Cp_2TiPh-coordinated cyano and ester groups as efficient ketyl radical acceptors in the reductive radical cyclization of γ- and δ-cyano ketones and δ-keto esters

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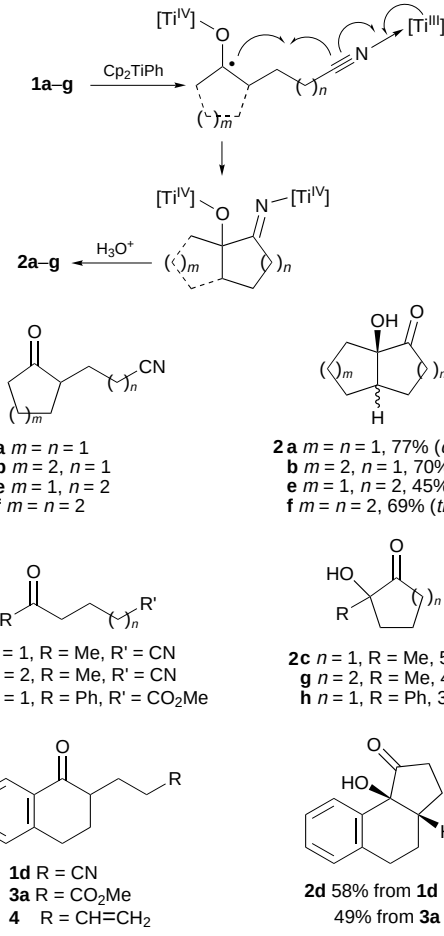
Cp_2TiPh promotes the reductive radical cyclization of γ- and δ-cyano ketones and δ-keto esters to give α-hydroxycycloalkanones in moderate to good yields; the titanium reagent coordinates to both the ketone and the cyano or ester terminus, the LUMO of the cyano or ester group is thus lowered, and cyclization proceeds irreversibly without formation of the unstable iminyl or alkoxy radical intermediates.

Radical cyclizations have been extensively utilized as powerful tools for the construction of carbocyclic skeletons, especially five-membered ring systems.[1] In these processes, C–C bonds are generally formed by the addition of a carbon-centered radical to a non-polar carbon–carbon multiple bond. On the other hand, radical additions to a carbonyl or cyano group are generally not efficient because they generate highly unstable alkoxy or iminyl radicals.[1] However, radical addition to these polar multiple bonds might be successful if the resulting unstable radical intermediates are effectively scavenged and converted into the desired products. With this in mind, we have developed a Ti^{III}-mediated reductive coupling of γ- and δ-cyano ketones leading to α-hydroxycycloalkanones, in which the Ti^{III} complex Cp_2TiPh coordinates to the cyano group so that the ketyl radical efficiently cyclizes to the coordinated cyano group without formation of the undesired iminyl radical intermediate (Scheme 1).[2] In addition, coordination of the Ti^{III} species lowers the LUMO of the cyano group and increases its ketyl trapping ability.[3]

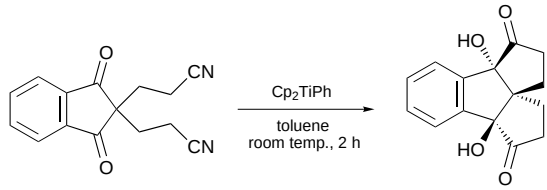
Cp_2TiPh was prepared according to the reported procedures[4] and used for further reactions without isolation. Typically, commercial Cp_2TiCl_2 (3 mmol) was treated sequentially with dry, degassed Et_2O solutions of Pr^iMgCl (3.3 mmol) and PhMgBr (3.3 mmol) in dry, degassed toluene (10 ml) under Ar at ambient temperature.[5] To the resultant dark green solution of Cp_2TiPh was added dropwise a 0.1 M toluene solution of 2-cyanoethylcyclopentanone **1a** (1 mmol) and the reaction mixture was stirred for 1 h at ambient temperature. Acid hydrolysis followed by silica gel chromatography afforded the 5-*exo* cyclization product **2a**[6] in 77% yield. The phenyl–titanium bond is essential, since analogous Ti^{III} species generated by the reduction of Cp_2TiCl_2 by Pr^iMgCl did not promote the cyclization under the same conditions. Similarly, intramolecular coupling product **2b**[6] was obtained from cycloalkanones **1b** in 70% yield. Acyclic ketone **1c** also gave **2c**,[6] but the yield was lower than those of the above cyclic precursors due to conformational flexibility around the carbonyl group. High dilution (0.04 M) and prolonged reaction time (2 h) was required to increase the yield to 50%. In contrast, the inverse addition of the Ti^{III} reagent to **1c** decreased the yield (17%). Thus the concentration of the Ti^{III} reagent is critical for the present cyclization. It is noteworthy that the present method is applicable to aryl-substituted ketone **1d** to afford tricyclic α-hydroxy ketone **2d**[6] in 58% yield, whereas the reported electrochemical reduction gave cyano alcohol due to simple reduction of the carbonyl group.[7,8] In the same manner, 6-*exo* cyclization of δ-cyano ketones **1e**,**f** and acyclic δ-cyano ketones **1g** gave the desired α-hydoroxycyclohexanones **2e**–**g**[6] in 45, 69 and 42% yields, respectively. It is interesting that the *trans*-fused product was selectively obtained from **1f**, whereas the *cis*-fused isomer was obtained for **2a**,**b**,**d** and **e**.

