J. Org. Chem. **2000,** *65,* 5066−5068

$TiCl_4$−*n*-Bu_4NI as a Reducing Reagent: Pinacol Coupling and Enolate Formation from α-Haloketones

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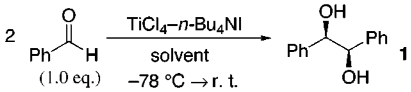
Received March 21, 2000

Low-valent metallic species such as $TiCl_3$[1] and $CrCl_2$[2] have a significant role as reducing reagents for organic molecules and their applications in organic synthesis have been extensively explored over the last three decades. Specifically, $TiCl_3$ is an extremely useful reagent for pinacol reactions,[3] McMurry couplings,[4] and Nef reactions.[5] In many cases, Ti(III) species are obtained via reduction of $TiCl_4$ by another metal or metallic hydride reagent such as Li, Mg, Zn, or $LiAlH_4$.[6] In these cases, however, concomitant formation of metal salts is inevitable. Because of their Lewis acidity, these metal residues sometimes cause undesirable side reactions, decrease of selectivities, or decomposition of functionalities. Herein we wish to report that $TiCl_4$−*n*-Bu_4NI (TBAI) mixed reagent[7] has the same reducing ability as low valent titanium reagents. These results clearly show that nonmetallic species such as ammonium iodide can reduce Ti(IV) species.[8]

Treatment of $TiCl_4$ with tetrabutylammonium iodide (TBAI) in dichloromethane at 0 °C provided a dark-red solution. After stirring for 10 min, benzaldehyde and hexane were added successively at −78 °C. The resulting biphasic mixture[9] was allowed to warm to ambient temperature during a period of 12 h. Aqueous workup provided the pinacol coupling product 1,2-diphenyl-1,2-ethanediol (**1**) in good yield with high stereoselectivity (*dl*/*meso* = 93/7) (Scheme 1).[10] In the absence of TBAI, the reaction did not proceed. The use of tetrabutylammonium bromide in place of TBAI also gave no pinacol product. Further investigation determined that optimal conditions were 1.5 equivalents of $TiCl_4$ and 2.2 equivalents of TBAI per 1.0 mmol of benzaldehyde (vide infra). The reaction temperature is crucial for the stereoselectivity. When the reaction was performed at 0 °C, the stereoselectivity of **1** decreased to 85/15. It was also essential to add hexane to enhance stereoselectivity.[11]

Scheme 1



Solvent	$TiCl_4$	*n*-Bu_4NI	Yield	*dl*/*meso*[a]
CH_2Cl_2	1.0 eq.	1.0 eq.	60%	91/9
CH_2Cl_2	2.0 eq.	2.0 eq.	70%	90/10
CH_2Cl_2	1.5 eq.	2.2 eq.	99%	90/10
CH_2Cl_2/hexane	1.5 eq.	2.2 eq.	99%	93/7

[a] Ratios were determined by ^1H NMR.

Pinacol coupling reactions of various aromatic aldehydes under these conditions are summarized in Table 1. Several comments are worth noting. (1) Only aromatic aldehydes were reactive under these conditions. Aliphatic aldehydes provided none of the desired diol, and the main product was an aldol condensation product. (2) Stereoselectivity of the product was generally high (>90/10) except in the cases of 2-bromo- and 2-benzoxybenzaldehyde.[12] In these cases, meso products were the major isomers (entries 9 and 10). (3) The reaction conditions are compatible with aldehydes containing the following functional groups: halides, ethers, esters, nitriles, or alcohols. (4) Methyltriphenylphosphonium iodide is as effective as TBAI (entry 11).[13] (5) $MePh_3PI$ or $MeEt_3NI$, which were prepared from Ph_3P or Et_3N with iodomethane in situ, gave similar results (entries 12 and 13).

The pinacol reaction of acetophenone was also investigated. The desired diol was obtained with extremely high stereoselectivity, although in modest yield. (Scheme 2). Unfortunately, the reaction of propiophenone under the same conditions was sluggish and the coupling product was obtained in only 7% yield. No reaction was observed in the case of naphthyl methyl ketone.

