**Abstract:** The Brønsted-acidic ionic liquid 1-methyl-3-(4-sulfobutyl)imidazolium triflate ([BMIM(SO$_3$H)][OTf]) was demonstrated to act efficiently as solvent and catalyst for the halogenation of activated organic compounds with N-halosuccinimides (NXS) under mild conditions with short reaction times. Methyl aryl ketones were converted into α-halo and α,α-dihaloketones, depending on the quantity of NXS used. Ketones with activated aromatic rings were selectively halogenated, however in some cases mixtures of α-halogenated ketone and ring-halogenated ketones were obtained. Activated aromatics were regioselectively ring halogenated to give mono- and dihalo-substituted products. The [BMIM(SO$_3$H)][OTf] ionic liquid (IL-A) was successfully reused eight times in a representative monohalogenation reaction with no noticeable decrease in efficiency. An effective halogenation scale-up in this IL is also presented. The reactivity trend and the observed chemo- and regioselectivities point to an ET process in these IL-promoted halofunctionalization reactions.
1. Introduction

Halogenated organic compounds are highly versatile starting materials and intermediates in organic and organometallic chemistry and their production has been under constant investigation. The topic has been extensively reviewed [1–4]. Halogenation reactions are often associated with extensive waste production and relatively high process costs. Increasing environmental and climate changes urge the development of safer and “greener” synthetic pathways at reduced costs. The main reaction waste is usually the organic solvent used as reaction medium; moreover volatile organics have severe environmental and health issues.

N-halosuccinimides are very popular as halogen-transfer reagents [5–9]; however they are usually not reactive enough for direct halogenation and require a Lewis acid or a Brønsted acid catalyst. The catalysts employed are usually moisture sensitive, they are often metallic or strongly acidic, produce toxic waste, and are costly.

Halogenation of aromatic compounds in different ILs has been recently reviewed [10,11] and further studied [12]. Fluorination of arenes with F-TEDA-BF₄ was examined in imidazolium-ILs [13]. Other earlier studies include chlorination of aromatics with trichloroisocyanuric acid in IL-A (Figure 1) [14], oxidative chlorination with HCl in [Hmim][NO₃] [15], bromination of aromatics in tribromide-based ILs [16–19], iodination with I₂/H₂O₂ in BMIM-IL [20], I₂/F-TEDA-BF₄ in imidazolium- and pyridinium-IL, also with I₂ or MeI/Koser’s reagent in BMIM-IL [21], iodination of alcohols in [Hmim][HSO₄] [22], and with N-iodosaccharin [23].

Brønsted-acidic ionic liquids such as [BMIM(SO₃H)][OTf] [24] (IL-A) have attracted considerable attention as dual solvent/catalysts and were employed in diverse acid-catalyzed transformations [25–30].

Figure 1. Structure of investigated imidazolium-based ionic liquids IL-A and IL-B.

In continuation of our previous studies on application of ionic liquids as solvents and catalysts in synthesis [31–43], we report on the utility of IL-A for halofunctionalization of organic molecules with NXS reagents.

2. Results and Discussion

Halogenation of acetophenone (1) with NIS, NBS and NCS was studied in IL-A and IL-B (Figure 1), and α-halogenation took place with all three reagents (Table 1). Iodination of 1 with 1.1 equiv. of NIS
at 55 °C gave 2a with significantly higher conversion in IL-A than in IL-B; albeit with slightly lower selectivity (Table 1, entries 1 and 2). Similar results were obtained in bromination with NBS (entries 3 and 4). Bromination with 2.2 equiv. of NBS in IL-A resulted in quantitative dibromination, whereas in IL-B only monobromination took place (entries 5 and 6). Chlorofunctionalization with 1.1 equivalents of NCS in the both IL-A and IL-B gave 2c as the main product; whereas regioselectivity in IL-A changed after prolonged heating and 3c was obtained as the major product (entries 7–9). Reaction with 2.2 equiv. of NCS in IL-B gave 2c as major and 3c as minor products, whereas 3c was formed exclusively in IL-A (entries 10 and 11). The results confirm the superior catalytic effect of the Brønsted acidic IL-A.

### Table 1. Halogenation of acetophenone 1 with N-halosuccinimides (NXS) in 1-butyl-3-methylimidazolium based ionic liquids a.

| Entry | X   | NXS (equiv.) | IL | T (°C) | Reaction time (min) | Conversion of 1 b (%) | 2 / 3 |
|-------|-----|--------------|----|--------|---------------------|-----------------------|-------|
| 1     | I   | 1.1          | IL-B | 55     | 10                  | 13                    | 100 / 0 |
| 2     | I   | 1.1          | IL-A | 55     | 10                  | 98                    | 93 / 7 |
| 3     | Br  | 1.1          | IL-B | 55     | 20                  | 22                    | 100 / 0 |
| 4     | Br  | 1.1          | IL-A | 55     | 20                  | 95                    | 86 / 14 |
| 5     | Br  | 2.2          | IL-B | 70     | 30                  | 60                    | 100 / 0 |
| 6     | Br  | 2.2          | IL-A | 70     | 30                  | 100                   | 0 / 100 |
| 7     | Cl  | 1.1          | IL-B | 70     | 30                  | 97                    | 85 / 15 |
| 8     | Cl  | 1.1          | IL-A | 70     | 30                  | 47                    | 90 / 10 |
| 9     | Cl  | 1.1          | IL-A | 70     | 90                  | 63                    | 15 / 85 |
| 10    | Cl  | 2.2          | IL-B | 70     | 30                  | 92                    | 91 / 9 |
| 11    | Cl  | 2.2          | IL-A | 70     | 30                  | 100                   | 0 / 100 |

*a Reaction conditions: 1 mmol of 1, 1.1 or 2.2 mmol of NXS stirred in 3 mmol of IL; b Conversion determined by 1H-NMR.

Focusing on the effect of the structure of aryl methyl ketones 4 on halogenation with N-halosuccinimides in IL-A (Table 2), compound 4a was selectively converted into its α-iodo derivative 5a (entry 1). Functionalization of 4a with 1.1 equiv. of NBS was less selective, furnishing α-bromo- and α,α-dibromo- substituted ketones 6a and 7a (entry 2), while reaction with 2.2 equiv of NBS yielded 7a in excellent yield (entry 3). Chlorination with 2.2 equiv. of NCS selectively produced the α,α-dichloroketone 8a (entry 4).

Halogenation of 2-acetylthiophene (4b) yielded the α-iodoketone 5b regioselectively (entry 5). Reaction of 4b with NBS (1.1 equiv.) exhibited a similar level of selectivity as with 4a, forming the mono- and dibrominated products 6b and 7b (entry 6), and with 2.2 equiv. of NBS 7b in high yield. Functionalization with 2.2 equiv. of NCS selectively furnished the α,α-dichloroketone 8b (entry 8). Compound 4c was regioselectively converted to its α-iodoketone 5c with NIS in high yield (entry 9). Bromination with NBS was somewhat less selective than in the previous cases giving a mixture of
α-bromo and α,α-dibromoketones 6c and 7c (entry 10), while with 2.2 equiv. of NBS 7c was selectively obtained in high yield (entry 11). The reaction temperatures were in 55–70 °C range, depending on the reactivity of the NXS reagent, and the reaction times varied from 10 to 150 minutes. It is noteworthy that no ring functionalization products were formed with ketones 4a, 4b and 4c, despite the additional activation of the aromatic ring with an EDG functionalization, which was obviously not enough for acetyl group deactivation of the aromatic part of the target.

**Table 2.** The effect of aryl methyl ketone 4 structure on halofunctionalization with N-halosuccinimides (NXS) in [BMIM(SO3H)][OTf] (IL-A).

| Entry | Ar | Reaction conditions | Products | Yield (%) b |
|-------|----|---------------------|----------|-------------|
| 1     | 4a | NIS (1.1) / 55 / 10 | 5a        | 94 (84)     |
| 2     | 4a | NBS (1.1) / 55 / 20 | 6a / 7a   | 72 (66) 19 (18) |
| 3     | 4a | NBS (2.2) / 70 / 60 | 7a        | 96 (94)     |
| 4     | 4a | NCS (2.2) / 70 / 150| 8a        | 97 (86)     |
| 5     | 4a | NIS (1.1) / 55 / 10 | 5b        | 91 (80)     |
| 6     | 4b | NBS (1.1) / 55 / 10 | 6b / 7b   | 75 (72) 16 (15) |
| 7     | 4b | NBS (2.2) / 70 / 30 | 7b        | 95 (85)     |
| 8     | 4b | NCS (2.2) / 70 / 60 | 8b        | 96 (67)     |
| 9     | 4c | NIS (1.1) / 55 / 10 | 5c        | 92 (80)     |
| 10    | 4c | NBS (1.1) / 55 / 20 | 6c / 7c   | 71 (62) 22 (20) |
| 11    | 4c | NBS (2.2) / 70 / 30 | 7c        | 100 (91)    |

*Reaction conditions: 1 mmol of 4, 1.1 or 2.2 mmol of NXS stirred in 3 mmol of IL-A at 55–70 °C for 10 to 150 min; b Relative yields determined by 1H-NMR, values in the brackets refer to the yields of isolated pure products.*

Halofunctionalization of 4c with excess of NCS was studied in IL-A at 70 °C (Scheme 1). With 2.2 equiv. of NCS a mixture of 2,2-dichloro-1-(p-anisyl)ethanone (8c) and 2,2-dichloro-1-(3-chloro-4-methoxyphenyl)ethanone (9) was obtained in 58:42 ratio, respectively, and with 3.3 equiv. of NCS selectively compound 9 was formed in high yield as the sole product.
Scheme 1. Chlorination of 4′-methoxyacetophenone (4c) with NCS.

In the next phase of this study halofunctionalization of isomeric dimethoxyacetophenones 10, 14, 18 and trimethoxyacetophenone 25 were examined (Schemes 2–4). Transformation of 10 with 1.1 equiv. of NBS furnished a mixture of α-bromoketone 12 and α,α-dibromo derivative 13, whereas with 2.2 equivalents of NBS, 13 was obtained as a sole product in high yield. Compound 10 was regioselectively converted into the α-iodoketone 11 with 1.1 equiv. NIS in good yield (Scheme 2).

Scheme 2. Halofunctionalization of 3′,4′-dimethoxyacetophenone (10) and 2′,4′-dimethoxyacetophenone (14) with NXS reagents in [BMIM(SO3H)][OTf] (IL-A) medium.

