J|A|C|S
ARTICLES
Published on Web 01/27/2004

Stereochemistry of Cyclopropane Formation Involving Group IV Organometallic Complexes

Charles P. Casey* and Neil A. Strotman
Contribution from the Department of Chemistry, University of Wisconsin, Madison, Wisconsin 53706

Received July 18, 2003; E-mail: casey@chem.wisc.edu

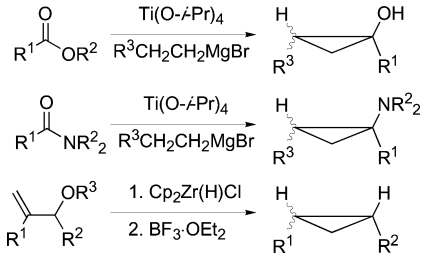
Abstract: The reaction of (*Z*)-HDC=CHCH(OCH$_3$)C$_6$H$_5$ (**1**) with Cp$_2$Zr(D)Cl followed by BF$_3$·OEt$_2$ gave phenylcyclopropanes **3a** and **3b**, both having cis deuterium. This stereochemical outcome requires inversion of configuration at the carbon bound to zirconium and is consistent with a "W-shaped" transition state structure for cyclopropane formation. In a Kulinkovich hydroxycyclopropanation, *trans*-3-deutero-1-methyl-*cis*-2-phenyl-1-cyclopropanol (**5**) was formed stereospecifically from Ti(O-*i*-Pr)$_4$, ethyl acetate, EtMgBr, and *trans*-β-deuterostyrene. This stereochemistry requires retention of configuration at the carbon bound to titanium and is consistent with frontside attack of the carbon−titanium bond on a carbonyl group coordinated to titanium. In a de Meijere cyclopropylamine synthesis, a 3:1 mixture of *N*,*N*-dimethyl-*N*-(*trans*-3-deutero-*trans*-2-phenylcyclopropyl)amine (**6a**) and *N*,*N*-dimethyl-*N*-(*cis*-3-deutero-*cis*-2-phenylcyclopropyl)amine (**6b**) was formed from Ti(O-*i*-Pr)$_4$, DMF, Grignard reagents, and *trans*-β-deuterostyrene. This stereochemistry requires inversion of configuration at the carbon bound to titanium and is consistent with a W-shaped transition structure for ring closure.

Introduction

Chemists' continuing fascination with cyclopropanes and their stereoselective synthesis was highlighted in a recent thematic issue of *Chemical Reviews*.[1] The cyclopropane unit plays an important role in pharmaceuticals, agrochemicals, theoretically interesting molecules, and intermediates in synthesis.[2] Group IV transition metal species are becoming widely used in the synthesis of diverse arrays of polysubstituted cyclopropanes.[3] For example, the Kulinkovich hydroxycyclopropanation of alkenes, discovered in 1989,[4] produces high yields of cyclopropanols from esters, Grignard reagents, and Ti(O-*i*-Pr)$_4$ (Scheme 1). Catalytic amounts of Ti can be employed.[5] The Kulinkovich reaction has been applied both diastereo- and enantioselectively.[6,7] The reaction is proposed to involve Ti(II)−alkene complexes generated from the Grignard reagent. The exchange of alkenes with the initial Ti(II)−alkene complex has broadened the scope of the procedure.

A similar methodology was developed by de Meijere for the synthesis of cyclopropylamines from *N*,*N*-dialkylamides, Grignard reagents, and Ti(O-*i*-Pr)$_4$ (Scheme 1).[8] Exchange of alkenes with a Ti(II)−alkene intermediate has broadened the scope of this cyclopropylamine synthesis.[9] The reaction requires stoichiometric Ti(IV) but provides an efficient route to polysubstituted cyclopropylamines not readily obtained by other routes. Primary cyclopropylamines have also been synthesized recently from Ti(O-*i*-Pr)$_4$, Grignard reagents, and nitriles.[10]

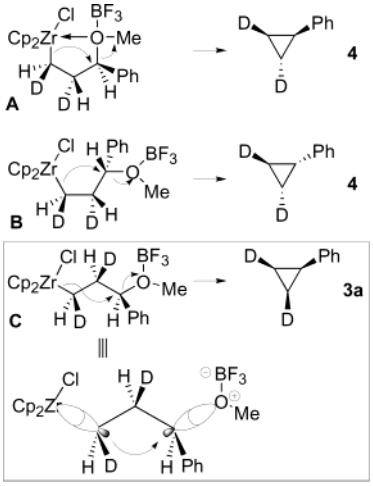
Scheme 1



Recently, an efficient new synthesis of cyclopropanes, via hydrozirconation of allylic ethers followed by addition of a Lewis acid, was reported by Gandon and Szymoniak (Scheme 1).[11] This procedure produced high yields of cyclopropanes under mild conditions and was compatible with a variety of alkyl, aryl, and alkenyl substituents.

