Improved Procedure for the Synthesis of Enantiomerically Enriched Cyclopropylmethanol Derivatives

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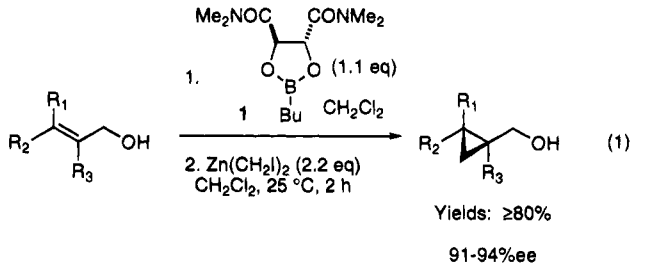
The propensity of the cyclopropyl subunit in natural and non-natural products has led to the development of numerous methods for the synthesis of enantiomerically enriched cyclopropylmethanol derivatives via the Simmons–Smith cyclopropanation reaction.[1,2]

We recently reported that substituted cyclopropylmethanol derivatives could be produced in high yields (≥80%) and enantioselectivities (91–93% ee) using a new amphoteric bifunctional chiral dioxaborolane ligand derived from (*R,R*)-(+)-*N,N,N′,N′*-tetramethyltartaric acid diamide (eq 1).[3]



(1)

The original procedure, reported on 0.5 mmol-scale, involved rapid addition (within few seconds) of a CH_2Cl_2 solution of the allylic alcohol and the dioxaborolane ligand **1** to the preformed $Zn(CH_2I)_2$ reagent at 0 °C. Subsequent warming to room temperature produced high yields of a variety of substituted cyclopropylmethanol derivatives in high enantioselectivities. For example, cinnamyl alcohol could be converted to the desired *trans*-(3-phenylcyclopropyl)methanol in quantitative yield and 93% ee. The increase of the temperature when mixing both solutions on this scale was barely noticeable. *However, when we tried to reproduce these exact conditions on a larger scale (8 mmol-scale), the increase of the temperature upon mixing the substrate with the reagent was such that it lead to a violent explosion.* Conversely, if the addition of a solution of the substrate and ligand to the preformed reagent was done at a rate to keep the internal temperature below −10 °C, the desired (phenylcyclopropyl)methanol was isolated in quantitative yield *but the enantiomeric excess was only 50%.* The numerous potential applications of this methodology to solve a variety of synthetic problems prompted us to immediately report a safer and improved procedure for the large scale synthesis of enantiomerically enriched cyclopropanes. We also disclose a detailed procedure for the extractive separation of the cyclopropylmethanol, the chiral diol, and the butylboronic acid and their recovery.

It appears from the results described above that addition of small amounts of an alcohol–ligand mixture to a large excess of the reagent (slow addition) is detrimental for obtaining high enantioselectivities. One approach that would potentially solve these problems would be to add the preformed reagent to the allylic alcohol–ligand mixture. The formation of large amounts of $Zn(CH_2I)_2$ in a nonethereal solvent is problematic since decomposition of the reagent prior to its complete formation is non negligible.[4] Furthermore, the manipulation of $Zn(CH_2I)_2$ in CH_2Cl_2 is not convenient and quantitative transfer is impossible due to the presence of large quantities of a precipitate.

These observations led us to consider using a homogeneous solution of $Zn(CH_2I)_2$·DME complex in CH_2Cl_2 as the reagent for these reactions.[5] This reagent is simply prepared by adding 2 equiv of CH_2I_2 to 1 equiv of Et_2Zn and DME in CH_2Cl_2 at −10 °C. Although we always used the freshly prepared solution, ^1H NMR analysis showed that little decomposition occurred after 24 h at room temperature in CD_2Cl_2.[6,7] Furthermore, the 24 h-old solution was as reactive as the freshly prepared solution. For example, the cyclopropanation of cinnamyl alcohol using 3 equiv of either the freshly prepared or of the 24 h/old solution was completed (>95%) after 2 h at room temperature.

The asymmetric cyclopropanation of allylic alcohols using this new reagent was then investigated. The desired cyclopropyl derivatives could be smoothly isolated in high yields if the preformed complex was added to a

(1) For recent interesting examples of natural and non-natural products containing a chiral, nonracemic cyclopropane see: (a) Curacin A: Gerwick, W. H.; Proteau, P. J.; Nagle, D. G.; Hamel, E.; Blokhin, A.; Slate, D. L. *J. Org. Chem.* **1994**, *59*, 1243–1245. (b) Constanolactones A and B: Nagle, D. G.; Gerwick, W. H. *Tetrahedron Lett.* **1990**, *31*, 2995–2998. (c) Halicholactone and neohalicholactone: Niwa, H.; Wakamatsu, K.; Yamada, K. *Tetrahedron Lett.* **1989**, *30*, 4543–4546.

