

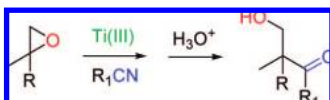
Titanocene-Promoted Intermolecular Couplings of Epoxides with Nitriles. An Easy Access to β -Hydroxyketones

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Received March 3, 2009



Radical couplings of epoxides and nitriles mediated by Cp_2TiCl provide a diastereoselective route to the synthesis of β -hydroxyketones. The conditions of this “aldol-like” reaction are mild enough to avoid the dehydration of the β -hydroxyketone. The scope of the coupling reaction with functionalized and tetrasubstituted epoxides has been studied. The radical character of the coupling reactions is demonstrated.

Introduction

The radical generation method based on titanocene-mediated opening of epoxides through single electron transfer introduced by Nugent and RajanBabu¹ and the catalytic version developed by Gansäuer and his group² have been the object of many interesting applications in synthesis.³ The main acceptors in all of these radical reactions are alkenes.

Although radical additions to polar multiple bonds such as a carbonyl group⁴ or a cyano group⁵ are in general unfavorable processes due to reversibility of the former and the slowness of the latter, our group has developed radical cyclizations, induced

by titanocene chloride, onto acceptors with polar multiple bonds such as aldehydes,⁶ ketones,⁶ esters,⁷ and nitriles.⁸ The products from these cyclizations are diols, hydroxyacetals, or hydroxyketones obtained in good yields from the corresponding epoxy derivatives. Thus, titanocene chloride has been used to broaden the range of useful radical traps; a recent mechanistic study⁹ of the cyclization of epoxy derivatives revealed the triple role of Ti(III): a radical initiator (homolytic cleavage of oxirane), a Lewis acid accelerator (coordination to CN or C=O), and a terminator (reduction of iminyl or alkoxy radicals). In a related cyclization of cyanoketones mediated by Cp_2TiPh reported by Itoh et al., the initial radical was generated from the carbonyl group, and the acceptor was the nitrile group.¹⁰

Recently, the group of Gansäuer has reported the catalytic radical cyclization of some epoxy derivatives.¹¹ They found that epoxy carbonyl compounds react with standard titanocene chlo-

(1) (a) Nugent, W. A.; RajanBabu, T. V. *J. Am. Chem. Soc.* **1988**, *110*, 8561. (b) RajanBabu, T. V.; Nugent, W. A. *J. Am. Chem. Soc.* **1994**, *116*, 986.

(2) (a) Gansäuer, A.; Pierobon, M.; Bluhm, H. *Angew. Chem., Int. Ed.* **1998**, *37*, 101. (b) Gansäuer, A.; Bluhm, H.; Pierobon, M. *J. Am. Chem. Soc.* **1998**, *120*, 12849.

(3) (a) Gansäuer, A.; Bluhm, H. *Chem. Rev.* **2000**, *100*, 2771. (b) Gansäuer, A.; Narayan, S. *Adv. Synth. Catal.* **2002**, *344*, 465. (c) Gansäuer, A.; Lauterbach, T.; Narayan, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 5556. (d) Cuerva, J. M.; Justicia, J.; Oller-López, J. L.; Oltra, J. E. *Top. Curr. Chem.* **2006**, *264*, 63. (e) Cuerva, J. M.; Justicia, J.; Oller-López, J. L.; Bazdi, B.; Oltra, J. E. *Mini Rev. Org. Chem.* **2006**, *3*, 23. (f) Barrero, A. F.; Quílez del Moral, J. F.; Sánchez, E. M.; Arteaga, J. F. *Eur. J. Org. Chem.* **2006**, 1627. (g) Gansäuer, A.; Justicia, J.; Fan, C.-A.; Worgull, D.; Piester, F. *Top. Curr. Chem.* **2007**, *279*, 25.

(4) (a) Kim, S. *Adv. Synth. Catal.* **2004**, *346*, 19–32, and references therein. (b) Curran, D. P. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, 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.

(5) (a) Fallis, A. G.; Brinza, I. M. *Tetrahedron* **1997**, *53*, 17543–17594, and references therein. (b) Beckwith, A. L. J.; O’Shea, D. M.; Westwood, S. W. *J. Am. Chem. Soc.* **1988**, *110*, 2565–2575. (c) Beckwith, A. L. J.; Hay, B. D. *J. Am. Chem. Soc.* **1989**, *111*, 230. (d) Beckwith, A. L. J.; Hay, B. D. *J. Am. Chem. Soc.* **1989**, *111*, 2674. (e) Curran, D. P.; Liu, W. *Synlett* **1999**, 117–119. (f) Bowman, W. R.; Bridge, C. F.; Brookes, P. *Tetrahedron Lett.* **2000**, *41*, 8989–8994. (g) Rychnovsky, S. D.; Swenson, S. S. *Tetrahedron* **1997**, *53*, 16489–16502. (h) Crich, D.; Bowers, A. A. *J. Org. Chem.* **2006**, *71*, 3452–3463.

