ChemPubSoc Europe

DOI: 10.1002/cctc.201900230

CHEMCATCHEM Communications

A Free-Radical Reduction and Cyclization of Alkyl Halides Mediated by $FeCl_2$

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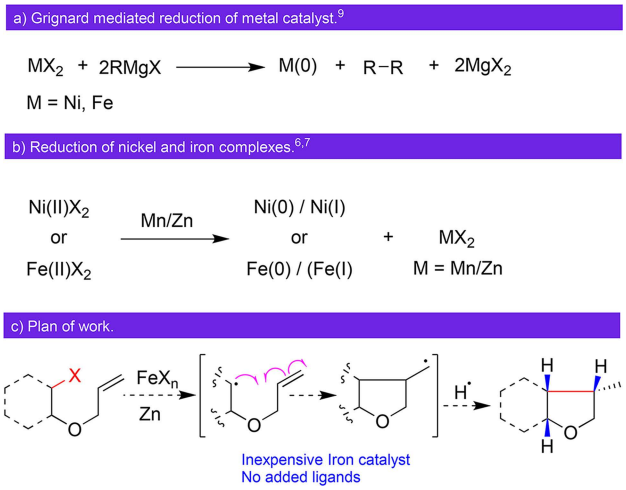
Iron mediated catalytic reactions are of great interest in the field of organic synthesis because they are economic and naturally abundant. However, the use of iron catalyst in the field of free radical cyclization or reduction of alkyl halides remains limited. Here we describe the use of an unprecedented combination of iron and zinc in the reduction and 5-*exo*-*trig* radical cyclization of alkyl halides under mild condition in the absence of added ligands or additives. The method is distinguished by its wide scope, functional group tolerance and the use of 1,4-cyclohexadiene as the source of hydrogen, which aids easy purification.

Sustainable chemical reactions play a vital role in industries and the search for an economical, environmentally benign and naturally abundant reagent is an important concern.[1] In this context, the development of iron mediated catalysis is very attractive. Over the past decade, iron catalysis has matured into a robust and attractive alternative to precious transition metal catalysts.[2] Despite the synthetic potential of iron catalysis, its application in the field of radical generation from alkyl halides is still lacking. Though the Bu_3SnH (stoichiometric) mediated radical reactions are very well established, the toxicity of tin reagents severely limits their potential use.[3] Photoredox catalysis has been proposed as an alternative to address these concerns raised by tin reagents, however, it often requires the use of expensive catalysts and is mostly limited to alkyl iodides.[4] Recently, there are developments based on iron catalysis appeared in the literature,[5] a close look into these studies reveals the requirement of either Grignard (Scheme 1a) or $NaBH_4$ reagents for the activation of iron catalyst, otherwise stoichiometric Fe(0) was used.[5a] Fensterbank et al. disclosed an elegant method to reduce the halogenoacetals in presence of 10 mol% of $FeCl_2$ and $NaBH_4$,[5b,c,h] Oshima et al. utilized PhMgBr for the activation of $FeCl_2$.[5g] Kang et al. used stoichiometric $Fe(CO)_5$ for the reductive radical cyclization.[5a] A methodology that can utilize iron and avoid the use of harsh conditions or reagents is highly desirable.



Scheme 1. Iron mediated reduction of alkyl halides.

Inspired by the recent literature on the *in-situ* reduction of nickel[6] and iron (Scheme 1b)[7] complexes by Mn/Zn and prompted by our perception that an activated iron may effectively catalyze the radical cyclization of unsaturated halogenoacetals (Scheme 1c), we envisaged a complementary strategy in which zinc can be used as a terminal reductant. We were also attracted towards the use of 1,4-cyclohexadiene (CHD) as the source of hydrogen atom since the resultant benzene could easily be removed, thus simplifying the purification process. As part of our ongoing interest in field of iron mediated catalytic reactions,[8] we present here an iron mediated reduction and cyclization of alkyl halides.

We commenced our study with the 1-(3-bromobutyl)-4-methoxybenzene **1a** which was readily prepared from the corresponding alcohol. After careful investigation, we pleasingly found that a combination of $FeCl_2$, Zn and CHD (1,4-cyclohexadiene) in CH_3CN at 50 °C offered the best result, affording **2a** in 99% isolated yield (Table 1, entry 1). As we speculated, a simple filtration followed by the removal of volatiles afforded the pure (by NMR) product **2a**. We found that CHD was more efficient to offer **2a** as the sole product, whereas MeOH (entry 2), catechol (entry 3) or Hantzsch ester (entry 4) offered the expected product **2a** in poor to moderate yield along with the alkene byproducts that complicate the isolation of **2a**. In the absence of CHD (similar to the reported condition),[7a] we observed only 44% of the protodehalogenated product (entry 5) along with traces of alcohol byproduct.

