Pinacol coupling of aromatic aldehydes and ketones by $TiCl_4$–Mg–THF under ultrasound irradiation

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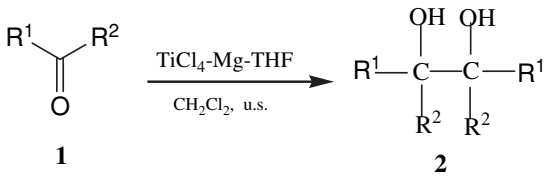
Pinacol coupling of aromatic aldehydes and ketones by $TiCl_4$–Mg–THF under ultrasound irradiation can lead to the corresponding pinacols in 20~89% yields.

Keywords: pinacol coupling, pinacol, synthesis, ultrasound irradiation

A number of 1,2-diols have been used in the synthesis of biologically important compounds, such as HIV protease inhibitors and natural products.[1] Several approaches to their syntheses have been described. Pinacol coupling reactions constitute one of the most straight forward methods.[2] Reagents such as Mg,[3] Mn,[4] Al,[5] In,[6] transition metal,[7, 8] and rare earth metal[9] promote the pinacol coupling.

The introduction of low-valent transition metal and lanthanoid based reducing systems, especially those based on titanium,[10] has provided dramatic advances in efficiency and selectivity. It is now possible to select appropriate conditions for efficient coupling of all types of carbonyl compounds, often with high chemo-, region- and stereo-selectivity.[2] in 1973, Mukaiyama reported that $TiCl_4$–Zn reduced aromatic aldehydes and ketones to produce the corresponding 1,2-diols in high yield,[11] but the stereoselectivity was not reported. In 1982, Clerici *et al.* reported that the pinacol coupling of aromatic aldehydes and ketones was promoted by aqueous titanium trichloride in basic media.[12] The reaction was complete in a few minutes, but the reducing power of Ti^{3+}/Ti^{4+} system was strongly pH dependent. The method has some limitations with respect to some aromatic aldehydes and ketones. Clerici *et al.* again reported pinacolisation of aromatic aldehydes mediated by titanium trichloride in dichloromethane in 1996.[13] The reaction had a 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 a monomeric titanocene (III) complex Cp_2TiPh.[14] Five aromatic aldehydes gave pinacols 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.[15] However, in spite of their potential utility, some of the reported methods suffer from drawbacks such as longer reaction times, lower reactivity for some aldehydes and ketones, lower yields, and lower *dl*-stereoselectivity.

Ultrasound is a convenient easily controlled technique which has increasingly been used in organic synthesis in the last three decades.[16] A number of organic reactions, involving metals, can be carried out in higher yields, shorter reaction time and milder conditions under ultrasound irradiation.[17-19] Recently, we reported the pinacolisation mediated by $TiCl_4$–Zn–THF or $TiCl_4$–Al–THF at room temperature under ultrasound irradiation.[20] We have now studied the pinacol coupling of aromatic aldehydes and ketones mediated by $TiCl_4$–Mg–THF system under ultrasound (Scheme 1).



1 **2**

Scheme 1

The effect of ultrasound on the pinacolisation reaction is summarised in Table 1. We used 3-ClC_6H_4CHO (1 mmol) as the substrate. When $TiCl_4$ (0.3 ml) and Mg (0.07 g) were added to the flask, after 30 min irradiation with a 25 kHz or 59 kHz ultrasonic cleaner, the yield of pinacol was 87% and 35%, respectively. When the irradiation time (25 kHz) was increased from 30 min to 60 min, the yield of pinacol remained the same. However on decreasing the reaction time from 30 min to 15 min, the yield of pinacol decreased from 87% to 50%. Adding Mg (0.140g) or Mg (0.035g) to the reaction system, the yield of pinacol (73% and 65%, respectively) was less than using Mg (0.070g) (87%). When $TiCl_4$ was 0.6 ml or 0.2 ml, pinacol was obtained in 35% and 44% yields, respectively. We chose the reaction conditions on the basis of these results: aldehyde or ketone (1 mmol), $TiCl_4$ (0.3 ml), Mg (0.07 g) and ultrasonic cleaner (25 kHz). The results of a series of pinacol couplings of aromatic aldehydes and ketones are shown in Table 2**.**