(6) (a) Fernández-Mateos, A.; Martín de la Nava, E.; Pascual Coca, G.; Ramos Silva, A.; Rubio González, R. *Org. Lett.* **1999**, *1*, 607. (b) 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. For applications of this method to the synthesis of β -lactams, see: (c) Ruano, G.; Martiñez, J.; Grande, M.; Anaya, J. *J. Org. Chem.* **2003**, *68*, 2024–2027. For applications of this method to the synthesis of bioactive terpenoids see: (d) Bermejo, F. A.; Fernández-Mateos, A.; Marcos-Escribano, A.; Martín-Lago, R.; Mateos-Burón, L.; Rodríguez-López, M.; Rubio González, R. *Tetrahedron* **2006**, *62*, 8933–8942. (e) Martín-Rodríguez, M.; Galán-Fernández, R.; Marcos-Escribano, A.; Bermejo, F. A. *J. Org. Chem.* **2009**, *74*, 1798–1801.

(7) Fernández-Mateos, A.; Herrero Teijón, P.; Rabanedo Clemente, R.; Rubio González, R. *Tetrahedron Lett.* **2006**, *47*, 7755–7758.

(8) (a) Fernández-Mateos, A.; Mateos Burón, L.; Rabanedo Clemente, R.; Ramos Silva, A. I.; Rubio González, R. *Synlett* **2004**, 1011. For a radical cascade polycyclization terminated on nitrile, see: (b) Fernández-Mateos, A.; Herrero Teijón, P.; Rabanedo Clemente, R.; Rubio González, R.; Sanz González, F. *Synlett* **2007**, 2718. For applications of this method to the synthesis of β -lactams, see: (c) Monleón, L. M.; Grande, M.; Anaya, J. *Tetrahedron* **2007**, *63*, 3017–3025. (d) Monleón, L. M.; Grande, M.; Anaya, J. *Synlett* **2007**, 1243–1246.

(9) Fernández-Mateos, A.; Herrero Teijón, P.; Mateos Burón, L.; Rabanedo Clemente, R.; Rubio González, R. *J. Org. Chem.* **2007**, *72*, 9973.

ride, but that a bulkier catalyst such as $(c\text{-C}_6\text{H}_{11}\text{C}_5\text{H}_4)_2\text{TiCl}$ was needed for epoxynitriles.

Epoxynitrile cyclization mediated by titanocene chloride, in both a stoichiometric and catalytic way, is a powerful route to β -hydroxycycloalkanones. Taking this reaction as a starting point, here we investigated the feasibility of the intermolecular reaction between epoxides and nitriles mediated by titanocene chloride, which would lead to the synthesis of aldols. To the best of our knowledge, little attention has been devoted to the topic apart from the paper published by Shono et al.¹² on intermolecular radical additions to nitriles. In that work the radicals were generated electrochemically from ketones.

Results and Discussion

Here we report our findings on the intermolecular reaction between epoxides and nitriles mediated by titanocene chloride (Scheme 1).

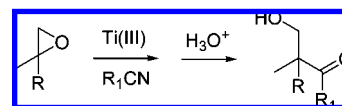
Reactions were carried out using 2 equiv of titanocene dichloride and 5 or 10 equiv of the nitrile acceptor. In almost all cases, the formation of the aldol products was observed. The regiochemical outcome of the reaction is in agreement with what has been previously observed with nonsymmetrical oxiranes.¹³ Epoxide opening is directed by nonbonding interactions during electron transfer.

The reaction takes place in two steps (Scheme 2). The initial step is based on the well-documented titanocene-mediated opening of epoxides, which affords the β -alkoxy radical intermediate (A) that further reacts with $\text{Cp}_2\text{Ti}(\text{CN})_2$ -coordinated nitrile^{8–10} to give B. The initial radical (A) could follow other alternative pathways, such as reacting with Cp_2TiCl_2 , which abstracts a hydrogen from the methyl group^{6a,9,14} when $\text{R} = \text{Me}$ to give C, or by coupling¹ when $\text{R} = \text{H}$ to give D. This coupling intermediate could evolve by elimination of $(\text{Cp}_2\text{TiO})_2^1$ to afford E, or after hydrolysis by hydrogen interchange¹ to give F.

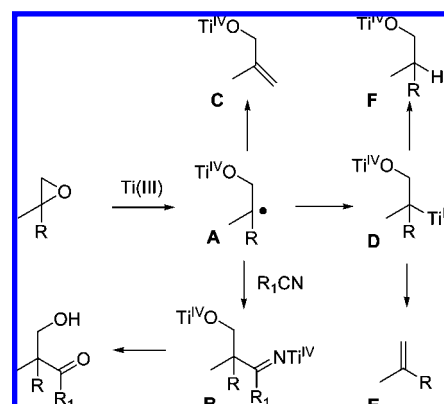
We carried out the work with a series of cyclic and acyclic oxiranes and several nitriles. Our results are summarized in Table 1.

