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Highly Diastereoselective Pinacol Coupling of Aldehydes Catalyzed by Titanium-Schiff Base Complexes

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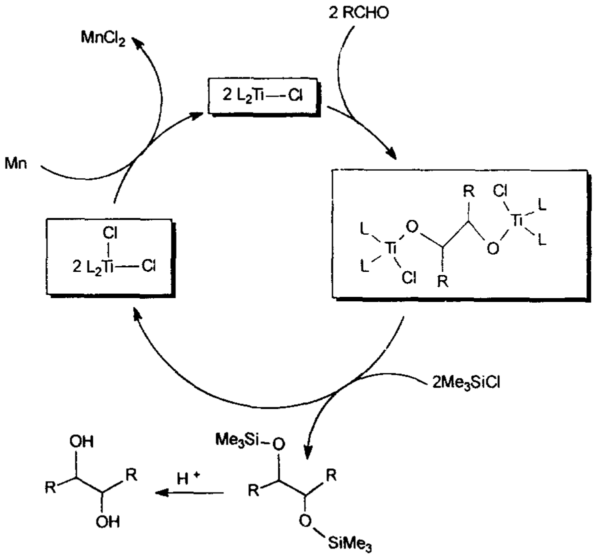
Abstract: A new effective methodology for a highly diastereoselective pinacol coupling of aldehydes is described. The method employs 3 mol % of a complex prepared *in situ* from $TiCl_4(THF)_2$ and a Schiff base in acetonitrile. The catalytic cycle is realized with Me_3SiCl and Mn as reducing agent. The dependence of the diastereoselectivity on the Schiff base used is reported.

The diasteroselective pinacol coupling of carbonyl compounds represents one of the most effective routes for the synthesis of 1,2-diols.[1] The reaction takes place *via* reductive coupling of the carbonyl moieties mediated by a metal in a low oxidation state.[2] Although the reaction is widely employed for the synthesis of alkenes, macrocyclics and diols,[1a] it suffers from the requirement of stoichiometric amounts of a reducing metal which may be difficult to prepare. A valid solution to this problem is the introduction of catalytic methodologies. Recently, Fürstner has described the McMurry coupling reaction using TMSCl and a bimetal redox system with Zn as the stoichiometric reducing metal and $TiCl_3$ in catalytic amounts.[3] In the light of this result, other bimetal redox systems were successfully employed.[4]



Scheme 1

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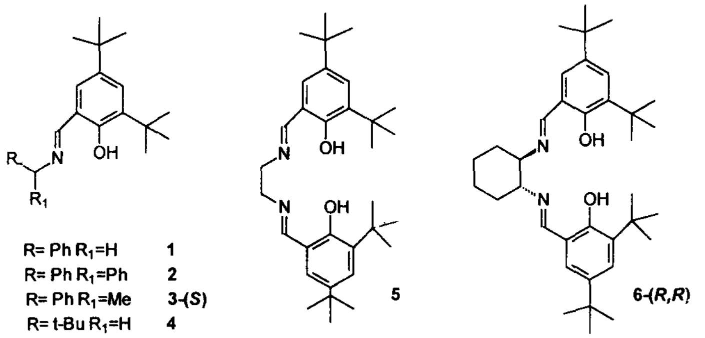
Moreover, the combined use of catalytic amounts of the expensive *rac*-ethylenebis(η^5-tetrahydroindenyltitanium)dichloride, TMSCl and Zn afforded a highly diastereoselective (up to 96:4) pinacol coupling of aromatic aldehydes. In spite of the effectiveness of the method, to achieve the highest diastereoselectivity it is necessary to employ $MgBr_2$ as additive and to add the aldehyde slowly to the reaction mixture.[5]

Herein, we describe a new simple method for the pinacol coupling of aldehydes based on the use of titanium complexes prepared from Schiff bases and titanium salts. These complexes have been utilized in several enantioselective transformations,[6] but to the best to our knowledge, their employment in redox mediated reactions has not yet been described. The reaction was carried out simply by adding the aldehydes, Mn and TMSCl to 3 mol % of titanium-Schiff base complex in acetonitrile. A plausible mechanism is shown in Scheme 1.

The structure determination of the imine-titanium complexes was recently reported,[7] and these showed themselves to be highly air- and moisture-sensitive. In order to avoid this drawback, we prepared the titanium complexes *in situ* by an exchange reaction between commercially available $TiCl_4(THF)_2$ and the Schiff base in a ratio 1:2. A large library of Schiff bases can be easily prepared by the reaction between amines or aminoalcohols with substituted salicylaldehydes.[8] We have synthesized and tested a series of Schiff bases (L=**1-6**) as ligands of $TiCl_4(THF)_2$ (Scheme 2).

