## Diastereoselective Ce(III)-Catalyzed Pinacol Couplings of Aldehydes<sup>1</sup>

Ulrich Groth,\* Mario Jeske

Fakultät für Chemie der Universität Konstanz, Universitätsstr. 10, Postfach M-720, 78457 Konstanz, Germany Fax +49-7531-882885; E-mail: ulrich.groth@uni-konstanz.de *Received 30 October 2000* 

**Abstract:** Aliphatic and aromatic aldehydes were converted into the corresponding pinacoles by using different cerium catalysts. Ce(OtBu)<sub>3</sub> proved to be superior over other cerium(III) catalysts. Especially the highly diastereoselective pinacol coupling of sterically non demanding aldehydes such as hexanal is remarkable.

Key words: catalysis, cerium, diastereoselectivity, lanthanides, pinacol coupling

Generally, 1,2-diols can be generated by bishydroxylation of olefinic double bonds<sup>2</sup> or reductive coupling of carbonyl compounds.<sup>3</sup> The last method plays an important role in the synthesis of HIV-protease inhibitors<sup>4</sup> and natural products<sup>5</sup> such as taxol. For an application in natural product synthesis a diastereoselective process is required.

Due to the economical, ecological and medicinal relevance transition metal catalyzed pinacol couplings are of fundamental importance. According to Hirao<sup>6</sup> and Endo<sup>7</sup> catalytic pinacol couplings can be initiated by low-valence vanadium and samarium. A broad variety of carbonyl compounds can be applied but high diastereoselectivities were only observed for sterically demanding substrates such as pivalaldehyde and cyclohexylcarbaldehyde. By applying these coupling reagents to  $\alpha$ -substituted aliphatic aldehydes the diastereoselectivities decreased to a 50: 50 ratio of rac to meso.

Gansäuer obtained high diastereoselectivities of up to 98.5: 1.5 in the pinacol coupling of aromatic aldeyhdes by using catalytic amounts of racemic ethylene-bis- $(\eta^5$ -tet-rahydroindenyl)titanium dichloride (EBTHITiCl<sub>2</sub>) <sup>8</sup> and in situ reduction with stoichiometric amounts of zinc.<sup>9</sup> This method can be applied only to aromatic and  $\alpha,\beta$ -un-saturated aldehydes but not to aliphatic aldehydes. Schiff base ligands were also utilized for titanium-catalyzed pinacol couplings by Cozzi and Umani–Ronchi.<sup>10</sup> In this case the obtained diastereoselectivities were comparable to the (EBTHITiCl<sub>2</sub>)-system, but in analogy to Gansäuer, aliphatic aldehydes cannot be coupled to the corresponding pinacoles.

With a manganese promoted and titanocene catalyzed pinacol coupling aliphatic aldehydes were converted to the 1,2-diols in good yields.<sup>11</sup> Nevertheless the observed diastereoselectivities were low. Hexanal was coupled with a diastereomeric ratio of 1.5: 1.

Recently, we reported a diastereoselective coupling of aldehydes to the corresponding pinacols using  $Ce(OiPr)_3^{12}$  as catalyst.<sup>13</sup> Diethyl zinc was utilized as reducing agent and, in analogy to Fürstner,<sup>14</sup> TMSCl served to cleave the oxygen cerium bond. This system allows not only the reductive coupling of aromatic aldehydes but also aliphatic aldehydes were converted to 1,2-diols in good yields. The diastereoselectivities ranged from 88:12 up to 98:2 in favor of the *rac* isomer. Nevertheless aliphatic aldehydes without  $\alpha$ -substitution such as hexanal cannot be coupled reductively with our catalytic system in which the limiting factor seems to be diethyl zinc. Instead, the addition product of an ethyl group to the carbonyl function was isolated exclusively.

Consequently, this side reaction had to be suppressed by a suitable variation of the reducing agent. Therefore, the cerium catalyzed pinacol coupling was investigated by applying highly electropositive metals such as magnesium, zinc and manganese instead of diethyl zinc. In order to prove scope and limitations of the pinacol coupling, benzaldehyde and hexanal were compared. Benzaldehyde was chosen because it yields the best results in coupling reactions with diethyl zinc as reducing agent whereas hexanal did not afford any coupling products.



Figure Cerium(III)-catalyzed pinacol couplings of aldehydes.

The results of the reductive couplings are summarized in Table 1.

