Asymmetric Synthesis of Enantiomerically Pure and Diversely Functionalized Cyclopropanes

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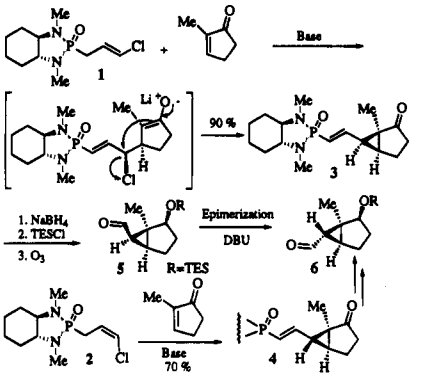
The asymmetric synthesis of cyclopropanes has been a topic of considerable interest and challenge over the past two decades.[1] Seminal contributions from various groups have described methods for the stoichiometric[2] and catalytic asymmetric[3] synthesis of disubstituted cyclopropane derivatives utilizing the addition of a methylene group to an alkene. These studies have been instrumental in the synthesis of cyclopropane motifs that are of industrial relevance,[4] cyclopropane components of natural products,[5] and other derivatives of biological importance.[6] In spite of much progress in the field, there are comparatively few methods for the asymmetric synthesis of enantiomerically pure tri- and tetrasubstituted cyclopropanes.[7] Although meritorious in several respects, some of these methods often afford *cis/trans* mixtures with acyclic substrates, and those generating bicyclic derivatives have been confined to a few examples only. These deficiencies have been addressed recently by Martin and co-workers.[8]

Scheme 1



We describe herein an efficient and versatile protocol for the synthesis of diastereomerically pure or highly enriched substituted cyclopropane derivatives endowed with functional diversity. The method consists in the highly stereocontrolled conjugate 1,4-addition of the anion of the *trans*-chloroallyl phosphonamide reagent **1** (BuLi, THF, −78 °C) to α,β-unsaturated carbonyl compounds, with the concomitant formation of the corresponding cyclopropanes as a result of an intramolecular attack of the enolate upon the intermediate allylic chloride.[9−11] The sequence is shown in Scheme 1 utilizing 2-methylcyclopentenone as an example which gives the crystalline *endo,endo* isomer **3** in 90% yield. Stereoselective reduction of the carbonyl group ($NaBH_4$, MeOH, −40 °C), protection, and oxidative cleavage by ozonolysis affords the aldehyde **5**, which can be epimerized to the *exo,endo* isomer **6**. Alternatively, utilization of the *cis*-chloroallyl phosphonamide reagent **2** with the same enone leads to the isomeric *exo,endo* product **4** as the major isomer (>90:10) (Scheme 1).

The nature of the α,β-unsaturated carbonyl compound can vary appreciably as can be seen from the results listed in Table 1. Thus, cyclopentenone and 2-methylcyclohexenone afford *endo,endo*-cyclopropanated bicyclic products **7** and **8**, respectively, in excellent diastereomeric purities (entries 1 and 2). The stereochemical identity of the products **3** and **7** was ascertained from single-crystal X-ray analysis of appropriate derivatives.[9]

The method is equally well adapted for the diastereoselective cyclopropanation of α,β-unsaturated γ-lactones,[8] δ-lactones, and γ-lactams (entries 3−5) using the reagent **1**. Again, the preponderant or exclusive product consisted of the *endo,endo* isomers **9**−**11** (entries 3−5), resulting from the same facial selectivity observed in the case of the cycloalkenones. Of particular significance were the results obtained with α,β-unsaturated esters, which further demonstrate the versatility of the method. Thus, *tert*-butyl cinnamate and *tert*-butyl sorbate afforded the corresponding *cis,trans,trans*-cyclopropane derivatives **12** and **13**, respectively, as virtually pure diastereoisomers with reagent **1** (entries 6 and 7).[12] Finally, *tert*-butyl crotonate gave diastereomerically pure cyclopropane analog **14** (entry 8),

(1) (a) Motherwell, W. B.; Nutley, C. J. *Contemp. Org. Synth.* **1994**, *1*, 219. (b) Doyle, M. P. *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH Publishers: New York, 1993; pp 63−99. (c) Doyle, M. P. *Recl. Trav. Chim. Pays-Bas* **1991**, *110*, 305. (d) Salaun, J. *Chem. Rev.* **1989**, *89*, 1247.

