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An Enantioselective Michael Addition of Soft Nucleophiles to Prochiral Enone Catalyzed by (2-Pyrrolidyl)alkyl Ammonium Hydroxide

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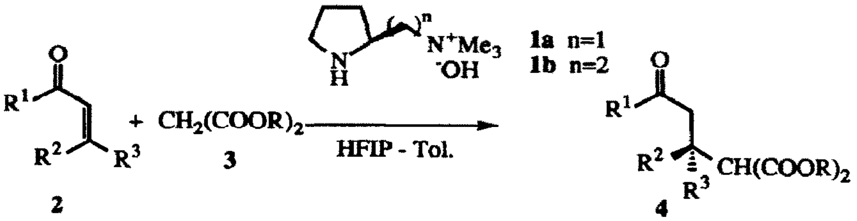
Abstract: (S)-N-(2-Pyrrolidylmethyl)-N,N,N-trimethylammonium hydoxide catalyzes the asymmetric Michael addition of soft nucleophiles to enones with moderate to high enantiomeric excess through ion-pair rather than steric control.

In recent years, great advances have been made in the study of asymmetric carbon-carbon bond forming reactions mediated by chiral catalysts.[1,2] Of these reactions, the catalytic asymmetric Michael addition has been extensively examined using chiral metal complex[3,4] or chiral amine.[5] Most of the asymmetric Michael addition with a chiral catalyst system which achieved a high level of asymmetric induction have been realized involving the differentiation of enantiofaces of the prochiral donor by its complexation with the chiral catalyst.[3] On the other hand, limited examples have been directed to the differentiation of enantiofaces of the prochiral acceptor through its interaction with the chiral catalyst.[4,5a]

In this paper we report that the chiral ammonium hydroxides (**1a** and **1b**) catalyze the asymmetric (enantioselective) Michael addition of soft nucleophiles to prochiral enones by the differentiation of acceptor enantiofaces through ion-pair rather than steric control.

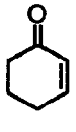
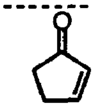
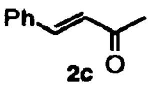
As chiral catalysts, we chose the ammonium hydroxides **1a** and **1b** easily prepared from (*S*)-proline,[6,7] which have five-membered secondary amino group to form iminium intermediate with carbonyl and basic ammonium hydroxide moiety attached at 2 position on the pyrrolidine ring at a distance of one or two carbons.



Scheme 1

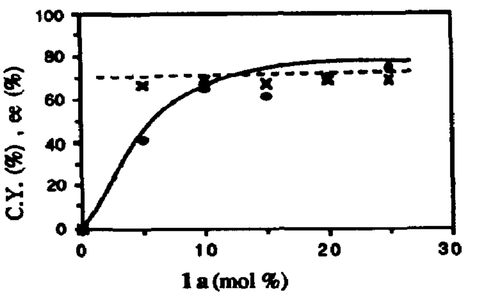
In the presence of **1a**, the Michael reaction of dibenzyl malonate **3a** with cyclohexenone **2a** gave the corresponding adduct **4a** in 88% yield with low asymmetric induction (3.5% ee) (Table 1, entry 1). Possibly due to the strong basicity of the catalyst of hydroxide form, direct attack of malonate to the enone may result in low ee of the product. Furthermore, in this reaction the dimer of the enone was also formed as a by-product.[8] To reduce the basicity of the catalyst and control the formation of the iminium intermediate (see Scheme 2), the reaction was conducted in the presence of an acidic additive. HFIP (1,1,1,3,3,3-hexafluoro-2-propanol) was found suitable for this purpose to obtain the addition product **4a** of ca 70% ee (entries 3, 5, 9).[9]

Table 1. Michael Addition of Malonate **3** with Enone **2** Catalyzed by **1a** or **1b**[a]

