

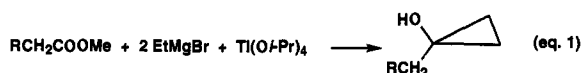
Catalytic Diastereoselective Synthesis of *Cis*-1,2-Disubstituted Cyclopropanols from Esters Using a Vicinal Dicarbanion Equivalent

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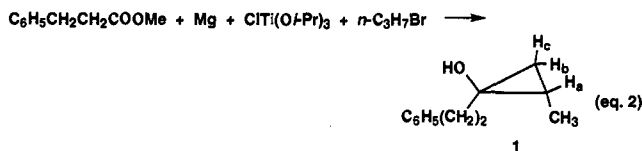
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The reaction of ethereal ethylmagnesium bromide (3 equiv) with *n*-alkanoic acid methyl esters in the presence of titanium isopropoxide (1 equiv) at -78 °C to -40 °C produces 1-alkylcyclopropanols in good yields.¹ This novel reaction (eq 1), which in a formal sense involves an ethylene dianion ($\text{CH}_2\text{--CH}_2^{2-}$) equivalent, can also be conducted with substoichiometric amounts of $\text{Ti}(\text{O-}i\text{-Pr})_4$ (0.05–0.1 equiv) at 20 °C.² It is likely that the



process is mediated by diisopropoxytitanacyclopropane, (*i*-PrO)₂TiCH₂CH₂.² Because of the simplicity and practicality of this route to cyclopropanols, and the possibility that it might be valuable for the stereoselective synthesis of more complex cyclopropanols, the investigation reported herein was undertaken. The results obtained to date indicate a remarkable intrinsic diastereoselectivity and the possibility of useful enantioselectivity as well. In addition, the observed stereopreference of the cyclopropanol synthesis is highly informative with regard to the detailed reaction pathway.

In the present research, two improvements have been made in the original procedures^{1,2} for the synthesis of cyclopropanols as summarized in eq 1. First, it was discovered that Grignard reagents with groups larger than ethyl give considerably better yields of cyclopropanols with $\text{CITi}(\text{O-}i\text{-Pr})_3$ as reagent rather than with $\text{Ti}(\text{O-}i\text{-Pr})_4$. Second, the preparation of the Grignard reagent can be obviated by the use of the process exemplified by eq 2, in which *n*-propyl bromide (2 equiv) in THF solution is added dropwise to a stirred mixture of methyl dihydrocinnamate (1 equiv), $\text{CITi}(\text{O-}i\text{-Pr})_3$ (0.1 equiv), and Grignard grade magnesium turnings (4 equiv) in THF at 18–20 °C to give, after quenching with aqueous acid and workup, *cis*-1-(2-phenylethyl)-2-methylcyclopropanol (1, 79% yield). The reaction is *completely*



diastereoselective for the *cis*-1,2-dialkylated cyclopropanol, as determined by 500 MHz NMR and chromatographic analysis. Proof of the *cis* disposition of alkyl substituents was obtained by ¹H NOE data, which revealed inter alia positive NOEs between the methyl substituent at C(2) and the methylene substituent at C(1) on the cyclopropanol ring, between these groups and H_b in 1, and between H_a and H_c in 1. ¹H NMR coupling constants, $J_{ac} = 9.7$ Hz and $J_{ab} = 5.9$ Hz, also confirmed this stereochemical assignment. The highly diastereoselective formation of *cis*-1,2-disubstituted cyclopropanols in the manner illustrated in eq 2 has

(1) Kulinkovich, O. G.; Sviridov, S. V.; Vasilevskii, D. A.; Pritыckaja, T. S. *Zh. Org. Khim.* 1989, 25, 2244.

(2) Kulinkovich, O. G.; Sviridov, S. V.; Vasilevskii, D. A. *Synthesis* 1991, 234. See also: Kulinkovich, O. G.; Sorokin, V. L.; Kel'in, A. V. *Russ. J. Org. Chem.* 1993, 29, 55.

