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Highly Enantioselective Decarboxylative Protonation of α-Aminomalonates Mediated by Thiourea *Cinchona* Alkaloid Derivatives: Access to Both Enantiomers of Cyclic and Acyclic α-Aminoacids

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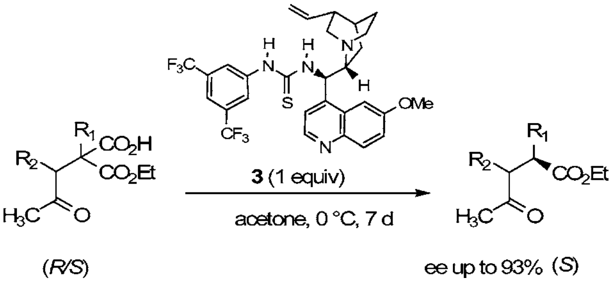
ABSTRACT



Thiourea derived *cinchona* alkaloids promote the asymmetric decarboxylative protonation of cyclic, acyclic, or bicyclic α-aminomalonate hemiesters under mild and metal-free conditions to afford enantioenriched aminoesters in high yields and enantioselectivities up to 93%. Both enantiomers of the aminoesters have been synthesized with the same selectivity when using organic base 3 and its pseudoenantiomer 6 derived from quinine.

Asymmetric decarboxylative protonation of substituted aminomalonates in the presence of a chiral base is a synthetically convenient and straightforward route to synthesize a variety of natural and unnatural optically pure α-aminoacids. This synthetic methodology is based on the more general malonic acid synthesis where the chirality of the product can be generated during the enolate protonation step (Scheme 1). In its enantioselective version, it is the first example of an asymmetric reaction reported as early as 1904.[1] Although enantioselective decarboxylative protonation is a century old reaction, it has not received much attention until recently.[2] Whereas high selectivity was obtained performing this chemical transformation in the presence of enzymes[3] or recently with organometallic complexes,[4] the highest enantiomeric excess achieved for this reaction catalyzed by an organic base was never more than 72%.[5] The enantiomeric excesses are strongly dependent both on the solvent and on the substrate.

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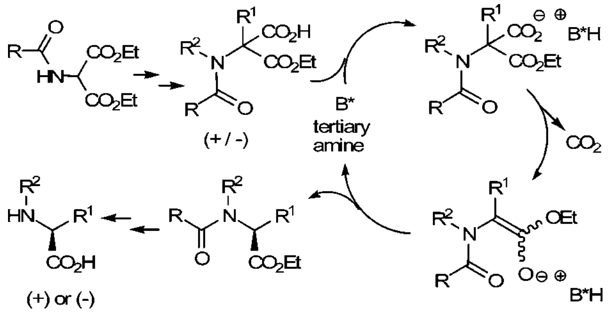
[1] (a) Marckwald, W. *Ber. Dtsch. Chem. Ges.* **1904**, *37*, 349. (b) Marckwald, W. *Ber. Dtsch. Chem. Ges.* **1904**, *37*, 1368.

[2] (a) Verbit, L.; Halbert, T. R.; Patterson, R. B. *J. Org. Chem.* **1975**, *40*, 1649−1650. (b) Glusker, J. P.; Carrell, H. L.; Job, R.; Bruice, T. C. *J. Am. Chem. Soc.* **1974**, *96*, 5741−5751. (c) Yashiro, M.; Ajioka, M.; Yano, S.; Toriumi, K.; Ito, T.; Yoshikawa, S. *Inorg. Chem.* **1986**, *25*, 1709−1715. (d) Toussaint, O.; Capdevielle, P.; Maumy, M. *Tetrahedron Lett.* **1987**, *28*, 539−542. (e) Roy, O.; Dieckmann, M.; Riahi, A.; Hénin, F.; Muzart, J. *Chem. Commun.* **2001**, 533−534. (f) Baur, M. A.; Riahi, A.; Hénin, F.; Muzart, J. *Tetrahedron*: *Asymmetry* **2003**, *14*, 2755−2761. (g) Roy, O.; Riahi, A.; Hénin, F.; Muzart, J. *Eur. J. Org. Chem.* **2002**, 3986−3994.

