4566 *J. Org. Chem.* **1997,** *62,* 4566−4567

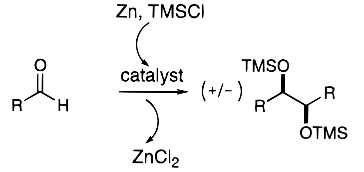
Ligand-Modified Catalysts for the McMurry Pinacol Reaction

Timothy A. Lipski, Mark A. Hilfiker, and
Scott G. Nelson*

*Department of Chemistry, University of Pittsburgh,
Pittsburgh, Pennsylvania 15260*

Received May 7, 1997

The McMurry pinacol reaction is an exceptionally versatile bond construction in organic synthesis and is, in many instances, the singular method for the preparation of highly strained alkenes and macrocyclic or polycyclic ring systems.[1] Despite the level of sophistication achieved in the McMurry reaction, intermolecular pinacol reactions continue to suffer from the requirement of stoichiometric quantities of expensive or difficult to prepare reducing agents and the notorious lack of stereoselection typically observed in these reactions.[2,3] Catalyzed reducing systems offer a potential solution to the operational and economic difficulties associated with these reactions, a fact that has undoubtedly contributed to recent reports of pinacol reactions catalyzed by Ti(III),[4] V(I),[5] Sn(IV),[3b] and Sm(II) complexes.[6] Intermolecular pinacol couplings promoted by Ti(III)[4b,7] and V(II) reagents[8] are among the rare examples of highly diastereoselective reductive carbonyl-coupling reactions. In the context of developing catalyzed reductive C−C bond constructions, we were interested in simultaneously addressing the issues of cost, operational simplicity, and stereochemical control by developing catalyzed pinacol reactions with the intent of modulating reaction stereoselection via the catalyst complex and its attendant ligands. We report herein the use of organic-soluble Ti(III) complexes as highly efficient catalysts for pinacol homocoupling reactions and the development of ligand-modified catalysts for controlling diastereoselectivity in the reductive coupling of aryl aldehydes (eq 1).



(1)

Catalyst = $TiCl_3(THF)_3$ or $TiCl_3(OC[N(Et)Ph]_2)$

Table 1. Catalyzed Pinacol Coupling of Aldehydes and Ketones[a]

entry	substrate	% yield[b]	*dl*:*meso*[c,d]
a	C_6H_5CHO	90	69:31
b	*p*-BrC_6H_4CHO	95	55:45
c	$C_6H_{11}CHO$	85	83:17
d	$PhCH_2CH_2CHO$	79	74:26
e	Me_2CHCH_2CHO	76	67:33
f	$C_6H_5COCH_3$	81	67:33
g	2-C_{10}-H_7COCH_3	84	62:38

[a] Reactions were carried out using the conditions given in ref 14. [b] Values reported are those for chromatographically purified materials after silyl ether hydrolysis. [c] Ratios determined by ^{1}H NMR analysis of crude reaction mixture. [d] Stereochemical assignments made by comparison of spectroscopic data to that reported in the literature.

While investigating the pinacol coupling of enolization-prone aldehydes, we discovered that the organic-soluble trichlorortris(tetrahydrofuran)titanium(III) complex[9] was the optimal reducing agent for effecting these bond constructions. In the course of this investigation, substoichiometric quantities of $TiCl_3(THF)_3$ were found to dramatically accelerate pinacol coupling reactions employing the Zn/TMSCl reducing system originally reported by Boudjouk.[10] Catalyst loadings of $TiCl_3(THF)_3$ as low as 1 mol % effect the pinacol homocoupling of benzaldehyde at −78 °C, in the presence of Zn (0.6−1.2 equiv) and TMSCl (1.2 equiv), to afford hydrobenzoin in quantitative yield (1.2:1 *dl*:*meso*).[11,12] Analogous reaction conditions provided no pinacol product in the absence of the titanium catalyst. While the $TiCl_3(THF)_3$-catalyzed reducing system proved effective for coupling benzaldehyde, reaction diastereoselection was unacceptably low, and coupling reactions of less electrophilic aromatic or aliphatic aldehydes proceeded only slowly or not at all under these reaction conditions. These limitations prompted us to pursue the development of modified catalyst complexes that would provide greater substrate generality and improved levels of diastereoselection.

Efforts to extend the $TiCl_3(THF)_3$-catalyzed pinacol couplings to less reactive substrates were advanced considerably by the observation that certain reaction additives dramatically enhance pinacol reaction rates. Substoichiometric quantities (5−30 mol %) of protic (*t*-BuOH, catechol, 2,2′-biphenol) or Lewis basic (DMPU, DMF, *N*,*N*-dimethylacetamide) additives afford ~5−10-fold rate accelerations relative to the parent $TiCl_3(THF)_3$ catalyst.[13] The catalyst system derived from $TiCl_3(THF)_3$−*t*-BuOH emerged from this investigation as the optimal pinacol catalyst on the basis of turnover rates and operational simplicity. Thus, in the presence of Zn (1.2 equiv) and TMSCl (1.2 equiv), $TiCl_3(THF)_3$−*t*-BuOH (5 mol %) catalyzes the reductive homocoupling of a variety of carbonyl compounds (Table 1), with diastereoselection ranging from *dl*:*meso* = 1.5−3:1 for aryl aldehydes (entries a and b), aliphatic aldehydes (entries d

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(1) (a) McMurry, J. E. *Chem. Rev.* **1989**, *89*, 1513−1524 and references cited therein.

