Pergamon

Tetrahedron Letters, Vol. 38, No. 22, pp. 3959-3962, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)00789-2

Chiral 2,2-Disubstituted Cyclopropanecarboxylic Acids: Effective Derivatizing Agents for Analysis of Enantiomeric Purity of Alcohols and for Resolution of 1,1'-Bi-2-naphthol.

Hyun Chang Kim, Soojin Choi, Hongdoo Kim, Kwang-Hyun Ahn,*

Department of Chemisty, Kyung Hee University, Yongin 449-701, Republic of Korea

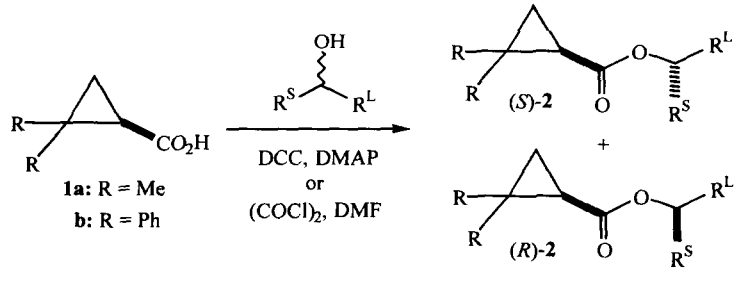
Jeong Hwan Koh, and Jaiwook Park*

Department of Chemisty, Center for Biofunctional Molecules, POSTECH, Pohang 790-784, Republic of Korea

Abstract: The enantiomeric purities of secondary alcohols can be easily analyzed by GC and HPLC through derivatization to the esters of 2,2-disubstituted cyclopropanecarboxylic acids **1**, and by ^{1}H NMR analysis of the esters of 2,2-diphenylcyclopropanecarboxylic acid (**1b**). In addition racemic 1,1'-bi-2-naphthol is easily resolved through derivatization to monoesters of 2,2-dimethylcyclopropanecarboxylic acid (**1a**), which are crystallized selectively and sequentially in high yields with high optical purities. © 1997 Elsevier Science Ltd.

The great interest in asymmetric reactions raises the need of efficient and convenient methods to determine the enantiomeric purity of the products.[1] Derivatization to the corresponding diastereomeric mixtures is a common way to measure the purity with readily accessible analytical methods, *e.g.*, GC, HPLC, and NMR spectroscopy.[2]

The most well-known chiral derivatizing reagent for alcohols and amines is α-methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA, Mosher's acid).[3] However, many chemists are interested in looking for more efficient chiral reagents in availability and economic aspect. For recent examples there are derivatives of (*R*)-lactic acid,[4] arylmethoxyacetic acids,[5] and others containing NMR active hetero atoms for ^{19}F, ^{31}P, and ^{77}Se NMR spectroscopic analyses.[5]



Now we wish to report 2,2-disubstituted cyclopropanecarboxylic acid derivatives **1** are versatile chiral derivatization reagents for the analyses of enantiomeric mixtures of secondary alcohols. The resulting diastereomeric esters are eligible in analyses with HPLC, GC, and ^{1}H NMR. In addition racemic 1,1'-bi-2-naphthol is easily resolved through derivatization to monoesters of the acid **1a**, which are crystallized selectively and sequentially in high yields with high optical purities.

The chiral acids, (*S*)-**1a** and (*R*)-**1b**, were prepared by hydrolysis of commercially available (*S*)-(+)-2,2-dimethylcyclopropanecarboxamide and Cu-catalyzed asymmetric cyclopropanation of 1,1-diphenylethylenes with diazoacetates and subsequent hydrolysis, respectively.[6,7] Secondary alcohols were easily derivatized to the corresponding esters by coupling with the acid chlorides generated from the reaction of the acids **1** with oxalyl chloride and *N,N*-dimethylformamide,[8] or by the reaction with the acids **1** in the presence of dicyclohexylcarbodiimide (DCC) and *N,N*-dimethylaminopyridine (DMAP) in CH_2Cl_2 at room temperature.[9] In the latter case the filtrate, which was obtained from a simple filtration of the resulting mixture through a celite pad, was analyzed directly with GC and HPLC. The chromatographic data for the esters are summarized in Table 1: In GC the esters of (*S*)-**1a** and (*R*)-alcohols have longer retention times than those of (*S*)-alcohols, while the esters of (*R*)-**1b** and (*S*)-alcohols have longer retention times than those of (*R*)-alcohols. Although the diastereomeric esters of 2-butanol are not separable with GC (entries 1 and 5), the diphenyl analogues coupled with (*R*)-**1b** have distinct retention times in HPLC equipped with UV detector (entry 5). Interestingly the elution orders of the esters of (*R*)-**1b** in HPLC are reverse to those in GC and the esters of (*S*)-alcohols come out first.