(2) For chiral auxiliaries in asymmetric Simmons–Smith see the following. Chiral acetals: (a) Charette, A. B.; Côté, B.; Marcoux, J.-F. *J. Am. Chem. Soc.* **1991**, *113*, 8166–8167. (b) Charette, A. B.; Marcoux, J.-F. *Tetrahedron Lett.* **1993**, *34*, 7157–7160. (c) Charette, A. B.; Turcotte, N.; Marcoux, J.-F. *Tetrahedron Lett.* **1994**, *35*, 513–516. (d) Mori, A.; Arai, I.; Yamamoto, H. *Tetrahedron* **1986**, *42*, 6447–6458. (e) Mash, E. A.; Hemperly, S. B.; Nelson, K. A.; Heidt, P. C.; Van Deusen, S. *J. Org. Chem.* **1990**, *55*, 2045–2055. Mash, E. A.; Hemperly, S. B. *J. Org. Chem.* **1990**, *55*, 2055–2060. (f) Mash, E. A.; Nelson, K. A. *Tetrahedron* **1987**, *43*, 679–692. (g) Arai, I.; Mori, A.; Yamamoto, H. *J. Am. Chem. Soc.* **1985**, *107*, 8254–8256. (h) Mash, E. A.; Nelson, K. A. *J. Am. Chem. Soc.* **1985**, *107*, 8256–8258. Chiral diols: (i) Sugimura, T.; Yoshikawa, M.; Futagawa, T.; Tai, A. *Tetrahedron* **1990**, *46*, 5955–5966. (j) Sugimura, T.; Futagawa, T.; Yoshikawa, M.; Tai, A. *Tetrahedron Lett.* **1989**, *30*, 3807–3810. (k) Sugimura, T.; Futagawa, T.; Tai, A. *Tetrahedron Lett.* **1988**, *29*, 5775–5778. Chiral acyl iron complexes: (l) Ambler, P. W.; Davies, S. G. *Tetrahedron Lett.* **1988**, *29*, 6979–6982. (m) Ambler, P. W.; Davies, S. G. *Tetrahedron Lett.* **1988**, *29*, 6983–6984. Chiral boronic esters: (n) Imai, T.; Mineta, H.; Nishida, S. *J. Org. Chem.* **1990**, *55*, 4986–4988. For the use of chiral ligands in the Simmons–Smith cyclopropanation see: (o) Ukaji, Y.; Sada, K.; Inomata, K. *Chem. Lett.* **1993**, 1227–1230. (p) Ukaji, Y.; Nishimura, M.; Fujisawa, T. *Chem. Lett.* **1992**, 61–64. (q) Takahashi, H.; Yoshioka, M.; Ohno, M.; Kobayashi, S. *Tetrahedron Lett.* **1992**, *33*, 2575–2578. (r) Denmark, S. E.; Edwards, J. P. *Synlett* **1992**, 229–230. (s) Imai, N.; Takahashi, H.; Kobayashi, S. *Chem. Lett.* **1994**, 177–180.

(3) Charette, A. B.; Juteau, H. *J. Am. Chem. Soc.* **1994**, *116*, 2651–2652.

(4) As expected, the addition of CH_2I_2 to Et_2Zn in CH_2Cl_2 at 0 °C is highly exothermic and the reagent's decomposition is significant after 20 min: Charette, A. B.; Brochu, C. Unpublished results. The reagent stability in benzene or toluene has also been discussed: Denmark, S. E.; Edwards, J. P.; Wilson, S. R. *J. Am. Chem. Soc.* **1992**, *114*, 2592–2602.

(5) The chemical shift of the $ZnCH_2I$ signal of the complex in CD_2Cl_2 is similar to that reported by Denmark for the same species in d_6-benzene: ^1H NMR (400 MHz, CD_2Cl_2) δ 3.71 (s, 4H, CH_3OCH_2), 3.54 (s, 6H, CH_3OCH_2), 1.38 (bs, 4H, $ZnCH_2I$).

(6) Significant decomposition is observed when the reagent is left on standing for 3–4 days. We have also observed that the complex solution can also be prepared in $CDCl_3$, and ^1H NMR analysis showed very little decomposition after 24 h at −20 °C (see supplementary material for spectra).

(7) In contrast, a solution of Et_2Zn in CH_2Cl_2 was not stable for long periods of time.

