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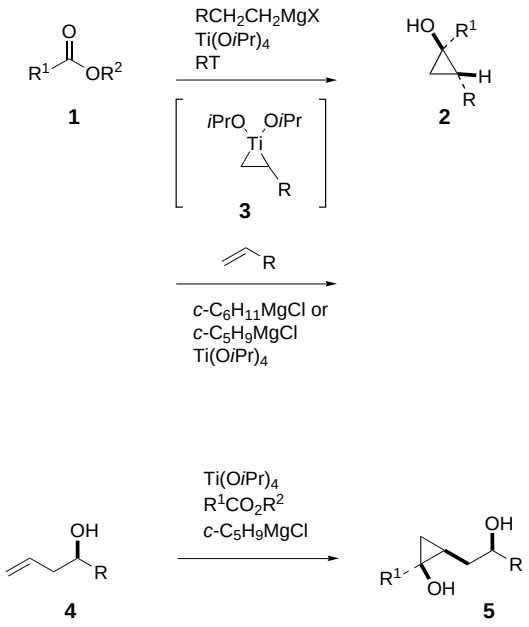
Diastereoselective Synthesis of *trans*-1,2-Dialkylcyclopropanols by the Kulinkovich Hydroxycyclopropanation of Homoallylic Alcohols**

Long Guo Quan, Se-Ho Kim, Jae Chol Lee, and Jin Kun Cha*

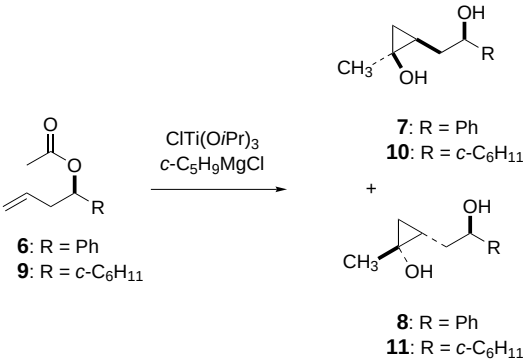
Kulinkovich and co-workers first reported an efficient preparation of cyclopropanols (**1** → **2**), by simple addition of a suitable Grignard reagent to a carboxylic ester, in the presence of titanium tetraisopropoxide (Scheme 1).[1] A key intermediate in the Kulinkovich cyclopropanation was presumed to be dialkoxytitanacyclopropane **3**.[2] An intramolecular process was developed independently by Sato's group and in our laboratories. Subsequently reported was a useful variant of the original Kulinkovich procedure, by facile olefin exchange of the initially formed titanacyclopropane with a terminal olefin, by employing a cyclohexyl or a cyclopentyl Grignard reagent.[1d, 3, 4] Other studies have included extension of the Kulinkovich cyclopropanation reaction to other



Scheme 1.

acyl derivatives and also applications of the resulting heteroatom-substituted cyclopropanes in organic synthesis.[2, 5] An enantioselective (70 – 78 % *ee*) synthesis of a *cis*-1,2-dialkylcyclopropanol was also achieved by Corey, who used a TADDOL-derived titanacyclopropane (TADDOL = (*R*,*R*)-$\alpha,\alpha,\alpha',\alpha'$-tetraaryl-1,3-dioxolane-4,5-dimethanol),[6] but its scope and generality remain untested. We report herein a diastereoselective synthesis of *trans*-1,2-dialkylcyclopropanols **5**, which starts with homoallylic alcohols **4**.[7]

Two different modes of the titanium-mediated hydroxycyclopropanation were available for homoallylic alcohols. One approach entailed an intramolecular cyclopropanation of the esters of homoallylic alcohols (Scheme 2). The related cyclopropanation reaction of but-3-enol esters was established to



Scheme 2.

give *trans*-1,2-dialkylcycloalkanols.[3a, 4a, 8] As a preliminary study with secondary homoallylic alcohols, an intramolecular cyclopropanation of acetate **6** was first examined by employing an excess of cyclopentylmagnesium chloride in the presence of $Ti(OiPr)_4$ or $ClTi(OiPr)_3$, to obtain cyclopropanols **7** and **8** as a ≈1:1 mixture in 73 % yield, along with trace

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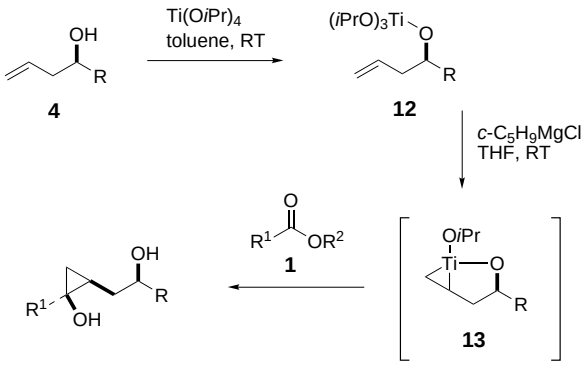
amounts of the corresponding *cis*-1,2-dialkyl isomers. Similarly, no diastereocontrol was observed for cyclopropanation of **9**, which lead to cyclopropanols **10** and **11** in 61% yield.