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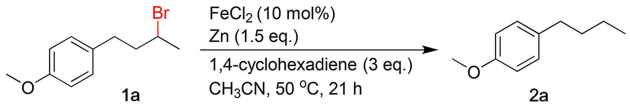
Supporting information for this article is available on the WWW under https://doi.org/10.1002/cctc.201900230

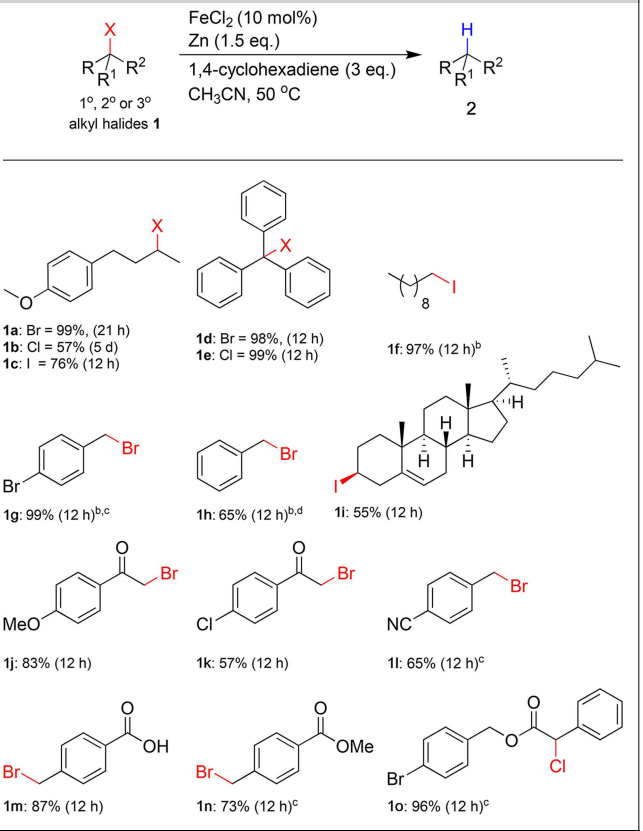
Table 1. Optimization of reaction condition.[a]



Entry	Deviation from standard condition	1a [%][b]	Yield 2a [%][b]
1	none	–	>99 (90)[c]
2	MeOH instead of CHD	9	70
3	Catechol instead of CHD	41	58
4	Hantzsch ester	80	18
5	without CHD in DMA	12	44[d]
6	without CHD	36	28
7	$FeCl_3$ instead of $FeCl_2$	18	78
8	$Fe(acac)_3$ instead of $FeCl_2$	85	9
9	Without Zn	97	0
10	without $FeCl_2$	96	0
11	Mn instead of Zn	–	99
12	DMF instead of CH_3CN	–	95
13	DMA instead of CH_3CN	–	94
14	Et_2O instead of CH_3CN	91	4
15	5 mol% $FeCl_2$	12	86 (96)[e]
16	1.0 eq. Zn	–	96
17	rt instead of 50 °C	45	42
18	1 eq. CHD	13	80

[a] General reaction condition: 0.5 mmol of **1a**, 1.5 mmol of CHD, 10 mol% of $FeCl_2$, 0.75 mmol of Zn, l.0 M CH_3CN, 50 °C, 21 h. [b] GC yield. [c] isolated yield. [d] 5 eq. of Zn, $FeBr_2$, DMA instead of CH_3CN. [e] 46 h instead of 21 h.

Table 2. Scope of substrates.[a]



[a] Reaction condition: 0.5 mmol of **1**, 1.5 mmol of CHD, 10 mol% of $FeCl_2$, 0.75 mmol of Zn, 1.0 M of CH_3CN, 50 °C, isolated yield. [b] GC yield. [c] 3 eq. of catechol was added instead of CHD. [d] 0.1 M of CH_3CN instead of 1.0 M of CH_3CN.

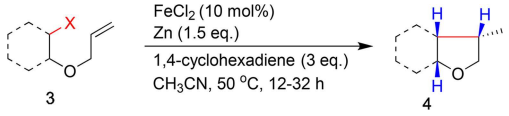
$FeCl_3$ also offered the protodehalogenated product, albeit in low yield (entry 7), while $Fe(acac)_3$ did not exhibit noticeable reactivity (entry 8). As shown in entries 9 and 10, no reactivity was found in the absence of either $FeCl_2$ or Zn, evidencing the role of $FeCl_2$ and Zn in the catalytic cycle.[10] Interestingly, the use of Mn as reductant resulted in a similar conversion (entry 11). In accordance with the literature on radical reactions, CH_3CN stands out to be the most suitable solvent for this transformation. DMF and DMA also offered **2a** in 95% and 94% yields respectively (entries 12 and 13). As expected, Et_2O was not suitable for this transformation (entry 14) and 91% of the starting material was left unreacted. Employing 5 mol% of $FeCl_2$ was sufficient to obtain 96% of **2a** (entry 15), albeit rather slowly (42 h vs 21 h). Carrying out the reaction at room temperature reduced the rate of the reaction (entry 17). Lowering the amount of CHD (entry 18) had significant effect on the yield.

