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# $InCl_3$-Catalyzed Reductive Coupling of Aromatic Carbonyl Compounds in the Presence of Magnesium and Chlorotrimethylsilane

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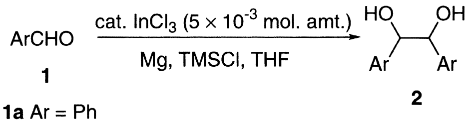
Reductive homocoupling of aromatic aldehydes and ketones has been achieved in tetrahydrofuran at room temperature using a catalytic amount of $InCl_3$ (0.005–0.1 molar amount) under nitrogen atmosphere in the presence of both chlorotrimethylsilane and magnesium metal (Mg turnings) to provide the corresponding 1,2-diols in good to moderate yields with a high diastereoselectivity.

Quite recently, we have reported that indium(III) chloride and some other indium compounds worked as effective catalysts in the reductive homocoupling of carbonyl compounds and imines in the presence of aluminum (Al) and chlorosilanes.[1] A similar catalytic effect of $InCl_3$ was also observed when magnesium (Mg) was employed as a reductant in the place of Al with a higher diastereoselectivity of the coupled products. We report here another example of $InCl_3$-catalyzed organic transformation of current interest[2] by comparing with those of the Al case.

Treatment of benzaldehyde (**1a**) with magnesium metal (Mg turnings, 4 mol amt.), TMSCl (4 mol amt.), and a catalytic amount of $InCl_3$ ($5 \times 10^{-3}$ mol amt.) in tetrahydrofuran (THF) under nitrogen atmosphere at room temperature for 2 h afforded 1,2-diphenyl-1,2-ethanediol (**2a**) in 67% yield (Table 1, entry 1). In this case the diastereoselectivity of **2a** was slightly higher (*dl*/*meso* = 68/32) than when using Al as a reductant (*dl*/*meso* = 57/43). Without either $InCl_3$ or TMSCl, the reaction did not proceed for 2 h (Table 1, entries 2,3). However, when the reaction time was elongated to 20 h, even in the absence of $InCl_3$ the coupling reaction proceeded, though both the product yield and diastereoselectivity were lower (entry 4). The yield of the expected diols was somewhat low despite a complete conversion of **1a**, partly because of the formation of a small amount of benzyl alcohol and small amounts of many unidentified compounds. The results of application of this optimized condition to *p*-substituted benzaldehydes are shown in Table 1. In these cases, although the reaction became slow, the corresponding coupling product was obtained in 43–69% yields, and especially in the case of *p*-methoxybenzaldehyde (**1d**) the highest diastereoselectivity (*dl*/*meso* = 85/15) was observed [50% yield (*dl*/*meso* = 59/41) in the case of Al].

Table 1. Reductive Coupling of Aromatic Aldehydes[a]



**1a** Ar = Ph
**1b** Ar = *p*-$ClC_6H_4$
**1c** Ar = *p*-$CH_3C_6H_4$
**1d** Ar = *p*-$CH_3OC_6H_4$

| Entry | Substrate | Product | Time/h | Isolated yield%[b] | *dl*/*meso*[c] |
|---|---|---|---|---|---|
| 1 | **1a** | **2a** | 2 | 67 | 68/32 |
| 2[d] | **1a** | **2a** | 2[e] | 0 | — |
| 3[f] | **1a** | **2a** | 2[e] | 0 | — |
| 4[d] | **1a** | **2a** | 20 | 45 | 59/41 |
| 5 | **1b** | **2b** | 17 | 59 | 50/50 |
| 6[d] | **1b** | **2b** | 17 | 16 | 50/50 |
| 7 | **1c** | **2c** | 18 | 69 | 56/44 |
| 8[d] | **1c** | **2c** | 18 | 43 | 57/43 |
| 9 | **1d** | **2d** | 10 | 43 | 85/15 |
| 10[d] | **1d** | **2d** | 10 | 5 | 51/49 |

a) Reaction conditions; **1** (5 mmol), $InCl_3$ (0.025 mmol), Mg (20 mmol), TMSCl (20 mmol), THF (50 mL), rt, $N_2$. b) The formation of 2.5 mmol of **2** corresponds to 100% yield. c) Determined by $^1H$ NMR. d) Without $InCl_3$. e) No reaction. f) Without TMSCl.

