# Effect of Fluoride Salts on Metal-Mediated Reactions. Aluminum/Fluoride Salt-Mediated Reduction and Pinacol Coupling of Carbonyl Compounds in Aqueous Media
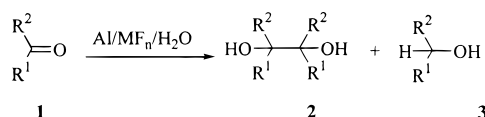
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### ABSTRACT



Metal fluoride salts were found to activate aluminum in water to react with carbonyl compounds to give the pinacol coupling products and/or the reduced alcohols. The metal ion of the fluoride salt was found to play a role in controlling the chemoselectivity and stereoselectivity of the reaction.

Dissolving metal reduction of carbonyl compounds is a venerable reaction in organic synthesis.[1] The carbonyl compound (**1**) can either be reductively coupled to the pinacol (**2**) or reduced to the corresponding alcohol **3** (Scheme 1).[2]

### Scheme 1
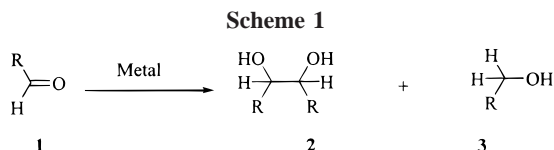


The metal used can be Li, Na, Mg, Ca, In, Zn, and Al, among others.[3] With the latter metal, aluminum amalgam with mercury has often been used.[4] The reaction media for the metal-mediated reductions can be either aprotic or protic organic solvents. For the protic solvents, ammonia, amines, and alcohols are often used, but water is rarely employed. Chemically, this is quite understandable. The reactive metals such as Li and Na are far too dangerous in water, whereas

the less reactive metals such as Mg, Ca, and Al often form water-insoluble oxides. The recent interest in green chemistry[5] has posed a new challenge for organic synthesis in

(2) For general reviews, see: (a) House, H. O. *Modern Synthetic Reactions*, 2nd ed.; W. A. Benjamin: New York, 1972; p 167. (b) McMurry, J. E. *Chem. Rev.* **1989**, *89*, 1513. (c) Khan, B. E.; Rieke, R. D. *Chem. Rev.* **1988**. *88*, 733. (d) Wirth, T. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 61. (e) Dushin, R. G. In *Comprehensive Organometallic Chemistry II*; Hegedus, L. S., Ed.; Pergamon: Oxford, 1995; Vol. 12, pp 1071−1095. (f) Fuerstner, A. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 164. (g) Robertson, G. M. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: New York, 1991; Vol. 3, pp 563−611. (h) Hirao, T. *Synlett* **1999**, 175. (i) Avalos, M.; Babiano, R.; Cintas, P.; Jiemenez, J. L.; Palacios, J. C. *Recent Res. Dev. Org. Chem.* **1997**, *1,* 159.

(3) (a) Zhang, W.-C.; Li, C.-J. *J. Org. Chem.* **1999**, *64*, 3230; *J. Chem. Soc., Perkin Trans. 1* **1998**, 3131 and references in both. (b) Rieke, R. D.; Kim, S.-H. *J. Org. Chem.* **1998**, *63*, 5235 and references therein. (c) Li, C.-J.; Meng, Y.; Yi, X.-H.; Ma, J.; Chan, T.-H. *J. Org. Chem.* **1997**, *62*, 8632 and reference therein. (d) Wang, L.; Sun, X.; Zhang, Y. *J. Chem. Res., Synop.* **1998**, 336 and reference therein.

(4) (a) Apblett, A. W. In *Encyclopedia of Inorganic Chemistry*; King, R. B., Ed.; John Wiley & Sons: Chichester, 1994; Vol. 1, pp 103−116. (b) Troyansky, E. I. In *Encyclopedia of Reagent for Organic Synthesis*; Paquette, L. A., Ed.; John Wiley & Sons: Chichester, 1995; Vol. 1, pp 150−153. (c) Fieser, M.; Fieser, F. L. *Reagents for Organic Synthesis;* John Wiley & Sons: New York, 1975; Vol. 5, p 9.

