Efficient Diastereoselective Pinacol Reaction of Aliphatic and Aromatic Aldehydes by Combined Use of Newly Utilized Titanium(II) Bromide and Copper

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Newly utilized low-valent titanium reductant, titanium(II) bromide, was conveniently prepared by treating titanium(IV) bromide with hexamethyldisilane. The pinacol reaction of aromatic and aliphatic aldehydes including primary aldehydes proceeded smoothly in dichloromethane-pivalonitrile at temperatures ranging from -23 to 0 °C by the combined use of soluble titanium(II) bromide and copper to give 1,2-diols in good to high yields with good to high *dl*-selectivities.

Reductive coupling of carbonyl compounds using low-valent metal species, known as pinacol reaction, is one of the most important methods for carbon-carbon bond formation, and many kinds of reducing reagent, especially low-valent titanium species, have been employed in this reaction.[1] Of these reactions, pinacols can be formed easily when aromatic aldehydes are used while yields and diastereoselectivities (*dl* and *meso*) of pinacols are usually found to be rather low in cases of aliphatic aldehydes. Recently, it was reported from our laboratory that a combination of titanium(II) chloride and zinc effectively promoted pinacol reaction of aliphatic carbonyl compounds in dichloromethane-pivalonitrile.[2] Under the condition, however, the diastereoselectivities of products were rather low, and combinations of titanium(II) chloride and other metals such as magnesium or copper were not effective for these reactions. Very recently, Matsubara and co-workers reported on enantioselective pinacol reaction of benzaldehyde using two moles of titanium(II) chloride and four moles of chiral diamines.[3] In order to find more efficient low-valent titanium species other than titanium(II) chloride, titanium(II) bromide was chosen and its preparation and its application to pinacol reaction were studied.

A few methods for the preparation of titanium(II) bromide from titanium(III) bromide or titanium metal have been reported, but these procedures are not convenient because the reactions are carried out at extremely high temperature (400 °C) or dangerous ignition was sometimes observed.[4] In our trial to develop a better procedure, titanium(IV) bromide was treated with hexamethyldisilane similar to that employed in the preparation of titanium(II) chloride.[5] After screening several reaction conditions, it was found that analytically pure titanium(II) bromide[6] was obtained as an air and moisture sensitive dark brown solid in high yield when five moles of hexamethyldisilane was added dropwise into the refluxing titanium(IV) bromide (at 230 °C). The mixture was further refluxed for additional 9 h, and the work up was carried out as mentioned in ref. 5.

Thus prepared titanium(II) bromide dissolved thoroughly in dichloromethane-pivalonitrile and the solution turned into a dark green. When an equimolar amount of benzaldehyde was added to this solution, the reductive coupling proceeded smoothly to give the corresponding pinacol in increased yield and diastereoselectivity.[7] On the other hand, the yield and diastereoselectivity were rather low when the reaction was carried out using a suspended titanium(II) chloride in the above mixed solvent (Table 1, entries 1, 2). In order to improve the coupling reaction, combinations of titanium(II) bromide with several metals[8] were tried (entries 3-11). When zinc was used as co-reductant, the aldehyde was consumed rapidly, but the diastereoselectivity decreased extremely in the case of using either titanium(II) bromide or chloride. On the contrary, combination of titanium(II) bromide and copper exhibited high reactivity in this reductive coupling reaction and sufficient diastereoselectivity was attained at -23°C (entry 7).[9] In this reaction, copper powder did not react with titanium(II) bromide in the mixed solvent unless aldehyde was added. After adding the aldehyde, copper disappeared soon. This observation suggested that copper(0) would help titanium(II) bromide to reduce aldehyde and there would be a one-to-one complex of titanium and copper because the yield decreased extremely when a half amount of copper was used (entry 8). On the other hand, zinc powder reacted with titanium(II) bromide in the absence of aldehydes and the solution turned into dark brown, suggesting that lower (zero or one) -valent titanium species would be produced. In the case of using iron or manganese, the reaction proceeded slowly even at room temperature and the yield of pinacol was rather low. In the case of using tin, the diastereoselectivity decreased though the aldehyde was reduced rapidly (entries 9-11).

