J. Org. Chem. **1998,** *63,* 2812−2813

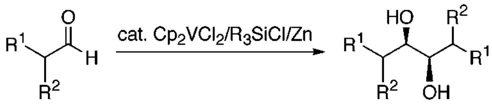
Highly Diastereoselective Pinacol Coupling of Secondary Aliphatic Aldehydes Induced by a Catalytic System Consisting of Vanadium Complex, Chlorosilane, and Zinc Metal

Toshikazu Hirao,* Motoki Asahara,
Yasuaki Muguruma, and Akiya Ogawa

Department of Applied Chemistry, Faculty of Engineering, Osaka University, Yamada-oka, Suita, Osaka 565-0871, Japan

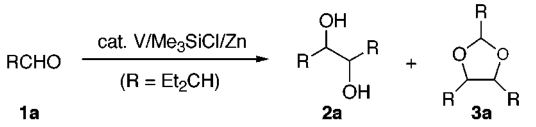
Received March 2, 1998

The reductive dimerization of carbonyl compounds, especially aldehydes and ketones, to give diols is an important method for constructing vicinally functionalized carbon−carbon bonds.[1] For this purpose, low-valent metals such as aluminum amalgam,[2] titanium,[3] vanadium,[4] zinc,[5] and samarium[6] have been employed conveniently. For example, pinacol coupling reactions using $TiCl_3/Zn-Cu$ and $[V_2Cl_3(THF)_6]_2[Zn_2Cl_6]$ are employed successfully for the synthesis of paclitaxel[7] and C_2-symmetrical HIV protease inhibitors,[8] respectively. To synthesize such complicated compounds, the efficient control of the stereochemistry in the coupling reactions is of great importance.[3f,h,j,4] In addition, another significant part of the pinacol coupling reaction includes the construction of a catalytic system of low-valent metals. It has recently been revealed that the use of chlorosilanes in combination with catalytic amounts of a transition-metal salt such as titanium and vanadium and a stoichiometric reducing agent successfully effects the catalytic pinacol coupling reactions.[9,10] Among these catalytic reactions, the low-valent titanium-catalyzed pinacol coupling of aromatic aldehydes exhibits the excellent diastereoselectivity.[10c−e] However, there are no examples of the highly diastereoselective pinacol coupling of simple aliphatic aldehydes in catalytic systems.[11,12] Herein, we report a highly diastereoselective catalytic pinacol coupling of secondary aliphatic aldehydes with the aid of $Cp_2VCl_2/R_3SiCl/Zn$ (eq 1).



(1)

Table 1. Selectivity of the Formation of 1,2-Diol[a]



entry	cat.	solvent	yield, % (*dl*/*meso*) **2a**	yield, % (*dl*/*meso*) **3a**
1	$CpV(CO)_4$	DME	0	80 (63/37)
2	$CpV(CO)_4$	THF	78 (91/9)	0
3	Cp_2VCl_2	DME	0	82 (88/12)
4	Cp_2VCl_2	THF	100 (88/12)	0
5[b]	$CpV(CO)_4$	THF	100 (92/8)	0
6[b]	Cp_2VCl_2	THF	100 (96/4)	0
7[c]	Cp_2VCl_2	THF	74 (70/30)	0
8[d]	Cp_2VCl_2	THF	0	39 (89/11)

[a] Reaction conditions unless otherwise stated: aldehyde (2 mmol), catalyst (0.06 mmol), Zn (4 mmol), Me_3SiCl (4 mmol), solvent (7 mL), 20 °C, 13 h. [b] $PhMe_2SiCl$ was used instead of Me_3SiCl. [c] 40 °C. [d] −20 °C.

A versatile catalytic system consisting of vanadium, chlorosilane, and zinc worked well for the reductive coupling of aliphatic aldehydes in dimethoxyethane (DME) to give 1,3-dioxolanes, but unfortunately, the diastereoselectivity of the dioxolanes obtained was generally very low. For example, 2-ethylbutanal (**1a**) reacted with cat. $CpV(CO)_4$, Me_3SiCl, and zinc powder in DME at room temperature, affording 1,3-dioxolane (**3a**) in 80% yield with low selectivity (*dl*/*meso* = 63/37, see entry 1 in Table 1).[9b,c] By switching the solvent simply from DME to THF, however, the product selectivity dramatically changed, providing 1,2-diol (**2a**) predominantly without formation of any olefinic products and 1,3-dioxolane (entry 2). Similar dependence of the product selectivity on the solvent was also observed with Cp_2VCl_2 catalyst (entries 3−4). More interestingly, both reactions of secondary aldehyde (**1a**) in THF using cat. Cp_2VCl_2 and cat. $CpV(CO)_4$ exhibited the excellent diastereoselectivity (entries 2 and 4). In the case of cat. Cp_2VCl_2, the diastereoselectivity could be further enhanced by using $PhMe_2SiCl$ in place of Me_3SiCl (entry 6). The result suggests that the bulkiness of the substituents on chlorosilanes somewhat contributes to the diastereoselection. Elevated temperature led to a significant decrease in both yield and stereoselectivity of **2a** (entry 7). At a lower temperature (−20 °C), the product selectivity changed, giving 1,3-dioxolane (**3b**) even in THF (entry 8).

