The Cp_2TiPh-Mediated Reductive Radical Cyclization of Cyanoketones and Related Reactions. Efficient Trapping of Ketyl Radicals by Cp_2TiPh-Coordinated Polar Multiple Bonds

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The reductive radical cyclization of cyanoketones was achieved using Cp_2TiPh. The Ti(III) reagent was prepared by the sequential addition of *i*-PrMgCl and PhMgBr to commercial Cp_2TiCl_2 in this order and used effectively without isolation. The cyclization of the γ- and δ-cyanoketones was performed in toluene at ambient temperature for several hours to give α-hydroxycyclopentanones and hexanones in moderate to good yields, respectively. The titanium reagent independently coordinates to both the carbonyl and cyano termini. As a result of lowering the LUMO of the cyano group upon coordination of the Ti(III) species, the irreversible cyclization successfully proceeds without formation of the unstable iminyl radical intermediate. The ester group can also be activated by the coordination of Cp_2TiPh, and aromatic ketones with an ester group at the γ position are cyclized to give the corresponding α-hydroxyketones.

Introduction

Radical additions to nonpolar C−C multiple bonds have been extensively employed as one of the commonest methods for making C−C bonds.[1] Especially, radical cyclizations has been elegantly applied to the synthesis of complex natural products.[2] On the other hand, radical additions to polar multiple bonds such as a carbonyl group or a cyano group are not generally efficient because they generate unfavorable alkoxy or iminyl radicals.[1] There has been a series of available kinetic data for the 5-exo radical cyclizations. They indicate such polar bonds are quite inefficient as a radical acceptor. As shown in Figure 1, the rate of β-scission of an alkoxy radical intermediate **D** [4.7×10^8 s^{-1} (25 °C), **D** → **C**] is about 500 times faster than that of the 5-exo cyclization of **C** [8.7×10^5 (25 °C), **C** → **D**]. That is why the 5-exo cyclization of the 5-oxa-5-hexenyl radical **C** is not general, although the cyclization is slightly faster compared to that of the parent 5-hexenyl radical **A**. As for the cyano group, cyclization itself is 25 times slower [4×10^3 s^{-1} (25 °C), **G** → **H**] than that of the corresponding 5-hexynyl radical **E** [1×10^5 s^{-1} (25 °C), **E** → **F**]. Despite these above facts, radical addition to polar multiple bonds might be successful if the resulting unstable radical intermediates are effectively scavenged. With this in mind, we developed a Ti(III)-mediated reductive coupling of cyanoketones and ketoesters leading to α-hydroxycycloalkanones, in which the Ti(III) complex, Cp_2TiPh, coordinates to a cyano group or an ester carbonyl group so that the

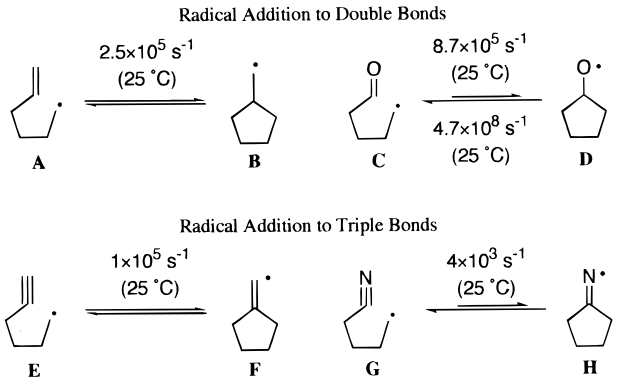

Figure 1. Rate constants for 5-exo radical cyclizations.

induced-titanium(IV)-substituted ketyl radical efficiently cyclizes to the Ti(III)-coordinated polar multiple bonds without formation of the undesirable iminyl or alkoxy radical intermediates (Scheme 1). In addition, coordination of the Lewis acidic Ti(III) species might lower the LUMO of these acceptors and increase their trapping ability of ketyl radicals. Herein, we report the full details of our study on the Cp_2TiPh-mediated cyanoketone cyclization and related reactions with ester carbonyl activation.[3]

Results and Discussion

Reduction of Nitriles by Titanocene(III) Complexes. Titanocene(III) reagents have received much attention as an efficient one-electron reducing reagent in organic synthesis.[4] For example, Cp_2TiCl induces the diastereoselective pinacol coupling of aromatic and α,β-unsaturated aldehydes.[4a−f] The Ti(III) reagent also promotes ring opening of epoxides to generate β-alkoxy radicals, which are utilized in the cyclization of epoxyolefins,[4i,l] the intermolecular addition of epoxides to

(1) (a) Beckwith, A. L. J.; Ingold, K. U. In *Rearrangements in Ground and Excited States*; de Mayo, P., Ed.; Academic Press: New York, 1980; Vol. 1, Chapter 4. (b) Surzur, J.-M. In *Reactive Intermediates*; Abramovitch, R. A., Ed.; Plenum Press: New York, 1982; Vol. 2, Chapter 3. (c) Curran, D. P. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, U.K., 1991; Vol. 4, Chapters 4.2.2 and 4.2.3. (d) Fossey, J.; Lefort, D.; Sorba, J. *Free Radicals in Organic Chemistry*; John Wiley & Sons: New York, 1995. (e) Curran, D. P. *Synthesis* **1988**, 417, 489. (f) Curran, D. P.; Porter, N. A.; Giese, B. *Stereochemistry of Radical Reactions*; VCH: Weinheim, 1995.

(2) (a) Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1237. (b) Koert, U. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 405.