(2) For recent examples, see: (a) Kang, J.; Lim, G. J.; Yoon, S. k.; Kim, M. Y. *J. Org. Chem.* **1995**, *60*, 564; (b) Charette, A. B.; Prescott, S.; Brochu, C. *J. Org. Chem.* **1995**, *60*, 1081. (c) Charette, A. B.; Juteau, H. *J. Am. Chem. Soc.* **1994**, *116*, 2651. (d) Ukaji, Y.; Sada, K.; Inomata, I. *Chem. Lett.* **1993**, 1227. (e) Romo, D.; Meyers, A. I. *J. Org. Chem.* **1992**, *57*, 6265. (f) Sugimura, T.; Katagiri, T.; Tai, A. *Tetrahedron Lett.* **1992**, *33*, 367. (g) Ukaji, Y.; Nishimura, M.; Fujisawa, T. *Chem. Lett.* **1992**, 61. (h) Mash, E. A.; Hemperly, S. B.; Nelson, K. A.; Heidt, P. C.; Van Deusen, S. *J. Org. Chem.* **1990**, *55*, 2045.

(3) For recent examples, see: (a) Denmark, S. E.; Christenson, B. L.; Diane, M. C.; O'Connor, P. S. *Tetrahedron Lett.* **1995**, *36*, 2215. (b) Imai, N.; Takahashi, H.; Kobayashi, S. *Chem. Lett.* **1994**, 177. (c) Nishiyama, H.; Itoh, Y.; Matsumoto, H.; Park, S.-B.; Itoh, K. *J. Am. Chem. Soc.* **1994**, *116*, 2223. (d) Evans, D. A.; Woerpel, K. A.; Hinman, M. M.; Faul, M. M. *J. Am. Chem. Soc.* **1991**, *113*, 726. (e) Muller, D.; Umbricht, G.; Weber, B.; Pfaltz, A. *Helv. Chim. Acta* **1991**, *74*, 232. (f) Masamune, S.; Lowenthal, R. E.; Abiko, A. *Tetrahedron Lett.* **1990**, *31*, 6005. (g) Noyori, R. *Science* **1990**, *248*, 1194. (h) Doyle, M. P.; Brandes, B. D.; Kazala, A. P.; Pieters, R. J.; Jarstfer, M. B.; Watkins, L. M.; Eagle, C. T. *Tetrahedron Lett.* **1990**, *31*, 6613.

(4) (a) Aratani, T. *Pure Appl. Chem.* **1985**, *57*, 1839. (b) Aratani, T.; Yoneyoshi, Y.; Nagase, T. *Tetrahedron Lett.* **1982**, *23*, 685. (c) Kropp, H. Eur. Pat. Appl. 48,025, 1982, Merck & Co. (d) Graham, D. W. Eur. Pat. Appl. 48,301, 1982, Merck & Co.

(5) (a) White, J. D.; Kim, T. S.; Nambu, M. *J. Am. Chem. Soc.* **1995**, *117*, 5612. (b) Ihara, M.; Taniguchi, T.; Tokunaga, Y.; Fukumoto, K. *J. Org. Chem.* **1994**, *59*, 8092. (c) Kende, A. S.; Fujii, Y.; Mendoza, J. S. *J. Am. Chem. Soc.* **1990**, *112*, 9645. (d) Barnes, N. J.; Davidson, A. H.; Hughes, L. R.; Procter, G.; Rajcoomar, V. *Tetrahedron Lett.* **1981**, *22*, 1751.

(6) For selected examples, see: (a) Inoue, T.; Kitagawa, O.; Ochiai, O.; Taguchi, T. *Tetrahedron: Asymmetry* **1995**, *6*, 691. (b) Dauben, W. G.; Hendricks, R. T.; Pandy, B.; Wu, S. C.; Zhang, X.; Luzzio, M. J. *Tetrahedron Lett.* **1995**, *36*, 2385. (c) Gooding, H.; Roberts, S. M.; Storer, R. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1890. (d) Cluet, F.; Haudrechy, A.; Le Ber, P.; Sinay, P.; Wick, A. *Synlett* **1994**, 913. (e) Hanafi, N.; Ortuno, R. M. *Tetrahedron: Asymmetry* **1994**, *5*, 1657. (f) Shimamoto, K.; Ohfune, Y. *Synlett* **1993**, 919. (g) Burgess, K.; Ho, K. K. *J. Org. Chem.* **1992**, *57*, 5931. (h) Dappen, M. S.; Pellicciari, R.; Natalini, B.; Monahan, J. B.; Chiorri, C.; Cordi, A. A. *J. Med. Chem.* **1991**, *34*, 161. (i) Shimamoto, K.; Ishida, M.; Shinozaki. H.; Ohfune, Y. *J. Org. Chem.* **1991**, *56*, 4167. (j) Williams, R. M.; Fegley, G. J. *J. Am. Chem. Soc.* **1991**, *113*, 8796.

