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Stereochemistry of the Kulinkovich Cyclopropanation of Nitriles

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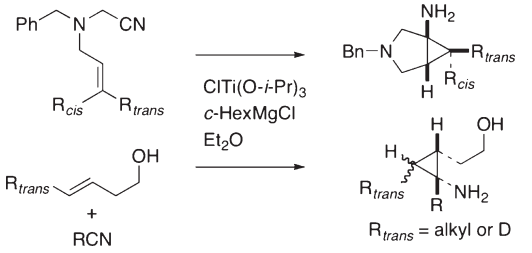

The stereochemistry of the Kulinkovich cyclopropanation of nitriles with alkenes has been examined by employing (*E*)-disubstituted alkenes and deuterium-labeled homoallylic alcohols as a stereochemical probe. An intramolecular cyclopropanation proceeds with preservation of the olefin configuration. On the other hand, intermolecular counterparts occur with both preservation and reversal of the olefin configuration, which corresponds to retention and inversion of configuration at the Ti−C bond, respectively, in the cyclopropane-forming step. These uncommon stereochemical outcomes contrast with that of the Kulinkovich cyclopropanation of tertiary amides.

Introduction

The exploration of cyclopropane's unique reactivity offers a useful tool in organic synthesis. The incorporation of a heteroatom substituent onto the ring enhances reactivity. For example, hydroxycyclopropanes (cyclopropanols) have been frequently utilized to exploit their facile ring cleavage. Kulinkovich and co-workers discovered an efficient method for preparing cyclopropanols from esters in 1989,[1] and the Kulinkovich cyclopropanation has since been extended to other carboxylic acid derivatives such as amides and nitriles to afford the corresponding heteroatom-substituted cyclopropanes.[2−6] An olefin exchange variant of the Kulinkovich cyclopropanation involving a dialkoxytitanacyclopropane or titanium(II)-alkene complex has broadened the scope of the Kulinkovich reaction.[7] An elegant deuterium labeling study by Casey and Strotman has established that the titanium homoenolate intermediates derived from esters undergo cyclization with retention of configuration at the Ti−C bond.[8] In contrast, the respective ring closure in the Kulinkovich cyclopropanation of amides entails addition of the Ti−C bond to the iminium ion intermediates with inversion of configuration in a W-shaped transition state.[8,9] The stereochemical course of the Kulinkovich cyclopropanation of nitriles is subtle in view of the likely intermediacy of imines (vis-à-vis iminium ions) and has been unexplored. By building on the recently disclosed cyclopropanation of nitriles with homoallylic alcohols, we report herein a stereochemical study of the Kulinkovich cyclopropanation of nitriles.

Results and Discussion

Our initial approach utilized a disubstituted olefin as the stereochemical probe by adaptation of Six's intramolecular

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cyclopropanation of disubstituted alkene-tethered amides, which proceeded in modest (20−40%) yields but with stereospecificity.[9] All known (intramolecular) cyclopropanation reactions of nitriles were limited to monosubstituted alkenes, except for one example of a *gem*-disubstituted alkene.[5c] However, we speculated that nitriles could be more amenable to coupling with disubstituted olefins than amides, as low-valent titanium species would bind more strongly to nitriles. Toward this end (*E*)- and (*Z*)-substrates **1** and **2** were subjected to intramolecular cyclopropanation (by the action of the cyclohexyl Grignard reagent) to produce cyclopropylamines **3** and **4**, respectively (Scheme 1). Both cyclopropanation reactions were stereospecific and occurred with retention of the olefin configuration, and the yields were higher than the cognate cyclopropanation reactions of amides. The stereochemical assignment rested on the coupling constants between two cyclopropane protons (J_{trans} = 3.7 Hz in **3** vs J_{cis} = 8.9 Hz in **4**), along with NOE measurements. Little difference in the product yield between (*E*)- and (*Z*)-alkenes was observed. Although details for ring closure of **B** to **4** are unknown, a plausible pathway likely involves **C** (where metal = Mg or Ti) or an open transition state (not shown).

