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# On the Mechanism and Kinetics of Radical Reactions of Epoxyketones and Epoxynitriles Induced by Titanocene Chloride

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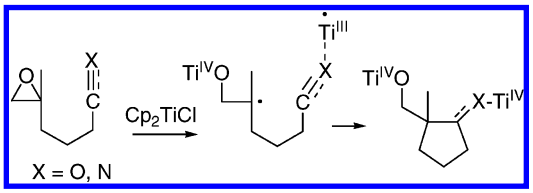


The reactions of a series of epoxynitriles and epoxyketones induced by titanocene chloride have been studied. The kinetics of the decyanogenation of $\beta,\gamma$-epoxynitriles with Ti(III) corresponds to a radical reaction ($k_{25} \approx 10^6$ s$^{-1}$), as demonstrated by competition experiments with H-transfer from 1,4-cyclohexadiene (1,4-CHD) or PhSH or conjugate addition to acrylonitrile. The 5-*exo* cyclization onto nitrile induced by Ti(III) is a radical reaction ($k_{25} \approx 10^7$ s$^{-1}$) as seen in competition experiments with H-transfer from PhSH or the titanocene−water complex. The iminyl or alkoxyl radicals generated by 5-*exo* cyclization onto nitriles or ketones only undergo a reduction with Ti(III). This reaction overwhelms any alternative process, such as tandem cyclization onto alkenes or $\beta$-scission. Iminyl radicals generated by 4-*exo* cyclizations onto nitriles undergo reduction with Ti(III) and $\beta$-scission reaction in a ratio of 96:4 when the α-substituent is CN. Alkoxyl radicals from 4-*exo* cyclizations onto ketone carbonyls undergo reduction with Ti(III) and $\beta$-scission in a ratio of 60:40 when the α-substituent is COOR. In nearly all the reactions studied, the role of Ti(III) is triple: a radical initiator (homolytic cleavage of oxirane), a Lewis acid (coordination to CN or C═O), and a terminator (reduction of iminyl or alkoxyl radicals).

## Introduction

Intramolecular additions of radicals to polar multiple bonds such as a carbonyl group or a cyano group are unfavorable processes,[1] the former due to reversibility and the latter to slowness. Despite these drawbacks, radical cyclization to polar multiple bonds might be successful if the alkoxyl or iminyl radical intermediate can be effectively trapped[2] and the cyano group can be activated. Radical cyclization onto nitriles has been reported to be an enigmatic reaction.[3] It is known that 5-*exo*-trig cyclization onto nitrile is a slow process, at the limit of the synthetic usefulness,[4] while 6-*exo* and 7-*exo* processes have received little attention.[1e,2c] We have not found examples of 4-*exo* cyclization onto nitriles except when the radicals are generated with Ti(III).[5a] Cyclic iminyl radicals generated with $Bu_3SnH$ could undergo reduction, $\beta$-scission, or tandem cyclization onto alkenes, depending on the nature of the α-substituents (Scheme 1).[3a] $\beta$-Scission is favored by ring strain[6] and

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(1) (a) Kim, S. *Adv. Synth. Catal.* **2004**, *346*, 19−32 and references cited therein. (b) Curran, D. P. In *Comprehensive Organic Synthesis*; Trost, B. M., Flemming, I., Eds.; Pergamon Press: Oxford, U.K. 1991; Vol. IV, pp 815−817. (c) Giese, B.; Kopping, B.; Göbel, T.; Dickhaut, J.; Thoma, G.; Kulicke, K. J.; Trach, F. *Org. React.* **1996**, *48*, 311−312. (d) Beckwith, A. L. J.; Raner, K. D. *J. Org. Chem.* **1992**, *57*, 4954−4962. (e) Fallis, A. G.; Brinza, I. M. *Tetrahedron* **1997**, *53*, 17543−17594.

(2) (a) Walton, R.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1991**, *113*, 5791−5799. (b) Devin, P.; Fensterbank, L.; Malacria, M. *Tetrahedron Lett.* **1999**, *40*, 5511−5514. (c) Curran, D. P.; Liu, W. *Synlett* **1999**, 117−119. (d) Yamamoto, Y.; Matsumi, D.; Itoh, K. *Chem. Commun.* **1998**, 875−876. (e) Alonso, R. A.; Burgey, C. S.; Rao, B. V.; Vite, G. D.; Vollerthun, R.; Zottola, M. A.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1993**, *115*, 6666−6672 and references cited therein. (f) Snider, B. B.; Buckman, B. O. *J. Org. Chem.* **1992**, *57*, 322−326. (g) Clive, D. L. J.; Beaulieu, P. L. *J. Org. Chem.* **1984**, *49*, 1314−1316. (h) Corey, E. J.; Pyne, S. G. *Tetrahedron Lett.* **1983**, *24*, 2821−2814. (i) Molander, G. A.; Wolfe, C. N. *J. Org. Chem.* **1998**, *63*, 9031−9036.

(3) (a) Bowman, W. R.; Bridge, C. F.; Brookes, P. *Tetrahedron Lett.* **2000**, *41*, 8989−8994. (b) Beckwith, A. L. J.; O'Shea, D. M.; Westwood, S. W. *J. Am. Chem. Soc.* **1988**, *110*, 2565−2575. (c) Rychnovsky, S. D.; Swenson, S. S. *Tetrahedron* **1997**, *53*, 16489−16502. (d) Crich, D.; Bowers, A. A. *J. Org. Chem.* **2006**, *71*, 3452−3463.

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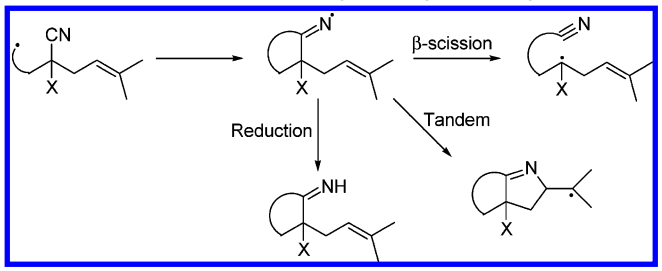
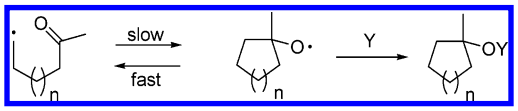
**SCHEME 1. Different Pathways for Cyclic Iminyl Radicals**




**SCHEME 2. Reversibility in Radical Cyclization onto Carbonyl Groups**

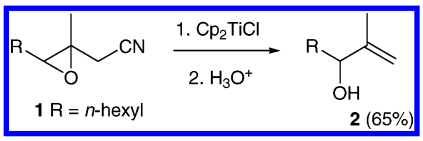



the formation of stabilized radicals (X = attractor group).[7] Tandem reactions onto alkenes are faster than reduction with $Bu_3SnH$.[3a,8]

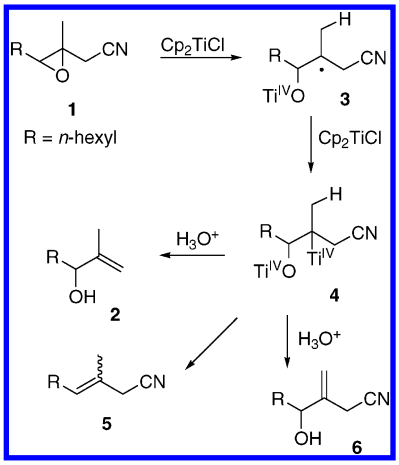
The intramolecular addition of radicals generated with $Bu_3SnH$ to aldehydes has been established for 5-*exo* and 6-*exo* ring closures.[2] Examples of radical cyclizations onto ketones by this method are rare, due to faster $\beta$-scission. To avoid reversibility in the radical cyclization onto aldehydes, and especially onto ketones, a method based on the fast trapping of the intermediate alkoxyl radicals with reagents such as triethylborane has been devised (Scheme 2). A 5-*exo*-trig cyclization onto ketone has been achieved with triethylborane in the presence of oxygen. Good yields of cyclopentanols need a large excess of $BEt_3/O_2$. This reagent is claimed to act as a Lewis acid, a radical initiator, and a terminator.[2b] However, no other size cycles have been obtained by this method.

We have recently reported high yield methods for the synthesis of cyclobutanones to cycloheptanones from epoxynitriles[5a] and cyclopropanols to cyclohexanols from epoxyaldehydes and epoxyketones, with titanocene chloride as reagent.[5b−d] It is well-known that Ti(III) promotes the homolytic cleavage of a epoxide

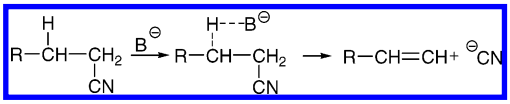
**SCHEME 3. CN Elimination**




**SCHEME 4. Hypothetical Heterolytic Pathways**




**SCHEME 5. Base-Catalyzed Elimination**




to a carbon radical,[9] but we are unaware of the actual role of Ti(III) in these reactions. Below we compare the behavior of $Cp_2TiCl$ with that reported for $Bu_3SnH$. The kinetics, mechanism, and synthetic usefulness of reactions induced by titanocene chloride on a series of epoxyketones and epoxynitriles are explored, and some interesting new reactions have been uncovered.

## Results and Discussion

The first reaction to be studied was the reported reaction of the epoxynitrile **1** with $Cp_2TiCl$, which affords exclusively the allylic alcohol **2** instead of the desired cyclopropanone (Scheme 3).[5a]

The reaction takes place in two steps. The initial step of this reaction is based on the well-documented titanocene-mediated opening of epoxides[9] such as **1** to give the radical **3**, which could further react following two pathways. The heterolytic way should be discarded due to the following: the attack of a second equivalent of the titanium reagent to the tertiary radical **3** to give the reduction product **4** is very improbable, due to steric factors (Scheme 4). The behavior of $Cp_2TiCl$ is comparable to that of bulky bases with tertiary alkyl halides.[10]

In the event of the intermediate **4** being formed, it would evolve in three ways to afford deoxygenation, decyanogenation,

(4) (a) Beckwith, A. L. J.; Hay, B. D. *J. Am. Chem. Soc.* **1989**, *111*, 230. (b) Beckwith, A. L. J.; Hay, B. D. *J. Am. Chem. Soc.* **1989**, *111*, 2674. (c) Beckwith, A. L. J. *Tetrahedron* **1981**, *37*, 3073.