(1) de Meijere, A. *Chem. Rev.* **2003**, *103*, 931.
(2) (a) Pietruszka, J. *Chem. Rev.* **2003**, *103*, 1051. (b) Gnad, F.; Reiser, O. *Chem. Rev.* **2003**, *103*, 1603. (c) Wessjohann, L. A.; Brandt, W.; Thiemann, T. *Chem. Rev.* **2003**, *103*, 1625. (d) Dolbier, W. R.; Battiste, M. A. *Chem. Rev.* **2003**, *103*, 1071.
(3) For recent reviews of cyclopropane formation using early transition metal reagents, see: (a) Kulinkovich, O. G.; de Meijere, A. *Chem. Rev.* **2000**, *100*, 2789. (b) Sato, F.; Urabe, H.; Okamoto, S. *Chem. Rev.* **2000**, *100*, 2835. (c) *Titanium and Zirconium in Organic Synthesis*; Marek, I., Ed.; Wiley-VCH: Weinheim, 2002; pp 390−434.
(4) Kulinkovich, O. G.; Sviridov, S. V.; Vasilevskii, D. A.; Prityts kaya, T. S. *Zh. Org. Khim.* **1989**, *25*, 2244.
(5) Kulinkovich, O. G.; Sviridov, S. V.; Vasilevski, D. A. *Synthesis* **1991**, 234.
(6) (a) Kulinkovich, O. G.; Savchenko, A. I.; Sviridov, S. V.; Vasilevski, D. A. *Mendeleev Commun.* **1993**, 230. (b) Kasatkin, A.; Sato, F. *Tetrahedron Lett.* **1995**, *36*, 6079. (c) Lee, J.; Kang, C. H.; Kim, H.; Cha, J. K. *J. Am. Chem. Soc.* **1996**, *118*, 291. (d) Epstein, O. L.; Savchenko, A. I.; Kulinkovich, O. G. *Tetrahedron Lett.* **1999**, *40*, 5935.
(7) Corey, E. J.; Rao, S. A.; Noe, M. C. *J. Am. Chem. Soc.* **1994**, *116*, 9345.
(8) (a) Chaplinski, V.; de Meijere, A. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 413. (b) Chaplinski, V.; Winsel, H.; Kordes, M.; de Meijere, A. *Synlett* **1997**, 111. (c) Williams, C. M.; de Meijere, A. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3699. (d) de Meijere, A.; Chaplinski, V.; Gerson, F.; Merstetter, P.; Haselbach, E. *J. Org. Chem.* **1999**, *64*, 6951.
(9) de Meijere, A.; Williams, C. M.; Kourdioukov, A.; Sviridov, S. V.; Chaplinski, V.; Kordes, M.; Savchenko, A. I.; Stratmann, C.; Noltemeyer, M. *Chem.-Eur. J.* **2002**, *8*, 3789.
(10) (a) Bertus, P.; Szymoniak, J. *Chem. Commun.* **2001**, 1792. (b) Bertus, P.; Szymoniak, J. *J. Org. Chem.* **2002**, *67*, 3965. (c) Bertus, P.; Szymoniak, J. *Synlett* **2003**, 265. (d) Laroche, C.; Bertus, P.; Szymoniak, J. *Tetrahedron Lett.* **2003**, *44*, 2485.
(11) Gandon, V.; Szymoniak, J. *Chem. Commun.* **2002**, 1308.

Scheme 2

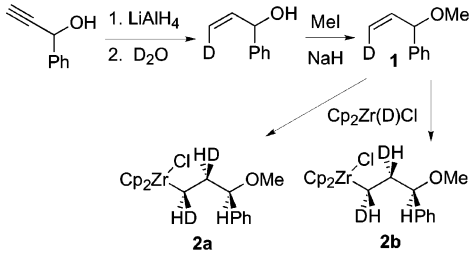


Gandon and Szymoniak envisioned that cyclopropane formation might result from coordination of the ether oxygen to both zirconium and the added Lewis acid, followed by a frontside displacement of the alkoxy group by the carbon−zirconium bond (structure **A**, Scheme 2). This mechanism retains the configuration of the carbon bound to zirconium and of the carbon bound to oxygen. However, this ring closure mechanism seemed questionable because an ether oxygen already coordinated to a Lewis acid would not be expected to coordinate to zirconium. Moreover, frontside displacement at an sp^3 hybridized ether center is very unfavorable.

We hypothesized that this cyclopropane formation might occur via a "W-shaped" transition state structure in which the backside of the carbon−zirconium bond attacks the backside of the carbon−oxygen bond of the Lewis acid coordinated ether (structure **C**, Scheme 2). The W-shaped transition structure results in inversion of configuration at both the carbon bound to zirconium and the carbon bound to the ether oxygen. Our group[12] and Brookhart's[13] have shown that W-shaped transition structures are involved in cyclopropane formation in organoiron chemistry. W-shaped transition structures were first established for cyclopropanations involving organotin compounds.[14] Because organometallic species most often react with retention of configuration at the carbon−metal bond, we decided to test our prediction that Gandon and Szymoniak's cyclopropane synthesis occurred with inversion of configuration at the carbon−zirconium bond.

Here, we report that cyclopropane formation from an allylic ether, $Cp_2Zr(H)Cl$, and a Lewis acid occurs with inversion of configuration at the zirconium−carbon bond consistent with a W-shaped transition structure. In addition, formation of cyclopropylamines from an amide, a Grignard reagent, and Ti(O-*i*-Pr)$_4$ is shown to proceed with inversion of configuration at the titanium−carbon bond and occurs via a W-shaped transition structure. In contrast, cyclopropanol formation from an ester, a Grignard reagent, and Ti(O-*i*-Pr)$_4$ is shown to proceed with retention of configuration at the titanium−carbon bond.

Scheme 3



Results

Stereochemistry of Cyclopropane Formation from Allylic Ethers, $Cp_2Zr(H)Cl$, and Lewis Acids. The reaction of $Cp_2Zr(H)Cl$ with an allylic ether produces a γ-alkoxy-alkylzirconium species, which upon treatment with a Lewis acid undergoes nucleophilic substitution of the alkoxy group by the carbon adjacent to zirconium.[11] Three different transition structures for cyclopropane ring closure and their stereochemical consequences are shown in Scheme 2: (1) transition structure **A** depicted by Gandon and Szymoniak which leads to retention of configuration at both the carbon bound to zirconium and the carbon bound to the ether oxygen,[11] (2) transition structure **B** in which the frontside of the carbon−zirconium bond attacks the backside of the carbon oxygen bond of the Lewis acid coordinated ether and results in retention of configuration at the carbon bound to zirconium and inversion at the carbon bound to the ether oxygen, and (3) our proposed W-shaped transition structure **C** which leads to inversion of configuration at both carbon centers.

