

Reduction and Coupling Reaction of Carbonyl Compounds by Aluminum Powder and a Small Amount of Oxalic Acid in Water

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A convenient pinacol coupling of aromatic aldehydes and aryl methyl ketones has been achieved with high yields by aluminum powder in the presence of oxalic acid in water. However, the diastereoselectivities of pinacols were not satisfying, and most aliphatic aldehydes and diaryl ketones have been found to be unreactive under the same conditions.

Keywords aluminum mediator, pinacol coupling reaction, aqueous media

Introduction

Pinacol coupling reaction is one of the most important reactions for the formation of carbon-carbon bond, and although discovered in 1859,¹ it can still find many applications to the diastereoselective synthesis of vicinal diols, which can be used as intermediates for the construction of biologically important natural product skeletons.² Numerous reagents for pinacol reactions are known, which include Al-Hg,³ Rieke Mg,⁴ active Mn,⁵ SmI₂,⁶ SmI₂-TMSCl (TMSCl=trimethylsilyl chloride),⁷ Cr(II) complexes,⁸ Zn-TMSCl-Ti(III),⁹ and TiCl₃.¹⁰ There were also reports of pinacolization in absolute methanol using Al-KOH¹¹ and Sm-I₂-Ti(OPr)₄,¹² however these methods required absolutely anhydrous conditions in an inert atmosphere. Moreover, many of these reagents are costly, moisture-sensitive and toxic. Therefore, it is very significant to develop a new methodology for C—C bond formation reaction by alternating reaction conditions and by utilization of less toxic reagents and solvents, in order to improve environmental performance. Recently, there has been growing interest to use water as reaction medium. Water offers several advantages with regard to low cost, safety, selectivity¹³ and operational simplicity compared with the use of organic solvents. Generally, the reactive metals such as Li and Na readily tend to react with water, while the less reactive metals have great inertia, so neither the reactive metals nor less reactive metals could cause pinacol coupling reactions in water. Lately, pinacol coupling reactions in aqueous media have been investigated by usage of Ti,¹⁴ Cu-Zn,¹⁵ Al,¹⁶ Mn,¹⁷ In,¹⁸ Mg,¹⁹ Ga,²⁰ etc. affording inter- or intramolecular coupling products of carbonyl compounds. Of these metals, aluminum is the most outstanding metal used for pinacol coupling reaction in aqueous media. Previously, pinacol coupling of

carbonyl compounds mediated by aluminum metal has been reported under suitable conditions, such as aluminum amalgam in aqueous THF,^{3a} aluminum-KOH in methanol,^{11b} aluminum-NaOH in aqueous media,^{16a} and aluminum-fluoride salts in aqueous media.^{16b}

We chose to examine the potential of aluminum metal in view of its low cost and ready availability. Aluminum has a lower first ionization potential (5.99 eV), and this should render it to situate among the most reducing metals. On the other hand, aluminum is resistant to water and carbonyl compounds, because it can form readily a thin film of insoluble Al₂O₃ as an armor to prevent itself from further reaction with carbonyl compounds in water. Generally, the challenge here is to find ways to overcome the well-known insolubility of aluminum oxide in water that so far has precluded the use of aluminum in aqueous media.

However, when sodium hydroxide was used as additive, it was found that reactions were too dramatic and could be completed within 5 min, but the yields of some pinacols were not high, and the corresponding unitary alcohols were sometimes main products. Perhaps, additive sodium hydroxide easily led to colloid suspension of aluminum hydroxide, which came from NaAlO₂ hydrolysis, and the suspension material adhered to surface of aluminum metal to obstruct aluminum metal to further react with carbonyl compounds, therefore, the yields of pinacols sometimes were not ideal.

Although aluminum metal was perhaps easily eroded by fluoride salts, it usually was rather difficult for fluoride salts to corrode thin film of Al₂O₃.²¹ If the surfaces of aluminum metal were compactly covered with Al₂O₃ film, it might result in that fluoride salts could not promote aluminum metal to carry out pinacol coupling reaction. Hereby, utilizing merely fluoride salts as addi-

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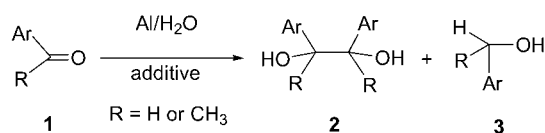
tive to complete pinacol coupling reaction, the yields of pinacols mostly depended on the oxidated degree of aluminum metal. This is why yields of pinacols are not high occasionally.

