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Enantioselective protonation of prochiral enolates in the asymmetric synthesis of (*S*)-naproxen

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Abstract—Racemic methyl, *iso*-propyl, and *tert*-butyl ester derivatives of naproxen were treated with achiral LDA base to give the corresponding prochiral enolates **2**-Li, **3**-Li, and **4**-Li. Protonation of these enolates with novel chiral proton sources (*S*)-**10** and (*S*,*S*)-**11**, containing the α-phenylethylamino group, proceeded in a highly enantioselective manner. Saponification of enantioenriched ester derivatives **2**–**4** afforded naproxen, (*S*)-**1**, with no loss of enantiopurity. © 2003 Published by Elsevier Science Ltd.

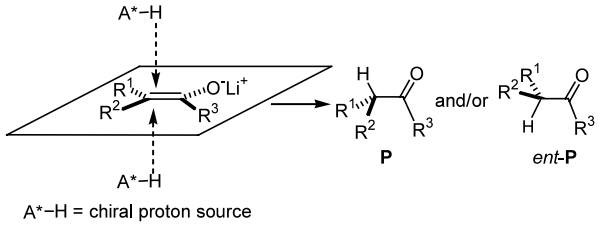
The diastereoselective alkylation of chiral carbonyl derivatives is now a well established strategy for asymmetric carbon–carbon bond formation.[1] A conceptually simple and potentially even more attractive methodology consists in the desymmetrization of prochiral enolates via enantioselective protonation with chiral acids. Indeed, enantiotopic faces in a prochiral substrate may be distinguished by chiral reagents to afford non-racemic derivatives (Scheme 1).[2–5]

(*S*)-2-(6-Methoxy-naphthalen-2-yl)propanoic acid [naproxen, (*S*)-**1**] is a powerful anti-inflammatory agent, whose asymmetric synthesis continues to be a challenging undertaking.[6] We report in this letter the results from the enantioselective protonation of prochiral enolates **2**–**4**-Li with novel chiral proton sources **5**–**8** (Scheme 2). Vedejs et al.[4] have previously reported a systematic study of the asymmetric protonation of **9**-Li with chiral aniline acids, to give predominantly (*R*)-**1**.

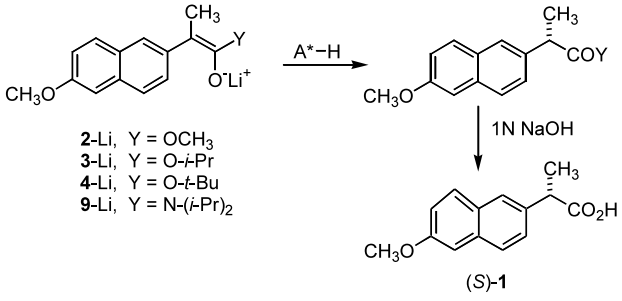
Racemic esters (±)-**2**, (±)-**3**, and (±)-**4** were readily prepared from commercially available racemic naproxen, according to the reaction conditions summarized in Scheme 3.[7]

Enantiomerically pure (*S*)-**2**, (*S*)-**3**, and (*S*)-**4** were similarly obtained by esterification of enantiomerically pure (*S*)-naproxen.[8] Table 1 summarizes the physical properties of the enantiopure esters (*S*)-**2**–**4**.

Finally, enantiopure (*S*)-naproxen was obtained by resolution of racemic naproxen, via fractional crystallization of diastereomeric salts of (*S*)-α-phenylethylamine.[9,10] Table 2 presents the enantiomeric excesses of naproxen samples isolated in first-crop crystals obtained under different conditions. Particularly efficient resulted the conditions specified in



Scheme 1.



Scheme 2.

Keywords: enantioselective protonations; chiral acids; resolution of racemates; prochiral enolates; enolate desymmetrization; naproxen.
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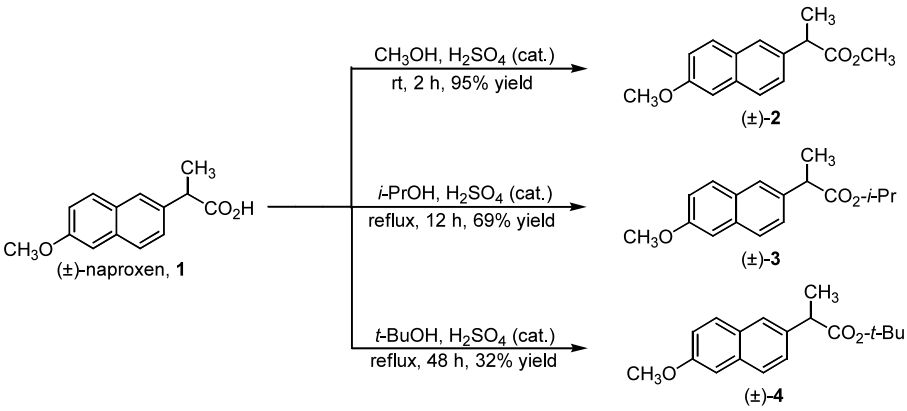
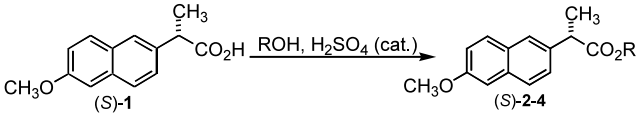


