ORGANIC
LETTERS

2001
Vol. 3, No. 24
3863−3865

Enantioselective Pinacol Coupling of Aldehydes Mediated and Catalyzed by Chiral Titanium Complexes

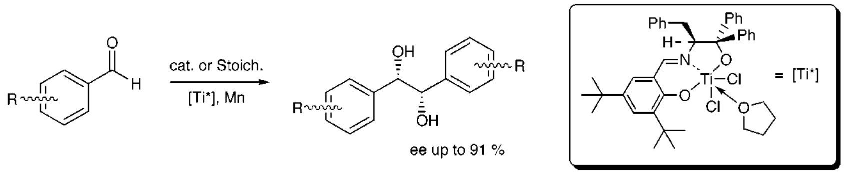
Ahlem Bensari,[‡] Jean-Luc Renaud,[†] and Olivier Riant*[,†,‡]

*Laboratoire de Chimie Organique et Médicinale, département de chimie,
place Louis Pasteur 1, Université catholique de Louvain, 1348 Louvain la Neuve,
Belgique, and Laboratoire de Catalyse Moléculaire, ICMO, Université Paris-Sud,
91405 Orsay, France*

riant@chim.ucl.ac.be

Received August 28, 2001

ABSTRACT



Starting from easily available chiral Schiff bases, a straightforward synthesis of air-stable titanium(IV) complexes was devised. Asymmetric pinacol coupling of aromatic aldehydes mediated and catalyzed by the corresponding low valent complexes afforded the chiral diols with high yields and enantioselectivities up to 91%.

The transition metal catalyzed formation of radicals anions is a very challenging process in organic methodology as it can lead to potential control of diastereoselectivity and enantioselectivity in a wide range of organic transformations.[1] The pinacol coupling of aldehydes remains one of the most studied reaction in this area, and various metals such as Ce,[2] Ti,[3] U,[4] Sm,[5] Cr[6] and V[7] have been shown to efficiently catalyze pinacol coupling. In some cases, careful optimization of the reaction parameters often leads to high diastereoselectivities for intramolecular as well as intermolecular coupling of either aliphatic and aromatic aldehydes. These results show that pinacol coupling is an excellent benchwork reaction for the study of the enantioselective catalyzed formation of radicals as no efficient system has been reported so far for this reaction. The very first example of a transition metal catalyzed enantioselective formation of radicals was reported in 1999 by Gansäuer et al. for the asymmetric opening of meso epoxides mediated by an enantiopure titanocene catalyst.[8] High enantioselectivities were observed when the α-titanoxyradicals were trapped either by an hydrogen source or an unsaturated ester. In the case of pinacol coupling of aromatic aldehydes, some reports have

---

[†] Université catholique de Louvain.

[‡] Université Paris-Sud.

(1) Reviews: (a) Hirao, T. *Synlett* **1999**, 175−181. (b) Gansäuer, A.; Bluhm, H. *Chem. Rev.* **2000**, *100*, 2771−2788.

(2) (a) Groth, U.; Jeske, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 574−575. (b) Groth, U.; Jeske, M. *Synlett* **2001**, 129−131.

(3) (a) Zhang, Y.; Liu, T. *Synth. Commun.* **1988**, *18*, 2173. (b) Gansäuer, A. *Chem. Commun.* **1997**, 457−458. (c) Gansäuer, A. *Synlett* **1997**, 363−364. (c) Lipski, T. A.; Hilfiker, M. A.; Nelson, S. G. *J. Org. Chem.* **1997**, *62*, 4566−4567. (d) Gansäuer, A.; Moschioni, M.; Bauer, D. *Eur. J. Org. Chem.* **1998**, 1923−1927. (e) Gansäuer, A.; Bauer, D. *J. Org. Chem.* **1998**, *63*, 2070−2071. (f) Gansäuer, A.; Bauer, D. *Eur. J. Org. Chem.* **1998**, 2573−2676. (g) Hirao, T.; Hatano, B.; Asahara, M.; Muguruma, Y.; Ogawa, A. *Tetrahedron Lett.* **1998**, *39*, 5247−5250. (h) Bandini, M.; Cozzi, P. G.; Morganti, S.; Umani-Ronchi, A. *Tetrahedron Lett.* **1999**, *40*, 1997−2000. (i) Yamamoto, Y.; Hattori, R.; Itoh, K. *Chem. Commun.* **1999**, 825−826.