(5) (a) Fernández-Mateos, A.; Mateos Burón, L.; Rabanedo Clemente, R.; Ramos Silvo, A. I.; Rubio González, R. *Synlett* **2004**, 1011−1014. (b) Fernández-Mateos, A.; Martín de la Nava, E. M.; Pascual Coca, G.; Rubio González, R. *Org. Lett.* **1999**, *1*, 607−610. (c) Fernández-Mateos, A.; Mateos Burón, L.; Rabanedo Clemente, R.; Martín de la Nava, E. M.; Rubio González, R.; Sanz González, F. *Synlett* **2004**, 2553−2557. (d) Fernández-Mateos, A.; Herrero Teijón, P.; Rabanedo Clemente, R.; Rubio González, R. *Tetrahedron Lett.* **2006**, *47*, 7755−7758. (e) Zhow, L.; Hirao, T. *Tetrahedron* **2001**, *57*, 6927−6933.

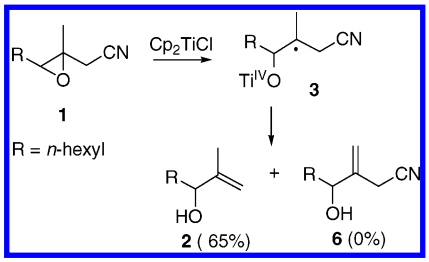
(6) (a) Quiclet-Sire, B.; Callier, A. C.; Zard, S. Z. *Tetrahedron Lett.* **1994**, *35*, 6109−6112. (b) Callier-Dublanchet, A.-C.; Quiclet-Sire, B.; Zard, S. Z. *Tetrahedron Lett.* **1997**, *38*, 2463−2466. (c) Boivin, J.; Callier-Dublanchet, A.-C.; Quiclet-Sire, B.; Scaiano, A.-M.; Zard, S. Z. *Tetrahedron* **1995**, *51*, 6517−6528. (d) Curran, D. P.; Seong, C. M. *Tetrahedron* **1992**, *48*, 2175−2190. (e) Boivin, J.; Fouquet, E.; Zard, S. Z. *Tetrahedron* **1994**, *50*, 1757−1768.

(7) (a) Kim, S.; Jon, S. Y. *J. Chem. Soc., Chem. Commun.* **1998**, 815−816. (b) Beckwith, A. L. J.; O'Shea, D. M.; Gerba, S.; Westwood, S. W. *J. Chem. Soc., Chem. Commun.* **1987**, 666−667. (c) Cossy, J.; Poitevin, C.; Pardo, D. G.; Peglion, J. L. *Synthesis* **1995**, 1368−1370. (d) Sulsky, R.; Gougoutas, J. Z.; DiMarco, J.; Biller, S. A. *J. Org. Chem.* **1999**, *64*, 5504−5510.

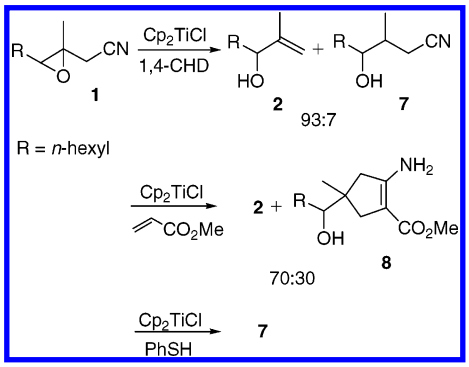
(8) Benati, L.; Bencivenni, G.; Leardini, R.; Minozzi, M.; Nanni, D.; Scialpi, R.; Spagnolo, P.; Zanardi, G.; Rizzoli, C. *Org. Lett.* **2004**, *6*, 417−420.

(9) (a) RajanBabu, T. V.; Nugent, W. A. *J. Am. Chem. Soc.* **1994**, *116*, 986−997. (b) RajanBabu, T. V.; Nugent, W. A. *J. Am. Chem. Soc.* **1988**, *110*, 8561−8562. (c) Daasbjerg, K.; Svith, H.; Grimme, S.; Gerenkamp, M.; Muck-Lichtenfeld, C.; Gansäuer, A.; Barchuk, A.; Keller, F. *Angew. Chem., Int. Ed.* **2006**, *45*, 2041. (d) Gansäuer, A.; Bluhm, H. *Chem. Rev.* **2000**, *100*, 2771−2788. (e) Gansäuer, A.; Lauterbach, T.; Narayan, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 5556−5573. (f) Barrero, A. F.; Quilez del Moral, J. F.; Sánchez, E. M.; Arteaga, J. F. *Eur. J. Org. Chem.* **2006**, 1627−1641. (g) Cuerva, J. M.; Justicia, J.; Oller-López, J. L.; Bazdi, B.; Oltra, J. E. *Mini-Rev. Org. Chem.* **2006**, *3*, 23.

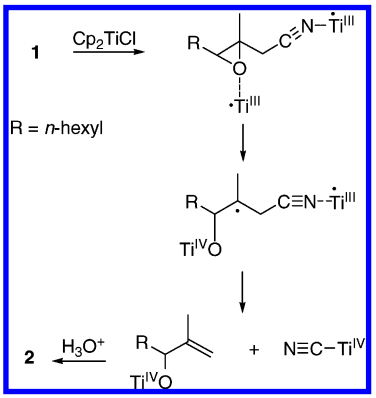
**SCHEME 6. Homolytic Pathway**




**SCHEME 7. Radical Competition Elimination versus Additions**




**SCHEME 8. Mechanistic Pathway for Radical Elimination**

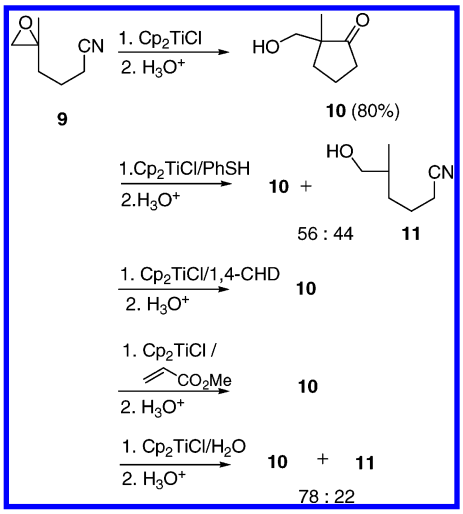



or dehydrogenation products. The deoxygenation pathway has mainly been observed for secondary radicals.[9a]

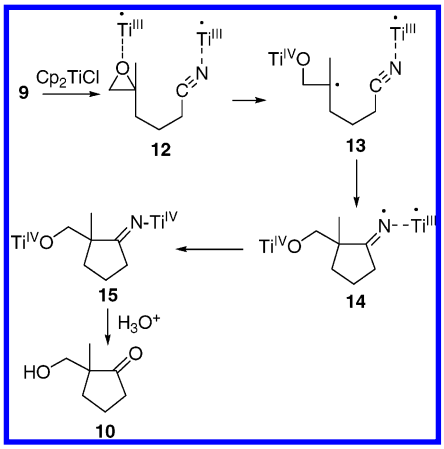
The elimination of $^{-}$CN would be the least likely. From previous work with base-catalyzed elimination, it is known that the cyano group is a very poor leaving group (Scheme 5).[11] For the depicted reaction, only 2% alkene was obtained after 117 h.

The dehydrogenation pathway would not be feasible because the s-alkyl complexes of the electron-poor transition metals (Ti, Zr), such as **4**, in high formal oxidation states, show a low tendency to be eliminated as hydride complexes to give alkenes.[12]

**SCHEME 9. Radical Competition Cyclization versus Additions**




**SCHEME 10. Mechanistic Pathway for Radical Cyclization of 9 with Ti(III)**




Following the homolytic pathway, the radical **3** would evolve in two directions: the well-known $\beta$-hydrogen elimination[5b,10a,b] and the unknown $\beta$-cyano elimination[5a] (Scheme 6).

The kinetics of the decyanogenation corresponds, as will be seen, to a radical reaction. The following experiments should demonstrate that the homolytic decyanogenation would be the real reaction pathway (Scheme 7). First, when we treated **1** with $Cp_2TiCl$ (2.5 equiv) in the presence of 1,4-CHD (10 equiv), two products were obtained, **2** and **7**, in a 93:7 ratio. The decyanogenation compound **2** was the main product. This result indicated that the elimination of CN is almost 13 times faster than the hydrogen atom transfer from 1,4-CHD ($k_{50} = 2 \times 10^5$ $M^{-1}$ $s^{-1}$).[13] Second, when we treated **1** with $Cp_2TiCl$ (2.5 equiv) in the presence of methylacrylate (10 equiv), two products were obtained, **2** and **8**, in a 70:30 ratio. The major product was the allylic alcohol **2**, resulting from the decyanogenation. The minor product **8** was the result of an intermolecular radical addition[9a] followed by a Thorpe-type cyclization and radical reduction. This result showed that elimination of CN is twice as fast as the radical addition to an activated alkene ($k_{20} = 1.1 \times 10^6$ $M^{-1}$ $s^{-1}$).[14]

(10) (a) Cuerva, J. M.; Campaña, A. G.; Justicia, J.; Rosales, A.; Oller-López, J. L.; Robles, R.; Cárdenas, D. J.; Buñuel, E.; Enrique Oltra, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 5522−5526. (b) Barrero, A. F.; Oltra, J. E.; Cuerva, J. M.; Rosales, A. *J. Org. Chem.* **2002**, *67*, 2566−2571. (c) Gansäuer, A.; Bluhm, H.; Pierebon, M. *J. Am. Chem. Soc.* **1998**, *120*, 12849−12859. (d) Gansäuer, A.; Rinker, B.; Pierobon, M.; Grimme, S.; Gerenkamp, M.; Mück-Lichtenfeld, C. *Angew. Chem., Int. Ed.* **2003**, *42*, 3687−3690.

(11) Wallace, T. J.; Hoffmann, J. E.; Schriesheim, A. *J. Am. Chem. Soc.* **1963**, *85*, 2739−2743; **1964**, *86*, 1561−1563.

(12) Colleman, J. P.; Hegedus, L. S.; Norton, J. R.; Finke, R. G. In *Principles and Applications of Organotransition Metal Chemistry*; University Science Books: Mill Valley, CA, 1987; pp. 698−700.

(13) Newcomb, M. *Tetrahedron* **1993**, *49*, 1151−1176.

