Highly *trans*-selective intramolecular pinacol coupling of dials catalyzed by bulky Cp₂TiPh

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$Cp_2Ti(Ph)Cl$ in the presence of Me_3SiCl and Zn provides an effective pinacol coupling catalyst for aromatic and aliphatic aldehydes.

Chiral 1,2-diols have found extensive use as asymmetric ligands for catalytic asymmetric reactions¹ and as chiral auxiliaries for diastereoselective transformation of carbonyl substrates.² Such valuable diols are commonly obtained by the resolution of racemic products prepared from a wide variety of aldehydes via threo-selective pinacol coupling.³ Pinacol coupling has also been employed as a key step in the construction of highly important natural and artificial compounds.3 For these purposes, stoichiometric reactions have so far been employed, however, catalytic methods are highly desirable as a metalatom-economical and practical entry to the above 1,2-diols. From this point of view, some catalytic methods have been developed,⁴ but few of them have been applied to the intramolecular coupling of dials.^{4g} This is partly because the intramolecular pinacol coupling of dials is often accompanied by side reactions such as intramolecular aldol condensation. With this in mind, we developed the Cp₂Ti(Ph)Cl-catalyzed intramolecular pinacol coupling of dials, which gave cyclic 1,2-diols in moderate to good yields with excellent transselectivity under mild conditions (Scheme 1).

Cp2TiCl has received much attention as an excellent singleelectron reductant in organic synthesis.⁵ In this context, Teuben et al. have reported the Cp2TiPh-mediated reductive coupling of benzonitrile leading to benzil,6 and recently we have found that the same titanium(III) reagent reacted with γ - and δ -ketonitriles to give α -hydroxycycloalkanones as reductive cyclization products in good yield.⁷ The importance of the Ti^{III}–Ph σ -bond is obvious from the fact that the parent Cp2TiCl was not effective for the above two reductive transformations. The phenyltitanium(III) reagent was readily prepared in situ via reduction of Cp2TiCl2 with PriMgCl followed by the addition of PhMgBr.^{6,7} The same reactive species may alternatively be generated by reducing Cp2Ti(Ph)Cl8 with Zn powder.9 Given this fact, Cp₂Ti(Ph)Cl should catalyze pinacol coupling reactions in the presence of a stoichiometric amount of Zn. In fact, stoichiometric reaction using equimolar amounts of Cp2Ti(Ph)Cl and Zn promoted the desired reductive coupling of benzaldehyde 1a to give hydrobenzoin 2a in 99% yield with a diastereoselectivity of *threo* : *erythoro* = 84 : 16. We carried out the catalyzed reaction as follows; a THF (5 ml) solution of 1a (3 mmol) and Me₃SiCl (1.5 equiv.) was added to a mixture of 3 mol% Cp₂Ti(Ph)Cl and Zn (1 equiv.) in THF (20 ml) and the mixture was stirred for 70 min at ambient temperature. Usual work-up gave 2a in 88% yield with a diastereomeric ratio of threo: erythro = 71:29 (Scheme 2). In the absence of the titanium catalyst, 2a was obtained in only 7% yield (threo: erythro = 50:50) along with the reduced product benzyl alcohol



(13%).¹⁰ The complete loss of diastereoselectivity demonstrated the importance of the titanocene catalyst. In addition to the aromatic aldehyde, less reactive aliphatic aldehyde **1b** was converted into the corresponding diol **2b** in good yield, although its *threo*-selectivity was lower than **2a**. These results demonstrate that Cp₂Ti(Ph)Cl is an efficient catalyst for the pinacol coupling of both aromatic and aliphatic aldehydes.

On the basis of the above results, we applied our new catalytic system to the intramolecular reductive coupling of dials (Table 1). In the presence of 6 mol% Cp₂Ti(Ph)Cl, the acid sensitive 1,5-dial **3a** was reduced at ambient temperature over 38 h to afford the desired diol **4a** in 40% yield with excellent *trans*-selectivity (*trans*: *cis* = 99:1). It is noteworthy that this high diastereoselectivity is in striking contrast to the *cis*-selectivity observed in the known methods using stoichiometric amounts of SmI₂¹¹ or TiCl₃(THF)₃–Bu'OH catalyst.^{4g} In a similar manner, 10 mol% of the catalyst transformed 1,6-diol **3b** into *trans*-cyclohexanediol **4b** in a higher yield (65%). Moreover, 1,6-dial **3c** having a bulky Bu^t group at the 3-position gave only a single stereoisomer **4c** in 52% yield. The relative



Table 1 Intramolecular pinacol coupling of dials 3a-d using Cp_Ti(Ph)Cl–Zn–Me_3SiCl^a

Dial	Catalyst/ mol%	t/h	Diol	Yield ^b (%)	trans : cis ^c
СНО СНО За	6	38	OH 4a ^{OH}	40%	99 : 1
СНО СНО 3b	10	14	OH 4b	65%	99 : 1
But CHO CHO 3c	10	14		1 52% 1	single isomer
СНО СНО	6	14	ОН	70%	91 : 9

^{*a*} Conditions: Cp₂Ti(Ph)Cl, Zn (1 equiv.), Me₃SiCl (1.5 equiv), THF (0.05 M), room temp. ^{*b*} Isolated yields. ^{*c*} Ratios determined by ¹H NMR analysis of isolated products.



Fig. 1 Mechanism of stereoselection.

configurations of all three stereogenic centers in **4c** were completely controlled. The stereochemistry of **4c** was determined by comparison of its spectral data with those previously reported.¹² In the ¹H NMR spectrum, the methyne protons α to the hydroxy groups have no H_{ax}-H_{ax} or H_{ax}-H_{eq} coupling with coupling constants over 10 Hz, indicating that both are constrained to occupy the equatorial positions. Among the four isomers, **4c** is the only one having no axial methyne proton α to the hydroxy groups, as shown in Fig. 1. In addition, the ¹³C NMR spectrum of **4c** and its melting point are in good agreement with reported data.¹²

These results clearly indicate that the bulky Ti^{IV} fragment surrounded by two cyclopentadienyl and one phenyl ligands cannot coordinate to the other carbonyl terminus, and cyclization must proceed *via* diradical intermediates such as **5**, in which two bulky $Cp_2(Ph)TiO$ moieties occupy axial positions in order to reduce steric repulsion (Fig. 1). This is in contrast to the intramolecular coupling of **3b** promoted by SmI₂ affording *cis*products *via* chelated intermediates such as **6**.¹¹

In addition to the aliphatic dials, a biphenylic dial **3d** was converted into a tricyclic diol **4d**¹³ in good yield (70%) with high *trans*-selectivity (*trans*: cis = 91:9).

In conclusion, we have demonstrated that $Cp_2Ti(Ph)Cl$ is an effective pinacol coupling catalyst for both aromatic and aliphatic aldehydes in the presence of Me₃SiCl and Zn. The catalytic intramolecular pinacol coupling of dials afforded cyclic *trans*-1,2-diols with excellent *trans*-selectivities of *trans*: cis = >90:10, indicative of non-chelation intermediates being involved in the present reductive cyclization. These results are in striking contrast to reported *cis*-selective methods.

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