The pinacol coupling of aromatic aldehydes in ethyl acetate mediated by $TiCl_4$–Al

Shu-Xiang Wang, Ke Wang, Guo-Biao Liu, Jin Cui and Ji-Tai Li*

College of Chemistry and Environmental Science, Hebei University, Baoding 071002, P.R. China

Titanium tetrachloride in ethyl acetate can be reduced by Al powder to the corresponding low valent titanium complexes, which can mediate the conversion of some aromatic aldehydes into the corresponding pinacols in 23–93 % yields within 25–120 min under stirring at r.t. When *N*,*N*,*N*′,*N*′-tetramethylethylene diamine (TMEDA) is added, the diastereoselectivities of the reactions are improved.

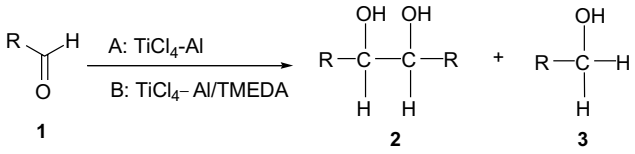
Keywords: aromatic aldehydes, pinacol coupling, pinacol, low valent titanium, ethyl acetate, TMEDA

The reductive coupling of carbonyl compounds, the pinacol coupling reaction,[1] is the most direct way to synthesise 1,2-diols by formation of the functionalised carbon–carbon bond. 1,2-Diols obtained in the reaction are very useful synthons for a variety of organic syntheses, and are also used as intermediates for the construction of biologically important natural product skeletons and asymmetric ligands for catalytic asymmetric reactions.[2] In particular, pinacol coupling has been employed as a key step in the construction of HIV-protease inhibitors.[3] Recent efforts have focused on the development of new reagents and reaction systems to improve the reactivity of the reagents and diastereoselectivity of the reactions.

Since the first report by Mukayama of pinacol coupling reactions mediated by a titanium reagent in 1973,[4] low valent titanium has attracted increasing attention. In 1982, Clerici and Porta reported pinacol coupling of aromatic aldehydes and ketones promoted by aqueous titanium trichloride in basic media.[5] The reaction was completed in a few minutes, but the method had some limitations with respect to some aromatic aldehydes and ketones. Clerici *et al.* reported pinacolisation of aromatic aldehydes mediated by titanium trichloride in dichloromethane in 1996.[6] The reaction was completed in high *dl*-stereoselectivity, but aromatic aldehydes bearing an electron-donating group showed lower reactivity. In 2000, Enders and Ullrich reported that asymmetric pinacol coupling of aromatic aldehydes under homogeneous conditions with $TiCl_2$ in the presence of enantiopure amines or hydrazines afforded 1,2-diols in moderate to excellent yields with good *dl*-diastereoselectivities.[7] In 2001, Itoh reported diastereoselective pinacol coupling of aldehydes promoted by the monomeric titanocene(III) complex Cp_2TiPh.[8] Five aromatic aldehydes gave desired pinacols in 54–96 % yields within 1–4 h. In 2004, Kulinkovich *et al.*[9] reported that the titanium(III) isopropoxide prepared by the reaction of titanium(IV) isopropoxide with one equivalent of a Grignard reagent transformed some aldehydes and aromatic ketones into the corresponding pinacols in good yields. However, in spite of their potential utility, some of the reported methods suffer from drawbacks such as long reaction times, expensive catalysts and harsh conditions. Our laboratory has also reported the pinacol coupling of aromatic aldehydes and ketones using $TiCl_4$–THF–Al, $TiCl_4$–THF–Zn[10] and $TiCl_4$–THF–Mg[11] in dichloromethane under ultrasound irradiation. For most of those methods, dichloromethane or tetrahydrofuran was chosen as the solvent. However, they are volatile, toxic and difficult to recover. In addition other solvents were chosen as extractants in the after-treatment procedures.

Ethyl acetate is a widely applied reagent; it is cheap, less poisonous than the above and easily obtained. Additionally, ethyl acetate is a good solvent for $TiCl_4$. As far as we are aware, there is no report of the pinacol coupling of aromatic aldehydes using MeCOOEt as solvent. Herein, we want to report our results on the pinacol coupling of aromatic aldehydes mediated by $TiCl_4$–Al and $TiCl_4$–Al/TMEDA in MeCOOEt at room temperature (see Scheme 1). In this system, ethyl acetate is both solvent and extractant.