(2) Robertson, G. M. In *Comprehensive Organic Synthesis: Carbon−Carbon σ-Bond Formation*; Trost, B. M., Fleming, I., Heathcock, C. H., Eds.; Pergamon Press: New York, 1991; Vol. 3, Chapter 2.6, pp 563−611.

(3) A number of highly diastereoselective intramolecular pinacol couplings have been reported; see: (a) Reference 1. (b) Raw, A. S.; Pedersen, S. F. *J. Org. Chem.* **1991**, *56*, 830−833. (c) Guidot, J. P.; Le Gall, T.; Mioskowski, C. *Tetrahedron Lett.* **1994**, *35*, 6671−6672. (d) Hays, D. S.; Fu, G. C. *J. Am. Chem. Soc.* **1995**, *117*, 7283−7284. (e) Kang, M.; Park, J.; Konradi, A. W.; Pedersen, S. F. *J. Org. Chem.* **1996**, *61*, 5528−5531.

(4) (a) Fürstner, A.; Hupperts, A. *J. Am. Chem. Soc.* **1995**, *117*, 4468−4475. (b) Gansäuer, A. *J. Chem. Soc., Chem. Commun.* **1997**, 457−458.

(5) Hirao, T.; Hasegawa, T.; Muguruma, Y.; Ikeda, I. *J. Org. Chem.* **1996**, *61*, 366−367.

(6) (a) Léonard, E.; Duñach, E.; Périchon, J. *J. Chem. Soc., Chem. Commun.* **1989**, 276−277. (b) Nomura, R.; Matsuno, T.; Endo, T. *J. Am. Chem. Soc.* **1996**, *118*, 11666−11667.

(7) (a) Raubenheimer, H. G.; Seebach, D. *Chimia* **1986**, *40*, 12−13. (b) Handa, Y; Inanaga, J. *Tetrahedron Lett.* **1987**, *28*, 5717−5718. (c) Barden, M. C.; Schwartz, J. *J. Am. Chem. Soc.* **1996**, *118*, 5484−5485.

(8) Konradi, A. W.; Kemp, S. J.; Pedersen, S. F. *J. Am. Chem. Soc.* **1994**, *116*, 1316−1323 and references cited therein.

(9) Manzer, L. E. *Inorg. Synth.* **1982**, *21*, 135−140.

(10) So, J.-H.; Park, M.-K.; Boudjouk, P. *J. Org. Chem.* **1988**, *53*, 5871−5875.

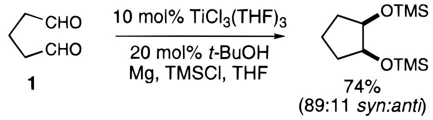
(11) The structure of the Ti(III) catalyst proved to be a determining factor in the success of the catalyzed pinacol reactions. Titanium(III) chloride that had not been precomplexed with THF was inactive as a catalyst under the indicated reaction conditions.

(12) For a discussion of possible mechanisms of low-valent metal-catalyzed pinacol reactions in the presence of TMSCl, see refs 4, 5, and 6b.

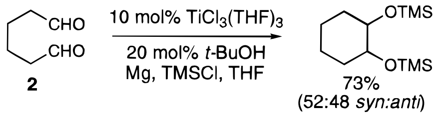
(13) The magnitude of the rate acceleration is substrate dependent; less reactive substrates (e.g., aliphatic aldehydes) exhibit the largest rate accelerations relative to the parent catalyst system.

S0022-3263(97)00792-5 CCC: $14.00

and e), and aryl methyl ketones (entries f and g) to *dl*:*meso* = 4.8:1 for an α-branched aliphatic aldehyde (entry c).[14] The sensitive 1,5- and 1,6-dialdehydes **1** and **2** also undergo annulative pinacol coupling under these catalytic reaction conditions (eqs 2 and 3).[15]



(2)



(3)