Scheme 3.

Table 1. Esterification of (*S*)-naproxen [(*S*)-**1**] to give enantiopure derivatives (*S*)-**2**–**4**[a]



R	Yield (%)	$[\alpha]_D^{28}$	mp
Me	95	+74.0	90–91
i-Pr	69	+22.4	65–66
t-Bu	22	+27.1	Wax

[a] For reaction conditions see Scheme 3 and Ref. 8.

entry 7, which afforded (*S*)-**1** of 92% ee and in high yield. This enantioenriched material was readily recrystallized to give enantiopure (*S*)-**1**.

Racemic naproxen ester derivatives (±)-**2**, (±)-**3**, and (±)-**4** (Scheme 3 and Table 1) were treated with the achiral base LDA to give the corresponding prochiral enolates **2**-Li, **3**-Li, and **4**-Li, which were then reprotonated with the novel chiral Brønsted acids (*S*)-**10** and (*S*,*S*)-**11** (Chart 1).[11,12]

As anticipated,[2–5] the above protocol afforded enantiomerically enriched **2**–**4** (Table 3). C_2-Symmetric phenol (*S*,*S*)-**11** proved to be a much better stereoinductor (ee = 78–93%) relative to (*S*)-**10** (ee = 69–76%).[13] Furthermore, the bulkier the substituent on the carboxylate group the higher the enantioselectivity (compare entries 4 and 6 in Table 3, ee = 90 and 93% for R = *i*-Pr and *t*-Bu, with entry 2 in Table 3, ee = 78% for R = CH_3).[14] Finally, verification of the absolute configuration and isolation of the desired (*S*)-naproxen was achieved by saponification under mild conditions (Eq. (1)).[15,16]

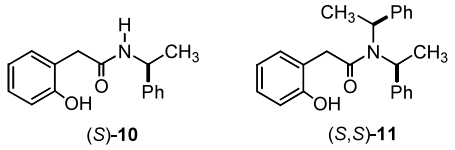
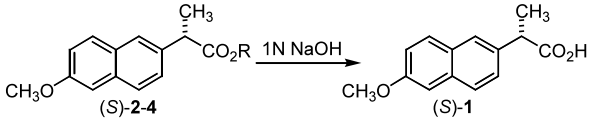


Chart 1.



(1)

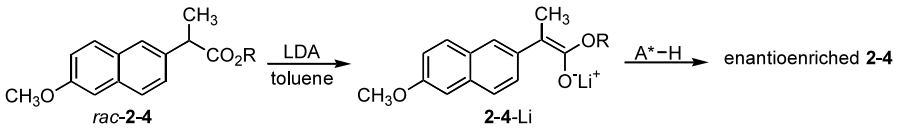
In conclusion, racemic ester precursors **2**–**4** are easily prepared by esterification of racemic naproxen, and highly enantioselective protonation of prochiral enolates **2**–**4**-Li is possible with novel phenols (*S*)-**10** and (*S*,*S*)-**11** as chiral proton sources. Since naproxen (**1**) is readily recovered by saponification of enantioenriched esters **2**–**4**, an alternative procedure for the preparation of (*S*)-naproxen is therefore available.