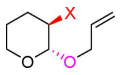
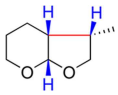
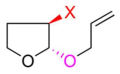
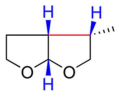
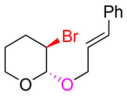
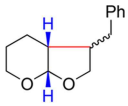
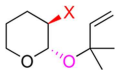
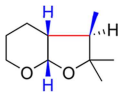
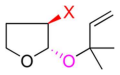
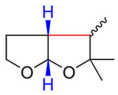
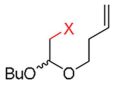
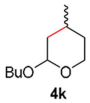
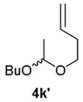
With the optimized condition in hand, we sought to investigate the scope of substrates. The results are summarized in table 2. As expected, the alkyl iodides **1c** and **1f**, benzyl bromides **1g** and **1h** were protodehalogenated efficiently (Table 2). The unreactive chloride **1b**, activated chlorides **1e** and **1o** were also suitable for this transformation and offered the corresponding protodehalogenated products in 57%, 99% and 96% yields respectively. Apart from the primary and secondary alkyl halides, sterically hindered tertiary halides **1d** and **1e** also underwent successful reduction to the corresponding protodehalogenated products in 98% and 99% yields respectively. 1-Bromoadamantane gave only 25% isolated yield (see SI).

We next examined the functional group tolerance; ketones **1j** and **1k** were compatible under the reaction condition and the corresponding products **2j** and **2k** were isolated in 83% and 57% yields respectively. The esters **1n** and **1o** were also compatible and offered the products **2n** and **2o** in 73% and 96% yields. Even the free carboxylic acid **1m** and nitrile **1l** were smoothly protodehalogenated in 87% and 65% yields. The cholesterol derivative **1i** offered the protodehalogenated product in 55% yield. Importantly, most of the products were obtained pure, just after the filtration of insoluble salts and removal of the volatiles.[11] The aryl halides and primary alkyl chlorides were intact under this reaction condition.[12] In the case of substrates **1g**, **1l**, **1n**, and **1o**, catechol was used instead of CHD.[13] In order to demonstrate the synthetic applicability of this methodology, we carried out a large-scale reaction in which 3.6 mmol of **1e** was subjected to the reaction condition with just 1 mol% of $FeCl_2$ and 1 eq. of Zn and CHD, to obtain the corresponding protodehalogenated product **2e** in 95% isolated yield.[14]

To further demonstrate the synthetic utility of this method, we subjected unsaturated halogenoacetals to the optimized condition and observed the formation of synthetically versatile cyclized products (Table 3).[3a–b,5a–c, g–h,15] The bromoacetal derivative **3a** offered the *cis*-fused *syn*-substituted 5-*exo*-*trig* cyclized product **4a** in 60% yield with 84:16 diastereoselectivity, reminiscent of recent literature that demonstrates the interme-

Table 3. Radical cyclization of alkyl halides.[a]

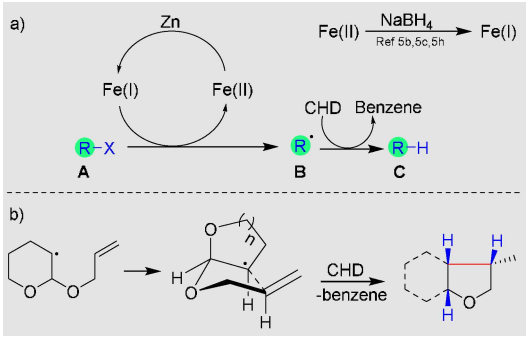


entry	3	t	Product 4 4	dr[b]	[%][c]
1					
	3a = Br	16 h	**4a**	84:16	60[d]
	3b = I	12 h		88:12	56
2					
	3c = Br	16 h	**4c**	95:5	74[d]
	3c = Br	16 h		90:10	93[d,e]
	3d = I	12 h		97:3	66
3	 3e	32 h	 4e	50:50	27
4					
	3f = Br	16 h	**4f**	33:67	52[d]
	3g = I	12 h		33:67	94
5					
	3h = Br	16 h	**4h**	50:50	56[d]
	3i = I	12 h		50:50	29
6	 3j	32 h	 4j	-	77[f]
7			 4k	 4k'	
	3k = Br	16 h	**4k**:**4k'**(36:64) *trans*:*cis* (65:35)		27[d]
	3l = I	12 h	**4k**:**4k'**(23:77) *trans*:*cis* (68:32)		46

