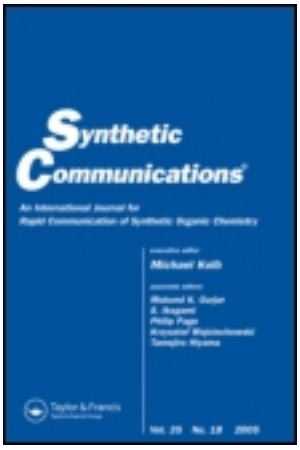

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Pinacol Coupling of Aromatic Aldehydes and Ketones Using $TiCl_3$-Al-EtOH Under Ultrasound Irradiation

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Pinacol Coupling of Aromatic Aldehydes and Ketones Using $TiCl_3$-Al-EtOH Under Ultrasound Irradiation

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ABSTRACT

Titanium trichloride in EtOH can be reduced by Al to the corresponding low-valent titanium complexes. This can reduce some aromatic aldehydes and ketones to the corresponding pinacols in 40–82% yields within 30–90 min at r.t. under ultrasound irradiation.

Key Words: Pinacol coupling; Pinacol; Synthesis; Low-valent titanium; Ultrasound irradiation.

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INTRODUCTION

One of the most powerful methods for constructing a carbon–carbon bond is the reductive coupling of carbonyl compounds giving olefins and 1,2-diols. Of these methods, the pinacol coupling, which was described in 1859, is still a useful tool for the synthesis of vicinal diols.[1,2] 1,2-Diols obtained in the reaction were very useful synthons for a variety of organic syntheses and were also used as intermediates for the construction of biologically important natural product skeletons and asymmetric ligands for catalytic asymmetric reaction.[3] In particular, pinacol coupling has been employed as a key step in the construction of HIV-protease inhibitors.[4] Recent efforts have focused on the development of new reagents and reaction systems to improve the reactivity of the reagents and diastereoselectivity of the products.

Low-valent titanium is a highly reactive reagent and is becoming increasingly attractive for carbonyl-coupling reactions.[5] In 1973, Mukaiyama first reported that $TiCl_4$-Zn reduced aromatic aldehydes and ketones to produce the corresponding 1,2-diols in high yield,[6] but the stereoselectivity was not reported. In 1982, Clerici et al. reported the pinacol coupling of aromatic aldehydes and ketones promoted by aqueous titanium trichloride in basic media.[7] The reaction was completed in a few minutes, but the reducing power of the Ti^{3+}/Ti^{4+} system is strongly pH dependent, and the method has some limitations with respect to some aromatic aldehydes and ketones. Clerici et al. again reported pinacolization of aromatic aldehydes mediated by titanium trichloride in dichloromethane in 1996.[8] The reaction was completed in high *dl*-stereoselectivity, but aromatic aldehydes bearing an electron-donating group showed lower reactivity. In 2001, Yamamoto et al. reported diastereoselective pinacol coupling of aldehydes promoted by monomeric titanocene (III) complex Cp_2TiPh.[9] Five aromatic aldehydes gave desired pinacol in 54–96% yields within 1–4 h. In 2000, Li et al. reported that 1,2-diols were obtained in pinacol coupling mediated by $TiCl_4$-Mg with a high stereoselectivity.[10] However, in spite of their potential utility, some of the reported methods suffer from drawbacks, such as longer reaction times, expensive catalysts, lower yields, and cumbersome product isolation procedures.

Ultrasound has increasingly been used in organic synthesis in the last three decades. Compared with traditional methods, this technique is more convenient and easily controlled.[11] A large number of organic reactions, especially many metal-involved reactions, can be carried out in higher yields, shorter reaction times and milder conditions under ultrasound irradiation.[12–14] Recently, we reported the pinacolization mediated by $TiCl_4$-THF-Zn or $TiCl_4$-THF-Al at room temperature under ultrasound irradiation.[15] Eight pinacols were obtained in 33–98% yield within 4–35 min under ultrasound irradiation. All of the results stated above prompted us to study the possibility of the pinacol

coupling of aromatic aldehydes mediated by $TiCl_3$-Al-EtOH system under ultrasound (Scheme 1).