The disappointing lack of 1,3-diastereoselectivity of the first approach prompted us to examine an alternative method involving the bicyclic titanacyclopropanes **13** via the titanate **12**, which was derived from alcohol **4** (Scheme 3).

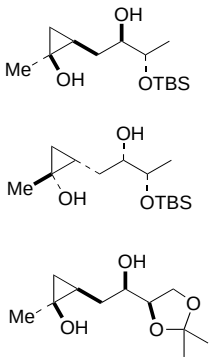


Product	R	R^1	Yield [%]	d.r.
7	Ph	Me	68	12.2:1
10	*c*-C_6H_{11}	Me	65	8.6:1
14	Ph	*n*-C_5H_{11}	62	8.0:1
15	Ph	*i*-C_5H_{11}	56	7.6:1
16	Ph	Bn	63	6.5:1
17	Ph	*i*Pr	51	3.5:1
18	Ph	*c*-C_6H_{11}	51	4.0:1
19	TMS	Me	48	6.0:1
20	*t*Bu	Me	58	8.3:1
21	2-furyl	Me	56	5.0:1
22	CH_2OTBS	Me	42	4.2:1
23	CH_2OTIPS	Me	56	7.4:1

Scheme 3. TMS = trimethylsilyl, TBS = *tert*-butyldimethylsilyl, TIPS = triisopropylsilyl, d.r. = diastereomeric ratio.

Surprisingly, the use of **13** has never been reported. For example, one-pot coupling of **12a** (R = Ph) with ethyl acetate in THF was diastereoselective and afforded a 12.2:1 diastereomeric mixture of **7** and **8** in 68–70% yield. Use of $ClTi(OiPr)_3$ in place of $Ti(OiPr)_4$ resulted in insignificant changes in diastereoselectivity and yield. Other solvents such as ether or toluene could also be employed, with comparable results (e.g., 11.4:1 diastereoselectivity in 61% yield in ether; 11:1 diastereoselectivity in 68% yield in toluene). The related cyclopropanation procedure starting with **4b** (R = *c*-C_6H_{11}) furnished **10** as the major isomer (8.6:1) in 65% yield. Also, coupling of **4a** (R = Ph) and several esters provided cyclopropanols **14**–**18** in comparable diastereoselectivity. Surprisingly, when branched esters were employed, diastereocontrol was decreased.

As can be seen from additional examples (e.g. **19**–**26**) of coupling of other respective homoallylic alcohols with ethyl acetate (Scheme 3 and 4), the hydroxycyclopropanation reaction via **13** appears to provide a general method for preparing *trans*-1,2-dialkylcyclopropanols with 1,3-diastereocontrol. As the starting alcohols are readily available in an



24: 60%, 3.3:1

25: 56%, 3.5:1

26: 32%, 5.6:1

Scheme 4.

enantiomerically pure form by standard methods,[9] the present method lends itself to a convenient enantioselective synthesis (e.g., of **24**–**26**). For example, (+)-(*R*)-**4a** was easily prepared from benzaldehyde in ≈90% *ee* by the Brown asymmetric allylation,[10] and its cyclopropanation with ethyl acetate gave (+)-**7**, $\alpha_D = 91.4$ ($c = 0.87$, benzene).

The ring configuration of the cyclopropanol products (**7**, **8**, **14**–**26**) was easily ascertained by NOE measurements and comparison of chemical shifts in the ^1H NMR spectra (with those of the corresponding *E* isomers, which were prepared independently). Initially, the pivotal relative stereochemistry of the major isomers was tentatively assigned on the basis of mechanistic considerations (Scheme 5). The bicyclic titanacyclopropane intermediate would exist as the two rapidly interconverting diastereomers **13A** and **13B**, and Curtin–Hammett kinetics are thus applicable here. The subsequent competing 1,3-diastereoselectivity-controlling steps involve the insertion of the ester carbonyl group between the Ti center and the less substituted carbon of the three-membered ring; here, formation of **28** is faster than that of **27**, because of steric considerations. As shown in Scheme 5, the insertion reaction (**13B** → **28** and also **13A** → **27**) may be diastereoselective at the acetal stereogenic center, but the latter stereocenter would be inconsequential in determining the stereochemistry of the final cyclopropanol products. Migration of the alkoxy group of **28** would then generate the titanium "homoenolate" intermediate **30**.[11] Finally, because of geometrical constraints, ring closure, driven by marked oxophilicity of Ti, should afford the cyclic titanate **32**, hydrolysis of which gives the indicated *Z* ring configuration. The stereochemical assignment was unequivocally established by single-crystal X-ray diffraction analysis of **20**,[12] and the remaining cyclopropanols were assumed, by analogy, to stem from the identical sense of diastereoselectivity (i.e., **13B** → **28** in preference to **13A** → **27**).

