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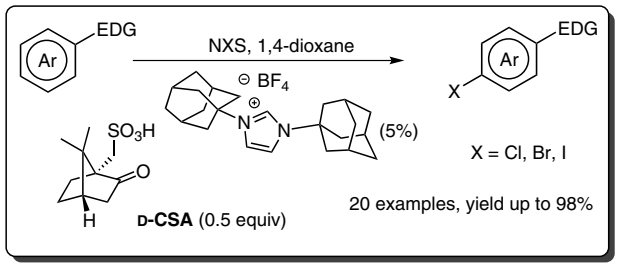
Imidazolium Salt Catalyzed *para*-Selective Halogenation of Electron-Rich Arenes

Jie Chen[a,b]
Xiaoyu Xiong[a,b]
Zenghua Chen[a,b]
Jianhui Huang*[a,b]

[a] Tianjin Key Laboratory for Modern Drug Delivery and High-Efficiency, School of Pharmaceutical Science and Technology, Tianjin University, Tianjin 300072, P. R. of China
[b] Collaborative Innovation Center of Chemical Science and Engineering (Tianjin), Tianjin 300072, P. R. of China
jhuang@tju.edu.cn



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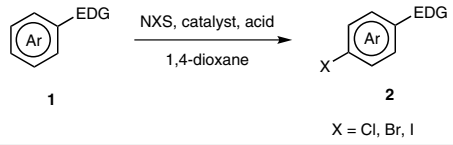
Abstract A highly *para*-selective halogenation of arenes bearing coordinating groups in the presence of a dimidazolium salt as a catalyst is reported. A series of electron-rich *p*-haloarenes were prepared in good yields and good to excellent selectivities. We also propose a plausible mechanism for the catalytic reaction.

Key words arenes, regioselectivity, halogenation, amides, ethers, catalysis

The electrophilic aromatic substitution reaction is one of the most popular reactions in organic synthesis.[1] The direct functionalization of arenes, in particular the synthesis of aryl halides by direct halogenation of electron-rich arenes, is among the most studied areas of synthetic chemistry, because of the versatility of aryl halides in many functional-group interconversions.[2] However, the regioselective synthesis of aryl halides is still a challenge in organic chemistry, as such reactions are generally nonselective, occurring at various sites.[3] Here, we describe a practical, imidazolium salt assisted, *para*-selective method for the halogenation of arenes (Scheme 1).



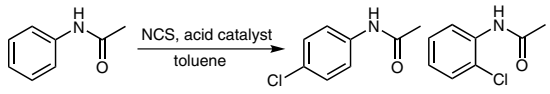
Scheme 1 Selective synthesis of *p*-haloarenes

During our studies on the direct C–H functionalization of various arenes,[4] we proposed, on the basis of the conventional Friedel–Crafts reaction,[5] that weak coordination might facilitate an improvement in the selectivity of the functionalization of arenes bearing coordinating electron-rich substituents. Here, we report our latest discoveries pertaining to imidazolium salt catalyzed[6] *para*-selective halogenation of electron-rich arenes.[7]

We began by examining the chlorination of *N*-phenylacetamide (**1a**). In the presence of a substoichiometric amount of acid, chlorination of **1a** with *N*-chlorosuccinimide (NCS) proceeded smoothly to give the corresponding regioisomeric chloroanilides **2a** and **2a′** as a 44:56 mixture in 74% total yield. The use of a catalytic amount of acid (10 mol%) resulted in a slow reaction with relatively low conversion. A screening of various acids resulted in an improved reactivity and selectivity. With sulfuric acid, methanesulfonic acid, or 4-toluenesulfonic acid, the reaction gave a good yield but poor selectivity, with the *o*-chloroanilide **2a′** as the major product (Table 1, entries 2, 5, and 8, respectively). Trifluoroacetic acid (entry 3) or the Lewis acid aluminum(III) chloride (entry 6) gave mixtures of similar amounts of the two isomers. Fortunately, acids such as benzoic acid (entry 7), D-camphorsulfonic acid (D-CSA; entry 9), or adamantane-1-carboxylic acid (entry 10) gave chloroanilides **2a** and **2a′** in a nearly 2:1 ratio in favor of the *para*-chlorinated product **2a**.