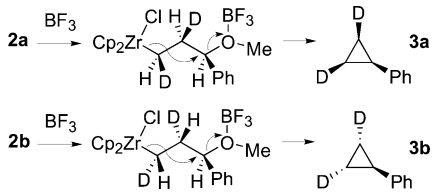
To distinguish between these stereochemical implications, we investigated the cyclopropane formation using deuterium labeling. Cis addition[15] of $Cp_2Zr(D)Cl$ to the allylic ether (*Z*)-HDC=CHCH(OCH$_3$)C$_6$H$_5$ (**1**) gave a mixture of diastereomeric alkyl zirconium compounds **2a** and **2b** (Scheme 3).[16] The stereochemistry of labeled phenylcyclopropanes obtained from reaction of this diastereomeric mixture of **2a** and **2b** with Lewis acids is determined by the mechanism of ring closure. Transition structures **A** and **B** predict formation of phenylcyclopropane bearing trans deuterium labels. In contrast, the W-shaped transition structure predicts formation of two isomers of phenylcyclopropane, both bearing cis deuterium labels.

Following a procedure similar to that of Gandon and Szymoniak,[11] deuterium labeled allyl ether **1** was added to a solution of $Cp_2Zr(D)Cl$ in CH_2Cl_2 at room temperature. After 30 min, the solution was cooled to 0 °C, the Lewis acid $BF_3{\cdot}OEt_2$ was added, and the solution was warmed to room temperature over 1 h. Labeled phenylcyclopropanes were isolated in 53% yield after flash column chromatography on silica gel (Scheme 4).[17]

1D and 2D ^{1}H NMR spectroscopy showed that the phenylcyclopropane was a 5:1 mixture of **3a**:**3b**, both of which have cis deuterium, and that less than 3% of **4**, which has trans

(12) (a) Casey, C. P.; Smith, L. J. *Organometallics* **1989**, *8*, 2288. (b) Casey, C. P.; Vosejpka, L. J. S. *Organometallics* **1992**, *11*, 738.
(13) (a) Brookhart, M.; Liu, Y. *Organometallics* **1989**, *8*, 1569. (b) Brookhart, M.; Liu, Y. *J. Am. Chem. Soc*. **1991**, *113*, 939.
(14) (a) Davis, D. D.; Chambers, R. L.; Johnson, H. T. *J. Organomet. Chem*. **1970**, *25*, C13. (b) Davis, D. D.; Black, R. H. *J. Organomet. Chem*. **1974**, *82*, C30. (c) Davis, D. D.; Johnson, H. T. *J. Am. Chem. Soc*. **1974**, *96*, 7576. (d) Fleming, I.; Urch, C. J. *Tetrahedron Lett*. **1983**, *24*, 4591. (e) Fleming, I.; Urch, C. J. *J. Organomet. Chem*. **1985**, *285*, 173.
(15) Hydrozirconation of olefins has been shown to proceed by cis addition. (a) Labinger, J. A.; Hart, D. W.; Seibert, W. E., III; Schwartz, J. *J. Am. Chem. Soc*. **1975**, *97*, 3851. (b) Schwartz, J.; Labinger, J. A. *Angew. Chem., Int. Ed. Engl*. **1976**, *15*, 333.
(16) In the ^{1}H NMR spectrum of the alkylzirconium species **2a** and **2b**, only resonances for the major isomer were readily discernible. The configuration of the major isomer could not be assigned.
(17) The reaction of the mixture of **2a** and **2b** with TMSOTf as the Lewis acid gave a 29% yield of a 5:1 mixture of labeled phenylcyclopropanes **3a**:**3b**.

Scheme 4



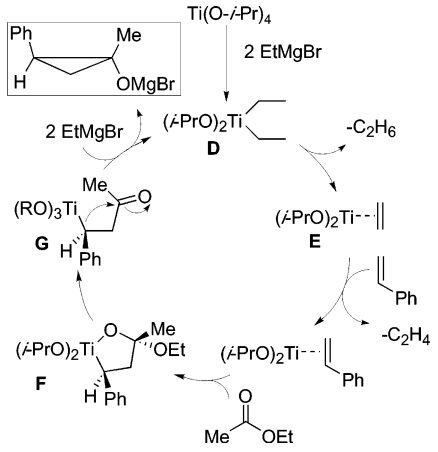
deuterium, was present (Scheme 4). In the ^{1}H NMR spectrum, the major isomer, **3a**, gave rise to a doublet (J = 8.4 Hz) at δ 0.927 corresponding to the two cis hydrogens each trans to phenyl, and to a triplet (J = 8.4 Hz) at δ 1.874 for the proton geminal to phenyl.[18,19] The minor isomer, **3b**, exhibited a doublet (J = 5.1 Hz) at δ 0.673 for the two protons cis to phenyl and a triplet (J = 5.1 Hz) at δ 1.872 for the proton geminal to phenyl, which was completely obscured by the resonance of **3a** at δ 1.874. Compound **4** would have produced a doublet of doublets (J = 8.4, 5.1 Hz) at δ 0.927 with the outermost peaks ~2.5 Hz outside of the doublet resulting from **3a**. Integration of this region put an upper limit of 5% on the amount of **4** produced.[20]

In a 1D TOCSY experiment in which the hydrogens trans to phenyl (δ 0.927) were pulsed, a major signal at δ 1.874 (t, J = 8.4 Hz) was observed due to magnetization transfer to the proton geminal to phenyl in **3a**, and a very minor signal (<3%) was seen at δ 0.67 due to hydrogens cis to phenyl either in monodeuterated phenyl cyclopropane or in **4**. In a second 1D TOCSY experiment in which the hydrogens cis to phenyl (δ 0.673) were pulsed, a major signal at δ 1.872 (J = 5.1 Hz) was observed due to magnetization transfer to the proton geminal to phenyl in **3b**, and a minor signal (<15%) was seen at δ 0.93 due to hydrogens trans to phenyl either in monodeuterated phenyl cyclopropane or in **4**. Observation of COSY cross-peaks demonstrated coupling between the protons of **3a** at δ 0.927 and δ 1.874 and between the protons of **3b** at δ 0.673 and δ 1.872. The failure to see a cross-peak between the resonances at δ 0.673 and δ 0.927 establishes that only negligible amounts of **4** were present.

