Note

Coupling Reaction of Carbonyl Compounds Mediated by Gallium Metal in Aqueous Media

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A simple and effective pinacol coupling of various aromatic aldehydes mediated by gallium in good yields has been carried out. The reaction is highly effective in water in the presence of KOH or HCl and was strongly affected by the steric environment surrounding the carbonyl group. Aliphatic aldehydes, ketones and aromatic ketones appear inert under the same reaction conditions.

Keywords coupling reaction, gallium mediator, aqueous media

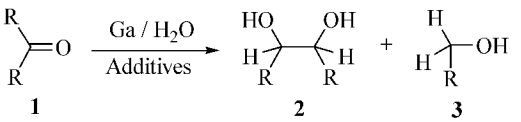
Introduction

Carbon-carbon bond formation is the essence of organic synthesis. One of the most powerful methods for constructing carbon-carbon bond is the reductive coupling of carbonyl compounds giving olefins and/or 1,2-diols.[1] Of these methods, the pinacol coupling is still a useful tool for the synthesis of vicinal diols. The corresponding products of this reaction can be used as intermediates for the preparation of ketones and olefins.[2] In addition, this method has been instrumental in the synthesis of some important natural products.[3] Traditionally, pinacol couplings have been effected by various metals such as sodium, lithium, or magnesium(I) iodide and Rieke Mg.[4] Other metallic reagents used for such a reaction include vanadium, VCl_3/$PhMe_2SiCl$/DME, Sm/TMEDA/THF, Sm/I_2 or SmI_2,[5] Ce(O-*t*-Bu)$_3$/TMSCl, $CeCl_3$/TMSCl,[6] Ce-I_2,[7] Yb,[8] Al(Hg),[9] and Rieke Mn,[10] as well as the versatile $TiCl_3$-based reducing agents,[11] and Ln/Me_3SiCl-THF (Ln: Ce, Pr, Nd, Gd, Dy, Tm, Yb, Lu).[12] Generally, these reagents were employed under anhydrous conditions. Because of economical and environmental concerns, the use of water as a solvent for metal-mediated carbon-carbon bond formation has generated considerable interest. Recently, pinacol coupling reactions in aqueous media have been investigated by using Ti,[13] Cu-Zn,[14] Al,[15] Mn,[16] In,[17] Mg,[18] *etc*., affording inter- or intra-molecular coupling products of carbonyl compounds. Up to date, Ga metal used for pinacol coupling reaction of carbonyl compounds either in organic media or in aqueous media has not been reported. Herein, we wish to report the study of using Ga for pinacol coupling reaction of carbonyl compounds in aqueous media.

Results and discussion

In our experiment, it was found that Ga, together with some KOH or HCl, was highly effective for pinacol coupling of carbonyl compounds in aqueous media to afford pinacol **2** in good yields at a slightly elevated temperature, as shown in Scheme 1. A small amount of corresponding alcohol **3** was formed as a by-product.

Scheme 1



1 **2** **3**

The Ga ingot was molten into a liquid for the present study. No pinacol product was observed in the absence of additives at different temperatures (Entries 1 and 11, Table 1). At room temperature, treatment of benzaldehyde with Ga and various additives in water for 12 h afforded very low yields of pinacol **2a** (< 10%) and alcohol **3a** (< 3%) accompanied by a 95% recovery of **1a**. The reaction was not significantly improved by either ultrasonic irradiation or the use of an excessive amount of Ga (Entry 10, Table 1). Although the introduction of methanol to the solvent (to increase the solubility of the substrate) enhanced the yields of pinacols (Entries 15, 17, 19, Table 1), the recent interest in green chemistry requires the use of a more benign solvent. When pinacol coupling reaction was performed in aqueous HCl solution, however, a certain amount of corresponding alcohol **3** was formed as by-products. To begin our study, the reaction of benzaldehyde with Ga was examined under various conditions in order to optimize the coupling condition (Table 1).

