



Reductive Coupling of Aromatic Aldehydes and Acetophenone Induced by $\text{TiCl}_4\text{-Al/CH}_2(\text{COOEt})_2$

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Induced by $\text{TiCl}_4\text{-Al/CH}_2(\text{COOEt})_2$ in CH_2Cl_2 , some aromatic aldehydes and acetophenone can afford the corresponding 1,2-diols in 13-91 % yields with good dl-diastereoselectivities within 45-60 min at room temperature.

Key Words: Aromatic aldehydes, Pinacol coupling, Pinacol, Low valent titanium, Esters.

INTRODUCTION

Pinacol coupling reaction of carbonyl compounds is an important organic reaction to form both the new C-C bond and pinacols^{1,2}, which has often been employed in total synthesis of many natural products^{3,4}. The chiral pinacols are also the prominent auxiliaries in many asymmetric synthesis⁵⁻⁷. In particular, pinacol coupling has been employed as a key step in the construction of HIV-protease inhibitors⁸. 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.

Since the first report by Mukayama⁹ of pinacol coupling reactions mediated with a titanium reagent in 1973, low valent titanium has attracted increasing attention. Clerici and Porta¹⁰ reported pinacol coupling of aromatic aldehydes and ketones promoted by aqueous titanium trichloride in basic media, the reaction was completed in a few minutes, but the method has some limitations with respect to some aromatic aldehydes and ketones and the diastereoselectivities of the pinacols are poor. Schwartz and Barden¹¹ reported the stereoselective pinacol coupling in aqueous media in 1996, the 1,2-diols with good yields and high diastereoselectivities were obtained. Gansäuer *et al.*¹² reported the titanocene-catalyzed pinacol coupling of aromatic aldehydes proceeding in good yields and with high diastereoselectivity under reagent control. Enders and Ullrich¹³ reported 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. Itoh *et al.*¹⁴ reported diastereoselective pinacol coupling of aldehydes promoted by monomeric titanocene(III) complex

Cp_2TiPh , five aromatic aldehydes gave desired pinacol in 54-96 % yields within 1-4 h. Kulinkovich *et al.*¹⁵, reported the titanium(III) isopropoxide prepared by the reaction of titanium(IV) isopropoxide with one equivalent of the Grignard reagent transformed the aldehydes and the 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 longer reaction time, expensive catalysts and harsh terms. Esters can coordinate with TiCl_4 , so we wish to report the results on the reductive coupling of aromatic aldehydes mediated by low valent titanium using esters as ligands.

EXPERIMENTAL

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

General procedure: A 50 mL two neck round bottom flask was charged with CH_2Cl_2 (5 mL), $\text{CH}_2(\text{COOEt})_2$ (3 mmol), TiCl_4 (2 mmol) under a nitrogen atmosphere. The two neck round flask was put into ultrasonic bath and then Al powder (4 mmol) was added. The reaction mixture was irradiated and turned into dark green immediately. After 5 min, the mixture was removed from ultrasonic bath. Then the desired aldehyde (**1**, 1 mmol) in 1 mL CH_2Cl_2 was added and the mixture was stirred at room temperature 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 extracted with ethyl

acetate (3 mL \times 15 mL). The combined organic layers were washed with saturated aqueous NaHCO₃ solution and brine, dried over anhydrous magnesium sulphate 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. The authenticity of the product was established by their ¹H NMR, MS and IR spectral data.

2a: ¹H 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} , cm⁻¹): 3480-3200.

2b: ¹H NMR: δ 3.03 (2H, s, OH, *meso*), 3.07 (2H, s, OH, dl), 5.42 (2H, d, CH, dl), 5.67 (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} , cm⁻¹): 3500-3100.

2c: ¹H NMR: δ 2.80 (2H, s, OH, *meso*), 3.37 (2H, s, OH, dl), 4.66 (2H, s, CH, dl), 4.85 (2H, s, CH, *meso*), 6.96-7.34 (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): 3318-3260.

2d: ¹H NMR: 2.96 (2H, s, OH, dl), 4.63 (2H, s, CH, dl), 7.02-7.28 (8H, m, Ph-H). *m/z* (%): 276 (14), 249 (32), 155 (100), 111 (8). IR (KBr, ν_{\max} , cm⁻¹): 3420-3380.

2e: ¹H NMR: δ 3.02 (2H, s, OH, *meso*), 3.06 (2H, s, OH, dl), 5.31 (2H, s, CH, dl), 5.60 (2H, s, CH, *meso*), 7.22-7.68 (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): 3400-3320.

2f: ¹H NMR: δ 2.32 (6H, s, CH₃, dl), 4.69 (2H, s, CH, dl), 7.04-7.09 (16H, m, Ph-H). *m/z* (%): 242 (1.2), 195 (6), 121 (100), 107 (12), 77 (13). IR (KBr, ν_{\max} , cm⁻¹): 3450-3280 cm⁻¹.