Reaction conditions: 1 mmol of ketone, NXS (1.1 or 2.2 mmol) stirred in 3 mmol of IL-A at 55 °C for 10–60 min. Relative yields determined by 1H-NMR. Values in brackets refer to the yields of isolated pure products.

Isomeric 2′,4′-dimethoxyacetophenone (14) exhibited different selectivity in reaction with 1.1 equiv. of NIS, forming a mixture of the α-iodoketone 15 as the major product along with 1-acetyl-5-iodo-2,4-dimethoxybenzene (16) and 2-iodo-1-(5-iodo-2,4-dimethoxyphenyl)ethanone (17) as minor products (Scheme 2). 2′,6′-Dimethoxyacetophenone (18) exhibited a similar reactivity trend as 14. Functionalization of 18 with 4.4 equiv. of NCS in IL-A selectively furnished 2,2-dichloro-1-(3,5-dichloro-2,6-dimethoxyphenyl)ethanone (21) in a good yield (Scheme 3). Reaction of 18 with 1.1
equiv. of NIS furnished a mixture of α-iodoketone 19 as major, and 2-iodo-1-(3-iodo-2,6-dimethoxyphenyl)ethanone (20) as minor product. Functionalization of 18 with 1.1 equiv. of NBS yielded the 3-bromo derivative 22 (as the main product), along with 2-bromo-1-(3-bromo-2,6-dimethoxyphenyl)ethanone (23) and 2,2-dibromo-1-(3,5-dibromo-2,6-dimethoxyphenyl)ethanone (24) as minor products. A similar reactivity trend was observed with 2.2 equiv. of NBS, forming 22 and 24 (but 23 was not formed). When 4.4 equiv. of NBS was employed, the tetrabromo-derivative 24 was isolated as the sole product in good yield.

Scheme 3. Halofunctionalization of 2′,6′-dimethoxyacetophenone (18) with NXS reagents in [BMIM(SO3H)][OTf] (IL-A) medium a.

2′,3′,4′-Trimethoxyacetophenone (25) was rapidly (within minutes) converted to the α-iodo derivative 26 with 1.1 equiv. of NIS (Scheme 4). Reaction of 25 with NBS gave a mixture of up to four compounds, depending on the quantity of the NBS. With 1.1 equiv. of NBS the α-bromoketone 27 was the main product, and α,α-dibromoketone 28, 2-bromo-1-(5-bromo-2,3,4-trimethoxyphenyl)ethanone (29) and tribromo-substituted ketone 30 were the minor products. With 2.2 equiv. of NBS 29 and 30 were the only isolated products (27 and 28 were not observed). Reaction of 25 with 3.3 equiv. of NBS exclusively yielded 30 in excellent yield (see Scheme 4).

To explore the potential utility of NXS/IL-A system in ring halogenation of activated arenes, halofunctionalization of anisole (31), 1,3-dimethoxybenzene (34), toluene (37), and 2-methylthiophene (40) were examined (Scheme 5).

Reaction of anisole (31) with 1.1 equiv. of NXS was highly para-selective, forming the corresponding iodo- 32a, bromo- 32b and chloro-derivative 32c (in 84-78% isolated yields) with no ortho-substitution being observed. Reaction of 31 with 2.2 equiv. of NXS selectively produced 2,4-dihaloanisoles 33a–c in high yields.
Scheme 4. Halofunctionalization of 2',3',4'-trimethoxyacetophenone (25) with NXS reagents in [BMIM(SO$_3$H)][OTf] (IL-A) medium $^a$.

\begin{align*}
&\begin{array}{cc}
\text{25} & \text{26} \\
\text{MeO} & \text{MeO}
\end{array}
\end{align*}

$^a$ Reaction conditions: 1 mmol of 25, NXS (1.1, 2.2 or 3.3 mmol) stirred in 3 mmol of IL A at 55 or 70 °C for 10–120 min. Relative yields determined by $^1$H-NMR. Values in brackets refer to the yields of isolated pure products.

Scheme 5. Transformation of activated aromatic molecules with $N$-halosuccinimides (NXS) in [BMIM(SO$_3$H)][OTf] (IL-A) $^a$.

\begin{align*}
&\begin{array}{cc}
\text{31} & \text{32a} \\
\text{MeO} & \text{X} = \text{I (84%)}
\end{array}
\end{align*}

$^a$ Reaction conditions: 1 mmol of substrate, NXS (1.1, 2.2 or 3.3 mmol) stirred in 3 mmol of IL A at 55 or 70 °C for 0.17–3 h. Relative yields determined by $^1$H-NMR. Values in brackets refer to the yields of isolated pure products.
1,3-Dimethoxybenzene (34) was transformed with 2.2 equiv. of NIS, NBS and NCS into 2,4-dihalo-1,5-dimethoxybenzenes 35a–c in high yields. Transformation of 34 with 3.3 equiv. of NCS led to a dearomatization of the target molecule and the formation of 2,4,4-trichloro-5-methoxycyclohexa-2,5-dienone (36) in 84% yield. This compound is the result of chlorination of aromatic ring resulting primarily in 35c and further regioselective 1,4-addition-elimination process following ipso-chlorination and demethylation of the para-methoxy group, what was confirmed by an independent experiment and the structure of 36 unequivocally distinguished from the possibly formed isomeric 4,6,6-trichloro-3-methoxycyclohexa-2,4-dienone using 2D-NMR measurement techniques HSQC and HMBC (Figure 2). The also expected 1,3,5-trichloro-2,4-dimethoxybenzene was not formed probably because of substantial sterical hindrance between the two methoxy substituents on the aromatic ring.

**Figure 2.** Copies of 2D-NMR spectra for 2,4,4-trichloro-5-methoxycyclohexa-2,5-dienone (36).

Halogenation of toluene (37) with 1.1 equiv. of NXS gave 4- and 2-halotoluene. The ortho/para ratio with NIS was 42:58, whereas with NBS and NCS this ratio changed in favor of the ortho-isomer. A similar regioselectivity was reported in halogenation of toluene with NBS and NCS in the presence of FeCl₃ [5].
2-Methylthiophene (40) was selectively converted into its 5-iodo derivative 41 in high yield with 1.1 equiv. of NIS. Reaction of 40 with NCS and NBS were also carried out successfully, however the isolated yields were low due to the volatility of the products.

Having discovered these highly efficient halofunctionalization reactions we then explored the possibility to make the process more economical through recycling and reuse of the IL. To explore this possibility, halogenation of acetophenone (1) with 1.1 equiv. of NIS was selected as a prototype reaction and the reaction was successfully repeated in reused/recycled IL-A for 8 cycles (Table 3) with no notable decrease in the conversions. To address the question of relative reactivity of the NXS reagent versus recycling and reuse, bromofunctionalization of 1 with 2.2 equivalents of NBS was examined (Table 3) over 5 repeated cycles, showing a gradual decrease in the dibromo derivative 3b with concomitant increase in monobromo product 2b. The data underscores the importance of IL-A as a promoter in these halogen-transfer reactions.

Table 3. The effect of [BMIM(SO3H)][OTf] (IL-A) recycling on transformation of acetophenone 1 with NXS reagents.

| Repetition number | Yield (%) |
|------------------|-----------|
| 1                | 86        |
| 2                | 90        |
| 3                | 90        |
| 4                | 88        |
| 5                | 90        |
| 6                | 89        |
| 7                | 87        |
| 8                | 92        |

Finally to explore the feasibility to perform these reactions on larger scales than reported thus far, bromination of 1 was carried out on a 9 mmol scale (a 9 fold increase), by using 19.8 mmols of NBS,
and 27 mmol of IL-A. The 2,2-dibromo-1-phenylethanone 3b was obtained in 90% isolated yield after 40 minutes at 70 °C.

Concerning a plausible mechanism for halofunctionalization with NXS/[BMIM(SO3H)][OTf] systems, previous studies [44–47] have shown that ring halogenations of activated aromatics with NIS, NBS and NCS proceed through an electron transfer (ET) pathway as the main reaction channel. Based on the fact that in the present study under the reaction conditions employed only activated aromatics could be halogenated, and considering the observed chemo- and regioselectivity patterns, in all probability the ET reaction pathway is also most likely operating in these reactions. The role of acidic IL as a catalyst is to enhance the electrophilic character of NXS reagents by additional polarization of N-X bond. In halogenation of phenyl methyl ketones the acidic IL could also act as enolization catalyst, accelerating electrophilic addition of halogen. With the studied ketones, side chain halogenation is the primary event with ring halogenation manifesting only when the ring is highly activated (two methoxy groups).

3. Experimental

3.1. General

All chemicals were purchased from commercial sources and used without further purification. Column chromatography was carried out using silica gel 60 (particle size: 0.063–0.2 mm) and preparative thin layer chromatography using PLC Silica gel 60 F254, 2 mm plates. Melting points were obtained with a Büchi 535 apparatus. For obtaining IR spectra on FTS3000-MX spectrometer, either a KBr pellet of the product was made or NaCl plates were used based on the physical state of product. NMR spectra were recorded on a Bruker Avance 300 DPX instrument (1H: 300 MHz, 13C: 75.5 MHz). The 1H spectra were referred to an internal standard (0 ppm for TMS) or to the residual 1H signal of CHCl3 at 7.26 ppm and for CD3COCD3 at 2.05 ppm (central line). The 13C spectra were referred to the residual signal of CDCl3 (77.0 ppm, central line) or CD3COCD3 (30.8 ppm, central line). Elemental analysis was performed on a Perkin-Elmer 2400-Series 2 apparatus.

3.2. Representative Procedure for Halogenation of Aromatic Compounds

To a stirred mixture of the aromatic compound (1 mmol) in ionic liquid (3 mmol), N-halo-succinimide (1.1–4.4 mmol) was added. The reaction mixture was stirred at 55, 70 or 85 °C until completion (monitored by TLC). The mixture was cooled to room temperature and washed three times with dichloromethane. The combined organic fractions were washed with aqueous Na2S2O3 and NaHCO3, dried over anhydrous Na2SO4 and filtered. Solvent was removed under reduced pressure and the crude reaction mixture was analyzed by 1H-NMR. Isolation of products from reaction mixtures was accomplished by preparative TLC or column chromatography and pure compounds were analyzed by NMR, MS and IR spectroscopy. Data for known compounds were verified from the literature while the new compounds were completely verified by spectroscopic data and C, H, N elemental analysis.