(3) Yamamoto, Y.; Matsumi, D.; Itoh, K. *Chem. Commun.* **1998**, 875.

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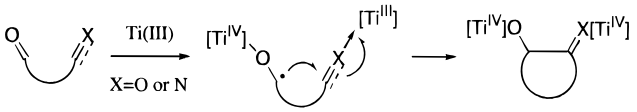
Scheme 1



Scheme 2

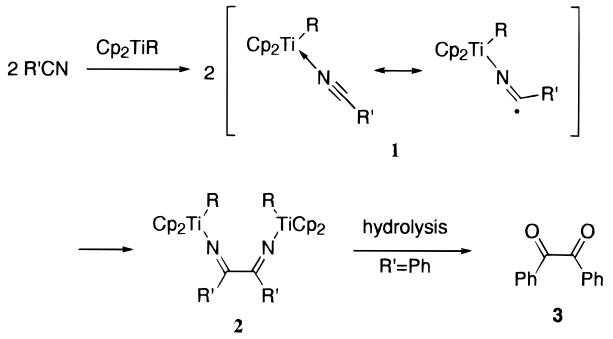


Table 1. Reaction of Nitriles and an Ester with Titanium(III) Reagents

entry	nitriles	Ti(III)	reaction time (h)	products (yield, %)
1	PhCN	Cp_2TiPh	1	PhCOCOPh (94%)
2	PhCN	Cp_2TiCl	overnight	no reaction
3	PhCN	Cp_2TiBn	overnight	PhCOCOPh (20%)
4	*n*-PrCN	Cp_2TiPh	1	*n*-PrCOPh (35%)
5	EtO_2CCH_2CN	Cp_2TiPh	1	Et_2OCCH_2COPh (30%)
6	$PhCH_2CN$	Cp_2TiPh	1	$PhCH_2COPh$ (24%)
7	$PhCH_2CO_2Me$	Cp_2TiPh	1	$PhCH_2COPh$ (23%)

activated olefins,[4j,l] and the stereoselective conversion of epoxy alcohols into diols.[4m,n] In 1977, Teuben et al. reported that Cp_2TiCl and related Cp_2TiR (R = Ar, CH_2-Ph) reacted with cyanides to produce titaniumdiimine complexes **2** via the *N*-titanaimidoyl radicals **1** (Scheme 2).[4g,h] We envisaged that if the imidoyl radical intermediate **1** can be applied to the radical addition chemistry, unprecedented transformations of nitriles to carbonyl compounds could be developed.[5] Therefore, at the outset of our study, we examined the generation of imidoyl radicals from a variety of nitriles by the one-electron reduction with several titanocene(III) reagents as summarized in Table 1. According to the reported procedures,[4g,h] Cp_2TiPh was prepared and used for further

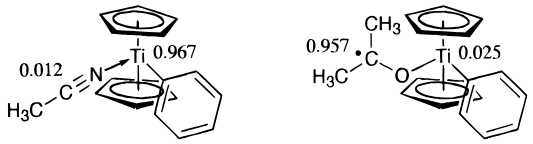
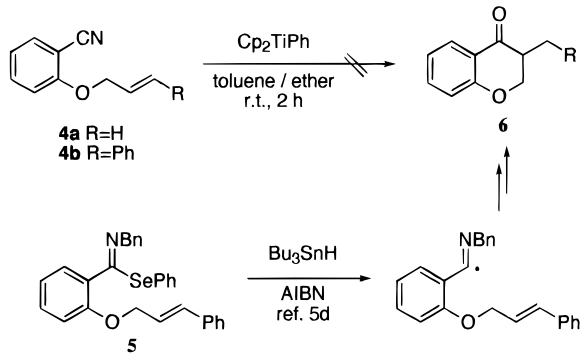


Figure 2. Spin densities of Cp_2TiPh-coordinated acetonitrile and acetone.

Scheme 3



reactions without isolation (see the Experimental Section). Benzonitrile reacted with 1.5 equiv[6] of Cp_2TiPh followed by acid hydrolysis to give the expected coupling product **3** in 94% yield (Table 1, entry 1). The phenyl–titanium bond is essential, since the coupling reaction did not take place under the same conditions using the analogous Cp_2TiCl generated by the reduction of Cp_2TiCl_2 with *i*-PrMgCl in sharp contrast to the report (Table 1, entry 2).[4g,h] An alkyl complex, Cp_2TiCH_2Ph, showed some reactivity but required a prolonged reaction time, and the yield of the coupling product was much lower (Table 1, entry 3). In addition, other aliphatic nitriles (*n*-PrCN, EtO_2CCH_2CN, $PhCH_2CN$) gave no coupling products at all. Phenylation products, instead, were obtained in 23–35% yields (Table 1, entries 4–6). These results indicate that the extensive resonance stabilization by the α-phenyl substituent allows the generation of the unstable sp^2-imidoyl radical **1** from benzonitrile. In other cases, however, the formation of *N*-titanaimidoyl radicals was unfavorable without a stabilizing group at the α-position. In such cases, the phenyl group transfers from the coordinating Cp_2TiPh to the coordinated cyano group. To intramolecularly trap the imidoyl radical more efficiently by an olefin acceptor, benzonitrile derivatives **4a** and **4b** were reacted with Cp_2TiPh, but no cyclization product was obtained (Scheme 3). This is in striking contrast to the successful radical cyclization of selenoimidate **5** to chromanone **6**.[5d] Moreover, this is consistent with PM3 semiempirical calculations,[7] suggestive of the unpaired spin being localized on the titanium center in Cp_2TiPh-(CH_3CN) whereas the unpaired spin is almost completely transferred to the carbonyl carbon from the titanium center in $Cp_2TiPh(CH_3COCH_3)$ as shown in Figure 2. In addition, the LUMO (β-spin) level of $CP_2TiPh(CH_3CN)$ (0.3 eV: UHF/PM3) is lower than that of CH_3CN (1.4 eV: RHF/PM3), indicative of the Cp_2TiPh-coordinated nitriles being an efficient radical acceptor.