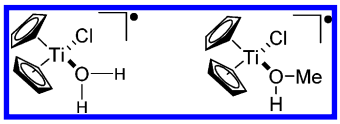
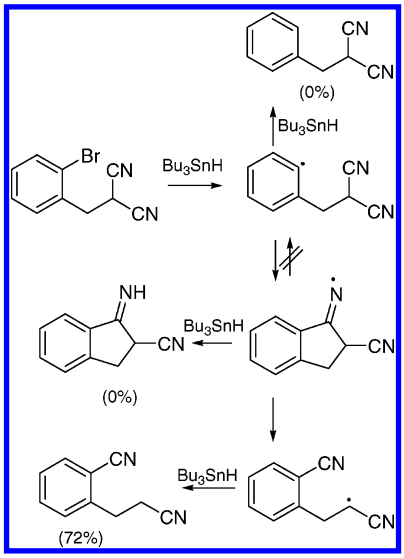
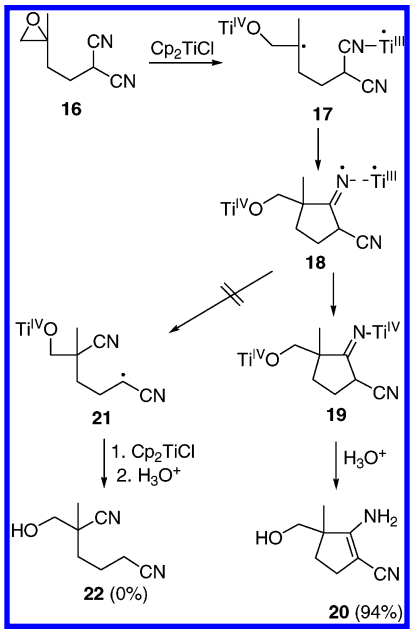


**FIGURE 1.** Titanocene complex with water or methanol.

**SCHEME 11. Effect of α-Substituent on Nitrile Radical Translocation**



**SCHEME 12. Reaction of 16 with Ti(III)**

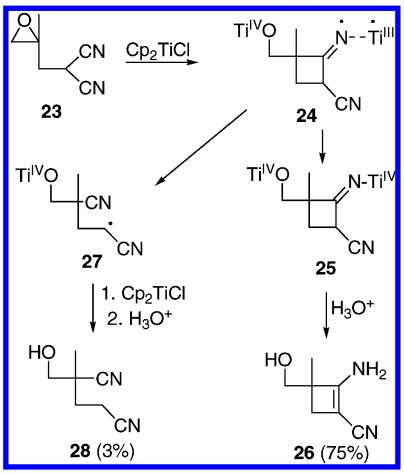


A third experiment with the epoxynitrile **1** was performed, adding PhSH (10 equiv) to the reaction with $Cp_2TiCl$ (2.5 equiv). This time only the reduction product **7** was obtained after the reaction of radical **3** with thiophenol hydrogen ($k_{20} = 9 \times 10^7$ $M^{-1}$ $s^{-1}$).[15] The former two reactions showed the rate constant for the decyanogenation to be close to $k_{25} = 2.5 \times 10^6$ $s^{-1}$, which is coherent with the result obtained for the reaction with added PhSH.[15] The reaction of **1** with $Cp_2TiCl$ was not altered by the presence of methanol or phenol.

(14) Fischer, H.; Radom, L. *Angew. Chem., Int. Ed.* **2001**, *40*, 1340−1371.

(15) Newcomb, M.; Choi, S. Y.; Horner, J. H. *J. Org. Chem.* **1999**, *64*, 1225−1231.

**SCHEME 13. Reaction of 23 with Ti(III)**



In light of these results, the decyanogenation of epoxynitrile **1** to give **2** could be explained in terms of two homolytic cleavages aided by coordination of $Cp_2TiCl$ to nitrile, as shown in Scheme 8, and indicate that $Cp_2TiCl$ acts as not only a radical initiator but also a Lewis acid and radical terminator.[16]

The second process to be studied was the reaction of epoxynitrile **9** with $Cp_2TiCl$ in THF, which gave only the cyclic hydroxyketone **10** after further hydrolysis.[5a] We have assumed a radical mechanism to explain this reaction. Here our aim is to test this hypothesis by carrying out several experiments (Scheme 9).

First, we observed that at least 2 equiv of $Cp_2TiCl$ was necessary for the reaction to be completed. Only one-third of conversion was reached using 1 equiv of $Cp_2TiCl$. These results are consistent with the formation of a titanium-coordinated nitrile, $ClCp_2Ti\cdots NC-R$, in which the nitrile group is an efficient radical acceptor as compared with the noncoordinated nitrile.[16,17] The titanium−nitrile complex would also explain the increased rate of radical cyclization when compared with that promoted by $Bu_3SnH$ in halonitriles.[18] The yield and conversion were independent of the addition order: reagent over substrate or vice versa.

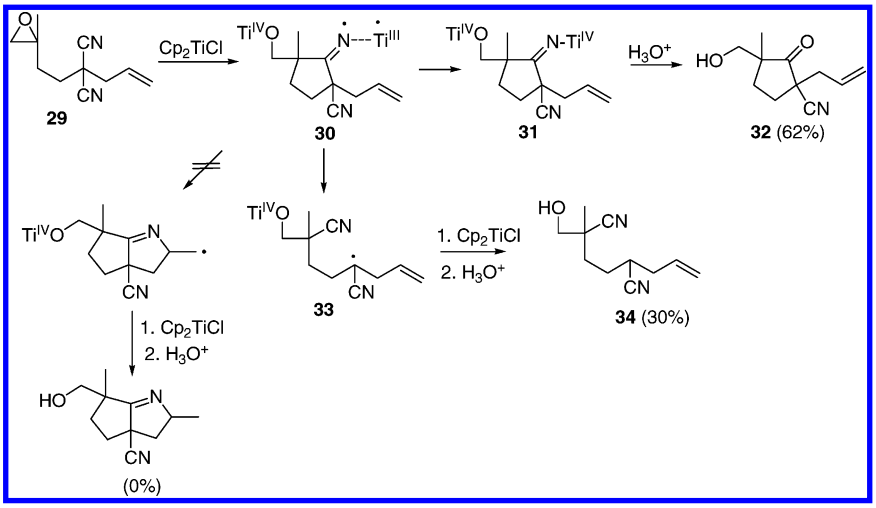
For a better understanding of the kinetic of the cyclization, we repeated the reaction using five additives. When PhSH (10 equiv) was added to the reaction of **2** with $Cp_2TiCl$, a mixture of hydroxyketone **10** and hydroxynitrile **11** in a 56:44 ratio was obtained. It is known that the rate constant for the reaction of radicals with PhSH is $k_{20} = 9 \times 10^7$ $M^{-1}$ $s^{-1}$.[15] This result shows that the cyclization and hydrogen transfer from PhSH rate are almost equal. This means that the rate constant for 5-*exo* radical cyclization onto nitrile is around $k_{25} = 9 \times 10^7$ $M^{-1}$ $s^{-1}$, which is farther away from that reported for the 5-cyanobutyl radical, $k_{25} = 4 \times 10^3$ $s^{-1}$.[18] This shows that titanocene accelerates the cyclization through a titanium-coordinated nitrile

(16) (a) Miyabe, H.; Ueda, M.; Yoshioka, N.; Naito, T. *Synlett* **1999**, 465−467. (b) Chareyron, M.; Devin, P.; Fensterbank, L.; Malacria, M. *Synlett.* **2000**, 83−85. (c) Renaud, P.; Gerster, M. *Angew. Chem., Int. Ed.* **1998**, *37*, 2562−2579. (d) Ollivier, C.; Renaud, P. *Chem. Rev.* **2001**, *101*, 3415−3434.

(17) (a) Yamamoto, Y.; Matsumi, D.; Hattori, R.; Itoh, K. *J. Org. Chem.* **1999**, *64*, 3224−3229. (b) de Boer, E. J. M.; Teuben, J. H. *J. Organomet. Chem.* **1977**, *140*, 41−45. (c) de Boer, E. J. M.; Teuben, J. H. *J. Organomet. Chem.* **1978**, *153*, 53−57.

(18) (a) Griller, D.; Smith, P.; Ingold, K. U. *Can. J. Chem.* **1979**, *57*, 831. (b) Beckwith, A. L. J.; Hay, B. D. *J. Am. Chem. Soc.* **1989**, *111*, 230−234.

**SCHEME 14. Reaction of 29 with Ti(III)**




$ClCp_2Ti\cdots NC-R$[17a] with a LUMO level lower than the uncoordinated nitrile **9** (Scheme 10). The cyclization gave an iminyl radical coordinated to Ti(III) **14**,[16] which further evolved to afford the N−Ti bond, as in **15**.

The addition of 1,4-CHD did not alter the result obtained without it. It is clear that cyclization is much faster than hydrogen transfer. The same happened when methyl acrylate was the additive.

Recently, water has been introduced as a source of hydrogen atoms in radical chemistry mediated by Ti(III).[10a] When water (10 equiv) was added to the reaction between **9** + Ti(III), a mixture of **10** and **11** was obtained in a 78:22 ratio, but conversion of the epoxide was 50%. An aqua complex such as that shown in Figure 1 has been proposed[10a] to explain the transfer of hydrogen atoms to radicals. This means that the reagent is partly consumed in this reaction. When methanol was added to the reaction, only **10** was obtained, but conversion was only 50%. The methanol seems to complex the Ti(III) (Figure 1) and inhibit the reaction with the epoxide but does not transfer atomic hydrogen as in the case of water.

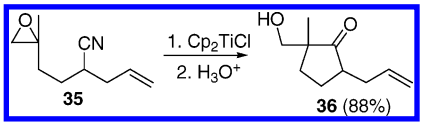
To corroborate the role of $Cp_2TiCl$ in the radical cyclization onto nitriles, we examined the reaction of precursors with electron-withdrawing α-substituents. Reported examples of radicals generated from nitrile halides with $Bu_3SnH$ indicate that only translocation products are obtained, due to stabilization of intermediate radicals (Scheme 11).[3]

In our case, from **16**, no translocation product **22** was obtained, only the cyclization product **20** (94%) (Scheme 12). This means that the reaction proceeds through the titanium-coordinated nitrile **17**, following with titanium-coordinated iminyl radical **18** and finally the imine Ti(IV) derivative **19**, which after hydrolysis and tautomerization gives the amino nitrile **20**. The reaction of the iminyl radical **18** with the coordinated Ti(III) is faster than translocation to **21**.