After hydrolysis, the reaction of cyclohexene oxide **1** with acetonitrile mediated by titanocene chloride affords a diastereomeric mixture of the aldols **2a** (*trans*) and **2b** (*cis*) at a 77:23 ratio. This result is in agreement with previous intermolecular additions of cyclohexyl radicals to activated alkenes^{1,15} or nitriles¹² in which the reaction took place preferentially at the less hindered side to give the *trans* product. The addition of benzonitrile occurs in a completely stereoselective manner to give only the *trans*-aldol **3**. The reaction with other nitriles such as methyl cyanoacetate or 1-cyclopentylacetonitrile also gives the coupling products **5a/b** and **4a/b**, respectively. The best couplings yields were obtained for acetonitrile. The reaction of methylcyclohexene oxide **6** with acetonitrile and benzonitrile afforded results similar to those described previously. The *trans*/

SCHEME 1. Coupling of Epoxides with Nitriles Induced by Titanocene



SCHEME 2. Reaction Pathways



cis diastereoselectivity for the addition of acetonitrile in this case was 86:14. The coupling reactions between the cyclopentene oxide **9** and nitriles were completely diastereoselective; only the *trans*-aldols were obtained in both examples (entries 7 and 8). Norbornene oxide **12** gave a 54:46 ratio of *trans/cis* aldols with acetonitrile (entry 9). The norbornyl radical in this example is attacked almost equally from both faces. The intrinsic stereochemical outcome observed for norbornyl radicals is *exo* selectivity, as reported in Giese's seminal studies¹⁶ and subsequent work by Gansäuer,^{15a} who for the reaction of norbornene oxide and acrylate as an acceptor, mediated by titanocene chloride, found an *exo/endo* ratio of 82:18. In the same work^{15a} Gansäuer reported that the bulky $(t\text{-BuCp})_2\text{TiCl}$ catalyst changed the *exo/endo* ratio to 53:47. The reaction of **12** with benzonitrile gave a 50:50 ratio of *trans/cis* aldols (entry 10). The terminal epoxides **15** and **18** gave the expected aldols in similar yields as the previous epoxides. Finally, the reaction of the tetrasubstituted epoxide, terpinolene oxide, **21**, gave only the reduction product α -terpineol **22** regioselectively. The lack of coupling products in the latter reaction means that it is sensitive to steric factors.

The scope and limitations of the coupling reaction shown above were studied with a new series of *functionalized* epoxides, which could react with titanocene chloride by alternative competing pathways.

The reaction of α,β -epoxyketones with Cp_2TiCl in THF/MeOH affords β -hydroxyketones in good yields.¹⁷ In the postulated reaction mechanism, a single electron transfer from Cp_2TiCl to the oxirane generates the radical intermediate, which upon reaction with Cp_2TiCl_2 produces the enolate.

(10) (a) Yamamoto, Y.; Matsumi, D.; Hattori, R.; Itoh, K. *J. Org. Chem.* **1999**, *64*, 3224–3229. See the Ti(III)–nitrile complex in (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.

(11) Gansäuer, A.; Piestert, F.; Huth, I.; Lauterbach, T. *Synthesis* **2008**, 3509.

(12) Shono, T.; Kise, N.; Fujimoto, T.; Tominaga, N.; Morita, H. *J. Org. Chem.* **1992**, *57*, 7175.

(13) (a) Daasbjerg, K.; Svith, H.; Grimme, S.; Gerenkamp, M.; Mück-Lichtenfeld, C.; Gansäuer, A.; Barchuk, A.; Keller, F. *Angew. Chem., Int. Ed.* **2006**, *45*, 2041. (b) Gansäuer, A.; Barchuk, A.; Keller, F.; Schmitt, M.; Grimme, S.; Gerenkamp, M.; Mück-Lichtenfeld, C.; Daasbjerg, K.; Svith, H. *J. Am. Chem. Soc.* **2007**, *129*, 1359–1371.


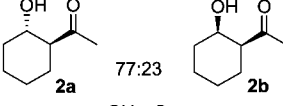
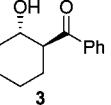

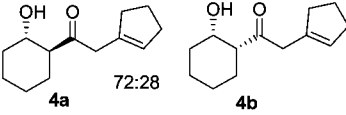

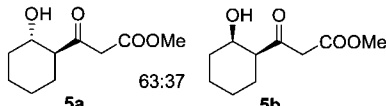
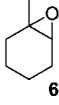
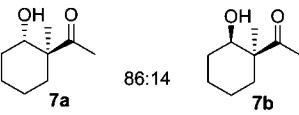
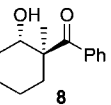

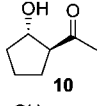
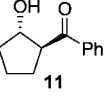