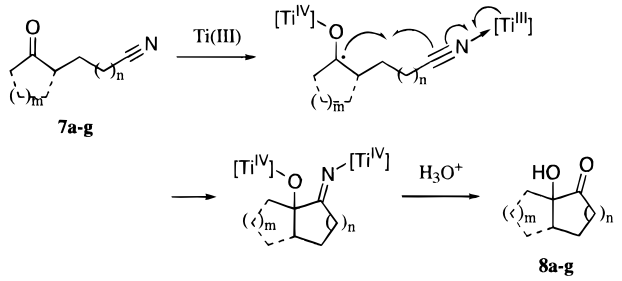
(4) (a) Hanada, Y.; Inanaga, J. *Tetrahedron Lett.* **1987**, *46*, 5717. (b) Schobert, R. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 855. (c) Gansäuer, A. *J. Chem. Soc., Chem. Commun.* **1997**, 457. (d) Gansäuer, A. *Synlett* **1997**, 363. (e) Gansäuer, A.; Bauer, D. *J. Org. Chem.* **1998**, *63*, 2070. (f) Barden, M. C.; Schwartz, J. *J. Am. Chem. Soc.* **1996**, *118*, 5484. (g) de Boer, E. J. M.; Teuben, J. H. *J. Organomet. Chem.* **1977**, *140*, 41. (h) de Boer, E. J. M.; Teuben, J. H. *J. Organomet. Chem.* **1978**, *153*, 53. (i) Nugent, W. A.; RajanBabu, T. V. *J. Am. Chem. Soc.* **1988**, *110*, 8561. (j) RajanBabu, T. V.; Nugent, W. A. *J. Am. Chem. Soc.* **1989**, *111*, 4525. (k) RajanBabu, T. V.; Nugent, W. A.; Beattie, M. S. *J. Am. Chem. Soc.* **1990**, *112*, 6408. (l) Gansäuer, A.; Bluhm, H.; Pierobon, M. *J. Am. Chem. Soc.* **1998**, *120*, 12849. (m) Yadav, J. S.; Srinivas, D. *Chem. Lett.* **1997**, 905. (n) Chakraborty, T. K.; Dutta, S. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1257. (o) Davies, S. G.; Thomas, S. E. *Synthesis* **1984**, 1027. (p) Yanlong, Q.; Guisheng, L.; Huang, Y.-Z. *J. Organomet. Chem.* **1990**, *381*, 29. (q) Spencer, R. P.; Schwartz, J. *J. Org. Chem.* **1997**, *62*, 4204.

(5) For radical addition of imidoyl radicals, see: (a) Leardini, R.; Pedulli, G. F.; Tundo, A.; Zanardi, G. *J. Chem. Soc., Chem. Commun.* **1984**, 1320. (b) Leardini, R.; Nanni, D.; Pedulli, G. F.; Tundo, A.; Zanardi, G. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1591. (c) Leardini, R.; Nanni, D.; Tundo, A.; Zanardi, G. *J. Chem. Soc., Chem. Commun.* **1989**, 757. (d) Bachi, M. D.; Denenmark, D. *J. Am. Chem. Soc.* **1989**, *111*, 1886. (e) Curran, D. P.; Liu, H. *J. Am. Chem. Soc.* **1991**, *113*, 2127. (f) Fukuyama, T.; Chen, X.; Peng, G. *J. Am. Chem. Soc.* **1994**, *116*, 3127. (f) Bachi, M. D.; Denenmark, D. *J. Org. Chem.* **1990**, *55*, 3442.

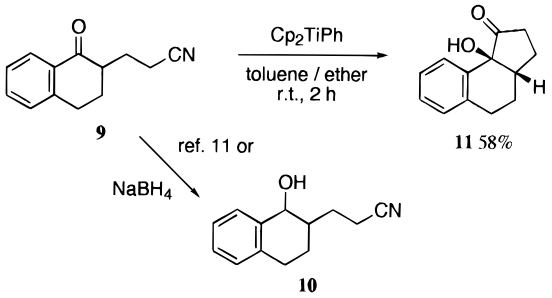
(6) Although 1 equiv of the Ti(III) reagent is theoretically required, 1.5 equiv of Cp_2TiPh was used to ensure the completion of reaction.

(7) Semiempirical calculations were carried out using MacSpartan *plus* (Wavefunction, Inc.). Geometries of $Cp_2TiPh(CH_3CN)$ and Cp_2-$TiPh(CH_3COCH_3)$ were optimized at the unrestricted Hartree–Fock (UHF) level with a PM3 Hamiltonian (Stewart, J. J. R. *J. Comput.-Aided Mol. Des.* **1990**, *4*, 1).