(4) Maury, O.; Villier, C.; Ephritikhine, M. *New J. Chem.* **1997**, *21*, 137−139.

(5) Nomura, R.; Matsuno, T.; Endo, T. *J. Am. Chem. Soc.* **1996**, *118*, 1666−1667.

(6) Svatos, A.; Boland, W. *Synlett* **1998**, 549−550.

(7) (a) Hirao, T.; Hasegawa, T.; Muguruma, Y.; Ikida, I. *J. Org. Chem.* **1996**, *61*, 366−367. (b) Hirao, T.; Asahara, M.; Muguruma, Y.; Ogawa, A. *J. Org. Chem.* **1998**, *63*, 2812−2813. (c) Hirao, T.; Hatano, B.; Imamoto, Y.; Ogawa, A. *J. Org. Chem.* **1999**, *64*, 7665−7667. (d) Hirao, T.; Takeuchi, H.; Ogawa, A.; Sakurai, H. *Synlett* **2000**, 1658−1660.

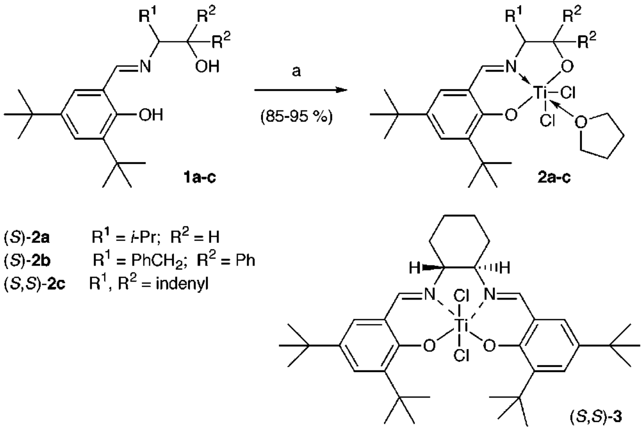
(8) Gansäuer, A.; Lautenbach, T.; Bluhm, H.; Noltemeyer, M. *Angew. Chem., Int. Ed.* **1999**, *38*, 2909−2910.

10.1021/ol016664a CCC: $20.00

already appeared in the literature concerning the use of catalytic amounts of chiral titanocenes[9] as well as stoichiometric amounts of titanium(II) halides and chiral ligands.[10] However, in most cases, enantioselectivities remain quite modest, and more studies are now required for better understanding of the mechanistic pathway of such reactions as well as optimization of the asymmetric induction. We wish to describe here our preliminary results concerning an efficent method for the enantioselective coupling of aromatic aldehydes using a new family of chiral titanium complexes.

As already shown by Gansäuer, chiral titanocenes can offer an elegant pathway for the generation of chiral titanium(III) catalysts, but their syntheses are often time-consuming and suffer low flexiblity for structure modification of the complex. In view of their easy access and wide applications in asymmetric catalysis, we turned our attention to the tetradentate salen and tridentate hemisalen ligands and designed a straightforward preparation of a new family of chiral titanium(IV) precursors. Complexes **2a**−**c** are easily prepared by mixing Schiff bases **1a**−**c** and titanium isopropoxide in THF followed by isopropoxide−chloride exchange by addition of an excess of TMSCl under inert atmosphere. The complexes were then precipitated by hexane and filtered at air (Scheme 1).

Scheme 1



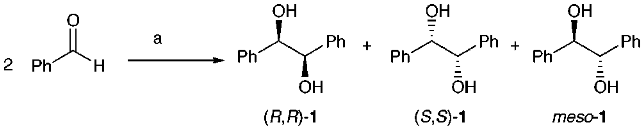
a. i. Ti(O-*i*Pr)$_4$, THF ii. TMSCl iii. hexane

We were very pleased to see that all of the complexes containing one molecule of THF were completely air-stable and nonhygroscopic in the crystalline state. They can be thus conserved in an open vessel at air for many months without any sign of decomposition.[11] As a result of the low cost of the Schiff bases used and the ease of the overall process, we were able to design a routine preparation of the complexes on a 20−50 g scale using standard benchwork material, and the yields were usually in the range of 85−95% starting from the chiral amino alcohols. The same procedure was also used for the synthesis of the known complex **3,** which was isolated in a 87% yield.