(5) See, for example: Anastas, P., Williamson, T., Eds. *Green Chemistry: Frontiers in Benign Chemical Synthesis and Processing*; Oxford University Press: New York, 1998.

(1) Fittig, R. *Justus Liebigs Ann. Chem.* **1859**, *110*, 23.

that new reaction conditions need to be found which reduce the emission of volatile organic solvents and the use of hazardous toxic chemicals. In this connection, organic reactions in aqueous media have attracted considerable recent interest because water is considered to be a safe and environmentally benign solvent.[6] We are therefore interested in exploring metal reduction reactions in water, but without the use of mercury amalgams due to the known toxicity of mercury. We have chosen to examine the potential of aluminum metal in view of its low cost and ready availability. Aluminum has a low first ionization potential of 5.986 eV, and this should render it among the most reducing metals. On the other hand, aluminum is resistant to water because it forms readily a thin film of insoluble $Al_2O_3$ as an armor to prevent itself from further reaction. The challenge here is to find ways to overcome the well-known insolubility of aluminum oxide in water that so far precluded the use of aluminum in aqueous media.[7]

Reports[8] that the presence of trace amount of fluoride anion in water dramatically increased the corrosion of aluminum metal drew our attention to the possibility of using fluoride salts to activate aluminum metal in water. Using benzaldehyde as the prototypal aldehyde, we examined its reaction with aluminum in aqueous media with various fluoride salts. The results are summarized in the following general conclusions.

(1) It is clear that fluoride salts have a special activating effect on aluminum metal in aqueous media. Comparing the series of KF, KCl, KBr, and KI (entries 1−4, Table 1), only

**Table 1.** Effects of Halide Ions on the Reaction of Benzaldehyde with Al/KX in Water[a]

| entries | reagent | time (h) | convn (%)[b] | products, %[b] meso-2 | dl-2 | 3 |
|---|---|---|---|---|---|---|
| 1 | 2.5Al/1 M KF | 16 | 100 | 41 | 45 | 13 |
| 2 | 2.5Al/1 M KCl | 16 | 0 | 0 | 0 | 0 |
| 3 | 2.5Al/1 M KBr | 16 | 0 | 0 | 0 | 0 |
| 4 | 2.5Al/1 M KI | 16 | 0 | 0 | 0 | 0 |
| 5 | 2.5Al/H2O | 1 week | 0 | 0 | 0 | 0 |
| 6 | 2.5Al/2 M KF | 16 | 100 | 42 | 42 | 13 |
| 7 | 2.5Al/3 M KF | 16 | 0 | 0 | 0 | 0 |
| 8 | 2.5Al/4 M KF | 16 | 0 | 0 | 0 | 0 |
| 9 | 2.5Al/5 M KF | 16 | 0 | 0 | 0 | 0 |

[a] For experimental conditions, see ref 9. [b] On the basis of the analysis of ^{1}H NMR of crude product.

the addition of KF to $Al/H_2O$ led to reaction with benzaldehyde.[9] Furthermore, in the absence of KF, $Al/H_2O$ is completely inactive (entry 5). On the other hand, too high a concentration of KF (greater than 3 M) also prevented the reaction from occurring (entries 7−9). With 1 M or 2 M

KF, the reaction gave a high yield of the pinacol (**2**, R = Ph) as a nearly 1:1 mixture of *dl* and *meso* isomers. However, the reduction product, benzyl alcohol (**3**, R = Ph) was formed to a significant extent as well.

(2) Unexpectedly, the cation of the fluoride salt has an effect on the partition of the products. Using the series of alkali metal fluoride salts under otherwise identical reaction conditions,[9] the yield of the reduction product **3** as a percentage of the total (**2** plus **3**) declined progressively from 24% to 8% as the cation changed from Li to Cs (entries 1−5, Table 2). We attributed this change to the size of the

