Practical iron-catalyzed dehalogenation of aryl halides†

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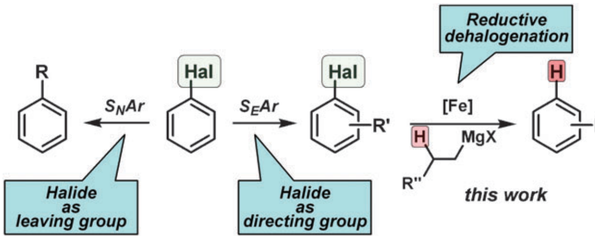
An operationally simple iron-catalyzed hydrodehalogenation of aryl halides has been developed with 1 mol% Fe(acac)$_3$ and commercial *t*-BuMgCl as reductant. The mild reaction conditions (THF, 0 °C, 1.5 h) effect rapid chemoselective dehalogenation of (hetero)aryl halides (I, Br, Cl) and tolerate F, Cl, OR, SR, CN, CO$_2$R, and vinyl groups.

Halogenated aromatic molecules are one of the most important structural motifs of natural and synthetic molecules and play a commanding role as intermediates for bulk and fine chemicals and materials.[1] The ability of halides to function as directing groups for arene derivatizations in *ortho* and (*para*) positions (S_EAr) has been known long before the advent of modern cross-coupling methodologies which consume the halide in a formal S_NAr reaction (Scheme 1). The non-consumptive directing $-I/+M$-effect of halides is key to electrophilic aromatic substitutions;[2] halides are also being extensively used as cheap and abundant protective groups in industrial arene processing.[3] Both strategies require efficient methods for the subsequent removal of the halide substituent.[4] Furthermore, the contamination of noxious down-stream chemicals and waste water poses a continuing challenge to the development of sustainable chemical technologies and thus demands effective dehalogenation protocols that go beyond the scope of microbial haloalkane degradations.[5]

Standard methods for the dehalogenation of aryl halides include either expensive, stoichiometric, or toxic metals, harsh and laborious reaction conditions or exhibit another detrimental environmental impact (*e.g.* catalytic Pd, Ni, Rh; stoichiometric Bu_3SnH, SmI_2; pressurized H_2, N_2H_4, $HSiR_3$ as reductants).[6] As part of our research program aiming at metal-catalyzed arene manipulations,[7] we developed a new protocol for the iron-catalyzed hydrodehalogenation of various (hetero)aryl halides under mild conditions (Scheme 1).

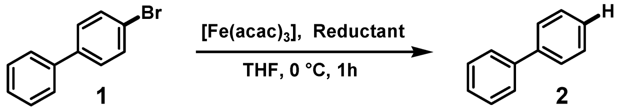


Scheme 1 The dual role of halides as leaving and directing groups and the iron-catalyzed hydrodehalogenation of arenes.

Modern iron-catalyzed reactions have matured to an advanced stage over the past years.[8] Especially cross-coupling reactions with aryl halides have been intensively studied.[9] We wondered whether the initial activation of an electrophilic aryl halide by a low-valent iron catalyst can be exploited for a cross-coupling with a hydride species in a formal reduction.[10] Initial experiments with 4-bromobiphenyl (**1**) and stoichiometric $LiAlH_4$ or $NaBH_4$ showed minimal reactivity, while alkyl-Grignard species effectively delivered a hydride *via* intramolecular β-hydride elimination (Table 1). With EtMgCl, competitive aryl–alkyl cross-coupling was observed (<10%). Upon employment of a commercial THF solution of *tert*-butylmagnesium chloride (*t*-BuMgCl, from Chemetall), no cross-coupling product was formed, but quantitative hydrodehalogenation was effected obviating chromatographic purification (entry 5). A related high temperature protocol with very limited substrate scope (4 products) was already reported by Takahashi *et al.*, which is not applicable to activated aryl chlorides, aryl bromides and iodides due to dominating cross-coupling.[11] Further optimization resulted in a procedure with 1 mol% Fe(acac)$_3$ and 1.5 equiv. *t*-BuMgCl. $FeCl_3$ and $FeCl_2$ showed slightly lower activities (90%); $CuCl_2$, $CoCl_2$, Pd(acac)$_2$, Ni(acac)$_2$ were ineffective (<8%).[11]

