$FeCl_2$-mediated Nucleophilic Chlorination of Iodoalkanes Accelerated by Phenanthroline Ligand

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Alkyl halides have been considered not only important building blocks but also useful intermediates in synthetic methods of nucleophilic substitution, metal-halogen exchange, and cross-coupling reactions. As the practical synthesis of various alkyl halides, the halogen exchange is one of the fundamental and efficient reactions, which is mainly used for preparing alkyl bromides or iodides. Finkelstein-type reactions[1] have been well studied for the conversion of alkyl chlorides to the corresponding bromides or iodides and alkyl bromides to iodides, which reaction is an equilibrium shifted by taking advantage of the different solubility of the resulting sodium salt in acetone. However, the reverse processes, the replacement of iodide by bromide or chloride, or of bromide by chloride, were not simple.

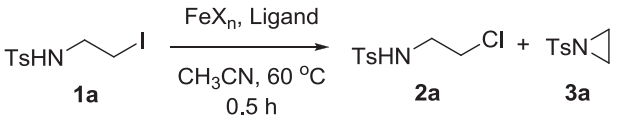
The early investigation on the chlorination of alkyl iodides were involved with the reaction of molecular chlorine or iodine monochloride,[2] which afforded the alkyl iodide-halogen intermediate (RI·ClX, X = Cl or I). The resulting trihalide ion could act as an electronegative leaving group and promote the chloride substitution, showing the preferred reactivity of tertiary and secondary iodides over primary iodides. Metal chlorides such as $MoCl_5$[3] and $BiCl_3$[4] were also discovered as the role of providing the chloride source as well as activating the carbon-halogen bond by Lewis acidic coordination to halogen leaving group. This strategy showed the 1,2-migration phenomena in the reaction with 1-iodooctane, supporting the intermediacy of carbocations. Another approach was the oxidatively-assisted substitution, where alkyl iodides were oxidized to iodoso compounds (RI═O) by mCPBA[5] or hypervalent iodine[6] compounds for consecutive nucleophilic chlorination. In a similar way, oxidative ligand transfers between alkyl iodides and aryliodine(III) reagents produced the requisite hypervalent alkyliodine intermediates for substitution. The methods described above make the iodide a good leaving group and the modified iodine functional group cannot act as a nucleophile again. On the other hand, a process of separating the generated alkyl chlorides by boiling point difference[7] or separating the leaving iodide into fluorous phase using fluorous phosphonium salt has been developed.[8]

As mentioned above, the conversion of iodides to the corresponding chlorides mostly required more than an equivalent of molecular chlorine, metal chloride, alkyl ammonium chloride, strongly acidic hydrogen chloride or oxidants under elevated temperature in long reaction time (sometimes 10 or more days).[9] Furthermore, much has been devoted to the transformation of secondary or tertiary iodides, but studies on primary iodide conversions are rare or the corresponding reactions require even more harsh conditions.

While we focused and investigated on the iron catalysis[10] in terms of new reactivity and alternative substitutes to the use of precious metals, under environmentally more acceptable 'green' conditions, iron chlorides were thought to provide the chloride source in the halogen exchange reaction. Moreover, to sufficiently activate the chloride and make the iron center soft, it was considered that the introduction of a bulky ligand was desperately needed. Herein, we report the scope and limitations of the ligand-accelerated nucleophilic chlorination of primary and secondary iodoalkanes with stoichiometric amount of iron chlorides under mild condition.

To examine the prospect of using $FeCl_n$ as potential chloride nucleophile, the reaction system of $FeCl_2$ and 1,10-phenanthroline monohydrate (phen-H_2O) ligand were subjected to a simple aliphatic iodoalkanes, toluene sulfonamide (**1a**). As described in Table 1, the reaction with stoichiometric amounts of $FeCl_3$ and 3 M equivalents of phen-H_2O smoothly promoted the formation of chloroalkane (**2a**) at 60 °C within 30 min, and $FeCl_2$ was determined to serve as an effective complex in the nucleophilic chlorination to afford **2a** in 79% yield (entries 1–2). The use of several types of ligands were tested: the reaction with 2,2′-bipyridine (bpy) resulted a comparable yield of 82% with phen-H_2O ligand. Other N or P-type ligands such as tetramethylethylenediamine (TMEDA), ethylenediamine (EDA), triphenylphosphine, or 1,2-bis(diphenylphosphino)ethane (dppe) did not exhibit noticeable reactivities (entries 4–7). Furthermore, the efficiency of the reaction system and role of each member in it was tested. In the absence of phen-H_2O ligand, the corresponding chloroalkane was not obtained, implying that the choice of ligand seemed to be

Table 1. Optimization of conditions for nucleophilic chlorination.[a]