Reductive coupling similarly proceeded with acetophenone (**3a**) as a substrate to afford 2,3-diphenyl-2,3-butanediol (**4a**) in moderate yield and high diastereoselectivity. In this case the diastereoselectivity of **4a** was also much higher (*dl*/*meso* = 82/18) compared with the case using Al as a reductant (*dl*/*meso* = 68/32). The use of 0.1 mol amt. of $InCl_3$ and 2 mol amt. of Mg to **4a** was revealed to give the best result. The reaction also occurred even without the addition of $InCl_3$, but a long induction period was observed and even so the product yield was much lower, similar to the case of Al as a reductant.[1] Figure 1 shows the relationship between the reaction time and the isolated yield of **4a** in this homocoupling in the presence and absence of $InCl_3$. Results of the reductive coupling of various aromatic ketones are summarized in Table 2. Especially in the case of *p*-methylacetophenone, the best product yield (98% yield) and high diastereoselectivity (*dl*/*meso* = 82/18) were obtained only for 4 h [72% yield (*dl*/*meso* = 65/35) for 5 h in the case of Al].

Next, we performed the reductive coupling of other various carbonyl compounds. Intramolecular reductive coupling of [1,1′-biphenyl]-2,2′-dicarbaldehyde (**5**) occurred under the same condition and only the *trans*-9,10-dihydrophenanthrene-9,10-diol (**6**) was obtained in good yield (76% yield). The reaction using Al as a reductant also gave only the *trans*-isomer in 39% yield under similar conditions. Such high *trans*-selectivity of the product from this substrate has already been observed in several cases.[4] In the case of aliphatic ketones such as 1-tetralone and cyclohexanone, the corresponding 1,2-diols were formed in low to moderate yield (< 33%), while in the case of aliphatic aldehydes such as octanal, only the reduction of carbonyl moiety occurred to give 1-octanol. On the other hand, the reaction of both substrates using Al as a reductant did

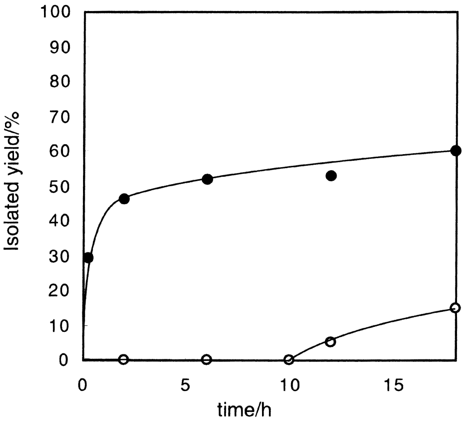
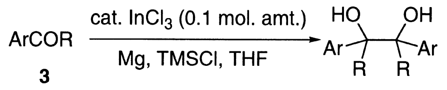
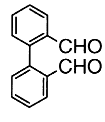


Fig. 1. Yield of **4a** in the Coupling of Acetophenone (**3a**) in the Presence (●) and Absence (○) of $InCl_3$. Reaction conditions; **3a** (1 mmol), $InCl_3$ (0.1 mmol), Mg (2 mmol), TMSCl (4 mmol), THF (10 mL), rt, $N_2$.

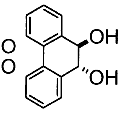
Table 2. Reductive Coupling of Aromatic Ketones[a)]



**3a** Ar = Ph, R = $CH_3$
**3b** Ar = $p$-$ClC_6H_4$, R = $CH_3$
**3c** Ar = $p$-$CH_3C_6H_4$, R = $CH_3$
**3d** Ar = 1-naphthyl, R = $CH_3$
**3e** Ar = 2-naphthyl, R = $CH_3$
**3f** Ar = Ph, R = Ph
**3g** Ar = 2-thienyl, R = $CH_3$



