

Pinacol coupling of aromatic aldehydes catalysed by a titanocene complex: a transition metal catalysed radical reaction

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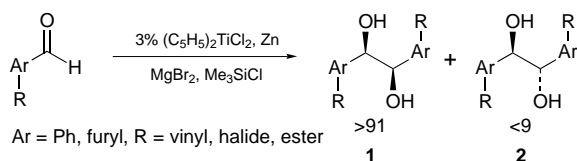
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A trinuclear complex derived from titanocene chloride and magnesium bromide is an efficient catalyst for the pinacol coupling of aromatic aldehydes; the 1,2-diols are obtained with good diastereoselectivity and a wide variety of sensitive functional groups are tolerated.

The reductive coupling of carbonyl compounds is the most direct way to 1,2-diols by forming a functionalized carbon-carbon bond.¹ Many stoichiometric reagents for this reaction have been developed² and the pinacol coupling has also been applied as a key step in the synthesis of several natural products.³ To avoid the use of expensive and toxic reagents the development of an efficient transition metal catalysed pinacol coupling is desirable. Here the first titanocene dichloride catalysed pinacol coupling of aromatic aldehydes is described yielding the corresponding 1,2-diols at room temperature in good yields with good diastereoselectivities. Pinacol coupling is not only a shortcut of the otherwise existing two-step sequence, coupling of the aldehydes to an (*E*)-stilbene with stoichiometric amounts of titanium reagents as in McMurry coupling reactions, and a *syn,vic*-dihydroxylation of the central double bond. More importantly the pinacol route to 1,2-diols tolerates certain functional groups that are sensitive to the McMurry reagent and/or to the dihydroxylation reaction. The pinacol coupling used here catalytically uses cheap, readily available, non-toxic reagents.

The only reported catalytic pinacol couplings involve harsh reaction conditions, low selectivities and low functional group tolerance.⁴ The catalysts, ruthenium complexes^{4a} or samarium iodide,^{4b} do not allow control of diastereoselectivity or enantioselectivity by ligand variations.

Based on the ability of cyclopentadienyl-bonded titanium(III) reagents^{2a,c} to induce stoichiometric pinacol couplings it seemed possible to develop a catalytic cycle. For this purpose the formed diol has to be removed from titanium with concomitant regeneration of (C₅H₅)₂TiCl₂.⁵ *In situ* reduction to the titanium(III) reagent then finishes the catalytic cycle.⁶ Benzaldehyde coupling in the presence of Zn and Me₂SiCl₂ with 10% (C₅H₅)₂TiCl₂ gives complete conversion to pinacol after hydrolysis in less than 10 min. Me₃SiCl as additive also gives clean product formation. Without the catalyst, conversion was not observed with Me₂SiCl₂ as additive. Me₃SiCl and Zn react to give pinacol over 20 h albeit without diastereoselectivity.⁷ Catalytic acceleration of the reaction was therefore significant as was the improvement in diastereoselectivity. Interestingly, however, lowering the temperature at which the catalytic coupling was performed leads to reduced selectivity and pronouncedly longer reaction times. One step in the catalytic cycle was slow and thus a competing, less selective



Scheme 1 Titanocene catalysed pinacol coupling of aromatic aldehydes

pathway operated. It is known that titanium alkoxides are less selective stoichiometric reagents in pinacol couplings⁸ and that both coupling and reduction of (C₅H₅)₂TiCl₂ are fast at and below room temperature.^{2,6} Thus, silylation is the rate determining step in the catalytic cycle. To improve the diastereoselectivity a solution of benzaldehyde and Me₃SiCl in THF was slowly added to a mixture of (C₅H₅)₂TiCl₂ and Zn in THF. The selectivity increased and the yield remained high. Selectivity is further improved by adding 1 equiv. of MgBr₂ to the benzaldehyde solution. This gave a tighter dimeric titanium catalyst by replacing Zn with Mg.

Diethyl ether and dichloromethane gave inferior results. Other silylating reagents, *e.g.* Me₂Bu^tSiCl, did not give any reaction.

Under the optimised conditions a variety of symmetrical 1,2-diols were synthesised in good yields and selectivities and could be obtained diastereomerically pure after a single recrystallisation. Functional groups interfering with McMurry couplings or dihydroxylation reactions such as chlorides, double bonds, phenolate esters and α,β -unsaturated esters are readily tolerated. Although initial experiments were performed on a small scale, the reaction can be readily scaled up and gave the same results using 0.5, 5 or 50 mmol of substrate. In the latter case 320 mg of catalyst was used. This compared favourably with the use of 24.9 g of (C₅H₅)₂TiCl₂ in the stoichiometric reaction. In effect (C₅H₅)₂TiCl₂ is replaced by the cheaper Me₃SiCl. A stoichiometric reductant was needed in both cases. Other stoichiometric or catalytic reagents, *e.g.* SmI₂, are even more expensive and less selective. The cheapest source of inherently toxic osmium for a dihydroxylation reaction is about 40 times more expensive than the essentially non-toxic (C₅H₅)₂TiCl₂.

Mechanistically it seems reasonable to assume that the catalytically active species in the catalytic cycle is a dimeric

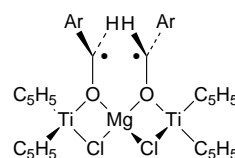


Fig. 1 Likely catalytically active species for the dimerisation of ketyl radicals both bound to the dimeric titanium catalyst

Table 1 Coupling of benzaldehyde at 0.1 m in the presence of Me₂SiCl₂ or Me₃SiCl

Amount of catalyst (%)	<i>t</i> /h	<i>T</i> /°C	Yield (%)	1 : 2
10	1.2	0	93	86 : 14
10	22	-40	92	70 : 30
3	0.25	25	96	84 : 16 ^a
3	3	25	88	89 : 11 ^{a,b}
3	3	25	90	95 : 5 ^{a,c}

^a 1.5 equiv. of Me₃SiCl. ^b Slow addition of PhCHO and Me₃SiCl. ^c Slow addition in the presence of MgBr₂

titanium complex binding both ketyl radicals. The observed *syn*-selectivity can then be readily explained by minimization of steric interference through *anti*-orientation of the R groups in the complex. This reaction is therefore an example of a transition metal catalysed radical reaction.

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Table 2 Pinacol coupling of substituted aldehydes under optimised conditions

R-Ar	t/h	Yield (%)	1:2
4-Methylphenyl	2.5	82	92:8
4-Chlorophenyl	3	78	93:7
3-Chlorophenyl	3	87	93:7
4-Vinylphenyl	2	91	92:8
4-Acetoxyphenyl	3	83	92:8
4-Crotonyloxy-phenyl	2	79	92:8
4- <i>tert</i> -Butylphenyl	3	80	94:6
2-Furyl	1.5	88	92:8

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