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Table 1 Pinacol coupling reaction of benzaldehyde (1 mmol) with gallium under various conditions

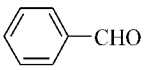
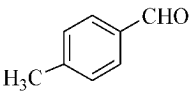
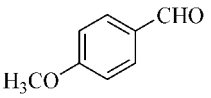
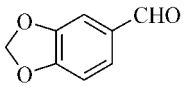
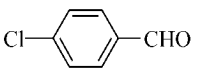
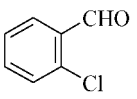
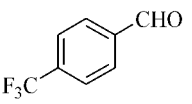
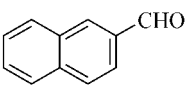
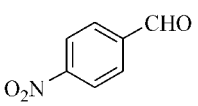
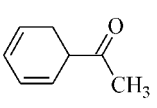
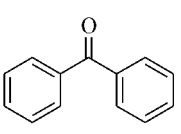
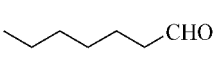
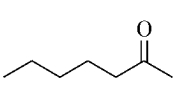
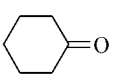
Entry	Reaction media (mmol)	Reaction time (h)	Pinacol **2a** yield[a,c] (%)	*dl*/*meso*[b]
1	H_2O (5 mL)	12	—	—
2	H_2O[e]/HCl (3 mmol)	12	4	1.1/1
3	H_2O/HCl (5 mmol)	12	6	1/1
4	H_2O/NH_4Cl (3 mmol)	12	2	1.4/1
5	H_2O/NH_4Cl (5 mmol)	12	3	1.2/1
6	H_2O/KOH (3 mmol)	12	4	1/2.5
7	H_2O/KOH (5 mmol)	12	6	1/1.7
8	KOH (3 mmol)/MeOH (5 mL)	12	7	1.3/1
9	KOH (5 mmol)/MeOH (5 mL)	12	9	1.4/1
10[d]	H_2O/KOH (5 mmol)	12	7	1/1.9
11[f]	H_2O (5 mL)	12	—	—
12	H_2O/HCl (5 mmol)	6	71	1/1
13	H_2O/NH_4Cl (5 mmol)	6	53	1.2/1
14	H_2O/KOH (5 mmol)	6	85	1/1.6
15	KOH (5 mmol)/MeOH (5 mL)	6	89	1.3/1
16	H_2O/KOH (5 mmol)	4	87	1/2
17	KOH (3 mmol)/MeOH (5 mL)	4	91	1.3/1
18	H_2O/KOH (5 mmol)	4	87	1/2
19	KOH (3 mmol)/MeOH (5 mL)	4	91	1.2/1

[a] The isolated yields are reported. [b] The ratios of *dl*/*meso* isomers were determined by the ^1H NMR analysis of the crude product mixtures. [c] The pure products were identified by IR, ^1H NMR, ^{13}C NMR and HRMS. [d] Irradiation in an ultrasonic bath (35 kHz). [e] The volume of H_2O is 5 mL in every situation. [f] Temperatures of reaction Entries 11—15 are 45 ℃, Entries 16—17 are 55 ℃, and Entries 18—19 are over 55 ℃.