The exclusive formation of **3a** and **3b**, both of which have cis deuterium, requires inversion of configuration at the carbon bound to zirconium and is consistent with a W-shaped transition state structure for this cyclopropanation. This stereochemistry excludes all ring closure mechanisms involving retention of stereochemistry at the carbon bound to zirconium including those involving transition structures **A** and **B**. In addition, the 5:1 ratio of **3a**:**3b** observed indicates a preference for addition of $Cp_2Zr(D)Cl$ to one face of the allylic ether and excludes a step in which the stereochemical information is lost.

Stereochemistry of Cyclopropanol Formation. In the Kulinkovich hydroxycyclopropanation, ring closure has been suggested to occur by intramolecular addition of a titanium alkyl to an electrophilic carbon γ to titanium (Scheme 5). This is an arrangement similar to that seen in cyclopropane formation via hydrozirconation of allylic ethers followed by addition of a Lewis acid. As shown above, this ring closure occurs with inversion of configuration at the carbon−zirconium bond via a W-shaped transition structure. We wondered whether the Kulinkovich hydroxycyclopropanation might also proceed with inversion of configuration at the carbon−titanium bond via a W-shaped transition structure.

Scheme 5

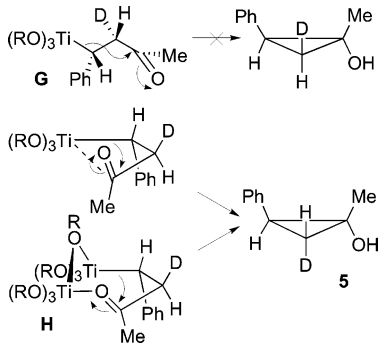


The well-studied variation of the Kulinkovich hydroxycyclopropanation in which 1-methyl-*cis*-2-phenyl-1-cyclopropanol is formed by reaction of Ti(O-*i*-Pr)$_4$, ethyl acetate, RMgBr, and styrene[6a,d,7] provides a convenient platform for studying the stereochemistry of ring closure if deuterium labeling is employed. In the proposed catalytic cycle (Scheme 5), reaction of 2 equiv of EtMgBr with Ti(O-*i*-Pr)$_4$ generates an unstable dialkyltitanium species (**D**) which eliminates ethane to form a Ti(II) ethylene complex (**E**). A sequence involving styrene displacement of ethylene, coordination of ethyl acetate, and reductive coupling of styrene and ethyl acetate leads to formation of a five-membered titanacycle (**F**).[21] **F** is shown with phenyl α to Ti by analogy with quenching studies of the reaction of ketones or imides with alkenes.[22] This regiochemistry is also suggested by DFT calculations.[23] Transfer of the ethoxy group to titanium and breaking of the Ti−O bond of titanacycle **F** produces an alkyltitanium species with a γ-ketone group (**G**). Intramolecular addition of the alkyltitanium to the ketone produces a titanium cyclopropoxide. Subsequent reaction with EtMgBr produces the magnesium cyclopropoxide and regenerates the catalyst.

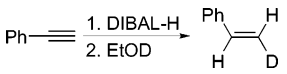
Three pathways for ring closure and their stereochemical consequences are shown in Scheme 6. In the first, the backside of the carbon−titanium bond of **G** attacks the ketone carbonyl via a W-shaped transition structure that involves inversion of configuration at the carbon bound to titanium. In the second, chelation of the ketone carbonyl to titanium via either σ- or π-complexation is followed by frontside attack of the carbon−titanium bond on the coordinated carbonyl to effect ring closure with retention of configuration at the carbon bound to titanium. The third is similar to the second but involves the alkoxy bridged dititanium species **H** with one titanium acting as a Lewis acid to activate the carbonyl and the other acting as a nucleophilic alkyl. This third pathway also involves the frontside of the

(18) These NMR data are similar to those reported by Brookhart.[13]
(19) In cyclopropanes, cis couplings are larger than trans couplings. Pretsch, E.; Bühlmann, P.; Affolter, C. *Structure Determination of Organic Compounds*; Springer: New York, 2000.
(20) Because of deuterium coupling, it was not possible to use line shape simulations to estimate the amount of **4**.
(21) The regiochemistry of insertion of styrene is shown as having the Ph α to Ti. If the titanacycle had formed with the alternative regiochemistry with Ph β to titanium, the observed stereochemistry of the cyclopropane would also have required retention of configuration at the carbon bonded to titanium.
(22) (a) Morlender-Vais, N.; Solodovnikova, N.; Marek, I. *Chem. Commun.* **2000**, 1849. (b) Lee, J.; Ha, J. D.; Cha, J. K. *J. Am. Chem. Soc.* **1997**, *119*, 8127.
(23) Wu, Y.-D.; Yu, Z.-X. *J. Am. Chem. Soc.* **2001**, *123*, 5777.

Scheme 6



Scheme 7



alkyltitanium species and leads to ring closure with retention of configuration at the carbon bound to titanium.

trans-β-Deuterostyrene was prepared by addition of $[(CH_3)_2CHCH_2]_2AlH$ (DIBAL-H) to phenylacetylene, followed by quenching with EtOD (Scheme 7). Residual phenylacetylene was removed by treatment with $AgNO_3$ in tributylamine, and pure *trans*-β-deuterostyrene was obtained by subsequent distillation.[24] Using a modification of Kulinkovich's procedure,[6d] we synthesized monodeuterated 1-methyl-*cis*-2-phenyl-1-cyclopropanol by slow addition of ethylmagnesium bromide (2.5 equiv) to ethyl acetate, Ti(O-*i*-Pr)$_4$ (0.2 equiv), and *trans*-β-deuterostyrene (2 equiv) in refluxing ether, followed by quenching with cold 10% sulfuric acid. Recrystallization from pentane/ether gave monodeuterated 1-methyl-*cis*-2-phenyl-1-cyclopropanol as a white crystalline solid. None of the related trans isomer was observed.[4,6,7]

^{1}H NMR spectroscopy established that the only cyclopropane isomer formed was *trans*-3-deutero-1-methyl-*cis*-2-phenyl-1-cyclopropanol (**5**) (Figure 1). In unlabeled 1-methyl-*cis*-2-phenyl-1-cyclopropanol, the hydrogen on C3 cis to the OH group appears at δ 1.25 and has a large cis coupling (J = 10.2 Hz) to the benzylic hydrogen, while the hydrogen on C3 trans to the OH group appears at δ 0.99 and has a small trans coupling (J = 6.0 Hz) to the benzylic hydrogen on C2. The ^{1}H NMR spectrum of **5** showed chemical shifts consistent with those observed for the unlabeled species, but lacked a resonance at δ 1.25 corresponding to a proton at C3 cis to the hydroxyl. Based on the integration of the δ 1.25 region, an upper limit of 2% can be placed on the amount of *cis*-3-deutero-1-methyl-*cis*-2-phenyl-1-cyclopropanol and nondeuterated 1-methyl-*cis*-2-phenyl-1-cyclopropanol formed.