The effect of the reaction conditions on the pinacolisation of benzaldehyde is summarised in Table 1.



Scheme 1

Table 1 The effect of the reaction conditions on pinacolisation of benzaldehyde

Entry	Metal	Molar ratio of PhCHO:$TiCl_4$:M	Additive	Time/min	Isolated yield/%		*dl*/*meso**
					2	**3**	
1	Mg	1:2:4	–	20	61	2	68/32
2	Zn	1:2:4	–	40	75	4	58/42
3	Al	1:2:2	–	60	70	5	–
4	Al	1:3:3	–	60	82	4	–
5	Al	1:4:4	–	60	84	4	–
6	Al	1:2:4	–	60	83	3	95.7/4.3
7	Al	1:3:4	–	60	83	3	–
8	Al	1:2:4	TMEDA[a]	60	80	4	98.6/1.4
9	Al	1:2:4	Pyridine[b]	60	28	5	–
10	Al	1:2:4	Triphenyl phosphine[c]	60	23	3	–

[a]The molar ratio of titanium tetrachloride and TMEDA is 1:1.5.
[b]The molar ratio of titanium tetrachloride and pyridine is 1:3.
[c]The molar ratio of titanium tetrachloride and triphenyl phosphine is 1:3.

* Correspondent. E-mail: orgsyn@mail.hbu.edu.cn

Table 2 Pinacolisation of carbonyl compounds mediated by $TiCl_4$–Al or $TiCl_4$–Al/TMEDA in ethyl acetate

Entry	Substrate	Reaction system	Time/min	Isolated yield/%		*dl*/*meso**
				2	**3**	
a	C_6H_5CHO	A	60	83	3	95.7/4.3
		B	60	80	4	98.6/1.4
b	2-ClC_6H_4CHO	A	40	91	2	44/56
		B	90	26	3	73/27
c	3-ClC_6H_4CHO	A	30	92	1	97.5/2.5
		B	90	78	4	*dl* only
d	4-ClC_6H_4CHO	A	30	93	2	95.2/4.8
		B	60	54	4	93/7
e	2,4-$Cl_2C_6H_3CHO$	A	50	92	2	48/52
		B	120	33	5	56/44
f	3-BrC_6H_4CHO	A	25	90	1	96.4/3.6
		B	90	42	3	98.5/1.5
g	Furaldehyde	A	50	68	5	61/39
h	4-$CH_3C_6H_4CHO$	A	120	51	4	92.3/7.7
		B	180	52	3	97.7/2.3
i	4-$CH_3OC_6H_4CHO$	A	70	33	6	*dl* only
j	3,4-$(OCH_2O)C_6H_3CHO$	A	120	23	3	96/4
		B	180	27	5	96.7/3.3
k	$C_6H_5CH{=}CHCHO$	A	120	37	3	0.7/99.3
		B	180	36	4	92.5/7.5
l	$C_6H_5COCH_3$	A	180	–	–	–
m	4-$ClC_6H_5COCH_3$	A	180	–	–	–

*The ratio of *dl*/*meso* was determined by ^1H NMR.
A, $TiCl_4$–Al; B, $TiCl_4$–Al/TMEDA.

The effect of metals on pinacolisation of benzaldehyde was investigated. When Mg and Zn powder were chosen to reduce $TiCl_4$, the yields of 1,2-diphenyl-1,2-ethanediol (**2a**) were 61 % and 75 %, but the ratios of *dl* to *meso* of **2a** were 68/32 and 58/42. Whereas using Al powder to reduce $TiCl_4$, the yield of **2a** was 83 % and the ratio of *dl* to *meso* of **2a** was 95.7/4.3. So Al powder was chosen to reduce $TiCl_4$.