---

(1) (a) Grame, M. R. In *Comprehensive Organic Synthesis;* Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 3, p 563. (b) Wirth, T. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 61.

(2) Schreibmann, A. A. *Tetrahedron Lett.* **1970**, *49*, 4271.

(3) (a) Mukaiyama, T.; Sato, T.; Hanna, J. *Chem. Lett.* **1973**, 1041. (b) Tyrlik, S.; Wolochowicz, I. *Bull. Chim. Soc. Fr.* **1973**, 2147. (c) McMurry, J. E.; Fleming, M. P. *J. Am. Chem. Soc.* **1974**, *96*, 4708. (d) Corey, E. J.; Danheiser, R. L.; Chandrasekaran, S. *J. Org. Chem.* **1976**, *41*, 260. (e) Suzuki, H.; Manabe, H.; Enokiya, R.; Hanazaki, Y. *Chem. Lett.* **1986**, 1339. (f) Handa, Y.; Inanaga, J. *Tetrahedron Lett.* **1987**, *28*, 5717. (g) McMurry, J. E. *Chem. Rev.* **1989**, *89*, 1513. (h) Barden, M. C.; Schwartz, J. *J. Am. Chem. Soc.* **1996**, *118*, 5484. (i) Balu, N.; Nayak, S. K.; Banerji, A. *J. Am. Chem. Soc.* **1996**, *118*, 5932. (j) Clerici, A.; Clerici, L.; Porta, O. *Tetrahedron Lett.* **1996**, *37*, 3035.

(4) (a) Freudenberger, J. H.; Konradi, A. W.; Pedersen, S. F. *J. Am. Chem. Soc.* **1989**, *111*, 8014. (b) Park, J.; Pedersen, S. F. *J. Org. Chem.* **1990**, *55*, 5924. (c) Konradi, A. W.; Pedersen, S. F. *J. Org. Chem.* **1992**, *57*, 28. (d) Konradi, A. W.; Kemp, S. J.; Pedersen, S. F. *J. Am. Chem. Soc.* **1994**, *116*, 1316.

(5) (a) Motherwell, W. B. *J. Chem. Soc., Chem. Commun.* **1973**, 935. (b) So, J.-H.; Park, M.-K.; Boudjouk, P. *J. Org. Chem.* **1988**, *53*, 5871. (c) Tanaka, K.; Kishigami, S.; Toda, F. *J. Org. Chem.* **1990**, *55*, 2981. (d) Tsukinoki, T.; Kawaji, T.; Hashimoto, I.; Mataka, S.; Tashiro, M. *Chem. Lett.* **1997**, 235.

(6) (a) Namy, J. L.; Kagan, H. B. *Tetrahedron Lett.* **1983**, *24*, 765. (b) Molander, G. A. *Chem. Rev.* **1992**, *92*, 29. (c) Taniguchi, N.; Kaneta, N.; Uemura, M. *J. Org. Chem.* **1996**, *61*, 6088.

(7) (a) Nicolaou, K. C.; Liu, J.-J.; Yang, Z.; Ueno, H.; Guy, R. K.; Sorensen, E. J.; Claiborne, C. F.; Hwang, C.-K.; Nakada, M.; Nantermet, P. G. *J. Am. Chem. Soc.* **1995**, *117*, 634. (b) Shiina, I.; Nishimura, T.; Ohkawa, N.; Sakoh, H.; Nishimura, K.; Saitoh, K.; Mukaiyama, T. *Chem. Lett.* **1997**, 419.

(8) (a) Kammermeier, B.; Beck, G.; Holla, W.; Jacobi, D.; Napierski, B.; Jendralla, H. *Chem. Eur. J.* **1996**, *2*, 307. (b) Kammermeier, B.; Beck, G.; Jacobi, D.; Jendralla, H. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 685.

(9) Fürstner's group and our group have independently demonstrated the catalytic McMurry coupling reaction and pinacol coupling reaction, respectively; see: (a) Fürstner, A.; Hupperts, A. *J. Am. Chem. Soc.* **1995**, *117*, 4468. (b) Hirao, T.; Hasegawa, T.; Muguruma, Y.; Ikeda, I. *J. Org. Chem.* **1996**, *61*, 366. (c) Hirao, T.; Hasegawa, T.; Muguruma, Y.; Ikeda, I. *Abstracts for the 6th International Kyoto Conference on New Aspects of Organic Chemistry*, 1994; p 175.