Table 2. Resolution of racemic naproxen with (*S*)-α-phenylethylamine[9]

Entry	Equiv. (*S*)-α-PEA	Solvent	Yield[a] (%)	$[\alpha]_D^{28}$	ee[b] (%)	Major enantiomer
1	1.0	EtOH	49	+17.0	26	(*S*)
2	1.0	EtOH–H_2O (1:1)	50	+22.3	34	(*S*)
3	1.0	EtOH–H_2O (7:3)	48	+28.8	43	(*S*)
4	1.0	*i*-PrOH	47	+17.8	27	(*S*)
5	1.0	*i*-PrOH–H_2O (1:1)	50	+24.7	37	(*S*)
6	0.5	*i*-PrOH–H_2O (4:1)	82	+42.0	63	(*S*)
7	0.5	*i*-PrOH–H_2O (3:7)	90	+61.1	92	(*S*)

[a] Calculated relative to the maximum theoretical yield.
[b] Determined by comparison of optical rotation with $[\alpha]_D^{28} = +65.9$ (*c* 1.2, $CHCl_3$) for enantiopure (*S*)-**1**.[6a]

Table 3. Enantioselective protonation of prochiral enolates **2**-Li, **3**-Li, and **4**-Li with chiral proton sources[17]



Entry	R	A*-H	Yield (%)	ee[a] (%)	Major enantiomer
1	CH_3	(*S*)-**10**	90	69	(*S*)
2	CH_3	(*S*,*S*)-**11**	94	78	(*S*)
3	*i*-Pr	(*S*)-**10**	91	72	(*S*)
4	*i*-Pr	(*S*,*S*)-**11**	93	90	(*S*)
5	*t*-Bu	(*S*)-**10**	87	76	(*S*)
6	*t*-Bu	(*S*,*S*)-**11**	88	93	(*S*)

[a] Enantiomeric excess, determined by comparison of optical rotations with that of enantiopure standards (see text).

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7. Cf. March, J. *Advanced Organic Chemistry*; 3rd ed.; Wiley: New York, 1985; p. 348.
8. *Typical experimental procedure for the preparation of enantiopure ester derivatives* **2**–**4**: To a 50 mL round-bottom flask containing (*S*)-**1** (0.5 g, 2.17 mmol) was added 30 mL of desired alcohol (MeOH, *i*-PrOH or *t*-BuOH), and a catalytic amount of H_2SO_4. The reaction mixture was filtered and concentrated in a rotary evaporator and extracted with CH_2Cl_2 (3×15 mL). The combined organic layers were washed with water (2×5 mL) and brine (1×10 mL), and dried with Na_2SO_4. Removal of the solvent left a residue that was recrystallized from hot MeOH:H_2O (3:7).
(*S*)-**2** ^{1}H NMR ($CDCl_3$): δ 1.57 (d, J=6.9 Hz, 3H), 3.65 (s, 3H), 3.85 (q, J=7.0 Hz, 1H), 3.89 (s, 3H), 7.02–7.89 (m, 6H). ^{13}C NMR ($CDCl_3$): δ 18.6, 45.4, 52.0, 55.3, 105.7, 118.9, 125.9, 126.1 127.1, 128.9, 129.2, 133.7, 135.6, 157.6, 174.9.
(*S*)-**3** ^{1}H NMR ($CDCl_3$): δ 1.11 (d, J=6.3 Hz, 3H), 1.25 (d, J=6.3 Hz, 3H), 1.54 (d, J=7.1 Hz, 3H), 3.80 (q, J=7.1 Hz, 1H), 3.89 (s, 3H), 5.01 (sept, J=6.3 Hz, 1H), 7.04–7.73 (m, 6H). ^{13}C NMR ($CDCl_3$): δ 18.7, 21.8, 22.6,

45.7, 55.3, 68.0, 105.7, 119.0, 125.9, 126.3 127.1, 129.1, 129.4, 133.8, 136.0, 157.7, 174.3.
(*S*)-**4** ^{1}H NMR ($CDCl_3$): δ 1.39 (s, 9H), 1.52 (d, $J=7.1$ Hz, 3H), 3.74 (q, $J=7.1$ Hz, 1H), 3.90 (s, 3H), 7.09–7.78 (m, 6H). ^{13}C NMR ($CDCl_3$): δ 18.6, 28.2, 46.3, 55.3, 68.1, 80.6, 105.6, 118.9, 125.7, 126.3, 127.1, 129.1, 129.4, 132.5, 136.4, 157.6, 174.1.