Li[15] *et al.* have reported that aromatic aldehydes bearing an electron-donating group and some ketones showed no reactivity in $TiCl_4$–Mg–THF system using the traditional method. Thus 4-methoxybezaldehyde (**1h**), acetophenone (**1i**) and 4-chloroacetophenone (**1m**) afforded no conversion *via*

Table 1 Influences of irradiation frequency and amount of Mg on the reductive coupling reaction[*]

Entry	Irradiation frequency / kHz	$TiCl_4$ / ml	Mg / g	Time / min	Isolated yield / % **2**
a	59	0.3	0.070	30	35
b	25	0.3	0.070	15	50
c	25	0.3	0.070	30	87
d	25	0.3	0.070	60	86
e	25	0.3	0.140	30	73
f	25	0.3	0.035	30	67
g	25	0.6	0.070	30	35
h	25	0.2	0.070	30	44

[*] Substrate: 3-ClC_6H_4CHO

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Table 2 Pinacolisation mediated by $TiCl_4$–Mg–THF under ultrasound irradiation

Entry	Substrate	Irradiation/ time min	Isolated yield/% **2**	*dl/meso**
a	C_6H_5CHO	20	68	77/23
b	3-ClC_6H_4CHO	30	87	92/8
c	4-ClC_6H_4CHO	20	89	85/15
d	2,4-$Cl_2C_6H_3CHO$	25	84	32/68
e	2-ClC_6H_4CHO	20	79	52/48
f	3-BrC_6H_4CHO	20	84	90/10
g	4-$CH_3C_6H_4CHO$	30	35	81/19
h	4-$CH_3OC_6H_4CHO$	40	25	91/9
i	3,4-$(OCH_2O)C_6H_3CHO$	40	27	88/12
j	Furfural	45	38	95/5
k	$C_6H_5COC_6H_5$	40	20	
l	$C_6H_5COCH_3$	25	64	80/20
m	4-$ClC_6H_4COCH_3$	5	45	77/23
n	$C_6H_5COCH_2Cl$	5	54	65/35
o	$C_6H_5COCH_2Br$	5	72	82/18
p	4- $H_2NC_6H_4COCH_3$	40	trace	

*Ratio of *dl/meso* was calculated by ^{1}H NMR.

TLC observation. Under ultrasound irradiation, pinacols were obtained in 25─45% yields. It is apparent that the reaction can be accelerated under ultrasound. We also used some ketones listed in Table 2 (**1n, 1o**) as the substrate gave pinacol in 54─72% yields.

As shown in Table 2**,** aromatic aldehydes possessing electron-withdrawing groups in the aromatic ring (**1b─1f**) had increased reactivity. In contrast, the aromatic aldehydes with electron-donating group (**1g─1j**) and ketones show less reactivity. Steric hindrance around the carbonyl group inhibits the coupling reaction. When 2-, 3- or 4-nitrobenzaldehyde and 4-aminoacetophenone were used as the substrates, little or no pinacol products were obtained.

Improved diastereoselectivity has been observed in our system compared with the $TiCl_4$─Zn─THF system. For example, using $TiCl_4$─Zn─THF system, when 4-ClC_6H_4CHO (**1c**), 3,4-$(OCH_2O)C_6H_3CHO$ (**1i**) and furfural (**1j**) as the substrate, the ratio of *dl*/*meso* of the 1,2-diols is 69/31, 25/75 and 53/47 respectively.[20] In the present system, the ratio of *dl*/*meso* of the corresponding 1,2-diols is 85/15, 88/12 and 95/5 respectively.

When 3- or 4-nitroacetophenones the substrates, 3- or 4-aminoacetophenone rather than a pinacol was obtained.

