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MANGANESE-PROMOTED, TITANOCENE-CATALYZED STEREOSELECTIVE PINACOL COUPLING OF ALDEHYDES

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ABSTRACT: Aromatic and aliphatic aldehydes undergo pinacol coupling when treated with Mn/Me_3SiCl in the presence of Cp_2TiCl_2 as catalyst. Good yields of bis-silyl pinacol ethers are obtained with varying degrees of diastereoselectivity. Enantioselective pinacolization has been achieved using an enantiomerically enriched catalyst.

Pinacol coupling provides a convenient method for generating carbon-carbon bonds with 1,2-difunctionality.[1] Unfortunately, traditional metal reductants for pinacolization rarely afford appreciable stereoselectivity or functional group tolerance. Recently several early transition metal reagents have been found to be effective for stoichiometric, dl-selective pinacol coupling of aromatic aldehydes.[2-5] As part of an effort to develop general stereoselective (including enantioselective), *catalytic* reductive coupling reactions of unsaturated substrates, we have investigated pinacolizations effected by a three component system: a titanocene-derived catalyst, a stoichiometric reductant, and a silyl halide to enable catalyst recycle. An attractive feature of such metallocene-based systems is the potential for tailoring the catalyst to enhance activity and selectivity, including

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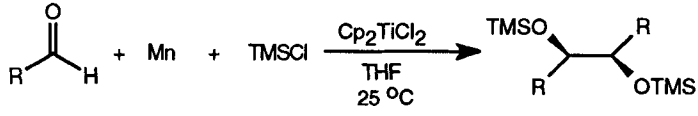
enantioselectivity.[6] Herein we present our findings on the successful pinacol coupling of aldehydes, *including saturated aldehydes,* employing Cp_2TiCl_2/Mn/Me_3SiCl. The first enantioselective pinacolization using a chiral titanocene catalyst is also demonstrated. While our investigation was underway, the catalytic pinacol coupling of aromatic aldehydes by other Ti-based systems[7a-c,8] and of aliphatic aldehydes by Zn/Cp_2VCl_2/TMSCl[9] was reported.

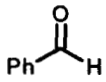
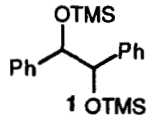
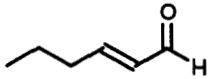
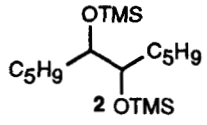
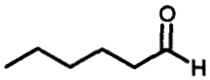
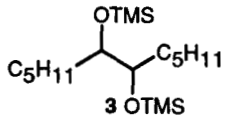
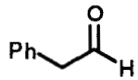
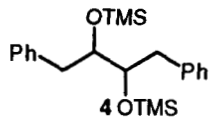
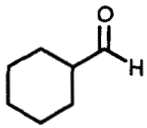
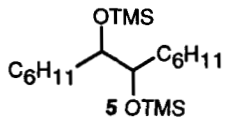
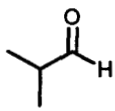
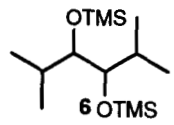
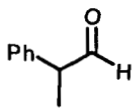
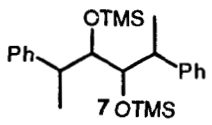
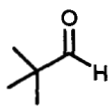
The viability of the Mn-promoted, Ti-catalyzed pinacolization method was first established using benzaldehyde as the substrate. Thus, stirring a mixture of benzaldehyde, excess manganese powder, Me_3SiCl, and Cp_2TiCl_2 (10 mol %) in THF for 24 hr at room temperature afforded hydrobenzoin-*bis*-TMS ether **1** in good yield and high *dl*- stereoselectivity (13:1) after flash chromatography (eq. 1, Table).[10] The stereoselectivity is comparable to that provided by the Cp_2TiCl_2/Zn/Me_3SiCl system.[7,11] The inexpensive, benign Mn reductant[13] is unreactive towards aldehydes under these conditions in the absence of Cp_2TiCl_2.[14] The unsaturated aldehyde 2-hexenal is regioselectively coupled in the head-to-head sense in moderate yield.