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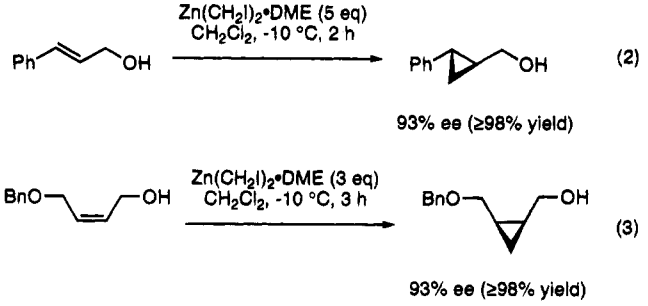
solution of cinnamyl alcohol and the dioxaborolane ligand at the rate to keep the internal temperature below −10 °C (20 min on a 8 mmol-scale). After considerable optimization, it was found that the highest enantioselectivities were obtained if 3−5 equiv of the complex were used (eq 2 and 3).[8] These new reaction conditions are compatible with large scale simply by adjusting the rate of addition of the reagent.[9]



We could separate and recover the three major components in the reaction using extractive procedures. When the reaction is complete, the organic layer is washed successively with saturated aqueous NH_4Cl to remove the chiral diol and the zinc byproducts. A subsequent base treatment of the organic layer removes 1-butaneboronic acid and leaves the almost pure cyclopropylmethanol in the organic layer. The cyclopropanemethanol (>95%), the diol derived from the ligand (85%), and 1-butaneboronic acid (50%) could all be recovered in relatively good yields.

In conclusion, we have described a safe and simple procedure for the generation of enantiomerically enriched cyclopropylmethanol derivatives on ≥1 mmol scale and for the efficient recovery of the reaction components. This procedure is general[10] and to the best of our knowledge is the first report on the use of a $Zn(CH_2I)_2$·DME complex solution in CH_2Cl_2 as the cyclopropanation reagent.

Experimental Section

General. Unless otherwise noted, all nonaqueous reactions were performed under an oxygen-free atmosphere of nitrogen with rigid exclusion of moisture from reagents and glassware. ^1H (and ^{13}C NMR) spectra were recorded in deuteriochloroform at 200.05 or 400.13 MHz (50 or 100 MHz). Diethylzinc was purchased neat and used without further purification (Aldrich or Akzo). When necessary, solvents and reagents were dried using standard procedures. Commercially available 1-butaneboronic acid was crystallized from CH_2Cl_2. Trimethyl borate was distilled over CaH_2 just prior to use.

1-Butaneboronic Acid. To a mixture 20.6 mL (0.182 mol) of freshly distilled trimethyl borate and 8.00 g (0.200 mol) of sodium hydride in 500 mL of anhydrous ether at −78 °C was added 100 mL (0.200 mol) of a 2.2 M solution of BuMgBr in ether at a rate to keep the internal temperature below −70 °C. After the addition, the mixture was stirred for an additional 2 h at −78 °C and then warmed to rt. The mixture was cooled to 0 °C, and H_2O (100 mL) was added followed by concd HCl (until pH = 1). The solution was stirred for an additional 1 h. The layers were separated, and the aqueous layer was washed with ether (3 × 100 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to produce an orange oil mixed with white crystals. The residue was crystallized from CH_2Cl_2 to produce the desired 1-butaneboronic acid. Two successive reevaporations of the filtrate and crystallization from CH_2Cl_2 afforded 18.5 g (87%) of 1-butaneboronic acid that was identical in all respects to authentic material:[11] mp 92.5−93 °C.

Preparation of Dioxaborolane 1. To a solution of 30.6 g (0.150 mol) of (+)-*N,N,N',*-tetramethyltartaric acid diamide in 100 mL of anhydrous toluene was added 18.3 g (0.180 mmol) of 1-butaneboronic acid. The mixture was heated under reflux to remove the H_2O produced in the reaction (Dean−Stark, 15 h). The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was dissolved in a minimum of CH_2Cl_2, filtered to remove excess 1-butaneboronic acid, and concentrated under reduced pressure to produce 37.8 g (93%) of the desired dioxaborolane **1**: ^1H NMR (300 MHz, $CDCl_3$) δ 5.53 (s, 2H, CHO), 3.20 (s, 6H, NMe), 2.98 (s, 6H, NMe), 1.40−1.29 (m, 4H, CH_2), 0.89−0.83 (m, 5 H, CH_3CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.9, 75.27, 36.5, 35.4, 25.4, 24.7, 13.2, 9.5; HRMS calcd for $C_{12}H_{23}BN_2O_4$ 270.1751, found 270.1746.