The use of a disubstituted alkene as the stereochemical probe was next extended to intermolecular cyclopropanation of nitriles by taking advantage of the directing effects of a homoallylic alcohol. We have recently shown that in situ formation of a temporary tether to the metal center is indispensable to the successful implementation of olefin-exchange mediated cyclopropanation to nitriles.[5e,6] Coupling between (*E*)-homoallylic alcohols **5**−**7** and nitriles **8a**−**c** was thus examined under previously reported conditions (Table 1 and Scheme 2).[10] The aminocyclopropane products **9a**−**c**/**9′a**−**c** **11a**−**c**, and **12b** were obtained in modest yields from alcohols **5**, **6**, and **7**, respectively, whereas significant amounts of uncyclized ketones (e.g., **10a**−**c**) were also isolated in most cases.[10d] The latter products were reduced when TMSOTf was added.[6] These examples represent the first successful cyclopropanation reactions of disubstituted alkenes with nitriles. Interestingly, the corresponding (*Z*)-olefin isomers of **5**−**7** was recovered unreacted.

The product ratios were influenced by several reaction variables, such as the structure of homoallylic alcohol or nitrile substrates, the reaction time (after the reaction mixture was allowed to warm to room temperature), and the presence of TMSOTf. Cyclopropanation of alcohols **6** and **7** yielded additional diastereomers in contrast with that of **5** (Scheme 2). A secondary alcohol was not examined to bypass complications arising from low 1,3-diastereocontrol by the resulting stereocenter.[6] The stereochemical assignment of the major isomers rested on the coupling constants

SCHEME 1

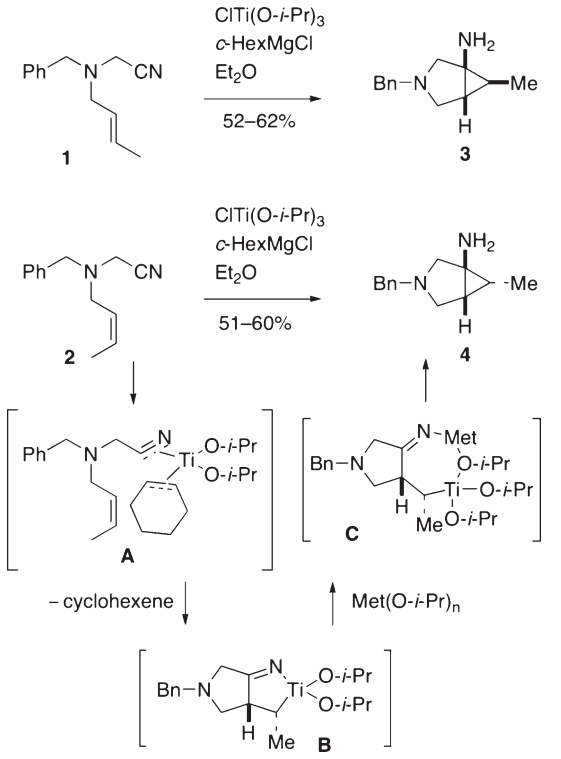
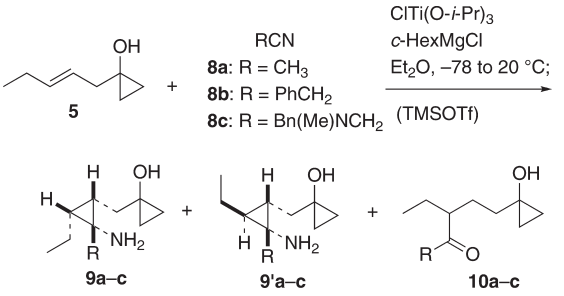