[a] Reaction conditions: 0.5 mmol of **3**, 1.5 mmol of CHD, 10 mol% of $FeCl_2$, 0.75 mmol of Zn, l.0 M of CH_3CN, 50 °C. [b] based on crude ^1H NMR. [c] isolated yield. [d] 80 °C instead of 50 °C. [e] catechol used instead of CHD. [f] DMA instead of CH_3CN.

diacy of alkyl radical in these reactions. The corresponding iodide **3b** also offered the cyclized product **4a** in 56% yield (88:12 dr). Traces of unsaturated product was seen along with the expected product **4a** which might account to the moderate yield of substrates **3a** and **3b**. Substrates **3c** and **3d** also underwent cyclization to offer the *cis*-fused *syn*-substituted bicyclic product **4c** with excellent diastereoselectivity control (entry 2). Substrate **3e** having an internal alkene also successfully offered the cyclized product albeit in lower yield (entry 3).[16] Further, the halogenoacetals **3f**–**3i** also resulted in the bicyclic products **4f** and **4h** with moderate to excellent yields. The acyclic halogenoacetal **3j** offered the corresponding cyclized product **4j** in 77% isolated yield. The *O*-homoallyl derivatives **3k** and **3l** gave the cyclized (6-*exo*-*trig*) product **4k** (entry 7) in relatively low yield along with the uncyclized protodehalogenated product **4k'** in 27% and 46% yields respectively.[5h] In accordance to the literature,[3a–b,5a–c,g–h,15] the observed selectivity towards *cis*-fused *syn* substitution can be explained by a transition state shown in Scheme 2b, where the endo cyclization of the alkene occurs predominantly.

It has been proposed in the previous studies[7] that the Fe(I) is generated upon mixing either $FeCl_2$ and Zn or $FeCl_2$ and $NaBH_4$,[5b,c,h] though Fe(0) cannot be ruled out. It is also noticed that the alkyl halide is intact in the absence of either $FeCl_2$ or Zn (entries 9 and 10, Table 1). The presence of a radical intermediate is evident from the formation of a *cis*-fused bicyclic product. Based on these results, we propose a catalytic cycle as shown in Scheme 2a. A single electron transfer (SET)



Scheme 2. Mechanistic proposal and a transition state model.

from Fe(I) to an alkyl halide A leads to the formation of a radical intermediate B, subsequent intramolecular endocyclic radical cyclization (5-*exo*-*trig*) followed by the abstraction of hydrogen atom from CHD led to the desired product C. The observed diastereoselectivity for substrates **3a–d** can be understood using the transition state model presented in Scheme 2b.[17,18]

In summary, we have developed an iron mediated free radical protodehalogenation of alkyl halides (1°, 2° and 3°) and cyclization of unsaturated halogenoacetals using Zn as a terminal reductant and CHD as the hydrogen donor. The developed catalytic system is compatible with various functional groups and sterically hindered halides. Initial studies revealed a radical intermediate during the reaction which serves as a useful alternative to the tin and photochemical mediated reactions.

Experimental Section

Under an inert atmosphere, the oven dried Schlenk tube was charged with iron (II) chloride (10 mol%, 0.05 mmol, 6.4 mg) and zinc (1.5 eq., 0.75 mmol, 49 mg) followed by the addition of acetonitrile (0.5 mL) and 1, 4-cyclohexadiene (3.0 eq., 1.5 mmol, 142 μL). After stirring for a minute at room temperature, the alkyl halide (1.0 eq., 0.5 mmol) was added and continued stirring at 50 °C. The completion of reaction was monitored using TLC. After the reaction was complete, the mixture was filtered through plug of Celite or silica, eluting with Et_2O/CH_2Cl_2/EtOAc (based on the volatility and polarity of the material) to remove metal salts and the filtrate was concentrated under vacuum to obtain protodehalogenated product. If needed the crude was subjected for further purification by flash column chromatography (petroleum ether/ethyl acetate) to give the corresponding product.

Acknowledgements

We thank the Science and Engineering Research Board, DST No: EMR/2015/001103/OC and Ramanujan Fellowship SB/S2/RJN059/2015 for financial support. FTP, RP and VM acknowledge IISER, Trivandrum for fellowship.

Conflict of Interest

The authors declare no conflict of interest.

Keywords: iron · catalysis · protodehalogenation · reductive cyclization · radicals · zinc

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[10] It is important to note that the traces of $FeCl_2$ (from an unclean stir bar) can catalyze the reaction.

[11] No silica column purification was required when CHD was used as the source of hydrogen atom, however, a silica column purification was necessary when we use catechol as the source of hydrogen atom.

[12] see SI for more details.

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[14] see page number S13 in SI for more details.

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Manuscript received: February 8, 2019
Revised manuscript received: March 28, 2019
Version of record online: April 17, 2019