**5**



**6**

| Entry | Substrate | Product | Time/h | Isolated yield%[b)] | *dl*/*meso*[c)] |
|---|---|---|---|---|---|
| 1 | **3a** | **4a** | 18 | 60 | 82/18 |
| 2[d)] | **3a** | **4a** | 18 | 12 | 55/45 |
| 3 | **3b** | **4b** | 24 | 43 | 76/24 |
| 4 | **3c** | **4c** | 4 | 98 | 82/18 |
| 5[d)] | **3c** | **4c** | 4 | 0 | — |
| 6 | **3d** | **4d** | 24 | 41 | — |
| 7 | **3e** | **4e** | 24 | 64 | 70/30 |
| 8 | **3f** | **4f** | 24 | 49 | — |
| 9 | **3g** | **4g** | 24 | 37 | 81/19 |

a) Reaction conditions; **3** (1 mmol), $InCl_3$ (0.1 mmol), Mg (2 mmol), TMSCl (4 mmol), THF (10 mL), rt, $N_2$. b) The formation of 0.5 mmol of **4** corresponds to 100% yield. c) Determined by $^1$H NMR. d) Without $InCl_3$. e) The ratio could not be determined because of the overlapping of methyl protons of **4d**.

not proceed. $\alpha,\beta$-Unsaturated carbonyl compounds such as *trans*-cinnamaldehyde yielded the corresponding 1,2-diols in 14% yield [27% yield (*dl*/*meso* = 60/40) in the case of Al].

Although the reductive coupling of an aromatic aldimine such as *N*-benzylideneaniline to the corresponding 1,2-diamine occurred (71% yield, *dl*/*meso* = 45/55) by using Al and a catalytic amount of $InCl_3$ (0.03 mol amt.) [0% yield without $InCl_3$], such a compound was not obtained in the case of Mg because of the facile decomposition of the substrate to the starting aldehyde **1a**. On the other hand, it was newly disclosed that using a catalytic amount of $InCl_3$ (0.05 mol amt.) and an equimolar amount of zinc (Zn) as a reductant, the corresponding 1,2-diamine was obtained in 92% yield (*dl*/*meso* = 51/49). The result that the reaction in the absence of $InCl_3$ afforded the product in 40% yield (*dl*/*meso* = 51/49) indicated a remarkable catalytic effect of $InCl_3$ also in this case. It is worth noting here, however, that the combination of Zn and $InCl_3$ is not suitable for reductive homocoupling of either aldehydes or ketones.

## Experimental

**General.** $^1$H and $^{13}$C NMR spectra were measured on JEOL EX-400, JNM-AL300, and JEOL GSX270 spectrometers for solutions in $CDCl_3$ with $Me_4Si$ as an internal standard. Analytical thin layer chromatographies (TLC) were performed with Merck silica gel 60 F-254 plates. Column chromatographies were performed with Merck silica gel 60.

$InCl_3$ was purchased from Aldrich and used without further purification. Magnesium metal (Mg turnings) was purchased from Nacalai Tesque and used without further purification. TMSCl and THF were distilled before use. All carbonyl compounds were commercial products and were used without further purification. All of imines were prepared by the condensation of carbonyl compounds and amines. The structures of 1,2-diols (**2a–d**, **4a–c**, **4e**, **4f**) and 1,2-diamines were determined by comparison of the spectral data with those of the authentic samples reported.[1] The compounds **4d**,[4] **4g**,[5] and **6**[3] are known.

**Typical Procedure for $InCl_3$-Catalyzed Reductive Coupling Reaction of Benzaldehyde (1a).** To a mixture of $InCl_3$ (5.5 mg, 0.025 mmol), magnesium (0.486 g, 20 mmol), chlorotrimethylsilane (2.5 mL, 20 mmol), and THF (40 mL) in a 200 mL two necked round-bottom flask was added **1a** (0.53 g, 5 mmol) in THF (10 mL) at room temperature under $N_2$. The mixture was kept at room temperature with magnetic stirring for 2 h, during which period the white turbid solution turned grey with a slight dissolution of Mg. Without $InCl_3$, such change was not observed and the reaction mixture remained colorless for 2–10 h. Diethyl ether (100 mL) and aqueous HCl (1.2 mol $L^{-1}$, 50 mL) were added to the resulting mixture and then the organic layer was separated, washed with saturated aqueous $NaHCO_3$ (50 mL × 3), dried over $Na_2SO_4$, and concentrated. The residue was purified by column chromatography on silica gel (eluent, hexane/ethyl acetate) to give 1,2-diphenyl-1,2-ethanediol **2a** (359 mg, 1.68 mmol, 67% yield; *dl*/*meso* = 68/32) and a complex mixture containing benzyl alcohol and many unidentified compounds (67 mg).

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