TABLE 1. Cyclopropanation of Homoallylic Alcohols with Nitriles

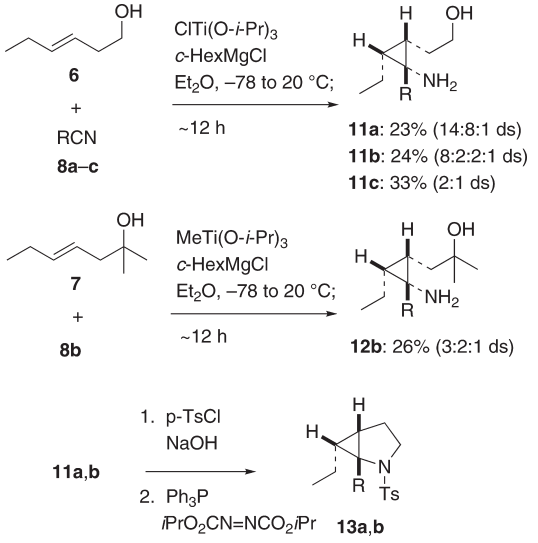


entry	nitrile	TMSOTf, time	% dr; **9**:**9′**	**10** (%)
1	**8a**	0 equiv, ∼12 h	39; 1:4	
2	**8a**	0 equiv, 24 h	42; 1:3	
3	**8a**	5 equiv, ∼12 h	50; 1:2	
4	**8b**	0 equiv, ∼12 h	25; 2:1	35
5	**8b**	0 equiv, 24 h	28; 2:1	37
6	**8b**	5 equiv, ∼12 h	35; 2:1	20
7	**8c**	0 equiv, ∼12 h	40; 1:6	35
8	**8b**	0 equiv, 24 h	43; 1:5	33
9	**8b**	5 equiv, ∼12 h	55; 1:2	15

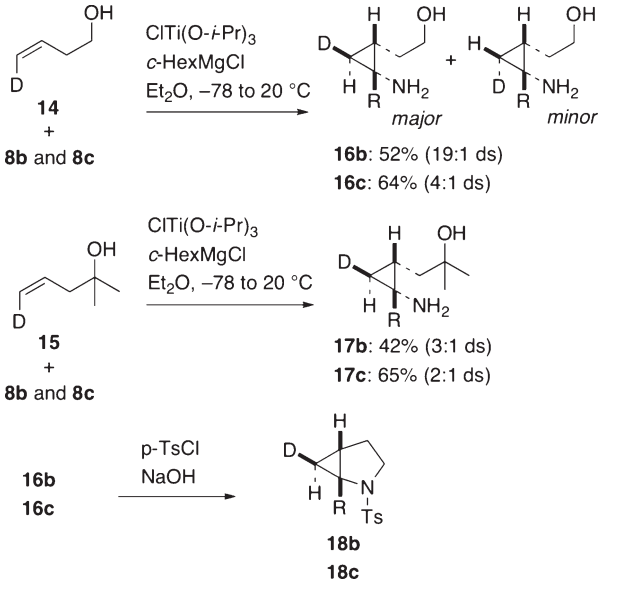
between two cyclopropane protons and was also corroborated by **11a,b** → **13a,b**. Most importantly, the formation of the major isomers from alcohols **6** and **7** entails reversal of the olefin configuration (i.e., *cis* products from (*E*)-alkenes) owing to inversion of configuration at the Ti−C bond in the cyclopropane-forming step (i.e., due to the overlap between the small lobe of the σ(C−Ti) orbital and the π^* orbital of the imine). However, there was no noticeable trend in the cyclopropanation of cyclopropanol **5** in that the major isomers arose from either retention (having J = 6.1−6.5

(10) (a) During the development of intermolecular coupling between nitriles and homoallylic alcohols, the use of MeTi(O-*i*-Pr)$_3$ (1 equiv) and the cyclohexyl Grignard reagent (2 equiv) was also found to be satisfactory but did not offer an advantage over the present procedure (except for **7**). (b) In the case of tertiary alcohol **7**, however, the pre-formation of the mixed titanate by the action of MeTi(O-*i*-Pr)$_3$ was required for the successful cyclopropanation. (c) Several cyclopropylamine products underwent slow decomposition during chromatography, which precluded isolation of pure minor isomers for full characterization. (d) The uncyclized ketones were isolated in 20−38% and 13% yields from cyclopropanation of **6** and **7**, respectively, but are not shown in Scheme 2 for convenience.