Scheme 4



Scheme 5



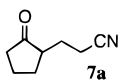
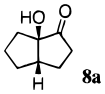
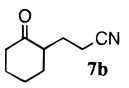
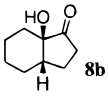
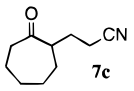
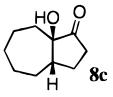
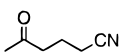
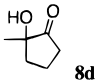
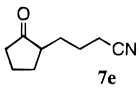
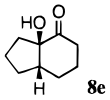
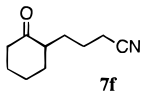
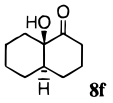
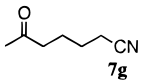
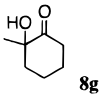
Intramolecular Ketyl Radical Additions to Cp_2-TiPh-Coordinated C−N Triple Bond. Although imidoyl radicals could not be generated by the single electron reduction of both aromatic and aliphatic nitriles with titanocene(III) reagents, Cp_2TiPh-coordinated nitriles are still fascinating as a radical acceptor (vide supra). To realize the radical addition to coordinated nitriles, we then investigated the reaction of ketonitriles with the Ti(III) reagent (Scheme 4).[8] To our knowledge, the intramolecular reductive coupling of ketonitriles is quite rare, and so far, only few examples using one-electron reducing agents such as Zn[9] and SmI_2[10] were reported in addition to the electroreductive method.[11] In a manner similar to the above nitrile coupling, 2-cyanoethylcyclopentanone **7a** was treated with the preformed solution of Cp_2TiPh in toluene at 0.1 M concentration to afford the 5-exo cyclization product **8a** in 77% yield after hydrolysis and chromatographic separation (Table 2, entry 1). The less reactive Cp_2TiCl again did not promote the coupling reaction under the same conditions.

Intramolecular coupling products **8b** and **8c** were similarly obtained from cyanoethylcyclohexanone **7b** and cyanoethylcycloheptanone **7c** in 70 and 43% yields, respectively (Table 2, entries 2 and 3). Acyclic ketone **7d** also gave **8d**, but the yield was lower than those of the above cyclic precursors due to the conformational flexibility around the carbonyl group (Table 2, entry 4). A high dilution and a prolonged reaction time were required to increase the yield up to 50% (Table 2, entry 5). In contrast, the inverse addition of the Ti(III) reagent to **7d** decreased the yield (17%). Thus, the high local concentration of the Ti(III) reagent is critical for the present cyclization. In general, aromatic ketones are more readily reduced than aliphatic ketones since the resultant ketyl radicals are highly stabilized by the α-phenyl group. Therefore, the aryl-substituted ketone **9** was reported to be over-reduced to give cyano alcohol **10** under electroreduction conditions (Scheme 5).[11] On the other hand, **9** was cleanly cyclized by our method to afford the tricyclic α-hydroxyketone **11** in 58% yield.

As already described, the 5-exo cyclization of γ-ketonitriles was achieved using Cp_2TiPh, and cyclic ketones **7a**−**c** and **9** were more readily cyclized than acyclic ketone **7d**. We next examined the 6-exo cyclization of δ-cyanoketones and the 7-exo cyclization of an ϵ-cyanoketone. Cyanopropylcyclopentanone **7e** was subjected to reductive cyclization to give the desired product **8e** in only 20% yield at a 0.1 M concentration (Table 1, entry 6). The high dilution conditions (0.04 M) again improved the yield (45%, entry 7). Similarly, the six-membered cyanoketone **7f** and acyclic cyanoketone **7g** afforded cyclized products **8f** and **8g** in 69 and 42% yields, respectively. It is interesting that the trans-fused product was selectively obtained from **7f**, whereas the cis-fused isomer was exclusive for **8a**−**c**, **11**, and **8e**. Furthermore, the reaction of ϵ-cyanoketone **7h** did not give the desired 7-exo reductive cyclization product. Instead, the carbonyl group and/or the nitrile moiety were phenylated by the titanium(III) reagent to give **12** and **13** (Scheme 6). The phenylation product **13** indicates that both the carbonyl and cyano termini are definitely coordinated by the Ti(III) complex.

To obtain further insight into the reaction mechanism, the cyclization of **9** was carried out in the presence of

Table 2. Cp_2TiPh-Mediated Reductive Coupling of Ketonitriles 7a−g

Entry	Ketonitriles	Concentrations/ reaction time	Products	Yields
1	 **7a**	0.1 M / 1 h	 **8a**	77%
2	 **7b**	0.1 M / 1 h	 **8b**	70%
3	 **7c**	0.1 M / 1 h	 **8c**	43%
4	 **7d**	0.1 M / 1 h	 **8d**	33%
5		0.04 M / 2 h		50%
6	 **7e**	0.1 M / 1 h	 **8e**	20%
7		0.04 M / 2 h		45%
8	 **7f**	0.04 M / 2 h	 **8f**	69%
9	 **7g**	0.04 M / 2 h	 **8g**	42%

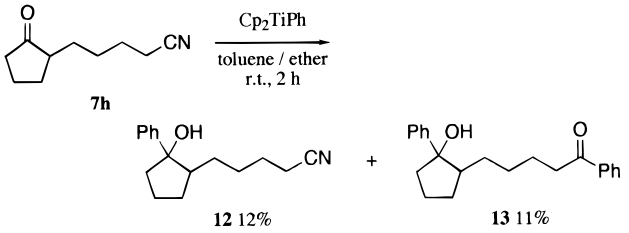
(8) For radical cyclization involving a nitrile group, see: (a) Clive, D. L. J.; Beaulieu, P. L.; Set, L. *J. Org. Chem.* **1984**, *49*, 1313. (b) Chenera, B.; Chuang, C.-P.; Hart, D. J.; Hsu, L.-Y. *J. Org. Chem.* **1985**, *50*, 5409. (c) Tsang, R.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1986**, *108*, 2116. (d) Snider, B. B.; Buckman, B. O. *J. Org. Chem.* **1992**, *57*, 322. (also see refs 9−11).