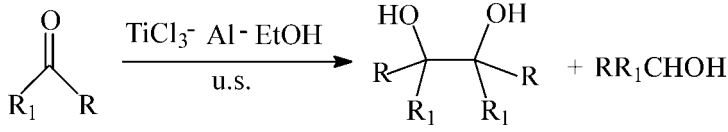
RESULTS AND DISCUSSION

The effect of the reaction conditions on pinacolization under ultrasound irradiation was summarized in Table 1. When the molar ratio of 4-ClC_6H_4-CHO : $TiCl_3$: Al was 1 : 2 : 3, 1,2-*di*(4-chlorophenyl)-1,2-ethanediol (**2a**) was obtained in 79% yield. Lowering the molar ratio to 1 : 1.5 : 3 lowers the yield of the 1,2-diol to 50%. The most important discovery was that changing the 4-ClC_6H_4CHO : $TiCl_3$: Al molar ratio to 1 : 2 : 4 lowers the yield of the 1,2-diol to 70%. Increasing this ratio to 1 : 2 : 8 caused a decrease in the yield to 52% (entry **c**, **f**). This finding is of interest especially from the environmental point of view. Increasing the 4-ClC_6H_4CHO : $TiCl_3$: Al molar ratio to 1 : 3 : 6, 1 : 3 : 8, and 1 : 4 : 8 increases the yield of the 1,2-diol to 67%, 80%, and 83% (entry **d**, **e**, **g**). The results showed that changing the molar ratio of $TiCl_3$ with Al powder had a significant effect on the yield of the 1,2-diol.

We also observed the effect of different frequencies of ultrasound irradiation on the reaction. When the frequency was 25 kHz, the coupling of benzaldehyde resulted in the desired product in 75% yield within 60 min (entry **h**). Under 40 kHz and 59 kHz ultrasound irradiation, the coupling of benzaldehyde was completed in 60 min with 74% and 55% yields, respectively (entry **k**, **l**). It was shown that a lower frequency of ultrasound irradiation improved the yield of pinacol coupling. The reason may be that the lower frequency irradiation produces better cavitations.[11,16] Therefore, all other couplings were carried out under 25 kHz ultrasound irradiation.

Moreover, when prolonging the reaction time from 60 min to 120 min, the yield of 1,2-diphenyl-1,2-ethanediol decreased from 75% to 73% (entry **h**, **i**). Additionally, after presonicating the Al powder for 60 min, the other reaction reagents were added in one portion, and benzaldehyde gave the desired 1,2-diol in 80% yield within 60 min (entry **j**).

In the absence of ultrasound, the coupling of 3-ClC_6H_4CHO mediated by $TiCl_3$-Al-EtOH was carried out in 43% yield (entry **n**) by using stirring



Scheme 1.

Table 1. The effect of the reaction conditions on pinacolization under ultrasound irradiation.

Entry	Substrate	Molar ratio of ArCHO/$TiCl_3$/Al	Frequency (kHz)	Time (min)	TSH Isolate yield (%)		*dl*/*meso**
					2	**3**	
a	4-ClC_6H_4CHO	1 : 2 : 3	25	30	79	12	66 : 34
b	4-ClC_6H_4CHO	1 : 1.5 : 3	25	30	50	20	
c	4-ClC_6H_4CHO	1 : 2 : 4	25	40	70	7	
d	4-ClC_6H_4CHO	1 : 3 : 6	25	20	67	10	
e	4-ClC_6H_4CHO	1 : 3 : 8	25	20	80	10	47 : 53
f	4-ClC_6H_4CHO	1 : 2 : 8	25	40	52	6	
g	4-ClC_6H_4CHO	1 : 4 : 8	25	20	83	14	
h	C_6H_5CHO	1 : 2 : 3	25	60	75	17	
i	C_6H_5CHO	1 : 2 : 3	25	120	73	9	
j	C_6H_5CHO	1 : 2 : 3	25	60	80[a]	9	
k	C_6H_5CHO	1 : 2 : 3	40	60	74	14	
l	C_6H_5CHO	1 : 2 : 3	59	60	55	3	
m	3-ClC_6H_4CHO	1 : 2 : 3	25	40	79	17	60 : 40
n	3-ClC_6H_4CHO	1 : 2 : 3	Stir[b]	40	43	6	
o	3-ClC_6H_4CHO	1 : 2 : 3	Stir[c]	40	56	28	

[a]After presonicating the Al powder for 60 min, the other reaction reagents were added in one portion.
[b]Stirred without ultrasound irradiation.
[c]After presonicating the reaction mixture for 10 min, the mixture was stirred without ultrasound for 40 min.
*The ratio of dl/meso is determined by ^{1}H NMR.

at 20°C within 40 min. After presonicating the reaction mixture for 10 min, under stirring at 20°C for 40 min, 1,2-*di*(3-chlorophenyl)-1,2-ethanediol was obtained with 56% yield (entry **o**). While under 25 kHz ultrasound irradiation, 1,2-*di*(3-chlorophenyl)-1,2-ethanediol was obtained with 79% yield within 40 min (entry **m**). It is clear that the ultrasound can accelerate the pinacolization. The reason may be that ultrasonic irradiation can cause Al particle rupture, decrease particle size, and increase the surface area available for reaction,[11,16] which can reduce Ti^{3+} to low-valent titanium complexes rapidly.