Stoichiometric conditions for the asymmetric pinacolization of benzaldehyde were first evaluated using in situ generated titanium(III) reagents. Optimization was performed with complex **2b** by studying reaction parameters such as solvent, concentration, temperature and coreductant.

Typical experiments were performed by reducing the titanium(IV) complex by an excess of reductant in acetonitrile under inert atmosphere and then adding freshly distilled benzaldehyde at the desired temperature. The pinacols were usually isolated after chromatographic purification in excellent yields and with high diastereoselectivities when precursor **2b** was employed. We found that optimum enantioselection was reached when the reaction was carried out at −10 °C and when acetonitrile was used instead of THF. Various coreductants were also compared with complex **2b** (entries 3−8, Table 1) and gave good enantioselectivities in most cases. Cerium metal proved the most efficient in terms of selectivity when the reaction was carried out at room temperature. However, in that latter case, no reaction was

Table 1. Asymmetric Pinacol Reaction of Benzaldehyde Promoted by Chiral Titanium **2a**−**c** and **3**



a. 1 equiv. [Ti*], 3 equiv. reduc., CH$_3$CN, T

entry	complex	reductant	*T* (°C)	yield (%)[b]	*dl*:*meso*[c]	ee (%)[d]
1	**2a**	Mn	−10	>95	61:39	31 (*S*,*S*)
2	**2b**[e]	Mn	25	>95	97:3	53 (*S*,*S*)
3	**2b**	Mn	25	93	98:2	61 (*S*,*S*)
4	**2b**	Mg	25	>95	97:3	64 (*S*,*S*)
5	**2b**	Zn	25	>95	69:31	65 (*S*,*S*)
6	**2b**	Sm	25	>95	97:3	67 (*S*,*S*)
7	**2b**	Ce	25	73	99:1	**76** (*S*,*S*)
8	**2b**	SmI$_2$	25	85	98:2	69 (*S*,*S*)
9	**2b**	Mn	−10	95	98:2	**77** (*S*,*S*)
10	**2c**	Mn	−10	94	81:19	37 (*R*,*R*)
11	**3**	Mn	−10	52	96:4	72 (*S*,*S*)

[a] Unless noted otherwise, all the reaction were carried out with 1 equiv of titanium(IV) complex and 3 equiv of reductant in acetonitrile ([Ti] = 0.05 M). When Mn was used, 325 mesh Mn powder was used. [b] Yield of isolated product after flash column chromatography on silica. [c] Measured by HPLC. [d] Enantiomeric excesses were measured by HPLC analysis; column, Pirkle (*S*,*S*)-Whelk; eluent, hexane/methanol/acetic acid (97/3/0.12); flow rate, 1 mL. min^{-1}; retention time, 30 min (*R*,*R*), 34 min (*S*,*S*), 39 min (*meso*). [e] The reaction was carried out in THF.

---

(9) (a) Dunlap, M. S.; Nicholas, K. M. *Synth. Commun.* **1999**, *29*, 1097−1106. (b) Halterman, R. L.; Zhu, C.; Chen, Z.; Dunlap, M. S.; Khan, M. A.; Nicholas, K. M. *Organometallics* **2000**, *19*, 3824−3829.

(10) (a) Matsubara, S.; Hashimoto, Y.; Okano, T.; Utimoto, K. *Synlett* **1999**, *9*, 1411−1412. (b) Enders, D.; Ullrich, E. C. *Tetrahedron: Asymmetry* **2000**, *11*, 3861−3865. (c) Hashimoto, Y.; Mizuno, U.; Matsuoka, H.; Miyahara, T.; Takakura, M.; Yoshimoto, M.; Oshima, K.; Utimoto, K.; Matsubara, S. *J. Am. Chem. Soc.* **2001**, *123*, 1503−1504.

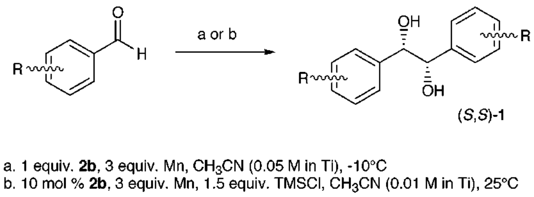
(11) Some complexes with similar structures have already been reported by the group of Braun and were described as air-sensitive compounds. Fleischer, R.; Wunderlich, H.; Braun, M. *Eur. J. Org. Chem.* **1998**, 1063−1070.