(9) Corey, E. J.; Pyne, S. G. *Tetrahedron Lett.* **1983**, *24*, 2821.

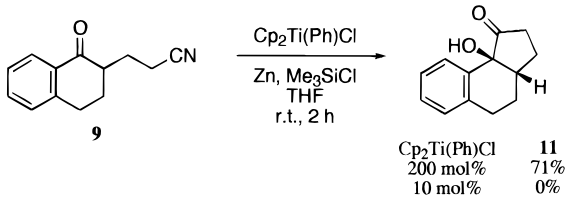
(10) Molander, G. A.; Kenny, C. *J. Am. Chem. Soc.* **1989**, *111*, 8236.

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

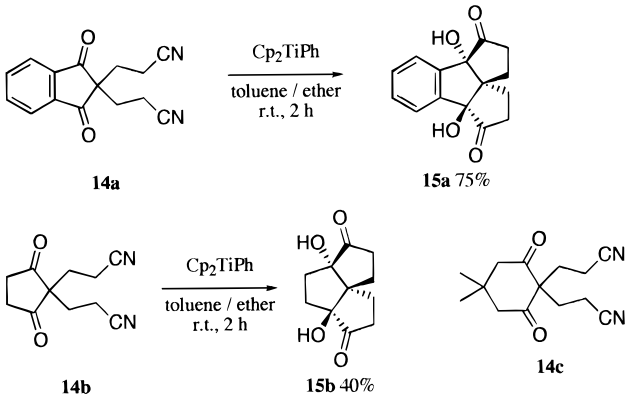
Scheme 6



Scheme 7



Scheme 8



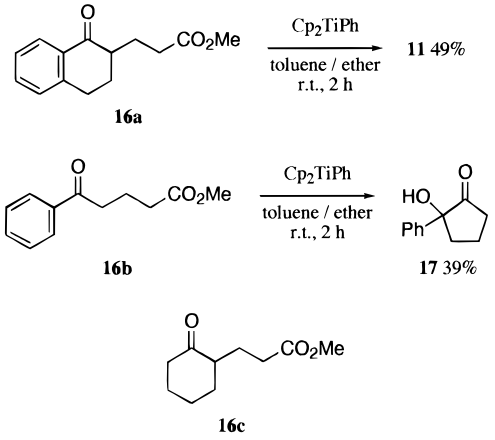
excess *i*-PrOH. As a result, the hydroxyketone **11** was obtained in 41% yield; however, the simple reduction product **10** was not formed at all.[11] This observation rules out an alternative anionic mechanism via a two-electron reduction of the ketones followed by cyclization of the resultant α-alkoxy anions to cyano groups. The intermediacy of Cp_2TiPh was supported by the experiment shown in Scheme 7. In situ reduction of the known complex $Cp_2Ti(Ph)Cl$[12] by Zn produces Cp_2TiPh, which mediated the cyclization of **9** to **11** in good yield (Scheme 7). The corresponding catalytic reaction did not take place because of the low concentration of the Ti(III) species (vide infra).

The present cyanoketone cyclization is a powerful route to α-hydroxycycloalkanones. The synthetic potential of this method was also demonstrated in the double cyclization of dicyanodiketones **14**, giving rise to interesting angular triquinane derivatives **15** (Scheme 8). Benzo-fused **14a** was treated with Cp_2TiPh to give the desired C_2-symmetric tetracyclic product **15a** in high yield. The parent dicyanodiketone **12b** showed a lower reactivity, but the double cyclization product **15b** was also obtained in 40% yield. In contrast, the less strained cyclohexanedione derivative **14c** gave no cyclization product.

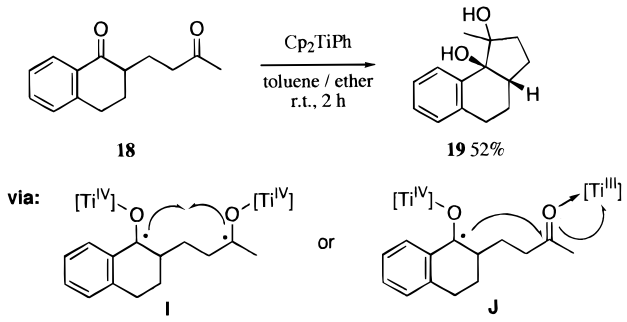
Intramolecular Ketyl Radical Additions to Cp_2-TiPh-Coordinated C−O Double Bonds. The ketyl radical accepting ability of the Ti(III)-coordinated ester carbonyl group is also demonstrated by the aromatic

(12) Waters, J. A.; Mortimer, G. A. *J. Organomet. Chem.* **1970**, *22*, 417.

Scheme 9



Scheme 10

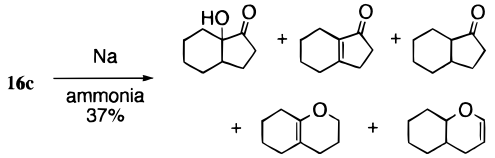


ketoester cyclization depicted in Scheme 9. Cyclic ketoesters **16a** and acyclic **16b** were treated with Cp_2TiPh under the high dilution conditions to selectively afford the α-hydroxycyclopentanones **11** and **17** in 49 and 39% yields, respectively. In these cases, the phenyl group α to the carbonyl is essential. The nonaromatic ketone **16c** gave no cyclized product.[13] Therefore, the ketoester cyclization was limited to aromatic ketones such as **16a** and **b** due to the less electrophilic character of the Cp_2-TiPh-coordinated ester group.