Fig. 1 shows a kinetic comparison of the iron-catalyzed hydrodehalogenation of **1** and the iron-free Grignard formation with metallic Mg. With only 1 mol% Fe(acac)$_3$ and 1.5 equiv. *t*-BuMgCl, the half-life of **1** was <3 min and the conversion complete after 1 h at 0 °C. The (iron-free) direct reaction of **1** with Mg exhibited a long induction period and a $t_{\frac{1}{2}}$ of 1.5 h for **1** at otherwise identical conditions

Table 1 Selected optimization experiments[a]



Entry	Mol% Fe(acac)$_3$	Reductant (equiv.)	Yield[b] (%)
1	5	EtMgCl (5)	87 (<10)
2	5	EtMgCl (3)	80 (<10)
3	1	EtMgCl (1.2)	67 (<10)
4	0.1	EtMgCl (1.2)	38 (<10)
5	**1**	***t*-BuMgCl (1.5)**	**>99 (0)**
6	—	*t*-BuMgCl (1.5)	0
7	10	$LiAlH_4$ or $NaBH_4$ (5)	<2
8	5	MeMgCl (1.5)	<1 (0)
9	—	Mg (1.2)	12

[a] Conditions: 1 mmol ArBr, 4 mL THF. [b] GC yields, yields in brackets refer to cross-coupling product 4-R-biphenyl (with R = Et, *t*-Bu, Me).

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† Electronic supplementary information (ESI) available: Experimental details and spectra. See DOI: 10.1039/c0cc01980a

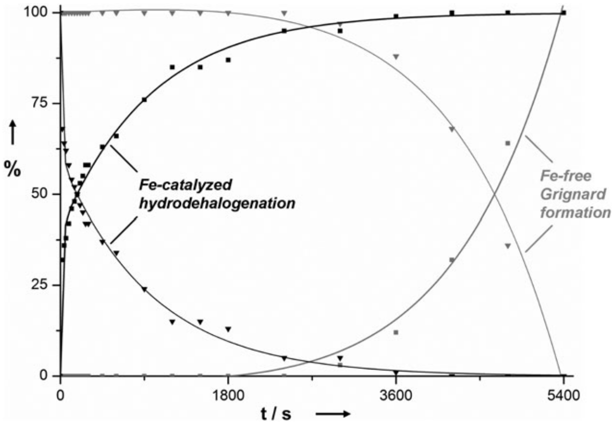


Fig. 1 Fe-catalyzed dehalogenation *vs.* magnesiation of **1** (▼) to **2** (■).

(entry 9, Table 1). The iron-catalyzed hydrodehalogenation is clearly devoid of an induction period, which is known to entail spontaneous heat release and unselective reactions in conventional Grignard formations.[12]

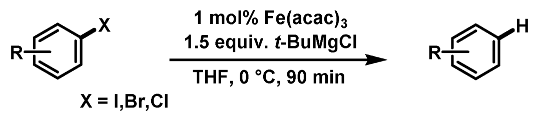
The optimized conditions effect reductive deiodination and debromination at 0 °C and display high chemoselectivity (I *vs.* Cl, Br *vs.* Cl) and functional group tolerance (F, Cl, ester, ether, thioether, CN, see Table 2). Sterically unhindered ester functions (*e.g.* CO_2Me) are subject to slow alkylation (> 1.5 h, 0 °C), while pivalates are stable under the conditions. Electron-withdrawing, -donating, and *ortho*-substituents are equally tolerated. The conversion of aryl chlorides requires elevated temperature (≥ 20 °C) and slightly extended reaction times (3 h). The observed selective mono-dechlorination of *o*- and *m*-dichlorobenzenes is especially surprising as both substrates are known to undergo elimination to arynes in the presence of strong bases. In no case formation of the corresponding homo-biaryl was observed. Aryl bromides with free OH and NH_2 residues required excess Grignard for *in situ* deprotonation and subsequent reduction (Table 3). Heteroaryl halides such as 5-bromoquinaldine, 3-bromothiophene and 4-chloroquinaldine gave the corresponding reduction products in good yields after stirring with 5 mol% $Fe(acac)_3$ and 3 equiv. *t*-BuMgCl in THF at 0 °C (Table 3).[13] Pyridines lacking 2-substitution showed competitive alkylation to 2-*tert*-butylpyridines.