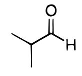
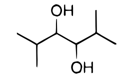
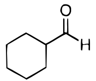
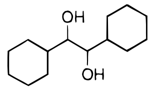
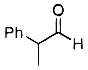
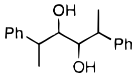
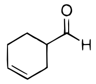
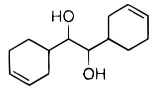
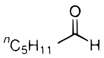
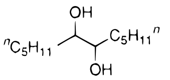
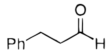
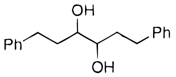
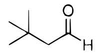
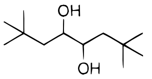
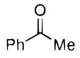
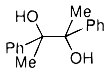
(10) For quite recent advances in the catalytic pinacol coupling, see: (a) Nomura, R.; Matsuno, T.; Endo, T. *J. Am. Chem. Soc.* **1996**, *118*, 11666. (b) Maury, O. Villiers, C. Ephritikhine, M. *New J. Chem.* **1997**, *21*, 137. (c) Gansäuer, A. *J. Chem. Soc., Chem. Commun.* **1997**, 457. (d) Gansäuer, A. *Synlett* **1997**, 363. (e) Lipski, T. A.; Hilfiker, M. A.; Nelson, S. G. *J. Org. Chem.* **1997**, *62*, 4566.

(11) For the diastereoselective pinacol coupling of aliphatic aldehydes by using a stoichiometric Nb(III), see: Szymoniak, J.; Besançon, J.; Moïse, C. *Tetrahedron* **1994**, *50*, 2841.

(12) Pedersen and co-workers reported a series of highly diastereoselective stoichiometric pinacol coupling of aliphatic aldehydes bearing chelating groups.[4]

S0022-3263(98)00376-4 CCC: $15.00

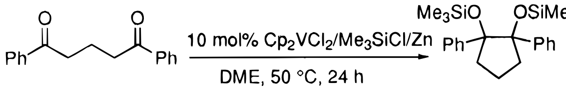
Table 2. $Cp_2VCl_2/R_3SiCl/Zn$-Induced Pinacol Coupling Reaction[a]

entry	aldehyde	coupling product	yield, %	[*dl*/*meso*]
1[b]	 **1b**	 **2b**	89	[91/9]
2[b]	 **1c**	 **2c**	71 (66)[c]	[90/10]
3	 **1d**	 **2d**	67 (66)[c]	[94/6]
4	 **1e**	 **2e**	100 (96)[c]	[85/15]
5	 **1f**	 **2f**	97	[50/50]
6	 **1g**	 **2g**	97	[64/36]
7	 **1h**	 **2h**	100	[56/44]
8	 **1i**	 **2i**	91	[57/43]
9[d]			17	[77/23]

[a] Reaction conditions unless otherwise stated: aldehyde (3 mmol), Cp_2VCl_2 (0.09 mmol), Zn (6 mmol), Me_3SiCl (6 mmol), THF (7 mL), 20 °C, 13 h. [b] $PhMe_2SiCl$ was used instead of Me_3SiCl. [c] Isolated yield (%). [d] −20 °C.

The representative results of the reductive coupling of aliphatic aldehydes by using the cat. $Cp_2VCl_2/R_3SiCl/Zn$ are shown in Table 2, which are strongly suggestive of a wide range of secondary aldehydes that participate in the highly diastereoselective pinacol coupling (entries 1−4). As well as secondary aldehydes, catalytic reactions of primary aldehydes in THF also provided the corresponding 1,2-diols selectively in excellent yields; however, their diastereoselectivities were very low (entries 5−7). These results strongly suggest that the diastereoselection is affected strongly by the bulkiness of the α-position of aldehydes.

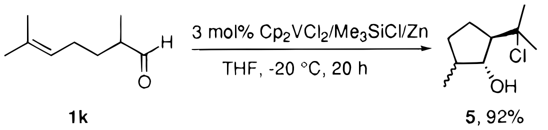
On the other hand, the catalytic pinacol coupling of ketones such as acetophenone proceeded efficiently with low diastereoselectivity (entries 8−9). Contrary to this, the intramolecular coupling reaction[3g,9a,10e,11,13] of 1,5-diketone (**1j**) successfully proceeded with excellent diastereoselectivity, as exemplified in eq 2.[14]



(2)

1j **4**, 74% (*dl*/*meso* = 91/9)