In summary, we have developed an enantio- and diastereoselective synthesis of *trans*-1,2-dialkylcyclopropanols by use of the bicyclic titanacyclopropanes derived from homoallylic alcohols, which provides moderate to good levels of diastereocontrol. The stereoselective formation of *trans*-1,2-dialkylcyclopropanols was made possible by seven-membered cyclic titanates and nicely complements the original Kulinkovich cyclopropanation procedure, which exhibits the opposite intrinsic preference for *cis*-1,2-dialkylcyclopropanols. Exten-

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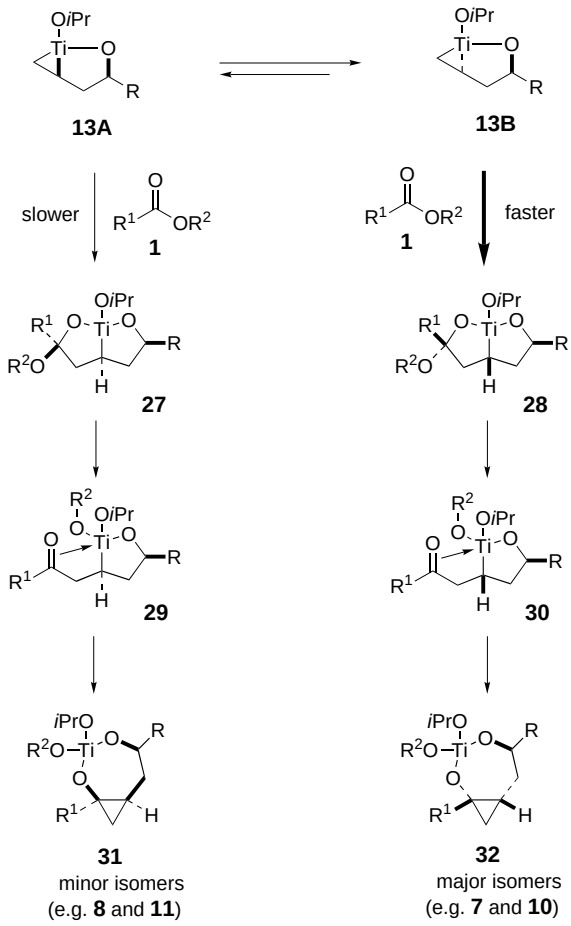

Scheme 5.

sion of the present strategy to an enantioselective synthesis of *cis*-1,2-dialkylcyclopropanols, as well as mechanistic studies to account for a marked divergence in levels of diastereoselectivity between the cyclopropanation reactions involving **6** and **12**, is under investigation.

Experimental Section

A solution of $Ti(OiPr)_4$ (0.16 mL, 0.55 mmol) and the alcohol (+)-**4a** (74 mg, 0.5 mmol) in toluene (1 mL) was stirred at room temperature for 1 h and then at 40 °C for 10 min. After volatile components were removed under vacuum, THF (5 mL) and ethyl acetate (44 mg, 0.5 mmol) were added at room temperature, followed by a 2 M solution of cyclopentylmagnesium chloride (1.1 mL) in tetrahydrofuran, over a period of 1 h (with a syringe pump). The reaction mixture was then stirred for an additional 10 min and quenched by addition of water (0.5 mL). The resulting mixture was stirred for 1 h, dried over anhydrous sodium sulfate, and filtered. The filter cake was washed with CH_2Cl_2 (10 mL), and the combined filtrates were concentrated under reduced pressure. Purification of the crude product by column chromatography on silica gel afforded 65 mg (68 %) of (+)-**7** as a colorless oil: $\alpha_D = 91.4$ ($c = 0.87$, benzene; ≈ 90 % *ee*); ^{1}H NMR (360 MHz, $CDCl_3$): $\delta = 0.34 - 0.43$ (m, 2H), 0.52 (m, 1H), 1.29 (s, 3H), 1.85 (ddd, J(H,H) = 5.3, 9.7, 14.8 Hz, 1H), 2.20 (apparent dt, J(H,H) = 14.8, 3.5 Hz, 1H), 3.65 (br s, 2H), 4.87 (dd, J(H,H) = 3.5, 5.3 Hz, 1H), 7.23 – 7.25 ppm (m, 5H); ^{13}C NMR (90 MHz, $CDCl_3$): $\delta = 19.8$, 20.1, 25.5, 37.3, 54.2, 73.1, 125.7, 127.0, 128.1, 144.0 ppm; HRMS [$M^+ - H_2O$] calcd for [$C_{12}H_{14}O$] 174.1044, found 174.1032.

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