A screening of solvents and additives was also fruitful, and the results are summarized in Table 2. Solvents such as *N*,*N*-dimethylformamide (Table 2, entry 4) or tetrahydrofuran (entry 6) gave low yields of the product, whereas 1,2-dichloroethane appeared to be a good solvent for the reaction, giving the desired product in quantitative yield, but with a slightly reduced regioselectivity (63:37) (entry 2). Toluene (entry 1) and 1,4-dioxane (entry 7) were the best solvents with respect to *para*-selectivity. A further improvement in the yield and regioselectivity was realized by the introduction of 5 mol% of an additive. When triphenylphosphine (entry 8) or 1,1′-ferrocenediylbis(diphenylphos-

Table 1 Screening of Reaction Conditions: Effects of Various Acids[a]

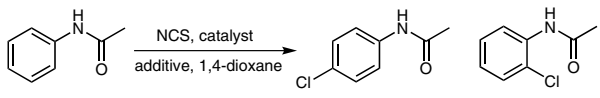


1a **2a** **2a'**

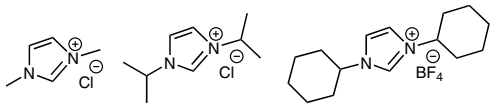
Entry	Acid	Yield	Ratio **2a**/**2a'**
1	–	n.r.[b]	–
2	H_2SO_4	74%	44:56
3	TFA	90%	50:50
4	AcOH	n.r.	–
5	MsOH	55%	22:78
6	$AlCl_3$	79%	55:45
7	BzOH	78%	69:31
8	TsOH	79%	47:53
9	**D-CSA**	**69%**	**74:26**
10	**Adamantane-1-carboxylic acid**	**67%**	**73:27**

[a] Reaction conditions: PhNHAc (**1a**; 0.2 mmol), NCS (0.26 mmol), acid (0.1 mmol), toluene (1 mL), r.t., under air.
[b] n.r. = no reaction.

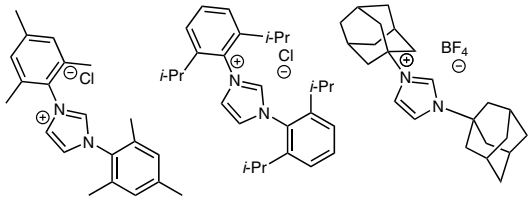
Table 2 Screening of Reaction Conditions: Solvents and Additives[a]



1a **2a** **2a'**



3 **4** **5**



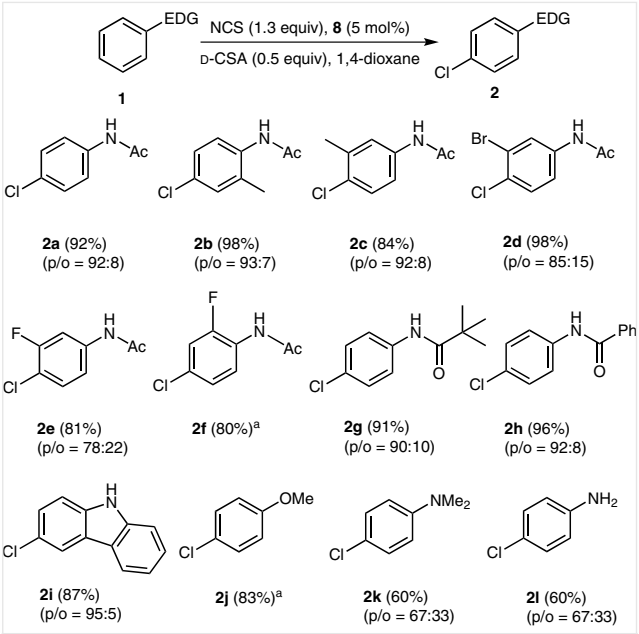
6 **7** **8**

Entry	Solvent	Additive	Yield (%)	Ratio[b] **2a**/**2a'**
1	toluene	–	69	74:26
2	DCE	–	quant	63:37
3	MeOH	–	60	64:36
4	DMF	–	38	69:31
5	MeCN	–	55	70:30
6	THF	–	15	67:33
7	1,4-dioxane	–	55	76:24
8	1,4-dioxane	PPh_3	80	88:12
9	1,4-dioxane	dppf	51	82:18
10	1,4-dioxane	d(^{t}BuPy)[c]	89	84:16
11	1,4-dioxane	TMEDA	32	74:26
12	1,4-dioxane	pyridine	51	81:19
13	1,4-dioxane	BINAP	94	79:21
14	1,4-dioxane	**3**	90	88:12
15	1,4-dioxane	**4**	74	83:17
16	1,4-dioxane	**5**	80	84:16
17	1,4-dioxane	**6**	81	90:10
18	1,4-dioxane	**7**	89	89:11
19	**1,4-dioxane**	**8**	**92**	**92:8**
20	1,4-dioxane	Bu_4NOAc	89	88:12