In addition to the cyano group, the ester group is an effective ketyl radical accepting group when coordinated by Cp_2TiPh.[2] Aromatic keto esters **3a** and **3b** were treated with the Ti^{III} reagent under high dilution conditions to afford 5-*exo* cyclization products **2d** and **2h** in 49 and 38% yields, respectively.

Recently, Molander and Kenny reported the SmI_2-promoted reductive cyclization of δ,ε-unsaturated keto esters, demonstrating that the ketyl-trapping ability of nitriles is lower than those of alkenes, alkynes, ketones and aldehydes.[9] In our hands, the double coordination to both carbonyl and cyano or ester groups by the Ti^{III} complex resulted in efficient reductive cyclization of a variety of keto nitriles and keto esters under mild conditions. In this context, alkenyl groups are no longer superior to the cyano group as a ketyl radical acceptor. In fact,



Scheme 1



5 **6** 75%

Scheme 2

α-butenyl ketone **4** did not give the expected cyclization product after treatment for 24 h with the Ti^{III} reagent, and the starting material was recovered with the carbonyl group intact (75% recovery).[10] This result shows that 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 **4** ineffective.

In conclusion, the Cp_2TiPh-mediated reductive radical cyclization of cyano ketones in both 5- and 6-*exo* modes was successful to provide an easy entry to 5- and 6-membered α-hydroxycycloalkanones. The coordination to the cyano group plays a key role in the present cyclization, *i.e.* the titanium reagent coordinates to both carbonyl and cyano moieties, and therefore, a low concentration of the Ti^{III} reagent is unfavorable. As a result, the LUMO of the cyano group is lowered and cyclization proceeds irreversibly without formation of the unstable iminyl radical intermediates. To the best of our knowledge, the intramolecular reductive coupling of keto nitriles is quite rare, and thus far only a few examples using one-electron reducing agents such as Zn[11] and SmI_2[9] have been reported in addition to the electroreductive method.[7] In our hands, intramolecular reductive radical cyclization of aromatic keto esters also gave the corresponding α- hydroxycycloalkanones, in which the Cp_2TiPh-coordinated ester group functions as a ketyl radical acceptor. Such an effect did not operate for the α-butenyl ketone, producing no reductive cyclization product. The synthetic utility of the cyano ketone cyclization was also demonstrated in the double cyclization of dicyano diketone **5**, giving rise to an interesting angular triquinane derivative **6**[6] in 75% yield (Scheme 2).

We gratefully acknowledge financial support (09750947 and 09305059) from the Ministry of Education, Science Sports and Culture, Japan.

Notes and References

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1 D. P. Curran, in *Comprehensive Organic Synthesis*, ed. B. M. Trost, Pergamon, Oxford, 1991, vol. 4, ch. 4.
2 Neither radical coupling products nor reduced products were obtained from the treatment of BnCN and $BnCO_2Et$ with Cp_2TiPh, demonstrating that no radical species are generated from aliphatic nitriles or esters with Cp_2TiPh.
3 PM3 theoretical calculations (Wavefunction, Inc. MacSpartan plus) for free and Cp_2TiPh-coordinated acetonitriles suggested that the LUMO level of MeCN (1.4 eV: RHF/PM3) is higher than the β-LUMO of Cp_2TiPh(MeCN) (0.3 eV: UHF/PM3).
4 E. J. M. de Boer and J. H. Teuben, *J. Organomet. Chem.*, 1978, **153**, 53.
5 Although only 2 equiv. of the Ti^{III} reagent is theoretically required, 3 equiv. of Cp_2TiCl_2 was used to ensure completion of cyclization.
6 The structures and stereochemistry of cyclized products **2a**–**c**, **e**–**g** were determined by comparison of their spectral features with those of reported compounds (ref. 7), and new compounds were characterized by the usual means.
7 T. Shono, N. Kise, T. Fujimoto, N. Tominaga and H. Morita, *J. Org. Chem.*, 1992, **57**, 7175.
8 In the presence of a large excess of Pr^iOH, the cyclization of **1d** afforded cyclized product **2** in 41% yield without formation of the simple reduced product cyano alcohol. This indicates that anionic species generated by the reduction of ketyl radicals are not involved in the present cyclization.
9 G. A. Molander and C. Kenny, *J. Am. Chem. Soc.*, 1989, **111**, 8236.
10 Similar results were reported in the reaction of hex-5-enal with SmI_2, where only a pinacol coupling product was obtained instead of a 5-*exo* cyclization product (E. J. Enholm and A. Trivellas, *Tetrahedron Lett.*, 1989, **30**, 1063.).
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Received in Cambridge, UK, 26th January 1998; 8/00661J