The translocations are favored not only by the stabilization of radicals but also by ring strain. All the reported examples of cyclobutyliminyl radical intermediates evolve to nitriles by *β*-fission.[19] We found that the major product from the reaction of epoxydinitrile **23** with Ti(III) was the enaminonitrile **26** (75%), which arose by tautomerization of the initial imine Ti-(IV) **25** after hydrolysis (Scheme 13). The minor compound was the translocation product **28** (3%). In this case, the results

(19) Zard, S. Z. *Synlett* **1996**, 1148−1154.

**SCHEME 15. Reaction of 35 with Ti(III)**



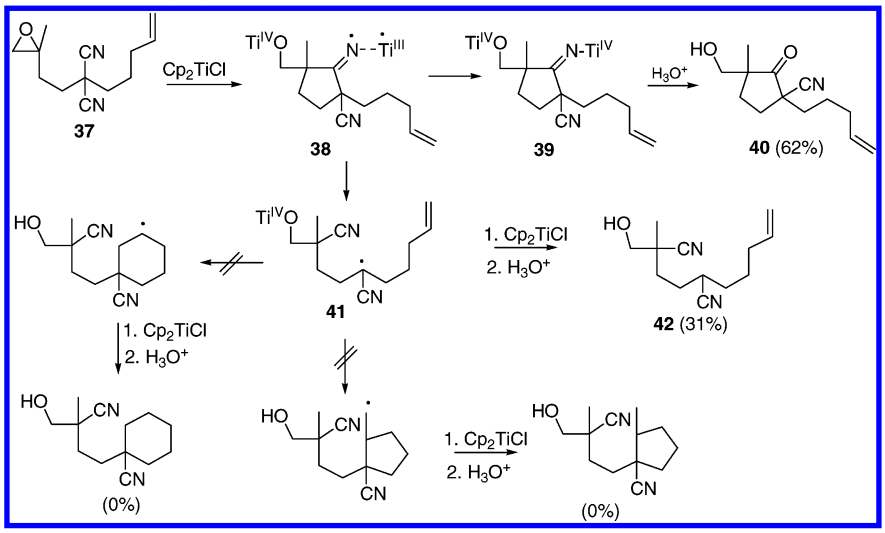

are best rationalized in terms of the cyclobutane ring strain, which competes, although to a low extent, with the reduction of the coordinated iminyl radical **24**.

Our next insight into the kinetics and mechanisms of radical reactions came from a tandem radical reaction involving cyclization onto nitriles to yield intermediate iminyl radicals followed by cyclization of the iminyl radicals onto alkenes. This kind of tandem reaction has been attempted from unsaturated dinitrile halides, with the translocation compound as the only reaction product.[3a] In our case, from **29**, two products were obtained: the cyclization diastereomeric mixture **32** in 62% yield, and the translocation diastereomeric mixture **34** in 30% yield (Scheme 14). No direct 6-*exo* cyclization onto the C=C double bond nor tandem cyclization takes place. The translocation product would not be expected if the earlier epoxydinitrile **16** were taken as reference. We attribute the difference in behavior to the very crowded environment of the nitrogen iminyl radical in the intermediate **30**, which is partly decoordinated from Ti(III).

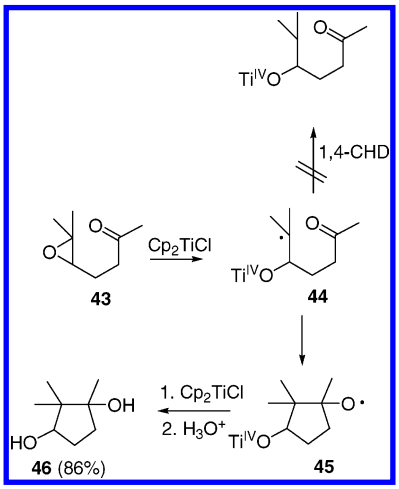
The substitution of a CN attractor group by a hydrogen group in the model dinitrile **29** would facilitate the tandem reaction against translocation, as has been reported.[3a] In our case, the mononitrile compound **35** afforded only the diastereomeric cyclization mixture onto nitrile **36** (88%); neither the tandem product nor the translocation product was obtained (Scheme 15).

To check whether the radical generated by a translocation, which is conjugated to the nitrile group as in **41**, reacted faster with Ti(III) than with the C=C bond in a 5-*exo* cyclization, we assayed a model involving the unsaturated epoxydinitrile **37** (Scheme 16). The unsaturated chain is longer than that of the model **29** and permits the 5-*exo* cyclization of the radical **41**. The reaction of **37** with Ti(III) afforded a diastereomeric mixture of the cyclization product onto nitrile **40** as the major product (62%) and the translocation compound **42** as the minor product (31%). No product derived from the 5-*exo* or 6-*endo* cyclization of the conjugated radical **41** onto the C=C bond was obtained. The reaction of the conjugated radical **41** with Ti(III) was faster.

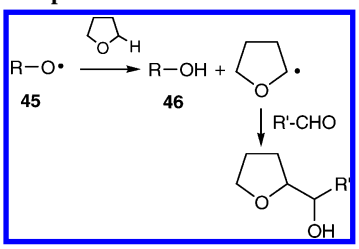
**SCHEME 16. Reaction of 37 with Ti(III)**



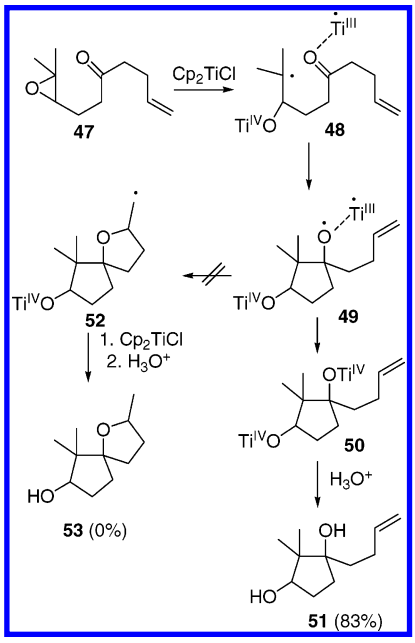
**SCHEME 17. Reaction of 43 with Ti(III)**



**SCHEME 18. Hydrogen Abstraction by Alkoxyl Radical and Aldehyde Trap**



**SCHEME 19. Reaction of 47 with Ti(III)**



In a previous work,[5b] we observed that radical cyclization of epoxyketones with Ti(III) is inhibited by PhSH but not by MeOH or PhOH. In the present work, we performed the reaction of **43** with Ti(III), adding 1,4-CHD. The result was the same as that without 1,4-CHD (Scheme 17).[5b] A mixture of diastereomeric diols **46** (86%) was the only product obtained. In light of this result, the rate constant for the cyclization of a tertiary radical onto C═O would be situated between $k_{20} = 9 \times 10^7$ $M^{-1}s^{-1}$ (ref 15) and $k_{50} = 2 \times 10^5$ $M^{-1}$ $s^{-1}$ (ref 13).

An interesting step in the radical cyclization is the fate of the alkoxyl radical **45**. It has been suggested that these highly electrophilic radicals abstract hydrogen from the solvent THF (Scheme 18).[20] If this hypothesis were correct, the tetrahydrofuranyl radical could be trapped by aldehydes, as has been shown recently by Yoshimitsu et al.[21]

The addition of 4-methoxybenzaldehyde to the reaction of epoxyketone **43** with Ti(III) in THF did not produce the expected α-substituted tetrahydrofuran-2-methanol, but unaltered aldehyde.

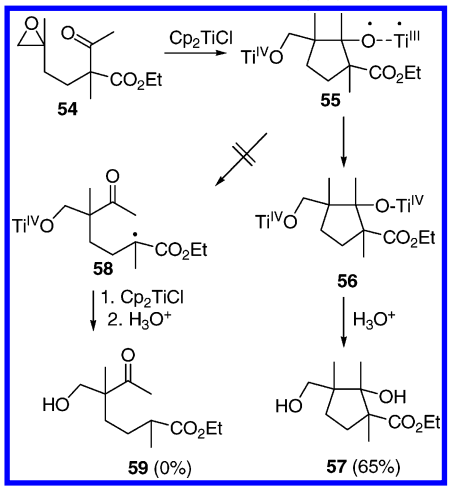
Another experiment to determine the evolution of the alkoxyl radical was carried out with the unsaturated epoxyketone **47** with the aim of trapping the alkoxyl radical **49** through a 5-*exo* cyclization process onto a C═C bond to **52** (Scheme 19). The rate constant for this type of cyclization is around $k = (4 \pm 2) \times 10^8$ $s^{-1}$.[22] The reaction of epoxyketone **47** with Ti(III) only afforded the diol **51** as a diastereomeric mixture (83%). No hydroxyether **53** was found. These results could be explained, as with the nitriles, in terms of a titanium-coordinated carbonyl

(20) Gansäuer, A.; Lauterbach, T.; Geich-Gimbel, D. *Chem.—Eur. J.* **2004**, *10*, 4983−4990 and references cited therein.

(21) Yoshimitsu, T.; Tsunoda, M.; Nagaoka, H. *Chem. Commun.* **1999**, 1745−1746.

(22) Hartung, J.; Gallou, F. *J. Org. Chem.* **1995**, *60*, 6706−6716.