(7) (a) Kanemasa, S.; Hamura, S.; Harada, E.; Yamamoto, H. *Tetrahedron Lett.* **1994**, *35*, 7985. (b) Davis, H. M. L.; Hutcheson, D. K. *Tetrahedron Lett.* **1993**, *34*, 7243. (c) Tanimori, S.; He, M.; Nakayama, M. *Synth. Commun.* **1993**, *23*, 2861. (d) Ito, I.; Katsuki, T. *Synlett* **1993**, 638. (e) Kotha, S. *Tetrahedron* **1991**, *50*, 3639. (f) Lowenthal, R. E.; Masamune, S. *Tetrahedron Lett.* **1991**, *32*, 7373. (g) Doyle, M.; Pieter, R. J.; Martin, S. F.; Austin, R. E.; Oalmann, C. J.; Muller, P. *J. Am. Chem. Soc.* **1991**, *113*, 1423. (h) Groth, U.; Schöllkopf, U.; Tiller, T. *Liebigs Ann. Chem.* **1991**, 857.

(8) (a) Martin, S. F.; Spaller, M. R.; Liras, S.; Hartman, B. *J. Am. Chem. Soc.* **1994**, *116*, 4493. (b) Martin, S. F.; Oalmann, C. J.; Liras, S. *Tetrahedron Lett.* **1992**, *33*, 6727.

(9) Experimental procedures and spectroscopic and X-ray data are provided in the supporting information.

(10) For conjugate additions with related phosphonamides, see: (a) Hanessian, S; Gomstyan, A. *Tetrahedron Lett.* **1994**, *35*, 7509. (b) Hanessian, S; Gomstyan, A.; Payne, A.; Hervé, Y.; Beaudoin, S. *J. Org. Chem.* **1993**, *58*, 5032. For applications to natural products synthesis, see: (c) Paquette, L. A.; Wang, T. Z.; Pinard, E. *J. Am. Chem. Soc.* **1995**, *117*, 1455. (d) Boyle, C. D.; Kishi, Y. *Tetrahedron Lett.* **1995**, *36*, 4579.

(11) For selected examples of asymmetric syntheses of cyclopropanes from anionic intermediates, see: Amputch, M. A.; Matamoros, R.; Little, R. D.; *Tetrahedron* **1994**, *50*, 5591. Paetow, M.; Kotthaus, M.; Grehl, M.; Fröhlich, R.; Hoppe, D. *Synlett* **1994**, 1034.

(12) The product **13** undergoes a slow 3,3-sigmatropic rearrangement to afford a mixture of two isomeric cycloheptadiene derivatives upon standing. The process is accelerated under thermal conditions or on silica gel. For X-ray data see the supporting information.

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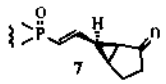
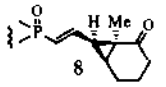
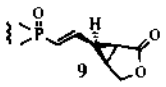
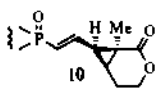
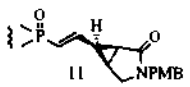
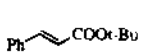
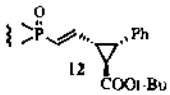
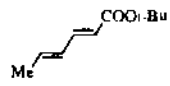
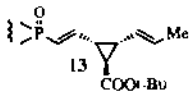
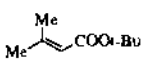
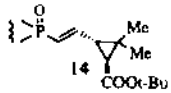
Table 1. Asymmetric Cyclopropanations

entry	substrate	product	ratio[a]; yield[b]
1		 7	96:4 ; 73 %
2		 8	95:5 ; 60[c] %
3		 9	99:1 ; 88[d,e] %
4		 10	92:8 ; 62 %
5		 11	99:1 ; 73 %
6		 12	99:1 ; 70 %
7		 13	99:1 ; 55[c]%
8		 14	95:5 ; 51[f] %

[a] Determined by ^{31}P-NMR and by isolation. [b] Yield of isolated, chromatographically homogeneous product(s). [c] Reaction performed at −100 °C; at −78 °C the ratio was 90:10; 80%. [d] The crude material could be used for subsequent transformations. Chromatography over silica gel requires 1% TEA in EtOAc (70%). [e] 3,3-Sigmatropic rearrangement was observed, ref 12. [f] Using Et_2O as solvent, in the presence of LiCl (4−5 equiv) and quenching with MeOH.