10.1021/ol070712v CCC: $37.00

Scheme 1. Proposed Route to Optically Enriched α-Aminoacids



As a part of our program on the synthesis of a selective M_2 muscarinic receptor antagonist[6] and on the development of new eco-friendly approaches to amino acid derivatives, we became involved in enantioselective organocatalyzed decarboxylative protonation.[7] This methodology was used for the preparation of enantioenriched pipecolic ester (72% ee) on a multigram scale in good yield and mild conditions, with 9-*epi*-cinchonine as the most efficient catalyst (10% amount).[5c]

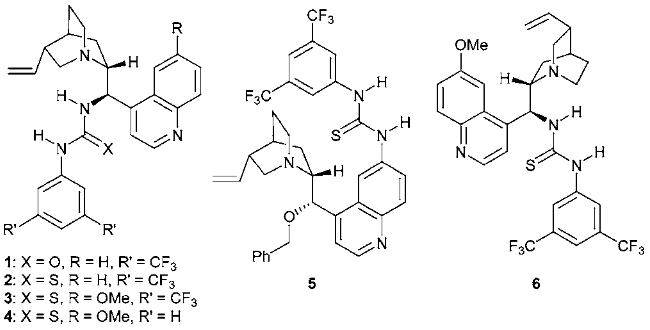
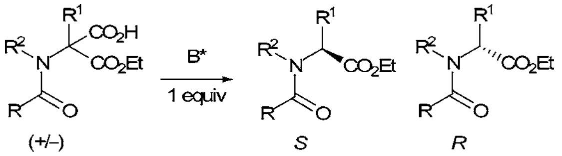
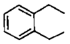


Figure 1. *Cinchona* derivatives tested in decarboxylative protonations.

Recently, urea/thiourea-based bifunctional catalysts have emerged as powerful catalysts in a wide range of asymmetric transformations.[8] Their high activity as well as their selectivity were assigned to their ability to activate both electrophilic and nucleophilic centers of the reacting partners. Since *cinchona* alkaloid derivatives were successfully used in previous decarboxylative protonations[5] we anticipated that the urea/thiourea bases **1**−**6** (Figure 1) would afford the conformational rigidity required for high selectivity.[9] The amine function could act as a chiral proton shuttle whereas the urea/thiourea group, a strong hydrogen-bond donor, would anchor the substrate to bring the chiral protonating agent in a close proximity to the prochiral enolate. We report here unprecedented enantioselectivities for metal-free decarboxylative protonations carried out in the presence of urea/thiourea *cinchona* bases **1**−**6**.

Scheme 2. (Thio)ureas Mediated Decarboxylation−Protonation of Hemimalonic Esters



	R	R^1	R^2	
7a	Ph	-$(CH_2)_4$-		**7b**
8a	OCH_2Ph	-$(CH_2)_4$-		**8b**
9a	2-thienyl	-$(CH_2)_4$-		**9b**
10a	Me	-$(CH_2)_4$-		**10b**
11a	Ph	CH_2Ph	H	**11b**
12a	OMe	CH_2Ph	H	**12b**
13a	Me	CH_2Ph	H	**13b**
14a	H	CH_2Ph	H	**14b**
15a	Me	*i*-Pr	H	**15b**
16a	Me			**16b**

Compounds **1**−**6** derived from *cinchona* alkaloids were prepared according to the described methods.[9] They were tested in a 1:1 ratio with substrate **7a** in THF at room temperature (Scheme 2). First, urea **1** afforded **7b** with a low 24% ee (Table 1, entry 1) as expected from literature precedent.[9c] By using the corresponding thiourea **2**, pipecolate **7b** was obtained in 80% yield and 64% ee (entry 2). Encouraged by this result, we screened the thioureas **3**−**6** in the decarboxylation of **7a** under similar reaction conditions, varying only the temperature and time. Increasing the temperature led to a decrease of the selectivity (entries 3 and 4). This result contrasts with those observed when the reaction was catalyzed by *cinchona* alkaloids,[5] the enantioselectivities being independent from the temperature, highlighting here the role of hydrogen bonding with thiourea-con-

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Table 1. Preliminary Results on the Decarboxylative Protonation[a] of the Model Substrate **7a** with Urea−Thioureas **1**−**5**

entry	base	temp (°C)	time (d)	yield[b] (%)	ee[c] (%)
1	**1**	25	2	80	24
2	**2**	25	2	80	64
3	**2**	40	2	95	58
4	**2**	60	1	98	24
5	**3**	25	2	85	70
6	**3**	0	7	94	82
7	**3**	−15	7	25	83
8	**4**	0	7	85	10
9	**5**	0	7	20	15

[a] **7a** (0.175 mmol), base (0.175 mmol) in THF (1 mL) under nitrogen. [b] Isolated yields after column chromatography. [c] Determined by chiral HPLC analysis. In all experiments, product **7b** with the *S* configuration was obtained as the major enantiomer.