When the molar ratio of PhCHO:$TiCl_4$:Al was 1:2:2, the yield of **2a** was 70 %. Increasing the molar ratio of PhCHO:$TiCl_4$:Al to 1:3:3 and 1:4:4, the yields of **2a** increased to 82 % and 84 % respectively. Increasing the amount of Al power and changing the molar ratio of PhCHO:$TiCl_4$:Al to 1:2:4 and 1:3:4, the yields of **2a** increased to 83 % and 83 % respectively. These results showed that changing the molar ratio of PhCHO:$TiCl_4$:Al had a significant effect on the yield of the 1,2-diol.

The effect of the additives on pinacolisation of benzaldehyde was also investigated. When *N*,*N*,*N*′,*N*′-tetramethylethylene diamine (TMEDA) was the additive, the yield of **2a** was 80 %. However, using pyridine and triphenyl phosphine as additives, the yields of **2a** were 28 % and 23 % respectively.

From the results above, the reaction conditions we chose were: system A: aldehyde (1 mmol), $TiCl_4$ (2 mmol), Al (4 mmol), MeCOOEt (5 ml); system B: aldehyde (1 mmol), $TiCl_4$ (2 mmol), Al (4 mmol), TMEDA (3 mmol), MeCOOEt (5 ml). Using the two reaction systems, we did a series of experiments on the pinacol coupling of aromatic aldehydes. The results are listed in Table 2.

The coupling of the aromatic aldehydes mediated by $TiCl_4$–Al in MeCOOEt was carried out in good yields. For example, using the present system under stirring at r.t. for 60 min and 30 min, **2a** and **2d** were obtained with 83 % and 93 % yields respectively. Whereas **2a** and **2d** were prepared in 50 % and 71 % yields respectively with $TiCl_4$–Al in Et_2O under stirring for 38 h and 29 h.[12]

Improved diastereoselectivity has been observed in the system A. When 4-ClC_6H_4CHO (**1d**), 4-$CH_3C_6H_4CHO$ (**1h**) and 4-$CH_3OC_6H_4CHO$ (**1i**) are substrates, the ratios of *dl* and *meso* of the corresponding 1,2-diols are 75/25, 74/26 and 72/28 respectively in Itoh's report.[8] Whereas in the present system, the ratios of *dl* and *meso* of the corresponding 1,2-diols are 95.2/4.8, 92.3/7.7 and *dl* only respectively.

On the other hand, when the substrate was $C_6H_5COCH_3$(**1l**) or 4-$ClC_6H_5COCH_3$(**1m**), we could not find the pinacol by TLC observation. These results showed that this system was without effect on aromatic ketones.

As shown in Table 2, benzaldehyde and the aromatic aldehydes with electron-withdrawing substituents in the benzene ring (**1a–1f**) had a high reactivity in the system A. Under stirring at r.t., **1a–1f** afforded **2a–2f** in 83–93 % yields within 25–60 min. In contrast, the aromatic aldehydes with electron-donating substituents in the benzene ring (**1h–1j**) showed lower reactivity. **1h–1j** only gave **2h–2j** with 23–51 % yields within 70–120 min under stirring at r.t.

TMEDA was an appropriate additive, which improved the *dl* selectivity of the coupling of aromatic aldehydes. The coupling of some aromatic aldehydes mediated by $TiCl_4$-Al/TMEDA in MeCOOEt was carried out in moderate yields. For example, **2c**, **2d**, **2f** and **2h** were prepared in 78 %, 54 %, 42 % and 52 % yields. However, the system B had good diastereoselectivity for the coupling of some aromatic aldehydes. When **1c** was substrate, the configuration of **2c** was *dl* only. For cinnamaldehyde(**1k**), the ratio of *dl* and *meso* of the corresponding 1,2-diol(**2k**) was 0.7/99.3 in the absence of TMEDA, however, in the presence of TMEDA the ratio of *dl* to *meso* of **2k** was 92.5/7.5. The results showed that the addition of TMEDA reversed the selectivity of the coupling of cinnamaldehyde.