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(8) Very recently, reduction of $TiCl_4$ to Ti(III) species by triethylamine has been reported, see: Periasamy, M.; Srinivas, G.; Karunakar, G. V.; Bharathi, P. *Tetrahedron Lett.* **1999**, *40*, 7577

(9) This mixed reagent is insoluble in hexane because of the low solubility of TBAI to hexane.

(10) For recent examples of titanium mediated pinacol reaction, see: (a) Li, T.; Cui, W.; Liu, J.; Zhao, J.; Wang, Z. *J. Chem. Soc., Chem. Commun.* **2000**, 139. (b) Matsubara, S.; Hashimoto, Y.; Okano, T.; Utimoto, K. *Synlett* **1999**, 1411. (c) Bandini, M.; Cozzi, P. G.; Morganti, S.; Umani-Ronchi, A. *Tetrahedron Lett.* **1999**, *40*, 1997. (d) Yamamoto, Y,; Hattori, R.; Ito, K. *J. Chem. Soc., Chem. Commun.* **1999**. 825. (e) Mukaiyama, T.; Kagayama, A.; Shiina, I. *Chem. Lett.* **1998**, 1107. (f) Hirao, T.; Hatano, B.; Asahara, M.; Muguruma, Y.; Ogawa, A. *Tetrahedron Lett.* **1998**, *39*, 5247. (g) Gansäuer, A.; Bauer, D. *J. Org. Chem.* **1998**, *63*, 2070. (h) Hayakawa, R.; Shimizu, M. *Chem. Lett.* **2000**, 724. (i) Mukaiyama, T.; Yoshimura, N.; Igarashi, K. *Chem. Lett.* **2000**, 838.

(11) The role of hexane is not clear at this stage.

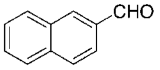
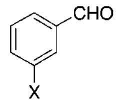
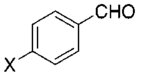
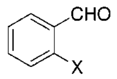
(12) Titanium-mediated pinacol reactions of 2-substituted aromatic aldehydes sometimes affords lower selectivity than reactions of 3- or 4-substituted benzaldehydes. For example, see ref 10b.

(13) The use of sodium iodide as an iodide source provided no pinacol product.

(14) For reductive coupling of imines, see: Hatano, B.; Ogawa, A.; Hirao, T. *J. Org. Chem.* **1998**, *63*, 9421 and references therein. See also ref 8.

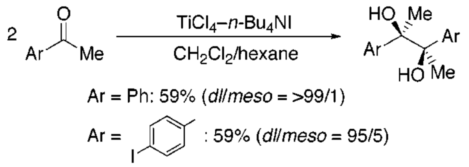
10.1021/jo0004254 CCC: $19.00

Table 1. Pinacol Coupling Reaction of Aromatic Aldehydes[a]

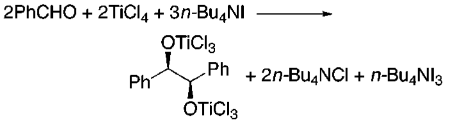
Entry	Substrate		yield(*dl*/*meso*)
1	PhCHO		99 (93/7)
2			88 (92/8)
3		X = Cl	96 (91/9)
4		X = OCH$_3$	86 (92/8)
5		X = OH	70 (92/8)
6		X = CN	90 (93/7)
7		X = CO$_2$CH$_3$	99 (91/9)
8		X = CH$_3$	71 (90/10)
9		X = Br	98 (33/67)
10		X = OCOPh	89 (27/73)
11	PhCHO		99 (94/6)[b]
12	PhCHO		99 (85/15)[c]
13	PhCHO		99 (89/11)[d]

[a] Substrate (1.0 mmol), TiCl$_4$ (1.5 mmol), and TABI (2.2 mmol) were employed unless otherwise noted. [b] Ph$_3$PMeI (2.2 mmol) was used instead of TBAI. [c] Et$_3$NMeI prepared in situ from Et$_3$N (2.2 mmol) and MeI (2.2 mmol) was used instead of TBAI. [d] Ph$_3$PMeI prepared in situ from Ph$_3$P (2.2 mmol) and MeI (2.2 mmol) was used instead of TBAI.

Scheme 2



Scheme 3



Unfortunately, the reaction of aromatic imines (PhCH=N-*n*-Pr and PhCH=NPh) under the same conditions provided no desired coupling products.[14] No reaction took place and only benzaldehyde was recovered after aqueous workup.