**Table 2.** Al/MF Promoted Pinacol Coupling of Carbonyl Compounds in Water[a]

| entries | aldehydes | promoter | time (h) | yield (%) of 2 (meso:dl)[b] | yield (%) of 3 |
|---|---|---|---|---|---|
| 1 | PhCHO | LiF | 5 days | 76[b] (1.1:1) | 24[b] |
| 2 | PhCHO | NaF | 2 days | 84[b] (1:1.0) | 16[b] |
| 3 | PhCHO | KF | 16 | 87[b] (1:1.0) | 13[b] |
| 4 | PhCHO | RbF | 16 | 90[b] (1:1.1) | 10[b] |
| 5 | PhCHO | CsF | 16 | 92[b] (1:1.0) | 8[b] |
| 6 | PhCHO | Bu4NF | 16 | 99[b] (1:1.5) | 1[b] |
| 7 | m-ClPhCHO | KF | 16 | 75 (1:1.2) | 5[b] |
| 8 | m-ClPhCHO | Bu4NF | 16 | 95 (1:2.2) | 6[b] |
| 9 | p-CF3PhCHO | KF | 16 | 100 (1:1.3) | / |
| 10 | p-CF3PhCHO | Bu4NF | 16 | 97 (1:2.5) | 2[b] |
| 11 | p-CH3PhCHO | KF | 16 | 92 (1:1.2) | 7[b] |
| 12 | p-CH3PhCHO | Bu4NF | 16 | 76 (1:2.3) | 5[b] |
| 13 | m-CH3PhCHO | KF | 16 | 90 (1:1.1) | 8[b] |
| 14 | o-CH3PhCHO | KF | 16 | 93 (1:1.1) | 6[b] |
| 15 | o-CH3PhCHO | Bu4NF | 16 | 94 (1:2.2) | 5[b] |
| 16 | PhCOCH3 | Bu4NF | 16 | 76 (1:2.1) | 10[b] |
| 17 | PhCOCH3 | KF | 16 | 60 (1:1.5) | 18[b] |
| 18 | c-C6H11CHO | KF | 16 | / | 10[b] |
| 19 | c-C6H11CHO | Bu4NF | 16 | / | / |
| 20 | cyclohexanone | KF | 16 | / | / |
| 21 | cyclohexanone | Bu4NF | 16 | / | / |

[a] For experimental conditions, see ref 9. [b] On the basis of the analysis of ^{1}H NMR of crude product.

cation. Consistent with this rationale, we found that when tetrabutylammonium fluoride (TBAF) was used as salt, the product was almost exclusively the pinacol **2** (entry 6).[10] Other substituted benzaldehydes can be similarly coupled in high yields (entries 7−15) using either KF or TBAF as the activating agent. Acetophenone reacted as well to give mainly the pinacol product (entries 16 and 17). In all these cases, the pinacol product **2** was formed as a mixture of *dl*

(6) For reviews, see: (a) Li, C. J.; Chan, T. H. *Organic Reactions in Aqueous Media*; John Wiley & Sons Inc.; New York, 1993. (b) Li, C. J. *Chem. Rev.* **1993**, *93*, 2023. (c) Chan, T. H.; Li, C. J.; Lee, M. C.; Wei, Z. Y. *Can. J. Chem.* **1994**, *72*, 1181. (d) Lubineau, A.; Auge, J.; Queneau, Y. *Synthesis* **1994**, 741. (e) Li, C. J. *Tetrahedron* **1996**, *52*, 5643. (f) Chan, T. H.; Issac, B. M. *Pure Appl. Chem.* **1996**, *68*, 919.
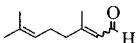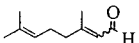
(7) Pinacol coupling of carbonyl compounds with Al powder in methanol promoted by KOH or NaOH had been reported: Khurana, J. M.; Sehgal, A. *J. Chem. Soc., Chem. Commun.* **1994**, 571. Khurana, J. M.; Sehgal, A.; Gogia, A.; Manian, A.; Maikap, G. C. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2213. Sahade, D. A.; Mataka, S.; Sawada, T.; Tsukinoki, T.; Tashiro, M. *Tetrahedron Lett.* **1997**, *38*, 3745.

