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A highly *dl*-stereoselective pinacolization of aromatic aldehydes mediated by $TiCl_4$–Zn

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Reduction of $TiCl_4(THF)_4$ with Zn in CH_2Cl_2 gave a green solution, which was found to promote the reductive coupling of aromatic aldehydes to yield 1,2-diols with high *threo* selectivity.

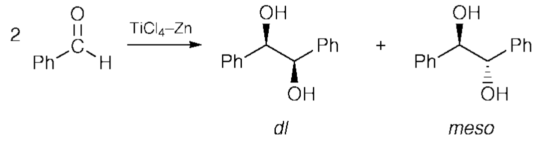
The pinacol coupling reaction, which allows the generation of 1,2-diols in one step, is a powerful synthetic reaction, and therefore has been recognized as one of the most significant C–C bond forming processes in synthetic organic chemistry.[1,2] In addition, *threo*-1,2-diols have, after resolution, frequently been utilized as auxiliaries in asymmetric synthesis.[3] Although a number of methods have been developed for the reductive coupling of carbonyl compounds,[4–6] selective pinacolization to *threo*-diols has only been found with stannylene precursors,[7] 'active titanium(III) reagents' prepared from $TiCl_4$/BuLi in Et_2O at −78 °C,[8] $TiCl_4/Bu^i{}_2Te$ in DME,[9] $TiCl_3/CH_2Cl_2$ solution[10] or $(Cp_2TiCl)_2$.[11,12] $(Cp_2TiCl)_2$, a binuclear complex, can be easily prepared from Cp_2TiCl_2 and used in stiochiometric or catalytic amounts in the pinacol coupling reaction. Many of these reagents are expensive and/or air sensitive.

Here we report the $TiCl_4$–Zn promoted reductive coupling of aromatic aldehydes in anhydrous solvent at room temperature. By the choice of an appropriate mole ratio of $TiCl_4$ and Zn and an appropriate coordinating additive such as TMEDA, TiCl-Zn and $TiCl_4$–Zn–TMEDA reduce benzaldehyde and other actived aromatic aldehydes to the corresponding pinacols in good yields and, what is more important, the coupling is highly *dl* selective.

It is noteworthy that the reagents used are readily available, inexpensive and stable to air oxidation, and the method is easier and more convenient compared with those so far reported. Thus, we produced 'actived titanium' and reduced aldehydes in one pot in only a short time.

In 1973, Mukaiyama[13] reported that $TiCl_4$–Zn reduced aromatic aldehydes or ketones to produce the corresponding 1,2-diols in high yield, but the stereoselectivity was not reported. At the outset of the study, we used THF as solvent, with an aldehyde to $TiCl_4$ to Zn ratio of 1:1.5:3, and obtained the hydrobenzoin with a *dl*:*meso* ratio of 3:1. When CH_2Cl_2 was selected as the solvent, with THF as a ligand and a mole ratio of $TiCl_4$ to Zn of 2:1, better results were obtained.

Table 1 Coupling of benzaldehyde mediated by $TiCl_4$–Zn



Entry	Additive (mmol)	Yield (%)[a]	*di*:*meso*[b]
1[c]		57	94:1
2[d]		55	108:1
3[e]		0	—
4[c]	Py[f] (10.95)	42	5.2:1
5[c]	DME[f] (5.48)	58	129:1
6[c]	TMEDA[f] (5.48)	77	*dl* only

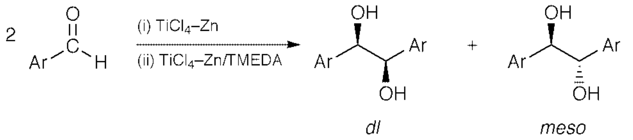
[a] Pinacol isolated yield. [b] Determined by ^1H NMR (400 MHz). [c] $TiCl_4$ reduction 3 min. [d] $TiCl_4$ reduction 18 min. [e] $TiCl_4$ reduction 1 h. [f] Added and stirred for 2 min prior to addition of benzaldehyde.