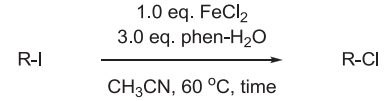
Entry	FeX_n	Ligand	Yield(%)[b] 1a	2a	3a
1	$FeCl_3$	phen-H_2O	—	61	—
2	$FeCl_2$	phen-H_2O	—	79	—
3	$FeCl_2$	bpy	—	82	—
4	$FeCl_2$	TMEDA	—	Decomp.	—
5	$FeCl_2$	EDA	—	Decomp.	—
6	$FeCl_2$	PPh_3	99	—	—
7	$FeCl_2$	dppe	99	—	—
8	$FeCl_2$	—	99	—	—
9[c]	$FeCl_2$	phen-H_2O	8	75	—
10[d]	$FeCl_2$	phen-H_2O	92	8	—
11	FeF_2	phen-H_2O	92	—	7
12	$FeBr_3$	phen-H_2O	8	—	43

[a] Reaction condition: **1a** (0.12 mmol), FeX_n (0.12 mmol, 1.0 equiv), ligand (0.36 mmol, 3.0 equiv), CH_3CN (0.1 M), 60 °C for 0.5 h.
[b] Isolated yield.
[c] Reaction with 2.0 equiv of ligand.
[d] Reaction with 1.0 equiv of ligand.

critical. When an amount of phen-H_2O was decreased, an equimolar amount of ligand sharply dropped the yield of product formation (entries 9–10). Additional possibility of other halogen nucleophile was investigated with the commercial source of iron salts, FeF_2 and $FeBr_3$. Instead of expected transfer-halogenation products, aziridine **3a** were obtained, which suggests that the intramolecular cyclization reaction was proceeded due to the Lewis acidic character of the iron complexes.

With the optimal reaction conditions in hand,[11] the substrate scope of chlorination of primary and secondary iodoalkanes was evaluated, and the results were summarized in Table 2. Various types of iodoalkanes were efficiently converted into corresponding chloroalkanes in moderate to high yields (entries 1–3). It is of interest to note that the pre-complexed $Fe(phen)_3Cl_2$ reagent were sufficiently comparable, which was thought to be the critical species generating a chloride nucleophile. However, Boc-protected tosylamide (**1d**) could not successfully afford the chlorinated product (**2d**, entry 4), suggesting that the neighboring group seems to have some effect on the chlorination reaction. Iodoalkanes having allyl and styrenyl group were also generally effective, but benzyl iodide (**1h**) and hydroxylated substrate (**1i**) significantly retarded the efficiency of reaction (entries 5–9). Ester and carbamate functional groups were well tolerated under the reaction conditions, delivering the corresponding chloroalkanes in up to 85% yield. Interestingly, α-chloromethyl carbonyl unit in **2j** could be an essential core in biologically active small molecules.[12] Remarkably, secondary chlorides were obtained by reacting iodides in acyclic substrates also converted into chlorides in high yield (entries 12–13).

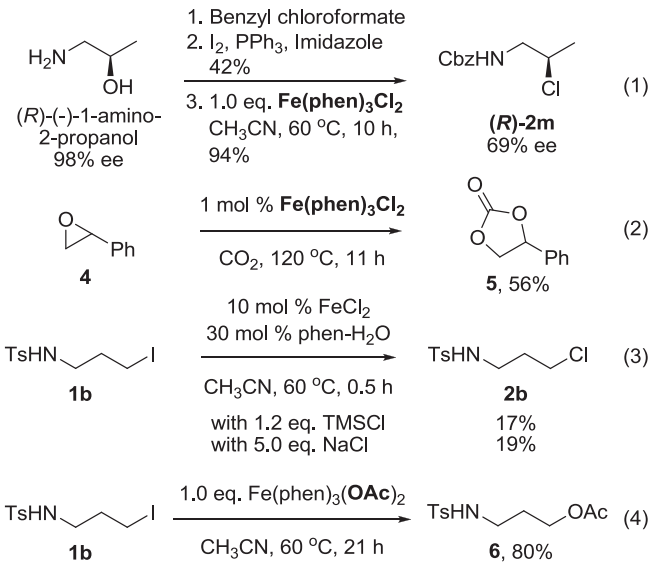
Table 2. Substrate scopes in nucleophilic chlorination.