(8) (a) Tennakone, K.; Wickramanayake, S. *Nature* **1987**, *325*, 202. (b) Hurlen, T.; Johansen, K. H. *Acta Chem. Scand., Ser. A* **1985**, *A39*, 545. (c) Foley, R. T.; Trzaskoma, P. P. *Corrosion (Houston)* **1977**, *33*, 435. (d) Tennakone, K.; Wickramanayake, S.; Fernando, C. A. N. *Environ. Pollut.* **1988**, *49*, 133. (e) Valand, T.; Nilsson, G. *Corros. Sci.* **1977**, *17*, 449.

and *meso* isomers with the *dl* isomer in slight excess. Aliphatic aldehydes and ketones, on the other hand, did not couple under these conditions or get reduced in low yield to the alcohols (entry 18−21).

(3) The fluoride salts of $Fe^{2+}$, $Co^{2+}$, and $Ni^{2+}$ were very chemoselective in promoting the reduction of benzaldehyde to the alcohol **3** (entries 1−3, Table 3). No pinacol was

**Table 3:** Al/MF$_2$-Promoted Reduction of Carbonyl Compounds to Alcohols in Water[a]

| Entries | Aldehydes | Promoter | Time (hr) | Yield% of 2 (*meso:dl*)[b] | Yield% of 3 |
|---|---|---|---|---|---|
| 1 | PhCHO | FeF$_2$ | 16 | / | 100[b] |
| 2 | PhCHO | CoF$_2$ | 16 | / | 100[b] |
| 3 | PhCHO | NiF$_2$ | 16 | / | 100[b] |
| 4 | PhCHO | NiCl$_2$ | 16 | / | 0[b] |
| 5 | PhCHO | NiBr$_2$ | 16 | / | 0[b] |
| 6 | PhCHO | FeCl$_2$ | 16 | / | 0[b] |
| 7 | p-CF$_3$PhCHO | FeF$_2$ | 16 | / | 100 |
| 8 | p-CF$_3$PhCHO | NiF$_2$ | 16 | / | 100 |
| 9 | 1-NaphthylCHO | FeF$_2$ | 16 | / | 97 |
| 10 | 1-NaphthylCHO | NiF$_2$ | 16 | / | 95 |
| 11 | c-C$_6$H$_{11}$CHO | FeF$_2$ | 24 | / | 96 |
| 12 | c-C$_6$H$_{11}$CHO | NiF$_2$ | 24 | / | 93 |
| 13 | p-ClPhCHO | FeF$_2$ | 16 | / | 93 |
| 14 | p-ClPhCHO | NiF$_2$ | 16 | / | 96 |
| 15 | [geranial structure] | FeF$_2$ | 24 | / | 96[c] |
| 16 | [geranial structure] | NiF$_2$ | 24 | / | 92[d] |
| 17 | PhCOCH$_3$ | FeF$_2$ | 16 | / | 95 |
| 18 | PhCOCH$_3$ | NiF$_2$ | 16 | / | 8[b] |
| 19 | n-C$_4$H$_9$COCH$_3$ | FeF$_2$ | 16 | / | /[b] |
| 20 | n-C$_4$H$_9$COCH$_3$ | NiF$_2$ | 16 | / | /[b] |

[a] For experimental conditions, see reference 9 ( only 1 mmol of NiF$_2$ or CoF$_2$ was used). [b] Based upon the analysis of $^1$H NMR of crude product. [c] Only 1,2-reduction was observed. [d] A mixture of 1,4-reduction and its corresponding saturated alcohol (1:2) without allylic alcohol derived from 1,2-reduction.

formed under these conditions. Previously, it had been reported that NiCl$_2$ and Al in THF was an efficient reagent for the reduction of aldehydes to alcohols.[11] In the present case, we found that, in water, only the fluoride salts had the activating effect. Neither NiCl$_2$, NiBr$_2$, nor FeCl$_2$ could effect the reduction (entries 4−6). Using NiF$_2$, or FeF$_2$, other aryl and aliphatic aldehydes were reduced efficiently in high

(10) Fluoride salts of a number of di- and polyvalent cations were also examined. No obvious pattern was discernible. MgF$_2$ and CaF$_2$ failed to activate the aluminum metal in water, whereas BaF$_2$, ZnF$_2$, MnF$_2$, AlF$_3$, CrF$_3$, TiF$_4$, and VF$_4$ all activated the metal to react with benzaldehyde to give varying proportions of **2** and **3**.
(11) Sarmah, B. K.; Barua, N. C. T. *Tetrahedron* **1991**, *47*, 8587.