After a comprehensive survey of the reaction conditions, it was found that Ga in KOH aqueous solution at 45 ℃ and 55 ℃ provided the optimal results in the absence of methanol (Entries 14 and 16, Table 1). Beyond 55 ℃, no any influence on pinacol product was observed, but the yield of by-product increased. Considering side reaction and energy consuming beyond 45 ℃, the reaction condition of Entry 14 was employed in pinacol coupling reaction, meanwhile, the ratio of KOH (7 mmol) was adjusted. Subsequently, the pinacol coupling reactions of other substrates were examined under the same conditions. The results are summarized in Table 2. In the most cases of Table 2, good yields of pinacols were obtained as mixtures of *dl* and *meso* isomers (Table 2). Benzaldehydes bearing trifluoromethyl and chloro group proceeded to give corresponding pinacols as the major products respectively (Entries 5, 6, 7, Table 2). As for piperonal and 2-naphthaldehyde (Entries 4 and 8, Table 2), HRMS demonstrated the generation of the corresponding pinacols. However, due to either piperonyl or naphthyl group in the corresponding pinacol hardly rotated freely and resulted in the decrease of the number of isomers. Actually, ^1H NMR spectra of both piperonyl and naphthyl pinacols showed one single peak at δ 4.48 and 5.02 respectively. This experimental result indicated that there were only *dl*-isomer for piperonyl pinacol and only *meso*-isomer for naphthyl pinacol (Entries 4 and 8, Table 2).[23-25, 27-29, 31-33] An increase in the steric hindrance around the carbonyl group inhibited carbon-carbon coupling reaction. No desired pinacol products were observed with acetophenone and diphenylmethanone (Entries 10 and 11, Table 2). As for nitrobenzaldehyde, no corresponding pinacol was obtained either (Entry 9, Table 2) probably due to the reduction of nitro group by gallium under the reaction condition.[19] Unlike aromatic carbonyl compounds, aliphatic aldehydes and ketones provided none of the desired diols, and the main products were mixtures of aldol condensation products under such conditions.

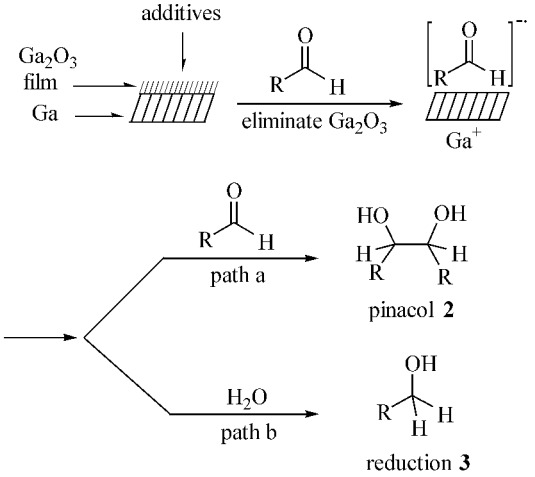
Based on our experimental results and the previous reports,[15(b),16,33] we propose the following possible mechanism (Scheme 2). The mechanism of metal reduction of carbonyl compound is generally believed to proceed through the intermediacy of a ketyl radical anion formed by electron transfer from metal to the carbonyl substrate. In the present case, it is likely that the additives activate the gallium metal surface by interaction with Ga_2O_3 to give the water-soluble complex compounds ($KGaO_2$), the exposed gallium metal can thus carry out the pinacol coupling or a reduction reaction of the carbonyl moiety.

Table 2 Gallium/KOH promoted pinacol coupling of carbonyl compounds in water

Entry	Substrate **1**	Time (h)	**2** (Yield, %)[a,c]	*dl*/*meso*[b]	**3** (Yield, %)[a,c]
1		6	**2a** (89)	1/2	6
2		6	**2b** (85)	1/3	7
3		6	**2c** (91)	3/1	5
4		6	**2d** (93)	single *dl*-type	2
5		6	**2e** (84)	1/1	7
6		6	**2f** (82)	1/1.5	6
7		6	**2g** (83)	1/2.3	3
8		6	**2h** (81)	single *meso*-type	7
9		6	—	—	—
10		6	—	—	—
11		6	—	—	—
12		6	—	—	—
13		6	—	—	—
14		6	—	—	—

[a] The isolated yields are reported. [b] The ratio of *dl* to *meso* isomers was determined by ^{1}H NMR analysis of the crude product mixture.
[c] The pure products were identified by IR, ^{1}H NMR, ^{13}C NMR and HRMS.[19]

Scheme 2 Postulated machanism for gallium-mediated pinacol coupling and reduction of carbonyl compounds



In conclusion, a highly effective pinacol coupling of aryl aldehyde was carried out mediated by gallium with KOH in water. The method here is an alternative approach to pinacol. This procedure provided a convenient and practical method for the formation of carbon-carbon bond.