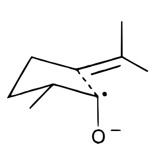
This successful result prompted us to examine catalytic intramolecular cyclization of olefinic aldehydes,[15] as indicated in eq 3. When the reaction of δ,ϵ-unsaturated aldehyde (**1k**) with cat. $Cp_2VCl_2/Me_3SiCl/Zn$ was conducted in THF at −20 °C,[16] trace amounts of vicinal diol were formed, and instead cyclic alcohol (**5**) was obtained as the major product with excellent diastereoselectivity (eq 3). The result is of great interest and may be explained by 5-*exo*-cyclization of the corresponding ketyl radical anion, followed by chlorination. In general, ketyl radical anions cyclize with excellent *trans* selectivities, suggesting that electronic repulsion between the forming radical center and the negatively charged ketyl oxygen is significant in the transition state leading to the disfavored *cis* isomer.[17] Considering also the 1,3-diaxial interaction between 2- and 6-methyl groups, model **A** is the most favorable, giving α-methyl located cyclic product (**5**) as the major product.



(3)

1k **5**, 92% (α-Me/β-Me = 77/23)

model A



In summary, this work describes a novel catalytic pinacol coupling of secondary aliphatic aldehydes with excellent diastereoselection. In this catalytic system, the additive of chlorosilane plays an important role in the construction of catalytic systems and also assists the stereoselection. An additive on the vanadium catalytic system also provides a versatile synthetic tools with high stereoselectivity, as exemplified by the highly stereoselective monodebromination of *gem*-dibromocyclopropanes with the vanadium catalyst in cooperation with diethyl phosphonate or triethyl phosphite.[18,19] Further studies on the scope and precise mechanism are underway, as well as the construction of new catalytic systems of low-valent metals.[20]

Acknowledgment. This research was supported in part by a Grant-in-Aid for Scientific Research on Priority Areas from the Ministry of Education, Science and Culture, Japan.

Supporting Information Available: Analytical data on the compounds prepared (IR, ^1H NMR, ^{13}C NMR, and mass spectra; elemental analyses) and NMR spectra of **2e** (8 pages).

JO980376J

---

(13) (a) Corey, E. J.; Danheiser, R. K.; Chandrasekaran, S. *J. Org. Chem.* **1977**, *42*, 2655. (b) McMurry, J. E.; Kees, K. L. *J. Org. Chem.* **1977**, *42*, 2655. (c) Molander, G. A.; Kenny, C. J. *J. Org. Chem.* **1988**, *53*, 2134. (d) McMurry, J. E.; Rico, J. G. *Tetrahedron Lett.* **1989**, *30*, 1169. (e) Raw, A. S.; Pedersen, S. F. *J. Org. Chem.* **1991**, *56*, 830. (f) Chiara, J. L.; Cabri, W.; Hanessian, S. *Tetrahedron Lett.* **1991**, *32*, 1125. (g) Hays, D. S.; Fu, G. C. *J. Am. Chem. Soc.* **1995**, *117*, 7283.

(14) In the case of ketones, the formation of dioxolanes is very slow even in DME, and therefore, DME can be employed as a solvent for the catalytic pinacol coupling to give 1,2-diol. On the other hand, the catalytic pinacol coupling reaction in THF at temperatures over 45 °C was accompanied by a ring opening reaction of THF.

(15) For the reductive intramolecular cyclization using stoichiometric amounts of SmI_2, see: (a) Molander, G. A.; Kenny, C. *J. Am. Chem. Soc.* **1989**, *111*, 8236. (b) Molander, G. A.; Harring, L. *J. Org. Chem.* **1990**, *55*, 6171. (c) Molander, G. A.; McKie, J. A. *J. Org. Chem.* **1992**, *57*, 3132. For V(II) induced reductive intramolecular cyclization, see: (d) Inokuchi, T.; Kawafuchi, H.; Torii, S. *J. Org. Chem.* **1991**, *56*, 4983.

(16) The same reaction at 20 °C provided 52% (α-Me/β-Me = 60/40) of **5** (*trans*-isomer) with the formation of its *cis*-isomer (ca. 20%).

(17) Curran, D. P.; Porter, N. A.; Giese, B. In *Stereochemistry of Radical Reactions;* VCH Press: Weinheim, 1995.

(18) Hirao, T.; Hirano, K.; Hasegawa, T.; Ohshiro, Y.; Ikeda, I. *J. Org. Chem.* **1993**, *58*, 6529.

(19) For some other catalytic system of early transition metals, see, for example: (a) Fürstner, A.; Shi, N. *J. Am. Chem. Soc.* **1996**, *118*, 2533. (b) Corey, E. J.; Zheng, G. Z. *Tetrahedron Lett.* **1997**, *38*, 2045.

(20) For YbI_2-catalyzed reduction with Al, see: Ogawa, A.; Ohya, S.; Sumino, Y.; Sonoda, N.; Hirao, T. *Tetrahedron Lett.* **1997**, *38*, 9017.