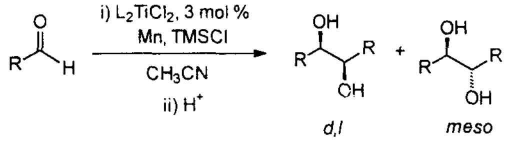


$$2\,L\,(1\text{-}6) + TiCl_4(THF)_2 \xrightarrow{CH_3CN} L_2TiCl_2$$

Scheme 2

The addition of solid $TiCl_4(THF)_2$ to **1-6** in CH_3CN yields the red titanium complexes. The protocol of this pinacol coupling reaction is really simple and consists in the formation of the titanium complex followed by the addition of Mn powder and TMSCl at 0°C. To the green-blue titanium(III) complex so obtained, the aldehyde is added at once. As shown in Table 1 the reaction affords diols in good yields and excellent diastereoselectivities with a variety of aldehydes. *It is important to note that the diastereoselectivity depends on the Schiff base used* (Table 1, entry 1-5, 7-8 and 9-10). Moreover we have found that the use of Mn as reductant affords the diols with higher yields than Zn, however Zn was necessary for the pinacol coupling of 3-phenylpropionaldehyde (entry 18). A remarkable aspect of this process is that the Schiff base increases the rate and the reaction yield. In fact, carrying out the reaction following this method 1,2-bis(phenyl)-1,2-ethanediol is obtained in 24 hours in a 80 % yield, while, without the ligand, product formation was only achieved in 48 h in a 40 % yield.

Table 1. Diastereoselective Pinacol Coupling of Aldehydes catalyzed by titanium-Schiff bases complexes



Entry	Ligand	RCHO	Yield[a] %	dl : meso[b]
1	**1**	PhCHO	75	**99:1**
2	**2**	PhCHO	80	**97:3**
3	**3**	PhCHO	60	92:8
4	**5**	PhCHO	43	95:5
5	**6**	PhCHO	40	90:10[c]
6	**2**	2-ThienylCHO	70	88:12
7	**3**	1- NaphtylCHO	66	70:30
8	**4**	1- NaphtylCHO	60	52:48
9	**1**	4-MeO-C_6H_4CHO	65	**92:8**
10	**4**	4-MeO-C_6H_4CHO	71	**94:6**
11	**2**	2-BrC_6H_4CHO	66	58:42
12	**1**	3-BrC_6H_4CHO	75	**96:4**
13	**1**	4-BrC_6H_4CHO	83	**95:5**
14	**1**	2-FurylCHO	76	88:12
15	**1**	4-Ph-C_6H_4CHO	83	**91:9**
16	**2**	4-AcOC_6H_4CHO	81	**91:9**[d]
17	**3**	PhCH=CHCHO	40	84:16[e]
18	**3**	PhCH_2CH_2CHO	48	62:32[e,f]

a) Isolated yield after flash chromatography. The rest being starting material. b) The dl : meso ratio was determined by GC or ^{1}H-NMR analysis. c) The diol was isolated with an enantiomeric excess of 10 %. d) A partial hydrolysis of the acetoxy group was observed after the acidic treatment. e) The rest being a mixture of starting material and the corresponding primary alcohol. f) The reaction was performed with Zn as reducing agent.

This result is particularly noteworthy and opens an access to the construction of tailored chiral Schiff bases and their employment in the enantioselective pinacol coupling.

Typical experimental procedure for the pinacol coupling:

To a solution of the Schiff base (0.06 mmol) in CH_3CN (2ml), $TiCl_4(THF)_2$ (0.03 mmol) was added under nitrogen. The resulting red solution was stirred 30 minutes at room temperature then cooled at 0°C. The Mn powder (99.9%, 50mesh, 6 mmol) was added followed by the addition of Me_3SiCl (2.2 mmol). The suspension becomes green-blue depending on the Schiff base used. After few minutes, the aldehyde (2 mmol) was added and the red-maroon suspension was stirred at room temperature for two days. The suspension was quenched with a saturated solution of $NaHCO_3$, diluted with ethyl acetate and then filtered through a sintered glass funnel. The aqueous phase was separated and extracted with ethyl acetate (2 x 5mL). The organic phases were combined and evaporated under reduced pressure. The resulting brown-red oil was dissolved in THF: HCl 1M (2:1, 5mL) and stirred at room temperature until the pinacol product was completely desilylated (checked by TLC). After 2 hours the reaction was diluted with water the THF was evaporated under reduce pressure and the product extracted with ethyl acetate. The organic phases were collected, dried (Na_2SO_4) and concentrated to give an oil purified by chromatography.

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