Table 1. Retention times (min) of esters in GC and HPLC

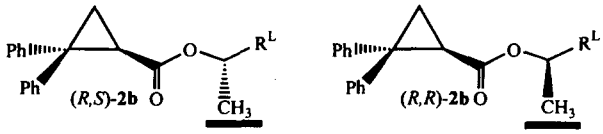
	Acid	Alcohols		GC				HPLC	
		R^S	R^L	(*S,S*)-**2a**	(*S,R*)-**2a**	(*R,S*)-**2b**	(*R,R*)-**2b**	(*R,S*)-**2b**	(*R,R*)-**2b**
1.[a]	(*S*)-**1a**	Me	Et	6.60	6.60				
2.[b]	(*S*)-**1a**	Me	*n*-Bu	9.36	9.48				
3.[c]	(*S*)-**1a**	Me	*n*-Hex	13.72	13.91				
4.[d]	(*S*)-**1a**	Me	Ph	9.72	9.98				
5.[e]	(*R*)-**1b**	Me	Et			23.56	23.56	6.48	6.90
6.[f]	(*R*)-**1b**	Me	*n*-Bu			26.72	26.39	4.93	5.45
7.[g]	(*R*)-**1b**	Me	*n*-Hex			22.87	22.49	4.94	5.55
8.[g]	(*R*)-**1b**	Me	Ph			24.44	24.04	7.44	8.54

GC condition: methyl silicone capillary column, 30m, injector pressure: 7.0 psi. [a]100 °C (initial temperature), 10 °C increase / min, 130 °C (10 min); [b]100 °C, 10 °C / min, 150 °C (10 min); [c]100 °C, 10 °C / min, 180 °C (10 min); [d]100 °C, 15 °C / min, 200 °C (10 min); [e]100 °C, 10 °C / min, 230 °C (10 min); [f]150 °C, 10 °C / min, 220 °C (20 min); [g]150 °C, 10 °C / min, 250 °C (20 min). HPLC condition: Hypersil® silica column (i.d. = 3 mm, o.d. = 4.6 mm, length = 100 mm), eluent: 1% ethyl acetate in *n*-hexane

The 2,2-diphenycyclopropanecarboxylic acid, (*R*)-**1b**, was found to be effective for ^{1}H NMR analysis. The diastereomeric esters **2b** showed well resolved resonance peaks for the easy analysis. In particular the

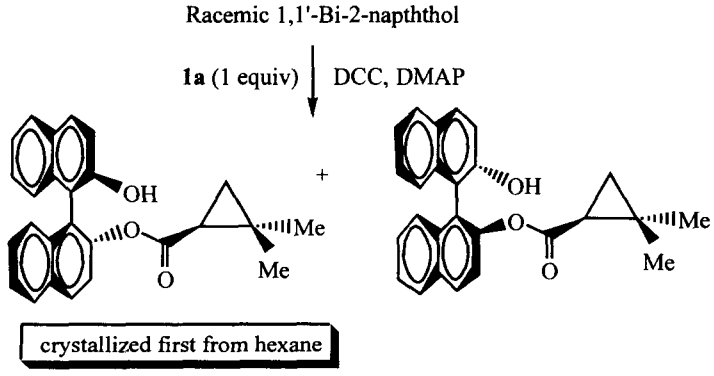
doublets of methyl protons, which are adjacent to the alkoxycarbonyl group, have distinct chemical shift values. The Δδ values of the doublets are summarized in Table 2: All the Δδ values (0.21~0.27 ppm) are much greater than those (0.06~0.1 ppm) of corresponding esters of Mosher's acid.[2b] And it is the consistent trend that the doublets of (*R,S*)-isomers appear at downfield to those of the (*R,R*)-isomers.

Table 2. ^{1}H NMR spectral data for the methyl protons of **2b**.



	R^L	(*R,S*)-**2b**	(*R,R*)-**2b**	
		δ (ppm)		Δδ (ppm)
1.	Et	1.10	0.88	0.22
2.	*n*-Bu	1.05	0.84	0.21
3.	*n*-hexyl	1.05	0.84	0.21
4.	Ph	1.47	1.20	0.27

Another interesting application of **1** was found in an efficient resolution of racemic 1,1'-bi-2-naphthol,[10] which is a well-known chiral ligand for asymmetric catalytic reactions.[11] Following the procedure similar to that mentioned above, racemic 1,1'-bi-2-naphthol was reacted with 1.1 equiv of (*S*)-**1a** to give a diastereomeric mixture of monoesters in 91% yield. The mixture was dissolved in hexane at 60 °C. After standing at room temperature for 12 h, the ester of (*R*)-binol was crystallized out selectively in almost quantitative yield with >95% *de*.[12] Then the ester of (*S*)-binol was obtained in 78% yield with >95% *de* from the filtrate. Hydrolysis of the resolved esters by KOH in 80% aqueous THF gave (*R*)-binol and (*S*)-binol in 94% and 97% yield, respectively.