2-Iodo-1-phenylethanone (2a). One mmol of substrate, 3 mmol IL-A, 1.1 mmol NIS, r.t. = 10 min, 55 °C, preparative chromatography SiO2, hexane/CH2Cl2 = 2.5/7.5, orange oil (86%), mp: lit [48] 33–35 °C;
**Molecules 2013, 18**

1H-NMR (CDCl$_3$): δ 8.03–7.97 (m, 2H), 7.64–7.57 (m, 1H), 7.54–7.45 (m, 2H), 4.37 (s, 2H); IR(NaCl): 3059, 2976, 2938, 1674, 1595, 1449, 1418, 1271, 1173, 1105, 1001, 791, 747, 703 cm$^{-1}$; MS (ESI): 247.0 (M+H)$^+$.  

**2-Bromo-1-phenylethanone (2b).** One mmol of substrate, 3 mmol IL-A, 1.1 mmol NBS, r.t. = 20 min, 55 °C, preparative chromatography, SiO$_2$, hexane/CH$_2$Cl$_2$ = 2.5/7.5, white solid (73%), mp: 46.8–48.2 °C (lit [49] 48.8–49.3 °C); 1H-NMR (CDCl$_3$): δ 8.02–7.97 (m, 2H), 7.66–7.57 (m, 1H), 7.55–7.45 (m, 2H), 4.46 (s, 2H); IR (KBr): 3058, 3002, 2951, 1694, 1593, 1447, 1397, 1209, 1198, 999, 769, 746, 685, 623 cm$^{-1}$; MS (ESI): 199.0 (M+H)$^+$, 201.0 (M+2+H)$^+$.  

**2-Chloro-1-phenylethanone (2c).** One mmol of substrate, 3 mmol IL-B, 1.1 mmol NCS, r.t. = 30 min, 70 °C, preparative chromatography SiO$_2$, hexane/CH$_2$Cl$_2$ = 2.5/7.5, white solid (74%), mp: 53.2–54.4 °C (lit [50] 55 °C); 1H-NMR (CDCl$_3$): δ 8.00–7.93 (m, 2H), 7.66–7.58 (m, 1H), 7.55–7.46 (m, 2H), 4.71 (s, 2H); IR (neat): 2951, 1692, 1595, 1580, 1448, 1397, 1209, 999, 769, 746, 685, 640 cm$^{-1}$; MS (ESI): 155.0 (M+H)$^+$, 157.0 (M+2+H)$^+$.  

**2,2-Dibromo-1-phenylethanone (3b).** One mmol of substrate, 3 mmol IL-A, 2.2 mmol NBS, r.t. = 30 min, 70 °C, CC SiO$_2$, CH$_2$Cl$_2$, white solid (82%), mp: 31.5–32.9 °C (lit [51] 33.5–34.5 °C); 1H-NMR (CDCl$_3$): δ 8.13–8.04 (m, 2H), 7.69–7.60 (m, 1H), 7.57–7.46 (m, 2H), 6.70 (s, 1H); IR (KBr): 1693, 1587, 1445, 1267, 1198, 983, 797, 705, 678, 625 cm$^{-1}$; MS (ESI): 276.9 (M+H)$^+$, 278.9 (M+2+H)$^+$, 280.9 (M+4+H)$^+$.  

**2,2-Dichloro-1-phenylethanone (3c).** One mmol of substrate, 3 mmol IL-A, 2.2 mmol NCS, r.t. = 120 min, 70 °C, CC SiO$_2$, CH$_2$Cl$_2$, yellow oil (96%); 1H-NMR (CDCl$_3$): δ 8.13–8.06 (m, 2H), 7.69–7.62 (m, 1H), 7.57–7.49 (m, 2H), 6.68 (s, 1H); IR (NaCl): 3065, 3008, 1705, 1595, 1449, 1278, 1222, 1182, 990, 932, 810, 774, 685, 654 cm$^{-1}$; MS (ESI): 154.0 (M−Cl+H)$^+$, 156.0 (M−Cl+2+H)$^+$.  

**2-Iodo-1-(2-naphthyl)ethanone (5a).** One mmol of substrate, 3 mmol IL-A, 1.1 mmol NIS, r.t. = 10 min, 55 °C, preparative chromatography SiO$_2$, hexane/CH$_2$Cl$_2$ = 2.5/7.5, yellow solid (84%), mp: 87.5–90.2 °C (lit [53] 87–87.5 °C); 1H-NMR (CDCl$_3$): δ 8.54–8.51 (m, 1H), 8.06–7.96 (m, 2H), 7.94–7.87 (m, 2H), 7.67–7.54 (m, 2H), 4.49 (s, 2H); IR(KBr): 1661, 1622, 1464, 1368, 1285, 1231, 1144, 1123, 1094, 1020, 991, 866, 804, 750 cm$^{-1}$; MS (ESI): 297.0 (M+H)$^+$.

**2-Iodo-1-(2-thienyl)ethanone (5b).** One mmol of substrate, 3 mmol IL -A, 1.1 mmol NIS, r.t. = 10 min, 55 °C, preparative chromatography SiO$_2$, hexane/CH$_2$Cl$_2$ = 2.5/7.5, yellow oil (96%); 1H-NMR (CDCl$_3$): δ 7.80 (dd, J = 3.9 Hz, J = 1.0 Hz, 1H), 7.69 (dd, J = 4.9 Hz, J = 1.0 Hz, 1H), 7.16 (dd, J = 4.9 Hz, J = 3.9 Hz, 1H), 4.30 (s, 2H); IR (NaCl): 3089, 3036, 2972, 2936, 1650, 1514, 1412, 1355, 1280, 1164, 1099, 1061, 963, 858, 727 cm$^{-1}$; MS (ESI): 252.9 (M+H)$^+$.  

**1-(p-Anisyl)-2-iodoethanone (5c).** One mmol of substrate, 3 mmol IL-A, 1.1 mmol NIS, r.t. = 10 min, 55 °C, preparative chromatography SiO$_2$, hexane/CH$_2$Cl$_2$ = 2.5/7.5, grey solid (80%), mp: 56.3–59.4 °C (lit [48] 57–59.5 °C); 1H-NMR (CDCl$_3$): δ 7.97 (d, J = 8.9 Hz, 2H), 6.95 (d, J = 8.9 Hz, 2H), 4.31 (s, 2H), 3.89 (s, 3H); IR (KBr): 3032, 2972, 1656, 1601, 1568, 1508, 1454, 1422, 1288, 1257, 1173, 1099, 1016, 1001, 845, 754 cm$^{-1}$; MS (ESI): 277.0 (M+H)$^+$.  

**1-(p-Anisyl)-2-iodoethanone**
2-Bromo-1-(2-naphthyl)ethanone (6a). One mmol of substrate, 3 mmol IL-A, 1.1 mmol NBS, r.t. = 20 min, 55 °C, preparative chromatography SiO2, hexane/CH2Cl2 = 2.5/7.5, grey solid (66%), mp: 80.3–82.2 °C (lit [55] 78–79.5 °C); 1H-NMR (CDCl3): δ 8.54–8.50 (m, 1H), 8.07–7.96 (m, 2H), 7.96–7.87 (m, 2H), 7.68–7.54 (m, 2H), 4.58 (s, 2H); IR (KBr): 2999, 2948, 1690, 1591, 1468, 1385, 1175, 1159, 1127, 1028, 853, 812, 740, 680 cm⁻¹; MS (ESI): 249.0 (M+H)⁺, 251.0 (M+2+H)⁺.

2-Bromo-1-(2-thienyl)ethanone (6b). One mmol of substrate, 3 mmol IL-A, 1.1 mmol NBS, r.t. = 10 min, 55 °C, preparative chromatography SiO2, hexane/CH2Cl2 = 2.5/7.5, yellow oil (72%), mp: lit [56] 31–33 °C; 1H-NMR (CDCl3): δ 7.81 (dd, J = 3.9 Hz, J = 1.0 Hz, 1H), 7.72 (dd, J = 4.9 Hz, J = 1.0 Hz, 1H), 7.17 (dd, J = 4.9 Hz, J = 3.9 Hz, 1H), 4.36 (s, 2H); IR (NaCl): 3098, 2942, 1652, 1514, 1412, 1287, 1194, 1061, 973, 939, 854, 727, 667 cm⁻¹; MS (ESI): 204.9 (M+H)⁺, 206.9 (M+2+H)⁺.

2-Bromo-1-(p-anisyl)ethanone (6c). One mmol of substrate, 3 mmol IL-A, 1.1 mmol NBS, r.t. = 20 min, 55 °C, preparative chromatography SiO2, hexane/CH2Cl2 = 2.5/7.5, pale red (62%), mp: 68.4–69.7 °C (lit [56] 69–71 °C); 1H-NMR (CDCl3): δ 7.97 (d, J = 8.9 Hz, 2H), 6.96 (d, J = 8.9 Hz, 2H), 4.40 (s, 2H), 3.89 (s, 3H); IR (KBr): 2938, 1688, 1597, 1510, 1326, 1263, 1208, 1167, 1115, 1016, 986, 745, 685 cm⁻¹; MS (ESI): 229.0 (M+H)⁺, 231.0 (M+2+H)⁺.

2,2-Dibromo-1-(2-naphthyl)ethanone (7a). One mmol of substrate, 3 mmol IL-A, 2.2 mmol NBS, r.t. = 60 min, 70 °C, CC SiO2, CH2Cl2, white solid (94%), mp: 78.1–80.7 °C (lit [57] 100–101.5 °C); 1H-NMR (CDCl3): δ 8.67–8.63 (m, 1H), 8.13–8.07 (m, 1H), 8.04–7.87 (m, 2H), 7.70–7.56 (m, 2H), 6.83 (s, 1H); IR (KBr): 1682, 1620, 1587, 1358, 1273, 1182, 1153, 820, 733, 632 cm⁻¹; MS (ESI): 326.9 (M+H)⁺, 328.9 (M+2+H)⁺, 330.9 (M+4+H)⁺.

2,2-Dibromo-1-(2-thienyl)ethanone (7b). One mmol of substrate, 3 mmol IL-A, 2.2 mmol NBS, r.t. = 30 min, 70 °C, preparative chromatography SiO2, hexane/CH2Cl2 = 2.5/7.5, orange oil (85%); 1H-NMR (CDCl3): δ 8.03–7.98 (m, 1H), 7.80–7.76 (m, 1H), 7.22–7.18 (m, 1H), 6.48 (s, 1H); IR (NaCl): 3098, 3013, 1669, 1512, 1411, 1354, 1279, 1179, 1065, 937, 858, 726, 665, 638 cm⁻¹; MS (ESI): 282.9 (M+H)⁺, 284.9 (M+2+H)⁺, 286.8 (M+4+H)⁺.