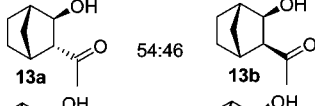
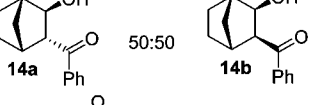
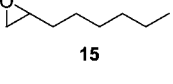
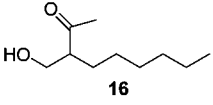
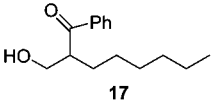
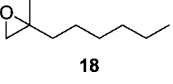
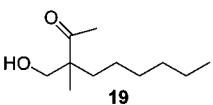
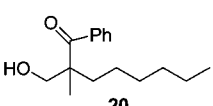
(14) (a) Barrero, A. F.; Oltra, J. E.; Cuerva, J. M.; Rosales, A. *J. Org. Chem.* **2002**, *67*, 2566–2571. (b) Bermejo, F.; Sandoval, C. *J. Org. Chem.* **2004**, *69*, 5275–5280. (c) Cuerva, J. M.; Campaña, A. G.; Justicia, J.; Rosales, A.; Oller-Lopez, J. L.; Robles, R.; Cárdenas, D. J.; Buñuel, E.; Enrique Oltra, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 5522–5526.

(15) (a) Gansäuer, A.; Bluhm, H.; Rinker, B.; Narayan, S.; Schick, M.; Lauterbach, T.; Pierobon, M. *Chem.–Eur. J.* **2003**, *9*, 531–542. (b) Curran, D. P.; Porter, N. A.; Giese, B. *Stereochemistry of Radical Reactions*; VCH: Weinheim, 1996; pp 128–135.

(16) Giese, B.; Heuck, K.; Lenhardt, H.; Lüning, U. *Chem. Ber.* **1984**, *117*, 2132.

(17) Hardouin, C.; Chevallier, F.; Rousseau, B.; Doris, E. *J. Org. Chem.* **2001**, *66*, 1046–1048.

TABLE 1. Cp_2TiCl -Mediated Coupling of Epoxides and Nitriles

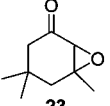
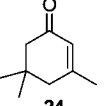
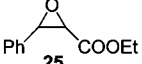
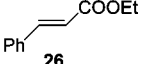

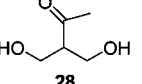
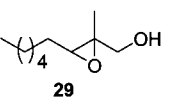
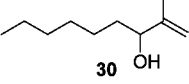

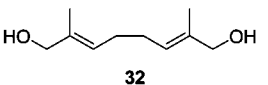

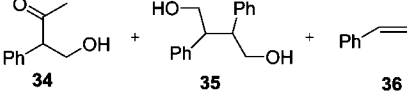
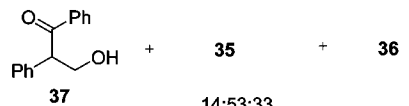

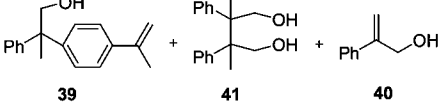
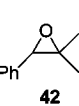
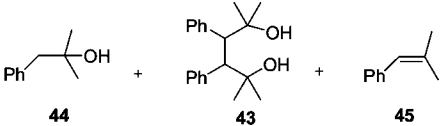
Entry	Epoxide	Nitrile	Aldol Products	Yield (%)
1		CH_3CN	 77:23	73
2	1	PhCN		65
3	1		 72:28	41
4	1		 63:37	53
5		CH_3CN	 86:14	61
6	6	PhCN		62
7		CH_3CN		60
8	9	PhCN		58
9		CH_3CN	 54:46	62
10	12	PhCN	 50:50	42
11		CH_3CN		76
12	15	PhCN		70
13		CH_3CN		46
14	18	PhCN		36

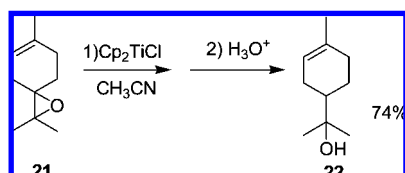
Subsequent protonation by methanol affords the β -hydroxyketone¹⁷ (Scheme 4).

The isophorone oxide **23** with acetonitrile (10 equiv) and titanocene chloride (2 equiv) gave only the deoxygenation product isophorone **24** (Table 2). The reaction was carried out under several conditions: reagent was added to a solution of the substrate and vice versa; acetonitrile was added to a solution

of the reagent followed by epoxide, and with different equivalents of the nitrile. Coupling with other acceptors such as acrylonitrile or ethyl acrylate was also attempted. The product was always isophorone **24**, in good yield. This result indicates that the initial stabilized radical generated by the opening of the oxirane is trapped faster by the Cp_2TiCl than the alternative acceptors. In the absence of a proton donor, deoxygenation¹

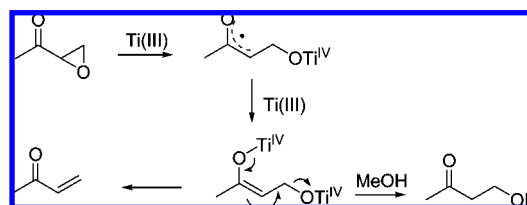
TABLE 2. Cp₂TiCl-Mediated Coupling of Functionalized Epoxides and Nitriles