Preparation of the $Zn(CH_2I)_2$·DME Complex Solution in CH_2Cl_2. To a solution of 3.8 mL (37.3 mmol) of Et_2Zn in 37 mL of CH_2Cl_2 and 3.9 mL (37.3 mmol) of freshly distilled DME at −15 °C was added 6.0 mL (75 mmol) of CH_2I_2 at a rate to keep the internal temperature below −10 °C (ca. 20 min). This clear colorless solution was used directly in the cyclopropanation reaction.

General Procedure for the Enantioselective Cyclopropanation of Cinnamyl Alcohol. (2*S*,3*S*)-*trans*-(3-Phenylcyclopropyl)methanol. To a mixture of 2.20 g (8.2 mmol, 1.1 equiv) of dioxaborolane **1**, 1.0 g (7.5 mmol, 1.0 equiv) of cinnamyl alcohol, and 300 mg of 4 Å molecular sieve in 37 mL of CH_2Cl_2 at −15 °C was added the previously prepared solution of $Zn(CH_2I)_2$·DME complex at a rate to keep the internal temperature below −10 °C (ca. 20 min). The resulting mixture was stirred at −10 °C for 2 h after which time TLC analysis showed complete consumption of starting material. A saturated aqueous NH_4Cl was added, and the layers were separated. The aqueous layer was washed three times with ether. The combined organic layers were then stirred vigorously for 12 h with aqueous KOH (5 M), and the layers were separated. The organic layer was then successively washed with 10% aqueous HCl, saturated aqueous $NaHCO_3$, H_2O, saturated aqueous NaCl, and concentrated under reduced pressure. The residue was chromatographed on silica gel (20% EtOAc:hexane) to afford 1.10 g (100%) of the desired cyclopropylmethanol that was identical in all respect to known material: $[\alpha]_D$ +66° (*c* 1.9, EtOH). The enantiomeric excess (93%) was determined by GC analysis of the trifluoroacetate ester derived from *trans*-(3-phenylcyclopropyl)methanol as previously described.[3] Recovery of the chiral diol: The saturated aqueous NH_4Cl (10 mL) layer was evaporated, and boiling MeOH (ca. 20 mL) was added to the residue and stirred to dissolve the diol (the MeOH was kept near boiling temperature). The mixture was then filtered, and the filtrate was concentrated under reduced pressure. The residue was crystallized using MeOH/EtOAc to produce 1.30 g (>95%) of chiral diol. Recovery of 1-butaneboronic acid: The KOH layer was acidified with concd HCl (until pH = 1) and extracted with ether (3 × 75 mL). The organic layer was concentrated under reduced pressure, and the residue was crystallized from CH_2Cl_2 to produce 420 mg (50%) of 1-butaneboronic acid.

***cis*-4-(Benzyloxy)-2-buten-1-ol.** The title compound[12] was prepared in >98% yield on a 5.6 mmol-scale using the general procedure described above except that 3 equiv of the $Zn(CH_2I)_2$·DME complex solution were used. The enantiomeric

(8) Slighly lower ee (90% ee vs 93% ee) were obtained if commercially available 1-butaneboronic acid was used without purification. Freshly prepared 1-butaneboronic acid was used throughout this publication. Much lower enantioselectivities (84% ee) were also obtained if less than 3 equiv of the reagent were used in the cyclopropanation of cinnamyl alcohol.

(9) The enantioselective cyclopropanation of cinnamyl alcohol on a 0.1 mol scale using this procedure gave the desired product in quantitative yield (92% ee). In this case, the complex solution was added over 1 h.

(10) Both, *cis*-2-penten-1-ol and 3-methyl-2-buten-1-ol gave the corresponding cyclopropylmethanol in quantitative yields and 92% ee when treated with 5 equiv of the $Zn(CH_2I)_2$·DME complex.

(11) (a) Srebnik, M.; Cole, T. E.; Ramachandran, V.; Brown, H. C. *J. Org. Chem.* **1989**, *54*, 6085−6096. (b) Washburn, R. M.; Levens, E.; Albright, C. F.; Billig, F. A. *Organic Syntheses*; Wiley: New York, 1963; Collect. Vol. IV, pp 68−72 and references cited therein.

(12) Identical in all respects to authentic material (see ref 2q).

excess was determined to be 93% by HPLC analysis of the crude product on a chiral stationary phase. [Chiralcel OD, 2% *i*-PrOH: hexanes, t_r (minor) 21.5 min, t_r (major) 18.4 min]: $[\alpha]_D$ +39° (*c* 4.8, $CHCl_3$).

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Supplementary Material Available: NMR spectra of the $Zn(CH_2I)_2$·DME complex in CD_2Cl_2 and $CDCl_3$ (4 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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