2,2-Dibromo-1-(p-anisyl)ethanone (7c). One mmol of substrate, 3 mmol IL-A, 2.2 mmol NBS, r.t. = 30 min, 70 °C, CC SiO2, CH2Cl2, white solid (91%), mp: 86.7–88.9 °C (lit [51] 93–94 °C); 1H-NMR (CDCl3): δ 8.08 (d, J = 9.0 Hz, 2H), 6.98 (d, J = 9.0 Hz, 2H), 6.66 (s, 1H), 3.90 (s, 3H); IR(KBr): 3032, 1674, 1597, 1566, 1504, 1420, 1314, 1263, 1202, 1177, 1146, 1020, 845, 810, 761, 706, 683 cm⁻¹; MS (ESI): 306.9 (M+H)⁺, 308.9 (M+2+H)⁺, 310.9 (M+4+H)⁺.

2,2-Dichloro-1-(2-naphthyl)ethanone (8a). One mmol of substrate, 3 mmol IL-A, 2.2 mmol NCS, r.t. = 150 min, 70 °C, CC SiO2, CH2Cl2, yellow solid (86%), mp: 66.6–69.8 °C (lit [59] 80–80.5 °C); 1H-NMR (CDCl3): δ 8.68–8.62 (m, 1H), 8.13–8.06 (m, 1H), 8.04–7.87 (m, 3H), 7.71–7.56 (m, 2H), 6.83 (s, 1H); IR (KBr): 3059, 1699, 1626, 1596, 1466, 1357, 1282, 1219, 1177, 1125, 866, 824, 785, 742, 657 cm⁻¹; MS (ESI): 239.0 (M+H)⁺, 241.0 (M+2+H)⁺.

2,2-Dichloro-1-(2-thienyl)ethanone (8b). One mmol of substrate, 3 mmol IL-A, 2.2 mmol NCS, r.t. = 90 min, 70 °C, preparative chromatography SiO2, hexane/CH2Cl2 = 3.5/6.5, orange oil [60]
(67%); δ 8.02 (dd, J = 3.9 Hz, J = 1.0 Hz, 1H), 7.80 (dd, J = 4.9 Hz, J = 1.0 Hz, 1H), 7.21 (dd, J = 4.9 Hz, J = 3.9 Hz, 1H), 6.47 (s, 3H); IR (NaCl): 3100, 3007, 1682, 1512, 1409, 1356, 1277, 1240, 1217, 1188, 1067, 944, 858, 802, 720, 668 cm⁻¹; MS (ESI): 194.9 (M+H)⁺.

2,2-Dichloro-1-(p-anisyl)ethanone (8c). One mmol of substrate, 3 mmol IL-A, 2.2 mmol NCS, r.t. = 90 min, 70 °C, preparative chromatography SiO₂, hexane/CH₂Cl₂ = 3.5/6.5, white solid (36%), mp: 76.9–78.2 °C (lit [61] 78–79 °C); δ 8.08 (d, J = 8.9 Hz, 2H), 6.99 (d, J = 8.9 Hz, 2H), 6.63 (s, 1H), 3.90 (s, 3H); IR (KBr): 3028, 1683, 1600, 1568, 1506, 1422, 1318, 1298, 1265, 1236, 1175, 1024, 847, 795, 745, 646 cm⁻¹; MS (ESI): 219.0 (M+H)⁺, 221 (M+2+H)⁺.

2,2-Dichloro-1-(3-chloro-4-methoxyphenyl)ethanone (9). One mmol of substrate, 3 mmol IL-A, 3.3 mmol NCS, r.t. = 180 min, 70 °C; preparative chromatography SiO₂, hexane/CH₂Cl₂ = 2.5/7.5; white solid (76%); mp: 99.3–100.9 °C; δ 8.14 (d, J = 2.3 Hz, 1H), 8.05 (dd, J = 8.8 Hz, J = 2.3 Hz, 1H), 7.02 (d, J = 8.8 Hz, 1H), 6.57 (s, 1H), 4.00 (s, 3H); δC-NMR (CD₃COCD₃): 185.7, 161.9, 133.1, 132.5, 127.0, 124.6, 114.3, 70.0, 58.2; IR (KBr): 2982, 1686, 1591, 1508, 1318, 1281, 1227, 1148, 1065, 1009, 824, 797, 750, 700, 631 cm⁻¹; MS (ESI): 253.0 (M+H)⁺, 255.0 (M+2+H)⁺; HRMS: calcd for C₉H₇Cl₃O₂: 252.9590; found: 252.9601; Anal. Calcd for C₉H₇Cl₃O₂: C, 42.64; H, 2.78. Found: C, 42.92; H, 2.72.

2-Iodo-1-(3,4-dimethoxyphenyl)ethanone (11). One mmol of substrate, 3 mmol IL-A, 1.1 mmol NIS, r.t. = 15 min, 55 °C, preparative chromatography SiO₂, CH₂Cl₂, yellow solid (69%), mp: 62.0–65.0 °C (lit [62] 65.2–66.2 °C); δ 7.62 (dd, J = 8.4 Hz, J = 2.0 Hz, 1H), 7.55 (d, J = 2.0 Hz, 1H), 6.90 (d, J = 8.4 Hz, 1H), 4.33 (s, 2H), 3.97 (s, 3H), 3.95 (s, 3H); IR (KBr): 2934, 2837, 1652, 1583, 1514, 1451, 1425, 1273, 1231, 1154, 1095, 1019, 877, 810, 768, 748, 617 cm⁻¹; MS (ESI): 307.0 (M+H)⁺.

2-Bromo-1-(3,4-dimethoxyphenyl)ethanone (12). One mmol of substrate, 3 mmol IL-A, 1.1 mmol NBS, r.t. = 60 min, 55 °C; preparative chromatography SiO₂, CH₂Cl₂, white solid (63%), mp: 80.5–81.6 °C (lit [63] 80–81 °C); δ 7.62 (dd, J = 8.4 Hz, J = 1.9 Hz, 1H), 7.55 (d, J = 1.9 Hz, 1H), 6.91 (d, J = 8.4 Hz, 1H), 4.41 (s, 2H), 3.97 (s, 3H), 3.95 (s, 3H); IR (KBr): 2966, 2940, 2843, 1682, 1586, 1515, 1466, 1420, 1283, 1244, 1155, 1020, 868, 798, 769, 683, 619 cm⁻¹; MS (ESI): 259.0 (M+H)⁺, 261.0 (M+2+H)⁺.

2,2-Dibromo-1-(3,4-dimethoxyphenyl)ethanone (13). One mmol of substrate, 3 mmol IL-A, 2.2 mmol NBS, r.t. = 120 min, 70 °C; column chromatography SiO₂, CH₂Cl₂; white solid (87%); mp: 79.0–81.7 °C; δ 7.74 (dd, J = 8.4 Hz, J = 2.0 Hz, 1H), 7.62 (d, J = 2.0 Hz, 1H), 6.92 (d, J = 8.4 Hz, 1H), 6.69 (s, 1H), 3.98 (s, 3H), 3.95 (s, 3H); δC-NMR (CD₃COCD₃): 186.8, 156.9, 151.6, 126.2, 125.4, 113.7, 112.8, 57.4, 57.3, 43.3; IR (KBr): 3017, 2967, 2933, 2837, 1676, 1587, 1518, 1454, 1416, 1350, 1279, 1238, 1190, 1155, 1016, 881, 800, 756, 689, 621 cm⁻¹; MS (ESI): 336.9 (M+H)⁺, 338.9 (M+2+H)⁺, 340.9 (M+4+H)⁺; HRMS: calcd for C₁₀H₁₁Br₂O₃: 336.9075; found: 336.9084.

2-Iodo-1-(2,4-dimethoxyphenyl)ethanone (15). One mmol of substrate, 3 mmol IL-A, 1.1 mmol NIS, r.t. = 10 min, 55 °C, preparative chromatography SiO₂, CH₂Cl₂, brown solid (34%), mp: 64.5–67.0 °C.
Molecules 2013, 18

(lit [48] 55–57.5 °C); 1H-NMR (CDCl3): δ 7.91 (d, J = 8.8 Hz, 1H), 6.56 (dd, J = 8.8 Hz, J = 2.3 Hz, 1H), 6.47 (d, J = 2.3 Hz, 1H), 4.46 (s, 2H), 3.94 (s, 3H), 3.87 (s, 3H); IR (KBr): 3009, 2940, 2838, 1657, 1595, 1499, 1454, 1414, 1333, 1267, 1211, 1161, 1109, 1023, 984, 826, 610 cm⁻¹; MS m/z (CI): 307.0 (M+H⁺).

1-Acetyl-5-iodo-2,4-dimethoxybenzene (16). One mmol of substrate, 3 mmol IL-A, 1.1 mmol NIS, r.t. = 10 min, 55 °C, preparative chromatography SiO₂, CH₂Cl₂, grey solid (3%); mp: 130.3–134.0 °C (lit [48] 142–145 °C); 1H-NMR (CDCl3): δ 8.23 (s, 1H), 6.39 (s, 1H), 3.94 (s, 3H), 3.94 (s, 3H), 2.56 (s, 3H); IR (KBr): 1647, 1591, 1464, 1391, 1357, 1329, 1271, 1231, 1017, 919, 818 cm⁻¹; MS (ESI): 307.0 (M+H)+, HRMS: calcd for C₁₀H₁₂IO₃: 306.9831; found: 306.9821.

2-Iodo-1-(5-iodo-2,4-dimethoxyphenyl)ethanone (17). One mmol of substrate, 3 mmol IL-A, 1.1 mmol NIS, r.t. = 10 min, 55 °C; preparative chromatography SiO₂, CH₂Cl₂, yellow solid (8%); mp: 148.5–148.6 °C; 1H-NMR (CDCl₃): δ 8.32 (s, 1H), 6.41 (s, 1H), 4.42 (s, 2H), 4.00 (s, 3H), 3.97 (s, 3H); 13C-NMR (CD₃COCD₃): δ 192.0, 165.2, 163.6, 143.4, 120.4, 98.1, 76.4, 58.4, 57.8, 10.7; IR (KBr): 1635, 1585, 1464, 1393, 1329, 1262, 1213, 1017, 919, 818 cm⁻¹; MS (ESI): 432.9 (M+H)+; HRMS: calcd for C₁₀H₁₁I₂O₃: 432.8798; found: 432.8788.