Entry	Epoxide	Nitrile	Products	Yield(%)
1		CH ₃ CN		88
2		CH ₃ CN		73
3		CH ₃ CN		59
4		CH ₃ CN		70
5		CH ₃ CN		99
6		CH ₃ CN		95
			9:50:41	
7	33	PhCN		90
			14:53:33	
8		CH ₃ CN		69
			18:62:20	
9		CH ₃ CN		72
			21:50:29	

SCHEME 3. Reaction of Terpineol with Cp₂TiCl and CH₃CN

was the predominant reaction (Scheme 4). Similar results were found with the epoxide **25** (Table 2, entry 2).

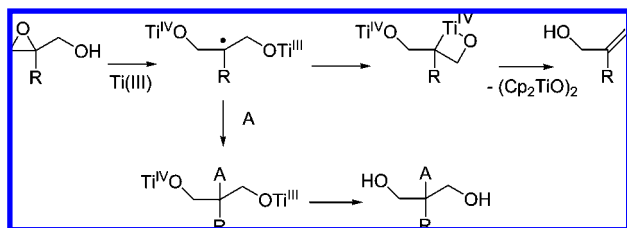
It is known that in the absence of H-atom donors 2,3-epoxyalcohols react with titanocene chloride to give allylic alcohols regioselectively¹⁸ (Scheme 5). This dehydroxylation has been explained as occurring through a radical intermediate,

SCHEME 4. Deoxygenation of α,β -Epoxyketones

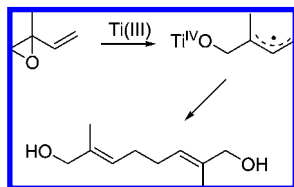
which could be trapped with different kinds of acceptors, such as hydrogen^{1b,19a,b} (from 1,4-cyclohexadiene), acrylates, or acrylonitrile.^{19c} In these cases it is clear that acceptor trapping is faster than the dehydroxylation step.

The epoxyalcohols **27** and **29** afforded opposite results (Table 2, entries 3 and 4), whereas the 2,3-epoxypropanol **27** gave only

SCHEME 5. Reaction Pathways of 2,3-Epoxyalcohols



SCHEME 6. Homocoupling of Vinyl Epoxides



the aldol coupling product **28** in good yield. The related epoxyalcohol **29** gave the dehydroxylation product **30**. These results can be explained by the different reaction rates of the radicals generated from **27** and **29** with the nitrile acceptor. The secondary radical arising from **27** is trapped quickly by the nitrile, but the tertiary radical from **29** is not. This means that dehydroxylation is faster than nitrile trapping when the radical arising from 2,3-epoxyalcohols is tertiary. We have previously shown²⁰ that the dehydroxylation rate constant for these compounds is higher than $1.1 \times 10^7 \text{ s}^{-1}$.

Radicals derived from the reaction of vinyl epoxides with Cp_2TiCl undergo homocoupling,^{21a} deoxygenation,^{21b,c} or reduction.^{21b,c} Homocoupling has been observed for catalytic conditions^{21a} and seems to be general (Scheme 6); the deoxygenation occurs with 2 equiv of Cp_2TiCl and has been observed for terminal alkenes,^{21b,c} while reduction has been reported for internal alkenes.^{21b,c}

The reaction of vinyl epoxide **31** with Cp_2TiCl (2.2 equiv) and acetonitrile (10 equiv) afforded quantitatively the homocoupling product **32** rather than the addition on the nitrile. Attempts to trap the allyl radical intermediate with methyl acrylate were fruitless. The same happened with acrylonitrile, as has been reported earlier.^{21a}

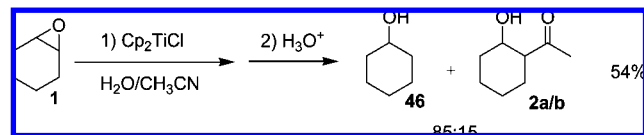
These results mean that in this case radical homocoupling is a very fast reaction, with a rate constant higher than $10^7 \text{ M}^{-1}\text{s}^{-1}$, since it is known that intermolecular addition of radicals to acrylates or acrylonitrile²² are in the order of $k = 10^6 \text{ M}^{-1}\text{s}^{-1}$.