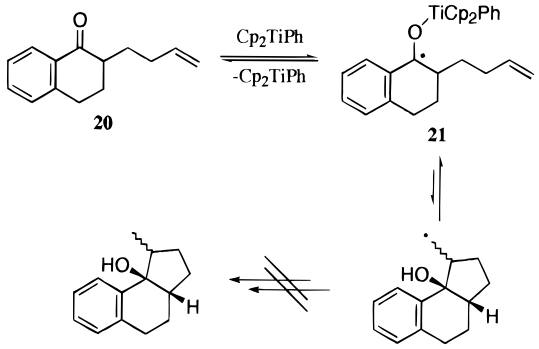
In addition to the heterocouplings of the ketonitriles and ketoesters, the homocoupling of diketone was then investigated (Scheme 10). Diketone **18** was treated with Cp_2TiPh to give the expected pinacol coupling product **19** in 52% yield via a simple intramolecular diradical coupling (**I**) or possibly, intramolecular addition of the more stable, long-lived phenyl-substituted ketyl radical to the Cp_2TiPh-coordinated nonaromatic ketone (**J**).

Intramolecular Ketyl Radical Addition to C−C Double Bonds. Recently, Molander et al. reported the SmI_2-promoted reductive cyclization of *δ*,*ϵ*-unsaturated ketoesters, demonstrating that the ketyl-trapping ability of nitriles is lower than those of alkenes, alkynes, ketones, or aldehydes.[10] In our hand, the double coordination to both the carbonyl and cyano groups by the

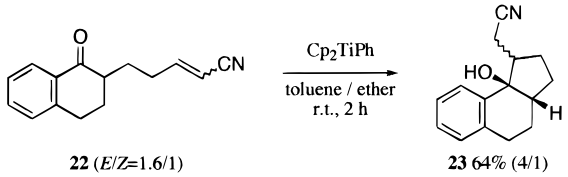
(13) The reductive cyclization of ketoester **12c** in Na/ammonia was reported to give a mixture of products given below (Gutsche, G. D.; Tao, I. Y. C.; Kozma, J. *J. Org. Chem.* **1967**, *32*, 1782.).



Scheme 11



Scheme 12



Ti(III) complex realized the efficient reductive cyclization of a variety of ketonitriles under mild conditions. In this context, alkenyl groups are no longer superior to the cyano group as a ketyl radical acceptor. In fact, α-butenyl ketone **20** did not give the expected cyclization product after 24 h and was recovered with the carbonyl group intact (75% recovery). This result showed that the ketyl radical formation is reversible, and this reversibility combined with the steric hindrance of the Cp_2TiPh-coordinated ketyl moiety makes the 5-exo-trig cyclization of **21** ineffective (Scheme 11). In contrast, a cyano group on the olefin terminus dramatically enhanced the cyclization ability, and as a result, intramolecular cyclization of **22** gave the cyano alcohol **23** in 64% yield (Scheme 12).[14] These facts again demonstrated the efficiency of the Cp_2TiPh-coordinated cyano group as a ketyl radical acceptor.

Conclusions

In conclusion, the Cp_2TiPh-mediated reductive radical cyclization of cyanoketones in both the 5- and 6-exo modes was successful to provide an easy entry to the 5- and 6-membered α-hydroxycycloalkanones. The coordination of Cp_2TiPh to the cyano group plays a key role in the present cyclization; i.e., the titanium reagent coordinates to both the carbonyl and cyano moieties. As a result, the LUMO of the cyano group is lowered, and cyclization proceeds irreversibly without formation of the unstable iminyl radical intermediates. In this situation, a low concentration of the Ti(III) reagent is unfavorable. In our hands, the intramolecular reductive radical cyclization of aromatic ketoesters also gave the corresponding α-hydroxycycloalkanones, in which Cp_2TiPh-coordinated ester group also functions as a ketyl radical acceptor. Such an effect did not occur for the α-butenyl ketone, producing no reductive cyclization product. Furthermore, a cyclohexanone with a cyanoolefin terminus gave an intramolecular Michael-type radical addition product.

(14) Similar chemoselectivity was observed in the reaction of 5-hexenal derivatives with SmI_2 (Enholm, E. J.; Trivellas, A. *Tetrahedron Lett.* **1989**, *30*, 1063).

Experimental Section

General Methods. ^1H and ^{13}C NMR spectra were obtained at 300 and 75 MHz, respectively, for samples in $CDCl_3$ solution. Flash chromatography was performed using a silica gel column (Merck Silica gel 60) eluted with mixed solvents (hexane/ethyl acetate). Ether and toluene were distilled from CaH_2, degassed, and stored over Na. Cp_2TiCl_2 was purchased from Kanto Chemical Co., Inc.

