Asymmetric Synthesis

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Chiral Phosphoric Acid Catalyzed Desymmetrization of *meso*-1,3-Diones: Asymmetric Synthesis of Chiral Cyclohexenones**

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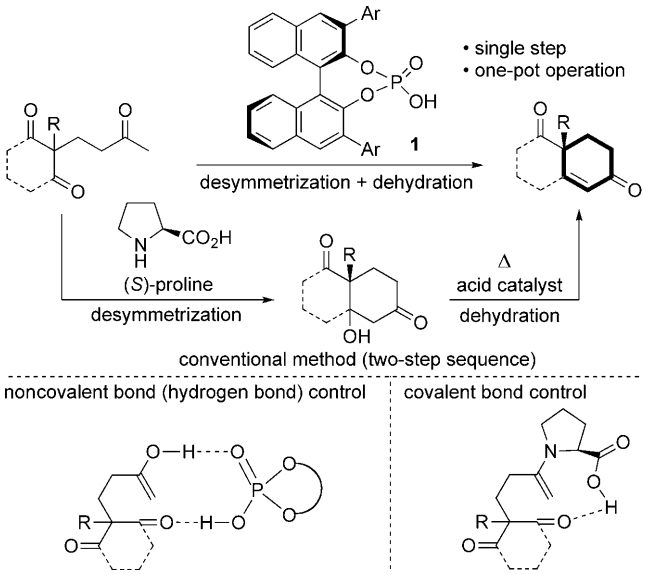
Cyclohexenones are important building blocks in synthetic organic chemistry. In particular, Hajos–Parrish[1] and Wieland–Miescher[2] ketones are useful synthetic intermediates not only for the preparation of steroids[3] but also for a range of natural products.[4] The most facile and conventional method used to obtain these ketones in enantiomerically pure form is the desymmetrization of *meso*-1,3-dicarbonyl compounds, in which (*S*)-proline is commonly used as a highly reliable chiral catalyst (Scheme 1).[1,2] This protocol consists of two consecutive transformations: 1) desymmetrization of *meso*-1,3-dione by (*S*)-proline-catalyzed aldol reaction, and 2) dehydration.

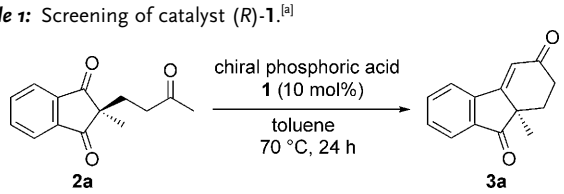


Scheme 1. Synthetic strategy for the preparation of chiral cyclohexenones.

As a result of our initial findings,[5] chiral phosphoric acids **1** derived from (*R*)-BINOL have been extensively studied as versatile chiral Brønsted acid catalysts. They exhibited remarkable asymmetric inducing ability in the nucleophilic addition to imine, the 1,4-addition to α,β-unsaturated compounds, and the transfer hydrogenation with Hantzsch ester.[6] Although the asymmetric ring-opening of *meso*-aziridines by means of chiral phosphoric acid had already been reported by Antilla and co-workers,[7a] the chiral phosphoric acid induced desymmetrization of *meso*-1,3-diones still remains a challenge.[7b,c] The control of stereoselectivity by weak, noncovalent bond interaction (hydrogen bond) is not a trivial issue in comparison with the control by covalent bonds ((*S*)-proline catalysis).[8] Herein, we report the asymmetric synthesis of synthetically useful chiral cyclohexenones through the desymmetrization of *meso*-1,3-dicarbonyl compounds induced by a chiral phosphoric acid.[9] By this method, both desymmetrization of the 1,3-dione compound and dehydration could be accomplished in a single-step, one-pot operation, to afford chiral cyclohexenones with excellent enantioselectivity.