SCHEME 2



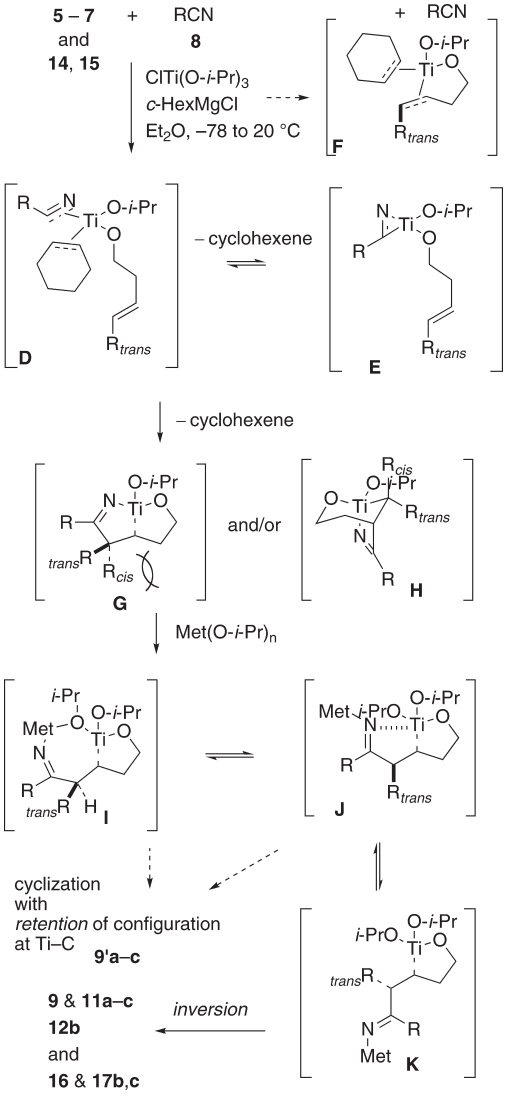
SCHEME 3



Hz between two cyclopropane protons) or reversal (having $J = 9.7$ Hz) of the olefin configuration. Taken together, these results suggest a small difference in activation energy between two stereochemical pathways.

Additional examples were examined by utilizing deuterium-labeled homoallylic alcohols **14** and **15** to probe subtle factors (including an R_{trans} substituent) that affect the stereochemical outcome of the nitrile cyclopropanation (Scheme 3).[11] As expected, these reactions gave the cyclopropylamine products in yields higher than those of the corresponding disubstituted homologues (Scheme 2). The stereochemical determination was established by the determination of J values (5.2−5.7 Hz between the *trans* cyclopropane protons) as well as clean formation of **18b,c** from

SCHEME 4



16b,c. Whereas the structure of a nitrile (**8b** vs **8c**) seems to affect the degree of stereoselectivity, the major products **16b, c** and **17b,c** arise from reversal of the olefin configuration in accord with inversion of configuration at the Ti−C bond in the ring-closure step. The minor products involve retention of the olefin configuration judging from $J = 8.9$−9.2 Hz.

A plausible mechanism starts with initial formation of **D** under typical Kulinkovich reaction conditions (Scheme 4). Subsequent olefin exchange is promoted by a temporary linker generated from the homoallylic alcohol functionality to afford bicyclic intermediate **G**. A dissociative pathway via **E** might also be possible.[12] As noted earlier, the intermediacy of **F** is deemed to be less likely.[13] The alternate mode of coupling leading to **H** can be envisioned, but its formation might be slower. (*Z*)-Disubstituted alkenes would be

(11) (a) Alcohols **14** and **15** were prepared by stereoselective hydroboration or hydrozirconation of deuterated alkynes to ensure complete deuterium labeling. (b) The cyclopropanation reactions of nondeuterated substrates were also undertaken to secure J_{trans} for comparison.

(12) Under otherwise identical conditions the cyclopentyl Grignard reagent was known to react with nitriles to give the corresponding bicyclic aminocyclopropanes.[5] This conspicuous difference between cyclohexyl and cyclopentyl Grignard reagents supports the intermediacy of **D** and can be rationalized in terms of different relative rates for ring closure versus olefin exchange.