Table 1. One-Step Catalytic Synthesis of *Cis*-1,2-Disubstituted Cyclopropanols at 20 °C in THF

R ₁	R ₂	% yield of 2 (isolated)
<i>n</i> -C ₃ H ₇	C ₂ H ₅	79
<i>n</i> -C ₆ H ₁₃	C ₂ H ₅	81
<i>n</i> -C ₆ H ₁₃	<i>n</i> -C ₆ H ₁₃	88
C ₆ H ₅ CH ₂ CH ₂	C ₂ H ₅	79
C ₆ H ₅ CH ₂ CH ₂	CH ₃	83
H	<i>n</i> -C ₆ H ₁₃	72 ^a
H	C ₆ H ₅	60 ^a
CH ₃	CH ₃	80 ^b
CH ₃	C ₆ H ₅	83 ^a

^a This reaction was conducted using preformed Grignard reagent.

^b Isolated as the 3,5-dinitrobenzoate ester.

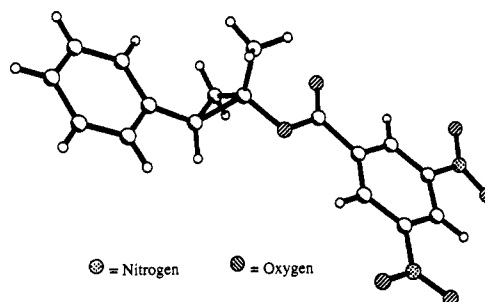


Figure 1. Molecular structure of the 3,5-dinitrobenzoate of *cis*-1-methyl-2-phenylcyclopropanol as determined by X-ray crystallographic analysis.

proven to be characteristic of this reaction, as is demonstrated by the data in Table 1.

Each of the *cis*-1,2-dialkylcyclopropanols listed in Table 1 was free of the corresponding *trans* isomer as determined by thin layer chromatographic analysis and high-field ¹H and ¹³C NMR studies. For each case, product stereochemistry was confirmed by ¹H NMR coupling constants and, whenever feasible, also by NOE studies. In addition, for the product 2, R₁ = CH₃ and R₂ = C₆H₅, the *cis* structure was demonstrated by single-crystal X-ray crystallographic analysis of the 3,5-dinitrobenzoate, mp 150–151 °C (Figure 1).³

Certain limitations in the scope of the cyclopropanol synthesis were discovered. Aromatic esters such as methyl, phenyl, or *p*-nitrophenyl benzoate resisted reaction under the standard conditions, as did α -branched esters such as methyl cyclohexanecarboxylate. Evidently, the formation of cyclopropanols by this method is very sensitive to the steric accessibility of the ester carbonyl group.

Preliminary studies on the development of an enantioselective version of the cyclopropanol synthesis have yielded promising results. Especially encouraging was the use of the chiral catalyst 3, which afforded chiral cyclopropanol 4 as shown in eq 3. In the case of 3, Ar = 3,5-bis(trifluoromethyl)phenyl,⁴ 0.3–1 equiv, cyclopropanol 4 was produced in 65–72% yield and 85:15 to 89:

(3) The colorless crystals of the 3,5-dinitrobenzoate of (\pm)-*cis*-1-methyl-2-phenylcyclopropanol, mp 150–151 °C, were found to contain four molecules per unit cell: empirical formula C₁₇H₁₄N₂O₆ (342.3); crystal size 0.5 × 0.4 × 0.3 mm³; space group P2₁/n; a = 10.119(2) Å, b = 15.299(3) Å, c = 10.321(2) Å, $\beta = 97.67(3)^\circ$; V = 1583.7(5) Å³; d = 1.436 g/cm³; (Mo K α radiation, 23 °C); 3566 reflections collected, of which 1664 with F_o > 4.0 σ (F_o) were used in the solution of the structure; R_w = 0.0579; GOF = 1.51. Detailed X-ray crystallographic data are available from the Cambridge Crystallographic Data Center, 12 Union Road, Cambridge, CB2 1EZ, U.K.

