Novel Catalytic Enantioselective Protonation (Proton Transfer) in Michael Addition of Benzenethiol to α-Acrylacrylates: Synthesis of (*S*)-Naproxen and α-Arylpropionic Acids or Esters†

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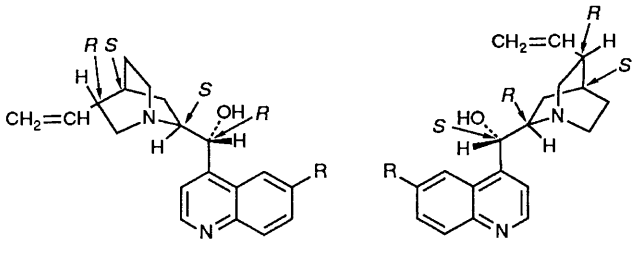
A novel synthesis of optically active 2-phenylpropionic acids or esters *via* catalytic enantioselective protonation in the Michael addition of benzenethiol to 2-phenylacrylates is described; the synthetic utility is further demonstrated by the asymmetric synthesis of (*S*)-Naproxen.

Synthesis of 2-arylpropionic acids, which constitute an important class of non-steroidal anti-inflammatory agents, has been an area of intense study.[1] Herein, we report new synthesis of 2-arylpropionic acids in optically active form.[2] The key step is the catalytic enantioselective protonation[3] of the prochiral carbanion generated in the addition of benzenethiol to α-arylacrylates catalysed by cinchona alkaloids.[4] The interesting feature of this Michael addition is the formation of a new chiral centre one carbon atom away from the incoming sulphur atom. The benzenethiol group can then be removed easily by standard Raney nickel desulphurization to give the corresponding α-arylpropionates.

Reaction of methyl **5a** or ethyl atropate[5] **5b** with benzenethiol under the conditions described (Table 1) using a catalytic amount of cinchonine **4** furnished the corresponding Michael adduct **6a** in poor enantiomeric excess (e.e.).‡ The enantioselectivity was almost doubled when the reaction was performed in the presence of cinchonidine **3**. These results prompted us to change the catalyst from **4** to the 6′-methoxy substituted quinidine. Use of **2** gave **6a** in 51% e.e. with a chemical yield of 84%. Similarly use of quinine **1** afforded **6a** in moderate e.e. enriched in the (*S*)-enantiomer. Encouraged by these results we decided to probe the effect of various groups on the ester moiety of atropic acid. Methyl and isopropyl substituents, **5c**, gave almost comparable results



Quinine **1** R = OMe **2** Quinidine

Cinchonidine **3** R = H **4** Cinchonine

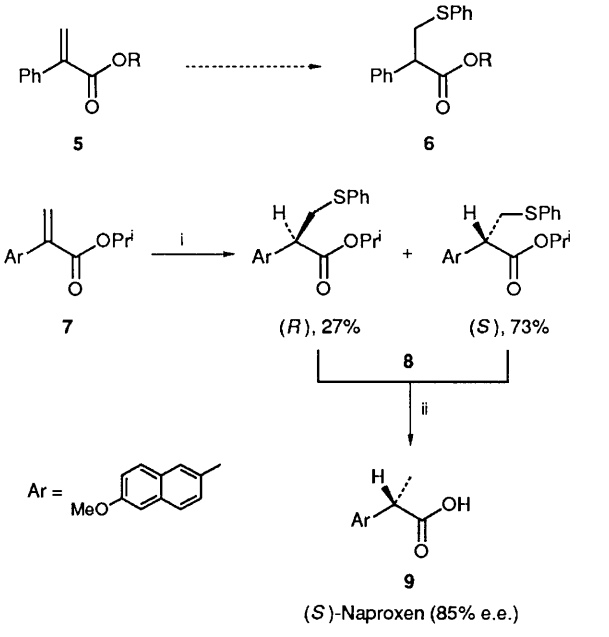
† Ind. Pat. Appl. 529/Cal/90, June 26, 1990.

‡ Cinchonine gave the highest enantioselectivity in the addition of benzenethiol to cyclohex-2-enone.[4a]

Table 1 Cinchona alkaloid-catalysed 1,4-addition of benzenthiol to α-phenylacrylates **5**[a]

Compound No.	R	Catalyst[b]	Major[c] enantiomer of **6**	E.e. (%)[d]	Chemical[e] yield%	*t*/day
5a	Me	**4**	*R*	17	65	2
5a	Me	**3**	*S*	32	78	2
5a	Me	**1**	*S*	43	83	4
5a	Me	**2**	*R*	51	84	4
5b	Et	**4**	*R*	18	71	2
5c	Pr^i	**4**	*R*	23	73	2
5c	Pr^i	**3**	*S*	22	90	2
5c	Pr^i	**1**	*S*	50	84	5
5c	Pr^i	**2**	*R*	45	80	4
5d	Bu^t	**1**	*S*	35	79	2
5e	$CH(Pr^i)_2$	**1**	*S*	27	74	6

[a] Typical experimental details: a solution of the α-arylacrylate (1 mmol), PhSH (1.05 mmol) and catalyst (0.2 mmol) in toluene (40 ml) was stirred under N_2 atmosphere in the dark at room temperature, followed by column chromatography. [b] Increasing or reducing the amounts of catalyst did not appreciably affect the enantioselectivity. [c] Absolute configurations of the products were confirmed by their conversion to ethyl or methyl α-phenylpropionate and comparison of the specific rotations with the reported values: O. Toussaint, P. Capdevielle and M. Maumy, *Tetrahedron Lett.* 1987, **28**, 539. [d] Unless otherwise stated optical purities (e.e.) of the products were determined by ^1H NMR measurements of desulphurised products (α-phenylpropionates) in the presence of the chiral shift reagent tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]-europium(III) [Eu(hfc)$_3$]. [e] Isolated yields after column chromatography.