We postulate a mechanism based upon a catalyst that forms by reduction of iron salts with alkylmagnesium halides bearing β-hydrogen atoms (Scheme 2).[10a,11,14] The resultant nucleophilic ferrate has a high propensity to activate $C(sp^2)$–halide bonds in an oxidative addition event.[14] While cross-coupling with *tert*-alkyl groups is not operative, a rapid β-hydride elimination internally delivers a formal hydride. Reductive elimination releases the arene (and *i*-butene as by-product).

Selected experiments in favour of the postulated mechanism: work-up of the model reaction (**1**, 1 mol% $Fe(acac)_3$, 1.5 equiv. *t*-BuMgCl, THF, 0 °C, 1.5 h) with D_2O did show any detectable deuterium incorporation. An identical result was obtained with THF-d_8 as solvent. Employment of EtMgBr-d_5 resulted in complete deuterium incorporation into **1** (^2H NMR (77 MHz, THF-d_8): δ 7.24 (s), see Scheme 2). Substitution of *t*-BuMgCl with PhMgCl or MeMgCl gave no dehalogenation product within 1.5 h at 0 °C. With *n*-dodecylmagnesium chloride (1.5 equiv.), equal amounts of 1-decene and biphenyl (**2**) formed (∼50%) over the course of the reaction. In the absence of $Fe(acac)_3$, conversion of **1** was < 1% after 1 h.

Subjection of alkyl bromides to the standard reaction conditions (1 mol% $Fe(acac)_3$, 1.5 equiv. *t*-BuMgCl, 0 °C, 1 h) selectively gave the hydrodebrominated alkanes (Scheme 3). The corresponding alkenes resulting from base-mediated dehydrobromination were not observed.

Table 2 Hydrodehalogenation of aryl halides



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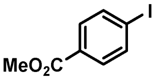
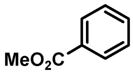
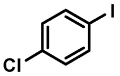
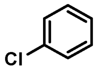
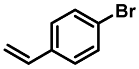
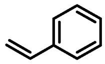
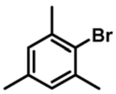
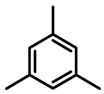
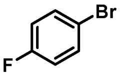
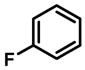
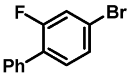
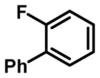
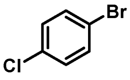
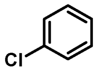
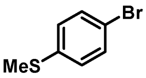
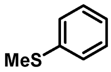
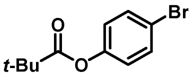
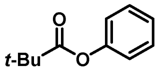
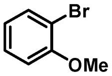
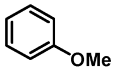
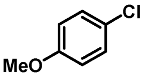
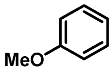
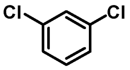
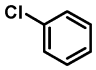
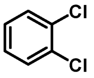
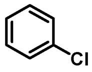
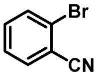
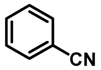
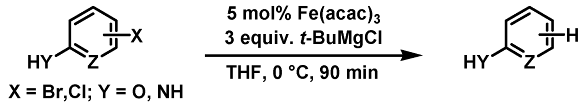
1			87[b]
2			95
3			65
4			87
5			95
6			86
7			89
8			93[c]
9			99[c,d]
10			87
11			84[e]
12			79[f]
13			95[f]
14			59