2-Iodo-1-(2,6-dimethoxyphenyl)ethanone (19). One mmol of substrate, 3 mmol IL-A, 1.1 mmol NIS, r.t. = 10 min, 55 °C, preparative chromatography SiO₂, CH₂Cl₂, yellow solid (47%); mp: 51.7–54.6 °C (lit [48] 58–60.5 °C); 1H-NMR (CDCl₃): δ 7.31 (t, J = 8.4 Hz, 1H), 6.57 (d, J = 8.4 Hz, 2H), 4.30 (s, 2H), 3.83 (s, 6H); IR (KBr): 2937, 2837, 1713, 1593, 1474, 1429, 1378, 1307, 1271, 1231, 1091, 980, 773, 722 cm⁻¹; MS (ESI): 307.0 (M+H)+.

2-Iodo-1-(3-iodo-2,6-dimethoxyphenyl)ethanone (20). One mmol of substrate, 3 mmol IL-A, 1.1 mmol NIS, r.t. = 10 min, 55 °C; preparative chromatography SiO₂, CH₂Cl₂, yellow oil (10%); 1H-NMR (CDCl₃): δ 7.75 (d, J = 8.8 Hz, 1H), 6.92 (s, 1H), 3.92 (s, 6H); 13C-NMR (CD₃COCD₃): δ 189.0, 154.8, 135.5, 129.7, 125.4, 72.5, 64.3; IR (KBr): 3016, 2946, 1738, 1568, 1462, 1462, 1343, 1395, 1282, 1244, 1165, 1084, 1003, 913, 805 cm⁻¹; MS (ESI): 432.9 (M+H)+; HRMS: calcd for C₁₀H₁₁I₂O₃: 432.8798; found: 432.8788.

2,2-Dichloro-1-(3,5-dichloro-2,6-dimethoxyphenyl)ethanone (21). One mmol of substrate, 3 mmol IL-A, 4.4 mmol NCS, r.t. = 1080 min, 85 °C; preparative chromatography SiO₂, hexane/CH₂Cl₂ = 1/1; white solid (65%); mp: 53.4–54.4 °C; 1H-NMR (CD₂COCD₂): δ 7.77 (s, 1H), 6.92 (s, 1H), 3.92 (s, 6H); 13C-NMR (CD₂COCD₂): δ 189.0, 154.8, 135.5, 129.7, 125.4, 72.5, 64.3; IR (KBr): 3016, 2946, 1738, 1568, 1462, 1414, 1214, 1070, 984, 926, 872, 818, 773, 714, 641 cm⁻¹; Anal. Calcd for C₁₀H₈Cl₄O₃: C, 37.77; H, 2.54. Found: C, 37.89; H, 2.36.

1-Acetyl-3-bromo-2,6-dimethoxybenzene (22). One mmol of substrate, 3 mmol IL-A, 1.1 mmol NBS, r.t. = 10 min, 55 °C, preparative chromatography SiO₂, CH₂Cl₂, yellow oil [64] (63%); 1H-NMR (CDCl₃): δ 7.48 (d, J = 8.9 Hz, 1H), 6.61 (d, J = 8.9 Hz, 1H), 3.83 (s, 3H), 3.81 (s, 3H), 2.49 (s, 3H); IR(NaCl): 3004, 2940, 2873, 2839, 1707, 1580, 1464, 1401, 1351, 1285, 1240, 1219, 1183, 1092, 1007, 971, 910, 801, 689, 652 cm⁻¹; MS (ESI): 259.0 (M+H)+, 261.0 (M+2+H)+.
2-Bromo-1-(3-bromo-2,6-dimethoxyphenyl)ethanone (23). One mmol of substrate, 3 mmol IL-A, 1.1 mmol NBS, r.t. = 10 min, 55 °C; preparative chromatography SiO₂, CH₂Cl₂; yellow oil (8%); ¹H-NMR (CDCl₃): δ 7.54 (d, J = 8.9 Hz, 1H), 6.64 (d, J = 8.9 Hz, 1H), 4.36 (s, 2H), 3.85 (s, 3H), 3.83 (s, 3H); ¹³C-NMR (CD₂COCD₃): δ 194.5, 158.9, 156.4, 137.1, 125.7, 111.1, 109.4, 64.1, 57.9, 38.6; IR (NaCl): 2941, 1707, 1580, 1464, 1403, 1285, 1227, 1180, 1132, 1088, 1005, 916, 803 cm⁻¹; MS (ESI): 336.9 (M+H)⁺, 338.9 (M+2+H)⁺, 340.9 (M+4+H)⁺; HRMS: calcd for C₁₀H₁₁Br₂O₃: 336.9075; found: 336.9082.

2,2-Dibromo-1-(3,5-dibromo-2,6-dimethoxyphenyl)ethanone (24). One mmol of substrate, 3 mmol IL-A, 4.4 mmol NBS, r.t. = 360 min, 85 °C; preparative chromatography SiO₂, hexane/CH₂Cl₂ = 1/1); white solid (72%); mp: 54.9–57.6 °C; ¹H-NMR (CD₃COCD₃): δ 8.05 (s, 1H), 6.88 (s, 1H), 3.90 (s, 6H); ¹³C-NMR (CD₃COCD₃): δ 188.5, 156.6, 140.9, 129.5, 114.4, 64.5, 45.2; IR (KBr): 3017, 2939, 1723, 1559, 1456, 1406, 1275, 1220, 1165, 1066, 982, 916, 799 615 cm⁻¹; MS (ESI): 494.7 (M+2+H)⁺, 496.7 (M+4+H)+, 498.7 (M+6+H)⁺; HRMS: calcd for C₁₀H₉Br₄O₃: 492.7285; found: 492.7296; Anal. Calcd for C₁₀H₈Br₄O₃: C, 24.23; H, 1.63. Found: C, 24.37; H, 1.61.

2-Iodo-1-(2,3,4-trimethoxyphenyl)ethanone (26). One mmol of substrate, 3 mmol IL-A, 1.1 mmol NIS, r.t. = 60 min, 55 °C, preparative chromatography SiO₂, CH₂Cl₂, yellow oil [63] (68%); ¹H-NMR (CDCl₃): δ 7.59 (d, J = 8.9 Hz, 1H), 6.73 (d, J = 8.9 Hz, 1H), 4.49 (s, 2H), 4.07 (s, 3H), 3.92 (s, 3H), 3.87 (s, 3H); IR (NaCl): 2941, 2840, 1661, 1587, 1493, 1464, 1410, 1287, 1099, 881, 808, 697 cm⁻¹; MS (ESI): 337.0 (M+H)+.

2-Bromo-1-(2,3,4-trimethoxyphenyl)ethanone (27). One mmol of substrate, 3 mmol IL-A, 1.1 mmol NBS, r.t. = 30 min, 55 °C; preparative chromatography SiO₂, CH₂Cl₂, white solid [65] (44%), mp: 39.8–42.0 °C; ¹H-NMR (CDCl₃): δ 7.61 (d, J = 8.9 Hz, 1H), 6.74 (d, J = 8.9 Hz, 1H), 4.05 (s, 3H), 3.93 (s, 3H), 3.87 (s, 3H); IR (NaCl): 2941, 2840, 1661, 1587, 1493, 1464, 1410, 1294, 1213, 1099, 999, 809, 668 cm⁻¹; MS (ESI): 289.0 (M+H)+, 291.0 (M+2+H)+.

2,2-Dibromo-1-(2,3,4-trimethoxyphenyl)ethanone (28). One mmol of substrate, 3 mmol IL-A, 1.1 mmol NBS, r.t. = 30 min, 55 °C; preparative chromatography SiO₂, CH₂Cl₂; white solid (14%); mp: 42.9–44.6 °C; ¹H-NMR (CDCl₃): δ 7.64 (d, J = 9.0 Hz, 1H), 7.09 (s, 1H), 6.76 (d, J = 9.0 Hz, 1H), 4.08 (s, 3H), 3.94 (s, 3H), 3.87 (s, 3H); ¹³C-NMR (CD₂COCD₃): δ 188.2, 161.0, 155.5, 149.2, 128.8, 121.3, 109.9, 63.6, 62.0, 57.7, 46.5; IR (KBr): 3020, 2942, 1723, 1588, 1495, 1462, 1410, 1293, 1217, 1097, 989, 814, 687 cm⁻¹; MS (ESI): 366.9 (M+H)⁺, 368.9 (M+2+H)⁺, 370.9 (M+4+H)⁺; HRMS: calcd for C₁₁H₁₂Br₂O₄: 366.9181; found: 366.9175; Anal. Calcd for C₁₁H₁₂Br₂O₄: C, 35.90; H, 3.29. Found: C, 36.29; H, 3.29.

2-Bromo-1-(5-bromo-2,3,4-trimethoxyphenyl)ethanone (29). One mmol of substrate, 3 mmol IL-A, 2.2 mmol NBS, r.t. = 120 min, 70 °C; preparative chromatography SiO₂, CH₂Cl₂; colorless oil (37%); ¹H-NMR (CDCl₃): δ 7.75 (s, 1H), 4.52 (s, 2H), 4.05 (s, 3H), 3.99 (s, 3H), 3.90 (s, 3H); ¹³C-NMR (CD₂COCD₃): δ 191.6, 157.3, 155.8, 149.2, 129.8, 128.0, 113.0, 63.2, 62.5, 62.5, 38.6; IR(NaCl): 3073, 2942, 1692, 1574, 1462, 1403, 1304, 1260, 1223, 1092, 1051, 995, 932, 889, 872, 791, 674
Molecules 2013, 18

2,2-Dibromo-1-(5-bromo-2,3,4-trimethoxyphenyl)ethanone (30). One mmol of substrate, 3 mmol IL-A, 3.3 mmol NBS, r.t. = 120 min, 70 °C; preparative chromatography SiO2, hexane/CH2Cl2 = 1/9); yellow oil (88%); 1H-NMR (CD3COCD3): δ 7.70 (s, 1H), 7.22 (s, 1H), 4.11 (s, 3H), 4.00 (s, 3H), 3.94 (s, 3H); IR (NaCl): 2943, 1690, 1574, 1463, 1403, 1304, 1258, 1216, 1090, 1047, 993, 797, 669 cm⁻¹; MS (ESI): 444.8 (M+H)+, 446.8 (M+2+H) +, 448.8 (M+4+H) +, 450.8 (M+6+H) +; HRMS: calcd for C11H11Br3O4: 444.8286; found: 444.8291; Anal. Calcd for C11H11Br3O4: C, 29.56; H, 2.48. Found: C, 29.44; H, 2.27.