Experimental

IR (Perkin-Elmer, 2000 FTIR), ^{1}H NMR (CD_3Cl, 500 MHz), ^{13}C NMR ($CDCl_3$, 125.7 MHz) and Micromass GCT-MS spectra were obtained at the Center of Analytical Configuration of University of Science and Technology of China. Flash chromatographic sheet employed was from the Factory of Reagent of Shanghai. All material was purchased from Aldrich and was used directly as received.

General procedure for pinacol coupling of aromatic aldehydes

Gallium ingot (2 mmol), additives (7 mmol) and water (5 mL), were sequentially placed in a round-bottomed flask, then carbonyl compound (1 mmol) was added successively to the mixture. The reaction mixture was stirred for the time indicated in Table 1 at certain temperature. The reaction mixture was then extracted with ethyl ether. Organic phase was washed with saturated brine, dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The crude product mixture contained pinacol *dl*-**2**, pinacol *meso*-**2** and alcohol **3** in certain ratio according to the ^{1}H NMR analysis. Pure pinacols were obtained by recrystallization from EtOAc/hexane (1∶6, *V*∶*V*) or by flash chromatography on silica gel eluting with petroleum ether/acetic ether (4∶1, *V*∶*V*).

1,2-*Biphenyl*-1,2-*ethanediol* (**2a**)[20-22,28] ^{1}H NMR ($CDCl_3$, 500 MHz) δ∶7.07—7.28 (m, 10H, Ph), 4.78 (*meso*), 4.64 (*dl*) (s, 2H, PhC**H**OH), 2.51—2.61 (brs, 2H, OH); ^{13}C NMR ($CDCl_3$, 125 MHz) δ∶78.26, 79.29, 127.17, 127.31, 128.10, 128.25, 128.31, 128.39, 139.95, 140.08; IR (KBr) ν∶3375.1, 2899.0, 1602.1, 1452.7, 1344.1, 754.0, 698.8 cm^{-1}; HRMS calcd for $C_{14}H_{14}O_2$ 214.0994, found 214.0993.

1,2-*Bi*(*p-methylphenyl*)-1,2-*ethanediol* (**2b**)[21,22,26,30] ^{1}H NMR ($CDCl_3$, 500 MHz) δ∶6.98 (d, *J* = 8.0 Hz, 4H), 7.10 (d, *J* = 8.0 Hz, 4H), 4.70 (*meso*), 4.60 (*dl*) (s, 2H, C**H**OH), 2.33 (brs, 2H, OH), 2.29 (s, 6H, CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ∶21.38, 21.41, 78.23, 79.01, 127.09, 127.26, 129.00, 129.16, 137.20, 137.92; IR (KBr) ν∶3354.3, 2915.2, 2888.6, 1614.1, 1516.1, 1321.3, 817.0 cm^{-1}; HRMS calcd for $C_{16}H_{18}O_2$ 242.1307, found 242.1295.

1,2-*Bi*(*p-methoxyphenyl*)-1,2-*ethanediol* (**2c**)[20,22,28,31] ^{1}H NMR ($CDCl_3$, 500 MHz) δ∶6.71 (d, *J* = 7.8 Hz, 4H), 6.96 (d, *J* = 7.8 Hz, 4H), 4.74 (*meso*), 4.56 (*dl*) (s, 2H, C**H**OH), 3.70 (s, 6H, CH_3), 3.20—3.34 (brs, 2H, OH); ^{13}C NMR ($CDCl_3$, 125 MHz) δ∶55.01, 78.81, 78.92, 113.38, 128.89, 134.08, 159.32; IR (KBr) ν∶3376.7, 2931.7, 2834.8, 1612.8, 1516.8, 1440.6, 1249.1, 1035.4, 833.0 cm^{-1}; HRMS calcd for $C_{16}H_{18}O_4$ 274.1205, found 274.1201.

