

Novel Concept for Efficient Transition-Metal-Catalyzed Reactions: A Highly Diastereoselective Titanocene-Catalyzed Pinacol Coupling under Buffered Protic Conditions

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Recently, a great deal of attention has been devoted to the development of catalytic reactions from stoichiometric transformations. Since the first report on the use of TMSCl to effect a McMurry coupling catalytic in titanium powder,¹ this concept was successfully applied in a number of reactions.^{2–4} Although powerful in most cases, this method has, however, two disadvantages. First, after hydrolysis during work-up hexamethyldisiloxane is generated in stoichiometric amounts that can not be readily recycled and must be disposed of as waste. Second, silylation frequently is the slowest step in the catalytic cycle, and therefore, TMSCl and similarly active or even more reactive silylating reagents, e.g., TMSOTf, have to be employed to render the reaction catalytic.

Herein, we address these disadvantages and disclose our results on the first example of achieving catalytic turnover by protonation of the metal–oxygen bond. Protonations are amongst the fastest reactions, and therefore, catalytic turnover could be increased compared to silylation. The proton donor used in the catalytic reaction should be readily recovered by protonation of the formed base with a strong acid. These advantages over silylation should become especially important in large-scale applications.

We decided to probe this novel concept in designing titanocene-catalyzed pinacol couplings⁵ as part of our ongoing program directed towards the development of transition-metal-catalyzed radical reactions (Figure 1). To achieve our goal, the utilized acid must be strong enough to protonate the titanium–oxygen bond. However, the stoichiometric reductant, i.e. a metal powder, should not be oxidized or the catalyst deactivated by complexation of the corresponding base. Clearly, this sets limitations on the acidity, i.e., the pK_a value, the steric accessibility of the acid, and the donor strength of the corresponding base. For our purpose, an ideal class of acids seemed to be pyridine hydrochlorides. According to their pK_a values in water, e.g., 5.25 for pyridine hydrochloride⁶ (**3**), 6.65 for 2,6-lutidine hydrochloride⁶ (**4**), 7.43 for 2,4,6-collidine hydrochloride⁶ (**5**), protonation of titanocene alkoxides seemed to be readily possible (Figure 2).

Initial experiments were conducted with benzaldehyde, 3 mol % titanocene dichloride as precatalyst, and manganese

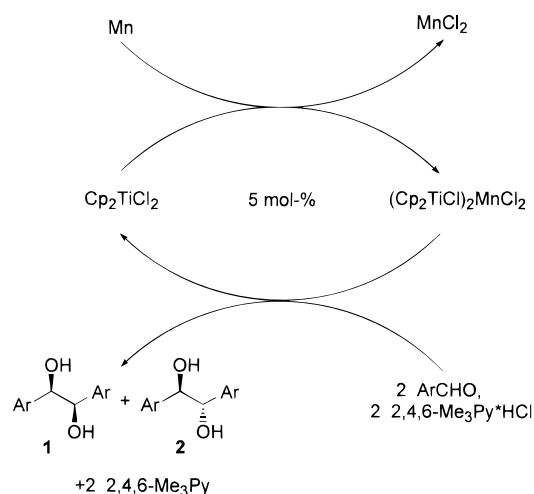


Figure 1. Titanocene-catalyzed pinacol couplings under buffered protic conditions.

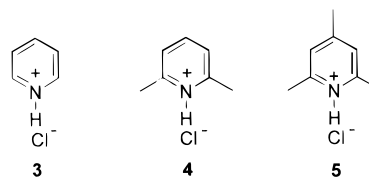


Figure 2. Pyridine hydrochlorides used in this study.

as stoichiometric reductant at 0.1 M concentration in THF with **3–5** as proton donors. The results of these studies are summarized in Table 1.

The effect of substitution on the pyridine hydrochlorides' ability to enable catalytic reactions was dramatic. Commercial pyridine hydrochloride **3** as acid did not lead to detectable conversion to products. No titanium(III) reagent was formed (Table 1, entry 1). 2,6-Lutidine hydrochloride **4** gave the 1,2-diol in 75 % yield but with low diastereoselectivity of 82:18 in favor of **1** (Table 1, entry 2). Gratifyingly, collidine hydrochloride **5** led to a noticeable improvement in diastereoselectivity (95:5), albeit with a reduced yield of 68% (Table 1, entry 3). A small amount of benzylalcohol was also formed, and about 20 % of benzaldehyde remained unreacted. It is reasonable to assume that the reason for the superiority of **5** for achieving catalytic turnover with high diastereoselectivity is a combination of its inability to promote electron transfer from Mn to benzaldehyde and its weak complexation tendency with titanium. When Zn was used instead of Mn diastereoselectivity decreased dramatically (Table 1, entry 4). Other metals used as stoichiometric reductants, e.g., Al, did not lead to catalytic turnover. Compared to the ability of Zn/TMSCl or Mn/TMSCl to initiate pinacol couplings of aldehydes⁷ and ketones, our stoichiometric reductive system Mn/**5** did not react with aliphatic or aromatic ketones at all and only very sluggishly with aliphatic aldehydes or benzaldehyde (Table 1, entry 5) without the presence of a catalyst. The reason for the superiority of Mn as stoichiometric reductant compared to Zn is unclear at present; however, Zn induces the uncatalyzed reaction significantly faster than Mn (Table 1, entry 6) presumably, because the formed ZnCl₂ is a stronger Lewis acid than MnCl₂. Thus, Mn/**5** constitutes an ideal

