because experiments on the activation of imines showed that catalyst **1** required modified phenyl substituents, typically bulky ones, to obtain high enantioselectivities.[6,7]

To gain mechanistic insight into the high enantioselectivity observed when using **1a**, we investigated a series of catalysts (**1**) bearing substituted phenyl rings. As shown in Table 1, there was a marked relationship between the substituent pattern on the phenyl ring and the catalytic performance in terms of both activity and enantioselectivity. The catalyst performance was maintained when the substituents were introduced to the *para* position of the phenyl ring, irrespective of their stereoelectronic properties (Table 1, entries 1–5). In contrast, if the phenyl ring was substituted by bulky groups at the 3,5-positions or by small substituents at the 2,6-positions (Table 1, entries 6–8) the catalytic activity and enantioselectivty was compromised.

Table 1: Enantioselective aza-ene-type reaction of glyoxylate (**3**) with enecarbamate (**4a**) catalyzed by (*R*)-**1** ([Eq. (2)]).[a]

Entry	**1**: Ar	Yield [%][b]	*ee* [%][c]
1	**1b**: 4-$CH_3C_6H_4$	93	95
2	**1c**: 4-$CF_3C_6H_4$	82	94
3	**1d**: 4-*t*BuC_6H_4	99	98
4	**1e**: 4-β-naphthylphenyl	81	95
5	**1f**: β-naphthyl	80	91
6	**1g**: 3,5-$tBu_2C_6H_3$	37	2
7	**1h**: 2,4,6-$(CH_3)_3C_6H_2$	40	8[d]
8	**1i**: 9-anthryl	35	18

[a] Unless otherwise noted, all reactions were carried out by using (*R*)-**1** (0.005 mmol ,5 mol%), freshly distilled **3** (0.17 mmol , 1.7 equiv), and **4a** (0.1 mmol) in CH_2Cl_2 (1.0 mL) for 1 h at room temperature in the presence of powdered 4 Å molecular sieves (85 mg). [b] Yield of **6a** after isolation. [c] Determined by chiral HPLC analysis. Absolute stereochemistry of **6a** was determined to be *S*.[13] [d] (*R*)-**6a** as a major enantiomer.

In an effort to understand the high enantioselectivity observed for catalyst (*R*)-**1a**, having simple phenyl substituents, we conducted a computational study into the hydrogen bonding between catalyst (*R*)-**1** and methyl glyoxylate (**3′**) at the B3LYP/6-31G** level of theory.[14] The lowest energy conformers of the (*R*)-**1a**/**3′** pair and the (*R*)-**1h**/**3′** pair are shown in Figures 1a and b, respectively. The key feature of the complexation mode is the presence of a double hydrogen bond,[15] where the hydrogen bond between the formyl hydrogen atom and the phosphoryl oxygen atom forces a coplanar orientation of the formyl group and the phosphoric acid subunit.[11] The experimental results can be rationalized by these double hydrogen-bonding models. In the 3D-structure of hydrogen-bonded pair **1a**/**3′** (Figure 1a), one enantiotopic face (*re* face) of the aldehyde is effectively shielded by one of the phenyl rings. In contrast, the other face (*si* face) is fully accessible and hence the enecarbamate attacks from the front side (blue arrow indicated in Figure 1a). This attack affords the product with the *S* configuration, which is the absolute configuration observed experimentally. Such a conformational arrangement of the

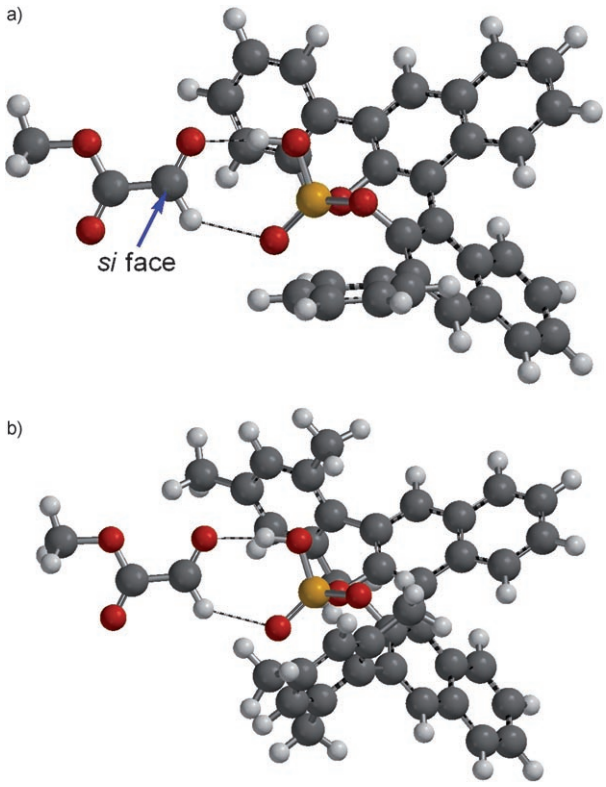

Figure 1. Three-dimensional structures of the hydrogen-bonded complexes formed between **1** and **3′**. P tan, O red, C gray, H white. a) (*R*)-**1a**/**3′**; b) (*R*)-**1h**/**3′**.

phenyl rings would be applicable to the *para*-substituted catalysts (**1b**–**1f**). In contrast, the mesityl rings of (*R*)-**1h** are forced into a perpendicular arrangement with respect to the basal naphthyl moiety because of the two *ortho*-methyl substituents, and hence overlapping with the aldehyde occurs (Figure 1b). Both enantiotopic faces are well shielded by the Ar groups and as a result there is a significant decrease in catalytic activity and enantioselectivty in catalysis by **1h**. Similar conformational restrictions would occur with the other catalysts having bulky Ar groups (**1g** and **i**).