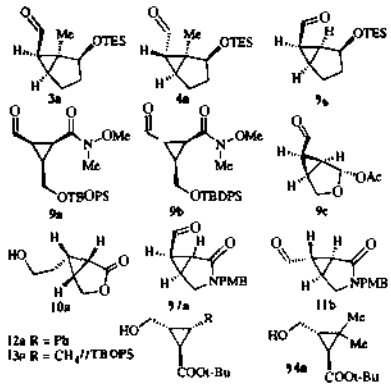


Figure 1.

which is enantiomeric with an immediate synthetic precursor to the antitumor agent anthoplanone.[15]

The phosphonamide derivatives listed in Table 1 can be further manipulated by chemoselective reactions to generate hitherto unavailable, enantiomerically pure (or highly enriched), and functionally diverse cyclopropanes[9] (Figure 1). For example, ring opening of the lactone **9** with the Weinreb reagent[14d] followed by ozonolysis gave **9a**, which was epimerized to **9b** by treatment with DBU. In the case of **10**, oxidative cleavage and reduction with sodium borohydride led to the ring-contracted γ-lactone **10a** exclusively. Oxidative cleavage of **11** afforded

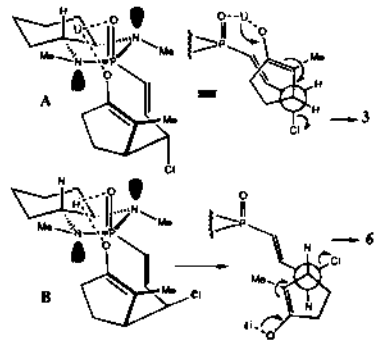


Figure 2.

the corresponding aldehyde **11a**, which was cleanly epimerized to **11b**. Selective ozonolysis[15] of the propenyl side chain in **13** (Table 1, entry 7) led to an aldehyde, which was further manipulated to give the differentially trisubstituted *cis,trans,trans* cyclopropane derivative **13a** as a single isomer.

The highly diastereoselective formation of trisubstituted cyclopropanes from the (*R,R*)-phosphonamide reagents **1** and **2** can be rationalized on the basis of previous observations from our laboratory.[11] The approach of the carbonyl substrate, as exemplified by 2-methylcyclopentenone in Figure 2, most probably occurs from the more accessible "left cleft" of the reagent.[16] This results in a favorable trajectory of attack of the γ-chloroallylic anion on the *re*-face of the cyclic enone, leading to a Li-chelated enolate intermediate which expels chloride to give the observed product. It is also remarkable that a high level of stereochemical character is maintained in the anionic transition state in order to undergo clean intramolecular S_N2-like ejection of the intermediate chloride by the enolate.[17]

The enantiomerically pure (or highly enriched) differentially substituted cyclopropane derivatives shown in Figure 1 and in Table 1 are versatile chirons in a variety of synthetic contexts. They should find extensive applications in the synthesis of natural and unnatural products of biological significance,[18] in the construction of polyfunctional chiral templates and scaffolds for molecular diversity,[19] and in further explorations of the fascinating chemistry of the cyclopropanes.[20]

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Supporting Information Available: Experimental procedures, spectral data, and X-ray crystallographic data of selected compounds (75 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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(13) Zheng, G.-C.; Hatano, M.; Ishitsuka, M. D.; Kusumi, T.; Kakisawa, H. *Tetrahedron Lett.* **1990**, *31*, 2617. McMurry, J. E.; Bosch, G. K. *J. Org. Chem.* **1987**, *52*, 4885. See also ref 5a.

(14) [a] Sibi, M. P. *Org. Prep. Proced. Int.* **1993**, *25*, 15. [b] Lipton, M.; Basha, A.; Weinreb, S. M. *Org. Synth.* **1988**, *59*, 49.

(15) Veysoglu, T.; Mitscher, L. A.; Swayze, J. K. *Synthesis* **1980**, 807.

(16) For a mechanistic interpretation of the results with acyclic esters, see refs 10a,d.

(17) The chloro precursor to **3** (Scheme 1) can be isolated after a short reaction time (10 min).

(18) Ho, T.-L. *Carbocyclic Construction in Terpene Synthesis*; VCH Publishers, Inc.: New York, 1988. For a recent review on sesquiterpenes containing a cyclopropane motif, see Jonniskens, L. H. D.; Wijnberg, J. B. P. A.; Degrrol, Ae. In *Studies in Natural Products Chemistry*; Atta-ur-Rahman, Ed.; Elsevier Science: New York, 1994; Vol. 14, p 355 and references cited therein. See also ref 6.

(19) For a recent example of carbocyclic scaffolds, see: Patek, M.; Drake, B. Lebl, M. *Tetrahedron Lett.* **1994**, *35*, 9169.

(20) For recent reviews, see: Sonnawane, H. R.; Bellur, N. S.; Kulkarni, D. G.; Ahuja, J. R. *Synlett* **1993**, 875. Hudlicky, T.; Reed, J. W. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, U.K., 1991; Vol. 5, p 899. Hudlicky, T.; Price, J. D. *Chem. Rev.* **1989**, *89*, 165 and references cited therein. Reissing, H. U. *Top. Curr. Chem.* **1988**, *144*, 73.