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Iron-mediated allylation of aryl aldehydes in aqueous media

Tak Chung Chan, Chak Po Lau and Tak Hang Chan*

Department of Applied Biology and Chemical Technology and the Open Laboratory for Chiral Technology, Institute of Molecular Technology for Drug Discovery and Synthesis, The Hong Kong Polytechnic University, Hung Hom, Hong Kong, SAR, China

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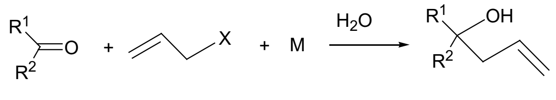
Abstract—Iron metal was found to be able to mediate the allylation reaction of aryl aldehydes in aqueous media with sodium fluoride as the promoter. The possible implication of an allyliron intermediate was examined.

Recently, there has been considerable interest in the metal mediated allylation of carbonyl compounds (**1**) in aqueous media to give the corresponding homoallylic alcohols (**2**) (Scheme 1). The development of such Grignard–Barbier type reactions in aqueous media is of interest because they reduce the environmental burden of organic solvents normally associated with organometallic reactions.[1] The metals used in Scheme 1 include Zn, In, Sn, Bi, Sb, Pb, Mn, Ga and Mg.[2] However, some of these metals are either toxic (Pb, Sn) or expensive (In, Bi, Sb and Ga) whereas others give extensive reductive side reactions (Mg, Zn and Mn). There is a need to search for additional metals so that a diversity of organometallic reactions of different reactivities and selectivities can be conducted in aqueous media.[3] We report here the first example of using inexpensive and nontoxic iron metal to mediate the allylation of carbonyl compounds.

In the preliminary experiment, benzaldehyde (1 mmol), allyl bromide (5 mmol) and iron powder (6–9 μm, 5 mmol) were stirred in water (5 mL) at room temperature. There was no detectable formation of the homoallylic alcohol product in 16 h (Table 1, entry 1). However, after 64 h, some product began to appear, albeit still in insignificant yield. Clearly, activation of the metal was required. The usual methods of activation, such as the use of THF cosolvent, or ammonium chloride solution,[2a] or the addition of hydrogen bromide,[4] or sodium dodecylsulfate (SDS)[5] or copper salts[6] did not lead to any meaningful improvements in yield. We had previously shown that in the case of antimony metal, fluoride salts have proven to be effective in activating the metal to perform the allylation reaction in aqueous media.[2e] We tried therefore a number of different fluoride salts on the iron-mediated allylation reaction and found that the yields of the homoallylic alcohol improved significantly (entries 2–13). While it was found that nearly any fluoride salt would manifest the activating effect, sodium fluoride at 2 M concentration gave the best result. To ensure that the activating effect was due to the fluoride ions and not the sodium ions, sodium chloride, bromide and iodide were also tried and none showed any effect on the reaction (entries 14–16). An isolated yield of 88% of the product could be obtained when the reaction was allowed to proceed for 96 h.



1 2

Scheme 1.

We have also examined other reaction variables. While increasing the reaction temperature seemed to improve the reaction, the temperature range was limited by the boiling point of allyl bromide. The optimal reaction temperature was found to be between room temperature and 50 °C. Lowering the ratios of allyl bromide or iron to benzaldehyde reduced the yield of the product. On the other hand, using a greater excess of allyl bromide or iron did not increase the yield. The application of sonication did not accelerate the reaction significantly.

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* Corresponding author. Tel.: +852-2766-5605; fax: +850-2364-9932; e-mail: bcchanth@polyu.edu.hk

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Table 1. Iron-mediated allylation of benzaldehyde[a]

Entry	Fluoride salts (Concn)	Yield %, 16 h[b]	Yield %, 64 h[b]
1	—	0	<5
2	LiF (1 M)	7	9
3	$NH_4{\cdot}HF_2$ (2 M)	14	20
4	NH_4F (2 M)	7	12
5	Bu_4NF (0.5 M)	<5	15
6	ZnF_2 (0.5 M)	10	27
7	NiF_2 (0.5 M)	12	24
8	RbF (0.5 M)	11	20
9	CsF (1 M)	23	35
10	KF (1 M)	18	40
11	NaF (1 M)	—	60
12	NaF (2 M)	30	70 (88)[c]
13	NaF (satd)	—	62
14	NaCl (2 M)	0	0
15	NaBr (2 M)	0	0
16	NaI (2 M)	0	0

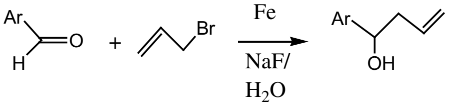
[a] Reaction conditions: benzaldehyde (1 mmol), allyl bromide (5 mmol) and iron (5 mmol) were stirred in water (5 mL) at room temperature for the indicated time with fluoride salts.

[b] Yield of the allylation product was determined by ^1H NMR of the crude reaction mixture.