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Table 1. Coupling of Benzaldehyde at 0.1 M Concentration in THF in the Presence of 3, 4, and 5 with 3 Mol % Cp₂TiCl₂ with Mn as Reductant after 8 h

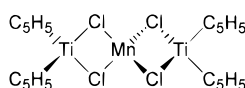
entry	acid	% cat.	% yield	1:2 ^a
1	3	3	<5	
2	4	3	75	82:18
3	5	3	68	95:5
4	5	3	77	78:22 ^b
5	5		42	72:28
6	5		68	86:14 ^{b,c}

^a By ¹H NMR of the crude product, see ref 5b. ^b Zn was used as reductant. ^c 7% of PhCH₂OH is also formed.

Table 2. Optimization of the Coupling Conditions with 5 as Acid

entry	% cat.	% yield	1:2 ^a	T/°C
1	3	60	92:8	0
2	3	62	87:13	40
3	5	82	98:2	25

^a By ¹H NMR of the crude product, see ref 5b.

**Figure 3.** Likely redox-active trinuclear titanium(III) complex.

system for conducting titanocene-catalyzed redox reactions. No special precautions to prevent interference of the non-catalyzed reaction pathway had to be taken. Further optimization studies of our catalytic system are summarized in Table 2.

When the coupling was performed at different temperatures, diastereoselectivity was 92:8 at 0 °C, 98:2 at room temperature, but decreased to 87:13 at 40 °C. The drop in selectivity at 0 °C can be explained by assuming somewhat slower protonation and thus interference of less selective pinacol coupling by titanium(III) alkoxides. Since the observed decrease in diastereoselectivity is more pronounced with TMSCl as additive it seems that protonation is indeed faster than silylation.^{3c,d} Collidine was recovered in greater than 95% yield after workup by simple acid–base extraction and could be reused without problems, thus amply demonstrating the economical advantages over silylation. The redox-active metal complex in our catalytic coupling seems to be a trinuclear complex⁸ where the two titanocene(III) units formed by reduction are bridged by manganese (Figure 3).

The optimized conditions were tested for a number of substrates. The results of these investigations are summarized in Table 3.

A variety of symmetrical 1,2-diols were synthesized with excellent diastereoselectivity and in good yields.⁹ It should

Table 3. Pinacol Coupling of Substituted Aldehydes under Optimized Conditions^a

entry	substrate	% yield	1:2 ^b
1	2-MePhCHO	90	97:3
2	3-MePhCHO	85	97:3
3	4-MePhCHO	84	97:3
4	4-ClPhCHO	89	97:3
5	4-BrPhCHO	82	98:2
6	4-MeOPhCHO	91	99:1
7	4-AcOPhCHO	85	99:1
8	4-PhPhCHO	87	97:3
9	4-vinylPhCHO	85	96:4
10	2-thienylCHO	82	95:5

^a See ref 9 for procedure. ^b By ¹H NMR of the crude product according to ref 5b.

be noted that ortho substitution is not problematic here but leads to failure of the catalytic reaction with TMSCl. Functional groups interfering with strong electron-donor reagents, e.g. Sml₂ (Table 3, entries 4, 5, and 7), McMurry couplings (Table 3, entries 5 and 7) or dihydroxylation reactions (Table 3, entry 9) were readily tolerated. The reaction seems to be superior to known stoichiometric⁵ or catalytic³ pinacol couplings in most (Table 3, entries 1, 2, and 4–9) and similar to in two cases (Table 3, entries 3 and 10) concerning diastereoselectivity and yield. We have thus convincingly demonstrated that catalytic turnover can indeed be achieved by protonation of a metal–oxygen bond in buffered protic media by properly adjusting the pK_a of the employed acid. The application of this concept to other carbon–carbon bond-forming reactions is in progress, and the results of these studies will be reported in due course.

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Supporting Information Available: Details of compound characterization (3 pages).

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(9) **General Experimental Procedure.** To a solution of Cp₂TiCl₂ (36.8 mg, 150 μmol) in dry THF (20 mL) was added Mn powder (165 mg, 3.0 mmol) under nitrogen. The solution was stirred until it became green, and 2,4,6-collidine hydrochloride (709 mg, 4.5 mmol) was then added. To the mixture was added 4-methoxybenzaldehyde (365 μL, 3.0 mmol) in THF (20 mL) over 3 h. After being stirred for 7 h, 2 M HCl (10 mL) was added, and the mixture was extracted with *t*-BuOMe (2 × 15 mL). The organic layer was washed with 2 M HCl (10 mL), saturated aqueous NaHCO₃ (10 mL), and brine. After drying (Na₂SO₄) and evaporation of the solvent, the crude product was purified by flash chromatography (petroleum ether, *t*-BuOMe, 1:1) to give 373 mg of (4,4'-dimethoxydiphenyl)-1,2-ethanediol as a 99:1 mixture of 1:2 (91%).