NOESY 1D spectroscopy confirmed the labeling assignment (Figure 1). When the methyl resonance of **5** at δ 1.20 was pulsed, magnetization transfer resulted in a 5.0% nOe enhancement of the δ 0.97 resonance of the proton on C3 cis to the methyl group and in a 2.1% nOe enhancement of the δ 7.14 resonance of the ortho phenyl protons, but only a 1.0% nOe enhancement of the δ 2.35 resonance of the benzylic proton (trans to methyl). These nOe observations support both the stereochemical assignment of 1-methyl-*cis*-2-phenyl-1-cyclopropanol and the labeling pattern of **5**.

(24) Fagan, M. A. Ph.D. Thesis, University of Wisconsin-Madison, 1999; p 166.

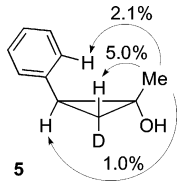
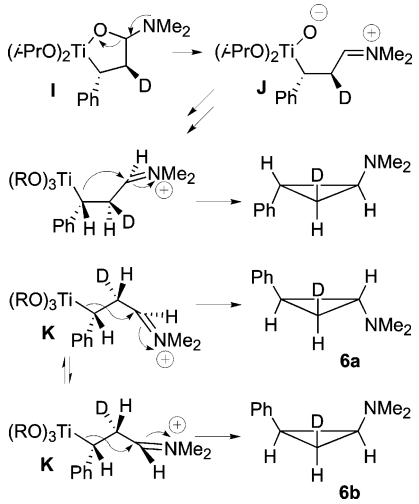


Figure 1. nOe enhancements upon irradiation of methyl resonance of **5**.

Scheme 8

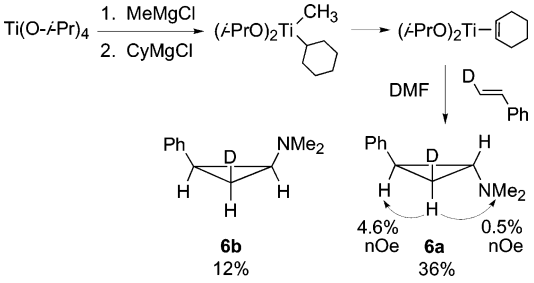


The exclusive formation of **5** indicates retention of configuration at the carbon bound to titanium. This result precludes a W-shaped transition state structure and requires a closure pathway involving frontside attack by the carbon−titanium bond. This is most likely facilitated by σ- or π-carbonyl coordination to the same titanium or to a second titanium.

Stereochemistry of Cyclopropylamine Formation. The proposed mechanism of cyclopropylamine formation from Ti(O-*i*-Pr)$_4$, Grignard reagents, an alkene, and a formamide is similar to that proposed for the Kulinkovich cyclopropanol synthesis up to the formation of a titanacycle intermediate.[3a,8a,b,9] In the case of cyclopropylamine formation, metallacycle **I** is suggested to ring open to give an iminium unit tethered to titanium in **J**. Ring closure is unlikely to proceed by the unfavorable coordination of a cationic iminium unit to an electropositive titanium. Two distinguishable processes for ring closure are shown in Scheme 8. The first involves frontside attack of the carbon−titanium bond on the iminium carbon, resulting in retention of configuration at the carbon bound to titanium. The second involves the W-shaped transition structure **K** in which the back lobe of the carbon−titanium bond attacks the iminium center, resulting in inversion of configuration at the carbon bound to titanium. These pathways are distinguishable when *trans*-β-deuterostyrene is employed: retention of configuration leads to cyclopropylamines with deuterium and phenyl trans to one another, while inversion of configuration leads to cyclopropylamines with deuterium and phenyl cis to one another.

trans-β-Deuterostyrene was converted to cis and trans isomers of *N*,*N*-dimethyl-*N*-(2-phenylcyclopropyl)amine using a modification of de Meijere's procedure.[9] $CH_3Ti(O\text{-}i\text{-}Pr)_3$ was generated from Ti(O-*i*-Pr)$_4$ and MeMgCl. DMF and *trans*-β-deuterostyrene were added, and then cyclohexylmagnesium chloride was added dropwise at 0 °C. Flash column chromatography gave a mixture of monodeuterated *N*,*N*-dimethyl-*N*-(*trans*-2-phenylcyclopropyl)amine (**6a**) and *N*,*N*-dimethyl-*N*-

Scheme 9



(*cis*-2-phenylcyclopropyl)amine (**6b**) in 36% and 12% yields, respectively (Scheme 9).

The minor isomer was shown to be *N*,*N*-dimethyl-*N*-(*cis*-3-deutero-*cis*-2-phenylcyclopropyl)amine (**6b**) by proton NMR spectroscopy (Scheme 9). The proton geminal to deuterium (δ 1.04) showed two large couplings of 9.0 and 6.9 Hz to cis protons. The other two cyclopropyl protons (δ 1.98, δ 1.84) each showed two large coupling constants, supporting the cis disposition of all three protons.[19] This requires that the deuterium, phenyl, and *N*,*N*-dimethylamino groups all be on the same face of the cyclopropane and establishes the structure of **6b**.