[a] Reaction conditions: PhNHAc (**1a**; 0.2 mmol), NCS (0.26 mmol), D-CSA (0.1 mmol), additive (0.01 mmol, 5 mol%), solvent (1 mL), r.t., under air.
[b] Determined by GC–MS.
[c] 4,4′-Di-*tert*-butyl-2,2′-bipyridine.

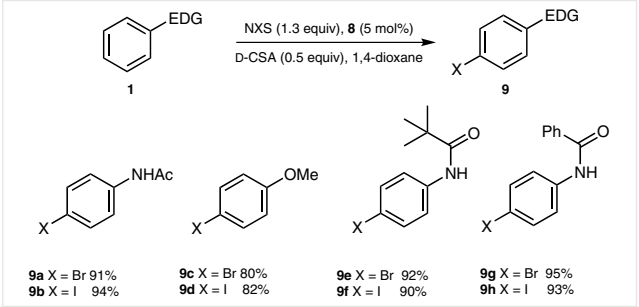
phine) (dppf; entry 9) was used as the additive, the chloroarenes **2a** and **2a′** were isolated in good yields with a high selectivity toward the former, with ratios of 88:12 and 82:18, respectively. The nitrogen-containing additives 4,4′-di-*tert*-butyl-2,2′-bipyridine [d(^{t}BuPy), entry 10], *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA, entry 11), and pyridine (entry 12) also provided the products with reasonably good selectivity. Interestingly, when the imidazolium salts **3**–**8** were investigated, the reactions gave high yields with good to excellent selectivities (entries 14–19). The simple methyl-substituted imidazolium salt **3** gave the isomeric chloroanilides in good yield and with good selectivity (entry 14). Similar results were obtained with the other imidazolium salts. In particular, imidazolium salt **8** gave the desired product **2a** in excellent yield (92%) and with excellent 92:8 selectivity in favor of the *para*-isomer (entry 19). The reaction in the presence of the phase-transfer catalyst tetrabutylammonium acetate (entry 20) also gave the desired product in good yield and with good regioselectivity.[8]

Having identified the optimal conditions, we evaluated the scope and limitations of this method (Scheme 2).[9] Acetanilides **1a**–**e** were good substrates for this type of transformation, giving the corresponding chlorinated products **2a**–**e** in good to excellent yields and with excellent regioselectivities. The reaction with a more hindered anilide was also successful; chloroanilide **2g** was isolated in an excellent 91% yield with 90:10 regioselectivity in favor of the *para*-substituted product. Carbazole **2i** was also successfully obtained; the corresponding isomeric *ortho*-substituted carbazole was a minor product in this reaction. However, the reactions with less coordinating electron-rich arenes were less successful; although the overall reaction yields were good, only moderate selectivity was observed for **2k** and **2l**, due to weak coordination by the secondary and primary amine groups, respectively.



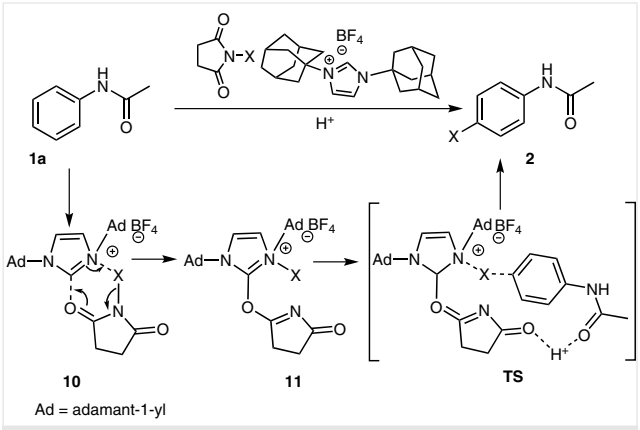
Scheme 2 Synthesis of *para*-chlorinated arenes. *Reagents and conditions*: arene **1** (0.2 mmol), NCS (0.26 mmol), D-CSA (0.1 mmol), imidazolium salt (0.01 mmol), 1,4-dioxane (1 mL), r.t., under air. All product ratios were measured by GC–MS. [a] Single regioisomer observed by GC–MS.