yields to the corresponding alcohols (entries 7−14). In the case of geranial, the two metal salts showed different regioselectivity. With FeF$_2$, only 1,2-reduction was observed (entry 15), whereas with NiF$_2$ the reaction gave a mixture of 1,4-reduction and its corresponding saturated alcohol with no allylic alcohol derived from 1,2-reduction (entry 16). Finally, acetophenone was reduced efficiently by FeF$_2$/Al/ H$_2$O (entry 17) but not NiF$_2$/Al/H$_2$O (entry 18). Aliphatic ketones appeared to resist reduction under these conditions (entries 19 and 20).

(4) Interestingly, copper(II) fluoride was found to have an effect on the stereoselectivity of the pinacol coupling reaction of substituted benzaldehyde. Not only is the pinacol **2** formed in high yield but the *meso* compound was also found to be the predominant isomer (*meso:dl* = 10−16:1, Table 4). While there were previous reports in the literature

**Table 4.** Reaction of Benzaldehydes with Al/CuF$_2$[a] in Water

| entries | aldehydes | yield by $^1$H NMR (%) | | isolated yield (%) of 2 (*meso:dl*) |
|---|---|---|---|---|
| | | **2** (*meso:dl*) | **3** | |
| 1 | PhCHO | 96 (16:1) | 4 | 95 (35:1) |
| 2 | p-ClPhCHO | 57 (15:1) | 18 | 54 (24:1) |
| 3 | p-CF$_3$PhCHO | 85 (3:1) | 15 | 84 (3:1) |
| 4 | p-MePhCHO | 83 (15:1) | 17 | 82 (21:1) |

[a] Modified conditions were used: under an Ar atmosphere, Al (2.5 mmol 99.95%, Aldrich) and CuF$_2$ (1 mmol) were stirred in distilled H$_2$O (5 mL) for 40 min; then another portion of Al (2.5 mmol) was added and followed by aldehyde (1 mmol) immediately. Reaction was worked up (ref 9) in 16 h.

of stereoselective reductive coupling of carbonyl compounds to *dl*-pinacols,[12] this is the first example of selective formation of the *meso*-isomer under metal reduction conditions and can therefore complement those methodologies.[13]

The mechanism of metal reduction of the carbonyl compound is generally believed to proceed through the intermediacy of a ketyl radical anion formed by electron transfer from the metal to the carbonyl substrate.[2] In the present case, it is likely that the fluoride anion activates the aluminum metal surface through interaction with Al$_2$O$_3$ to give the water-soluble fluoroaluminates.[14] The exposed aluminum metal can thus cause the pinacol coupling or a reduction reaction of the carbonyl moiety to occur. Further experimental studies are clearly required to determine whether the reaction then follows the usual ketyl mechanism or, because the presence of the other metal cation, some other modified mechanisms. Our results demonstrate, however, that

(12) (a) Barden, M. C.; Schwartz, J. *J. Am. Chem. Soc.* **1996**, *118*, 5484. (b) Szymoniak, J.; Besancon, J.; Moise, C. *Tetrahedron* **1994**, *50*, 2841. (c) Szymoniak, J.; Besancon, J.; Moise, C. *Tetrahedron* **1992**, *48*, 3867.
(13) Carbonyl compounds can be reductively coupled to *meso*-pinacols under electrochemical conditions. See: Grimshaw, J.; Ramsey, J. S. *J. Chem. Soc. C* **1966**, 653.
(14) The corrosion of aluminum metal with fluoride ion is believed to proceed through the formation of various fluoroaluminates. However, the exact structures of these species have not been elucidated. See: refs 8b−e.

aluminum-mediated reduction and pinacol coupling of carbonyl compounds can be achieved in aqueous media with the assistance of the fluoride salt. The use of fluoride anion provides a method to overcome the refractory metal oxide surface problem in aqueous media. Finally, through judicious choice of the counterion of the fluoride salt, the chemo- selectivity as well as the stereoselectivity of the reaction can be modulated.