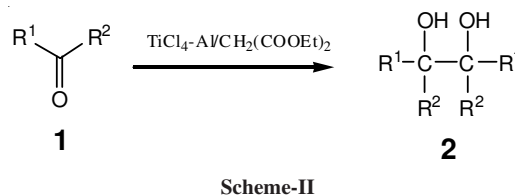
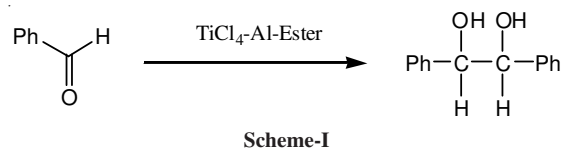
2g: ¹H NMR: δ 3.75 (6H, s, CH₃O, dl), 3.79 (6H, s, CH₃O, *meso*), 5.13 (2H, s, CH, dl), 5.34 (2H, s, CH, *meso*) 6.85-7.25 (16H, m, Ph-H) ppm. Anal. calcd. (%) for C₁₆H₁₈O₄: C 70.06, H 6.61; found (%) C 70.02, H 6.63. IR (KBr, ν_{\max} , cm⁻¹): 3640-3130 cm⁻¹.

2h: ¹H NMR: δ 4.59 (2H, s, CH, dl), 4.67 (2H, s, CH, *meso*), 5.96 (4H, s, CH₂, dl), 6.06 (4H, s, CH₂, *meso*), 6.56-6.81 (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} , cm⁻¹): 3600-3100 cm⁻¹.

2j: ¹H NMR: δ 1.51 (6H, s, CH₃, dl), 1.59 (6H, s, CH₃, *meso*), 2.30 (2H, s, OH, *meso*), 2.60 (2H, s, OH, dl), 7.20-7.26 (20H, m, Ph-H) ppm. *m/z* (%): 225 (4), 206 (4), 181 (32), 165 (9), 121 (100), 105 (12), 77 (11), 43 (80). IR (KBr, ν_{\max} , cm⁻¹): 3600-3100 cm⁻¹.

RESULTS AND DISCUSSION

The effect of different esters on the benzaldehyde were investigated (Table-1). As shown in Table-1, the coupling of benzaldehyde mediated by TiCl₄-Al using different esters as ligands was carried out in good yields for a short time. For example, using ethyl acetate (Entry 1), diethyl oxalate (Entry 3), diethyl butanedioate (Entry 5), diethyl (*o*-)phthalate (Entry 6),



dibutyl (*o*-)phthalate (Entry 7), diethyl camphorate (Entry 8), diethyl malonate (Entry 9) and ethyl acetoacetate (Entry 10) as ligands under stirring at room temperature within 40-50 min, 1,2-diphenyl-1,2-ethanediol was obtained with 90-93 % yields.

However, the structure of esters had obvious effect on the diastereoselectivity of 1,2-diphenyl-1,2-ethanediol. When the ligand was single ester, the *dl/meso* of 1,2-diphenyl-1,2-ethanediol was low. For example, when ethyl acetate, isopentyl acetate and ethyl acetoacetate were used as ligands, the *dl/meso* of 1,2-diphenyl-1,2-ethanediol was 68/32, 66/34 and 65/35, respectively. For the double ester, using diethyl oxalate, diethyl butanedioate, diethyl *o*-phthalate, dibutyl *o*-phthalate, diethyl camphorate as ligands, the *dl/meso* of 1,2-diphenyl-1,2-ethanediol was 76/24, 77/23, 82/18, 83/17 and 70/30, respectively. Using diethyl malonate as ligand, the *dl/meso* of 1,2-diphenyl-1,2-ethanediol was 97.4/2.6. When diethyl (*trans*)-butenedioate was used as ligand, the *dl/meso* of 1,2-diphenyl-1,2-ethanediol was 16/84.

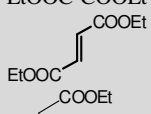
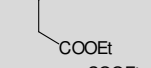
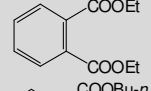
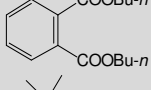
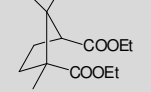
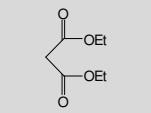
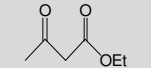
From the results above, using CH₂(COOEt)₂ as ligand, the 1,2-diphenyl-1,2-ethanediol could be obtained in high yield and good *dl*-diastereoselectivity. So we did a series of experiments on the pinacol coupling of aromatic aldehydes and ketones using CH₂(COOEt)₂ as ligand. The results are listed in Table-2.

The coupling of some aromatic aldehydes mediated by TiCl₄-Al using CH₂(COOEt)₂ as ligand was carried out in good yields. For example, using the present system under stirring at room temperature for 45 and 60 min, **2a** and **2d** were obtained with 90 and 91 % yields, respectively. Whereas **2a** and **2d** were prepared in 50 and 71 % yields, respectively with TiCl₄-Al in Et₂O under stirring for 38 and 29 h¹⁶.