(4) See: (a) Narasaka, K.; Iwasawa, N.; Inoue, M.; Yamada, T.; Nakashima, M.; Sugimori, J. *J. Am. Chem. Soc.* 1989, 111, 5340. (b) Corey, E. J.; Matsumura, Y. *Tetrahedron Lett.* 1991, 32, 6289. (c) Schmidt, B.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* 1991, 30, 99, 1321.

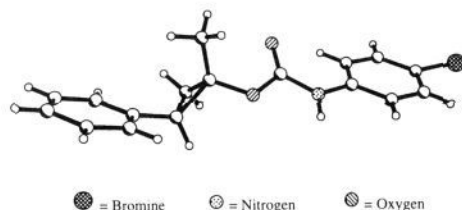
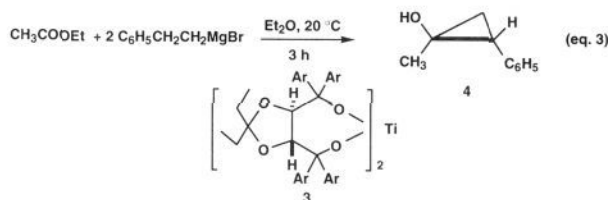


Figure 2. Molecular structure and absolute configuration of the (*p*-bromophenyl)urethane of chiral *cis*-1-methyl-2-phenylcyclopropanol (**4**), prepared as shown in eq 3) as determined by X-ray crystallography.

11 enantioselectivity.⁵ The absolute configuration of the predominating enantiomer was determined after conversion to the (*p*-bromophenyl)urethane derivative (reaction with *p*-bromophen-



yl isocyanate and 4-(dimethylamino)pyridine in CH_2Cl_2 at 23 °C for 3 h, 88% yield), separation of enantiomers using a Chiralcel OD chiral HPLC column at 23 °C with 5% isopropyl alcohol in hexane for elution (elution times 14.5 min for the major enantiomer and 18.8 min for the minor enantiomer at 1 mL/min flow rate), and recrystallization from heptane. X-ray single-crystal analysis of the major enantiomer, mp 133 °C, $[\alpha]_{\text{D}}^{23} +67^\circ$ ($c = 1.1$, CHCl_3), revealed the molecular structure and absolute configuration shown in Figure 2.⁶ The use of other catalysts of structure **3**, for example, Ar = 6-methoxy-2-naphthyl, 1-naphthyl, or 3,5-dimethylphenyl, also favored the formation of the enantiomer **4**, but with distinctly lower enantioselectivity than found for **3**, Ar = 3,5-bis(trifluoromethyl)phenyl.

The observed absolute and relative stereochemical preferences for the formation of chiral *cis*-1,2-disubstituted cyclopropanols such as **4** are consistent with the titanacyclopentane^{2,7} pathway which is shown in Scheme 1. Reaction of the chiral titanate reagent **3** with 2 equiv of Grignard reagent leads stereoselectively in this scheme to the more stable diastereomeric titanacyclopentane **5**, in which the substituent R_2 is maximally distant from the nearest (axial, Ar^*) Ar group.⁸ The next step, **5** \rightarrow **6**, involves position-selective expansion of the titanacyclopentane ring by insertion of the ester carbonyl group between Ti and the more substituted carbon. This bond-selective insertion finds precedent in recent work on the zirconium-catalyzed carbomagnesiation of olefins.⁹ The insertion reaction **5** \rightarrow **6** is also *diastereoselective* for the geometry in which the two larger groups R_1 and R_2 are

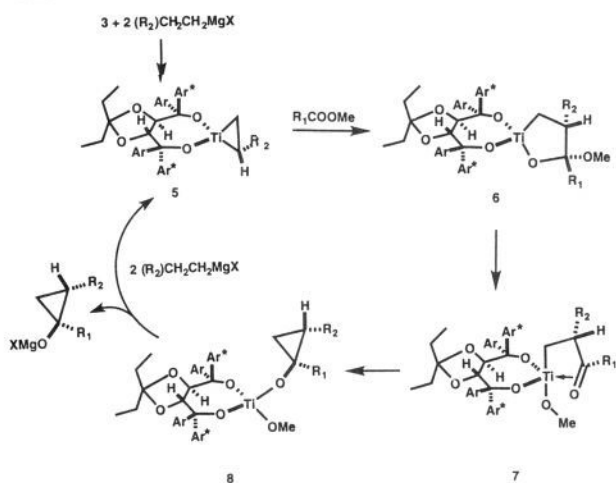
(5) Determined by conversion to the levorotatory Mosher MTPA ester and analysis by 500 MHz ^1H NMR. See: Dale, J.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512.