Styrene oxide **33** undergoes homocoupling, addition, and deoxygenation processes in the reaction with Cp_2TiCl (2.2 equiv) and acetonitrile (10 equiv). The initial benzyl radical reacts more

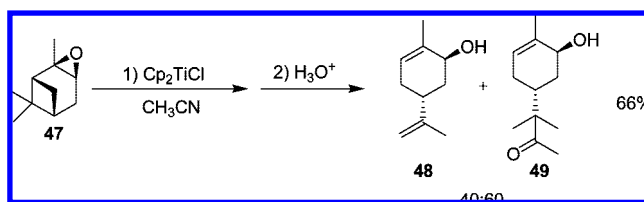
TABLE 3. Influence of Nitrile/Epoxyde Ratio

entry	epoxide	MeCN equiv	aldol products
1	1	10	2a 57%; 2b 17%
2	1	5	2a 60%; 2b 11%
3	1	2.5	2a 20%; 2b 1.9%
4	1	1	2a 8.6%; 2b 2.4%

SCHEME 7. Competition between Hydrogen Transfer and Coupling



SCHEME 8. Reaction of Pinene Oxide and Acetonitrile with Titanocene



slowly²³ than the allyl radical to give three kinds of products, among which is the aldol resulting from the addition of the benzyl radical to acetonitrile. A similar result was found when benzonitrile was used as an acceptor. The methyl homologue **38** did not afford addition products with acetonitrile, but two kinds of homocoupling products, **39** and **41**, and a deoxygenation product, **40**. This result must be due to steric factors. Finally, the dimethyl styrene oxide **42** was assayed to observe the regioselectivity on the oxirane cleavage (benzyl versus tertiary radical). This time, no addition products were obtained; instead homocoupling, reduction, and deoxygenation products were observed. The benzyl radical seems to be the only one generated. The addition of this radical to nitrile failed presumably as a result of steric requirements.

A series of reactions with different amounts of acetonitrile were performed to check the influence of the radical acceptor concentration on product yield (Table 3). As can be seen, the yield of aldol products was similar for 10 or 5 equiv of acetonitrile; below these amounts, the reaction yield decreased. Diastereoselectivity was better for 2.5 equiv (entry 3).

It turned out that all above-reported reactions have a radical character. The aldol product stereochemistry shown above is a proof of this character. Indeed, the following three experiments corroborate this hypothesis. The reaction of cyclohexene oxide with titanocene chloride and a mixture of 5 equiv of acetonitrile and 5 equiv of water gave a mixture of cyclohexanol **46** and the aldol **2** at a ratio of 85:15, respectively. This means that the addition of the radical to acetonitrile is nearly five times slower than hydrogen transfer from the $\text{Ti}^{\text{III}}\text{-H}_2\text{O}$ complex.²⁴

Another fact in favor of the radical mechanism is the reaction of pinene oxide **47** with Cp_2TiCl and acetonitrile. The products obtained were the *trans*-carveol **48** and the hydroxyketone **49**, at a ratio of 40:60. This result could be explained in terms of the homolytic cleavage of oxirane, further cyclobutane open-

(18) (a) RajanBabu, T. V.; Nugent, W. A.; Beattic, M. S. *J. Am. Chem. Soc.* **1990**, *112*, 6408–6409. (b) Yadav, J. S.; Shekharam, T.; Gadgil, V. R. *J. Chem. Soc., Chem. Commun.* **1990**, 843.

(19) (a) Chakraborty, T. K.; Das, S. *Tetrahedron Lett.* **2002**, *43*, 2313–2315. (b) Chakraborty, T. K.; Dutta, S. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1257–1259. (c) Chakraborty, T. K.; Samanta, R.; Das, S. *J. Org. Chem.* **2006**, *71*, 3321–3324, and references therein.

(20) Fernández-Mateos, A.; Herrero Teijón, P.; Rabanedo Clemente, R.; Rubio González, R. *Synlett* **2008**, 3208–3212.

(21) (a) Barrero, A. F.; Quílez del Moral, J. F.; Sánchez, E. M.; Arteaga, J. F. *Org. Lett.* **2006**, *8*, 669–672. (b) Yadav, J. S.; Shekharam, T.; Srinivas, D. *Tetrahedron Lett.* **1992**, *33*, 7973–7976. (c) Yadav, J. S.; Shekharam, T.; Gadgil, V. R. *J. Chem. Soc., Chem. Commun.* **1990**, *11*, 843–844. (d) The dimerization of phenyl-substituted radicals is unique for epoxide opening but has been observed for oxetane opening; Gansäuer, A.; Ndene, N.; Lauterbach, T.; Justicia, J.; Winkler, I.; Mück-Lichtenfeld, C.; Grimme, S. *Tetrahedron* **2008**, *64*, 11839–11845.

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

(23) Newcomb, M. *Tetrahedron* **1993**, *49*, 1167.

(24) Jin, J.; Newcomb, M. *J. Org. Chem.* **2008**, *73*, 7901–7905. The rate constant for hydrogen atom transfer reaction of the water complex $\text{Cp}_2\text{Ti}^{\text{III}}\text{Cl-H}_2\text{O}$ to alkyl radicals using indirect kinetic methods is $k_{25} = 1.0 \times 10^5 \text{ M}^{-1}\text{s}^{-1}$.

ing,²⁰ and trapping of the tertiary radical by acetonitrile. The carveol product is formed by hydrogen elimination from the tertiary radical. This means that the radical addition to acetonitrile is slower than cyclobutane radical cleavage^{20,25} and faster than hydrogen elimination. The rate constant of the cyclobutane radical cleavage in pinene derivatives²⁰ by the radical clock method was $1.1 \times 10^7 \text{ s}^{-1}$.