In order to conquer two shortages mentioned above, we attempted to find a new additive to cause pinacol coupling reaction. It is very effective for oxalic acid to erode aluminum oxide. Because oxalic acid is able to readily form coordinated metal complex with Al^{3+} , this method can avoid producing suspension insoluble $\text{Al}(\text{OH})_3$. This drew our attention to possibility of adopting coordination agents to implement pinacol coupling reaction. As expected, the experiments indicated that high yields of pinacols were acquired by adding aluminum and oxalic acid in water. Herein, we wish to report the study of using aluminum powder and some complex for pinacol coupling reactions of carbonyl compounds in water.

Results and discussion

It was found that aluminum powder could well mediate pinacol coupling reactions of carbonyl compounds by addition of a small quantity of complexant in water. pinacol **2** was got in good yields at certain temperature, as shown in Scheme 1. A small amount of the corresponding unitary alcohol **3** was formed as a by-product.

Scheme 1



To begin our study, the reaction of benzaldehyde with Al was examined under various conditions in order to optimize the coupling condition (Table 1).

It was observed that additives had a special activat-

ing effect on aluminum mediated pinacol coupling of benzaldehyde in aqueous media, high yield of pinacol was obtained as a mixture of *meso* to *dl* isomers with the ratio of *meso* to *dl* isomer approximately 1 : 1. However, no pinacol products were observed in the absence of additives (Entry 1, Table 1). Raising temperature helped enhancing the yields of pinacols below 50 °C (Entries 10, 11 and 12, Table 1). After a comprehensive survey of the reaction conditions, it was found that coupling of benzaldehyde (1 mmol) with Al (2 mmol) in water (5 mL) at 45 °C could provide the high yield of pinacol in the presence of oxalic acid (0.2 mmol).

Subsequently, oxalic acid was used as additive to investigate the coupling reaction of other substrates under the same conditions. The results are listed in Table 2.

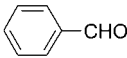
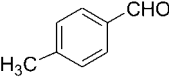
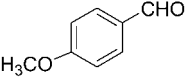
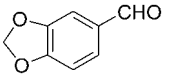
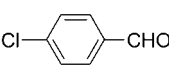
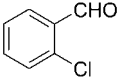
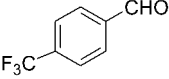
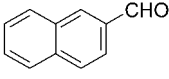
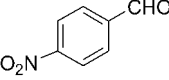
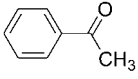
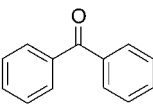
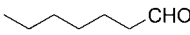
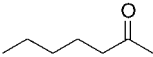
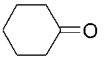
In most cases, high yields of pinacols were obtained as mixtures of *dl* and *meso* isomers under such reaction conditions. It was noteworthy that electrostatic effect on the aromatic ring and steric hindrance around the carbonyl group could affect the yields of diols. Aromatic aldehydes substituted by electron-withdrawing group gave higher yields than by electron-donating group at the same position, and for example, benzaldehyde bearing trifluoromethyl, chloro or bromo group proceeded similarly to yield pinacol **2** as the major products (Entries 5, 6, 7, Table 2). However, as for nitrobenzaldehyde, no corresponding pinacol was obtained (Entry 9, Table 2), due to the reduction of nitro group by aluminum powder under such reaction condition. An increase in the steric hindrance around the carbonyl group affected distribution of ratio of *meso* to *dl* isomer, the preponderant product was compound of smaller steric hindrance, such as diols from piperonal and 1-naphthaldehyde (Entries 4, 8, Table 2), and the yields of pinacols were reduced (Entry 10, Table 2). Furthermore, as group substituted was big enough, no desired pinacols were observed with phenylphenone (Entry 11, Table 2). Unlike aromatic carbonyl compounds, most aliphatic