[a] GC yields. [b] 2.5 mol% $Fe(acac)_3$. [c] Isolated yields. [d] 10 °C. [e] 5 mol% $Fe(acac)_3$, 1.5 equiv. *t*-BuMgCl, 35 °C, 4 h. [f] 5 mol% $Fe(acac)_3$, 1.5 equiv. *t*-BuMgCl, 20 °C, 3 h.

Table 3 Hydrodehalogenation of acidic substrates and heteroarenes



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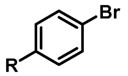
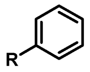
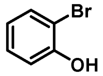
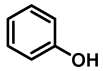
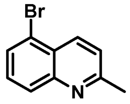
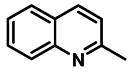
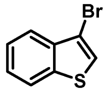
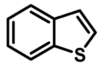
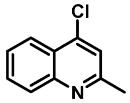
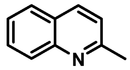
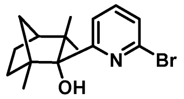
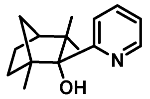
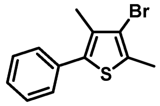
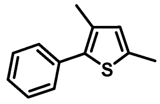
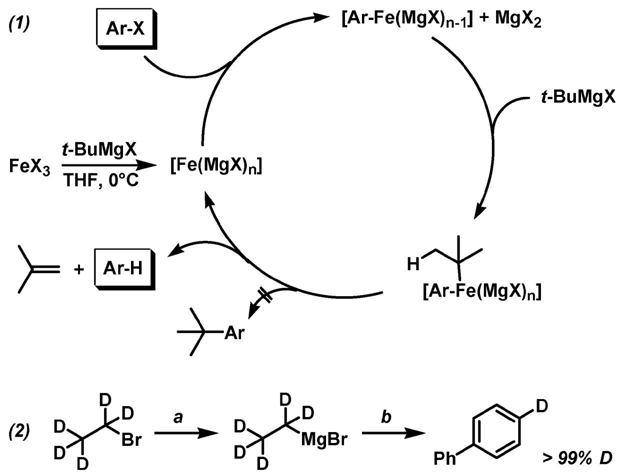
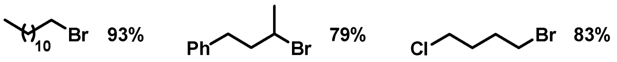
1 2		 R = OH R = NH_2	72[a] 62[a]
3			87[a]
4			77[b]
5			72
6			82[c]
7			78[d]
8			54[e]

[a] 4 h. [b] 1 mol% $Fe(acac)_3$, 1.5 equiv. t-BuMgCl. [c] 20 °C. [d] GC yield.[13] [e] NMR yield.



Scheme 2 Mechanistic rationale. a: 1.5 equiv. Mg, 1.2 equiv. LiCl, 0.01 mol% Dibal-H, THF, 0 °C, 3 h; b: **1**, 5 mol% $Fe(acac)_3$, THF, 0 °C, 1 h.

In summary, we have developed a highly practical iron-catalyzed hydrodehalogenation of aryl and heteroaryl halides. Commercial t-BuMgCl (from Chemetall) serves as a hydride source *via* an iron-centered β-hydride elimination. The mild reaction conditions (THF, 0 °C, 90 min) tolerate various functional groups, electron-deficient heteroarenes and allow highly chemoselective reactions in the vicinity of halide, ester, nitrile, thioalkyl and vinyl substituents. The practical and rapid methodology may suggest further applications to the selective dehalogenation of complex molecules and scavenging of environmentally noxious halo aromatics.



Scheme 3 Isolated yields for reductive debromination of alkyl bromides.

Notes and references

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