From the results above, the reaction conditions we chose are as follows: aldehyde (1 mmol), $TiCl_3$ (2 mmol), Al (3 mmol)/EtOH (4 mL). Using this reaction system, we did a series of experiments for pinacol coupling of aromatic aldehydes under 25 kHz ultrasound irradiation. The results are summarized in Table 2.

Table 2. Pinacolization mediated by $TiCl_3$-Al-EtOH under ultrasound irradiation.

Entry	Substrate	Time (min)	Isolated yield (%)		*dl*/*meso**
			2	**3**	
a	C_6H_5CHO	60	75	17	63 : 37
b	3-BrC_6H_4CHO	35	82	14	60 : 40
c	4-ClC_6H_4CHO	30	79	12	66 : 34
d	3-ClC_6H_4CHO	40	79	17	60 : 40
e	2-ClC_6H_4CHO	45	68	23	20 : 80
f	2,4-$Cl_2C_6H_3CHO$	30	71	21	21 : 79
g	4-$CH_3C_6H_4CHO$	80	69	6	91 : 9
h	4-$CH_3OC_6H_4CHO$	80	62	19	8 : 92
i	3,4-$(OCH_2O)C_6H_3CHO$	50	69	22	66 : 34
j	Furaldehyde	50	58	18	59 : 41
k	Cinnamaldehyde	50	40	14	57 : 43
l	PhCOPh	90	0	0	—
m	$PhCOCH_3$	90	Trace	—	—

*The ratio of dl/meso is determined by ^{1}H NMR.

As shown in Table 2, the coupling of some aromatic aldehydes was carried out in good yields using $TiCl_3$-Al in EtOH under ultrasound irradiation. For example, 1,2-*di*(4-methylphenyl)-1,2-ethanediol (**2g**) and 1,2-diphenyl-1,2-ethanediol (**2a**) were previously prepared in 35% and 65% yields, respectively, using $TiCl_3$-CH_2Cl_2 under stirring for 30 min.[8] Under ultrasonication, 1,2-*di*(4-methylphenyl)-1,2-ethanediol (**2g**) and 1,2-diphenyl-1,2-ethanediol (**2a**) were obtained with 69% and 75% yields, respectively.

From the data given in Table 2, the $TiCl_3$-Al-EtOH system can be seen to have high chemoselectivity for some aromatic aldehydes, especially for 3-BrC_6H_4CHO (**1b**), and 4-ClC_6H_4CHO (**1c**) gave the desired 1,2-diols with 82% (**2b**) and 79% (**2c**) yields, respectively, within 30–35 min. In the Tyrlik report,[17] $TiCl_3$-Mg, gave alkenes with aromatic systems but coupled aliphatic carbonyls to pinacols in moderate yields. In addition, in 1989, McMurry et al.[5] reported that the titanium-induced coupling reaction gave pinacols at 0°C, but at solvent reflux temperature, it gave alkene through deoxygenation. In our system, the coupling was carried out at room temperature and gave pinacol in high yields. Besides, the competing Cannizzaro reaction, giving alcohol and carboxylic acid, was not observed, and there was no olefin formation arising from McMurry reactions.

Improved diastereoselectivity has been observed in our system compared to the analogous process in THF at room temperature.[9] When 4-$CH_3C_6H_4CHO$ (**1g**), 4-$CH_3OC_6H_4CHO$ (**1h**) were used as a substrate, the

ratio of *dl* and *meso* of the 1,2-diols is 74 : 26 and 72 : 28, respectively, in the Yamamoto et al. report. In the present system, the ratio of *dl* and *meso* of the corresponding 1,2-diols is 91 : 9 and 8 : 92, respectively.

As shown in Table 2, some aromatic aldehydes via pinacol coupling can give pinacols in good yields under ultrasound irradiation. The electron-withdrawing substituents in the benzene ring (**1b**–**1d**) can increase the rapidity of the reaction. In contrast, the electron-donating substituents in the benzene ring (**1g**–**1i**) show less reactivity. In addition, the substituents in the benzene ring have some effects on the ratio of *dl* and *meso*. When 4-ClC_6H_4CHO (**1c**), 3-ClC_6H_4CHO (**1d**), 2-ClC_6H_4CHO (**1e**), and 2,4-$Cl_2C_6H_3CHO$ (**1f**) are as used substrates, the ratio of *dl* and *meso* of the 1,2-diols is about 1/1–1/4; when 4-$CH_3C_6H_4CHO$ (**1g**) is used as a substrate, the ratio of *dl* and *meso* of the 1,2-diols is about 10/1; in contrast, when 4-$CH_3OC_6H_4CHO$ (**1h**) is used as a substrate, the ratio of *dl* and *meso* of the 1,2-diols is about 1 : 10. It is shown that the aromatic aldehydes with electron-donating substituents in the benzene ring have higher stereoselectivity than those with electron-withdrawing substituents in the benzene ring.