Next, we examined the corresponding bromination and iodination reactions. Both transformations were successful when anilides or methoxybenzenes were used, and the corresponding aryl bromides and iodides **9a**–**h** were isolated in 80–95% yield. (Scheme 3) Interestingly, excellent regioselectivities (*para*/*ortho* >98:2) were observed by ^{1}H NMR spectroscopic analyses of the crude reaction mixtures.



Scheme 3 Synthesis of bromo- and iodoarenes

With respect to the roles of the acid and imidazolium salt, by taking anilide **1a** as an example, we propose that preliminary coordination of the *N*-halosuccinimide (NXS) with the imidazolium salt **8** results in the formation of a complex **10**, which subsequently rearranges to give the intermediate **11** (Scheme 4). Transition state **TS** is then formed, which leads to the final product **2** in a *para*-selective fashion that avoids steric repulsion at the *ortho*-position. During the formation of **TS**, the added acid is hydrogen-bonded to both the acetyl group of the anilide and one carbonyl group of NXS, and the resulting interaction of the imidazolium salt with NXS delivers the halogen to the remote position of the anilide, avoiding reaction at the *ortho*-position.



Scheme 4 A plausible reaction pathway

In conclusion, we have developed a practical synthesis for the preparation of halogenated arenes by selective *para*-substitution in the presence of an imidazolium salt. A series of electron-rich aryl chlorides were successfully prepared under mild conditions. Further experimental and computational studies to elucidate the reaction mechanism are in progress.

Acknowledgment

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1560376.

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(8) Makosza, M. *Pure Appl. Chem.* **2009**, *72*, 1399.
(9) **Chloroarenes 2a–j; General Procedure**
A mixture of anilide or ether **1** (0.2 mmol), NCS (0.26 mmol), D-CSA (0.1 mmol), and imidazolium salt **8** (0.01 mmol) in 1,4-dioxane (1 mL) was stirred at r.t. (25 °C) under air for 24 h. When the substrate was completely consumed (GC–MS), the reaction was quenched with sat. aq $NaHCO_3$ (4 mL), and the mixture was extracted with EtOAc (3 × 4 mL). The organic layer was washed with H_2O (3 × 4 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel).

***N*-(4-Chloro-2-methylphenyl)acetamide (2b)**
The general procedure gave a 93:7 mixture of products **2b** and **2b′** in 98% yield. **2b** was isolated as a white solid; yield: 33.4 mg (91%); mp 140–141 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.69 (d, *J* = 9.2 Hz, 1 H), 7.16 (d, *J* = 6.3 Hz, 2 H), 6.99 (br s, 1 H), 2.22 (s, 3 H), 2.19 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.4, 134.2, 131.1, 130.3, 130.3, 126.7, 124.5, 24.3, 17.7. HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_9H_{11}{}^{35}ClNO$: 184.0524; found: 184.0520.

***N*-(3-Bromo-4-chlorophenyl)acetamide (2d) and *N*-(3-Bromo-2-chlorophenyl)acetamide (2d′)**
The general procedure gave an 85:15 mixture of the products **2d** and **2d′** in 98% yield.
2d: White solid; yield: 41.4 mg (83%); mp 118–119 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.87 (d, *J* = 2.1 Hz, 1 H), 7.51 (br s, 1 H), 7.38 (dt, *J* = 15.8, 5.4 Hz, 2 H), 2.18 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.4, 137.2, 130.3, 129.5, 124.6, 122.5, 119.7, 24.5. HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_8H_8Br^{79}Cl^{35}NO$: 247.9472; found: 247.9468.
2d′: White solid; yield: 7.3 mg (15%); mp 118–119 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.62 (s, 1 H), 7.65–7.45 (m, 1 H), 7.22 (d, *J* = 8.5 Hz, 1 H), 7.17 (dd, *J* = 8.5, 2.1 Hz, 1 H), 2.25 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.4, 137.3, 130.3, 129.5, 124.6, 122.5, 119.7, 24.5. HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_8H_7Br^{79}Cl^{35}NO$: 247.9472; found: 247.9467.