Entry	Enone 2	Malonate 3	Cat.	HFIP (eq)	Yield (%)[b]	ee (%)[c]	Confign.
1			1a	0	4a 88	3.5	S[d]
2		$CH_2(COOBn)_2$	1a	1	4a 52	21	S
3		3a	1a	10	4a 61	71	S
4	2a		1b	10	4a 96	49	S
5	2a	$CH_2(COOMe)_2$	1a	10	4b 65	69	S[e]
6		3b	1b[f]	10	4b 61	67	S
7	 2b	3a	1a	10	4c 62	58	S[d]
8		3b	1a	10	4d 56	56	S[e]
9		3b	1a	10	4e 21	68	R[g]
10	2c	3b	1b	10	4e 53	22	R[g]

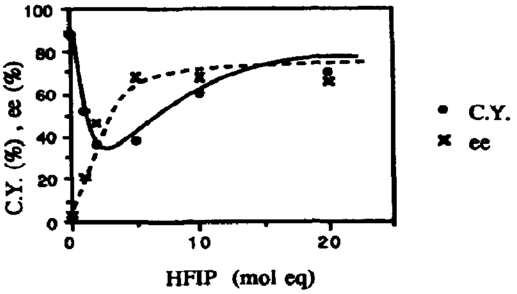
[a] Reaction conditions: enone (1 mmol), malonate (1 mmol), catalyst (0.1 mmol), HFIP (indicated in Table 1) in toluene, rt, 1week. [b] Isolated yield. [c] Determined by HPLC analysis with chiral stationary phase column (DAICEL CHIRALCEL OB-H, CHIRALPAK AS). [d] Benzyl ester **4a** and **4c** were converted to dimethyl ester **4b** and **4d**, respectively (H_2/5% Pd-C, then $TMSCHN_2$) for determination of their absolute configurations. [e] **4b** and **4d** were converted to the known acetate derivative by hydrolysis, decarboxylation and esterification for determination of their absolute configurations (see ref. 10). [f] 15 mol % of **1b** was used. [g] See ref. 11.

The effects of the molar ratio of catalyst **1a** on chemical yield and ee of the Michael adduct **4a** formed by the reaction of **2a** with **3a** in the presence of 10 molar equivalents of HFIP can be seen from Graph 1. The amount of catalyst affected the reaction rate (chemical yield), but not very much the ee of the product **4a**, which was optimized at ca 10 mol % of catalyst **1a**. Graph 2 shows the effects of the amount of HFIP at 10 mol % of catalyst **1a**.[9] Although ee of the product **4a** gradually increased with the amount of HFIP reaching a maximum (ca 70% ee) at more than 5 molar equivalents, the chemical yield showed a minimum point (at ca 3 molar equivalents of HFIP) where the dimer of cyclohexenone[8] was formed in appreciable amount. In consideration of these results, 10 mol % of catalyst **1a** or **1b** and 10 molar equivalents of HFIP were thus used in subsequent experiments as shown in Table 1.



