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Stereoselective Pinacol Coupling in Aqueous Media

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Reductive coupling of aldehydes and ketones to glycols (pinacol coupling) is a standard reaction of organic synthesis,[1] and Mg metal[2] or various low-valent complexes of Ti,[3] Zr,[4] V,[5] Nb,[5a,6] Sn,[7] or Sm[8] can be used for efficient synthesis of inter- or intramolecular pinacol coupling, often with high diastereoselectivity. However, most conventional reductive-coupling methods are incompatible with aqueous conditions or protic functionality,[1] and reagents possessing aqueous stability might not be stereoselective.[3n−p,9] For example, although aqueous $TiCl_3$ can be used for pinacol coupling of aromatic ketones and aldehydes in basic solution, the intermediate aquo titanium complex is apparently sterically undemanding: the "pinacol" coupling of benzaldehyde using aqueous $TiCl_3$ (pH = 10−12) gives hydrobenzoin in good yield (88%) but with poor diastereoselectivity (*dl:meso* = 1.3:1).[3o] Inexpensive and easy to prepare green titanocene chloride, $[Cp_2Ti^{III}Cl]_2$ (**1**),[10] readily hydrolyzes to give blue $[Cp_2Ti^{III}(H_2O)]^+$ (**2**) which is stable in water in the absence of oxygen.[11] Complex **1** is a good reducing agent, reacting with activated alkyl halides[12] or epoxides[13] by heteroatom abstraction to give Cp_2Ti^{IV} halide or alkoxy complexes and alkyl radicals. We now report that **1** effectively reductively couples aromatic and α,*β*-unsaturated aldehydes to give 1,2-diols in high yield under either anhydrous or aqueous conditions. Perhaps because the metallocene moiety "Cp_2Ti-X" is sterically demanding,[14] pinacol coupling also occurs with high diastereoselectivity.

In a general procedure,[15] benzaldehyde (200 mg; 2 mmol) dissolved in 20 mL of THF was added dropwise to a green solution of **1** (462 mg; 1.1 mmol of the dimer; 1.1 equiv) in 20 mL of THF at −78 °C. The reaction mixture slowly turned red−brown, and the reaction mixture was allowed to warm to room temperature. After 1 h, hydrolysis (aqueous NaOH; Et_2O extraction) followed by chromatography gave 200 mg of hydrobenzoin (95%; 98:2 *dl:meso*). When a similar procedure was attempted in THF:H_2O (4:1) but starting at 0 °C, the only reaction noted was hydrolysis of **1**. However, when NaCl (8 g; 62 equiv per Ti) was added, the reaction mixture rapidly turned green. It was allowed to warm to room temperature, and after 5 h, it had become red. Hydrolysis and gas chromatographical analysis of an aliquot showed complete consumption of the benzaldehyde. Workup was accomplished by pouring the reaction mixture into 1 N NaOH followed by extraction with Et_2O to give hydrobenzoin. The crude residue was analyzed by ^1H NMR and GC of the corresponding acetonides[3i] to determine the product *dl:meso* distribution by comparison with authentic materials. Results (84%; *dl:meso* = 94:6) compare favorably with those reported for coupling using simple reducing agents under aprotic conditions.[3,9,16] Other examples of pinacol coupling in mixed solvent systems are given in Table 1. It is especially interesting to note that methyl glyoxylate and glyoxylic acid are easily converted to dimethyl tartrate and tartaric acid, respectively, with no adverse participation of the carboxylic functionality. Also, even though Cp_2Ti^{III} can react with aryl halides,[17] no reduction of that functionality was noted for the case studied.

We believe that the mechanism of pinacol coupling involves formation of an intermediate Cp_2Ti(aldehyde)Cl complex, **3** (Scheme 1). A hydride complex analog has been analyzed by EPR,[18] and **3** likely has significant unpaired electron density on the carbonyl carbon atom, as shown in the ketyl complex

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[1] For comprehensive reviews, see: (a) Wirth, T. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 61. (b) Dushin, R. G. In *Comprehensive Organometallic Chemistry II*; Hegedus, L. S., Ed.; Pergamon: Oxford, 1995; Vol 12, pp 1071−1095. (c) Furstner, A. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 164. (d) Robertson, G. M. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: New York, 1991; Vol. 3, pp 563−611. (e) McMurry, J. E. *Chem. Rev.* **1989**, *89*, 1513. (f) Kahn, B. E.; Rieke, R. D. *Chem. Rev.* **1988**, *88*, 733.