(1)

Using longer reaction times (18-72 hr) this same method also was found to be effective for the pinacolization of aliphatic aldehydes (Table). It is noteworthy that other Ti(III) systems have generally proven ineffective in coupling the less reactive saturated aliphatic aldehydes.[2,5] Product yields, which range from excellent to moderate, decrease with increasing steric bulk of the aldehyde; the hindered pivaldehyde (R=^{t}Bu) was unreactive under these conditions. The

Table. Aldehyde Pinacolization by $Mn/Cp_2TiCl_2/TMSCl$

Aldehyde	Product	Time (hr)	Yield (%)[a]	Diastereomer ratio
	 **1**	24	73	13:1
	 **2**	18	45	2:1
	 **3**	18	80	1.5:1
	 **4**	40	93	3:1
	 **5**	48	81	2:1
	 **6**	48	60	2.5:1
	 **7**	72	47	2:1:1
	—	48	no rxn.	—

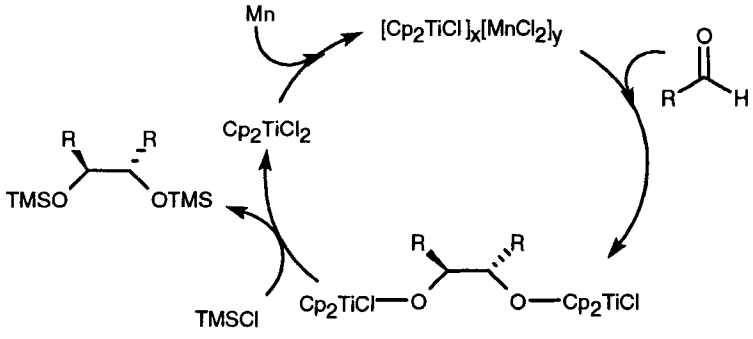
[a]After flash chromatography

diastereoselectivity in the reactions of aliphatic aldehydes, however, is modest relative to that for benzaldehyde. The predominant pinacol isomer in these cases is also assigned as *dl* based on comparison of the pinacol mixture obtained from hydrolysis of **5** with authentic samples of the *dl* and *meso* compounds.

A preliminary evaluation of the potential of chiral metallocene catalysts to direct enantioselective pinacolization was carried out employing chiral, non-racemic Brintzinger's catalyst[15], (*RR*)-ethylenebis(tetrahydroindenyl)titanium dichloride (**8**). Under the previously established conditions homochiral **8** catalyzed the conversion of benzaldehyde to pinacol ether **1** in good yield and diastereoselectivity (7:1 *dl/meso*). The chiral isomer of **1** was 60% ee (unoptimized), demonstrating the viability of this approach to asymmetric synthesis of pinacols.

Although the precise catalyst species and mechanistic details remain to be established, Scheme 1 outlines a plausible catalytic cycle. Given the aforementioned precedents a Ti(III) species, either monometallic (Cp_2TiCl)[16], bimetallic ($[Cp_2TiCl]_2$)[17] or trimetallic ($[Cp_2TiCl]_2MnCl_2$)[18], probably is responsible for the key coupling step and TMSCl likely mediates both product formation and recycle of the Ti.

Scheme 1



Current efforts are directed towards expanding the scope of titanocene-catalyzed pinacolizations and enhancing their stereoselectivity, including enantioselective variants.

Experimental

General.

THF was distilled from sodium benzophenone ketyl. Gas chromatographic analysis was carried out on a 2 m column with 0V 101 as the stationary phase. Silica gel (30-60 micron) was used for flash chromatography. Complex *rac* -**8** was resolved according to the method of Brintzinger (68 % ee).[14]

Pinacol Coupling of Aldehydes

To a side arm round bottom flask was added activated 4Å molecular sieves (one scupula), titanocene dichloride (0.05 g, 0.20 mmol), and manganese (50 mesh; 0.55 g, 10 mmol) under nitrogen. Distilled THF (20 ml) was added and the mixture was stirred for 5 min while changing from red to green. Trimethylsilylchloride (0.63 ml, 5.0 mmol) was added *via* syringe followed by the aldehyde (2.0 mmol) and the mixture was stirred at 20 °C for 15 to 48 hr. After GC analysis indicated that all the aldehyde had reacted, the volatiles were removed by rotary evaporation, the residue was triturated with 4:1 petroleum ether/ether, and the washings filtered through Celite. Concentration of the filtrate produced the crude products as orange or yellow oils. Further purification was accomplished by flash chromatography over silica gel using petroleum ether/ether as eluant providing the pinacol-bis-silyl ethers as colorless oils. The products were characterized by ^{1}H and ^{13}C NMR and mass spectrometry .