(6) The colorless crystals of the (*p*-bromophenyl)urethane of **4** were found to contain four molecules per unit cell: empirical formula $\text{C}_{17}\text{H}_{16}\text{BrNO}_2$ (346.2); crystal size $0.1 \times 0.2 \times 0.6 \text{ mm}^3$; space group $P2_12_12_1$; $a = 5.2010(10)$ Å, $b = 13.790(3)$ Å, $c = 21.510(4)$ Å; $V = 1542.6(5)$ Å³; $d = 1.491 \text{ g/cm}^3$; (Mo $\text{K}\alpha$ radiation, -80°C); 3996 reflections collected, of which 1934 with $F_o > 4.0\sigma(F_o)$ were used in the solution of the structure; $\eta \approx 1.02(4)$; $R_w = 0.0445$; GOF = 1.00. Detailed X-ray crystallographic data are available from the Cambridge Crystallographic Data Center, 12 Union Road, Cambridge, CB2 1EZ, U.K.

(7) For recent reviews on titana- and zirconacyclopentane chemistry, see: (a) Broene, R. D.; Buchwald, S. L. *Science* **1993**, *261*, 1696. (b) Buchwald, S. L.; Nielsen, R. B. *Chem. Rev.* **1988**, *88*, 1047. (c) Negishi, E.-I.; Takahashi, T. *Acc. Chem. Res.* **1994**, *27*, 124.

(8) Inspection of scale models reveals that the steric interactions between the equatorial Ar groups (Ar) and R_2 are small compared to those involving the axial (Ar^*) groups in **5**. In addition, it is easily seen that for $\text{Ar}^* = \text{phenyl}$ or 6-methoxy-2-naphthyl the interactions are considerably smaller than for $\text{Ar}^* = 3,5\text{-bis(trifluoromethyl)phenyl}$.

Scheme 1



trans to one another. Oxidative addition of the MeO-C linkage of **6** to Ti leads to intermediate **7** (face-specific π -donor coordination of C=O to Ti(IV)), which by reductive elimination affords the *cis*-1,2-disubstituted cyclopropanol complex **8**, the absolute configuration of which agrees with that experimentally determined for **4**. This and other possible mechanisms are under further investigation, especially toward the design of more highly enantioselective catalytic systems.¹⁰⁻¹²

(9) Hoveyda, A. H.; Morken, J. P.; Hour, A. F.; Xu, Z. *J. Am. Chem. Soc.* **1992**, *114*, 6692.