In summary, we have demonstrated that 2,2-disubstituted cyclopropanecarboxylic acids **1** can be used as

efficient chiral derivatization reagents for secondary alcohols to analyze their enantiomeric purities by GC, HPLC, and ^{1}H NMR. We are currently investigating the extended applications of the acids **1** to variable alcohols, amines, and thiols.

ACKNOWLEDGEMENT. We gratefully thank POSCO (JP, Grant for Technology Development, Grant No. 96F011) and Korea Research Foundation (KHA, University Research Center Program) for financial support.

REFERENCES AND NOTES

1. Morrison, J. D. *Asymmetric Synthesis*, Academic Press, New York 1983, Vol. I.
2. (a) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1968**, *90*, 3732-3738. (b) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543-2549. (c) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512-519. (d) Sullivan, G. R.; Dale, J. A.; Mosher, H. S. *J. Org. Chem.* **1973**, *38*, 2143-2147.
3. Tottie, L.; Moberg, C.; Heuman, A. *Acta Chem. Sca,* **1993**, *47*, 492-499.
4. Latypov, S. K.; Seco, J. M.; Quiñoá, E.; Riguera, R. *J. Org. Chem.* **1995**, *60*, 1538-1545 and references therein.
5. (a) Takeuchi, Y.; Itoh, N.; Note, H.; Koizumi, T.; Yamaguchi, K. *J. Am. Chem. Soc.* **1991**, *113*, 6318-6320. (b) Alexakis, A.; Mutti, S.; Mangeney, P. *J. Org. Chem.* **1992**, *57*, 1224-1237. (c) Silks, L. A.; Peng, J.; Odom, J. D.; Dunlap, R. B. *J. Org. Chem.* **1991**, *56*, 6733-6736.
6. Evans, D. A.; Woerpel, K. A.; Hinman, M. M.; Faul, M. M. *J. Am. Chem. Soc.* **1991**, *113*, 726-728.
7. (*S*)-**1a**: $[\alpha]_D^{23}$ +154° ($CHCl_3$, c=1; lit.[6] +148°); ^{1}H NMR ($CDCl_3$): δ 1.50 (dd, 1H, *J*=8.4Hz, 5.6Hz), 1.25 (s, 3H), 1.17 (s, 3H), 1.12 (dd, 1H, *J*=5.6Hz, 4.6Hz), 0.92 (dd, 1H, *J*=8.4Hz, 4.6Hz). (*R*)-**1b**: mp 148-150 °C; $[\alpha]_D^{23}$ -213° ($CHCl_3$, c=1; lit.[6] +212° for (*S*)-**1b** isomer); ^{1}H NMR ($CDCl_3$): δ 7.35-7.17 (m, 10H), 2.50 (dd, 1H, *J*=8.4Hz, 6.3Hz), 2.11 (dd, 1H, *J*=6.3Hz, 5.0Hz), 1.66 (dd, 1H, *J*=8.4Hz, 5.0Hz).
8. Ward, D. E.; Rhee, C. K. *Tetrahedron Lett.* **1991**, *32*, 7165-7166.
9. Neises, B.; Steglich, W. *Org. Synth., Coll. Vol. VII* **1990**, 93-95.
10. (a) Chow, H. -F.; Wan, C. -W.; Ng, M. -K. *J. Org. Chem.* **1996**, *61*, 8712-8714. (b) Cai, D.; Hughes, D. L.; Verhoeven, T. R.; Reider, P. J. *Tetrahedron Lett.* **1995**, *36*, 7991-7994. (c) Hu, Q. -S.; Vitharana, D.; Pu, L. *Tetrahedron: Asymmetry* **1995**, *6*, 2123-2126.
11. For reviews, see: (a) Mikami, K.; Shimizu, M. *Chem. Rev.* **1992**, *92*, 1021-1050. (b) Singh, V. K. *Synthesis* **1992**, 605-617. (c) Rosini, C.; Franzini, L.; Raffaelli, A.; Salvadori, P. *Synthesis* **1992**, 503-517.
12. Only the ester of (*R*)-binol was detected in the ^{1}H NMR, of which stereochemistry was confirmed by comparison with the authentic sample prepared from (*R*)-binol and (*S*)-**1a**.

(*Received in Japan* 18 *March* 1997; *revised* 14 *April* 1997; *accepted* 21 *April* 1997)