A Practical and Controllable Enantioselective Synthesis of 2-Phenyl-1cyclopropanecarboxylates via a Camphor-Derived Sulfonium Ylide

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Abstract: We have developed a practical and controllable enantioselective synthesis of 2-phenyl-1-cyclopropane-carboxylates via camphor-derived sulfonium ylide. The procedure has many advantages such as cheap starting materials, facile synthetic procedures, good yields, excellent diastereoselectivities and high enantioselectivities.

Key words: enantioselective synthesis, practical method, cyclopropanecarboxylate, sulfonium ylide, diastereoselectivity

Optically active 2-substituted-1-cyclopropanecarboxylates, especially 2-phenyl-1-cyclopropanecarboxylates are very useful intermediates in the synthesis of chiral compounds and are present in many biologically important substances.¹ Recently the cyclopropanation via chiral ylides has become one of the most common methods for the enantioselective synthesis of cyclopropane derivatives.² However, only one report^{2b} appeared in the literature on the enantioselective synthesis of 2-substituted-1cyclopropanecarboxylates via ylides. In this protocol, chiral sulfide 1 is prepared in a poor 30% yield from expensive (R)-pulegone. The reaction of sulfide 1 with aliphatic bromide does not occur unless expensive silver tetrafluoroborate is employed. Although excellent enantioselectivities are achieved, one serious limitation is that only one configuration of 2-aryl-1-cyclopropanecarboxylate is obtained.³ Another serious limitation for its practical application, especially on a large scale, is that an phosphazene base $[EtN=P(NMe_2)_2N=$ expensive $P(NMe_2)_3$ is used to form the sulfonium ylides.³ Very recently it was reported that chiral vinylcyclopropanes can be synthesized by camphor-derived sulfonium ylide 2 with excellent diastereoselectivity and enantioselectivity.^{2c} Herein, we wish to report a practical and controllable enantioselective synthesis of 2-phenyl-1-cyclopropanecarboxylate via a camphor-derived sulfonium ylide.





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Initially, we employed camphor-derived sulfide 3 in a reaction with ethyl bromoacetate (Scheme 1) and obtained sulfonium salt 4^4 in 89% yield. Treatment of salt 4 with sodium hydroxide gave stabilized sulfonium ylide 5^4 in about 90% yield. We tried to obtain pure ylide 5, however, this failed because the so called 'stabilized ylide' 5 was found to gradually decompose. However, we were pleased to find that, in the presence of potassium tert-butoxide, the reaction of sulfonium salt 4 with α , β -unsaturated compound 6 in one-pot proceeded smoothly in an ice-bath, affording trans-2-substituted-1-cyclopropanecarboxylate 7a,b stereoselectively in good yield (Scheme 2). This is the first example of a cyclopropanation via camphor-derived stabilized sulfonium ylide. Although the trans/cis ratio was high, the ee value for the trans-isomers was rather low.



Scheme 1 Asymmetric cyclopropanation reaction via camphorderived stabilized sulfonium ylide 5.

We then tried to employ camphor-derived semi-stabilized sulfonium ylide **9**. This underwent reaction with a range of α,β -unsaturated esters and resulted in the enantioselective synthesis of 2-phenyl-1-cyclopropanecarboxylate **7** (Scheme 2). It was found that the reaction of sulfide **3** with benzyl bromide afforded camphor-derived sulfonium salt **8**⁴ in good yield at 0 °C. Further experiments showed that in the presence of potassium *tert*-butoxide, sulfonium salt **8** reacted smoothly with various α,β -unsaturated esters or propenenitrile to give 2-phenyl-1-cyclopropanecarboxylates **7c–f** or 2-phenyl-1-cyclopropanenitrile **7g** in good yields (Table 1).⁵ No epoxides were observed in this cyclopropanation reaction. Excellent

diastereoselectivities were achieved with the *trans*-isomer dominant in all cases. The experimental results also indicated that (1R,2R)-2-phenyl-1-cyclopropanecarboxylates **7c-f** or (1R,2R)-2-phenyl-1-cyclopropanenitrile **7g** could be obtained with excellent enantioselectivities when potassium *tert*-butoxide was used as the base (Table 1, entries 1–7).