Finally, we investigated the catalytic version of the reaction using the conditions reported by Gansäuer.² We found that the reaction of cyclohexene oxide with 5 equiv of acetonitrile and 0.5 equiv of Cp_2TiCl gave a mixture of aldols **2a** and **2b** at a ratio of 76:24 and a 21% yield. For 0.2 equiv of Cp_2TiCl the ratio of **2a** and **2b** was 75:25 and the yield was 4%. For 0.1 equiv of Cp_2TiCl no aldol products were observed. This result also demonstrates the radical character of the reaction, because in the catalytic conditions the double role of titanocene (coordination to CN and reduction of iminyl radicals) seems less likely due to the relatively low catalyst loading.

Experimental Section

General Procedure 1 (GP1). Reaction of epoxides and nitriles with Cp_2TiCl . A mixture of Cp_2TiCl_2 (2.20 mmol) and Zn (6.60 equiv) in strictly deoxygenated THF (10 mL) was stirred at room temperature until the red solution turned green. In a separate flask, the epoxy compound (1 mmol) and the nitrile were dissolved in strictly deoxygenated THF (10 mL). The green Ti(III) solution was slowly added via cannula to the epoxide and nitrile solution. After 30 min, an excess of saturated NaH_2PO_4 was added, and the mixture was stirred for 20 min. The mixture was filtered to remove insoluble titanium salts. 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 $\text{Cp}_2\text{TiCl}/\text{CH}_3\text{CN}$.** According to GP1, reaction of **1** (100 mg, 1.02 mmol) and CH_3CN (0.27 mL, 5.09 mmol) with Cp_2TiCl followed by flash chromatography (hexane 7:3 diethyl ether) furnished **2a** (81 mg, 56%) and **2b** (30 mg, 21%).

Data for *trans* isomer **2a**: IR, ν 3395, 2975, 1701, 1430, 1059 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.20 (4H, m), 1.72 (2H, m), 1.93 (2H, m), 2.15 (3H, s), 2.34 (1H, m), 2.83 (1H, bs), 3.75 (1H, m) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 24.3 (CH_2), 25.2 (CH_2), 27.9 (CH_2), 29.0 (CH_3), 33.7 (CH_2), 58.8 (CH), 70.6 (CH), 212.8 (C) ppm; MS EI, *m/z* (relative intensity) 124 ($\text{M}^+ - 18$, 3), 81 (45), 71 (100), 55 (38); HRMS (ESI) 165.0894 ($\text{M}^+ + \text{Na}$, $\text{C}_8\text{H}_{14}\text{O}_2\text{Na}$), calcd 165.0886. Anal. Calcd for $\text{C}_8\text{H}_{14}\text{O}_2$: C, 67.57; H, 9.92. Found: C, 67.67; H, 9.94.

Data for *cis* isomer **2b**: IR, ν 3427, 2970, 1698, 1434, 1062 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.1–2.0 (8H, m), 2.18 (3H, s), 2.46 (1H, m), 3.18 (1H, bs), 4.20 (1H, m) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 19.7 (CH_2), 23.3 (CH_2), 25.3 (CH_2), 28.7 (CH_3), 31.8 (CH_2), 53.9 (CH), 66.2 (CH), 213.9 (C) ppm; MS EI, *m/z* (relative intensity) 124 ($\text{M}^+ - 18$, 2), 81 (42), 71 (100), 55 (22); HRMS (ESI) 165.0891 ($\text{M}^+ + \text{Na}$, $\text{C}_8\text{H}_{14}\text{O}_2\text{Na}$), calcd 165.0886. Anal. Calcd for $\text{C}_8\text{H}_{14}\text{O}_2$: C, 67.57; H, 9.92. Found: C, 67.64; H, 9.95.

Reaction of **9 with $\text{Cp}_2\text{TiCl}/\text{PhCN}$.** According to GP1, reaction of **9** (100 mg, 1.19 mmol) and PhCN (1.21 mL, 11.90 mmol) with Cp_2TiCl followed by flash chromatography (hexane 7:3 diethyl ether) furnished **11** (131 mg, 58%) as a colorless oil: IR, ν 3401, 2948, 1669, 1361, 1229, 1084, 995 cm^{-1} ; ^1H NMR (400 MHz,

CDCl_3) δ 1.7–2.2 (6H, m), 3.69 (1H, m), 4.61 (1H, q, $J = 5.2$ Hz), 7.4–7.6 (3H, m), 8.0–8.1 (2H, m) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 22.8 (CH_2), 28.7 (CH_2), 34.9 (CH_2), 55.2 (CH), 75.8 (CH), 128.5 (3CH), 133.1 (2CH), 136.6 (C), 201.9 (C) ppm; MS EI, *m/z* (relative intensity) 172 ($\text{M}^+ - 18$, 31), 148 (1), 144 (3), 133 (13), 105 (100), 77 (91), 51 (36); HRMS (ESI) 213.0884 ($\text{M}^+ + \text{Na}$, $\text{C}_{12}\text{H}_{14}\text{O}_2\text{Na}$), calcd 213.0886. Anal. Calcd for $\text{C}_{12}\text{H}_{14}\text{O}_2$: C, 75.76; H, 7.42. Found: C, 75.87; H, 7.44.