**SCHEME 20. Reaction of 54 with Ti(III)**




$ClCp_2Ti\cdots O{=}CR_2$, as in **48** in which the carbonyl group is an efficient radical acceptor.[16,17] The reaction of **47** with Ti(III) must proceed through similar intermediates as seen in Scheme 10. The reaction of the alkoxyl radical with Ti(III) is faster than (a) intramolecular addition to the C=C bond, (b) abstraction of hydrogen from THF ($k = 10^7$ $M^{-1}$ $s^{-1}$),[23] or (c) $\beta$-scission ($k_{25} = 9.1 \times 10^7$ $s^{-1}$).[18b]

Previously, we have seen (Scheme 14) that the iminyl−titanium radical complex undergoes $\beta$-scission when the environment of the N−Ti bond is very crowded and if the radical formed after the fission is stabilized by an attractor group. Regarding this issue, we investigated the behavior of some analogue alkoxyl radicals.[3b] Treatment of epoxyketoester **54** with Ti(III) gave a diastereomeric mixture of diol esters **57** (65%) (Scheme 20). No translocation product, such as **59**, was obtained from the reaction of **54** with $Cp_2TiCl$, but only the cyclization product resulting from radical alkoxyl trapping with Ti(III). In this case, the R−O•···Ti(III) coordination must be stronger than R−CN•···Ti(III).[17a] The PM3 semiempirical calculations developed by Itoh et al. suggest that the unpaired spin is localized on the titanium center in the complex $Cp_2PhTi\cdots NC{-}CH_3$, whereas the unpaired spin is almost completely transferred to the carbonyl carbon from the titanium center in the complex $PhCp_2Ti\cdots O{=}C(CH_3)_2$.[17]

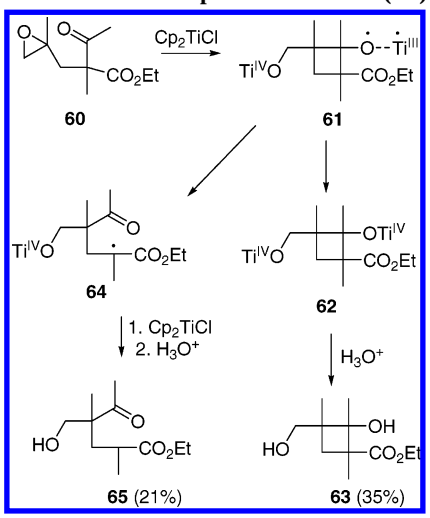
To force the cleavage of the alkoxyl radical intermediate, we tackled the cyclization of epoxyketoester **60**, which must occur through the highly strained cyclobutane intermediate **61** (Scheme 21). The reaction of **60** with $Cp_2TiCl$ gave a diol ester **63** (35%) and a diastereomeric mixture of hydroxyketoesters **65** (21%). The acyclic product **65** is the result of the radical **61** $\beta$-scission.

The syntheses of the epoxides whose radical reactions have been studied in the present work are described in the Supporting Information.

## Conclusion

The results above show that the kinetics of CN elimination induced by $Cp_2TiCl$ in $\beta,\gamma$-epoxynitriles is in the range expected for a radical reaction. Epoxynitriles and epoxyketones cyclizations induced by titanocene chloride are mediated radical processes.

**SCHEME 21. Reaction of Epoxide 60 with Ti(III)**




The role of titanocene chloride, substantial in this kind of process, is to promote the homolytic regioselective cleavage of oxirane rings and also to complex the cyano and carbonyl groups. The complexation facilitates radical cyclization by making accessible a low-lying LUMO level of complex. Finally, the titanocene chloride acts as a radical terminator.

The rate of iminyl or alkoxyl radical reductions with titanocene chloride is much faster than radical cyclization or the $\beta$-scission reaction. Only cyclobutane alkoxyl or iminyl radicals gave some $\beta$-scissions.

## Experimental Section

**General Methods.** Melting points are uncorrected. $^1H$ NMR spectra were measured at either 200 or 400 MHz, and $^{13}C$ NMR were measured at 50 or 100 MHz in $CDCl_3$ and referenced to TMS ($^1H$) or solvent ($^{13}C$), except where indicated otherwise. IR spectra were recorded for neat samples on NaCl plates, unless otherwise noted. Standard mass spectrometry data were acquired by using GC−MS system in EI mode with a maximum *m*/*z* range of 600. When required, all solvents and reagents were purified by standard techniques: tetrahydrofuran (THF) was purified by distillation from sodium and benzophenone ketyl and degassed before use. Dimethylformamide (DMF) was dried over $CaH_2$, distilled under reduced pressure, and degassed before use. All reactions were conducted under a positive pressure of argon, utilizing standard benchtop techniques for the handling of air-sensitive materials. Chromatographic separations were carried out under pressure on silica gel using flash column techniques on Merck silica gel 60 (0.040−0.063 mm). Yields reported are for chromatographically pure isolated products unless otherwise mentioned.

**General Procedure 1 (GP 1). Reaction of Epoxides with $Cp_2TiCl$.** A mixture of $Cp_2TiCl_2$ (2.50 mmol) and Zn (7.50 equiv) in strictly deoxygenated THF (4 mL) was stirred at room temperature until the red solution turned green. In a separate flask, the epoxy compound (1 mmol) was dissolved in strictly deoxygenated THF (20 mL). The green Ti(III) solution was slowly added via cannula to the epoxide solution. After 30 min, an excess of saturated $NaH_2PO_3$ was added, and the mixture was stirred for 20 min. The product was extracted into ether, and the combined organic layers were washed with saturated $NaHCO_3$ and brine, dried ($Na_2SO_4$), and filtered. After removal of the solvent, the crude product was purified by flash chromatography.

**Reaction of 1 with $Cp_2TiCl$.** According to GP 1, reaction of **1** (200 mg, 1.10 mmol) with $Cp_2TiCl$ followed by flash chromatography (hexane/diethyl ether 85:15) furnished 2-methylnon-1-en-3-ol **2** (111 mg, 65%), as a colorless oil: IR, $\nu$ 3370, 1653, 1030

(23) (a) Malatesta, V.; Ingold, K. U. *J. Am. Chem. Soc.* **1981**, *103*, 609−614. (b) Malatesta, V.; Scaiano, J. C. *J. Org. Chem.* **1982**, *47*, 1455−1459. (c) Busfield, W. K.; Grice, I. D.; Jenkins, I. D. *J. Chem. Soc., Perkin Trans. 2* **1994**, 1079−1086.

cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 0.88 (3H, t, $J$ = 7 Hz), 1.2−1.6 (10H, m), 1.72 (3H, s), 4.05 (1H, t, $J$ = 6.5 Hz), 4.83 (1H, s), 4.93 (1H, s) ppm; $^{13}$C NMR ($CDCl_3$) $\delta$ 13.9 ($CH_3$), 17.4 ($CH_3$), 22.5 ($CH_2$), 25.4 ($CH_2$), 29.1 ($CH_2$), 31.7 ($CH_2$), 34.9 ($CH_2$), 75.9 (CH), 110.8 ($CH_2$), 147.6 (C) ppm; MS EI, *m*/*z* (relative intensity) 156 ($M^+$, 3), 99 (11), 94 (12), 86 (18), 71 (100), 55 (20); HRMS (ESI) 157.1566 ($M^+$ + H, $C_{10}H_{21}O$), calcd 157.1587. Anal. Calcd for $C_{10}H_{20}O$: C, 76.86; H, 12.90. Found; C, 76.91; H, 12.96.

**Reaction of 1 with $Cp_2TiCl$/1,4-CHD.** According to GP 1, reaction of **1** (70 mg, 0.39 mmol) with $Cp_2TiCl$ and 1,4-CHD (312 mg, 3.90 mmol) followed by flash chromatography (hexane/diethyl ether 85:15) furnished **2** (38 mg, 63%) and a 1:1 mixture of diastereoisomeric 4-hydroxy-3-methyldecanonitrile **7** (3.5 mg, 5%), as a viscous oil: IR, $\nu$ 3488, 2248, 1028, cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 0.88 (6H, t, $J$ = 6.6 Hz), 1.02 (3H, d, $J$ = 6.8 Hz), 1.09 (3H, d, $J$ = 6.8 Hz)*, 1.2−1.5 (20H, m), 1.84 (1H, m)*, 1.94 (1H, m), 2.30 (1H, dd, $J_1$ = 7.6 Hz, $J_2$ = 16.1 Hz), 2.48 (3H, m), 3.45 (1H, m)*, 3.64 (1H, m) ppm; $^{13}$C NMR ($CDCl_3$) $\delta$ 12.9 ($CH_3$), 14.0 ($2CH_3$), 16.4 ($CH_3$)*, 20.3 ($CH_2$)*, 21.4 ($CH_2$), 22.52 ($2CH_2$), 25.3 ($CH_2$)*, 25.9 ($CH_2$), 29.1 ($2CH_2$), 31.7 ($2CH_2$), 34.2 (CH), 34.5 ($CH_2$)*, 35.6 (CH), 36.1 (CH)*, 73.0 (CH), 74.2 (CH)*, 119.4 (C) 120.1 (C)* ppm; MS EI, *m*/*z* (relative intensity) 138 ($M^+$ − 45, 1), 96 (24), 68 (100), 55 (20); HRMS (ESI) 206.1532 ($M^+$ + Na, $C_{11}H_{21}NONa$), calcd 206.1520.

**Reaction of 1 with $Cp_2TiCl$/Methyl Acrylate.** According to GP 1, reaction of **1** (50 mg, 0.28 mmol) with $Cp_2TiCl$ and methyl acrylate (240 mg, 2.80 mmol) followed by flash chromatography (hexane/diethyl ether 85:15) furnished **2** (29 mg, 67%) and two diastereoisomers of methyl 2-amino-4-(1-hydroxy-hepthyl)-4-methylcyclopent-1-enecarboxylate **8**: less polar isomer (11 mg, 16%), more polar isomer (12 mg, 16%).

Data for less polar isomer: IR, $\nu$ 3451, 3360, 1735, 1668 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 0.88 (3H, t, $J$ = 6.6 Hz), 1.06 (3H, m), 1.2−1.7 (10H, m), 1.98 (2H, d, $J$ = 16.5 Hz), 2.23 (1H, d, $J$ = 14.0 Hz), 2.55 (1H, d, $J$ = 14.0 Hz), 2.66 (1H, d, $J$ = 16.5 Hz), 3.49 (1H, m), 3.68 (3H, s) ppm; $^{13}$C NMR ($CDCl_3$) $\delta$ 14.0 ($CH_3$), 22.5 ($CH_2$), 23.4 ($CH_3$), 26.7 ($CH_2$), 29.2 ($CH_2$), 31.8 ($CH_2$), 32.4 ($CH_2$), 39.9 ($CH_2$), 43.4 (C), 44.8 ($CH_2$), 50.2 ($CH_3$), 78.8 (CH), 93.4 (C), 159.9 (C), 168.3 (C) ppm; MS EI, *m*/*z* (relative intensity) 269 ($M^+$, 7), 154 (100), 122 (36), 115 (90), 94 (37), 83 (25), 67 (20), 55 (65); HRMS (ESI) 292.1883 ($M^+$ + Na, $C_{15}H_{27}NO_3Na$), calcd 292.1888. Anal. Calcd for $C_{15}H_{27}NO_3$: C, 66.88; H, 10.10; N, 5.20. Found: C, 66.69; H, 10.19; N, 5.34.