In addition, the position of substituents in the benzene ring has some effect on the ratio of *dl* and *meso* in the two systems. The coupling of the aromatic aldehydes with *meta*- or *para*-substituents in the benzene ring has high diastereoselectivity, whereas the coupling of aromatic aldehydes with *ortho*-substituents in the benzene ring show low diastereoslectivity. For example, the ratios of *dl* and *meso* of **2c**, **2d**, **2f**, **2h**, **2i** and **2j** are 92.3/7.7 to *dl* only in the two systems. However, using 2-ClC_6H_4CHO (**1b**) and 2,4-$Cl_2C_6H_3CHO$ (**1e**) as substrates, the ratios of *dl* and *meso* of the corresponding 1,2-diols are 44/56 and 48/52 in the system A. In the system B, the ratios of *dl* and *meso* of the corresponding 1,2-diols are 73/27 and 56/44 respectively.

In summary, we have found an efficient and convenient method for the preparation of pinacols diastereoselectively from some aromatic aldehydes by using $TiCl_4$–Al or $TiCl_4$–Al/TMEDA in ethyl acetate under stirring. The main advantages of the present procedure are the milder reaction conditions, the inexpensive catalyst and its operational simplicity.

Experimental

Liquid aldehydes were distilled before use. IR spectra were recorded on Bio-Rad FTS-40 spectrometer (KBr). MS was determined on a VG-7070E spectrometer (EI, 70 eV). ^{1}H NMR spectra was measured on Bruker AVANCE 400 (400 MHz) spectrometer using TMS as internal standard and $CDCl_3$ as solvent.

The purity of ethyl acetate: A 500 ml round-bottomed flask was charged with 300 ml of ethyl acetate, 30 ml of acetic anhydride and three drops of concentrated sulfuric acid, then the solution was heated under reflux to remove ethanol and water. After 4 h, the solution was distilled and the distillate was dried over anhydrous potassium carbonate. Then the distillate was distilled again to obtain anhydrous ethyl acetate.

General procedure for the preparation of pinacols: A 50 ml two neck round-bottomed flask was charged with MeCOOEt (5 ml), $TiCl_4$ (2 mmol) and Al powder (4 mmol) under a nitrogen atmosphere. The mixture was stirred at room temperature and it turned into violet-black. After 15 min, the desired aldehyde (**1**, 1 mmol) in 1 ml MeCOOEt was added and the mixture was stirred at r.t for a period as indicated in Tables 1 and 2 (the reaction was followed by TLC). After the completion of the reaction, the resulting suspension was quenched with 10 ml of 10 % K_2CO_3 and extracted with ethyl acetate (3 × 15 ml). The combined organic layers were washed with saturated aqueous $NaHCO_3$ solution and brine, dried over anhydrous magnesium sulfate for 12 h and filtered. Ethyl acetate was evaporated under reduced pressure to give the crude product, which was separated by column chromatography on silica (200–300 mesh), eluted with petroleum ether or a mixture of petroleum ether and diethyl ether.

In a similar procedure, TMEDA (3 mmol) was added as an additive, and stirring was continued for 5 min prior to the addition of aldehyde.

The authenticity of the products was established by their ^{1}H NMR, MS and IR spectroscopic data.[13]

2a: ^{1}H NMR: δ 2.52 (2H, s, OH, *meso*), 3.18 (2H, s, OH, *dl*), 4.68 (2H, s, CH, *dl*), 4.82 (2H, s, CH, *meso*), 7.11–7.32 (20H, m, Ph–H). *m/z* (%): 214 (1), 180 (7.6), 167 (12.5), 149 (6.0), 107 (93.8), 79 (100), 77 (73.8). IR (KBr) ν_{max}: 3200–3480 cm^{-1}.

2b: ^{1}H NMR: δ 2.82 (2H, s, OH, *meso*), 2.91 (2H, s, OH, *dl*), 5.33 (2H, d, CH, *dl*), 5.58 (2H, d, CH, *meso*), 7.14–7.28 (16H, m, Ph–H). *m/z* (%): 282 (1), 165 (47), 141 (89), 113 (13), 107 (14), 77 (100), 51 (38). IR (KBr) ν_{max}: 3100–3500 cm^{-1}.