**Table 1** $Ce(OiPr)_3$ -Catalyzed Pinacol Couplings of Benzaldehydeand Hexanal wit Different Reducing Agents (M = Mn, Zn, Mg).

entry	metal	R = Ph		$\mathbf{R} = \mathbf{n} - \mathbf{C}_{5} \mathbf{H}_{11}$		
		yield of <b>2</b> [% ]	2a : 2b	yield of <b>2</b> [%]	2a : 2b	
1	Mg	94	65 : 35	74	53 : 47	
2	Zn	90	77 : 23	79	83:17	
3	Mn	96	80 : 20	82	85 : 15	

Benzaldehyde could be coupled in high yields (>90%) and also in good diastereoselectivities of up to 80: 20 to the corresponding pinacol. Best results were obtained by using manganese as reducing agent (entry 3). Applying the Downloaded by: Florida State University Libraries. Copyrighted material

above described systems allows for the first time the diastereoselective coupling of hexanal. The 1,2-diol was isolated in yields of up to 82% and diastereoselectivities of up to 85: 15 (entry 3). The reductive coupling of pentanal and heptanal gave similar results. To the best of our knowledge this reaction achieves the highest diastereoselectivities in the coupling of sterically non demanding aliphatic aldehydes published until now. Based on its ability of highly diastereoselective pinacol couplings manganese was favored over magnesium and zinc (entries 1-3). Consequently, all further coupling reactions were carried out with manganese.<sup>15</sup>

Since all above mentioned studies were carried out with  $Ce(OiPr)_3$  the influence of the cerium ligand was investigated next.

 Table 2
 Cerium(III)-Catalyzed Pinacol Couplings of Benzaldehyde

 and Hexanal by Variation of the Cerium Ligand.

entry	cerium reagent	R = Ph		$R = n - C_5 H_{11}$	
		yield of <b>2</b> [%]	2a : 2b	yield of <b>2</b> [%]	2a : 2b
1	CeCl <sub>3</sub>	86	58 : 42	68	64 : 36
2	ClCe(OiPr) <sub>2</sub>	90	68 : 32	75	<b>80 : 20</b>
3	Ce(OiPr) <sub>3</sub>	96	80 : 20	82	85 : 15
4	Ce(OCHiPr <sub>2</sub> ) <sub>3</sub>	91	83:17	75	85 : 15
5	$Ce(OtBu)_3$	94	85 : 15	73	87:13

As shown in Table 2 remarkable differences between cerium chlorides and cerium alkoxides were observed. Accordingly, the use of catalytic amounts of  $CeCl_3$  leads to acceptable yields but very low diastereoselectivities (entry 1). Similar results were obtained using  $ClCe(OiPr)_2$  (entry 2). Nevertheless the yield and especially the diastereoselectivity were increased by changing from cerium(III)chlorides to cerium(III)alkoxides (entries 3-5). Best results could be achieved by using more bulky ligands such as *tert*-butoxide (entry 5).<sup>16</sup>

In summary, we have presented an efficient method for the highly diastereoselective pinacol coupling of aldehydes. Best results were obtained by using Ce(OtBu)<sub>3</sub> as catalyst. To the best of our knowledge aliphatic  $\alpha$ -unsubstituted aldehydes could be coupled with high diastereoselectivity for the first time. The pinacol coupling of functionalized aldehydes is under current investigation in our group. These results should be of broad interest in natural product synthesis.

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- (16) Typical Experimental Procedure: The reactions were carried out under argon atmosphere using Schlenk techniques. Substances which are sensitive against moisture and oxidation were stored in a glove box. The cerium alkoxides Ce(OtBu)<sub>3</sub> and Ce(OCHiPr<sub>2</sub>)<sub>3</sub> were synthesized by refluxing Ce(OiPr)<sub>3</sub> with 10 equivalents of the corresponding alcohol in toluene. After 15 h the excess of alcohol was removed in vacuo. In a Schlenk tube 5 mL THF were added to 32 mg (0.1 mmol; 3 mol%) Ce(OtBu)<sub>3</sub> and 326 mg (6.0 mmol; 2.0 equivalents) manganese powder. Subsequently, 3.0 mL (3.0 mmol) of an 1.0M aldehyde solution in THF and 3.0 ml (4.5 mmol; 1.5 equivalents) of an 1.5 M TMSCl solution in THF were added slowly by use of a syringe pump. After 24 h 25 mL of

an aqueous 2 N HCl solution were added. The reaction mixture was extracted with diethyl ether  $(3 \times 50 \text{ mL})$ . The combined organic layers were washed with a saturated aqueous NaHCO<sub>3</sub> solution  $(3 \times 50 \text{ mL})$  and brine  $(3 \times 50 \text{ mL})$  and dried over magnesium sulfate. The solvent was removed by evaporation and the residue was purified by flash chromatography on silica gel (petroleum ether / diethyl ether 3:1). The *rac-/meso*-ratios were determined by <sup>1</sup>H NMR-analysis of the crude reaction products.

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