In the ^{1}H NMR spectrum of the major isomer, *N*,*N*-dimethyl-*N*-(*trans*-3-deutero-*trans*-2-phenylcyclopropyl)amine (**6a**), a doublet of doublets at δ 1.08 was seen for the proton geminal to deuterium with one large coupling constant (J = 9.6 Hz) to a cis proton and one smaller coupling constant (J = 4.5 Hz) to a trans proton. Although this established the trans relationship of the phenyl and *N*,*N*-dimethylamino groups, the orientation of the deuterium could not be definitively assigned because the protons adjacent to the phenyl and amino groups had very similar frequencies.

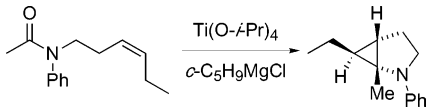
1D NOESY spectroscopy definitively established the configuration at the carbon bearing deuterium in **6a**. When the CHD resonance at δ 1.08 was pulsed, magnetization transfer resulted in a 0.5% nOe enhancement of the δ 2.38 resonance of the NMe_2 group and a 4.6% nOe enhancement of the δ 1.96 resonance of the benzylic proton, but no enhancement of any of the phenyl resonances (Scheme 9). This requires that the proton geminal to deuterium (δ 1.08) be cis to NMe_2 and trans to phenyl.

In the major product **6a**, the two large substituents are trans to one another, while in the minor isomer **6b** they are cis. More significantly, in both **6a** and **6b**, deuterium and phenyl are cis to one another. This stereochemical outcome requires inversion of configuration at the carbon bearing titanium and is consistent with a W-shaped transition state structure for ring closure (Scheme 8).

Discussion

The Kulinkovich hydroxycyclopropanation occurs with retention of configuration at the carbon bound to titanium. This is the usual stereochemical result for reactions of organolithium and magnesium reagents with electrophiles.[25] Coordination of the carbonyl group to titanium in either a mononuclear (**G**) or a bridged dititanium (**H**) transition structure for ring closure would favor attack by the frontside of the carbon titanium bond and result in retention of configuration (Scheme 6). A rationale for production of only the thermodynamically less stable cis isomer **5**[26] has been proposed. On the basis of DFT calculations, Wu suggested that the cis preference derives from steric

Scheme 10



interaction within a transition state having an agostic interaction between an α carbon−hydrogen bond and titanium.[23]

Inversion of configuration at the carbon bound to the metal center was observed in the de Meijere cyclopropylamine synthesis of **6a** and **6b** (Scheme 9). Reaction at the frontside of the carbon metal bond is disfavored by steric effects, and reaction at the backside of the carbon metal bond with a γ-electrophile is sterically more accessible. Ouhamou and Six observed a similar inversion of stereochemistry at a titanium carbon bond in an intramolecular cyclopropylamine synthesis (Scheme 10).[27]

Inversion of configuration at the carbon bound to the metal center was also observed in the formation of phenylcyclopropane from $Cp_2Zr(D)Cl$, an allylic ether, and $BF_3{\cdot}OEt_2$ (Scheme 4). The W-shaped transition structure **C** suggested for phenylcyclopropane formation is well precedented in both iron and tin chemistry (Scheme 2). The 5:1 ratio of **3a**:**3b** is mechanistically significant. It requires that the zirconium hydride add selectively to one diastereoface of the alkene and that the stereochemical information not be lost in a subsequent step. Thus, a mechanism in which Lewis acid assisted ionization of the carbon−oxygen bond occurred to give a carbocation intermediate can be excluded,[28] because rotation about the carbon−carbon bond of such a carbocation intermediate would have given a 1:1 ratio of **3a**:**3b**.

The switch from retention of configuration at the carbon bound to titanium in the Kulinkovich hydroxycyclopropanation to inversion of configuration in the de Meijere cyclopropylamine synthesis can be readily explained. In the Kulinkovich hydroxycyclopropanation, frontside attack of the carbon−titanium bond on a carbonyl group is strongly favored by its coordination to titanium. In contrast, the positively charged iminium group in the de Meijere cyclopropylamine synthesis cannot coordinate to the electrophilic titanium. Ring closure therefore occurs via the less sterically demanding W-shaped transition state structure **K** in which the backside of the carbon−titanium bond attacks the electrophilic γ-iminium group to produce a cyclopropylamine with inversion at the carbon bound to titanium (Scheme 8).

Experimental Section

(*Z*)-CHD═CHCH(OH)C$_6$H$_5$.[29] 1-Phenyl-2-propyn-1-ol (1.32 g, 10.0 mmol) was added to a solution of $LiAlH_4$ (380 mg, 10.0 mmol) in THF (30 mL) at 0 °C and was stirred for 24 h at room temperature. D_2O (1 mL) was added dropwise over 15 min followed by an additional 6 mL of D_2O. The reaction mixture was poured into Et_2O (600 mL). The ether solution was washed with H_2O (3 × 150 mL) and dried ($MgSO_4$). Evaporation of solvent gave (*Z*)-3-deutero-1-phenyl-2-propen-

(25) (a) Jensen, F. R.; Nakamaye, K. L. *J. Am. Chem. Soc*. **1966**, *88*, 3437. (b) Hoffmann, R. W.; Hölzer, B. *Chem. Commun*. **2001**, 491.
(26) The configuration of **5** had been confirmed by X-ray diffraction.[7]
(27) Ouhamou, N.; Six, Y. *Org. Biomol. Chem.* **2003**, *1*, 3007.
(28) Brookhart found evidence for intermediate carbocations γ to iron in cyclopropane formation from the reaction of a cationic iron carbene complex with (*Z*)-HDC═CHC$_6$H$_4$-*p*-OMe. Brookhart, M.; Kegley, S. E.; Husk, G. R. *Organometallics* **1984**, *3*, 650. He also suggested involvement of γ-carbocation intermediates in cyclopropane formation in the reaction of (γ-methoxy)alkyliron compounds with Lewis acids.[13]
(29) (a) Grant, B.; Djerassi, C. *J. Org. Chem*. **1974**, *39*, 968. (b) Kang, M. J.; Jang, J.-S.; Lee, S.-G. *Tetrahedron Lett*. **1995**, *36*, 8829.