2c: ^{1}H NMR: δ 2.80 (2H, s, OH, *meso*), 3.37 (2H, s, OH, *dl*), 4.56 (2H, s, CH, *dl*), 4.75 (2H, s, CH, *meso*), 6.87–7.28 (16H, m, Ph–H). *m/z* (%): 263 (1.2), 251 (1.6), 178 (4.6), 165 (4.6), 141 (100), 113 (23.8), 77 (71.0). IR (KBr) ν_{max}: 3260–3318 cm^{-1}.

2d: ^{1}H NMR: δ 2.45 (2H, s, OH, *meso*), 3.02 (2H, s, OH, *dl*), 4.62 (2H, s, CH, *dl*), 4.83 (2H, s, CH, *meso*), 7.02–7.28 (16H, m, Ph–H). *m/z* (%): 276 (14), 249 (32), 155 (100), 111 (8). IR (KBr) ν_{max}: 3380–3420 cm^{-1}.

2e: ^{1}H NMR: δ 2.98 (2H, s, OH, *meso*), 3.02 (2H, s, OH, *dl*), 5.22 (2H, s, CH, *dl*), 5.52 (2H, s, CH, *meso*), 7.15–7.59 (12H, m, Ph–H). *m/z* (%): 352 (1), 305 (1.4), 233 (10), 175 (100), 145 (10), 111 (25), 77 (15). IR (KBr) ν_{max}: 3320–3400 cm^{-1}.

2f: ^{1}H NMR: δ 2.55 (2H, s, OH, *meso*), 3.12 (2H, s, OH, *dl*), 4.60 (2H, s, CH, *dl*), 4.76 (2H, s, CH, *meso*), 6.95–7.41 (16H, m, Ph–H). *m/z* (%): 325 (6), 186 (16), 157 (8), 107 (7), 77 (100), 51 (13). IR (KBr) ν_{max}: 3200–3500 cm^{-1}.

2g: ^{1}H NMR: δ 4.99 (2H, s, CH, *dl*), 5.02 (2H, s, CH, *meso*), 6.24–6.34 and 7.36–7.39 (m, 12H, furyl-H). *m/z* (%): 196 (10), 178 (25), 152 (73), 137 (33), 98(100), 84(22), 49 (30). IR (KBr) ν_{max}: 3240–3300 cm^{-1}.

2h: ^{1}H NMR: δ 2.33 (6H, s, CH_3, *dl*), 2.37 (6H, s, CH_3, *meso*), 4.68 (2H, s, CH, *dl*), 4.76 (2H, s, CH, *meso*) 7.04–7.21 (16H, m, Ph–H). *m/z* (%): 242 (1.2), 195 (6), 121 (100), 107 (12), 77 (13). IR (KBr) ν_{max}: 3280–3450 cm^{-1}.

2i: ^{1}H NMR: δ 3.78 (6H, s, CH_3O, *dl*), 4.63 (2H, s, CH, *dl*), 6.76–7.06 (8H, m, Ph–H). *m/z* (%): 302 (1), 284 (2.5), 268 (5.0), 255 (11.8), 151(100), 123(32), 93 (77.1), 65 (39.0). IR (KBr) ν_{max}: 3100–3600 cm^{-1}.

2j: ^{1}H NMR: δ 4.56 (2H, s, CH, *dl*), 4.65 (2H, s, CH, *meso*), 5.96 (4H, s, CH_2, *dl*), 6.06 (4H, s, CH_2, *meso)*, 6.53–6.81 (12H, m, Ph–H). *m/z* (%): 302 (1), 284 (2.5), 268 (5.0), 255 (11.8), 151 (100), 123 (32), 93 (77.1), 65 (39.0). IR (KBr) ν_{max}: 3100–3600 cm^{-1}.

2k: ^{1}H NMR: δ 2.53 (4H, s, OH), 4.32 (2H, d, CH, *dl*), 4.47 (2H, d, CH, *meso*), 6.31 (2H, m, –CH=CH–), 6.74 (2H, m, –CH=CH–), 7.29–7.42 (20H, m, Ph–H). *m/z* (%): 282 (1), 266 (15), 221 (12), 177 (24), 162 (26), 151 (30), 135 (23), 120 (70), 85 (38), 77 (17), 57 (90). IR (KBr) ν_{max}: 3360–3450 cm^{-1}.

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