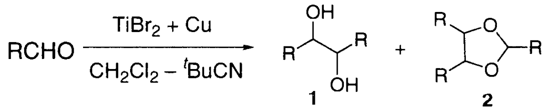
Table 1. Pinacol reactions of benzaldehyde[a]

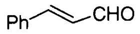
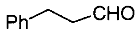
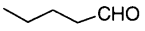
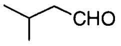
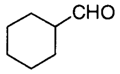
entry	reductant	temp	time /h	yield /%	[*dl* / *meso*][b]
1	$TiCl_2$	rt	6	36	[90/10]
2	$TiBr_2$	rt	6	43	[99/1]
3	$TiCl_2$ + Zn	0 °C	6	79	[49/51]
4	$TiBr_2$ + Zn	0 °C	6	50[c]	[51/49]
5	$TiCl_2$ + Cu	rt	6	79	[71/29]
6	$TiBr_2$ + Cu	rt	6	90	[90/10]
7	$TiBr_2$ + Cu	–23 °C	6	95	[97/3]
8	$TiBr_2$ + Cu[d]	–23 °C	6	36	[98/2]
9	$TiBr_2$ + Fe	rt	18	80	[93/7]
10	$TiBr_2$ + Mn	rt	18	53	[80/20]
11	$TiBr_2$ + Sn	rt	3	80	[75/25]

[a] PhCHO / TiX_2 / co-reductant / ^tBuCN = 0.5 / 0.5 / 0.5 / 2 (mmol), CH_2Cl_2 = 1.8 mL. [b] Ratios determined by ^1H-NMR analysis of crude reaction mixture. [c] 1,3-dioxolane was obtained in 15% yield. [d] Cu; 0.25 mmol.

The yields and diastereoselectivities of the pinacol reaction

Table 2. Pinacol reactions using $TiBr_2$ and Cu

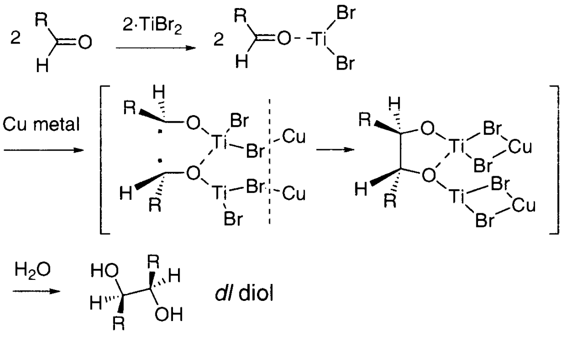


entry	aldehyde	condition[a]	yield /% 1 [*dl* / *meso*][b]	2
1	PhCHO	A	95 [96/4]	2
2	*p*-Cl-PhCHO	A	97 [99/1]	0
3	*p*-MeO-PhCHO	A	74 [94/6]	13
4		A	80 [91/9]	12
5		B	82 [80/20]	7
6		B	70 [74/26]	17
7		B	75 [75/25]	trace
8		B	70 [95/5]	23

[a] Reference 10. Condition A: Ti / Cu / CHO = 1/1/1, -23 °C, 8 h; B: Ti / Cu / CHO = 1.3/1.3/1, 0 °C, 18 h. [b] Ratios determined by ^{1}H-NMR analysis of crude reaction mixture.

of several aldehydes using titanium(II) bromide and copper are summarized in Table 2. Aromatic and α,β-unsaturated aldehydes were transformed to the corresponding pinacols in high yields with high diastereoselectivities (entries 1-4).