Scheme 1 *Reagents and conditions*: i, PhSH, **1**, toluene; ii, Raney Ni, AcOH–HCl, crystallisation

whereas more sterically demanding esters (*e.g.* t-butyl, **5d**, diisopropyl **5e**) gave lower optical inductions (Table 1).

In order to demonstrate the synthetic utility of this reaction, benzenethiol was added to the acrylate[5] **7** in the presence of **1**; the corresponding Michael adduct **8** was obtained in 85% isolated yield and 46% e.e. Raney nickel desulphurization followed by acid hydrolysis of **8** afforded **9** in 45% e.e. and 72% overall yield. Compound **9** after a single crystallization from benzene gave (*S*)-Naproxen in 85% e.e. (Scheme 1).

The mechanistic basis of the enantioselectivity can be rationalized by the following considerations[4b] and the proposed transition state based on the minimum energy conformations of quinine and α-methylatropate (Fig. 1).

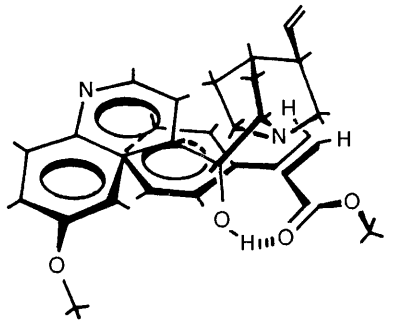


Fig. 1

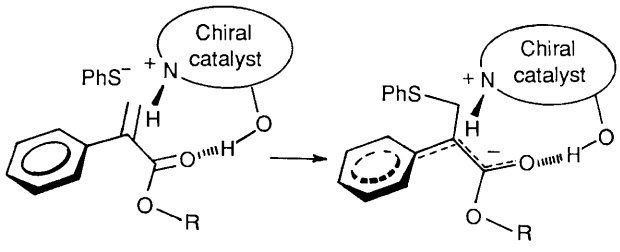


Fig. 2

The important features include hydrogen bonding between the hydroxy group of the catalyst and the carbonyl group of the ester as well as the presence of the 6′-methoxy group in the catalyst. The tertiary nitrogen of the quinuclidine forms an ion pair by abstracting a proton from benzenethiol followed by delivery of a proton from one face to the generated prochiral carbanion as depicted in Fig. 2. Since quinine-catalysed benzenethiol addition to **5c** leads to the product enriched in the (*S*)-enantiomer, the proposed transition state appears to be in agreement with these results.

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References

1 J. P. Rieu, A. Boucherle, H. Consse and G. Mouzin, *Tetrahedron*, 1986, **42**, 4095.

2 Recent lead references: R. Noyori, K. Nagai, M. Kitamura, T. Ohta and H. Takaya, *J. Org. Chem.*, 1987, **52**, 3174; R. D. Larsen, E. G. Corley, P. Davis, P. J. Reider and E. J. J. Grabowski, *J. Am. Chem. Soc.*, 1989, **111**, 7650 and references cited therein; G. Castaldi, S. Cavicchioli, C. Giordano and F. Uggeri, *J. Org. Chem.*, 1987, **52**, 4243.

3 For a recent example see: C. Fehr and J. Galindo, *J. Am. Chem. Soc.*, 1988, **110**, 6909 and references cited therein.

4 (*a*) H. Wynberg and H. Hiemstra, *J. Am. Chem. Soc.*, 1981, **103**, 417, and references cited therein; (*b*) G. D. H. Dijekstra, R. M. Kellog and H. Wynberg, *Rec. Trav. Chim. Pays Bas*, 1989, **108**, 195; (*c*) N. Kobayashi and K. Iwai, *J. Org. Chem.*, 1981, **46**, 1823; (*d*) N. Kobayashi and K. J. Iwai, *J. Am. Chem. Soc.*, 1978, **100**, 7071; (*e*) H. Yamashita and T. Mukaiyama, *Chem. Lett.*, 1985, 363; (*f*) G. D. H. Dijkstra, R. M. Kellog, H. Wynberg, J. S. Svendessen, I. Marko and K. B. Sharpless, *J. Am. Chem. Soc.*, 1989, **111**, 8069.

5 Various atropates were prepared by esterification of atropic acid. For synthesis of atropic acid, see: S. Campolmi, M. G. Felicioli, V. Carletti and R. Santi, Ger. Offen. 2,919,919/1979 (*Chem. Abstr.* 1979, **92**, 146491g).