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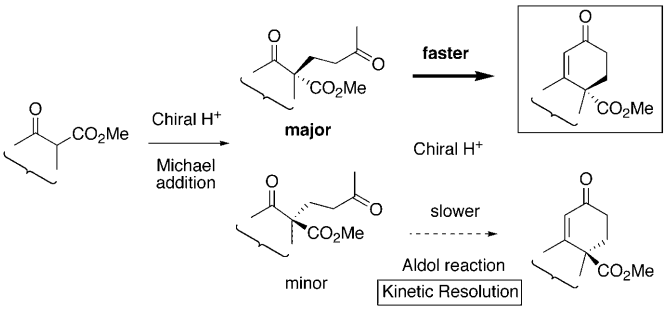
Enantioselective Robinson-Type Annulation Reaction Catalyzed by Chiral Phosphoric Acids**

Takahiko Akiyama, Takuya Katoh, and Keiji Mori*

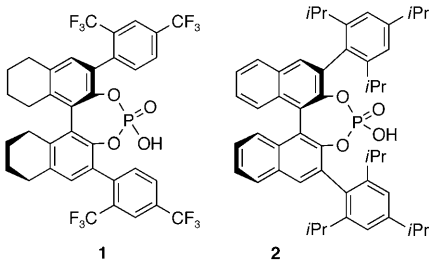
The Robinson annulation reaction is one of the most useful methods for the construction of the cyclohexenone structure and is widely employed in the synthesis of complex natural products.[1] It consists of three consecutive processes: 1) Michael addition of a carbonyl compound to an α,β-unsaturated ketone, 2) an intramolecular aldol reaction, and 3) dehydration. Both acid and base catalysts have been extensively utilized in the Robinson annulation reaction. To synthesize the cyclohexenone substructures in an optically pure form with the Robinson annulation reaction, a chiral ketone is used as the starting material and an enantioenriched Robinson annulation product is furnished by the diastereoselective Michael addition reaction.[2] Alternatively, the enantioselective Michael addition reaction is a key reaction for the enantioselective Robinson annulation reaction.[3] In the 1970s Hermann and Wynberg conducted seminal work on the enantioselective conjugate addition of β-keto esters to methyl vinyl ketone in the presence of cinchona alkaloid as catalyst.[4,5] Sasai and Shibasaki disclosed the highly enantioselective conjugate addition reaction of β-keto esters with methyl vinyl ketone.[6] Chiral scandium(III) catalysts,[7] palladium catalysts,[8] and ruthenium catalysts[9] have been also employed. Maruoka and co-workers have reported phase-transfer catalysis.[10] Recently, Deng and co-workers have developed an efficient cinchona alkaloid catalyst.[11]

In our ongoing studies of synthetic methods which are catalyzed by phosphoric acid,[12–14] we found a novel strategy for the enantioselective Robinson-type annulation reaction which includes: 1) a chiral Brønsted acid catalyzed enantioselective Michael addition reaction of α-alkyl-β-keto esters with methyl vinyl ketone, and 2) a chiral Brønsted acid catalyzed kinetic resolution in the intramolecular aldol reaction followed by dehydration. The enantiomer that was obtained selectively by the Michael addition reaction reacted preferentially to give the corresponding Robinson-type annulation product with excellent enantioselectivities (Scheme 1). Herein, we wish to describe the details of our strategy.



Scheme 1. Strategy for the asymmetric Robinson-type annulation reaction.

At the outset, the Michael addition reaction of β-keto ester **3a** (X = Y = H, Z = CH_2) with methyl vinyl ketone in the presence of a chiral phosphoric acid was examined. Screening for the phosphoric acid revealed that phosphoric acid **1** was the most effective as a catalyst for the Michael



1 **2**

addition reaction in terms of both chemical yield and enantioselectivity. The corresponding Michael adduct **4a** was obtained in 99% yield with 78% *ee* (Table 1, entry 1). The enantioselectivity was determined by HPLC analysis.[15] The substrate scope of the Michael addition reaction is shown in Table 1. Substituted indanone derivative **3** (Z = CH_2) proved to be a suitable substrate (Table 1, entries 1–4). β-Keto esters **3** (Z = O) obtained from salicylic acid also gave the corresponding adducts with high enantioselectivities (Table 1, entries 5–8). Notably, a catalyst loading of as low as 2 mol% was enough for the Michael addition reactions (Table 1, entries 5 and 8). Methyl 2-oxocyclopentanecarboxylate also afforded the corresponding adduct with high enantioselectivity (Table 1, entry 9).

Next, we investigated the kinetic resolution in the phosphoric acid catalyzed aldol reaction of **4a**. Treatment of racemic **4a** with 10 mol% of **1** in *m*-xylene at 100°C for 13 hours furnished **5a** in 13% yield with 48% *ee*. This product was accompanied by recovered **4a** in 56% yield with 25% *ee*.

[*] Prof. Dr. T. Akiyama, T. Katoh, Dr. K. Mori
Department of Chemistry, Gakushuin University
1-5-1, Mejiro, Toshima-ku, Tokyo 171-8588 (Japan)
Fax: (+81) 3-5992-1029
E-mail: takahiko.akiyama@gakushuin.ac.jp

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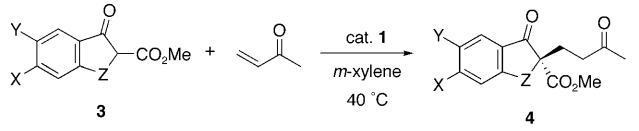
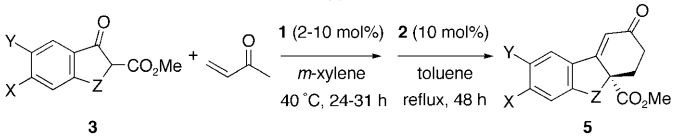
Table 1: Enantioselective Michael addition reaction.