Reaction of **15 with $\text{Cp}_2\text{TiCl}/\text{CH}_3\text{CN}$.** According to GP1, reaction of **15** (100 mg, 0.78 mmol) and CH_3CN (0.40 mL, 7.80 mmol) with Cp_2TiCl followed by flash chromatography (hexane 6:4 diethyl ether) furnished **16** (101 mg, 76%); IR, ν 3408, 2941, 1701, 1462, 1361, 1191, 1046 cm^{-1} ; ^1H NMR (200 MHz, CDCl_3) δ 0.86 (3H, t, $J = 6.8$ Hz), 1.2–1.6 (10H, m), 2.18 (3H, s), 2.67 (1H, m), 3.71 (2H, m) ppm; ^{13}C NMR (50 MHz, CDCl_3) δ 14.2 (CH_3), 22.7 (CH_2), 27.4 (CH_2), 28.2 (CH_2), 29.5 (CH_2), 29.9 (CH_3), 31.8 (CH_2), 54.7 (CH), 62.9 (CH_2), 213.3 (C) ppm; MS EI, *m/z* (relative intensity) 139 ($\text{M}^+ - 33$, 1), 125 (1), 111 (2), 97 (2), 88 (91), 70 (88), 55 (100); HRMS (ESI) 195.1343 ($\text{M}^+ + \text{Na}$, $\text{C}_{10}\text{H}_{20}\text{O}_2\text{Na}$), calcd 195.1356. Anal. Calcd for $\text{C}_{10}\text{H}_{20}\text{O}_2$: C, 69.72; H, 11.70. Found: C, 69.84; H, 11.73.

Reaction of **27 with $\text{Cp}_2\text{TiCl}/\text{CH}_3\text{CN}$.** According to GP1, reaction of **27** (99 mg, 1.35 mmol) and CH_3CN (0.71 mL, 13.51 mmol) with Cp_2TiCl followed by flash chromatography (hexane 4:6 diethyl ether) furnished **28** (94 mg, 59%); IR, ν 3382, 2929, 1695, 1443, 1096 cm^{-1} ; ^1H NMR (200 MHz, CDCl_3) δ 2.27 (3H, s), 2.75 (1H, t, $J = 4.6$ Hz), 3.97 (4H, dq, $J_1 = 4.6$ Hz, $J_2 = 7.4$ Hz) ppm; ^{13}C NMR (50 MHz, CDCl_3) δ 29.3 (CH_3), 55.5 (CH), 61.9 (2 CH_2), 210.6 (C) ppm; HRMS (ESI) 141.0528 ($\text{M}^+ + \text{Na}$, $\text{C}_5\text{H}_{10}\text{O}_3\text{Na}$), calcd 141.0528. Anal. Calcd for $\text{C}_5\text{H}_{10}\text{O}_3$: C, 50.84; H, 8.53. Found: C, 50.91; H, 8.52.

Conclusion

The titanocene-promoted intermolecular coupling of epoxides with nitriles was successful in providing easy access to β -hydroxyketones diastereoselectively. The coordination of Cp_2TiCl to the cyano group plays a key role in the reaction addressed here. As a result, the LUMO of the cyano group is lowered, and radical coupling proceeds irreversibly without the formation of unstable iminyl radical intermediates. In this situation, a low concentration of the Ti(III) reagent is unfavorable. An excess of the nitrile is required for better yields of the coupling products. Functionalized epoxides such as epoxyketones, epoxyalcohols, vinyloxyepoxides, aryloxyepoxides, and tetra-substituted epoxides do not generally give addition products with nitriles because of alternative faster radical reactions or steric factors. Several proofs of the reactions' radical mechanism are given.

Acknowledgment. Financial support for this work from the Ministerio de Ciencia y Tecnología of Spain (CTQ2005-05026/BQU) and the Junta de Castilla y León (SA079A06) is gratefully acknowledged. We also thank the Universidad de Salamanca for the fellowship to P.H.T.

Supporting Information Available: Experimental procedures and copies of ^1H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

JO900479V

(25) (a) Kang, Y. H.; Kice, J. L. *J. Org. Chem.* **1984**, *49*, 1507–1511. (b) Kenney, R. L.; Fisher, G. S. *J. Org. Chem.* **1974**, *39*, 682–686.