9. *Typical experimental procedure for the resolution of racemic naproxen [(±)-**1**] with (S)-α-phenylethylamine*. To a 25 mL three-necked flask containing (±)-**1** (1.0 g, 4.34 mmol) was added 10 mL of a mixture of solvents [*i*-PrOH:H_2O (7:3)] and heated at 70°C for 30 min. Subsequently, slow addition of (*S*)-α-PEA (0.26 g, 2.17 mmol) dissolved in 5 mL of the mixture used was carried out with continued heating for a period of 30 min. Finally, the reaction mixture was brought without stirring ring to room temperature. The diastereoisomeric salts were recrystallized [*i*-PrOH:H_2O (7:3)]. A solution of the diastereomerically pure salt was treated with HCl 10% and extracted with CH_2Cl_2 (3×20 mL), washed with water, brine (1×10 mL), dried with Na_2SO_4 and concentrated to afford 0.45 g (90% yield) of (*S*)-**1**. $[\alpha]_D^{28}=+61.1$ (*c* 1.5, $CHCl_3$), 92% ee.
10. (a) For a review on the use of α-phenylethylamine as resolving agent, see: Juaristi, E.; Escalante, J.; León-Romo, J. L.; Reyes, A. *Tetrahedron: Asymmetry* **1998**, *9*, 715; (b) See also: Reyes, A.; Juaristi, E. *Synth. Commun.* **1995**, *25*, 1053.
11. For a review on the use of α-phenylethylamine as chiral auxiliary, see: Juaristi, E.; León-Romo, J. L.; Reyes, A.; Escalante, J. *Tetrahedron: Asymmetry* **1999**, *10*, 2441.
12. *2-(2-Hydroxyphenyl)-N-(1-phenylethyl)acetamide, (S)-**10***. Mp 105°C. $[\alpha]_D^{28}=-34.7$ (*c* 1.1 $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 1.42 (d, $J=7.3$ Hz, 3H), 3.55 (dd, $J=11.6$ Hz, $J=4.1$ Hz, 2H), 5.04 (m, 1H), 6.89–7.32 (m, 9H), 9.96 (bs, 1H). ^{13}C NMR ($CDCl_3$): δ 21.8, 40.6, 49.6, 117.6, 120.5, 121.7, 126.1, 127.5, 128.8, 129.1, 130.9, 142.5, 155.8, 177.7.
*2-(2-Hydroxyphenyl)-N,N-bis-(1-phenylethyl)acetamide, (S,S)-**11***. Oil, $[\alpha]_D^{28}=-75.4$ (*c* 1.0 $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 1.29 (d, $J=7.2$ Hz, 3H), 1.37 (d, $J=7.2$ Hz, 3H), 3.58 (q, $J=7.2$ Hz, 1H), 3.70 (dd, $J=11.9$ Hz, $J=6.9$ Hz, 2H) 4.21 (q, $J=7.1$ Hz, 1H), 7.11–7.55 (m, 14H), 9.37 (bs, 1H). ^{13}C NMR ($CDCl_3$): δ 21.9, 22.1, 40.6, 40.8, 49.9, 50.2, 117.6, 120.4, 121.9, 127.5, 129.1, 129.2, 130.4, 142.6, 155.9, 179.8.
13. For a discussion on the benefits of using C_2-symmetric, chiral ligands in asymmetric synthesis, see: Whitesell, J. K. *Chem. Rev.* **1989**, *89*, 1581.
14. It is anticipated that, by analogy with naproxen amide enolate **9**-Li,[4] the *Z* configured enolates **2**–**4**-Li are formed upon treatment of **2**–**4** with LDA.
15. The absolute (*S*) configuration in recovered esters **2**–**4** (Table 3) indicates *like*[16] stereoinduction in the proton transfer from (*S*)-**10** and (*S*,*S*)-**11** to prochiral enolates **2**–**4**-Li.
16. For a definition of the *like*/*unlike* stereochemical descriptors, see: Seebach, D.; Prelog, V. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 654.
17. *General procedure for the enantioselective protonation of rac **2**–**4** with chiral proton sources (S)-**10**, and (S,S)-**11***. A solution of (i-Pr)$_2$NH (1.1 equiv.) in toluene was cooled to 0°C before the slow addition of BuLi (1.1 equiv., ca. 1.8 M in hexane). The resulting solution was stirred for 30 min., and then cooled to −78°C before the dropwise addition of *rac*-**2**–**4** (1.0 equiv.) in toluene (10 mL). Stirring was continued for 1 h at −78°C in order to secure the complete formation of the corresponding enolate. The protonation source (*S*)-**10** or (*S*,*S*)-**11** (1.2 equiv.) in toluene was then added dropwise via syringe, and the reaction mixture was stirred at −78°C for 30 min, at ambient temperature for 5 min, and finally cooled at −78°C before it was quenched by the addition of saturated aqueous NH_4Cl solution and extracted with CH_2Cl_2 (3×25 mL). The combined extracts were washed with water and brine, and dried over anhydrous Na_2SO_4, filtered and concentrated at reduced pressure. The residue was purified by flash chromatography using hexanes–ethyl acetate (7:3) as eluent.