An initial study was conducted by treatment of triketone **2** with 10 mol% of **1a** in toluene. Gratifyingly, enone **3a** was obtained in the enantioenriched form (46% *ee*; Table 1,

Table 1: Screening of catalyst (*R*)-**1**.[a]



Entry	Ar	Yield [%][b]	*ee* [%][c]
1	Ph (**1a**)	56 (43)	46
2	$SiPh_3$ (**1b**)	85 (5)	84
3	9-anthryl (**1c**)	91 (4)	70
4	2,4,6-(iPr)$_3C_6H_2$ (**1d**)	92 (5)	90
5[d]	2,4,6-(iPr)$_3C_6H_2$ (**1d**)	>99	90
6[d,e]	2,4,6-(iPr)$_3C_6H_2$ (**1d**)	95	90
7[f]	(S)-proline	57[g]	−60

[a] Unless otherwise noted, all reactions were conducted with 0.2 mmol of **2a** in toluene (2.0 mL). [b] Determined by ^{1}H NMR spectroscopy. Amount of recovered starting material in parenthesis. [c] Determined by HPLC on a chiral stationary phase using a Daicel Chiralcel OD-H column; flow rate = 0.5 mL min^{-1}; eluent = *n*-hexane/*i*PrOH = 5:1. [d] *n*-Hexane was used as the reaction solvent. [e] 5 mol% catalyst loading. [f] Triketone **2** was treated with 10 mol% of (*S*)-proline in DMF at 25 °C for 48 h, and the resulting product was treated with TsOH·H_2O (10 mol%) in benzene at reflux for 20 min. [g] Yield of isolated product. DMF = *N*,*N*-dimethylformamide, Ts = 4-toluenesulfonyl.

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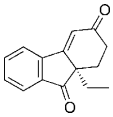
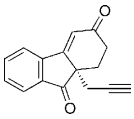
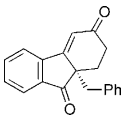
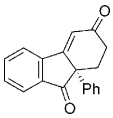
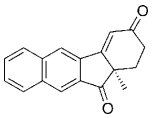
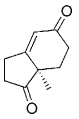
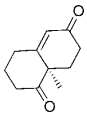
entry 1), even when the reaction was performed at 70 °C. Screening of catalysts and reaction conditions (Table 1, entries 2–5) revealed that the use of 5 mol % of 2,4,6-triisopropylphenyl-substituted catalyst **1d** in *n*-hexane at gentle reflux (70 °C) was the optimal set of the conditions, and gave **3a** in excellent yield and enantioselectivity (95 %, 90 % *ee*; Table 1, entry 6).[10] Significantly, the selectivity of the chiral phosphoric acid was overwhelmingly higher than that of (*S*)-proline (57 %, 60 % *ee*; Table 1, entry 7).

The generality of this method was examined under the optimal reaction conditions (Table 2). Ethyl-substituted **3b** was obtained in excellent yield and enantioselectivity (89 %, 92 % *ee*; Table 2, entry 1). In the case of propargyl substrate **3c**, a key synthetic intermediate in the synthesis of the gibbane framework,[11] the enantioselectivity was also excellent (94 % *ee*; Table 2, entry 2). Benzyl- and phenyl-substituted substrates (**3d** and **3e**) were obtained in good enantioselectivity (87 and 90 % *ee*; Table 2, entries 3 and 4). In these two reactions, higher catalyst loading (10 mol %) and prolonged reaction times (96 and 48 h, respectively) were required. In particular, in the case of the phenyl-substituted substrate **3e** the use of toluene as the reaction solvent was essential owing to the poor solubility of the substrate. Excellent yield and enantioselectivity were also observed in the case of naphthalene derivative **3f** (90 %, 84 % *ee*; Table 2, entry 5). Chiral phosphoric acid was applied to the asymmetric synthesis of Hajos–Parrish and Wieland–Miescher ketones (**3g** and **3h**), and gave moderate to high yields with good enantioselectivity (70 and 82 % *ee*; Table 2, entries 6 and 7).[12] The absolute configurations of these cyclohexenone derivatives were surmised by analogy with **3a**.