Entry	R-I		Time (h)	R-Cl		Yield (%)[a]
1	TsHN–I	**1a**	0.5	TsHN–Cl	**2a**	79
2	TsHN–I	**1b**	0.5	TsHN–Cl	**2b**	79 (84)[b]
3[b]	TsHN–I	**1c**	0.5	TsHN–Cl	**2c**	67
4	TsBocN–I	**1d**	3	TsBocN–Cl	**2d**	8
5	N(Ts)–I	**1e**	6	N(Ts)–Cl	**2e**	83
6[c]	Ph–I	**1f**	0.5	Ph–Cl	**2f**	83
7	Ph–I	**1g**	0.5	Ph–Cl	**2g**	83
8[c]	MeO–I	**1h**	0.5	MeO–Cl	**2h**	34
9[c]	OH–I	**1i**	5	OH–Cl	**2i**	40
10	Ph–O–C(=O)–I	**1j**	0.5	Ph–O–C(=O)–Cl	**2j**	85
11[c]	O(=C)–O–I	**1k**	0.5	O(=C)–O–Cl	**2k**	61
12[c]	BocHN–I	**1l**	16	BocHN–Cl	**2l**	64
13[c]	CbzHN–I	**1m**	10	CbzHN–Cl	**2m**	71

[a] Isolated yield.
[b] Accompanied with 1-tosylpyrrolidine (16%).
[c] Reaction condition: iodide (0.12 mmol), $Fe(phen)_3Cl_2$ (0.12 mmol, 1.0 equiv), CH_3CN (0.1 M), 60 °C.

To investigate the nucleophilic chlorination processes mediated by the $FeCl_2$/phen system, we performed mechanistic experiments employing the enantio-rich secondary alcohol compound (Scheme 1, Eq. (1)). (*R*)-(−)-1-Amino-2-propanol (98% *ee*) was converted to the corresponding secondary iodide by Cbz protection and iodination reaction, and the expected (*S*)-**1m** substrate was treated with the isolated $Fe(phen)_3Cl_2$ compound. The chlorination reaction was smoothly proceeded and predominantly afforded the (*R*)-**2m** enantiomer as a major product in the ratio of approximately 85:15, which verifies that $Fe(phen)_3Cl_2$-mediated chlorination is mainly proceeded by S_N2 reaction pathway.[13] Additional evidence of the phenomenon of



Scheme 1. Experiments for mechanistic investigations.

generating applicable chloride anions from $Fe(phen)_3Cl_2$ was also found in the following cyclic carbonate synthesis (Eq. (2)). A catalytic amount of $Fe(phen)_3Cl_2$ could be used for the conversion of styrene oxide (**4**) into cyclic carbonate (**5**), while an ammonium halide ($R_4N^+X^-$) is generally employed in the oxide ring opening pathway during the carbonate synthesis.[14] The feasibility of an iron catalysis accompanied with external chloride sources was examined under the reaction condition with 10 mol % of $FeCl_2$, however, experiments conducted with TMSCl or NaCl failed to generate the measurable amount of the chlorinated product **2b**.[15] Interestingly, the deiodinative acetoxylation was successfully achieved by $Fe(phen)_3(OAc)_2$ complex to afford the acetate **4b** even under the elongated reaction time (21 h). These results indicated that it was advantageous for the $Fe(phen)_3^{2+}$ complex ion to bind to the I^- ion (soft base) rather than Cl^- or OAc^- (hard bases) ions acting as a nucleophile, while the Fe^{2+} ion (hard acid) was converted to the $Fe(phen)_3^{2+}$ complex ion (soft acid).[4]

In summary, a ligand accelerated nucleophilic chlorination of alkyl iodides is described, and the reaction is performed using stoichiometric amount of iron dichloride with phen-H_2O ligand, in which metal chloride is considered as a chloride source. This reaction provides a convenient method for the efficient access to diverse primary or secondary chlorides under the mild reaction conditions. Reaction mechanism is mainly suggested to the S_N2 type substitution approved by overall inversion of configuration in the reaction of an enantio-rich secondary iodide. Moreover, the isolated $Fe(phen)_3Cl_2$ complex was found to be the critical species generating a chloride nucleophile.

Experimental

General Procedure for the Nucleophilic Chlorination Reaction. To a solution of iodoalkane (**1a**) (0.12 mmol, 1.0 equiv) in CH_3CN (1.2 mL) was added $FeCl_2$ (0.12 mmol, 1.0 equiv) and 1,10-phenanthroline monohydrate (0.36 mmol, 3.0 equiv). After being stirred at 60 °C for 0.5 h, solvent evaporation and silica gel column chromatography afforded *N*-(2-chloroethyl)-4-methylbenze-nesulfonamide (**2a**).[16] Yield 22 mg (79%); white solid; R_f = 0.49 (Hex:EtOAc = 2:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (d, 2H, *J* = 8.3 Hz), 7.33 (d, 2H, *J* = 8.2 Hz), 5.01 (t, 1H, *J* = 6.1 Hz), 3.55 (t, 2H, *J* = 5.9 Hz), 3.30 (q, 2H, *J* = 5.9 Hz), 2.44 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.9, 136.9, 129.9, 127.1, 44.6, 43.5, 21.4 ppm; HRMS (EI): calcd for $C_9H_{12}ClNO_2S$ (M^+) 233.0277, found 233.0276.

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Supporting Information. Additional supporting information is available in the online version of this article.

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