Scheme 4

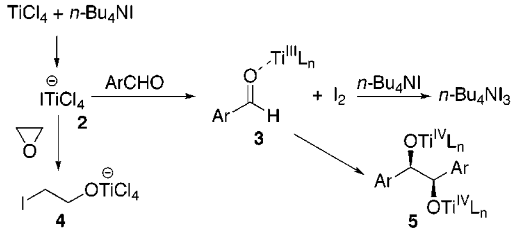
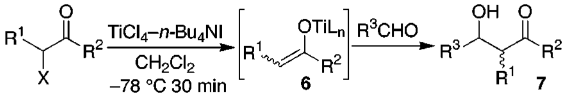
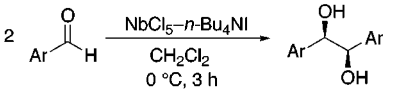


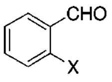
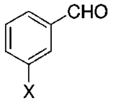
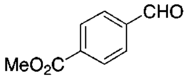
Table 2. Enolate Formation from α-Haloketones



Entry	R^1	R^2	R^3	X	yield (*syn*/*anti*)
1	*n*-C$_8$H$_{17}$	CH$_3$	Ph	I	91% (92/8)
2	-(CH$_2$)$_{10}$-		Ph	I	93% (89/11)
3	CH$_3$	Ph	Ph	I	81% (93/7)
4	CH$_3$	Ph	Ph	Br	83% (99/1)
5	CH$_3$	CH$_3$	Ph	Cl	no reaction
6	H	Ph	Ph	I	62%
7	*n*-C$_8$H$_{17}$	CH$_3$	*n*-C$_6$H$_{13}$	I	77% (86/14)
8	H	OCH$_2$Ph	Ph	I	67%
9	CH$_3$	OEt	Ph	I	52% (65/35)

Scheme 5



Aldehyde		Yield	*dl*/*meso*
PhCHO		99%	>99/1
	X = Br	87%	>99/1
	X = OCOPh[a]	65%	95/5
	X = OH[a]	40%	88/12
	X = OH	75%	>99/1
	X = OMe	93%	>99/1
		99%	>99/1

[a] Reaction temperature, –78 °C to 0 °C. Hexane (3 mL) was added.

To elucidate the reaction mechanism, further experiments were performed. After quenching the reaction mixture with water, addition of hexane to the organic phase provided a black precipitate. This was identified as *n*-Bu$_4$NI$_3$ by examination of the NMR spectra and elemental analysis.[15] Thus, the course of this pinacol reaction is outlined in Scheme 3. Iodide ion can formally serve as a reducing reagent of Ti(IV) into Ti(III).[16] However, only a small amount of I$_3^-$ could be detected in the mixture of TiCl$_4$ and TBAI at −78 °C.[17] This result could indicate that practically no reduction of Ti(IV) occurred in the absence of aromatic aldehyde. Additionally, it has already been reported that this mixed reagent can induce the nucleophilic attack of iodide to epoxides or unsaturated carbonyl compounds.[7] Based on these facts, we propose the following mechanism (Scheme 4). (1) The reaction of TiCl$_4$ with TBAI would form pentacoordinate titanium ate-complex **2**. (2) Coordination of a carbonyl oxygen to the titanium center of **2** would facilitate the reduction of **2** to Ti(III) species **3**. (3) Finally, **3** could form the corresponding ketyl radical which would dimerize to afford coupling product **5**. Instead of aldehyde, the use of epoxide would result in nucleophilic opening by the iodotitanate compound to form iodoalkoxytitanium compound **4**.

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[15] Both ^{1}H and ^{13}C spectra were identical with those of the authentic sample of *n*-Bu$_4$NI$_3$ which was prepared by mixing of *n*-Bu$_4$NI and I$_2$. UV absorbance in CH$_2$Cl$_2$ was also identical with that of the authentic sample. Elemental analysis of this precipitate was also consistent with *n*-Bu$_4$NI$_3$. Found: C, 30.81; H, 5.84%. Calcd for C$_{16}$H$_{36}$I$_3$N: C, 30.84; H, 5.82%.