(10) The following procedure for the preparation of **2**, $\text{R}_1 = n\text{-C}_6\text{H}_{13}$ and $\text{R}_2 = \text{C}_2\text{H}_5$, illustrates the catalytic synthesis of *cis*-1,2-dialkylcyclopropanols. To a suspension of Grignard grade magnesium turnings (20.0 mmol, 0.48 g, activated with 1,2-dibromomethane (1.0 mmol, 0.187 g)), methyl heptanoate (5.0 mmol, 0.721 g), and $\text{ClTi(O-}i\text{-Pr)}_3$ (0.5 mmol, 0.5 mL, 1.0 M) in THF (30 mL) was slowly added dropwise a solution of bromobutane (1.0 mmol, 1.5 g) in THF (10 mL) over 1 h at 18–20 °C. The resulting colored solution was stirred for 2–3 h and poured into ice-cold 10% H_2SO_4 (75 mL), and the organic product was extracted with ether ($3 \times 30 \text{ mL}$). The combined extracts were washed with saturated NaHCO_3 (50 mL) and with NaCl (50 mL) and dried over MgSO_4 . Filtration and evaporation of the solvent under vacuum gave an oil, which was purified by silica gel column chromatography (hexane-ether, 8:2) to afford 0.638 g (75%) of *cis*-1-*n*-hexyl-2-ethylcyclopropanol as a colorless oil (one diastereomer only): R_f 0.3 (hexane-ether, 7:3, PMA); FTIR (neat) 3365 (br), 2930 (s), 2875 (s), 1454 (s), 1266 (s) cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 1.79 (s, OH), 1.68–1.6 (m, 1H), 1.56–1.4 (m, 4H), 1.38–1.28 (m, 7H), 1.15–1.05 (m, 1H), 0.98 (t, 3H, $J = 7.5 \text{ Hz}$), 0.91 (t, 3H, $J = 6.5 \text{ Hz}$), 0.78 (dd, 1H, $J = 5.0, 10.0 \text{ Hz}$), 0.05 (t, 1H, $J = 5.5 \text{ Hz}$); ^{13}C NMR (100 MHz, CDCl_3) δ 59.0, 34.0, 31.8, 29.5, 27.6, 25.9, 22.7, 22.6, 19.2, 14.0, 13.8 ppm; mass spectrum (EI, 70 eV) m/z (rel intensity) 170 (10) $[\text{M}]^+$, 155 (5), 141 (90), 128 (15), 113 (100); HRMS calcd for $[\text{C}_{11}\text{H}_{22}\text{O}]^+$ 170.1671, found 170.1665.

(11) The following procedure illustrates the enantioselective synthesis of 1(*S*)-methyl-2(*R*)-phenylcyclopropanol (**4**). To a solution of (4*R*,5*R*)-2,2-diethyl- α,α,α' -tetrakis[3,5-bis(trifluoromethyl)phenyl]-1,3-dioxolane-4,5-dimethanol^{4b} (0.8 mmol, 0.830 g) in toluene (2.0 mL) was added titanium ethoxide (0.4 mmol, 88 μL) under an argon atmosphere. The light yellow reaction mixture was warmed to 40–45 °C, stirred for 15 h, and then heated for 5 h at reflux. The resulting light yellow solution was cooled to 23 °C, and the toluene was removed in vacuo to afford a light yellow waxy solid, which was dissolved in ether (15 mL). To this solution of the spiroitanate (0.4 mmol) and ethyl acetate (0.4 mmol, 39 μL) in ether was added dropwise an ether solution of phenethylmagnesium bromide (0.88 mmol, 2.0 mL, 0.444 M) at 18–20 °C over 1–2 h. The reaction mixture was stirred for another 1 h at 23 °C. After the workup,¹⁰ the crude product was purified by SGC (hexane-ether) to afford the chiral diol ligand and **4** in 64% yield (38.0 mg) and 70% ee as determined by ^1H NMR analysis of the Mosher (MTPA) ester. In another experiment the cyclopropanol **4** was obtained in 78% ee. Found for **4**: R_f 0.3 (hexane-ether, 7:3, PMA); FTIR (thin film) 3323 (br, OH), 2929 (s), 1603 (s), 1416 (m), 1227 (s), 1109 (m) cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.32–7.27 (m, 2H), 7.22–7.12 (m, 3H), 2.38 (dd, 1H, $J = 7.0, 10.2 \text{ Hz}$), 2.0 (s, OH), 1.25 (dd, 1H, $J = 5.8, 10.2 \text{ Hz}$), 1.2 (s, 3H), 0.99 (t, 1H, $J = 6.0 \text{ Hz}$); ^{13}C NMR (100 MHz, CDCl_3) δ 138.5, 128.3, 128.1, 125.9, 57.5, 30.6, 20.6, 18.8 ppm; mass spectrum (EI, 70 eV) m/z (rel intensity) 148 (85) $[\text{M}]^+$, 133 (25), 115 (15), 105 (100); HRMS calcd for $[\text{C}_{10}\text{H}_{12}\text{O}]^+$ 148.0238, found 148.0242.

(12) This research was assisted financially by grants from the National Institutes of Health and the National Science Foundation and a graduate NSF fellowship to M.C.N.