Data for more polar isomer: IR, $\nu$ 3458, 3380, 1739, 1669 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 0.88 (3H, t, $J$ = 6.6 Hz), 1.03 (3H, m), 1.2−1.7 (10H, m), 2.10 (1H, d, $J$ = 16.5 Hz), 2.17 (1H, d, $J$ = 13.7 Hz), 2.46 (1H, d, $J$ = 13.7 Hz), 2.69 (1H, d, $J$ = 16.5 Hz), 3.49 (1H, m), 3.68 (3H, s) ppm; $^{13}$C NMR ($CDCl_3$) $\delta$ 14.0 ($CH_3$), 22.1 ($CH_3$), 22.5 ($CH_2$), 26.7 ($CH_2$), 29.2 ($CH_2$), 31.7 ($CH_2$), 32.4 ($CH_2$), 40.5 ($CH_2$), 43.5 (C), 45.7 ($CH_2$), 50.2 ($CH_3$), 78.8 (CH), 93.2 (C), 159.9 (C), 168.3 (C) ppm; MS EI, *m*/*z* (relative intensity) 269 ($M^+$, 4), 154 (53), 122 (26), 115 (100), 94 (25), 83 (27), 67 (13), 55 (38); HRMS (ESI) 292.1881 ($M^+$ + Na, $C_{15}H_{27}NO_3Na$), calcd 292.1888. Anal. Calcd for $C_{15}H_{27}NO_3$: C, 66.88; H, 10.10; N, 5.20. Found: C, 66.71; H, 10.16; N, 5.22.

**Reaction of 1 with $Cp_2TiCl$/PhSH.** According to GP 1, reaction of **1** (80 mg, 0.44 mmol) with $Cp_2TiCl$ and PhSH (404 mg, 4.40 mmol) followed by flash chromatography (hexane/diethyl ether 85:15) furnished **7** (75 mg, 93%), as a 1:1 mixture of diastereoisomers.

**Reaction of 9 with $Cp_2TiCl$.** According to GP 1, reaction of **9** (125 mg, 1.0 mmol) with $Cp_2TiCl$ followed by flash chromatography (hexane/diethyl ether 50:50) furnished 2-(hydroxymethyl)-2-methylcyclopentanone **10** (102 mg, 80%), as a colorless oil: IR, $\nu$ 3445, 1732 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 0.98 (3H, s), 1.6−2.4 (6H, m), 3.42 (1H, d, $J$ = 10.9 Hz), 3.58 (1H, d, $J$ = 10.9 Hz) ppm; $^{13}$C NMR ($CDCl_3$) $\delta$ 18.74 ($CH_2$), 19.2 ($CH_3$), 33.05 ($CH_2$), 38.3 ($CH_2$), 50.2 (C), 66.9 ($CH_2$), 224.3 (C) ppm; MS EI, *m*/*z* (relative intensity) 128 ($M^+$, 9), 82 (27), 69 (89), 57 (100); HRMS (ESI) 129.0905 ($M^+$ + H, $C_7H_{13}O_2$), calcd 129.0910. Anal. Calcd for $C_7H_{12}O_2$: C, 65.60; H, 9.44. Found: C, 65.83; H, 9.41.

**Reaction of 9 with $Cp_2TiCl$/PhSH.** According to GP 1, reaction of **9** (40 mg, 0.32 mmol) with $Cp_2TiCl$ and PhSH (352 mg, 3.20 mmol) followed by flash chromatography (hexane/diethyl ether 50:50) furnished **10** (22 mg, 56%) and 6-hydroxy-5-methylhexanenitrile **11** (18 mg, 44%), as a viscous oil: IR, $\nu$ 3409, 2248, 1047 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 0.94 (3H, d, $J$ = 6.5 Hz), 1.20 (2H, m), 1.5−1.8 (3H, m), 2.35 (2H, t, $J$ = 6.7 Hz), 3.48 (2H, d, $J$ = 5.3 Hz) ppm; $^{13}$C NMR ($CDCl_3$) $\delta$ 16.2 ($CH_3$), 17.3 ($CH_2$), 22.9 ($CH_2$), 32.2 ($CH_2$), 35.0 (CH), 67.6 ($CH_2$), 119.5 (C) ppm; MS EI, *m*/*z* (relative intensity) 96 ($M^+$ − 31, 44), 82 (51), 69 (86), 54 (100); HRMS (ESI) 150.0734 ($M^+$ + Na, $C_7H_{13}NONa$), calcd 150.0734. Anal. Calcd for $C_7H_{13}NO$: C, 66.10; H, 10.30; N, 11.01. Found: C, 66.23; H, 10.36; N, 11.13.

**Reaction of 9 with $Cp_2TiCl$/1,4-CHD.** According to GP 1, reaction of **9** (40 mg, 0.32 mmol) with $Cp_2TiCl$ and 1,4-CHD (256 mg, 3.20 mmol) followed by flash chromatography (hexane/diethyl ether 50:50) furnished **10** (38 mg, 95%)

**Reaction of 9 with $Cp_2TiCl$/Methyl Acrylate.** According to GP 1, reaction of **9** (100 mg, 0.80 mmol) with $Cp_2TiCl$ and methyl acrylate (688 mg, 8.0 mmol) followed by flash chromatography (hexane/diethyl ether 50:50) furnished **10** (77 mg, 75%).

**Reaction of 9 with $Cp_2TiCl/H_2O$.** According to GP 1, reaction of **9** (40 mg, 0.32 mmol) with $Cp_2TiCl$ and $H_2O$ (58 mg, 3.2 mmol) followed by flash chromatography (hexane/diethyl ether 50:50) furnished **10** (16 mg, 39%) and **11** (4.5 mg, 11%).

**Reaction of 9 with $Cp_2TiCl$/MeOH.** According to GP 1, reaction of **9** (50 mg, 0.40 mmol) with $Cp_2TiCl$ and MeOH (128 mg, 4.0 mmol) followed by flash chromatography (hexane/diethyl ether 50:50) furnished **10** (24 mg, 50%).

**Reaction of 16 with $Cp_2TiCl$.** According to GP 1, reaction of **16** (100 mg, 0.66 mmol) with $Cp_2TiCl$ followed by flash chromatography (hexane/ethyl acetate 30:70) furnished 2-amino-3-hydroxy-3-methylcyclopent-1-enecarbonitrile **20** (94 mg, 94%), as a colorless oil: IR, $\nu$ 3363, 2179, 1614, 1052 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 1.20 (3H, s), 1.65 (2H, m), 2.45 (2H, m), 3.53 (1H, d, $J$ = 10.4 Hz), 3.62 (1H, d, $J$ = 10.4 Hz) ppm; $^{13}$C NMR ($CDCl_3$) $\delta$ 20.5 ($CH_3$), 27.5 ($CH_2$), 33.5 ($CH_2$), 49.3 (C), 69.3 ($CH_2$), 73.1 (C), 118.8 (C), 166.9 (C); HRMS (ESI) 175.0857 ($M^+$ + Na, $C_8H_{12}N_2ONa$), calcd 175.0847. Anal. Calcd for $C_8H_{12}N_2O$: C, 63.13; H, 7.95; N, 18.41. Found: C, 63.25; H, 7.91; N, 18.49.

**Reaction of 23 with $Cp_2TiCl$.** According to GP 1, reaction of **23** (80 mg, 0.58 mmol) with $Cp_2TiCl$ followed by flash chromatography (hexane/diethyl ether 75:25) furnished 2-(hydroxymethyl)-2-methylpentanedinitrile **28** (2 mg, 3%), as a colorless oil: IR, $\nu$ 3429, 2220, 1057 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 1.38 (3H, s), 1.90 (1H, m), 2.20 (1H, m), 2.62 (2H, m), 3.63 (1H, d, $J$ = 11.0 Hz), 3.74 (1H, d, $J$ = 11.0 Hz) ppm; $^{13}$C NMR ($CDCl_3$) $\delta$ 13.4 ($CH_2$), 20.7 ($CH_3$), 31.6 ($CH_2$), 39.0 (C), 67.3 ($CH_2$), 118.4 (C), 121.3 (C) ppm; HRMS (ESI) 161.0693 ($M^+$ + Na, $C_7H_{10}N_2ONa$), calcd 161.0690. Anal. Calcd for $C_7H_{10}N_2O$: C, 60.85; H, 7.30; N, 20.28. Found: C, 60.88; H, 7.32; N, 20.22.

2-Amino-3-hydroxymethyl-3-methylcyclobut-1-enecarbonitrile **26** (60 mg, 75%) was obtained as a colorless oil: IR, $\nu$ 3442, 2249, 1093 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 1.60 (3H, s), 1.68 (1H, d, $J$ = 5.3 Hz), 1.79 (1H, d, $J$ = 5.3 Hz), 4.20 (1H, d, $J$ = 9.6 Hz), 4.30 (1H, d, $J$ = 9.6 Hz) ppm; $^{13}$C NMR ($CDCl_3$) $\delta$ 15.2 ($CH_3$), 26.4 ($CH_2$), 35.6 (C), 72.3 ($CH_2$), 77.6 (C), 114.0 (C), 168.7 (C) ppm; MS EI, *m*/*z* (relative intensity) 136 ($M^+$ − 2, 6), 122 (13), 93 (23), 80 (87), 66 (25), 52 (100); HRMS (ESI) 161.0684 ($M^+$ + Na, $C_7H_{10}N_2ONa$), calcd 161.0690. Anal. Calcd for $C_7H_{10}N_2O$: C, 60.85; H, 7.30; N, 20.28. Found: C, 60.69; H, 7.39; N, 20.21.