In summary, we have found an efficient and convenient method for the preparation of pinacols from some aromatic aldehydes by using $TiCl_4$–Mg–THF with ultrasound irradiation. The main advantage of the present procedure is the milder reaction conditions and operational simplicity.

Experimental

Liquid aldehydes were distilled before use. IR spectra were recorded on Bio-Rad FTS-40 spectrometer (KBr). MS were 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. Sonication was performed in Shanghai Branson-CQX ultrasonic cleaner (with a frequency of 25kHz and a nominal power 250W) and SK 250 LH ultrasonic cleaner (with a frequency of 40kHz, 59kHz and a nominal power 250W; Shanghai Kudos ultrasonic instrument Co., Ltd). The reaction flasks were located in the maximum energy area in the cleaner, where the surface of reactants is slightly lower than the level of the water. The reaction temperature was controlled by addition or removal of water from ultrasonic bath.

General procedure for the pinacol coupling of aromatic aldehydes and ketones by $TiCl_4$–Mg–THF under ultrasound irradiation: A 50 ml two-neck round flask was charged with CH_2Cl_2 (5 ml), THF (1 ml) and $TiCl_4$ (0.3 ml) and under an atmosphere of nitrogen at room temperature. To this solution Mg (0.07 g) was added in one portion. The colour of the solution changed to green immediately. Then a solution of the desired aldehyde (**1**, 1 mmol) in 1ml CH_2Cl_2 was added in one portion. The mixture was irradiated in the water bath of the ultrasonic cleaner at r.t. for a period as indicated in Table 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 filtered to remove the solid residues. 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. The 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. All the products were confirmed by comparing their R_f value with that of the authentic samples, and IR, MS, ^{1}H NMR spectral data.

2a ^{1}H NMR: δ 2.27 (2H, s, OH, *meso*), 2.92 (2H, s, OH, *dl*), 4.73 (2H, s, CH, *dl*), 4.85 (2H, s, CH, *meso*), 7.14–7.32 (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} cm^{-1}: 3200–3480.

2b: ^{1}H NMR: δ 2.38 (2H, s, OH, *meso*), 2.95 (2H, s, OH, *dl*), 4.65 (2H, s, CH, *dl*), 4.82 (2H, s, CH, *meso*), 7.16–7.43 (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} cm^{-1}: 3260–3318.

2c: ^{1}H NMR: δ 2.39 (2H, s, OH, *meso*), 2.97 (2H, s, OH, *dl*), 4.63 (2H, s, CH, *dl*), 4.84 (2H, s, CH, *meso*) 7.02–7.26 (16H, m, Ph-H). *m/z* (%): 276 (14), 249 (32), 155 (100), 111 (8). IR (KBr) ν_{max} cm^{-1}: 3380–3420.

2d: ^{1}H NMR: δ 3.46 (4H, s, OH), 5.16 (2H, s, CH, *dl*), 5.47(2H, s, CH, *meso*), 7.10–7.28 (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} cm^{-1} : 3320–3400.

2e: ^{1}H NMR: δ 2.66 (2H, s, OH, *meso*), 2.76 (2H, s, OH, *dl*), 5.39 (2H, s, CH, *dl*), 5.63 (2H, s, CH, *meso*), 7.17–7.70 (16H, m, Ph-H). *m/z* (%): 282 (1), 165 (47), 141 (89), 113 (13), 107 (14), 77 (100), 51 (38). IR (KBr) ν_{max} cm^{-1}: 3100–3500.

2f: ^{1}H NMR: δ 2.36 (2H, s, OH, *meso*), 2.93 (2H, s, OH, *dl*), 4.65 (2H, s, CH, *dl*), 4.81 (2H, s, CH, *meso*), 6.97–7.46 (16H, m, Ph-H). *m/z* (%): 325 (6), 186 (16), 157 (8), 107 (7), 77 (100), 51 (13). IR (KBr) ν_{max} cm^{-1}: 3200–3500.