Interestingly, the enantioselectivity in the asymmetric synthesis of 2-phenyl-1-cyclopropanecarboxylate can be



Scheme 2 Highly stereoselective synthesis of trans-(2R,3R)-2-phenyl-1-cyclopropanecarboxylates **7c–f** or cyclopropanenitrile **7g** via camphor-derived sulfonium ylide **9**.

tuned at will just by changing the base. When sodium hydride was used instead of potassium *tert*-butoxide, (1S,2S)-2-phenyl-1-cyclopropanecarboxylates **7c**-**f** were obtained with good opposite enantioselectivities (Scheme 3). The absolute configuration of **7c**-**f** was assigned through the comparison of the sign of their optical rotations with that of the known compounds. The (1R,2R)-isomers of the known compounds **7c**-**g** are levorotatory in ethanol whereas (1S,2S)-isomers of the known compounds **7c**-**f** are dextrorotatory.⁷ It is noteworthy that chiral sulfide **3** could be recovered almost quantitatively and reused conveniently.



Scheme 3 Highly stereoselective synthesis of *trans*-(2*S*,3*S*)-2-substituted-1-cyclopropanecarboxylates 7c–f via camphor-derived sulfonium ylide 9

In conclusion, we have developed an efficient method for the enantioselective synthesis of *trans*-(2R,3R)-2-phenyl-1-cyclopropanecarboxylates with excellent enantioselectivities and diastereoselectivities. Either enantiomer can be obtained, at will just by changing the base, with good to excellent enantioselectivities. The cheap starting materials, the facile preparation of chiral sulfonium ylide, excellent diastereoselectivities, and high enantioselectivities make this synthetic method practical for organic synthesis as well as having possible industrial applications.

Entry	COOR	Base	Temp (°C)	Time (h)	Yield (%) ^{a,b}	trans/cis ^c	ee (%) ^d	Configuration
1	COOEt	t-BuOK	-50	12	84	99:1	91	R,R
2	COOEt	t-BuOK	-10	12	87	97:3	90	R,R
3	COOMe	t-BuOK	-50	12	82	100:0	93	R,R
4	COOMe	t-BuOK	-10	12	88	100:0	90	R,R
5	COOn-Bu	t-BuOK	-50	12	91	99:1	91	R,R
6	COOCH ₂ Ph	t-BuOK	-50	12	79	98:2	95	R,R
7	CN	t-BuOK	-10	24	75	100:0	91	R,R
8	COOEt	NaH	-10	24	76	99:1	80	<i>S</i> , <i>S</i>
9	COOMe	NaH	-10	24	71	98:2	85	<i>S</i> , <i>S</i>
10	COOn-Bu	NaH	-10	24	80	100:0	72	<i>S</i> , <i>S</i>
11	COOCH ₂ Ph	NaH	-10	24	76	98:2	82	<i>S,S</i>

 Table 1
 Controllable Enantioselective Synthesis of 2-Phenyl-1-cyclopropanecarboxylates 7 via Camphor-Derived Sulfonium Ylide 9

^a Isolated yields.

^b All products are known compounds⁶ and were confirmed by ¹H NMR, IR and mass spectroscopy.

^c Determined by ¹H NMR spectroscopy or GC.

^d Determined by chiral HPLC on a Chiralcel OD-H column.