1,2-*Bipiperonyl*-1,2-*ethanediol* (**2d**)[23,25,27,32] ^{1}H NMR ($CDCl_3$, 500 MHz) δ∶3.03 (s, 2H, OH), 4.50 (s, 2H), 5.91 (s, 4H), 6.71—6.78 (m, 4H), 6.81 (s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ∶64.83, 100.96, 107.85, 108.12, 120.45, 134.95, 146.92, 147.83; IR (KBr) ν∶3332.4, 2909.1, 1605.2, 1503.4, 1443.6, 1250.4, 1034.6, 1016.5, 804.2 cm^{-1}; HRMS calcd for $C_{16}H_{14}O_6$ 302.0790, found 302.0800.

1,2-*Bi*(*p-chlorophenyl*)-1,2-*ethanediol* (**2e**)[21,28,31,32] ^{1}H NMR ($CDCl_3$, 500 MHz) δ∶7.09—7.25 (m, 8H, Ar), 4.85 (*meso*), 4.70 (*dl*) (s, 2H, C**H**OH), 4.08—4.25 (brs, 2H, OH); ^{13}C NMR ($CDCl_3$, 125 MHz) δ∶76.77, 77.76, 127.53, 127.72, 128.96, 129.06, 132.32, 132.53, 140.20, 140.46; IR (KBr) ν∶3332.1, 2918.2, 1596.8, 1491.7, 1311.8, 1090.2, 823.0 cm^{-1}; HRMS calcd for $C_{14}H_{12}Cl_2O_2$ 282.0214, found 282.0211.

1,2-*Bi*(*o-chlorophenyl*)-1,2-*ethanediol* (**2f**)[20,32,33] ^{1}H NMR ($CDCl_3$, 500 MHz) δ∶7.10—7.83 (m, 8H, Ph), 5.51 (*meso*), 5.27 (*dl*) (s, 2H, C**H**OH), 3.35 (2H, OH); ^{13}C NMR ($CDCl_3$, 125 MHz) δ∶71.66, 72.50, 126.19, 126.59, 128.23, 128.44, 128.71, 128.79, 129.76, 130.20, 131.94, 132.93, 138.14, 139.26; IR (KBr) ν∶3376.9, 2923.9, 1595.2, 1573.0, 1440.3, 1031.8, 749.2 cm^{-1}; HRMS calcd for $C_{14}H_{12}Cl_2O_2$ 282.0214, found 282.0208.

1,2-*Bi*(*p-trifluoromethylphenyl*)-1,2-*ethanediol* (**2g**)[16] ^{1}H NMR ($CDCl_3$, 500 MHz) δ∶7.43 (d, *J* = 6.2 Hz, 4H, Ar), 7.55 (d, *J* = 6.2 Hz, 4H, Ar), 4.96 (*meso*), 4.92 (*dl*) (s, 2H, C**H**OH), 3.25—3.47 (brs, 2H, OH); ^{13}C NMR ($CDCl_3$, 125 MHz) δ∶77.72, 78.19, 125.26, 128.78, 128.94, 146.98; IR

(KBr) ν: 3408.4, 2885.0, 1623.0, 1333.3, 1119.7, 1070.3, 840.0 cm^{-1}; HRMS calcd for $C_{16}H_{11}F_6O$ ($M + H^- - H_2O$) 333.0714, found 333.0689.

1,2-Bi(2-naphthyl)-1,2-ethanediol (**2h**)[24,28,29,31,32]

^1H NMR ($CDCl_3$, 500 MHz) δ: 3.58—3.70 (br, 2H), 5.02 (s, 2H), 7.42—7.50 (m, 4H), 7.52—7.60 (m, 4H), 7.84 (d, J = 8.0 Hz, 2H), 7.93 (t, J = 4.0, 5.0 Hz, 2H), 8.06 (t, J = 4.0, 5.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 77.26, 124.55, 125.41, 125.76, 125.95, 126.32, 128.06, 128.71, 131.77, 133.95, 134.54; IR (KBr) ν: 3389.8, 3051.1, 2900.0, 1599.1, 1507.8, 1041.4, 817.8, 742.2 cm^{-1}; HRMS calcd for $C_{22}H_{18}O_2$ 314.1967, found 314.1964.

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