Table 1 Pinacol coupling reaction of benzaldehyde (1.0 mmol) with Al (2.0 mmol) under various conditions

Entry	Reaction media (mmol)	Reaction time/h	Pinacol 2 yield ^{a,b} /%	<i>Meso/dl</i> ^c
1	H ₂ O (5)	18	—	—
2	Acetylacetone (0.2)	18	34	1.1/1
3	Xylenolorange (0.2)	18	57	1/1
4	Sulfocarbamide (0.2)	18	42	1/1.4
5	EDTA (0.1)	18	53	1/1.2
6	Triethanolamine (0.2)	18	47	1/2.5
7	Sulfosalicylic acid (0.2)	18	58	1/1.7
8	Tartaric acid (0.2)	18	53	1.3/1
9	Citric acid (0.2)	18	59	1.4/1
10	Oxalic acid (0.2)	18	61	1/1.5
11 ^d	Oxalic acid (0.2)	18	84	1/1.2
12 ^e	Oxalic acid (0.2)	18	76	1/1.1

^aThe isolated products were reported. ^bThe pure products were identified by IR, ¹H NMR, ¹³C NMR and HRMS. ^cThe ratio of *meso* to *dl* isomer was determined by the ¹H NMR analysis of crude product mixture. ^dReaction temperature at 45 °C. ^eReaction temperature at 50 °C.

Table 2 Aluminum/oxalic acid promoted pinacol coupling of carbonyl compounds in water

Entry	Substrate 1	Time/h	Yield ^{a,b} /%	Meso/dl ^c	Yield ^{a,b} /%
1		18	2a (84)	1.1/1	3a (7)
2		18	2b (81)	1.3/1	3b (9)
3		18	2c (83)	1/2	3c (6)
4		18	2d (80)	dl-type	3d (11)
5		18	2e (89)	1.1/1	3e (8)
6		18	2f (86)	1.2/1	3f (5)
7		18	2g (91)	1/1	3g (6)
8		18	2h (79)	meso-type	3h (9)
9		18	—	—	—
10		18	2i (63)	1.5/1	—
11		18	—	—	—
12	CH ₂ O	18	2j (43)	—	3j (4)
13	CH ₃ CHO	18	2k (35)	—	3k (2)
14		18	—	—	—
15		18	—	—	—
16		18	—	—	—

^aThe isolated products were reported. ^bThe pure products were identified by IR, ¹H NMR, ¹³C NMR and HRMS. ^cThe ratio of meso to dl isomer was determined by the ¹H NMR analysis of crude product mixture.

aldehydes and ketones provided none of the desired diols, while the main products were complex mixtures.

The mechanism of metal reduction of carbonyl compound has generally believed to proceed through the intermediate of a ketyl radical anion formed by electron transfer from the metal to the carbonyl substrate. In the present case, it is likely that the oxalic acid may activate the aluminum metal surface through interaction with Al₂O₃ to afford the water-soluble coordinated metal complex, and exposed aluminum metal can cause the pinacol coupling or a reduction reaction of the carbonyl

moiety to occur. In order to prove such reaction mechanism mentioned, two experiments below were conducted.

(1) It was found that the yield of pinacol **2** was significantly increased when enhancing oxalic acid amounts within certain fields, and it probably was explained that the layers of aluminum oxide were gradually corroded with oxalic acid (curve A of Figure 1). However, when more surfaces of aluminum metal were exposed, activating aluminum metal was saturated, and the yields of pinacol **2** tended to drop, meanwhile, the

yield of corresponding unitary alcohol **3** was increased (curve B of Figure 1).

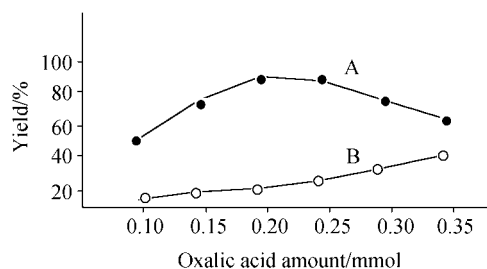


Figure 1 Effect of oxalic acid amount on the yields of pinacols **2** (A) and unitary alcohol **3** (B) from benzaldehyde (1.0 mmol) in water.