Next we used various enecarbamates **4** in the aza-ene-type reaction to investigate the stereochemical aspects of diastereoselection [Eq. (2)]. Among the catalysts (**1**) that were examined (Table 1), **1d** exhibited excellent performance in terms of both catalytic activity and enantioselectivity and hence the subsequent reactions were carried out by using **1d**. As shown in Table 2, the (*Z*)-enecarbamates required longer

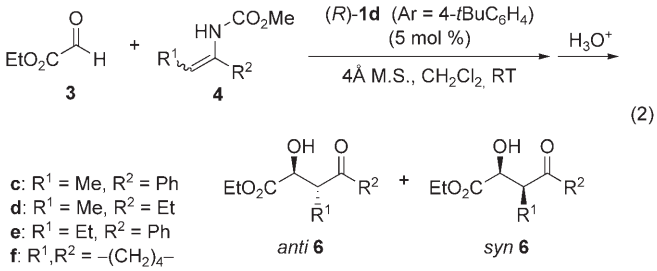

Table 2: Aza-ene-type reaction of various enecarbamates (**4**) with **3** catalyzed by (*R*)-**1d** ([Eq. (2)]).[a]

Entry	4	*t* [h]	Yield [%][b]	*anti*:*syn*	*ee* [%][c]	
					anti	*syn*
1	(*E*)-**4c**	2	73	>99:<1	>99	53
2	(*E*)-**4d**	2	73	96:4	99	56
3[d]	(*E*)-**4e**	4	75	99:1	99	74
4	**4f**	1	89	89:11	99	98
5	(*Z*)-**4c**	24	11	72:28	26	88
6	(*Z*)-**4d**	2	74	50:50	28	69
7[d]	(*Z*)-**4e**	24	67	92:8	8	74

[a] Unless otherwise noted, all reactions were carried out by using 0.005 mmol of (*R*)-**1d** (5 mol%), 0.17 mmol of freshly distilled **3** (1.7 equiv), and 0.1 mmol of **4** in 1.0 mL of CH_2Cl_2 in the presence of powdered 4 Å molecular sieves (85 mg). [b] Yield of **6** after isolation. [c] Determined by chiral HPLC analysis. [d] 0.3 mmol of freshly distilled **3** (3.0 equiv).

reaction times and low enantioselectivities were observed in the major isomers (*anti*) (Table 2, entries 5–7). However, extremely high enantioselectivities and *anti* selectivities were observed in the reactions of the *E* isomers (Table 2, entries 1–4). It seems likely that the reaction proceeds through a cyclic transition state because of the significant difference in both the reactivity and the enantioselectivity observed between each geometric isomer. The slower reaction observed with *Z* enecarbamates could be caused by unfavorable interactions between the enecarbamate (**4**) and the hydrogen-bonded complex of **1d** and **3**. Whereas the exclusive formation of *anti* products from the *E* isomers could be attributed to the well defined *exo* transition state.[10b]

In conclusion, we have demonstrated the highly enantio- and diastereoselective aza-ene-type reaction of glyoxylate with enecarbamates catalyzed by a chiral phosphoric acid. DFT computational analysis of the complexation modes allowed us to demonstrate that the double hydrogen bonding interaction between the phosphoric acid and the glyoxylate is crucial in providing the high enantioselectivity. The present hydrogen-bonding model could be applicable to other enantioselective reactions of aldehydes, and also provides a guiding principle for the design of novel chiral Brønsted acid catalysts. Additional studies to develop other enantioselective transformations of aldehydes and to elucidate the transition states of the phosphoric acid catalyzed aza-ene-type reaction are in progress.

Experimental Section

Representative procedure for aza-ene-type reaction of glyoxylate with enecarbamates catalyzed by chiral phosphoric acid (Table 1): Freshly distilled ethyl glyoxylate (**3**) (16.9 μL, 0.17 mmol) was added to a suspension of phosphoric acid (*R*)-**1d** (2.5 mg, 5 μmol) and activated 4 Å molecular sieves (< 5 micron powder, 85 mg) in CH_2Cl_2 (1 mL) at room temperature under N_2 gas. After stirring the mixture for 5 min, enecarbamate **4a** (18.5 μL, 0.1 mmol) was introduced and the reaction mixture was stirred at room temperature for 1 h. The resulting mixture was quenched with saturated $NaHCO_3$ aq. at room temperature and then extracted with CH_2Cl_2 (×4). The organic layer was dried over Na_2SO_4, filtrated, and concentrated to give crude **5a**. A solution of crude **5a** in EtOH (1.5 mL) was treated with HBr (47% aqueous solution, 150 μL) at room temperature and the resulting mixture was stirred at room temperature for 1 h. The reaction mixture was then quenched with saturated $NaHCO_3$ aq. at 0 °C, and extracted with CH_2Cl_2 (×4). The organic layer was dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography to give **6a** (20.6 mg, 0.0927 mmol) in 99% yield as a slightly yellow liquid. The enantioselectivity of **6a** was determined to be 98% *ee* by using chiral HPLC analysis.

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