p-Iodoanisole (32a). One mmol of substrate, 3 mmol IL-A, 1.1 mmol NIS, r.t. = 20 min, 55 °C, preparative chromatography SiO2, hexane/CH2Cl2 = 7.5/2.5, white solid (84%), mp: 42.1–44.4 °C (lit [48] 47–49.5 °C); 1H-NMR (CDCl3): δ 7.55 (d, J = 9.0 Hz, 2H), 6.68 (d, J = 9.0 Hz, 2H), 3.78 (s, 3H); IR (KBr): 2965, 2936, 2835, 1584, 1481, 1450, 1285, 1173, 1026, 993, 807 cm⁻¹.

p-Bromoanisole (32b). One mmol of substrate, 3 mmol IL-A, 1.1 mmol NBS, r.t. = 20 min, 55 °C, CC (SiO2, hexane, colorless oil [9] (81%); 1H-NMR (CDCl3): δ 7.37 (d, J = 9.0 Hz, 2H), 6.78 (d, J = 9.0 Hz, 1H), 3.78 (s, 3H); IR (NaCl): 3004, 2957, 2937, 2835, 1579, 1487, 1460, 1290, 1249, 1171, 1072, 1032, 1003, 822 cm⁻¹.

p-Chloroanisole (32c). One mmol of substrate, 3 mmol IL-A, 1.1 mmol NCS, r.t. = 30 min, 55 °C, preparative chromatography SiO2, hexane/CH2Cl2 = 7.5/2.5, colorless oil [66] (78%); 1H-NMR (CDCl3): δ 7.24 (d, J = 9.0 Hz, 2H), 6.83 (d, J = 9.0 Hz, 1H), 3.79 (s, 3H); IR (NaCl): 3006, 2959, 2940, 2906, 2837, 1593, 1492, 1460, 1290, 1245, 1181, 1169, 1092, 1063, 1032, 824, 750, 686, 639, 626 cm⁻¹.

2,4-Diiodoanisole (33a). One mmol of substrate, 3 mmol IL-A, 2.2 mmol NIS, r.t. = 30 min, 70 °C, CC (SiO2, CH2Cl2, white solid (92%), mp: 65.8–67.0 °C (lit [67] 67.5–68.5 °C); 1H-NMR (CDCl3): δ 8.04 (d, J = 2.1 Hz, 1H), 7.58 (dd, J = 8.6 Hz, J = 2.1 Hz, 1H), 6.58 (d, J = 8.6 Hz, 1H), 3.86 (s, 3H); IR (KBr): 1582, 1469, 1429, 1275, 1246, 1184, 1169, 1092, 1063, 1032, 824, 750, 686, 639, 626 cm⁻¹.

2,4-Dibromoanisole (33b). One mmol of substrate, 3 mmol IL-A, 2.2 mmol NBS, r.t. = 180 min, 85 °C, CC SiO2, hexane/CH2Cl2 = 7.5/2.5, white solid (90%), mp: 53.5–56.0 °C (lit [67] 61–62 °C); 1H-NMR (CDCl3): δ 7.67 (d, J = 2.3 Hz, 1H), 7.38 (dd, J = 8.8 Hz, J = 2.3 Hz, 1H), 6.77 (d, J = 8.8 Hz, 1H), 3.88 (s, 3H); IR (NaCl): 3080, 2973, 2936, 2835, 1574, 1476, 1456, 1379, 1289, 1250, 1052, 1020, 876, 804, 679, 619 cm⁻¹.

2,4-Dichloroanisole (33c). One mmol of substrate, 3 mmol IL-A, 2.2 mmol NCS, r.t. = 30 min, 70 °C, CC SiO2, hexane/CH2Cl2 = 7.5/2.5, colorless oil [66] (89%); 1H-NMR (CDCl3): δ 7.37 (d, J = 2.5 Hz, 1H), 7.19 (dd, J = 8.8 Hz, J = 2.5 Hz, 1H), 6.85 (d, J = 8.8 Hz, 1H), 3.89 (s, 3H); IR (NaCl): 3075, 3011, 2965, 2940, 2901, 2841, 1580, 1484, 1439, 1389, 1292, 1263, 1184, 1106, 1065, 1025, 870, 835, 805, 716, 642 cm⁻¹.
1,5-Diiodo-2,4-dimethoxybenzene (35a). One mmol of substrate, 3 mmol IL-A, 2.2 mmol NIS, r.t. = 20 min, 70 °C, column chromatography (SiO₂, CH₂Cl₂, white solid (89%), mp: 193.6–196.5 °C (lit [68] 201–202 °C); ¹H-NMR (CDCl₃): δ 8.04 (s, 1H), 6.37 (s, 1H), 3.89 (s, 6H); IR (neat): 1568, 1556, 1458, 1452, 1428, 1357, 1275, 1207, 1177, 1034, 1014, 886, 813, 652 cm⁻¹; MS (ESI): 389.9 (M⁺).

1,5-Dibromo-2,4-dimethoxybenzene (35b). One mmol of substrate, 3 mmol IL-A, 2.2 mmol NBS, r.t. = 30 min, 70 °C, preparative chromatography SiO₂, hexane/CH₂Cl₂ = 2.5/7.5, white solid (70%), mp: 135.5–138.4 °C (lit [69] 138–139 °C); ¹H-NMR (CDCl₃): δ 7.66 (s, 1H), 6.50 (s, 1H), 3.91 (s, 6H); IR (neat): 1579, 1570, 1487, 1463, 1432, 1367, 1287, 1208, 1175, 1061, 1052, 1019, 877, 864, 813, 804, 687, 680 cm⁻¹.

1,5-Dichloro-2,4-dimethoxybenzene (35c). One mmol of substrate, 3 mmol IL-A, 2.2 mmol NCS, r.t. = 120 min, 70 °C, preparative chromatography SiO₂, hexane/CH₂Cl₂ = 2.5/7.5, white solid (82%), mp: 111.6–114.2 °C (lit [70] 118–119 °C); ¹H-NMR (CDCl₃): δ 7.36 (s, 1H), 6.54 (s, 1H), 3.91 (s, 6H); IR (neat): 1738, 1578, 1492, 1466, 1454, 1428, 1374, 1295, 1229, 1206, 1171, 1085, 1021, 861, 804, 740 cm⁻¹.

2,4,4-Trichloro-5-methoxycyclohexa-2,5-dienone (36). One mmol of substrate, 3 mmol IL-A, 3.3 mmol NCS, r.t. = 45 min, 70 °C; preparative chromatography SiO₂, hexane/CH₂Cl₂ = 2.5/7.5; yellow solid (84%); mp: 114.6–116.2 °C; ¹H-NMR (CDCl₃): δ 7.13 (s, 1H), 5.65 (s, 1H), 3.94 (s, 3H); ¹³C-NMR (CD₃COCD₃): δ 178.3, 169.5, 139.7, 132.4, 101.2, 76.3, 59.3; IR (neat): 1738, 1657, 1595, 1459, 1347, 1269, 1217, 1156, 1034, 974, 934, 898, 838, 783, 698, 686, 608 cm⁻¹; MS (ESI): 226.9 (M⁺), 228.9 (M+2⁺), 230.9 (M+4⁺); HRMS: calcd for C₇H₆Cl₃O₂: 226.9433; found: 226.9431; Anal. Calcd for C₇H₅Cl₃O₂: C, 36.96; H, 2.22. Found: C, 37.13; H, 2.23.

p-Iodotoluene+o-Iodotoluene (38a, 39a). One mmol of substrate, 3 mmol IL-A, 1.1 mmol NIS, r.t. = 20 min, 55 °C, preparative chromatography SiO₂, hexane/CH₂Cl₂ = 99.7/0.3, yellow oil [71] (49%); ¹H-NMR (CDCl₃): δ 7.80 (d, J = 7.8 Hz, 1H), 7.56 (d, J = 8.1 Hz, 2H), 7.23 (d, J = 4.1 Hz, 2H), 6.92 (d, J = 8.1 Hz, 2H), 6.90-6.82 (m, 1H), 2.43 (s, 3H), 2.29 (s, 3H).

p-Bromotoluene+o-Bromotoluene (38b, 39b). One mmol of substrate, 3 mmol IL-A, 1.1 mmol NBS, r.t. = 20 min, 55 °C; ¹H-NMR (CDCl₃): δ 7.55–7.49 (m, 1H), 7.36 (d, J = 8.3 Hz, 2H), 7.29–7.14 (m, 2H), 7.08–6.99 (m, 3H), 2.40 (s, 3H), 2.30 (s, 3H) [72].

p-Chlorotoluene+o-Chlorotoluene (38c, 39c). One mmol of substrate, 3 mmol IL-A, 1.1 mmol NCS, r.t. = 180 min, 70 °C; ¹H-NMR (CDCl₃): δ 7.37–7.31 (m, 1H), 7.25–7.07 (m, 7H), 2.39 (s, 3H), 2.32 (s, 3H) [73].

5-Iodo-2-methylthiophene (41). One mmol of substrate, 3 mmol IL-A, 1.1 mmol NIS, r.t. = 10 min, 55 °C, CC SiO₂, hexane/CH₂Cl₂ = 7.5/2.5, yellow oil [74] (81%); ¹H-NMR (CDCl₃): δ 7.00 (d, J = 3.5 Hz, 1H), 6.44 (dq, J = 3.5 Hz, J = 0.9 Hz, 1H), 2.49 (d, J = 0.9 Hz, 3H).
3.3. Scale up Experiment

To a stirred mixture of acetophenone (1, 9 mmol, 1.08 g) in IL-A (27 mmol, 9.95 g), N-bromo succinimide (19.8 mmol, 3.52 g) was added. The reaction mixture was stirred at 70 °C for 40 min. Then the mixture was cooled to room temperature and washed three times with dichloromethane. The combined organic fractions were washed with aqueous Na₂S₂O₃ and NaHCO₃, dried over anhydrous Na₂SO₄ and filtered. Solvent was removed under reduced pressure and the crude reaction mixture was analyzed with ¹H-NMR. Purification of crude reaction mixture by chromatography yielded 2.25 g (90%) of 3b.

3.4. Recycling/Reuse of IL-A in Iodination of Acetophenone (1) with NIS

To a stirred mixture of acetophenone (1, 1 mmol, 120 mg) in IL-A (3 mmol, 368 mg), N-iodo succinimide (1.1 mmol, 225 mg) was added. The reaction mixture was stirred at 55 °C for 10 minutes. Then the mixture was cooled to room temperature and washed three times with dichloromethane. The combined organic fractions were washed with aqueous Na₂S₂O₃ and NaHCO₃, dried over anhydrous Na₂SO₄ and filtered. Solvent was removed under reduced pressure and the crude reaction mixture was analyzed with ¹H-NMR. Purification of crude reaction mixture with chromatography yielded 212 mg (86%) of 2a. The IL-A from reaction was dried under reduced pressure and reused.