(2) The experiments demonstrated that different reaction media only affected the yields of pinacols, and hardly changed ratio of *meso* to *dl* isomer whether in organic solvents or aqueous media. This further showed that the reaction mechanism of pinacol coupling in aqueous media was the same as in organic solvents. The diastereoselectivities of pinacols are listed in Table 3.

Experimental

IR (Perkin-Elmer, 2000 FTIR), ^1H NMR (CDCl_3 , 500 MHz), ^{13}C NMR (CDCl_3 , 125.7 MHz) and MS-GC (HP5890 (II)/HP 5972, EI) spectra were obtained at the Center of Analytical Configuration of University of

Science and Technology of China. Flash chromatographic sheet employed was purchased from the Factory of Reagent of Shanghai and all material from Aldrich and used directly as received.

General procedure for pinacol coupling of aromatic aldehydes and aryl methyl ketones

Aluminum powder (2 mmol), additive (0.2 mmol) and water (5 mL), were sequentially placed in a round-bottomed flask, then carbonyl compounds (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 ^1H 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). All compounds obtained were consistent with authentic ones in literatures.²⁰

1,2-Dimethyl-1,2-biphenyl-1,2-ethanediol (2i): ^1H NMR (CDCl_3 , 500 MHz) δ : 6.87–7.16 (m, 10H, Ph), 2.01–2.13 (brs, 2H, OH), 1.01 (s, 3H, CH_3), 1.04 (s, 3H, CH_3); ^{13}C NMR (CDCl_3 , 125 MHz) δ : 19.65, 19.89, 79.34, 79.87, 127.23, 127.27, 127.50, 128.24, 128.31, 128.45, 138.67, 138.86; IR (KBr) ν : 3341.5, 2897.0, 1381.3, 1043.4, 697.8 cm^{-1} . HRMS calcd for $\text{C}_{16}\text{H}_{18}\text{O}_2$ 242.1307, found 242.1295.

Table 3 Diastereoselectivities of pinacol coupling applying aluminum metal as mediator and oxalic acid as additive in different media

Entry ^a	Media (V : V)	<i>Meso/dl</i> ^b	Entry ^a	Media (V : V)	<i>Meso/dl</i> ^b
1 ^c	THF	2a (1/1.6)	13	THF-H ₂ O (1 : 1)	2e (1.5/1)
2	THF	2b (1/1.3)	14	THF-H ₂ O (1 : 1)	2f (1/1)
3	THF	2c (1/1.5)	15	THF-H ₂ O (1 : 1)	2g (1/1.3)
4	THF	2d (1/9)	16	THF-H ₂ O (1 : 1)	2h (14/1)
5	THF	2e (1/1.2)	17	H ₂ O-(CO ₂ H) ₂ (0.2)	2a (1/1.1)
6	THF	2f (1.1/1)	18	H ₂ O-(CO ₂ H) ₂ (0.2)	2b (1/1.3)
7	THF	2g (1/1.4)	19	H ₂ O-(CO ₂ H) ₂ (0.2)	2c (2/1)
8	THF	2h (11/1)	20	H ₂ O-(CO ₂ H) ₂ (0.2)	2d (1/12)
9	THF-H ₂ O (1 : 1)	2a (1/1)	21	H ₂ O-(CO ₂ H) ₂ (0.2)	2e (1/1.1)
10	THF-H ₂ O (1 : 1)	2b (1/1)	22	H ₂ O-(CO ₂ H) ₂ (0.2)	2f (1.5/1)
11	THF-H ₂ O (1 : 1)	2c (1/1.4)	23	H ₂ O-(CO ₂ H) ₂ (0.2)	2g (1/1.2)
12	THF-H ₂ O (1 : 1)	2d (1/7)	24	H ₂ O-(CO ₂ H) ₂ (0.2)	2h (13/1)

^aThe reaction temperatures was 45 °C and time was 12 h. ^bThe ratios of *meso/dl* were determined by ^1H NMR under conditions of mixtures.

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