[2] (a) Furstner, A.; Csuk, R.; Rohrer, C.; Weidmann, H. *J. Chem. Soc., Perkin Trans. 1* **1988**, 1729 and references therein. (b) Chan, T. H.; Vinokur, E. *Tetrahedron Lett.* **1972**, *1*, 75.

[3] (a) Swindell, C. S.; Fan, W.; Klimko, P. G. *Tetrahedron Lett.* **1994**, *35*, 4959. (b) McMurry, J. E.; Siemers, N. O. *Tetrahedron Lett.* **1994**, *35*, 4505. (c) Nicolaou, K. C.; Yang, Z.; Sorenson, E. J.; Nakada, M. *J. Chem. Soc., Chem. Commun.* **1993**, 1024. (d) McMurry, J. E.; Siemers, N. O. *Tetrahedron Lett.* **1993**, *34*, 7891. (e) Swindell, C. S.; Chandler, M. C.; Heerding, J. M.; Klimko, P. G.; Rahman, L. T.; Raman, J. V.; Venkataraman, H. *Tetrahedron Lett.* **1993**, *34*, 7005. (f) Davey, A. E.; Schaeffer, M. J.; Taylor, R. J. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2657. (g) McMurry, J. E.; Dushin, R. G. *J. Am. Chem. Soc.* **1990**, *112*, 6942. (h) McMurry, J. E.; Rico, J. G.; Shih, Y.-N. *Tetrahedron Lett.* **1989**, *30*, 1173. (i) McMurry, J. E.; Rico, J. G. *Tetrahedron Lett.* **1989**, *30*, 1169. (j) Pierrot, M.; Pons, J.-M.; Santelli, M. *Tetrahedron Lett.* **1988**, *29*, 5925. (k) Handa, Y.; Inanaga, J. *Tetrahedron Lett.* **1987**, *28*, 5717. (l) Suzuki, H.; Manabe, H.; Enokiya, R.; Hanazaki, Y. *Chem. Lett.* **1986**, 1339. (m) Raubenheimer, H. G.; Seebach, D. *Chimia* **1986**, *40*, 12. (n) Clerici, A.; Porta, O. *J. Org. Chem.* **1983**, *48*, 1690. (o) Clerici, A.; Porta, O. *Tetrahedron Lett.* **1982**, *23*, 3517. (p) Clerici, A.; Porta, O. *Tetrahedron* **1982**, *38*, 1293. (q) Trylik, S. Wolochowicz, I. *Bull. Chem. Soc. Fr.* **1973**, 2147. (r) Mukaiyama, T.; Sato, T.; Hanna, J. *Chem. Lett.* **1973**, 1041.

[4] Askham, F. R.; Carroll, K. M. *J. Org. Chem.* **1993**, *58*, 7328.

[5] (a) Kammermeier, B.; Beck, G.; Jacobi, D.; Jendralla, H. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 685. (b) Park, J.; Pederson, S. F. *Tetrahedron* **1992**, *48*, 2069. (c) Kempf, D. J.; Sowin, T. J.; Doherty, E. M.; Hannick, S. M.; Codavoci, L.; Henry, R. F.; Green, B. E.; Spanton, S. G.; Norbeck, D. W. *J. Org. Chem.* **1992**, *57*, 5692. (d) Annunziata, R.; Benaglia, M.; Cinquini, M.; Cozzi, F.; Giaroni, P. *J. Org. Chem.* **1992**, *57*, 782. (e) Raw, A. S.; Pederson, S. F. *J. Org. Chem.* **1991**, *56*, 830. (f) Park, J.; Pederson, S. F. *J. Org. Chem.* **1990**, *55*, 5924. (g) Konradi, A. W.; Pederson, S. F. *J. Org. Chem.* **1990**, *55*, 4506. (h) Annunziata, R.; Cinquini, M.; Cozzi, F.; Giaroni, P. *Tetrahedron: Assymetry* **1990**, *1*, 355. (i) Takahara, P. M.; Freudenberger, J. H.; Konradi, A. W.; Pederson, S. F. *Tetrahedron Lett.* **1989**, *30*, 7177. (j) Freudenberger, J. H.; Konradi, A. W.; Pederson, S. F. *J. Am. Chem. Soc.* **1989**, *111*, 8014.