(13) Isolation of uncyclized ketones (e.g., **10**) is consistent with the regiochemistry of intermediate **G**.

recalcitrant to the requisite formation of **G** presumably as a result of unfavorable nonbonding interactions with R_{cis} placed in the concave face. The involvement of **D** in place of **F** is consistent with the atypical reversal in the order of reactivity of (*E*)- and (*Z*)-alkenes toward a transition metal.[14,15]

Three possible modes of ring closure, **I**, **J**, and **K**, can be envisioned, where intervention of an iminium ion intermediate is not obligatory for the formation of a cyclopropane ring. The first two trigger frontside attack (i.e., retention of configuration) of the Ti−C bond at the imine. On the other hand, **K** is poised to cyclize via a sterically less encumbered W-shaped transition state with inversion of configuration at the Ti−C bond.[8] This inversion of configuration results in the *cis* relationship between R_{trans} and the alcohol-tethered side chain from an (*E*)-alkene substrate. Possible interactions between the imine nitrogen and the metal center favor the formation of the seven-membered titanate intermediate to account for the *cis* relationship of the primary amine and the alcohol-tethered side chain.

Conclusion

In summary, an intramolecular cyclopropanation of an alkene-tethered nitrile proceeds with retention of the olefin configuration, but intermolecular coupling between a homoallylic alcohol and a nitrile is not stereoselective. This remarkable dichotomy in the stereochemical outcome between intramolecular and intermolecular cyclopropanations of nitriles might be attributed to geometrical constraints imposed by the bicyclic titanate **B** in the former reaction.[16] The remarkable disparity in stereochemistry between intramolecular cyclopropanation reactions of nitriles and amides (bearing an *N*-alkenyl tether)[9] is also noteworthy.

Experimental Section

Representative Procedure for Intramolecular Cyclopropanation of Olefin-Tethered Nitriles. To a solution of nitrile **1** (0.1 g, 0.5 mmol) and titanium(IV) isopropoxide (0.16 mL, 0.55 mmol) in diethyl ether (3 mL) under an atmosphere of nitrogen was added at rt (∼20 °C) slowly (over a period of 1 h) a 2 M solution of cyclohexylmagnesium chloride in diethyl ether (0.6 mL, 1.2 mmol). The reaction mixture was stirred for an additional 2 h, treated with 10% NaOH (0.6 mL) at 0 °C, and allowed to stir for 1 or 2 h. Inorganic precipitates were filtered off through a pad of Celite, and the filter cake was washed thoroughly with ether. The combined filtrates were washed with brine and dried with Na_2SO_4. The solvent was removed under reduced pressure. Purification of the residue by silical gel chromatography using a gradient (0:100 to 1:5 MeOH−CH_2Cl_2) afforded 53−63 mg (52−62%) of pure cyclopropylamine **3**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.78 (apparent t, J = 3.7 Hz, 1H), 1.11 (d, J = 6.4 Hz, 3 H), 1.31 (dq, J = 6.4, 3.7 Hz, 1H), 1.51 (br s, 2 H), 2.38 (d, J = 8.6 Hz, 1H), 2.48 (dd, J = 8.3, 3.7 Hz, 1H), 2.87 (d, J = 8.6 Hz, 1H), 2.98 (d, J = 8.3 Hz, 1H), 3.58 (s, 2H), 7.18−7.28 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.8, 19.1, 30.4, 44.2, 55.2, 59.2, 62.3, 126.7, 128.1, 128.5, 139.4; MS (ESI) m/z 203.36 ($M + H^+$), 204.34 ($M + 2H^+$); HRMS calcd for $C_{13}H_{19}N_2$ ($M + H^+$) 203.1548, found 203.1554.

Cyclopropylamine **4** was obtained in 52−62% yield from nitrile **2** under identical conditions: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.04−1.11 (m, 1H), 1.21 (dt, J = 8.9, 2.6 Hz, 1H), 1.25 (d, J = 6.4 Hz, 3H), 1.85 (br s, 2 H), 2.56 (d, J = 9.0 Hz, 1H), 2.79 (d, J = 2.6 Hz, 2H), 3.06 (d, J = 9.0 Hz, 1H), 3.59 (s, 2H), 7.19−7.35 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 7.3, 23.3, 27.7, 44.6, 52.7, 59.8, 60.2, 126.7, 128.1, 128.3, 139.7; MS (ESI) m/z 203.33 ($M + H^+$), 204.34 ($M + 2H^+$); HRMS calcd for $C_{13}H_{19}N_2$ ($M + H^+$) 203.1548, found 203.1555.