1,2-bis(trimethylsiloxy)-1,2-diphenylethane (1):

^{1}H NMR: ($CDCl_3$) minor isomer (min): -0.29 (s, 18H), 4.24 (s, 2H), 7.00-7.18 (m, 10H); major isomer (maj) : -0.09 (s, 18H), 4.63 (s, 2H), 7.20, 7.31 (m, 10H)

^{13}C NMR: ($CDCl_3$) maj + min: -0.50, 0.05, 79.38, 79.76, 126.85,127.12, 127.34, 141.80, 143.10

GCMS (12 ev EI) m/e (intensity): 179.1 (M^{+}-179.1, 100) for both GC peaks

GC and NMR purity $\geq$ *93%.*

6,7-bis(trimethylsiloxy)-dodeca-4,8-diene (2):

^{1}H NMR ($CDCl_3$) maj + min: 0.83-0.89 (m, 12H), 1.33-1.38 (m,8H), 1.96 (m, 8H), 5.47-5.58 (m, 4H); min: 0.05 (s, 18H), 3.84 (d, J=6 Hz, 2H), 5.35 (dd, J=4.8 Hz, 1.2 Hz, 2H); maj: 0.08 (s, 18H), 3.87 (d, J=6 Hz, 2H), 5.39 (dd, J=4.8 Hz, 1.2 Hz, 2H)

^{13}C NMR ($CDCl_3$) maj + min: 0.36, 0.95, 10.69, 13.58, 22.26, 29.64, 34.30, 129.94, 130.58, 131.99; (in d_6-benzene) additional peak at 78.0

GCMS, m/e (relative intensity) isomers not resolved by GC: 171.1 (M^+-171.1, 100)

GC and NMR purity ≥ 92%.

6,7-bis(trimethylsiloxy)-dodecane (3):

^{1}H NMR ($CDCl_3$) maj + min: 0.09 (s, 36H), 0.87 (t, J=6.8 Hz, 12 H), 1.18-1.32 (m, 16H), 1.38-1.39 (m, 8H), 1.50 -1.55 (m, 8H); maj: 3.47-3.50 (m, 2H); min: 3.51-3.52 (m, 2H); (in d_6-benzene) min: 3.63 (d, J=5.2 Hz, 2H); maj: 3.73 (d, J=8.4 Hz, 2H)

^{13}C NMR ($CDCl_3$) maj + min: 0.48, 1.27, 14.09, 22.59, 25.54, 25.99, 30.46, 31.82, 32.97, 32.69, 34.02, 73.00, 75.33

GCMS (12 ev EI) m/e (intensity): GC peak 1: 331.3 (M^+-15, 0.6), 173.1 (M^+-173.1, 100); GC peak 2: 331.3 (M^+-15.1, 1.2), 275.2 (M^+-056, 0.8), 173 (M^+-173.1, 100)

GC and NMR purity ≥ 80%.

2,3-bis(trimethylsiloxy)-1,4-diphenylbutane (4):

^{1}H NMR ($CDCl_3$): maj + min: 3.73-3.75 (m, 4H), 7.15-7.40 (m, 20H); min: -0.24 (s,18H), 2.65 (dd,J=9.2 Hz, 13.2 Hz, 2H), 2.89 (dd, 3.6 Hz, 13.4 Hz, 2H); maj: -0.20 (s,18H), 2.54 (dd, J=9.2 Hz, 9.6 Hz, 2H), 3.05 (broad d, J=12 Hz, 2H)

^{13}C NMR ($CDCl_3$) min + maj: 0.29, 0.76, 38.43, 40.91, 74.01, 75.51, 127.36, 128.83, 129.80, 138.19.

GCMS (12 ev EI) m/e (intensity): isomers not resolved by GC: 295 (M^+-91.2, 61.2), 206.1 (M^+-180.1, 6.6), 193.1 (M^+-193.1, 100)

GC and NMR purity ≥ 98%.

1,2-bis(trimethylsiloxy)-1,2-dicyclohexylethane (5):

^{1}H NMR ($CDCl_3$) maj + min: 0.8-2.0 (m, 44H), 3.30 (d, J=6 Hz, 4H);

maj: 0.10 (s, 18H); min: 0.11 (s, 18H); (in d_6-benzene) maj: 3.34 (d, J=4 Hz, 2 H); min: 3.49 (d, J=8 Hz, 2H)

^{13}C NMR ($CDCl_3$) maj + min: 0.90, 1.09, 26.15, 26.30, 26.63, 29.92, 30.62, 31.88, 39.10, 39.77, 78.30, 78.80.