Table 2: Substrate scope of the desymmetrization reaction.[a]

Entry	Product		*t* [h]	Yield [%]	*ee* [%][b]
1	**3b**		48	89	92
2	**3c**		72	82	94
3[c]	**3d**		96	94	87
4[c,d]	**3e**		48	72	90
5[c]	**3f**		24	90	84
6[c]	**3g**		24	86	70
7[c]	**3h**		24	64	82

[a] Unless otherwise noted, all reactions were conducted with 0.2 mmol of **2** and 5 mol % **1d** in *n*-hexane (2.0 mL) at 70 °C. [b] Determined by HPLC on a chiral stationary phase. [c] 10 mol % of **1d** was employed. [d] In toluene at 90 °C.

To clarify the origin of the enantioselectivity, ONIOM (B3LYP/6-31G*:HF/3-21G) calculations[13] were carried out based on the transition state (TS) controlled by hydrogen bonding, as shown in Scheme 1. In the TS, chiral phosphoric acid could simultaneously activate carbonyl and enol moieties with Brønsted acidic and Lewis basic sites, respectively.[14] The attack of the TS from the *si* face ($\mathbf{TS}_{si}$) was 1.3 kcal mol^{-1} more stable than attack from the *re* face ($\mathbf{TS}_{re}$), which is in agreement with the experimental results (Figure 1). The energy difference would be mainly caused by the steric repulsion between the aryl moiety of the substrate and the 3,3′-triisopropylphenyl group.

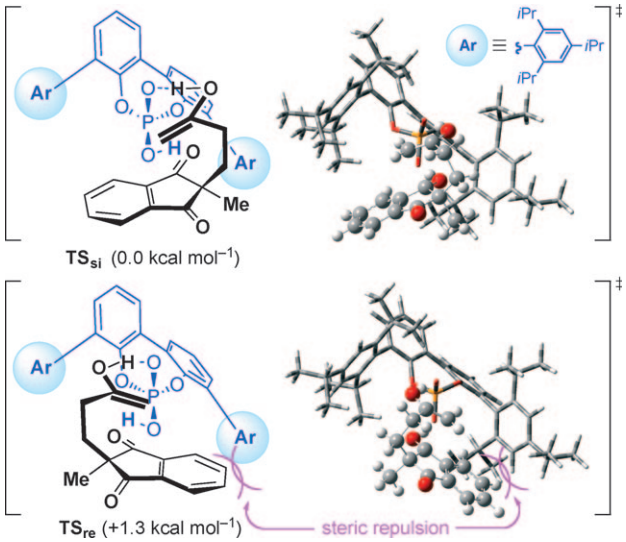


Figure 1. 3D structures and schematic representation of models of $\mathbf{TS}_{re}$ and $\mathbf{TS}_{si}$ calculated by ONIOM (B3LYP/−31G*:HF/3-21G).

In summary, we have developed the first example of chiral phosphoric acid catalyzed desymmetrization of *meso*-1,3-dicarbonyl compounds. This method could be applied to a wide variety of substrates to give chiral cyclohexenones in high yields and with excellent enantioselectivity. Further investigation of its application to the synthesis of natural products is currently under way in our laboratory.

Experimental Section

General procedure for Table 1, entry 6: Chiral phosphoric acid **1d** (7.5 mg, 0.010 mmol) was added to a solution of triketone **2a** (46 mg, 0.20 mmol) in *n*-hexane (2.0 mL) at room temperature, and the reaction mixture was heated at 70 °C. After heating for 24 h, the reaction mixture was directly purified by column chromatography on

silica gel (eluent: CH_2Cl_2/AcOEt 10:1) to give **3a** (40 mg, 0.19 mmol) in 95% yield.

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