On the other hand, we found that aliphatic aldehydes and aromatic ketones show less reactivity in the pinacol coupling (**1k**–**1m**).

We have done the experiments using reducing agents Mg, Zn, or Mn in combination with the $TiCl_3$-EtOH system. When the substrate was 4-ClC_6H_4CHO, the yields of pinacol were 92%,[18] 91%, and 70%, respectively.

It is noteworthy that the reagents used are readily available, inexpensive, and stable to air oxidation, and the method is easier and more convenient compared with those so far reported.[9,10]

CONCLUSION

In summary, we have found an efficient and convenient method for the preparation of pinacols from some aromatic aldehydes by using $TiCl_3$-Al-EtOH under ultrasound. The main advantages of the present procedure are the milder reaction conditions, inexpensive catalyst, and operational simplicity.

EXPERIMENTAL

Liquid aldehydes were distilled prior to use. Infrared (IR) spectra were recorded on a Bio-Rad FTS-40 spectrometer (KBr). Mass spectra (MS) were determined on a VG-7070E spectrometer (EI, 70 eV). ^{1}H NMR spectra were measured on a Bruker AVANCE 400 (400 MHz) spectrometer using

tetramethylsilane (TMS) as the internal standard and $CDCl_3$ as a solvent. Sonication was performed in Shanghai Branson-CQX ultrasonic cleaner (with a frequency of 25 kHz and a nominal power 250 W) and SK 250 LH ultrasonic cleaner (with a frequency of 40 kHz, 59 kHz, and a nominal power 250 W; Shanghai Kudos Ultrasonic Instrument Co., Ltd.). The reaction flask was located in the maximum energy area in the cleaner, where the surfaces of reactants are slightly lower than the level of the water. The reaction temperature was controlled by adding or removing of water from the ultrasonic bath.

General Procedure

A 50 mL two-neck round flask was charged with a 15% $TiCl_3$ solution in dilute HCl (2 mmol) and 4 mL EtOH under a nitrogen atmosphere. After 2 min of irradiation, Al powder (4 mmol) was added. When the reaction mixture turned into a dark color, a solution of the desired aldehyde (**1**, 1 mmol) in 1 mL EtOH was added. The mixture was irradiated in the water bath of the ultrasonic cleaner for a period as indicated in Table 1 [the reaction was followed by thin-layer chromatography (TLC)]. After the completion of the reaction, the resulting suspension was quenched with 1 mL H_2O and filtered to remove the Al powder. The filtrate was 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) and eluted with petroleum ether or a mixture of petroleum ether and diethyl ether. The authenticity of the product was established by their ^{1}H NMR, ^{13}C NMR, MS, and IR spectral data.

2a: ^{1}H NMR: δ 2.32 (2H, *s*, OH, *meso*), 2.96 (2H, *s*, OH, *dl*), 4.72 (2H, *s*, CH, *dl*), 4.84 (2H, *s*, CH, *meso*), 7.15–7.32 (20H, *m*, Ph-H) ppm. ^{13}C NMR: 78.45, 79.50, 127.39, 127.53, 128.30, 128.46, 140.16, 140.29; *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 2.45 (2H, *s*, OH, *meso*), 3.04 (2H, *s*, OH, *dl*), 4.63 (2H, *s*, CH, *dl*), 4.79 (2H, *s*, CH, *meso*), 6.96–7.41 (16H, *m*, Ph-H) ppm. *m*/*z* (%): 325 (6), 186 (16), 157 (8), 107 (7), 77 (100), 51 (13). IR (KBr) ν_{max}: 3200–3500 cm^{-1}.

2c: ^{1}H NMR: δ 2.32 (2H, *s*, OH, *meso*), 2.89 (2H, *s*, OH, *dl*), 4.63 (2H, *s*, CH, *dl*), 4.84 (2H, *s*, CH, *meso*), 7.02–7.33 (16H, *m*, Ph-H) ppm. ^{13}C NMR: 78.82, 128.75, 129.00, 134.14, 134.20, 138.16, 138.37; *m*/*z*

(%): 276 (14), 249 (32), 155 (100), 111 (8). IR (KBr) ν_{max}: 3380–3420 cm^{-1}.