**Reaction of 29 with $Cp_2TiCl$.** According to GP 1, reaction of **29** (100 mg, 0.57 mmol) with $Cp_2TiCl$ followed by flash chromatography (hexane/ethyl acetate 60:40) furnished a mixture of isomers of 1-allyl-3-(hydroxymethyl)-3-methyl-2-oxocyclopentanecarbonitrile **32** (61 mg, 62%), in a ratio of 1.5:1, as a viscous liquid: IR, $\nu$ 3480, 2242, 1755 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 1.06 (3H, s)*, 1.13

(3H, s), 1.80−2.60 (12H, m), 3.44 (1H, d, $J$ = 10.5 Hz), 3.52 (1H, d, $J$ = 10.7 Hz)*, 3.73 (1H, d, $J$ = 10.7 Hz)*, 3.76 (1H, d, $J$ = 10.5 Hz), 5.22 (2H, d, $J$ = 15.3 Hz), 5.25 (2H, d, $J$ = 24.1 Hz), 5.80 (2H, m) ppm; $^{13}$C NMR ($CDCl_3$) $\delta$ 19.8 ($CH_3$)*, 20.7 ($CH_3$), 29.2 ($CH_2$), 29.9 ($CH_2$), 30.1 ($CH_2$)*, 30.2 ($CH_2$)*, 36.7 ($CH_2$), 38.6 ($CH_2$)*, 48.3 (C), 49.3 (C)*, 51.3 (C)*, 51.4 (C), 66.6 ($CH_2$), 67.6 ($CH_2$)*, 118.5 (C)*, 119.2 (C), 120.7 ($CH_2$), 120.9 ($CH_2$)*, 130.6 (CH)*, 130.7 (CH), 212.9 (C) 213.2 (C)* ppm; MS EI, *m*/*z* (relative intensity) 192 ($M^+ - 1$, 3), 150 (14), 136 (16), 122 (19), 94 (32), 67 (26), 57 (100); HRMS (ESI) 194.1132 ($M^+ + H$, $C_{11}H_{16}NO_2$), calcd 194.1176. Anal. Calcd for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.42; H, 7.84; N, 7.28.

A mixture of isomers of 5-allyl-2-(hydroxymethyl)-2-methylhexanedinitrile **34** (30 mg, 30%) was obtained in a ratio 1.5:1, as a viscous liquid: IR, $\nu$ 3455, 2242, 1060 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 1.34 (3H, s), 1.36 (3H, s), 1.75−2.10 (8H, m), 2.40 (4H, m), 2.66 (2H, m), 3.63 (4H, m), 5.20 (1H, d, $J$ = 11.3 Hz), 5.22 (1H, d, $J$ = 16.6 Hz), 5.81 (2H, m) ppm; $^{13}$C NMR ($CDCl_3$) $\delta$ 20.5 ($CH_3$)*, 21.0 ($CH_3$), 26.9 ($CH_2$)*, 27.1 ($CH_2$), 31.4 (CH), 31.5 (CH)*, 33.0 ($CH_2$), 33.1 ($CH_2$)*, 35.9 ($CH_2$)*, 36.1 ($CH_2$), 39.1 (C)*, 39.2 (C), 67.5 ($CH_2$)*, 67.9 ($CH_2$), 119.3 ($2CH_2$), 120.8 (2C), 122.4 (2C), 132.4 (2CH) ppm; MS EI, *m*/*z* (relative intensity) 177 ($M^+ - 15$, 3), 175 (12), 161 (31), 147 (49), 134 (40), 122 (19), 108 (17), 94 (62), 81 (89), 68 (100), 54 (92); HRMS (ESI) 193.1375 ($M^+ + H$, $C_{11}H_{17}N_2O$), calcd 193.1336. Anal. Calcd for $C_{11}H_{16}N_2O$: C, 68.72; H, 8.39; N, 14.57. Found: C, 68.97; H, 8.32; N, 14.53.

**Reaction of 35 with $Cp_2TiCl$.** According to GP 1, reaction of **35** (120 mg, 0.73 mmol) with $Cp_2TiCl$ followed by flash chromatography (hexane/diethyl ether 70:30) furnished 5-allyl-2-(hydroxymethyl)-2-methylcyclopentanone **36**, major isomer (58 mg, 48%) and minor isomer (49 mg, 40%).

Data for major isomer, as a viscous liquid: IR, $\nu$ 3444, 1730 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 1.09 (3H, s), 1.65 (2H, m), 2.07 (3H, m), 2.41 (2H, m), 3.47 (1H, d, $J$ = 10.8 Hz), 3.55 (1H, d, $J$ = 10.8 Hz), 5.02 (1H, d, $J$ = 7.6 Hz), 5.07 (1H, d, $J$ = 13.0 Hz), 5.74 (1H, m) ppm; $^{13}$C NMR ($CDCl_3$) $\delta$ 20.3 ($CH_3$), 25.0 ($CH_2$), 31.6 ($CH_2$), 33.7 ($CH_2$), 47.9 (CH), 50.1 (C), 67.1 ($CH_2$), 116.6 ($CH_2$), 135.6 (CH), 224.3 (C) ppm; MS EI, *m*/*z* (relative intensity) 168 ($M^+$, 5), 122 (14), 107 (12), 100 (23), 81 (53), 67 (100), 57 (96); HRMS (ESI) 169.1245 ($M^+ + H$, $C_{10}H_{17}O_2$), calcd 169.1223. Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.45; H, 9.53.

Data for minor isomer, as a viscous liquid: IR, $\nu$ 3444, 1737 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 0.98 (3H, s), 1.64 (2H, m), 1.96 (1H, m), 2.12 (2H, m), 2.26 (1H, m), 2.50 (1H, m), 3.48 (1H, d, $J$ = 10.8 Hz), 3.65 (1H, d, $J$ = 10.8 Hz), 5.02 (1H, d, $J$ = 9.2 Hz), 5.06 (1H, d, $J$ = 12.3 Hz), 5.73 (1H, m) ppm; $^{13}$C NMR ($CDCl_3$) $\delta$ 18.9 ($CH_3$), 24.9 ($CH_2$), 30.7 ($CH_2$), 34.1 ($CH_2$), 49.6 (CH), 50.5 (C), 67.4 ($CH_2$), 116.5 ($CH_2$), 135.5 (CH), 224.0 (C) ppm; MS EI, *m*/*z* (relative intensity) 168 ($M^+$, 5), 122 (17), 107 (12), 100 (30), 81 (49), 67 (100), 57 (96); HRMS (ESI) 169.1228 ($M^+ + H$, $C_{10}H_{17}O_2$), calcd 169.1223. Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.35; H, 9.57.

**Reaction of 37 with $Cp_2TiCl$.** According to GP 1, reaction of **37** (100 mg, 0.47 mmol) with $Cp_2TiCl$ followed by flash chromatography (70:30 hexane/ethyl acetate) furnished 3-(hydroxymethyl)-3-methyl-2-oxo-1-(pent-4-enyl)cyclopentanecarbonitrile **40** (64 mg, 62%), as a mixture of isomers in a ratio of 2:1: IR, $\nu$ 3487, 3078, 2242, 1748 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 1.09 (3H, s)*, 1.15 (3H, s), 1.50−2.50 (20H, m), 3.46 (1H, d, $J$ = 10.5 Hz), 3.55 (1H, d, $J$ = 10.7 Hz)*, 3.75 (1H, d, $J$ = 10.7 Hz)*, 3.78 (1H, d, $J$ = 10.5 Hz), 5.04 (4H, m), 5.78 (2H, m) ppm; $^{13}$C NMR ($CDCl_3$) $\delta$ 20.1 ($CH_3$)*, 20.9 ($CH_3$), 24.0 ($CH_2$), 24.2 ($CH_2$)*, 29.6 ($CH_2$), 30.2 ($CH_2$)*, 31.0 ($CH_2$), 31.2 ($CH_2$)*, 32.2 ($CH_2$), 33.1 ($CH_2$), 33.1 ($CH_2$)*, 34.1 ($CH_2$)*, 48.6 (C), 49.7 (C)*, 51.1 (C)*, 51.2 (C), 67.0 ($CH_2$), 67.7 ($CH_2$)*, 115.4 ($CH_2$), 115.6 ($CH_2$)*, 118.6 (C)*, 119.4 (C), 137.2 (CH)*, 137.3 (CH), 213.3 (C) 213.71 (C)* ppm; MS EI, *m*/*z* (relative intensity) 206 ($M^+ - 15$, 2), 154 (40), 122 (19), 110 (18), 94 (25), 80 (23), 72 (39), 57 (100); HRMS (ESI) 222.1456 ($M^+ + H$, $C_{13}H_{20}NO_2$), calcd 222.1483. Anal. Calcd for $C_{13}H_{19}NO_2$: C, 70.56; H, 8.65; N, 6.33. Found: C, 70.67; H, 8.64; N, 6.34.

2-(Hydroxymethyl)-2-methyl-5-(pent-4-enyl)hexanedinitrile **42** (32 mg, 31%) was obtained as a mixture of isomers in a ratio of 1:1: IR, $\nu$ 3461, 2242, 1644, 1073 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 1.35 (3H, s), 1.36 (3H, s), 1.50−2.20 (12H, m), 2.58 (2H, m), 3.64 (4H, m), 5.00 (2H, d, $J$ = 9.2 Hz), 5.03 (2H, d, $J$ = 17.2 Hz), 5.78 (2H, m) ppm; $^{13}$C NMR ($CDCl_3$) $\delta$ 20.5 ($CH_3$), 21.0 ($CH_3$), 26.2 ($2CH_2$), 27.5 ($CH_2$), 27.7 ($CH_2$), 31.2 ($CH_2$), 31.3 ($CH_2$), 31.5 (CH), 31.6 (CH), 32.9 ($2CH_2$), 33.1 ($CH_2$), 33.2 ($CH_2$), 39.1 (C), 39.3 (C), 67.6 ($CH_2$), 68.0 ($CH_2$), 115.4 ($2CH_2$), 121.3 (2C), 122.4 (2C), 137.4 (2CH) ppm; MS EI, *m*/*z* (relative intensity) 205 ($M^+ - 15$, 3), 190 (3), 189 (12), 175 (16), 161 (20), 134 (14), 122 (74), 109 (85), 94 (95), 81 (63), 69 (100), 54 (97); HRMS (ESI) 221.1693 ($M^+ + H$, $C_{13}H_{21}N_2O$), calcd 221.1649. Anal. Calcd for $C_{13}H_{20}N_2O$: C, 70.87; H, 9.15; N, 12.72. Found: C, 70.77; H, 9.21; N, 12.79.

**Reaction of 43 with $Cp_2TiCl$.** According to GP 1, reaction of **43** (200 mg, 1.41 mmol) with $Cp_2TiCl$ followed by flash chromatography (hexane/ethyl acetate 70:30) furnished 1,2,2-trimethylcyclopentane-1,3-diol **46**, minor isomer (75 mg, 37%), major isomer (99 mg, 49%).