GCMS (12 ev EI) m/e (relative intensity): GC peak 1 185.1 (M^+-185.1, 100): GC peak 2: 185.1 (M^+-185.1, 100)

GC and NMR purity $\geq$ *98%.*

3,4-bis(trimethylsiloxy)-2,5-dimethylhexane (6):

^1H NMR ($CDCl_3$) maj: 0.10 (s, 18H), 0.08 (d, J=6.4 Hz, 6H), 0.84 (d, J=6.4 Hz, 6H), 1.80 (m, 2H), 3.26 (d, J=5.6 Hz, 2H); min: 0.10 (s, 18H), 0.88 (d, J=7.6 Hz, 6H), 0.89 (d, J=7.8 Hz, 6H), 1.88 (m, 2H), 3.38 (bs, 2H).

^{13}C NMR ($CDCl_3$) maj + min: 0.79, 1.03, 16.11, 19.51, 20.45, 21.11, 29.94, 30.14, 79.00, 79.85

GCMS (12 ev EI) m/e (intensity): GC peak 1: 247.3 (M^+-43, 1.5), 145.1 (M^+-145.1, 100); GC peak 2: 275.2 (M^+-15, 1.1), 247 (M^+-43, 19.7), 158 (M^+-132.2, 1.6), 146.2 (M^+-144, 100)

GC and NMR purity $\geq$ *95%.*

3,4-bis(trimethylsiloxy)-2,5-diphenylhexane (7):

^1H NMR ($CDCl_3$) min A: -0.31 (s, 9H), 0.00 (s, 9H), 1.15 (d, 7.2 Hz, 3H), 1.27 (d, 7.6 Hz, 3H), 2.52 (m, 1H), 3.10 (m, 1H), 3.53 (dd, 8.4 Hz, 2.4-3.2 Hz, 1 H), 3.82 (dd, 7.6 Hz, 3.2 -3.6 Hz, 1H), 7.00 -7.40 (m, 10 H).

maj: -0.130 (s, 18H), 1.10 (d, 3 Hz, 6H), 2.82-2.96 (m, 2H), 3.65 (d, 4 Hz, 2H), 7.00-7.40 (m, 10 H).

min B: -0.28 (s, 18H), 1.10-1.20 (m, 6H), 3.03 (m, 2H), 3.77 (m, 2H), 7.00-7.40 (m, 10H).

^{13}C NMR: ($CDCl_3$) min A: -0.04, 0.40, 17.95, 18.94, 41.72, 42.59, 80.41, 80.78, 125.71, 126.24, 127.65, 128.26, 128.30, 128.67

GC MS (12 ev EI) m/e (intens.) min A: 309.2 (M^+-105.2, 37.8), 220.2 (M^+-194.2, 4.4), 207.2 (M^+-207.2, 100.0)

GC and NMR purity $\geq$ *99%.*

Enantioselective Pinacol Coupling Catalyzed by ***8***

Pinacolization of benzaldehyde catalyzed by Brintzinger's catalyst (*RR*-**8**)

was carried out as above. The dominant *dl* diastereomeric silyl ether was separated from the *meso* isomer (12:1) by preparative TLC (silica, 15:1 petroleum ether/ether). It was then hydrolyzed by heating with Bu_4NF in wet THF (reflux, 4 hr). Following addition of ether and water the phases were separated, the organic phase dried over Na_2SO_4, and the solvent evaporated. The specific rotation of the isolated *syn* (*dl*) isomer ($[\alpha]_D$ 38.6°) indicated (after correction for the optical purity of **8**) a 60 % ee.

Hydrolysis of Pinacol Silyl Ether **5**

A mixture of the *dl/meso* pinacol *bis*-ether **5** (0.067 mmol), methanol (8 ml), 1 N HCl (4 ml), and THF (10 ml) was stirred at 20 °C for 5 to 6 hr while monitoring by TLC. After rotary evaporation of the organic solvents the resulting aqueous phase was extracted three times with ethyl acetate. The combined organic extracts were washed with saturated aqueous $NaHCO_3$ and then with brine. The organic phase was dried over Na_2SO_4, concentrated, and flash chromatographed (4:1 petroleum ether/ether) to afford *dl/meso*-1,2-bis(cyclohexyl)-1,2-ethanediol, identified by comparison with authentic samples. These were prepared by separate catalytic hydrogenation of *dl* - and *meso*-hydrobenzoin.[17]

Acknowledgments.

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