2d: ^{1}H NMR: δ 2.35 (2H, *s*, OH, *meso*), 2.92 (2H, *s*, OH, *dl*), 4.67 (2H, *s*, CH, *dl*), 4.83 (2H, *s*, CH, *meso*), 6.93–7.30 (16H, *m*, Ph-H) ppm. ^{13}C NMR: 78.68, 125.62, 127.34, 128.72, 129.85, 134.64, 141.94; *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}.

2e: ^{1}H NMR: δ 2.64 (2H, *s*, OH, *meso*), 2.75 (2H, *s*, OH, *dl*), 5.39 (2H, *s*, CH, *dl*), 5.63 (2H, *s*, CH, *meso*), 7.17–7.34 (16H, *m*, Ph-H) ppm. *m/z* (%): 282 (1), 165 (47), 141 (89), 113 (13), 107 (14), 77 (100), 51 (38). IR (KBr)ν_{max}: 3100–3500 cm^{-1}.

2f: ^{1}H NMR: δ 2.67 (2H, *s*, OH, *meso*), 2.75 (2H, *s*, OH, *dl*), 5.28 (2H, *s*, CH, *dl*), 5.56 (2H, *s*, CH, *meso*), 7.16–7.65 (12H, *m*, Ph-H) ppm. ^{13}C NMR: 71.71, 73.02, 127.26, 127.64, 128.74, 129.58, 130.12, 130.51, 133.53, 134.20, 134.53, 134.85, 135.05, 136.00; *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}.

2g: ^{1}H NMR: δ 2.32 (6H, *s*, CH_3, *dl*), 2.37 (6H, *s*, CH_3, *meso*), 4.70 (2H, *s*, CH, *dl*), 4.77 (2H, *s*, CH, *meso*) 7.07–7.28 (16H, *m*, Ph-H) ppm. ^{13}C NMR: 21.59, 21.62, 78.38, 79.18, 127.33, 127.49, 129.20, 129.35, 137.38, 137.43, 137.82, 138.11; *m/z* (%): 242 (1.2), 195 (6), 121 (100), 107 (12), 77 (13). IR (KBr) ν_{max}: 3280–3450 cm^{-1}.

2h: ^{1}H NMR: δ 3.79 (6H, *s*, CH_3O, *dl*), 3.83 (6H, *s*, CH_3O, *meso*), 4.65 (2H, *s*, CH, *dl*), 4.76 (2H, *s*, CH, *meso*), 6.77–7.28 (16H, *m*, Ph-H) ppm. *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}.

2i: ^{1}H NMR: δ 4.60 (2H, *s*, CH, *dl*), 4.67 (2H, *s*, CH, *meso*), 5.95 (4H, *s*, CH_2, *dl*), 5.98 (4H, *s*, CH_2, *meso*), 6.56–6.88 (12H, *m*, Ph-H) ppm. ^{13}C NMR: 40.28, 40.49, 77.57, 78.15, 101.38, 108.02, 108.09, 108.34, 108.52, 121.31, 121.45, 137.18, 138.04, 146.64, 147.28; *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 4.98 (2H, *s*, CH, *dl*), 5.02 (2H, *s*, CH, *meso*), 6.22–6.33 (12H, *m*, furyl-H) ppm. *m/z* (%): 196 (10), 178 (25), 152 (73), 137 (33), 98(100), 84(22), 49 (30). IR (KBr) ν_{max}: 3240–3300 cm^{-1}.

2k: ^{1}H NMR: δ 2.29 (2H, *s*, OH, *meso*), 2.52 (2H, *s*, OH, *dl*), 4.31 (2H, *d*, CH, *dl*), 4.47 (2H, *d*, CH, *meso*), 6.32 (2H, *m*, –CH═CH–), 6.74 (2H, *m*, –CH═CH–), 7.18–7.42 (20H, *m*, Ph-H) ppm.

2m: ^{1}H NMR: δ 1.53 (6H, *s*, CH_3, *dl*), 1.61 (6H, *s*, CH_3, *meso*), 2.29 (2H, *s*, OH, *meso*), 2.59 (2H, *s*, OH, *dl*), 7.22–7.29 (20H, *m*, Ph-H) ppm. ^{13}C NMR: 25.36, 25.52, 79.01, 79.27, 127.31, 127.34, 127.56, 127.79, 143.83, 144.20; *m*/*z* (%): 225 (4), 206 (4), 181 (32), 165 (9), 121 (100), 105 (12), 77 (11), 43 (80). IR (KBr) ν_{max}: 3100–3600 cm^{-1}.

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