Table 2. Ee Values as a Function of Solvents and Substrates[a]

entry	substrate	solvent	product	yield[b] (%)	ee[c] (%)
1	**7a**	THF	**7b**	94	82
2	**8a**	THF	**8b**	88	83
3	**9a**	THF	**9b**	92	88
4	**10a**	THF	**10b**	90	90
5	**11a**	THF	**11b**	89	73
6	**12a**	THF	**12b**	84	83
7	**13a**	THF	**13b**	82	82
8	**14a**	THF	**14b**	74	61
9	**10a**	THF/H_2O[d]	**10b**	86	75
10	**10a**	Et_2O	**10b**	94	81
11	**10a**	MeCN	**10b**	88	92
12	**10a**	acetone	**10b**	88	93
13	**10a**	toluene	**10b**	92	91
14	**10a**	CH2Cl2	**10b**	80	63
15	**10a**	DMF	**10b**	75	35
16	**10a**	EtOH	**10b**	82	63

[a] **7a** (0.175 mmol), base **3** (0.175 mmol), solvent (1 mL), 0 °C, 7 d. [b] Isolated yields after column chromatography. [c] Determined by chiral HPLC analysis. In all experiments, the *S* configuration of the product was obtained as the major enantiomer. [d] 3/1 mixture.

taining *cinchona* bases.[10] Thiourea **3**, the quinidine analogue of cinchonine derivative **2**, afforded a slightly better enantioselectivity at room temperature (entry 5). Decreasing the temperature led to a notable improvement of selectivity with an ee of 82−83%, while slowing the reaction rate (entries 6 and 7). At −15 °C, the isolated yield of **7b** reached only 25% after 7 days (entry 7). Base **4**, with no CF_3 groups on the *N*-phenylthiourea moiety, led to **7b** with a poor selectivity confirming the major role of the trifluoromethyl substituents. By increasing the acidity of the NH protons of the thiourea group, stronger H-bonds are formed with the substrate (entry 8). Surprisingly, **5** with the thiourea moiety on the quinoline ring gave poor yield and enantiomeric excess (entry 9).

All compounds **1**−**5** generated the *S* configuration of **7b** as the major enantiomer.[11] From this preliminary study **3** was found to be the best among all organic bases tested. Therefore quinidine-based **3** and its pseudoenantiomer **6**, prepared from quinine, were employed in the following part of this work. Further, we investigated the effect of *N*-acyl substituents on both cyclic and acyclic substrates. For a given substrate, the bulky benzoyl group gave lower ee values while the acetyl provided higher selectivity (Table 2, compare entries 1, 4, and 5, 7). Noteworthy are both the low yield and the enantioselectivity obtained with the *N*-formyl derivative (entry 8). It appeared that both steric and electronic properties of the acyl group influence the selectivity. Therefore to increase H-bond acceptor properties of the substrate, a 2-thiophenecarbonyl moiety was appended on the nitrogen as compound **9a**. Amino ester **9b** was obtained with a selectivity (88% ee) similar to that obtained with **10b** (compare entries 3 and 4). However, in this case we cannot exclude a self-decarboxylation.[12] Equally high levels of stereoinduction (83% ee) were observed with the Cbz and methoxycarbonyl derivatives **8a** and **12a** (entries 2 and 6). The easy removal of these *N*-protecting groups shows the practical utility of this chemistry.

In our previous work on decarboxylative protonation catalyzed by *cinchona* alkaloids, where the selectivity was mainly governed by ion-pair interactions, the highest enantioselectivities were obtained in solvents of low polarity.[5c] Here, a wide range of solvents either polar aprotic (CH_3CN, acetone) or apolar aprotic (toluene, ether, or THF) afforded both good yields and high selectivities. Among the best solvents, namely, THF, CH_3CN, acetone, and toluene (Table 2, entries 4, 11−13), the observed enantioselectivities are similar (within experimental error). Hence, further decarboxylations with thioureas **3** and **6** were carried out in THF, acetone, or acetonitrile.

The decarboxylation of hemiester **7a** by using 20 mol % of thiourea **3** under optimized conditions (THF, 0 °C, 12 days) afforded **7b** in 70% yield and 69% ee.[13] This lower selectivity could result from a competitive protonation of the intermediate enolate by the carboxylic acid group of unreacted starting compound due to the slow reaction rate. Although low efficiency of base **3** was observed under catalytic conditions, this compound could be considered as a catalyst. Indeed, no reaction occurred without it and it was recovered unchanged at the end of the reaction allowing its recycling by acid−base workup.