In the cases of aliphatic aldehydes, the corresponding pinacol coupling products were obtained at 0 °C, along with a small amount of 1,3-dioxolanes **2** produced from initially formed pinacols and remaining aldehydes (entries 5-8). Concerning high diastereoselective pinacol reaction of primary aliphatic aldehydes, Szymoniak et al. isolated pinacols as their dioxolane compounds like **2** with high diastereoselectivities (*dl* / *meso* ~ 9 / 1) using low-valent niobium reagent.[11] Hirao et al. improved pinacol reactions of aliphatic aldehydes without producing 1,3-dioxolanes using catalytic amount of vanadium(IV) complex together with excess amounts of zinc and chlorotrimethylsilane, but diastereoselectivities of these reactions using primary aldehydes were rather low (*dl* / *meso* < 2 / 1).[12] In the present reaction of using titanium(II) bromide and copper, pinacols were obtained mainly as 1,2-diol in good to high yields with good to higher diastereoselectivities. These results may be explained by considering initial formation of a titanium-bridged intermediate which can be readily formed by the interaction of an aldehyde with titanium(II) bromide soluble in the above mentioned solvent. By reductive coupling of the above intermediate on the surface of copper metal, titanium alcoholate and copper complex were in turn produced as sketched in Scheme 1.[13]



Scheme 1. Supporsed reduction mechanism.

Thus *dl*-selective pinacol reaction of several aldehydes including primary aliphatic aldehydes was effectively achieved by combined use of titanium(II) bromide and copper in dichloromethane-pivalonitrile.

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References and Notes

1 Review articles, see: a) G. M. Robertson, in "Comprehensive Organic Synthesis," ed. by B. M. Trost and I. Fleming, Pergamon Press, Oxford(1991), Vol. 3, p 563. b) T. Wirth, *Angew. Chem., Int. Ed. Engl.*, **35**, 61 (1996). c) A. Fürstner and B. Bogdanovic, *Angew. Chem., Int. Ed. Engl.*, **35**, 2442 (1996).

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3 S. Matsubara, Y. Hashimoto, T. Okano, and K. Utimoto, *Synlett*, **1999**, 1411.

4 a) R. C. Young and W. M. Leaders, *Inorg. Synth.*, **2**, 116 (1965). b) G. Brauer, "Handbook of Preparative Inorganic Chemistry," vol. 2, p 1185 (1965).

5 S. P. Narula and H. K. Sharma, *Inorg. Synth.*, **24**, 181 (1985).

6 Elemental Anal. of titanium(II) bromide, Found: Br 77.10%, Ti 22.89%. Calcd for $TiBr_2$: Br 76.95%, Ti 23.05%.

7 It was reported that soluble low-valent titanium species improved the diastereoselectivity because of the readiness of forming the titanium-bridged intermediate: A. Clerici, L. Clerici, and O. Porta, *Tetrahedron Lett.*, **37**, 3035 (1996).

8 Copper powder was purchased from Soekawa Chemical Co., Ltd. and used as received. Zinc powder was activated before use by 1 M aqueous HCl and washed with H_2O and ether, then dried under vacuum at 100 °C. Other metals were dried under vacuum at 100 °C.

9 Benzaldehyde was reduced slowly at -23 °C by using the combination of titanium(II) chloride and copper: T. Mukaiyama, A. Kagayama, K. Igarashi, and I. Shiina, *Chem. Lett.*, **1999**, 1157.

10 A typical procedure for the pinacol coupling reaction: To a suspension of $TiBr_2$ (0.5 mmol) and Cu powder (0.5 mmol) in CH_2Cl_2 (1.0 mL) was added ^{t}BuCN (2 mmol) under argon atmosphere. After the resulting Cu suspended dark green solution was cooled to –23 °C, a solution of benzaldehyde (0.5 mmol) in CH_2Cl_2 (0.8 mL) was added. The reaction mixture was stirred for 6 h, then the work up was carried out as mentioned in ref. 2. The crude product was purified by TLC to afford the desired pinacol (95%).

11 J. Szymoniak, J. Besançon, and C. Moïse, *Tetrahedron*, **50**, 2841 (1994).

12 a) T. Hirao, M. Asahara, Y. Muguruma, and A. Ogawa, *J. Org. Chem.*, **63**, 2812 (1998). For similar reactions using catalytic amount of titanium(III) complex, see: b) T. A. Lipski, M. A. Hilfiker, and S. G. Nelson, *J. Org. Chem.*, **62**, 4566 (1997).

13 The reductive coupling also proceeded when titanium(IV) bromide was employed instead of titanium(II) bromide. However, complex mixtures were produced and yields of the pinacols were poor. For example, in the case of using benzaldehyde or 3-phenylpropanal as a substrate, the yield of pinacol was 60% or 14%, respectively.