General Procedure for Intermolecular Cyclopropanation of Nitriles with Alcohols 5, 6, 14, and 15. (A) Without TMSOTf. A solution of chlorotitanium triisopropoxide (0.12 mL, 0.5 mmol) in diethyl ether (1.0 mL) was cooled to −78 °C under an atmosphere of nitrogen. A 2 M solution of cyclohexylmagnesium chloride in diethyl ether (0.63 mL, 1.26 mmol) was added dropwise within 5 min at the same temperature. After the mixture had been stirred for an additional 45 min, a solution of a homoallylic alcohol (0.25 mmol) and a nitrile (0.5 mmol) in ether (1.0 mL) was added in one portion at −78 °C. The reaction mixture was allowed to slowly warm to rt (∼20 °C) (over approximately 1.5 h), stirred for an additional 12 or 24 h, and then treated with 10% NaOH (3 mL) at 0 °C. Two phases separated in 30 min, and the aqueous layer was extracted with ether (4 × 5 mL). The combined organic extracts were dried with Na_2SO_4. The solvent was removed under reduced pressure. Purification of the concentrate by silica gel chromatography using a MeOH−CH_2Cl_2 gradient gave the corresponding cyclopropylamine products.

General Procedure for Intermolecular Cyclopropanation of Nitriles with Alcohols 5 and 6. (B) With TMSOTf. A solution of chlorotitanium triisopropoxide (0.12 mL, 0.5 mmol) in diethyl ether (1.0 mL) was cooled to −78 °C under an atmosphere of nitrogen. A 2 M solution of cyclohexylmagnesium chloride in diethyl ether (0.63 mL, 1.26 mmol) was added dropwise within 5 min at the same temperature. After the mixture had been stirred for an additional 45 min, a solution of a homoallylic alcohol (0.25 mmol) and a nitrile (0.5 mmol) in ether (1.0 mL) was added in one portion at −78 °C. The reaction mixture was allowed to slowly warm to rt (over approximately 1.5 h), stirred for an additional 3 h, and then recooled to −78 °C. TMSOTf (0.23 mL, 1.25 mmol) was added in one portion. The reaction mixture was allowed to slowly warm to rt (∼20 °C), stirred overnight (∼ 15 h), and then treated with 10% NaOH (3 mL) at 0 °C. Two phases separated in 30 min, and the aqueous layer was extracted with ether (4 × 5 mL). The combined organic extracts were dried with Na_2SO_4. The solvent was removed under reduced pressure. Purification of the concentrate by silical gel chromatography using MeOH−CH_2Cl_2 gradient gave the corresponding cyclopropylamine products.

Cyclopropylamine 9′a (Major Isomer). ^{1}H NMR (400 MHz, C_6D_6) δ 0.24 (ddd, J = 8.1, 6.1, 3.7 Hz, 1H), 0.38−0.48 (m, 2H), 0.50 (apparent q, J = 6.1 Hz, 1H), 0.89−0.94 (m, 2H), 0.92 (t, J = 7.3 Hz, 3H), 0.95 (s, 3H), 1.08 (m, 1H), 1.23 (m, 1H), 1.65 (dd, J = 15.0, 8.1 Hz, 1H), 1.87 (dd, J = 15.0, 3.7 Hz, 1H), 2.32 (br s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 13.0, 13.8, 14.5, 22.7, 23.3, 29.6, 32.6, 36.2, 36.9, 55.0; MS (ESI) m/z 170.36 ($M + H^+$); HRMS calcd for $C_{10}H_{20}NO$ ($M + H^+$) 170.1545, found 170.1539.