As shown in Table-2, benzaldehyde and the aromatic aldehydes with electron-withdrawing substituents in the benzene ring (**1a-1e**) had high reactivity in the present system. Under stirring at room temperature, **1a-1e** afforded **2a-2e** in 86-91 % yields within 45-60 min. In contrast, the aromatic aldehydes with electron-donating substituents in the benzene ring (**1f-1i**) showed lower reactivity. Compounds of **2g** and **2h** were obtained with 38 and 28 % yields within 1 h under stirring at room temperature. When **1g** was as substrate, trace amount of **2g** was obtained.

On the other hand, when the substrate were C₆H₅COCH₃ (**1j**) and 4-ClC₆H₄COCH₃ (**1k**), the yields of the corresponding 1,2-diols were 13 and 0 %, respectively. The results showed that aromatic ketones had little reactivity induced by this system.

TABLE-1
EFFECT OF THE STRUCTURE OF ESTER ON PINACOLIZATION OF BENZALDEHYDE

Entry	Ester	Temperature (°C)	Time (min)	Isolated yield (%)	<i>dl/meso</i> *
1	CH_3COOEt	26	40	91	68/32
2	$\text{CH}_3\text{COOCH}_2\text{CH}_2\text{CH}(\text{CH}_3)_2$	26	50	65	66/34
3	EtOOC-COOEt	25	45	93	76/24
4		25	50	67	16/84
5		27	45	91	77/23
6		28	40	92	82/18
7		26	45	90	83/17
8		28	50	90	70/30
9		25	45	90	97.4/2.6
10		26	45	91	65/35

*Ratio of *dl*- and *meso*- isomer is determined by $^1\text{H NMR}$.

TABLE-2
PINACOLIZATION OF AROMATIC ALDEHYDES AND KETONES MEDIATED BY $\text{TiCl}_4\text{-Al/CH}_2(\text{COOEt})_2$

Entry	Substrate	Temperature (°C)	Time (min)	Yield (%)	<i>dl/meso</i> *
a	$\text{C}_6\text{H}_5\text{CHO}$	25	45	90	97.4/2.6
b	2- $\text{ClC}_6\text{H}_4\text{CHO}$	22	50	86	80/20
c	3- $\text{ClC}_6\text{H}_4\text{CHO}$	21	60	90	98.7/1.3
d	4- $\text{ClC}_6\text{H}_4\text{CHO}$	21	60	91	<i>dl</i> only
e	2,4- $\text{Cl}_2\text{C}_6\text{H}_3\text{CHO}$	22	60	87	68/32
f	4- $\text{CH}_3\text{C}_6\text{H}_4\text{CHO}$	20	60	73	<i>dl</i> only
g	2- $\text{CH}_3\text{OC}_6\text{H}_4\text{CHO}$	22	60	38	67/33
h	3,4-(OCH_2O) $\text{C}_6\text{H}_3\text{CHO}$	21	60	28	80/20
i	4- $\text{CH}_3\text{OC}_6\text{H}_4\text{CHO}$	21	60	Trace	—
j	PhCOCH_3	22	60	13	77/23
k	PhCOPh	22	60	0	—

Improved diastereoselectivity has been observed in the present system. When 4- $\text{ClC}_6\text{H}_4\text{CHO}$ (**1d**) and 4- $\text{CH}_3\text{C}_6\text{H}_4\text{CHO}$ (**1f**) are substrates, the *dl/meso* of the corresponding 1,2-diols were 75/25 and 74/26, respectively in Itoh's report⁸, whereas in the present system, **2d** and **2f** are both *dl*-only.

In addition, the position of substituents in the benzene ring has some effects on the *dl/meso* in the system. The coupling of the aromatic aldehydes with *meta*- or *para*-position substituents in the benzene ring has high diastereoselectivities, whereas the coupling of aromatic aldehydes with *ortho*-position substituents in the benzene ring showed low diastereoselectivities. For example, the *dl/meso* of **2c**, **2d** and **2f** were 98.7/1.3, *dl*-only and *dl*-only. However, using 2- $\text{ClC}_6\text{H}_4\text{CHO}$ (**1b**), 2,4- $\text{Cl}_2\text{C}_6\text{H}_3\text{CHO}$ (**1e**) and 2- $\text{CH}_3\text{OC}_6\text{H}_4\text{CHO}$ (**1g**) as substrates, the *dl/meso* of the corresponding 1,2-diols were 80/20, 68/32 and 67/33, respectively.

In summary, we have found an efficient and convenient method for the preparation of diastereoselective pinacols from

some aromatic aldehydes by using $\text{TiCl}_4\text{-Al/CH}_2(\text{COOEt})_2$ in CH_2Cl_2 under stirring at room temperature. The main advantage of the present procedure is the milder reaction conditions, inexpensive catalyst and operational simplicity.

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