Highly *trans*-selective intramolecular pinacol coupling of dials catalyzed by bulky Cp_2TiPh

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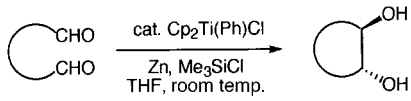
$Cp_2Ti(Ph)Cl$ in the presence of Me_3SiCl and Zn provides an effective pinacol coupling catalyst for aromatic and aliphatic aldehydes.

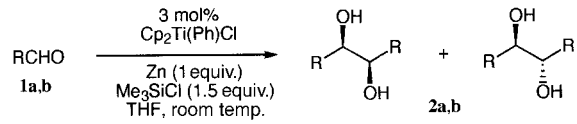
Chiral 1,2-diols have found extensive use as asymmetric ligands for catalytic asymmetric reactions[1] and as chiral auxiliaries for diastereoselective transformation of carbonyl substrates.[2] Such valuable diols are commonly obtained by the resolution of racemic products prepared from a wide variety 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 metal-atom-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 $Cp_2Ti(Ph)Cl$-catalyzed intramolecular pinacol coupling of dials, which gave cyclic 1,2-diols in moderate to good yields with excellent *trans*-selectivity under mild conditions (Scheme 1).

Cp_2TiCl has received much attention as an excellent single-electron reductant in organic synthesis.[5] In this context, Teuben *et al.* have reported the Cp_2TiPh-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 Cp_2TiCl was not effective for the above two reductive transformations. The phenyltitanium(III) reagent was readily prepared *in situ via* reduction of Cp_2TiCl_2 with Pr^iMgCl followed by the addition of PhMgBr.[6,7] The same reactive species may alternatively be generated by reducing $Cp_2Ti(Ph)Cl$[8] with Zn powder.[9] Given this fact, $Cp_2Ti(Ph)Cl$ should catalyze pinacol coupling reactions in the presence of a stoichiometric amount of Zn. In fact, stoichiometric reaction using equimolar amounts of $Cp_2Ti(Ph)Cl$ 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 Me_3SiCl (1.5 equiv.) was added to a mixture of 3 mol% $Cp_2Ti(Ph)Cl$ 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 $Cp_2Ti(Ph)Cl$ is an efficient catalyst for the pinacol coupling of both aromatic and aliphatic aldehydes.



Scheme 1

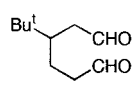
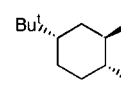
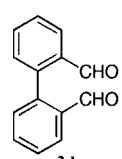
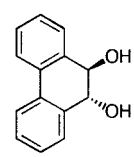
On the basis of the above results, we applied our new catalytic system to the intramolecular reductive coupling of dials (Table 1). In the presence of 6 mol% $Cp_2Ti(Ph)Cl$, the acid sensitive 1,5-dial **3a** was reduced at ambient temperature over 38 h to afford the desired diol **4a** in 40% yield 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 SmI_2[11] or $TiCl_3(THF)_3$–Bu^tOH 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



2a R = Ph, 0.12 M, 70 min, 88% (*threo* : *erythro* = 71 : 29)
2b R = CH_2CH_2Ph, 0.2 M, 18 h, 80% (*threo* : *erythro* = 64 : 36)

Scheme 2

Table 1 Intramolecular pinacol coupling of dials **3a–d** using $Cp_2Ti(Ph)Cl$–Zn–Me_3SiCl[a]

Dial	Catalyst/ mol%	*t*/h	Diol	Yield[b] (%)	*trans* : *cis*[c]
 **3a**	6	38	 **4a**	40%	99 : 1
 **3b**	10	14	 **4b**	65%	99 : 1
 **3c**	10	14	 **4c**	52%	single isomer
 **3d**	6	14	 **4d**	70%	91 : 9

[a] Conditions: $Cp_2Ti(Ph)Cl$, Zn (1 equiv.), Me_3SiCl (1.5 equiv), THF (0.05 M), room temp. [b] Isolated yields. [c] Ratios determined by ^1H NMR analysis of isolated products.

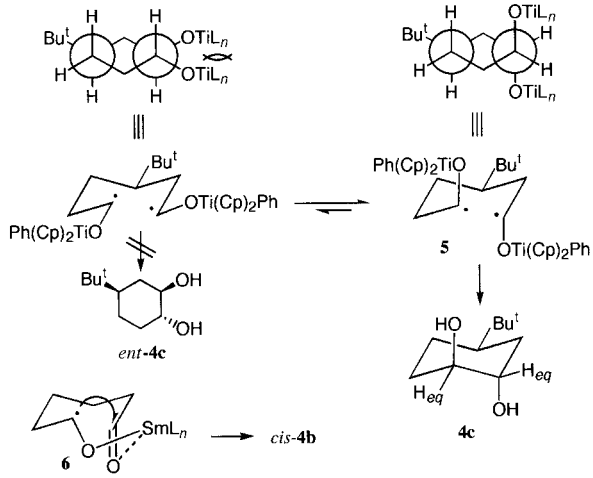


Fig. 1 Mechanism of stereoselection.

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 ^{1}H 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 ^{13}C 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 SmI_2 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 Me_3SiCl 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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