1 a(mol %) vs C.Y. (%) and ee (%) of 4 a

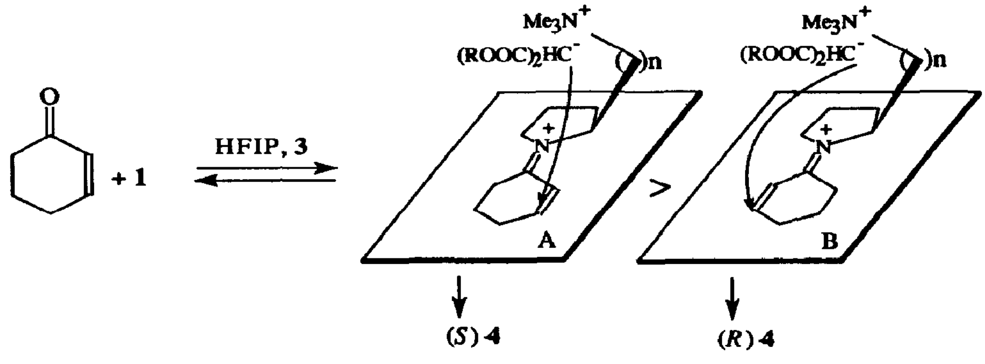
Graph 1



HFIP (mol eq) vs C.Y. (%) and ee (%) of 4 a

Graph 2

With cyclic enone (Z-enone) **2a** or **2b**, the addition reaction of malonate **1** catalyzed by (*S*)-enantiomer **1a** or **1b** gave the Michael adduct **4a-4d** in an (*S*)-enantiomer enriched manner (entries 1-8). With acyclic (*E*)-enone **3c**, the (*R*)-enantiomer of **4e** was predominantly formed on using the same catalyst (entries 9, 10). Comparison of the catalyst **1a** with **1b** indicated a higher asymmetric induction when **1a** was used (entries 3, 4 and 9, 10). These results may suggest that the facial selectivity of enone at the time of nucleophilic attack of malonate can be controlled by the configuration of the catalyst used through the reversible formation of iminium intermediate **A**, in which malonate with ammonium counter cation is situated at suitable position to approach the ß-carbon of the enone from the same site of the armed alkylammonium substituent (Scheme 2).[12] In the case of iminium intermediate **B**, the distance between malonate and ß-cabon of the enone seems relatively too far to react.



Scheme 2

Further examinations using various Michael donors and investigation of the mechanistic aspects are currently carried out.

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3. For example: a) Sasai, H.; Arai, T.; Shibasaki, M. *J. Am. Chem. Soc.* **1994**, *116*, 1571. b) Kanai, M.; Tomioka, K. *Tetrahedron Lett.* **1993**, *35*, 895. c) Sawamura, M.; Hamashima, H.; Ito, Y. *J. Am. Chem. Soc.* **1992**, *114*, 8295. d) Yura, T.; Iwasawa, N.; Narasaka, K.; Mukaiyama, T. *Chem. Lett.* **1988**, 1025. e) Iwasawa, N.; Yura, T.; Mukaiyama, T. *Tetrahedron* **1989**, *45*, 1197. f) Cram, D. J.; Sogah, G. D. Y. *J. Chem. Soc., Chem. Commun.* **1981**, 625. g) Aoki, S.; Sasaki, S.; Koga, K. *Tetrahedron Lett.* **1989**, *30*, 7229.
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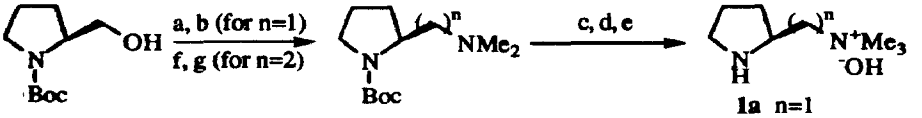
6. The ammonium hydroxides **1a** and **1b** were prepared from (*S*)-*N*-Boc-2-pyrrolidylmethanol^7 as shown below.



1a n=1
1b n=2

a, CBr_4, Ph_3P / CH_3CN; b, Me_2NH / CH_2Cl_2; c, MeBr / CH_2Cl_2; d, HBr / MeOH; e, IRA-400 (ammonium hydroxide form); f, TsCl / Py then KCN, 18-crown-6; g, H_2, Raney-Ni, $(CH_2O)n$ / EtOH

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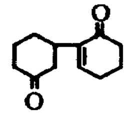
8. The dimer of cyclohexenone formed in this reaction was determined as the Michael adduct **5**.



5

9. Low nucleophilicity of HFIP and its acidity (pKa=9.3) may be suitable for the present reactions. Under similar reaction conditions except that 2,2,2-trifluoroethanol (pKa=12.8) was used instead of HFIP as an additive, **4a** was obtained in 29% yield with 41% ee (compare with the result in Table 1, entry 3). In the presence of AcOH (pKa=4.7), no reaction occurred.
10. Posner, G. H.; Weitzberg, M.; Hamill, T. G.; Sivathan, E. A.; Cun-Heg, H.; Clardy, J. *Tetrahedron* **1986**, *42*, 2919.
11. Tomioka, K.; Yasuda, K.; Koga, K. *Tetrahedron Lett.* **1983**, *24*, 4967.
12. The asymmetric Michael addition reaction of malonate with enone catalyzed by alkaline metal salt of (*S*)-proline was reported by Yamaguchi and Hirama's group.^{5a} They indicated the efficiency of the catalyst to depend on the alkaline metal used and Rb(I) salt to be most suitable based on ee of the product. For this salt, the sence of asymmetric induction is opposite to that in our case, although the catalysts have similar structures and the same configurations in both cases.

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