1-ol as a yellow oil (1.36 g, 109%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40−7.25 (m, aromatic), 6.04 (ddt, J_{HH} = 10.2, 6.0 Hz, J_{HD} = 3.3 Hz, HDC=C*H*), 5.18 (dd, J = 10.2, 1.2 Hz, HDC=C), 5.20 (broad dd, J = 5.9, 2.8 Hz, HCO), 2.06 (broad s, OH). ^{13}C NMR {^{1}H} (75 MHz, $CDCl_3$): δ 142.78, 140.33, 128.76 (2C), 127.95, 126.52 (2C), 115.04 (t, J_{CD} = 23.8 Hz), 75.51. HRMS (ESI) calcd for C_9H_9DO (M^+) 135.0794, found 135.0795.

(*Z*)-HDC=CHCH(OCH$_3$)C$_6$H$_5$ (1). (*Z*)-3-Deutero-1-phenyl-2-propen-1-ol (1.00 g, 7.41 mmol) in THF (7.4 mL) was added dropwise to a suspension of NaH (800 mg, 60% dispersion in mineral oil, 20 mmol) in a THF (12 mL) solution of CH_3I (1.21 mL, 19.4 mmol) at 45 °C. After 45 min, H_2O was added dropwise at room temperature until hydrogen evolution ceased. An additional 30 mL of H_2O was added, and the mixture was extracted with Et_2O (2 × 200 mL). The combined Et_2O layers were washed with H_2O (4 × 100 mL), dried ($MgSO_4$), and concentrated on a rotary evaporator. Flash column chromatography (silica gel, 20:1 pentane:ether) gave **1** as a colorless oil (0.76 g, 69%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.4−7.2 (m), 5.92 (ddt, J_{HH} = 10.2, 6.9, J_{HD} = 2.5 Hz, HDC=C*H*), 5.19 (dd, J = 10.2, 0.9 Hz, HDC=C), 4.62 (dd, J = 6.6, 0.9 Hz, CHO), 3.32 (s, OCH_3). ^{13}C NMR {^{1}H} (75 MHz, $CDCl_3$): δ 141.1, 138.9, 128.7 (2C), 127.9, 127.0 (2C), 116.2 (t, J_{CD} = 23.8 Hz), 84.9, 56.6. HRMS (ESI) calcd for $C_{10}H_{11}DONa$ ($M + Na^+$) 172.0848, found 172.0844.

2-*cis*-3-*cis*-Dideuterophenylcyclopropane (3a) and 2-*trans*-3-*trans*-Dideuterophenylcyclopropane (3b).[11] A solution of **1** (298 mg, 2.0 mmol) in 1 mL of CH_2Cl_2 was added to a suspension of $Cp_2Zr(D)Cl$ (518 mg, 2.00 mmol) in 6 mL of CH_2Cl_2. After 30 min, the solution was cooled to 0 °C, and BF_3·OEt_2 (279 mL, 2.2 mmol) was added by syringe. After 5 min at 0 °C and 1 h at room temperature, saturated aqueous $NaHCO_3$ (10 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined extracts were washed with H_2O (2 × 10 mL), dried ($MgSO_4$), and concentrated on a rotary evaporator. Flash column chromatography (silica gel, 20:1 pentane:ether) gave a 5:1 mixture of **3a**:**3b** as a colorless oil (127 mg, 53%). HRMS (EI) calcd for $C_9H_8D_2$ (M^+) 120.0908, found 120.0904. ^{13}C NMR {^{1}H} (75 MHz; $CDCl_3$): δ 144.160, 128.468 (2C), 125.86 (2C), 125.547, 15.40, 8.94 (t, J_{CD} = 24.6 Hz). ^{1}H NMR (300 MHz, $CDCl_3$) assigned to **3a**: δ 7.25 (t, J = 7.2 Hz, meta), 7.13 (tt, J = 7.4, 1.4 Hz, para), 7.07 (d, J = 7.6 Hz, ortho), 1.874 (t, J = 8.4 Hz, *H*CPh), 0.927 (d, J = 8.4 Hz, CHDCHD); assigned to **3b**: δ 0.673 (d, J = 5.1 Hz, CHDCHD), CHPh of **3b** obscured. 1D TOCSY (500 MHz, $CDCl_3$) pulsed at δ 0.673 ⇒ δ 1.872 [t, J = 5.1 Hz, HCPh (**3b**)], pulsed at δ 0.927 ⇒ δ 1.874 [t, J = 8.4 Hz, HCPh (**3a**)].

***trans*-β-Deuterostyrene.**[24] $[(CH_3)_2CHCH_2]_2AlH$ (DIBAL-H) (182 mL, 1 M solution in hexane, 0.182 mol) was added to a solution of phenylacetylene (20.0 mL, 0.182 mol) and hexane (160 mL) and stirred at 60 °C for 5 h. Evaporation of hexane and unreacted phenylacetylene under vacuum (4 × 10^{-2} Torr) overnight gave a red oil. The red oil was dissolved in 40 mL of ether, and EtOD (2 mL) was added slowly at −78 °C. After the vigorous reaction had subsided, additional EtOD (25 mL) was added, and the solution warmed to room temperature. The resulting solution was poured into a 2 M solution of sodium potassium tartrate (500 mL) and was extracted with ether (2 × 200 mL). The combined organic layer was washed with H_2O (200 mL) and was concentrated on a rotary evaporator. The resulting mixture of styrene and phenylacetylene was added to a suspension of $AgNO_3$ (10.2 g, 0.060 mol) in tributylamine (17.2 mL, 0.070 mol) and tetraglyme (20 mL). A gray precipitate (silver acetylides) formed over 1.5 h. The volatiles were vacuum transferred (4 × 10^{-2} Torr) from the reaction mixture into a flask cooled with liquid nitrogen. This material was distilled (37 °C, 10−20 Torr) through a Vigreux column to give *trans*-β-deuterostyrene as a colorless oil (9.5 g, 50%). This material was shown by ^{1}H NMR spectroscopy to contain less than 1% phenylacetylene and less than 2% undeuterated styrene.