Our success in influencing pinacol reaction rates through modifying the catalyst complex led us to explore catalyst architecture as a vehicle for establishing stereochemical control in the pinacol bond constructions. Modified catalyst structures could readily be accessed from the parent $TiCl_3(THF)_3$ complex by exploiting the lability of coordinated THF toward ligand exchange.[16] This analysis and the Lewis base-induced rate acceleration exhibited by the Ti-catalyzed pinacol reactions prompted us to assay the sensitivity of reaction diastereoselection to the steric and electronic characteristics of various amide and urea ligands.[17] The catalyst complex derived from 5 mol % $TiCl_3(THF)_3$−*t*-BuOH and 30 mol % 1,3-diethyl-1,3-diphenylurea (DEPU) proved to be the most successful catalyst system, delivering the chiral pinacol diastereomers with substantially enhanced levels of stereoselectivity relative to reactions employing the parent $TiCl_3(THF)_3$−*t*-BuOH catalyst (Table 2).[18] Thus, aromatic aldehydes undergo catalyzed diastereoselective homocoupling to afford the chiral pinacol products with diastereomeric ratios of *dl*:*meso* = 87:13 to 91:9. The insensitivity of diastereoselection in the coupling of aliphatic aldehydes to the DEPU-modified catalyst suggests that π-stacking interactions between substrate and ligand may contribute to defining the stereochemical course of these reactions.[19]

Table 2. Diastereoselective Homocoupling of Aryl Aldehydes[a]

entry	substrate	% yield[b]	*dl*:*meso*[c,d]
a	C_6H_5CHO	89	88:12 (69:31)
b	*p*-$CH_3OC_6H_4CHO$	83	90:10 (70:30)
c	*o*-$CH_3C_6H_4CHO$	90	87:13
d	*p*-(*i*-Pr)C_6H_4CHO	90	87:13
e	*p*-$(C_6H_5)C_6H_4CHO$	94	91:9
f	$PhCH_2CH_2CHO$	95	67:33

[a] Reactions were carried out using the conditions given in ref 14 with 30 mol % 1,3-diethyl-1,3-diphenylurea (DEPU). [b] Reported yields are for chromatographically purified materials after silyl ether hydrolysis. [c] Ratios determined by ^{1}H NMR analysis of crude reaction mixture. [d] Values in parentheses are for reaction in the absence of DEPU.

The present study establishes ligand-modified Ti(III) complexes as effective catalysts for executing the reductive homocoupling of various carbonyl compounds. The capacity of catalyst architecture to influence reaction diastereoselection in the catalyzed pinacol reactions has been demonstrated for the first time. The insights enumerated herein are expected to prove valuable in devising catalyzed asymmetric variants of these important C−C bond constructions.

Acknowledgment. The donors of the Petroleum Research Fund, administered by the American Chemical Society, the American Cancer Society, and the University of Pittsburgh are gratefully acknowledged for support of this work. The authors wish to thank Dennis Curran and Peter Wipf for helpful suggestions in the preparation of this manuscript.

Supporting Information Available: Experimental procedures and details of compound characterization are provided (3 pages).

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(14) General experimental procedure for coupling 1.1 mmol of substrate: under a nitrogen atmosphere, 20 mg of trichlorotris-(tetrahydrofuran)titanium (III) (54 μmol), 87 mg of 1,3-diethyl-1,3-diphenylurea (0.32 mmol), and 85 mg of Zn powder (1.3 mmol) were suspended in 22 mL of THF. The resulting gray suspension was cooled to 0 °C, and 10 μL of 2-methyl-2-propanol (0.11 mmol), 164 μL of TMSCl (1.30 mmol), and 1.1 mmol of the aldehyde were added to the catalyst mixture via syringe. Once TLC analysis indicated that all the aldehyde had been consumed (~6 h), the excess Zn powder was removed by filtration. Methanol (4 mL) and 1 N aqueous HCl (2 mL) were added to the filtrate, and the reaction was stirred at room temperature for 2 h. The volatiles were evaporated *in vacuo*, the resulting aqueous residue was diluted with ethyl acetate, and the layers were separated. The aqueous portion was extracted with ethyl acetate (2 × 5 mL), and the combined organic layers were washed successively with a saturated aqueous solution of $NaHCO_3$ and brine. The organic portion was dried over $MgSO_4$ and concentrated *in vacuo*. Flash chromatography (hexanes/ethyl acetate) afforded the desired diol in the indicated yield and diastereoselectivity (Table 2). Results reported in Table 1 were for reactions employing this same experimental procedure but excluding the 1,3-diethyl-1,3-diphenylurea.

(15) Use of magnesium as the stoichiometric reductant, in place of zinc, provided substantially improved chemical yields in the annulative pinacol coupling of glutaraldehyde (**1**) and adipaldehyde (**2**).

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(17) Ligand effects in stoichiometric McMurry pinacol reactions have been examined, see: Balu, N.; Nayak, S. K.; Banerji, A. *J. Am. Chem. Soc.* **1996**, *118*, 5932−5937.

(18) The structure of the added ligand and $TiCl_3$:ligand stoichiometry proved to influence reaction diastereoselectivity. The reported $TiCl_3$−DEPU catalyst system was deduced by optimizing both of these reaction variables.

(19) Stoichiometric quantities of other urea additives (e.g., DMPU) do not afford improved stereoselectivity, suggesting that enhanced diastereoselection due to the DEPU ligand is not simply an artifact of a modified catalyst aggregation state.