A typical procedure is as follows: THF (11.7 mmol) was added dropwise to a solution of $TiCl_4$ (3.65 mmol) in 10 ml of CH_2Cl_2 under an atmosphere of argon at room temperature. To this solution Zn (1.82 mmol) was added in one portion. The color of the solution changed to green immediately. After stirring for 3 min benzaldehyde (3.65 mmol) in 3 ml of CH_2Cl_2 was added in one portion. After 30 min of stirring, the reaction was quenched with 15 ml of 10% K_2CO_3 and extracted with EtOAc followed by chromatography to give 0.22 g of hydrobenzoin (57%, 94:1 *dl*:*meso*).

When the reduction time was less than 20 min, acceptable yields and high *dl* selectivities were obtained. However, when the reduction time was greater than 1 h, the color of solution changes from green to black, and no product was obtained. According to the reports of Piotr Sobota[14] and Kirrsten Foling,[15] we assume that the $TiCl_4(THF)_2$ was first reduced to $[Ti_2(\mu\text{-Cl})_2Cl_4(THF)_4]$ by Zn in CH_2Cl_2; $ZnCl_2$ can then abstract chlorine from $[Ti_2(\mu\text{-Cl})_2Cl_4(THF)_4]$ and form ionized $[TiCl_2(THF)_4{}^+\cdot ZnCl_3(THF)^-]$. We think the binuclear complex $[Ti_2(\mu\text{-Cl})_2Cl_4(THF)_4]$ is the active compound which reduces the benzaldehyde to pinacol with high *dl*-selectivity, exactly as $(Cp_2TiCl)_2$ has high *dl*-selectivity. The ionized $[TiCl_2(THF)_4{}^+\cdot ZnCl_3(THF)^-]$ has no activity to benzaldehyde. In order to lower the Lewis activity of the $ZnCl_2$ and suppress ionization of the $[Ti_2(\mu\text{-Cl})_2Cl_4(THF)_4]$, a coordinating additive, especially Lewis bases such as Py and TMEDA, is added. When the reduction was carried out in the presence of 1.5 equiv. of TMEDA as an additive the yield improved to 76% and only the *dl*-isomer was obtained.

Under the optimised conditions, a variety of symmetrical 1,2-diols were synthesized in good yields and excellent selectivity, and could be obtained diastereomerically pure after

Table 2 Reductive coupling of aldehyes under optimised conditions



Entry	Ar	Yield (%)[a]	*dl*:*meso*[b]
1[c]	Ph	57	94:1
2[d]	Ph	77	*dl* only
3[c]	*p*-FC_6H_4	80	25:1
4[d]	*p*-FC_6H_4	88	*dl* only
5[c]	*p*-ClC_6H_4	86	52:1
6[d]	*p*-ClC_6H_4	86	*dl* only
7[c]	*p*-BrC_6H_4	90	51:1
8[d]	*p*-BrC_6H_4	92	*dl* only
9[c]	*m*-BrC_6H_4	92	54:1
10[d]	*m*-BrC_6H_4	94	346:1
11[c]	*p*-CNC_6H_4	92	*dl* only
12[d]	*p*-CNC_6H_4	96	*dl* only

[a] Pinacol isolated yield. [b] Ratio determined by ^1H NMR (400 MHz). [c] Conditions (i). [d] Conditions (ii).

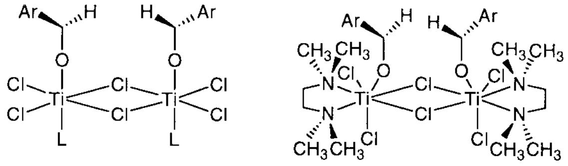


Fig. 1

a single recrystallization. Functional groups, such as halide and cyano groups, are tolerated. Aromatic aldehydes bearing an electron-donating group showed lower reactivity, for example, *p*-anisaldehyde afforded no significant conversion *via* TLC observation.

Mechanistically it seems reasonable to assume that the active species is a binuclear titanium complex binding both ketyl radicals, in which the Ar groups are arranged *anti* to each other to minimized steric interaction. When the binuclear titanium complex is coordinated with TMEDA, the sterically crowded environment drastically improved the pinacol diastereoselectivities (Fig. 1).

Notes and references

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