[16] As shown in Scheme 3, 3 mol of TBAI is needed to reduce 2 mol of TiCl$_4$. Therefore, the stoichiometry in Scheme 1 can be explained by Scheme 3.

[17] After the mixture of TiCl$_4$ (1.2 mmol) and TBAI (1.8 mmol) in CH$_2$Cl$_2$ was stirred for 30 min at −78 °C, 0.06 mmol of I$_3^-$ was detected by titration with aqueous Na$_2$S$_2$O$_3$.

This $TiCl_4$−TBAI mixed system could also reduce α-iodoketones or α-bromoketones to provide the corresponding titanium enolates **6**.[18] The resulting enolates afforded aldol-type adducts **7** in good yields upon treatment with various aldehydes (Table 2). Under these conditions, 3-chlorobutanone did not react and the chloroketone was recovered quantitatively (entry 5). While α-iodoesters could be converted into enolates (entry 8 or 9), no reduction proceeded in the case of an α-bromoester.

We examined another quaternary ammonium iodide-metal halide combination and found that the $NbCl_5$−*n*-Bu_4NI mixed system could also induce pinacol coupling reaction of aromatic aldehydes (Scheme 5).[19] Interestingly, stereoselectivities were higher than the corresponding reactions run in the presence of $TiCl_4$−*n*-Bu_4NI. Contrary to the reaction with $TiCl_4$−*n*-Bu_4NI system, the reaction of 2-substituted benzaldehydes showed high *dl*-selectivities.

In summary, reduction systems based on $TiCl_4$ (or $NbCl_5$)-quaternary ammonium iodide combinations were found. Reduction of aromatic aldehydes or α-haloketones by this mixed reagent can be performed easily without using another reducing reagent.

Experimental Section

General Procedure for Pinacol Reaction with $TiCl_4$−TBAI System. To a solution of $TiCl_4$ (1.5 mmol) in CH_2Cl_2 (1.5 mL) was added a solution of tetrabutylammonium iodide (2.2 mmol) in CH_2Cl_2 (3 mL) at 0 °C. After stirring for 10 min at 0 °C, the resulting dark-red solution was cooled to −78 °C and benzaldehyde (1.0 mmol) and hexane (3 mL) were added. The mixture was allowed to warm to ambient temperature during a period of 12 h. Then the whole mixture was poured into aqueous NH_4Cl and was extracted with ethyl acetate. The organic layer was washed with aqueous $Na_2S_2O_3$ and dried over Na_2SO_4. Concentration and purification by chromatography afforded 1,2-diphenyl-1,2-ethanediol (106 mg, 0.49 mmol) in 99% yield.

General Procedure for Pinacol Reaction with $NbCl_5$−TBAI System. To a suspension of $NbCl_5$ (1.2 mmol) in CH_2Cl_2 (2 mL) was added a solution of tetrabutylammonium iodide (1.8 mmol) in CH_2Cl_2 (2.5 mL) at 0 °C. After stirring for 10 min at 0 °C, to the resulting black solution was added benzaldehyde (1.0 mmol). The mixture was stirred for 3 h at 0 °C. Then, saturated aqueous NH_4Cl (3 mL) was added to the mixture. The whole mixture was dried over Na_2SO_4. Ethyl acetate was added and the solution was washed with aqueous $Na_2S_2O_3$ and dried over Na_2SO_4. Concentration and purification by chromatography afforded 1,2-diphenyl-1,2-ethanediol (106 mg, 0.49 mmol) in 99% yield.

Acknowledgment. This work was supported by a Grant-in-Aid for Scientific Research on Priority Area (B) (No. 10208208) from the Ministry of Education, Science, Sports, and Culture, Japan.

Supporting Information Available: Spectral data for new compounds and *n*-Bu_4NI_3. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) $TiCl_2$-induced enolate formation from α-haloketone has been reported. Mukaiyama, T.; Kagayama, A.; Igarashi, K.; Shiina, I. *Chem. Lett.* **1999**, 1157.

(19) Niobium based reduction of carbonyl compounds has been reported, see: (a) Szymoniak, J.; Besancon, J.; Moïse, C. *Tetrahedron* **1992**, *48*, 3867. (b) Szymoniak, J.; Besancon, J.; Moïse, C. *Tetrahedron* **1994**, *50*, 2841.