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References

- (a) Li, Z. N.; Liu, G. S.; Zheng, Z.; Chen, H. *Tetrahedron* 2000, *56*, 7187. (b) Högberg, M.; Sahlberg, C.; Engelhardt, P.; Norèen, R.; Kangasmetsä, J.; Johansson, N. G.; Öberg, B.; Vrang, L.; Zhang, H.; Sahlberg, B. L.; Unge, T.; LÖvgren, S.; Fridborg, K.; Bäckbro, K. *J. Med. Chem.* 1999, *42*, 4150. (c) Ikeda, T.; Kawai, A.; Mano, T.; Okumura, Y.; Stevens, R. W. Japanese Patent 90/323 814 27, 1990. (d) Lebel, H.; Marcoux, J. F.; Molinaro, C.; Charette, A. B. *Chem. Rev.* 2003, *103*, 971.
- (2) (a) Li, A. H.; Dai, L. X.; Aggarwal, V. K. *Chem. Rev.* 1997, 97, 2341. (b) Solladié-Cavallo, A.; Diep-Vohuule, A.; Isarno, T. *Angew. Chem. Int. Ed.* 1998, *37*, 1689. (c) Ye, S.; Huang, Z. Z.; Xia, C. A.; Tang, Y.; Dai, L. X. *J. Am. Chem. Soc.* 2002, *124*, 2432.
- (3) Aggarwal, V. K.; Winn, C. L. Acc. Chem. Res. 2004, 37, 611.
- (4) 4: Mp 103–105 °C. ¹H NMR: $\delta = 5.77$ (s, 1 H), 5.57 (d, J = 16.6 Hz, 1 H), 5.39 (d, J = 16.6 Hz, 1 H), 5.22 (d, J = 7.1Hz, 1 H), 4.33 (q, J = 7.0 Hz, 2 H), 4.25 (m, 1 H), 3.19 (s, 3 H), 2.04 (d, J = 4.5 Hz, 1 H), 2.03–1.87 (m, 2 H), 1.56–1.50 (m, 2 H), 1.35 (t, J = 7.1 Hz, 3 H), 1.23 (s, 3 H), 1.01 (s, 3 H), 0.87 (s, 3 H). MS (ESI): m/z = 287.1 (M – Br). **5**: 4.16– 4.14 (m, 1 H), 4.15–3.90 (m, 3 H), 3.85 (d, J = 7.2 Hz, 1 H),

2.96 (s, 1 H), 2.82 (s, 3 H), 1.85–1.81 (m, 3 H), 1.56–1.48 (m, 2 H), 1.26 (t, J = 7.0 Hz, 3 H), 1.21 (s, 3 H), 0.97 (s, 3 H), 0.84 (s, 3 H). **8**: Mp 107–109 °C. ¹H NMR: δ = 7.60 – 7.27 (m, 5 H), 6.21 (d, J = 7.4 Hz, 1 H), 5.71 (d, J = 12.0 Hz, 1 H), 5.51 (d, J = 12.0 Hz, 1 H), 4.54 (d, J = 7.4 Hz, 1 H), 4.11 (t, J = 7.4 Hz, 1 H), 2.86 (s, 3 H), 1.97 (d, J = 4.5 Hz, 1 H), 1.84–1.80 (m, 1 H), 1.66 (s, 1 H), 1.46–1.29 (m, 2 H), 1.15 (s, 3 H), 0.95 (s, 3 H), 0.81 (s, 3 H). MS (ESI): m/z = 291.1 (M – Br).

- (5) General procedure for the controllable enantioselective synthesis of 2-phenyl-1-cyclopropanecarboxylates **7c**–**f** via camphor-derived sulfonium ylide **9**: To a stirred suspension of sulfonium salt **8** (445 mg, 1.2 mmol) and α , β -unsaturated ester (1.0 mmol) in THF (6 mL) was added *t*-BuOK (336 mg, 3.0 mmol) or NaH (72 mg, 3.0 mmol) in one portion at the desired temperature (Table 1). After stirring for the time indicated (Table 1), the reaction mixture was passed through a short silica gel column, which was eluted with ethyl acetate. After concentration of the eluent, the residue was purified by flash column chromatography or preparative TLC, giving 2-phenyl-1-cyclopropanecarboxylate **7c–f**.
- (6) (a) Johnson, C. R.; Rogers, P. E. J. Org. Chem. 1973, 38, 1793. (b) Charett, A. B.; Janes, M. K.; Lebel, H. *Tetrahedron: Asymmetry* 2003, 14, 867. (c) Li, Z. N.; Zheng, Z.; Chen, H. L. *Tetrahedron: Asymmetry* 2000, 11, 1157. (d) Doyle, M. P.; Dorow, R. L.; Tamblyn, W. H. J. Org. Chem. 1982, 47, 4095.
- (7) (a) Inouye, Y.; Sugita, T.; Walborsky, H. M. *Tetrahedron* 1964, 20, 1695. (b) Evans, D. A.; Woerpel, K. A.; Scott, M. J. *Angew. Chem. Int. Ed.* 1992, *31*, 430.