***trans*-3-Deutero-1-methyl-*cis*-2-phenyl-1-cyclopropanol (5).**[6d] Over 1 h, EtMgBr (8.33 mL, 3 M solution in ether, 25 mmol) in ether (7 mL) was added dropwise to a solution of EtOAc (0.98 mL, 10 mmol), *trans*-β-deuterostyrene (2.10 g, 20 mmol), and Ti(O-*i*-Pr)$_4$ (0.59 mL, 2.0 mmol) in ether (15 mL) heated at reflux. After an additional 30 min at reflux, the reaction mixture was poured into ice-cold 10% sulfuric acid (50 mL), and the organic layer was separated. The aqueous layer was extracted with ether (2 × 20 mL), and the combined organic layers were washed with saturated aqueous sodium bicarbonate (40 mL) and then H_2O (40 mL). Evaporation of solvent and subsequent recrystallization from pentane/ether gave **5** (0.43 g, 29%) as a white crystalline solid, mp 78−80 °C (lit[30] 80−81 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.28 (t, J = 7.2 Hz, meta), 7.22−7.12 (m, ortho/para), 2.35 (d, J = 6.9 Hz, HCPh), 2.11 (br s, OH), 1.20 (s, CH_3), 0.97 (d, J = 6.9 Hz, HDC). NOESY 1D (500 MHz, $CDCl_3$): the methyl resonance at δ 1.20 was pulsed and integrated for −3.000 H, the resonance at δ 0.97 for the proton on C3 cis to the methyl group integrated for 0.050 H (5.0%), the resonance at δ 2.35 for the benzylic hydrogen integrated for 0.010 H (1.0%), and the resonance at δ 7.14 for the ortho phenyl protons integrated for 0.042 H (2.1%). ^{13}C NMR {^{1}H} (75 MHZ, $CDCl_3$): δ 138.75, 128.60 (2C), 128.36 (2C), 126.18, 57.68, 30.80, 20.88, 18.77 (t, J_{CD} = 24.8 Hz). HRMS (EI) calcd for $C_{10}H_{11}OD$ (M^+) 149.0951, found 149.0950.

***N*,*N*-Dimethyl-*N*-(*trans*-3-deutero-*trans*-2-phenylcyclopropyl)-amine (6a) and *N*,*N*-Dimethyl-*N*-(*cis*-3-deutero-*cis*-2-phenylcyclopropyl)amine (6b).**[9] A solution of $CH_3Ti(O\text{-}i\text{-}Pr)_3$ was prepared by adding MeMgCl (1.79 mL, 3.0 M solution in THF, 5.37 mmol) dropwise over 10 min to Ti(O-*i*-Pr)$_4$ (1.43 mL, 4.88 mmol) in THF (15 mL) at 0 °C. After the mixture was stirred for an additional 5 min, *N*,*N*-dimethylformamide (0.344 mL, 4.44 mmol) in THF (6 mL) and then *trans*-β-deuterostyrene (0.560 mL, 4.88 mmol) were added. While the solution was maintained at 0 °C, cyclohexylmagnesium chloride (2.69 mL, 2.0 M solution in Et_2O, 5.38 mmol) was added dropwise over 50 min. The mixture was stirred at room temperature for 20 h and then quenched with H_2O (2.5 mL) to give a gray precipitate. The solution was vacuum filtered, and the solid was washed with Et_2O (20 mL). The combined yellow filtrate was concentrated by rotary evaporation and was purified by flash column chromatography (silica gel, 100:2−100:6 pentane:ether). Compound **6b** (84 mg, 12%) eluted first as a colorless oil, followed by **6a** (257 mg, 36%) as a pale yellow oil.

For **6a**, ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.25 (t, J = 7.2 Hz, meta), 7.15 (tt, J = 7.2, 1.5 Hz, para), 7.06 (d, J = 7.7 Hz, 2H, ortho), 2.38 (s, NMe_2), 1.96 (dd, J = 9.6, 3.0 Hz, *H*CPh), 1.78 (dd, J = 3.9, 3.3 Hz, HCN), 1.08 (dd, J = 9.6, 4.5 Hz, HCD). NOESY 1D (500 MHz, $CDCl_3$): the proton geminal to deuterium at δ 1.08 was pulsed and integrated for −1.000 H, the resonance at δ 1.96 for the benzylic hydrogen integrated for 0.046 H (4.6%), and the resonance at δ 2.38 for the dimethylamino group integrated for 0.033 H (0.5%). ^{13}C NMR {^{1}H} (125 MHz, $CDCl_3$): δ 142.33, 128.42 (2C), 126.25 (2C), 125.76, 50.30, 45.20 (2C), 25.39, 17.11 (t, J_{CD} = 25.0 Hz). 1D NOESY (500 MHz, $CDCl_3$): δ 1.08 ⇒ δ 2.38 (0.5%), δ 1.96 (4.6%). HRMS (EI) calcd for $C_{11}H_{14}DN$ (M^+) 162.1266, found 162.1258.

For **6b**, ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.28 (d, J = 7.6 Hz, ortho), 7.24 (t, J = 7.9 Hz, meta), 7.15 (tt, J = 6.9, 1.8 Hz, para), 2.13 (s, NMe_2), 1.98 (t, J = 8.0 Hz, *H*CPh), 1.84 (t, J = 7.1 Hz, HCN), 1.04 (dd, J = 9.0, 6.9 Hz, HCD). ^{13}C NMR {^{1}H} (75 MHz, $CDCl_3$): δ 139.10, 128.44 (2C), 127.72 (2C), 125.48, 47.46, 45.37 (2C), 24.13, 13.36 (t, J_{CD} = 24.2 Hz). HRMS (EI) calcd for $C_{11}H_{14}DN$ (M^+) 162.1266, found 162.1266.

Acknowledgment. Financial support from the National Science Foundation is gratefully acknowledged.

JA030436P

(30) DePuy, C. H.; Breitbeil, F. W.; DeBruin, K. R. *J. Am. Chem. Soc.* **1966**, *88*, 3347.