Entry	X	Y	Z	Yield [%][a]	*ee* [%][b]
1[c]	H	H	CH_2	99	78
2[c,d]	H	H	CH_2	99	80
3[c]	Br	H	CH_2	89	78
4[c]	Cl	H	CH_2	99	81
5[e]	H	H	O	99	83
6[c]	H	Cl	O	99	78
7[c]	H	Br	O	79	75
8[e]	H	Me	O	87	70
9[c,f]	methyl 2-oxocyclopentane-carboxylate			88	78

[a] Yield of isolated product. [b] Enantiomeric excess was determined by HPLC methods on a chiral stationary phase. [c] Reactions were carried out with **3** (0.2 mmol), and methyl vinyl ketone (0.6 mmol; 3 equiv) in the presence of **1** (10 mol%) in *m*-xylene (1.0 mL). [d] Benzyl ester was employed instead of methyl ester. [e] Reactions were carried out with **1** (2 mol%) and methyl vinyl ketone (2 equiv) at 20°C. [f] The reaction was carried out at 50°C for 48 h.

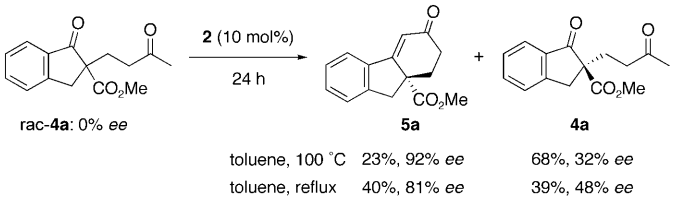
Table 2: Enantioselective Robinson-type annulation reaction.[a]



Entry	X	Y	Z	Yield [%][a]	*ee* [%][b]
1	H	H	CH_2	64	96
2[c]	H	H	CH_2	61	99
3[d]	H	H	CH_2	74	97
4	Br	H	CH_2	67[e]	99
5	Cl	H	CH_2	64	98
6	H	H	O	66	99
7	H	Cl	O	72	97
8	H	Br	O	71	96
9	H	Me	O	54	99
10	methyl 2-oxocyclopentane-carboxylate			53	83

[a] Yield of isolated product. [b]Enantiomeric excess was determined by HPLC methods on a chiral stationary phase. [c] The second reaction was carried out at 100°C. [d] Benzyl ester was employed instead of methyl ester. [e] Yield based on ^{1}H NMR spectroscopy.

Although phosphoric acid **1** was not effective, a detailed survey of other chiral phosphoric acids revealed that prominent kinetic resolution was observed by using **2** at high temperature (Scheme 2). Treatment of racemic **4a** with



Scheme 2. Kinetic resolution in the Aldol reaction.

10 mol% of **2** in toluene at 100°C for 24 hours resulted in the formation of **5a** in 23% yield with 92% *ee*. Further increasing the reaction temperature (heating at reflux in toluene) improved the chemical yield, albeit with a the slight decrease of the enantioselectivity. Overall notable kinetic resolution was achieved by means of a chiral Brønsted acid, even at high temperature.

The pronounced kinetic resolution observed in the aldol reaction inspired us to study the enantioselective Robinson-type annulation reaction in combination with the enantioselective Michael addition reaction. Compound **3** was treated with methyl vinyl ketone under identical reaction conditions with those used in Table 1, and subsequent purification of the reaction mixture gave 1,4-adducts **4**. Compounds **4** were treated with 10 mol% of **2** in toluene at reflux and furnished Robinson-type annulation products **5** with high yields and with excellent enantioselectivities (Table 2). In the case of methyl 2-oxocyclopentanecarboxylate, kinetic resolution was not observed in the aldolization process (compare Table 1, entry 9 with Table 2, entry 10).

The present aldol reaction is considered to proceed via the following cyclic transition state model in which the phosphoric acid worked as a multifunctional catalyst: The phosphoric acid hydrogen atom activated the ketone group by acting as a Brønsted acid and thus promoted the formation of an enol from the ketone unit (Figure 1). Furthermore, the phosphoryl oxygen atom formed a hydrogen bond with the enol hydrogen atom, acting as a Lewis base.

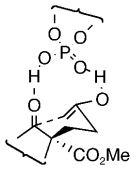


Figure 1. Proposed transition state.

In summary, we have developed a chiral phosphoric acid catalyzed enantioselective Robinson-type annulation reaction based on the enantioselective Michael addition reaction and the subsequent aldol reaction. Further investigations to clarify the reaction mechanism and its application to other enantioselective reactions are underway.

Experimental Section

Typical procedure for the Robinson-type annulation reaction: Methyl vinyl ketone (49 μL, 0.60 mmol) was added to a solution of keto ester **3a** (38 mg, 0.20 mmol) and chiral phosphoric acid **1** (16 mg, 0.02 mmol) in *m*-xylene (1 mL) at 40°C. After the reaction was stirring at that temperature for 24 h, the mixture was directly purified by column chromatography on silica gel (hexanes/EtOAc = 3:1)to give the corresponding Michael adduct **4a**. The adduct was dissolved in toluene (1 mL) and chiral phosphoric acid **2** (15 mg, 0.020 mmol) was added. The reaction mixture was heated to reflux for 48 h. Upon cooling, **2** was removed by column chromatography on silica gel (CH_2Cl_2/AcOEt = 10:1). The crude mixture was further purified by preparative TLC to give **5a** (32 mg, 0.12 mmol) in 64% yield (Table 2, entry 1).

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