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(9) Thiourea catalysts of *cinchona* alkaloids: (a) Tillman, A. L.; Ye, J.; Dixon, D. J. *Chem. Commun.* **2006**, 1191−1193. (b) Ye, J.; Dixon, D. J.; Hynes, P. S. *Chem. Commun.* **2005**, 4481−4483. (c) McCooey, S. H.; Connon, S. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 6367−6370. (d) Vakulya, B.; Varga, S.; Csampai, A.; Soós, T. *Org. Lett.* **2005**, *7*, 1967−1969. (e) Marcelli, T.; van der Haas, R. N. S.; van Maarseveen, J. H.; Hiemstra, H. *Angew. Chem., Int. Ed.* **2006**, *45*, 929−931. Song, J.; Wang, Y.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 6048−6049.

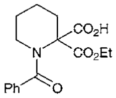
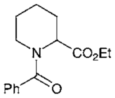
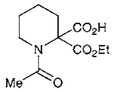
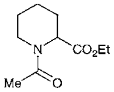
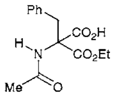
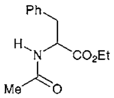
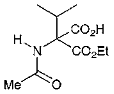
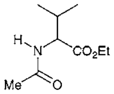
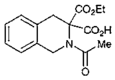
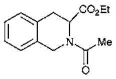
(10) Connon, S. J. *Chem. Eur. J.* **2006**, *12*, 5418−5427.

(11) Absolute stereochemistry was determined by comparison with known data (ref 5). New compounds were independently synthesized from the corresponding optically pure aminoacids.

(12) We observed the formation of 5% of product **9b** in a $CDCl_3$ sample kept at rt for 7 days, whereas no decarboxylation was observed with **7a**, **11a**, or **15a** under the same conditions. This suggests that the sulfur atom of the thiophene ring is basic enough to promote self-decarboxylation.

(13) This result is similar to our previous attempt of a catalytic reaction with substrate **7a**. **7b** was obtained with 72% ee with use of 10% of epicinchonine at room temperature, see ref 5c.

Table 3. Enantioselective Decarboxylation Mediated by Pseudoenantiomers **3** and **6** with *N*-Acetyl Substrates[a]

entry	substrate	solvent	base	product	yield[b] (%)	ee[c] (%)
1	 **7a**	Me_2CO	**6**	 **7b**	92	89, *R*
2	 **10a**	Me_2CO	**3**	 **10b**	90	93, *S*
3		Me_2CO	**6**		88	89, *R*
4	 **13a**	MeCN	**3**	 **13b**	86	82, *S*
5	 **15a**	THF	**3**	 **15b**	85	89, *S*
6		MeCN	**3**		85	86, *S*
7		Me_2CO	**6**		83	88, *R*
8	 **16a**	MeCN	**3**	 **16b**	90	86, *S*
9		Me_2CO	**3**		92	85, *S*
10		Me_2CO	**6**		89	88, *R*

[a] Substrate (0.35 mmol), base (0.35 mmol), solvent (2 mL), 0 °C, 7 d. [b] Isolated yields after column chromatography. [c] Determined by chiral HPLC analysis.

Finally, we chose the cheap and commercially available *N*-acetyl aminomalonate to prepare hemimalonates **15a** and **16a**. We examined the scope of pseudoenantiomeric bases **3** and **6** by testing the decarboxylation with structurally distinct substrates—acyclic, cyclic, and bicyclic. Gratifyingly, good consistency in the selectivity was observed with all substrates. Furthermore, excellent enantioselectivities were achieved with quinine derivative **6**, which was found to be equally efficient but opposite to **3** in terms of enantioselection in the asymmetric decarboxylative protonation of all substrates (Table 3, entries 1, 3, 7, and 10).

In summary, this work reports an asymmetric decarboxylative protonation reaching 93% ee, the highest enantioselectivity achieved for this reaction mediated by an organic base. Unlike previous reports, the selectivity was shown to be highly dependent on the temperature, due to supramolecular association of the intermediates controlled by H-bonding. Although 1 equiv of the base was used, its ready access and reusability in combination with the broad range of solvents that can be used and the *very* mild conditions make this transformation synthetically attractive. The general applicability of the reaction for the synthesis of α-aminoacid derivatives was demonstrated with structurally different types of amino hemiester precursors. Both enantiomers of these amino-esters could be synthesized with the same selectivity when using organic bases **3** and **6**. Easily removable *N*-protecting groups such as CBz or methoxycarbonyl can be used in place of acetyl with the same efficiency. In its current achievment, this enantioselective decarboxylative protonation mediated by an organic base is a valuable metal-free alternative to asymmetric protonation of lithium enolates and represents the first step toward highly selective organocatalyzed asymmetric protonation. We are currently searching for bases that can be used in catalytic amounts to overcome the slow reaction rate observed with the thioureas used in this work.

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Supporting Information Available: Details of the procedure, spectral data for unknown compounds, and an HPLC chromatogram. This material is available free of charge via the Internet at http://pubs.acs.org.

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