[6] (a) Szymoniak, J.; Besançon, J.; Moise, C. *Tetrahedron* **1994**, *50*, 2841. (b) Szymoniak, J.; Besançon, J.; Moise, C. *Tetrahedron*, **1992**, *48*, 3867.

[7] Hays, D. S.; Fu, G. C. *J. Am. Chem. Soc.* **1995**, *117*, 3867.

[8] For example, benzaldehyde reacts with SmI_2 to yield hydrobenzoin (95%), but stereoselectivity is poor (*dl:meso* = 55:45). See: (a) Namy, J.-L.; Souppe, J.; Kagan, H. B. *Tetrahedron Lett.* **1983**, *24*, 765. For other examples, see: (b) Anies, C.; Pancrazi, A.; Lallemand, J.-Y.; Prange, T. *Tetrahedron Lett.* **1994**, *35*, 7771. (c) Chiara, J. L.; Martin-Lomas, M. *Tetrahedron Lett.* **1994**, *35*, 2969. (d) Lebrun, A.; Namy, J.-L.; Kagan, H. B. *Tetrahedron Lett.* **1993**, *34*, 2311. (e) Arseniyadis, S.; Yashunsky, D. V.; Freitas, R. P.; Dorado, M. M.; Toromanoff, E.; Potier, P. *Tetrahedron Lett.* **1993**, *34*, 1137. (f) Uenishi, J.; Masuda, S.; Wakabayashi, S. *Tetrahedron Lett.* **1991**, *32*, 5097. (g) Chiara, J. L.; Cabri, W.; Hanessian, S. *Tetrahedron Lett.* **1991**, *32*, 1125. (h) Molander, G. A.; Kenny, C. *J. Am. Chem. Soc.* **1989**, *111*, 8236. (i) Molander, G. A.; Kenny, C. *J. Org. Chem.* **1988**, *53*, 2134.

[9] Tanaka, K.; Kishigami, S.; Toda, F. *J. Org. Chem.* **1990**, *55*, 2981.

[10] Coutts, R. S. P.; Wailes, P. C.; Martin, R. L. *J. Organomet. Chem.* **1973**, *47*, 375.

[11] Wailes, P. C.; Coutts, R. S. P.; Wiegold, H. In *Organometallic Chemistry of Titanium, Zirconium, and Hafnium*; Academic Press: New York, 1974; Chapter VI, pp 206 and references therein.

[12] (a) Cavallaro, C. L.; Schwartz, J. *J. Org. Chem.* **1995**, *60*, 7055. (b) Yanlong, Q.; Guisheng, L.; Huang, Y.-Z. *J. Organomet. Chem.* **1990**, *381*, 29.

[13] RajanBabu, T. V.; Nugent, W. A. *J. Am. Chem. Soc.* **1994**, *116*, 986.

[14] Jungst, R.; Sekutowski, D.; Davis, J.; Luly, M.; Stucky, G. *Inorg. Chem.* **1977**, *16*, 1645.

[15] All manipulations were performed either using standard Schlenk techniques or, for nonaqueous systems, in a glove box under a purified nitrogen atmosphere. Except when mixed aqueous procedures were used, THF was distilled from sodium/benzophenone ketyl. Deionized H_2O was thoroughly purged with argon to remove dissolved oxygen. Titanocene chloride dimer, $(Cp_2TiCl)_2$, was prepared[10] and stored in the dry box. Aldehydes were distilled prior to use.

[16] So, J.-H.; Park, M.-K.; Boudjouk, P. J. *J. Org. Chem.* **1988**, *53*, 5871.

[17] Liu, Y.; Schwartz, J. *Tetrahedron* **1995**, *51*, 4471; *J. Org. Chem.* **1994**, *59*, 940.