4. Conclusions

In summary, the Brønsted acidic ionic liquid 1-methyl-3-(4-sulfobutyl)imidazolium triflate ([BMIM(SO₃H)][OTf]; IL-A) exhibited a notable catalytic effect in the halofunctionalization of aromatics with NXS and transformations were significantly faster as compared to IL-B. Aryl methyl ketones were α- and α,α-dihalogenated with high selectivity and in respectable yields. In the case of methoxy-substituted acetophenones, competing ring halogenation occurred. Activated arenes were selectively mono- and dihalogenated. A noteworthy feature is exclusive para-halogenation of anisole with NXS/IL-A. Recycling and reuse of [BMIM(SO₃H)][OTf] was demonstrated in a prototype iodination reaction in eight cycles with no decrease in the conversion. The catalytic role of IL-A in dibromination with NBS is manifested in higher mono- to dihalogenation ratios when the reaction is repeated in the used IL. The feasibility for scale-up was also demonstrated in a representative case.

Acknowledgments

The authors are grateful to the staff of the Mass Spectroscopy Centre at Jožef Stefan Institute for mass spectrometric measurements and prof. B. Stanovnik for elemental analysis. The Slovenian Research Agency (contracts: Programme ARRS P1-0134, Young Researchers Fellowship ARRS 1000-08-310039, and USA/Si bilateral project BI-US/12-13-004) and European Regional Development Found (OP 13.1.1.2.02.0005) are acknowledged for financial support.
References

1. French, A.N.; Bissmire, D.; Wirth, T. Iodine electrophiles in stereoselective reactions: ecent developments and synthetic applications. *Chem. Soc. Rev.* **2004**, *33*, 354–362.

2. Stavber, S.; Jereb, M.; Zupan, M. Electrophilic Iodination of Organic Compounds Using Elemental Iodine or Iodides. *Synthesis** **2008**, *18*, 1487–1513.

3. Podgoršek, A.; Zupan, M.; Iskra, J. Oxidative Halogenation with “Green” Oxidants: Oxygen and Hydrogen Peroxide. *Angew. Chem. Int. Ed.* **2009**, *48*, 8424–8450.

4. Zhdankin, V.V.; Stang, P.J. Chemistry of Polyvalent Iodine. *Chem. Rev.* **2008**, *108*, 5299–5358.

5. Golebiewski, W.M.; Gucma, M. Applications of *N*-Chlorosuccinimide in Organic Synthesis. *Synthesis* **2007**, 3599–3619.

6. Tanemura, K.; Suzuki, T.; Nishida, Y.; Satsumabayashi, K.; Horaguchi, T. Halogenation of Aromatic Compounds by *N*-chloro-, *N*-bromo-, and *N*-iodosuccinimide. *Chem. Lett.* **2003**, *32*, 932–933.

7. Pravst, I.; Zupan, M.; Stavber, S. Halogenation of ketones with *N*-halosuccinimides under solvent-free reaction conditions. *Tetrahedron* **2008**, *64*, 5191–5199.

8. Bucos, M.; Villalonga-Barber, C.; Micha-Screttas, M.; Steele, B.R.; Screttas, C.G.; Heropoulos, G.A. Microwave assisted solid additive effects in simple dry chlorination reactions with *n*-chlorosuccinimide. *Tetrahedron* **2010**, *66*, 2061–2065.

9. Mo, F.; Yan, J.M.; Qiu, D.; Li, F.; Zhang, Y.; Wang, J. Gold-Catalyzed Halogenation of Aromatics by *N*-Halosuccinimides. *Angew. Chem. Int. Ed.* **2010**, *49*, 2028–2032.

10. Borodkin, G.I.; Shubin, V.G. Electrophilic Reactions of Aromatic and Heteroaromatic Compounds in Ionic Liquids. *Russ. J. Org. Chem.* **2006**, *42*, 1745–1770.

11. Pavlinac, J.; Zupan, M.; Laali, K.K.; Stavber, S. Halogenation of organic compounds in ionic liquids. *Tetrahedron* **2009**, *65*, 5625–5662.

12. Kumar, V.; Yap, J.; Muroyama, A.; Malhotra, S.V. Highly Efficient Method for C-5 Halogenation of Pyrimidine-Based Nucleosides in Ionic Liquids. *Synthesis* **2009**, 3957–3962.

13. Laali, K.K.; Borodkin, G.I. First application of ionic liquids in electrophilic fluorination of arenes; Selectfluor™ (F-TEDA-BF₄) for “green” fluorination. *J. Chem. Soc. Perkin Trans.* **2002**, *2*, 953–957.

14. Hubbard, A.; Okazaki, T.; Laali, K.K. Chlorination of Aromatics with Trichloroisocyanuric Acid (TCICA) in Brønsted-Acidic Imidazolium Ionic liquid [BMIM(SO₃H)][OTf]: An Economical, Green Protocol for the Synthesis of Chloroarenes. *Aust. J. Chem.* **2007**, *60*, 923–927.

15. Chiappe, C.; Leandri, E.; Tebano, M. [Hmim][NO₃]—An efficient solvent and promoter in the oxidative aromatic chlorination. *Green Chem.* **2006**, *8*, 742–745.

16. Chiappe, C.; Sanzone, A. Using the ‘Chemical Tunability’ of Ionic Liquids to Increase Sustainability in the Electrophilic Bromination of Unsaturated Compounds. *Synthesis* **2011**, 2392–2396.

17. Borikar, S.P.; Daniel, T.; Paul, V. An efficient, rapid, and regioselective bromination of anilines and phenols with 1-butyl-3-methylpyridinium tribromide as a new reagent/solvent under mild conditions. *Tetrahedron Lett.* **2009**, *50*, 1007–1009.

18. Salazar, J.; Dorta, R. Pentylypyridinium Tribromide: A Vapor Pressure Free Room Temperature Ionic Liquid Analogue of Bromine. *Synlett* **2004**, 1318–1320.
19. Borikar, S.P.; Daniel, T. Aromatic Bromination of Aldehydes and Ketones Using 1,3-Di-n-butylimidazolium Tribromide [BBIm]Br₃ Ionic Liquids under Solvent-Free Conditions. *J. Iran. Chem. Soc.* 2011, 8, 531–536.

20. Pavlinac, J.; Laali, K.K.; Zupan, M.; Stavber, S. Iodination of Organic Compounds with Elemental Iodine in the Presence of Hydrogen Peroxide in Ionic Liquid Media. *Aust. J. Chem.* 2008, 61, 946–955.

21. Lee, J.C.; Kim, J.; Park, H.J.; Kwang, B.; Lee, S.B. Direct Metal-free α-iodination of Arylketones Induced by Iodine or Iodomethane with HTIB in Ionic Liquid. *Bull. Korean Chem. Soc.* 2010, 31, 1385–1386.

22. Hajipour, A.R.; Rafiee, F.; Ruoho, A. Efficient and Selective Iodination of Benzylic Alcohols Using NaI/Bronsted Ionic Liquid System at Room Temperature. *Synth. Commun.* 2011, 41, 603–611.

23. Bailey, L.; Handy, S.T. Aromatic iodination using N-iodosaccharin in room temperature ionic liquids. *Tetrahedron Lett.* 2011, 52, 2413–2414.

24. Cole, A.C.; Jensen, J.L.; Ntai, I.; Tran, K.L.T.; Weaver, K.J.; Forbes, D.C.; Davis, J.H., Jr. Novel Bronsted Acidic Ionic Liquids and Their Use as Dual Solvent–Catalysts. *J. Am. Chem. Soc.* 2002, 124, 5962–5963.

25. Kore, R.; Srivastava, R. Influence of –SO₃H functionalization (N-SO₃H or N-R-SO₃H, where R = alkyl/benzyl) on the activity of Brönsted acidic ionic liquids in the hydration reaction. *Tetrahedron Lett.* 2012, 53, 3245–3249.

26. Akbari, J.; Heydari, A. A sulfonic acid functionalized ionic liquid as a homogeneous and recyclable catalyst for the one-pot synthesis of α-aminophosphonates. *Tetrahedron Lett.* 2009, 50, 4236–4238.

27. Garima; Srivastava, V.P.; Yadav, L.D.S. Direct sulfonylation of Baylis-Hillman alcohols and diarylmethanols with TosMIC in ionic liquid-[Hmim]HSO₄: an unexpected reaction. *Tetrahedron Lett.* 2011, 52, 4622–4626.

28. Hajipour, A.R.; Ghayeb, Y.; Sheikhan, N.; Ruoho, A.E. Brønsted acidic ionic liquid as an efficient and reusable catalyst for one-pot synthesis of 1-amidoalkyl 2-naphthols under solvent-free conditions. *Tetrahedron Lett.* 2009, 50, 5649–5651.

29. Chen, Z.; Zhu, Q.; Su, W. A novel sulfonic acid functionalized ionic liquid catalyzed multicomponent synthesis of 10,11-dihydrochromeno[4,3-b]chromene-6,8(7H,9H)-dione derivatives in water. *Tetrahedron Lett.* 2011, 52, 2601–2604.

30. Chen, X.; Liu, R.; Xu, Y.; Zou, G. Tunable protic ionic liquids as solvent-catalysts for improved synthesis of multiply substituted 1,2,4-triazoles from oxadiazoles and organoamines. *Tetrahedron* 2012, 68, 4813–4819.

31. Laali, K.K.; Gettwert, V.J. Electrophilic Nitration of Aromatics in Ionic Liquid Solvents. *J. Org. Chem.* 2001, 66, 35–40.

32. Sarca, V.D.; Laali, K.K. Triflic acid-promoted transacylation and deacylation reactions in ionic liquid solvents. *Green Chem.* 2004, 6, 245–248.

33. Laali, K.K.; Sarca, V.D.; Okazaki, T.; Brock, A.; Der, P. Triflic acid-catalyzed adamantylation in [BMIM][OTf] ionic liquid; synthetic scope and mechanistic insight. *Org. Biomol. Chem.* 2005, 3, 1034–1042.
34. Sarca, V.D.; Laali, K.K. Facile benzylation of aromatics in ionic liquid solvents promoted by TfOH, Sc(OTf)3, and Yb(OTf)3·xH2O; New life for a classic transformation. *Green Chem.*, **2006**, 8, 615–620.