[c] Yield in parenthesis was the isolated yield of the product from the reaction mixture after 96 h of reaction time.

Allylation of a number of aromatic aldehydes were examined under similar reaction conditions (Table 2). In general, the product homoallylic alcohols were obtained in moderate to excellent yields. It seemed that electron withdrawing substituents favoured the reaction. For *p*-phthaldehyde, a good yield of the bis-allylated product was obtained in excellent yield (entry 11). Aryl ketones, aliphatic aldehydes and ketones were not allylated under these reaction conditions. In this sense, the chemoselectivity of iron is similar to that of manganese in allylating only aryl aldehydes.[2g] Allyl chloride can be used in lieu of allyl bromide in the allylation of benzaldehyde, but the yield of the product alcohol was lower (55%) under similar reaction conditions. Crotyl or cinnamyl bromide can also be used as the allylating agent. In both cases, the reaction was regioselective, giving mainly the γ-regioisomer. The reaction was, however, less diastereoselective, giving a mixture of nearly amounts of the *syn*- and *anti*-diastereomers (Scheme 2).

Table 2. Iron-mediated allylation of aryl aldehydes[a]

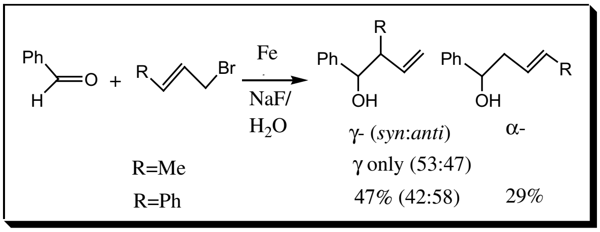


Entry	Ar =	Time	Temp.	Yield (%)[b]
1	Ph–	96	rt	88
2	*p*-ClPh–	96	rt	95
3	*o*-ClPh–	96	rt	90
4	*o*,*p*-Cl_2Ph–	96	rt	88
5	*p*-FPh–	96	rt	53
6	*p*-BrPh–	96	rt	50
7	*p*-CF_3Ph–	96	rt	60
8	*p*-CNPh–	96	rt	97
9	*p*-MePh–	144	rt	40
10	*p*-MeOPh–	96	rt	21
11	*p*-CHO–Ph–	96	50	95[c]

[a] Reaction conditions: aryl aldehyde (1 mmol), allyl bromide (5 mmol) and iron (5 mmol) were stirred in NaF solution (2 M, 5 mL).

[b] Isolated yield.

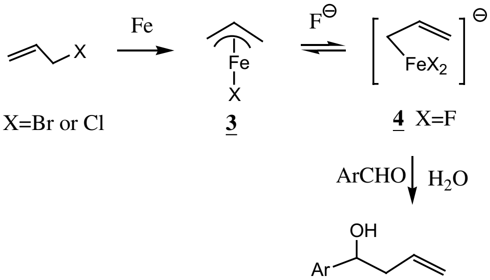
[c] Yield of the bis-allyated product.



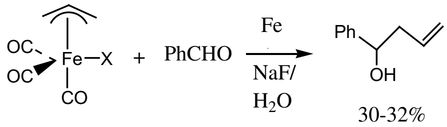
Scheme 2. Regio- and diastereoselectivity in iron-mediated allylation.

In several metal mediated allylation reactions in aqueous media, true organometallic intermediates were detected as the metallating agents by NMR spectroscopy.[7] For example, tin was found to insert into allyl bromide to give the corresponding allyltin bromide in aqueous media.[7a] A plausible mechanism of the iron-mediated allylation is outlined in Scheme 3. Insertion of Fe(0) into allyl bromide gives the π-allyliron(II) intermediate **3**. Such π-allyliron(II) compounds are normally not sufficiently electrophilic to react with aldehydes.[8] One possible role of the fluoride ions is to activate the π-allyl species through the formation of the σ-allyliron compound **4**, which is expected to be more electrophilic and reacts with aryl aldehydes.

Since iron compounds are paramagnetic, it was not possible to study the intermediates in iron-mediated allylation reactions using ^1H NMR spectroscopy. Supporting evidence for the involvement of allyliron intermediates was provided by the following experiments. The known complexes $(\eta^3\text{-}C_3H_5)Fe(CO)_3Br$ (**5a**) and $(\eta^3\text{-}C_3H_5)Fe(CO)_3I$ (**5b**) were prepared according to literature procedures.[9] Under the same reaction conditions as the iron-mediated allylation reactions, a mixture of a 5:1 ratio of complex **5** to benzaldehyde was stirred in 2 M NaF aqueous solution at room temperature for 96 h. A moderate yield (30–32%) of the homoallylic alcohol product was obtained (Scheme 4). In contrast



Scheme 3.



5 **a**: X=Br
b: X=I

Scheme 4.

and as expected, in the absence of NaF, no allylation product was observed in aqueous media under the same conditions.

Acknowledgements

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