observed with cerium when the temperature was lowered to −10 °C. We chosed Mn (325 mesh) as the best compromise in term of efficiency and reproducibility in this reaction, and this choice was retained in the optimized system. Salen-based complex **3** also gave good enantioselection when it was used as a stoichiometric reagent (entry 11) ,but it showed lower reactivity and was then discarded in further experiments. Various structures were also tested by changing the nature of the salicycladehyde and the amino alcohol in the ligand in order to optimize the enantioselection, three representative structures being given here by the complexes **2a**−**c**. During the optimization of the reaction procedure using complex **2b**, we found that the complex could be partially recovered when the reaction mixture was treated with an excess of TMSCl before workup in order to regenerate the dichloro complex **2b** and the pinacol bis-TMS ether. Complex **2b** could then be selectively extracted by precipation from the crude reaction mixture and recrystallized (60% recovery) for further reuse.

Efforts were then made toward the use of a catalytic amount of the titanium complex. We found that, according to previous studies in this area of research,[12] the use of TMSCl as a mediator for catalysis allowed us to lower the amount of titanium catalyst up to 2−10 mol % when the reaction was carried out at room temperature; the results are summarized in Table 2.

The loss of enantioselectivity observed when the reaction was carried out under catalytic condition was attributed to the fact that similar ee's were obtained when the reaction was carried out at room temperature with a stoichiometric amount of **2b**. Unfortunately, reactivity was lost in the catalytic system when the reaction temperature was lowered. A 10 mol % amount of the titanium complex was used in all catalytic runs, but we also found out that little decrease in enantioselectivity was observed when the amount of the catalyst was lowered to 2 mol % (entry 2). Examination of various substituted aryl aldehydes showed a crucial electronic effect on the enantioselectivity. Whereas electron-donating substituents gave a noticeable increase in the ee of the pinacol (entries 4 and 5), introduction of an electron-withdrawing group showed a strongly negative effect in the selectivity (entries 7 and 8). However, we were able to reach a 91% ee with *p*-anisaldehyde when a stoichiometric amount of the complex was used (entry 5). Other coreductants were also used, such as the inexpensive cerium Mishmetall[13] for which high enantioselectivities were observed at room temperature in the stoichiometric system.

Table 2. Asymmetric Pinacol Coupling of Various Aromatic Aldehydes



		stoichiometric[a]			catalytic		
entry	R	yield (%)[b]	*dl*:*meso*[c]	ee (%)[d]	yield (%)[b]	*dl*:*meso*[c]	ee (%)[d]
1	H	>95	98:2	77	94	96:4	63
2	H[e]				80	91:9	60
3	*o*-CH_3	>95	95:5	**85**	>95	86:14	64
4	*p*-CH_3	>95	97:3	**86**	>95	95:5	52
5	*p*-OCH_3	>95	98:2	**91**	84	95:5	58
6	*p*-OCH_3[f]	73	99:1	**88**			
7	*p*-Br	>95	95:5	48	81	83:17	16
8	*p*-CF_3	>95	81:19	7	90	63:17	5

[a] For the conditions used, see above. [b] Yield of isolated product after flash column chromatography on silica. [c] Measured by HPLC. [d] Enantiomeric excesses were measured by HPLC analysis on a Pirkle (*S*,*S*)-Whelk column (entries1 and 2) or a Chiralcel AD column (entries 3−8). [e] Two mole percent of **2b** was used. [f] Cerium Mishmetall was used instead of Mn, and the reaction was carried out at room temperature.

In summary, we have been able to devise a new family of chiral titanium complexes that could be efficiently used in the promoted and catalyzed asymmetric pinacol coupling of aromatic aldehydes. More work is now required in order to understand the mechanistic pathway of this reaction[14] and the application to synthetically useful redox catalyzed reactions.

Acknowledgment. We thank CNRS and Université catholique de Louvain for financial support. We warmly thank Prof. A. Gansäuer for sharing information with us and for fruitful discussions. The Algerian Government is acknowledged for a fellowship (A.B.).

OL016664A

---

(12) Fürstner, A.; Huppert, A. *J. Am. Chem. Soc.* **1995**, *117*, 4468−4475.

(13) Helion, F.; Namy, J.-L. *J. Org. Chem.* **1999**, *64*, 2944−2946.

(14) Enemærke, R. J.; HjØllund, G. H.; Daasbjerg, Skrydstrup, T. *C. R. Acad. Sci.* **2001**, 435−438.