Data for minor isomer, colorless oil: IR, $\nu$ 3381, 1036 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 0.76 (3H, s), 1.03 (3H, s), 1.14 (3H, s), 1.88 (3H, m), 2.09 (1H, m), 2.96 (1H, br s), 3.73 (1H, d, $J$ = 5.9 Hz) ppm; $^{13}$C NMR ($CDCl_3$) $\delta$ 15.8 ($CH_3$), 21.5 ($CH_3$), 23.8 ($CH_3$), 30.7 ($CH_2$), 37.8 ($CH_2$), 48.2 (C), 82.8 (CH), 83.3 (C) ppm; MS EI, *m*/*z* (relative intensity) 126 ($M^+ - 18$, 14), 111 (59), 93 (71), 69 (80), 55 (89), 43 (100); HRMS (ESI) 167.1053 ($M^+$ + Na, $C_8H_{16}O_2Na$), calcd 167.1047. Anal. Calcd for $C_8H_{16}O_2$: C, 66.63; H, 11.18. Found: C, 66.87; H, 11.07.

Data for major isomer, white solid: mp 85−89 °C; IR, $\nu$ 3391, 1055 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 0.77 (3H, s), 0.95 (3H, s), 1.17 (3H, s), 1.4−2.2 (5H, m), 4.17 (1H, t, $J$ = 8.5 Hz) ppm; $^{13}$C NMR ($CDCl_3$) $\delta$ 17.4 ($CH_3$), 18.8 ($CH_3$), 23.3 ($CH_3$), 29.0 ($CH_2$), 35.9 ($CH_2$), 47.3 (C), 79.4 (CH), 81.7 (C) ppm; MS EI, *m*/*z* (relative intensity) 126 ($M^+ - 18$, 13), 108 (92), 93 (40), 83 (39), 71 (100), 55 (55); HRMS (ESI) 167.1043 ($M^+$ + Na, $C_8H_{16}O_2Na$), calcd 167.1047. Anal. Calcd for $C_8H_{16}O_2$: C, 66.63; H, 11.18. Found: C, 66.98; H, 11.13.

**Reaction of 47 with $Cp_2TiCl$.** According to GP 1, reaction of **47** (150 mg, 0.82 mmol) with $Cp_2TiCl$ followed by flash chromatography (hexane/ethyl acetate 70:30) furnished of 1-but-3-enyl-2,2-dimethylcyclopentane-1,3-diol **51**, minor isomer (30 mg, 20%) and major isomer (96 mg, 63%)

Data for minor isomer, colorless oil: $^1$H NMR ($CDCl_3$) $\delta$ 0.79 (3H, s), 1.07 (3H, s), 1.48 (1H, m), 1.61 (1H, s), 1.81 (2H, m), 1.97 (1H, m), 2.12 (2H, m), 2.31 (1H, m), 3.75 (1H, br s), 4.96 (1H, d, $J$ = 10 Hz), 5.05 (1H, d, $J$ = 16.2 Hz), 5.87 (1H, m) ppm; $^{13}$C NMR ($CDCl_3$) $\delta$ 16.0 ($CH_3$), 23.7 ($CH_3$), 28.4 ($CH_2$), 30.8 ($CH_2$), 34.4 ($CH_2$), 35.6 ($CH_2$), 48.8 (C), 83.5 (CH), 85.4 (C), 114.4 ($CH_2$), 139.3 (C) ppm; HRMS (ESI) 207.1345 ($M^+ + Na$, $C_{11}H_{20}O_2Na$), calcd 207.1355. Anal. Calcd for $C_{11}H_{20}O_2$: C, 71.70; H, 10.94. Found: C, 71.87; H, 10.96.

Data for major isomer, white solid: mp 88−89 °C; $^1$H NMR ($CDCl_3$) $\delta$ 0.78 (3H, s), 1.09 (3H, s), 1.2−1.7 (4H, m), 1.84 (1H, m), 2.12 (2H, m), 2.21 (1H, m), 4.20 (1H, dd, $J$ = 8.2 Hz, $J_1$ = 8.3 Hz), 4.96 (1H, d, $J_2$ = 10.1 Hz), 5.04 (1H, d, $J$ = 17.2 Hz), 5.86 (1H, m) ppm; $^{13}$C NMR ($CDCl_3$) $\delta$ 16.9 ($CH_3$), 18.8 ($CH_3$), 27.80 ($CH_2$), 28.7 ($CH_2$), 33.5 ($CH_2$), 35.2 ($CH_2$), 47.8 (C), 79.3 (CH), 83.5 (C), 114.5 ($CH_2$), 139.2 (C) ppm; HRMS (ESI) 207.1318 ($M^+$ + Na, $C_{11}H_{20}O_2Na$), calcd 207.1355. Anal. Calcd for $C_{11}H_{20}O_2$: C, 71.70; H, 10.94. Found: C, 71.63; H, 11.07.

**Reaction of 54 with $Cp_2TiCl$.** According to GP 1, reaction of **51** (125 mg, 0.55 mmol) with $Cp_2TiCl$ followed by flash chromatography (hexane/diethyl ether 60:40) furnished a diastereomeric mixture of ethyl 2-hydroxy-3-hydroxymethyl-1,2,3-trimethylcyclopentanecarboxylate **57** (82 mg, 65%) in a ratio of 7:3, as a viscous liquid: IR, $\nu$ 3426, 1720, 1033 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ (major) 0.88 (3H, s), 1.19 (3H, s), 1.24 (3H, t, $J$ = 7.0 Hz), 1.24 (3H, s),

1.4−2.4 (4H, m), 3.53 (2H, br s), 4.16 (2H, m); (minor) 0.99 (3H, s)*, 1.16 (3H, s)*, 1.24 (3H, t, $J$ = 7.0 Hz)*, 1.24 (3H, s)*, 1.4−2.4 (4H, m)*, 3.92 (2H, br s)*, 4.16 (2H, m, $J$ = 7.0 Hz)* ppm; $^{13}$C NMR ($CDCl_3$) $\delta$ (major) 14.0 ($CH_3$), 20.2 ($CH_3$), 22.5 ($CH_3$), 22.8 ($CH_3$), 32.5 ($CH_2$), 32.8 ($CH_2$), 48.6 (C), 57.7 (C), 60.4 ($CH_2$), 69.5 ($CH_2$), 85.8 (C), 176.5 (C); (minor) 13.5 ($CH_3$)*, 14.0 ($CH_3$)*, 14.7 ($CH_3$)*, 17.2 ($CH_3$)*, 33.8 ($CH_2$)*, 34.3 ($CH_2$)*, 45.5 (C)*, 55.6 (C)*, 60.4 ($CH_2$)*, 77.6 ($CH_2$)*, 78.61 (C)*, 176.5 (C)* ppm; MS EI, *m*/*z* (relative intensity) 166 ($M^+$ − 64, 1), 141 (20), 125 (22), 116 (50), 98 (48), 85 (93), 69 (100), 57 (99); HRMS (EI) 253.1399 ($M^+$ + Na, $C_{12}H_{22}O_4Na$), calcd 253.1410. Anal. Calcd for $C_{12}H_{22}O_4$: C, 62.58; H, 9.63. Found: C, 62.88; H, 9.69.

**Reaction of 60 with $Cp_2TiCl$.** According to GP1, reaction of **60** (90 mg, 0.43 mmol) with $Cp_2TiCl$ followed by flash chromatography (hexane/ethyl acetate 40:60) furnished a diastereomeric mixture of ethyl 4-hydroxymethyl-2,4-dimethyl-5-oxohexanoate **65** (19 mg, 21%) in a ratio 12:1, as a viscous liquid: $^1$H NMR ($CDCl_3$) $\delta$ 1.11 (3H, s), 1.13 (3H, s), 1.18 (6H, d, $J$ = 7.0 Hz), 1.26 (3H, t, $J$ = 7.1 Hz), 1.27 (3H, t, $J$ = 7.1 Hz), 1.58 (4H, m), 2.15 (3H, s), 2.19 (3H, s), 2.48 (2H, m), 3.4−3.6 (4H, m), 4.17 (4H, m) ppm; $^{13}$C NMR ($CDCl_3$) $\delta$ 14.0 ($CH_3$), 14.2 ($CH_3$), 19.4 ($CH_3$), 19.6 ($CH_3$), 19.9 ($CH_3$), 20.2 ($CH_3$), 22.7 ($CH_3$), 26.0 ($CH_3$), 33.5 ($CH_2$), 35.4 (CH), 35.7 (CH), 38.0 ($CH_2$), 43.0 (C), 49.6 (C), 60.4 ($CH_2$), 60.7 ($CH_2$), 67.3 ($CH_2$), 69.2 ($CH_2$), 177.1 (C), 177.2 (C), 213.5 (C), 213.7 (C) ppm; MS (EI, *m*/*z*) 186 ($M^+$ − 30, 1), 140 (8), 102 (10), 83 (100), 69 (25), 56 (52); HRMS (ESI) 239.1276 ($M^+$ + Na, $C_{11}H_{20}O_4Na$), calcd 239.1259. Anal. Calcd for $C_{11}H_{20}O_4$: C, 61.09; H, 9.32. Found: C, 61.34; H, 9.16.

Ethyl 2-hydroxy-3-hydroxymethyl-1,2,3-trimethylcyclobutanecarboxylate **63** (32 mg, 35%) was obtained as a viscous oil: IR, $\nu$ 3414, 1707, 1027 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 1.26 (3H, t, $J$ = 7.2 Hz), 1.28 (3H, s), 1.33 (3H, s), 1.44 (3H, s), 2.24 (1H, s), 2.27 (1H, s), 3,41 (1H, d, $J$ = 10.8 Hz), 3.61 (1H, d, $J$ = 10.8 Hz), 4.14 (2H, q, $J$ = 7.2 Hz) ppm; $^{13}$C NMR ($CDCl_3$) $\delta$ 14.2 ($CH_3$), 19.4 ($CH_3$), 20.6 ($CH_3$), 21.4 ($CH_3$), 33.5 ($CH_2$), 43.5 (C), 49.6 (C), 60.4 ($CH_2$), 68.6 ($CH_2$), 76.2 (C), 175.71 (C) ppm; MS (EI, *m*/*z*) 141-($M^+$ − 75, 10), 102 (20), 83 (100), 69 (22), 56 (56); HRMS (ESI) 239.1264 ($M^+$ + Na, $C_{11}H_{20}O_4Na$), calcd 239.1254. Anal. Calcd for $C_{11}H_{20}O_4$: C, 61.09; H, 9.32. Found: C, 61.23; H, 9.35.

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**Supporting Information Available:** Preparation and characterization of epoxides, and NMR spectra of compounds **2**, **7**, **8**, **10**, **11**, **20**, **26**, **28**, **32**, **34**, **36**, **40**, **42**, **51**, **57**, **63**, and **65**. This material is available free of charge via the Internet at http://pubs.acs.org.

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