Cp_2TiPh-Mediated Reductive Coupling of Benzonitrile. To a suspension of Cp_2TiCl_2 (747 mg, 3.0 mmol) in dry degassed toluene (10 mL) was added a solution of freshly prepared *i*-PrMgCl [*i*-PrCl (259 mg, 3.3 mmol) and Mg (160 mg, 6.6 mmol)] in dry degassed ether (5 mL) under Ar atmosphere at room temperature. The reaction mixture was stirred for 30 min. To the resultant green solution was added a solution of freshly prepared PhMgBr [PhBr (471 mg, 3.0 mmol) and Mg (146 mg, 6.0 mmol)] in dry degassed ether (5 mmol) at room temperature, and the reaction mixture was stirred for further 30 min. To the obtained dark-green Cp_2TiPh solution was added benzonitrile (206 mg, 2 mmol) at room temperature, and the reaction mixture was stirred for 1 h. The reaction was quenched by 1 N HCl (10 mL), and the mixture was stirred for 30 min. The organic layer was separated and washed with brine (20 mL). The aqueous layer was extracted with ethyl acetate (20 mL × 3). The combined organic layer was dried with $MgSO_4$ and concentrated in vacuo. The crude mixture was purified by silica gel flash column chromatography (hexane−AcOEt 20:1) to give benzil **3** (198 mg, 94%) as white needles. The reactions of Cp_2TiPh with other nitriles and methyl phenylacetate are performed in the same manner. Products and yields are summarized in Table 1.

General Procedure for Cp_2TiPh-Mediated Cyclization of Cyanoketones. To a suspension of Cp_2TiCl_2 (747 mg, 3.0 mmol) in dry degassed toluene [10 mL (25 mL for **7d**−**h**)] was added a solution of freshly prepared *i*-PrMgCl [*i*-PrCl (259 mg, 3.3 mmol) and Mg (160 mg, 6.6 mmol)] in dry degassed ether (5 mL) under Ar atmosphere at room temperature. The reaction mixture was stirred for 30 min. To the resultant green solution was added a solution of freshly prepared PhMgBr [PhBr (471 mg, 3.0 mmol) and Mg (146 mg, 6.0 mmol)] in dry degassed ether (5 mL) at room temperature, and the reaction mixture was stirred for a further 30 min. To the obtained dark-green Cp_2TiPh solution was added a solution of cyanoketone **7** (1 mmol) in dry degassed toluene [10 mL (20 mL for **7d**−**h**, **9**)] at room temperature, and the reaction mixture was stirred for 1 h (2 h for **7d**−**h**, **9**). The reaction was quenched by 1 N HCl (10 mL), and the mixture was stirred for 30 min. The organic layer was separated and washed with brine (20 mL). The aqueous layer was extracted with ethyl acetate (20 mL × 3). The combined organic layer was dried with $MgSO_4$ and concentrated in vacuo. The crude mixture was purified by silica gel flash column chromatography to give α-hydroxycycloalkanone **8**. The yields are summarized in Table 2, and α-hydroxycycloalkanones **8a**−**g**, **11** are reported in ref 11. Compound **17** is reported in ref 15. The reductive cyclizations of unsaturated cyanides **4a**,**b**, ketoester **16a**,**b**, diketone **18**, and ketonitrile **22** were also performed in the same manner with **7d**−**h**.

Spectral data for 11: oil (eluant, hexane−AcOEt 3:1); IR (neat) 3427 (OH) 1742 (C=O) cm^{-1}; ^1H NMR δ 1.74 (1 H, ddt, J = 13.1, 10.8, 9.6 Hz), 1.86−2.04 (2 H, m), 2.17 (1 H, dddd, J = 14.3, 11.4, 6.6, 4.2 Hz), 2.31 (1 H, dd, J = 19.5, 9 Hz), 2.39 (1 H, ddd, J = 19.5, 9.6, 5.4 Hz), 2.50 (1 H, ddd, J = 15.2, 7.5, 3.9 Hz), 2.86 (1 H, ddd, J = 17.7, 6.6, 3 Hz), 2.95 (1 H, ddd, J = 17.7, 11.4, 6 Hz), 3.10 (1 H, br s), 7.14−7.27 (3 H, m), 7.42 (1 H, dd, J = 7.5, 1.5 Hz); ^{13}C NMR δ 19.3, 20.7, 24.5, 33.5, 41.3, 77.2, 126.6, 127.9, 128.3, 129.5, 132.2, 136.8, 217.6; MS (EI) *m*/*z* (rel intensity) 202 (M^+, 99), 174 (47), 146 (100). Anal. Calcd for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98. Found: C, 77.18; H, 6.98.

Spectral data for 12: oil (eluant, hexane−AcOEt 1:1); IR (neat) 3447 (OH), 2246 (C≡N) cm^{-1}; ^1H NMR δ 1.00−2.50 (15

(15) Syper, L. *Tetrahedron* **1987**, *43*, 2853.

H, m), 7.00−7.65 (5 H, m); ^{13}C NMR δ 16.8, 21.5, 25.47, 27.1, 27.5, 29.6, 43.7, 50.9, 76.3, 76.9, 84.0, 120.0, 125.0, 126.7, 128.3, 146.0. Anal. Calcd for $C_{16}H_{21}NO$: C, 78.97; H, 8.70; N, 5.76. Found: C, 79.11; H, 9.04; N, 5.57.

Spectral data for 13: oil (eluant, hexane−AcOEt, 5:1); IR (neat) 3493 (OH), 1682 (C═O) cm^{-1}; ^{1}H NMR δ 1.00−3.10 (16 H, m), 7.00−8.10 (10 H, m); ^{13}C NMR δ 21.5, 24.2, 27.6, 28.0, 29.5, 38.2, 43.6, 50.7, 80.0, 125.1, 126.5, 128.2, 128.3, 128.7, 133.0, 137.2, 146.3, 200.8. Anal. Calcd for $C_{22}H_{26}O_2$: C, 81.95; H, 8.13. Found: C, 81.84; H, 8.23.