Cyclopropylamine 9a (Minor Isomer). ^{1}H NMR (400 MHz, C_6D_6) δ 0.34−0.43 (m, 3H), 0.63 (dt, J = 9.7, 4.1 Hz, 1H), 0.85−0.95 (m, 2H), 0.90 (t, J = 7.3 Hz, 3H), 1.09 (s, 3H), 1.23 (dq, J = 7.3,

(14) In recent examples of intramolecular cyclopropanation reactions of (*E*)- and (*Z*)-disubstituted alkenes bearing amide groups, faster reactions were presumed for (*Z*)-isomers.[9c]

(15) (a) These putative intermediates in Scheme 4 have eluded isolation for full characterization. For a computational study on the related Kulinkovich cyclopropanation of esters, see: Wu, Y.-D.; Yu, Z.-X. *J. Am. Chem. Soc.* **2001**, *123*, 5777. (b) The reactivity of the Kulinkovich reagent is conceptually related to that of the Negishi reagent: Negishi, E.; Huo, S. In *Titanium and Zirconium in Organic Synthesis*; Marek, I., Ed.; Wiley-VCH: Weinheim, 2002; pp 1−49. See also : Buchwald, S. L.; Watson, B. T.; Wannamaker, M. W.; Dewan, J. C. *J. Am. Chem. Soc.* **1989**, *111*, 4486.

(16) (a) The atypical dichotomy is indicative of a small difference in activation energy between two modes of the final cyclization step: complexation between the titanium metal and the imine functional group predisposes to retention of configuration; on the other hand, inversion of configuration is favored on grounds of steric effects. (b) It is interesting to note that an idealized W-shaped transition state is unattainable for the bicyclic titanate **B**, which might help reinforce ring closure with retention of configuration.

3.2 Hz, 2H), 1.28 (dd, $J = 14.6$, 4.1 Hz, 1H), 1.87 (ddd, $J = 14.6$, 9.7, 1.6 Hz, 1H), 2.10 (br s, 3H); HRMS calcd for $C_{10}H_{20}NO$ ($M + H^+$) 170.1545, found 170.1543.

Preparation of Cyclopropylamine 12b by Cyclopropanation with MeTi(O-*i*-Pr)$_3$. To a solution of methyltitanium triisopropoxide (0.07 mL, 0.3 mmol) in diethyl ether (1.0 mL) under nitrogen was added at rt dropwise (over 5 min) a solution of alcohol **7** (38.4 mg, 0.3 mmol) in ether (0.5 mL). After the mixture had been stirred for 30 min, a solution of nitrile **8b** (29.5 mg, 0.25 mmol) in ether (0.5 mL) was added in one portion, followed by slow addition (over 1 h by using a syringe pump) of a 2 M solution of cyclohexylmagnesium chloride in ether (0.25 mL, 0.5 mmol). The reaction mixture was stirred at rt for an additional 3 h and then treated with 10% NaOH (3 mL) at 0 °C. Two phases separated in 30 min, and the aqueous layer was extracted with ether (4 × 5 mL). The combined organic extracts were dried with Na_2SO_4. The solvent was removed under reduced pressure. Purification of the concentrate by silical gel chromatography using a MeOH−CH_2Cl_2 gradient (1:100 to 1:10) afforded the cyclopropylamine products as a mixture of isomers. **12b** (major isomer): ^{1}H NMR (500 MHz, C_6D_6) δ 0.63 (dt, $J = 9.2$, 7.0 Hz, 1H), 0.73 (dt, $J = 9.2$, 4.7 Hz, 1H), 0.88 (t, $J = 7.3$ Hz, 3H), 1.15 (s, 3H), 1.16 (s, 3H), 1.17 (br s, 3H), 1.27−1.34 (m, 2H), 1.49 (dd, $J =$ 13.4, 4.7 Hz, 1H), 1.54 (dd, $J =$ 13.4, 9.2 Hz, 1H), 2.36 (d, $J = 13.7$ Hz, 1H), 2.59 (d, $J = 13.7$ Hz, 1H), 7.03−7.11 (m, 4H), 7.12−7.18 (m, 1H); ^{13}C NMR (125 MHz, C_6D_6) δ 14.6, 17.1, 21.8, 22.8, 28.7, 29.2, 30.6, 37.0, 39.4, 49.4, 70.0, 126.6, 128.6, 129.7, 139.9; MS (ESI) m/z 263.37 ($M + H^+$), 264.38 ($M + 2H^+$); HRMS calcd for $C_{16}H_{27}N_2O$ ($M + H^+$) 263.2123, found 263.2115.

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Supporting Information Available: Full characterization data for all new cyclopropyl amines and copies of their ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.