[18] Barden, M. C.; Schwartz, J. *J. Org. Chem.* **1995**, *60*, 5963.

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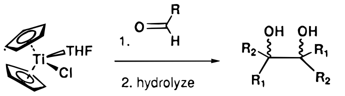
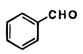
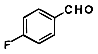
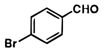
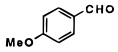
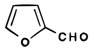
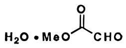
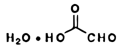
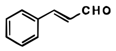
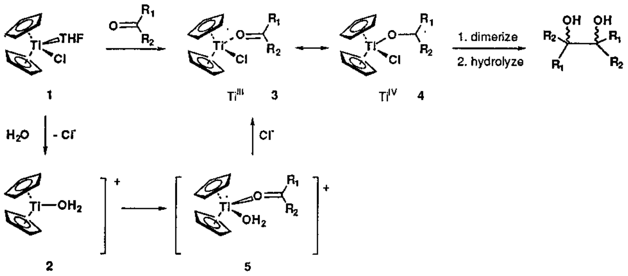
Table 1. Reductive Coupling of Aldehydes by Cp_2TiCl



Aldehyde	THF:H_2O[a]	Temp (°C)[b]	Yield (%)[c]	*dl:meso*[d]
	100:0	-78	95	98:2
	80:20	0	84	94:6
	50:50	0	89	95:5
	20:80	0	82	95:5
	100:0	-78	91	98:2
	80:20	0	85	94:6
	100:0	-78	91	95:5
	80:20	0	84	91:9
	100:0	-78	93	98:2
	80:20	0	88	94:6
	100:0	-78	82	99:1
	80:20	0	75	95:5
	100:0	-78	79	98:2
	100:0	-78	68[e]	98:2
	100:0	-78	88	98:2
	80:20	0	83	93:7

[a] All reactions were run in the presence of excess NaCl. [b] Initial temperature; final temperature was room temperature in all cases. [c] Combined yields for isolated *dl* and *meso* products. [d] Determined by ^1H NMR (300 MHz) of the crude reaction mixtures following hydrolysis. [e] Requires 8 equiv of Cp_2TiCl.[20]

Scheme 1



"resonance structure" **4**. Dimerization of **4** would give the glycolate. According to this hypothesis, strong bonding between the carbonyl group oxygen and Ti is an *a priori* requirement for glycolate formation; perhaps the requirement for strong Ti—O bonding in a sterically crowded environment is the origin of the pinacol diastereoselectivities observed. Cationic, hydrated species **2**[11] could coordinate an aldehyde to give $[Cp_2Ti(H_2O)(aldehyde)]^+$ (**5**) which is apparently unreactive for such reductive coupling; no reductive coupling occurs in the absence of added Cl^- or when noncoordinating triflate is used instead. Simple chloride ion addition to **5** affords **3**; it is reasonable that replacement of H_2O by Cl^- could favor transfer of electron density from Ti to the coordinated carbonyl group. Studies to elucidate the reaction mechanism and to expand the scope of the coupling reaction are now in progress.[19]

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(19) The complex $(EBTHI)_2TiCl$ was more stereoselective than was $[Cp_2TiCl]_2$ for aldehyde reductive coupling. For example, benzaldehyde yielded hydrobenzoin *dl:meso* = 36:1 (95%) at 0 °C using $[Cp_2TiCl]_2$; *dl:meso* = >50:1 (92%) using $(EBTHI)_2TiCl$. $[Cp_2TiCl]_2$ shows low reactivity toward pinacol coupling of aromatic ketones or aliphatic aldehydes and ketones.

(20) Workup was accomplished by quenching the reaction with 1 N NaOH followed by filtration and washing with Et_2O. The aqueous layer was concentrated to *ca.* 5 mL, and saturated solution of $BaCl_2$ was added. The mixture was heated to 70 °C, and the Ba salt precipitated on standing. See: Katsaros, N.; Vrachnou-Astra, E.; Konstantatos, J.; Stassinopoulou, C. I. *Tetrahedron Lett.* **1979**, *20*, 4319.