2g: ^{1}H NMR: δ 2.28 (12H, s, CH_3), 2.45 (2H, s, OH, *meso*), 2.81 (2H, s, OH, *dl*), 4.70 (2H, s, CH, *dl*), 4.77 (2H, s, CH, *meso*) 7.07–7.28 (16H, m, Ph-H). *m/z* (%): 242 (1.2), 195 (6), 121 (100), 107 (12), 77 (13). IR (KBr) ν_{max} cm^{-1} : 3280–3450.

2h: ^{1}H NMR: δ 2.95 (4H, s, OH), 3.75 (6 H, s, OCH_3, *dl*), 3.79 (6 H, s, OCH_3, *meso*), 4.64 (2H, s, CH, *dl*), 4.72 (2H, s, CH, *meso*), 6.84–7.52 (16H, m, Ph-H). *m/z* (%): 276 (14), 249 (32), 155 (100), 111 (8). IR (KBr) ν_{max} cm^{-1} : 3300–3600.

2i: ^{1}H NMR: δ 4.44 (4H, s, OH), 5.14 (2H, s, CH, *dl*), 5.27 (2H, s, CH, *meso*), 5.96 (8H, s, CH_2), 6.57–6.94 (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} cm^{-1}: 3100–3600.

2j: ^{1}H NMR: δ 5.03 (2H, s, CH, *dl*), 5.10 (2H, s, CH, *meso*), 6.29–6.37 (12H, m, furyl-H). *m/z* (%): 196 (10), 178 (25), 152 (73), 137 (33), 98 (100), 84 (22), 49 (30). IR (KBr) ν_{max} cm^{-1} : 3240–3300.

2k: ^{1}H NMR: δ 3.04 (2H, s, OH,), 7.17–7.19 (20H, m, Ph-H). *m/z* (%): 184 (16), 183 (99), 165 (7), 106 (8), 105 (100), 78 (6), 77 (72), 51 (11), 43 (2). IR (KBr) ν_{max} cm^{-1}: 3200–3600.

2l: ^{1}H NMR: δ 1.53 (6H, s, CH_3, *dl*), 1.61 (6H, s, CH_3, *meso*), 2.34 (2H, s, OH, *meso*), 2.66 (2H, s, OH, *dl*), 7.21–7.35 (20H, m, Ph-H). *m/z* (%): 225 (4), 206 (4), 181 (32), 165 (9), 121 (100), 105 (12), 77 (11), 43 (80). IR (KBr) ν_{max} cm^{-1}: 3100–3600.

2m: ^{1}H NMR: δ 1.47 (6H, s, CH_3, *dl*), 1.54 (6H, s, CH_3, *meso*), 2.26 (2H, s, OH, *meso*), 2.56 (2H, s, OH, *dl*), 7.11–7.34 (16H, m, Ph-H). *m/z* (%): 276 (14), 249 (32), 155 (100), 111 (8). IR (KBr) ν_{max} cm^{-1}: 3140–3650.

2n: ^{1}H NMR: δ 1.53 (4H, s, CH_2, *dl*), 1.64 (4H, s, CH_2, *meso*), 2.27 (2H, s, OH, *meso*), 2.57 (2H, s, OH, *dl*), 7.20–7.24 (20H, m, Ph-H). *m/z* (%): 155 (3), 121 (13), 105 (100), 77 (13), 51 (2), 43 (18). IR (KBr) ν_{max} cm^{-1}: 3140–3620.

2o: ^{1}H NMR: δ 1.53 (4H, s, CH_2, *dl*), 1.55 (4H, s, CH_2, *meso*), 2.27 (2H, b, OH, *meso*), 2.58 (2H, s, OH, *dl*), 7.21–7.25 (20H, m, Ph-H). *m/z* (%): 303 (11), 301 (12), 240 (4), 239 (23), 201 (2), 199 (2), 123 (8), 121 (23), 105 (100), 81 (26), 43 (2). IR (KBr) ν_{max} cm^{-1}: 3160–3640.

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