Spectral data for 19: solid; mp 115.5−116.0 °C (eluant, hexane−AcOEt 5:1); IR (CH_2Cl_2) 3586 (OH) cm^{-1}; ^{1}H NMR δ 0.66 (1 H, br s), 1.40 (3 H, s), 1.66−2.09 (6 H, m), 1.73 (1 H, br s), 2.33 (1 H, q, J = 6.6 Hz), 2.62 (1 H, ddd, J = 15.3, 6.9, 4.5 Hz), 2.79 (1 H, ddd, J = 15.3, 9.3, 4.8 Hz), 7.13−7.29 (3 H, m), 7.66 (1 H, dd, J = 7.5, 1.5 Hz); ^{13}C NMR δ 22.4, 27.7, 27.8, 27.9, 37.5, 48.9, 81.9, 83.8, 126.0, 126.8, 127.3, 128.1, 137.9, 140.9; MS (EI) *m*/*z* (rel intensity) 218 (M$^+$, 98), 200 (85), 159 (63), 145 (100). Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 77.00; H, 8.34.

Spectral data for 23: oil (eluant, hexane−AcOEt 2:1); IR (neat) 3446 (OH), 2249 (C≡N) cm^{-1}; ^{1}H NMR δ 1.20−1.80 (12 H, m), 1.90−2.25 (4 H, m), 2.46 (1 H, dd, J = 16, 5 Hz) [minor isomer δ 1.05−1.71 (8 H, m), 1.75 (1 H, m), 1.84−2.19 (3 H, m), 2.22−2.51 (2 H, m)]; ^{13}C NMR δ 16.4, 19.8, 20.7, 22.8, 23.5, 25.6, 27.4, 44.2, 46.9, 77.5, 119.5 [minor isomer δ 17.1, 22.9, 24.3, 27.3, 27.8, 30.0, 34.2, 39.3, 47.6, 80.1, 120.4]; MS (EI) *m*/*z* (rel intensity) 179 (M$^+$, 31), 162 (8), 111 (100). Anal. Calcd for $C_{11}H_{17}NO$: C, 73.70; H, 9.56; N, 7.81. Found: C, 73.53; H, 9.73; N, 7.50.

Cp_2TiPh-Mediated Reductive Cyclization of 9 in the Presence of *i*-PrOH. To the Cp_2TiPh solution prepared as above [Cp_2TiCl_2 (747 mg, 3.0 mmol)/toluene (10 mL) with *i*-PrMgCl (3.3 mmol)/ether (5 mL) and PhMgBr (3.0 mmol)/ether (5 mL)] was added a solution of cyanoketone **9** (199 mg, 1 mmol) in toluene (10 mL) and *i*-PrOH (10 mL) at room temperature, and the reaction mixture was stirred for 2 h. The standard workup as described above gave **11** (83 mg, 41%).

Reductive Cyclization of 5e Using Cp_2Ti(Ph)Cl/Zn/Me_3SiCl. To a solution of Cp_2Ti(Ph)Cl (149 mg, 0.6 mmol) and Zn (39 mg, 0.6 mmol) in dry degassed THF (7 mL) was added Me_3SiCl (0.11 mL, 0.9 mmol), and the solution was stirred for 1 h under Ar atmosphere at room temperature. To the resultant green solution was added a solution of **9** (60 mg, 0.3 mmol) in dry degassed THF (5 mL) at room temperature, and the reaction mixture was stirred for a further 2 h. The standard workup as described above gave **11** (43 mg, 71%).

Cp_2TiPh-Mediated Double Cyclization of Dicyanodiketone. According to the procedure for **7d**−**h**, dicyanodiketone **14a** (126 mg, 0.5 mmol) was cyclized to afford 96 mg of tetracyclic α-hydroxyketone **15a** (0.37 mmol, 75%) as a solid: mp 171.5−172.0 °C (eluant, hexane−AcOEt 2:1); IR (CH_2Cl_2) 3530 (OH), 1744 (C═O) cm^{-1}; ^{1}H NMR δ 1.71 (2 H, dt, J = 12.5, 7 Hz), 2.30 (1 H, dd, J = 17, 1.5 Hz), 2.32 (1 H, dd, J = 16.5, 0.5 Hz), 2.57 (2 H, ddd, J = 16.5, 12.5, 7 Hz), 2.64 (1 H, dd, J = 9.5, 0.5 Hz), 2.66 (1 H, dd, J = 9.5, 1.5 Hz), 7.32−7.35 (2 H, m), 7.36−7.39 (2 H, m); ^{13}C NMR δ 26.8, 35.3, 56.1, 87.2, 123.9, 130.5, 142.7, 216.0; MS (EI) *m*/*z* (rel intensity) 258 (M$^+$, 85), 240 (82), 185 (93), 159 (100). Anal. Calcd for $C_{15}H_{14}O_4$: C, 69.76; H, 5.46. Found: C, 69.85; H, 5.37.

In the same manner, **14b** was converted into **15b**: solid; mp 122.5−123.8 °C (eluant, hexane−AcOEt 1:1); IR (CH_2Cl_2) 3550 (OH), 1742 (C═O) cm^{-1}; ^{1}H NMR δ 1.67 (4 H, m), 2.15 (2 H, m), 2.35−2.64 (6 H, m), 2.79 (2 H, br s); ^{13}C NMR δ 26.2, 35.6, 35.8, 58.8, 86.8, 219.6; MS (EI) *m*/*z* (rel intensity) 210 (M$^+$, 10), 192 (19), 182 (50), 137 (100). Anal. Calcd for $C_{11}H_{14}O_4$: C, 62.85; H, 6.71. Found: C, 62.75; H, 6.81.

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