35. Laali, K.K.; Okazaki, T.; Bunge, S.D. N-(Trifluoromethylsulfonyl)aryloxytrifluoromethyl-sulfoximines [Ar-SO(CF3)=NTf] and N-Aryltriflimides Ar-N(Tf)2 by Thermal and Photolytic Dediazonium of [ArN2][BF4] in [BMIM][Tf2N] Ionic Liquid: Exploiting the Ambident Nucleophilic Character of a “Nonnucleophilic” Anion. *J. Org. Chem.*, **2007**, 72, 6758–6762.

36. Hubbard, A.; Okazaki, T.; Laali, K.K. Halo- and Azidodediazoniation of Arenediazonium Tetrafluoroborates with Trimethylsilyl Halides and Trimethylsilyl Azide and Sandmeyer-Type Bromodediazoniation with Cu(I)Br in [BMIM][PF6] Ionic Liquid. *J. Org. Chem.*, **2008**, 73, 316–319.

37. Kalkhambkar, R.G.; Laali, K.K. Arenediazonium salts immobilized in imidazolium ionic liquids as electrophilic partners in the Pd(OAc)2-catalyzed Matsuda–Heck arylation. *Tetrahedron Lett.*, **2011**, 52, 1733–1737.

38. Kalkhambkar, R.G.; Laali, K.K. Pd(OAc)2-catalyzed cross-coupling of polyfluoroarenes with simple aromatics in imidazolium ionic liquids (ILs) without oxidant and additive and with recycling/reuse of the IL. *Tetrahedron Lett.*, **2011**, 52, 5525–5529.

39. Aridoss, G.; Laali, K.K. Condensation of propargylic alcohols with 1,3-dicarbonyl compounds and 4-hydroxycoumarins in ionic liquids (ILs). *Tetrahedron Lett.*, **2011**, 52, 6859–6864.

40. Aridoss, G.; Sarca, V.D.; Ponder, J.F., Jr.; Crowe, J.; Laali, K.K. Electrophilic chemistry of propargylic alcohols in imidazolium ionic liquids: Propargylation of arenes and synthesis of propargylic ethers catalyzed by metallic triflates [Bi(OTf)3, Sc(OTf)3, Yb(OTf)3], TfOH, or B(C6F5)3. *Org. Biomol. Chem.*, **2011**, 9, 2518–2529.

41. Aridoss, G.; Laali, K.K. Ethylammonium Nitrate (EAN)/Tf2O and EAN/TFAA: Ionic Liquid Based Systems for Aromatic Nitration. *J. Org. Chem.*, **2011**, 76, 8088–8094.

42. Aridoss, G.; Laali, K.K. Highly Efficient Synthesis of 5-Substituted 1H-Tetrazoles Catalyzed by Cu–Zn Alloy Nanopowder, Conversion into 1,5- and 2,5-Disubstituted Tetrazoles, and Synthesis and NMR Studies of New Tetrazolium Ionic Liquids. *Eur. J. Org. Chem.*, **2011**, 6343–6355.

43. Kumar, G.G.K.S.N.; Aridoss, G.; Laali, K.K. Condensation of propargylic alcohols with indoles and carbazole in [bmim][PF6]/Bi(NO3)3·5H2O: a simple high yielding propargylation method with recycling and reuse of the ionic liquid. *Tetrahedron Lett.*, **2012**, 53, 3066–3069.

44. Eberson, L.; Hatshorn, M.P.; Radner, F.; Persson, O. Radical cation mechanism of aromatic halogenation by halogens or iodine chloride in 1,1,1,3,3,3-hexafluoropropan-2-ol. *J. Chem. Soc. Perkin Trans.* **1998**, 2, 59–70.

45. Fabbrini, M.; Galli, C.; Gentili, P.; Macchitella, D.; Petridi, H. Aromatic iodination: a new investigation on the nature of the mechanism. *J. Chem. Soc. Perkin Trans.* **2001**, 2, 1516–1521.

46. Fokin, A.A.; Schreiner, P.R.; Gunchenko, P.A.; Peleshanko, S.A.; Shubina, T.E.; Isaev, S.D.; Tarasenko, P.V.; Kulik, N.I.; Schiebel, H.-M.; Yurchenko, A.G. Oxidative Single-Electron Transfer Activation of σ-Bonds in Aliphatic Halogenation Reactions. *J. Am. Chem. Soc.*, **2000**, 122, 7317–7326.

47. Vasilyev, A.V.; Lindeman, S.V.; Kochi, J.K. Molecular structures of the metastable charge-transfer complexes of benzene (and toluene) with bromine as the pre-reactive intermediates in electrophilic aromatic bromination. *New J. Chem.*, **2002**, 26, 582–592.
48. Stavber, G.; Iskra, J.; Zupan, M.; Stavber, S. Aerobic Oxidative Iodination of Organic Compounds with Iodide Catalyzed by Sodium Nitrite. *Adv. Synth. Catal.* 2008, 350, 2921–2929.

49. Podgoršek, A.; Stavber, S.; Zupan, M.; Iskra, J. Bromination of ketones with H2O2–HBr “on water”. *Green Chem.* 2007, 9, 1212–1218.

50. Ram, R.N.; Manoj, T.P. Copper(I)-Promoted Synthesis of Chloromethyl Ketones from Trichloromethyl Carbinols. *J. Org. Chem.* 2008, 73, 5633–5635.

51. Kajigaeshi, S.; Kakinami, T.; Tokiyama, H.; Hirakawa, T.; Okamoto, T. Synthesis of Dibromoacetyl Derivatives by Use of Benzyltrimethylammonium Tribromide. *Bull. Chem. Soc. Jpn.* 1987, 60, 2667–2668.

52. Chen, Z.; Zhou, B.; Cai, H.; Zhu, W.; Zou, X. Simple and efficient methods for selective preparation of α-mono or α,α-dichloro ketones and β-ketoesters by using DCDMH. *Green Chem.* 2009, 11, 275–278.

53. Okamoto, T.; Kakinami, T.; Nishimura, T.; Hermawan, I.; Kajigaeshi, S. Preparation of Aromatic Iodoacetyl Derivatives by Direct Iodination with a Potassium Iodide-Potassium Iodate-Sulfuric Acid System. *Bull. Chem. Soc. Jpn.* 1992, 65, 1731–1733.

54. Arcoria, A.; Fisichella, S.; Maccarone, E.; Scarlata, G. Reactions of Triethyl Phosphite with 2-Haloacetyl-furan, -thiophene, -pyrrole and -N-methylpyrrole. *J. Heterocyclic. Chem.* 1975, 12, 215–218.

55. Kourounakis, A.P.; Matralis, A.N.; Nikitakis, A. Design of more potent squalene synthase inhibitors with multiple activities. *Bioorg. Med. Chem.* 2010, 18, 7402–7412.

56. Song, G.-L.; Zhu, H.-J.; Chen, L.; Luo, Z.-H. Novel Disubstituted Phenylene-Linked Bis-imidazole Derivatives: Facile Synthesis and Optical Properties. *Helv. Chim. Acta* 2010, 93, 2397–2405.

57. Terent’ev, A.O.; Khodykin, S.V.; Krylov, I.B.; Ogibin, Y.N.; Nikishin, G.I.A Convenient Synthesis of 2,2-Dibromo-1-aryl ethanones by Bromination of 1-Arylethanones with the H2O2-HBr System. *Synthesis* 2006, 1087–1092.

58. Kim, K.; Cho, J.; Yoon, S.C. Reactions of Tetrasulfur Tetranitride with Aryl Dibromomethyl Ketones: One-pot Synthesis of 3-Aroylformamido-4-aryl-1,2,5-thiadiazoles and their Reactions. *J. Chem. Soc. Perkin Trans.* 1995, 1, 253–259.

59. Kinbara, K.; Harada, Y.; Saigo, K. A high-performance, tailor-made resolving agent: remarkable enhancement of resolution ability by introducing a naphthyl group into the fundamental skeleton. *J. Chem. Soc. Perkin Trans.* 2 2000, 2, 1339–1347.

60. Nobrega, J.A.; Gonçalves, S.M.C.; Peppe, C. Selective Preparation of α,α-dichloroketones with Copper(II) chloride. *Synth. Commun.* 2002, 32, 3711–3717.

61. Kurosawa, K.; Yamaguchi, K. The Reaction of Acetophenones with Manganese(III) Acetate. *Bull. Chem. Soc. Jpn.* 1981, 54, 1757–1760.

62. Jereb, M.; Stavber, S.; Zupan, M. Direct α-Iodination of Aryl Alkyl Ketones by Elemental Iodine Activated by 1-Chloromethyl-4-fluoro-1,4-diaziobiocyclo[2.2.2]octane Bis(tetrafluoroborate). *Synthesis* 2003, 853–858.

63. Shang, G.; Liu, D.; Allen, S.E.; Yang, Q.; Zhang, X. Asymmetric Hydrogenation of α-Primary and Secondary Amino Ketones: Efficient Asymmetric Syntheses of (–)-Arbutamine and (–)-Denopamine. *Chem. Eur. J.* 2007, 13, 7780–7784.
64. Lindh, J.; Sjöberg, P.J.R.; Larhed, M. Synthesis of Aryl Ketones by Palladium(II)-Catalyzed Decarboxylative Addition of Benzoic Acids to Nitriles. *Angew. Chem. Int. Ed.* **2010**, *49*, 7733–7737.
65. Liu, X.-H.; Lv, P.-C.; Xue, J.-Y.; Song, B.-A.; Zhu, H.-L. Novel 2,4,5-trisubstituted oxazole derivatives: Synthesis and antiproliferative activity. *Eur. J. Med. Chem.* **2009**, *44*, 3930–3935.
66. Maraš, N.; Polanc, S.; Kočevar, M. Microwave-assisted methylation of phenols with tetramethy lammonium chloride in the presence of K₂CO₃ or Cs₂CO₃. *Tetrahedron* **2008**, *64*, 11618–11624.
67. Muraki, T.; Togo, H.; Yokoyama, M. Reactivity and Synthetic Utility of 1-(Arenesulfonyloxy)benziodoxolones. *J. Org. Chem.* **1999**, *64*, 2883–2889.
68. Hamamoto, H.; Hattori, S.; Takemaru, K.; Miki, Y. Hypervalent Iodine(III)–LiX Combination in Fluoroalcohol Solvent for Aromatic Halogenation of Electron-Rich Arenecarboxylic Acids. *Synlett* 2011, *1563–1566.
69. Pahari, P.; Rohr, J. Total Synthesis of Psoralidin, an Anticancer Natural Product. *J. Org. Chem.* **2009**, *74*, 2750–2754.
70. Testaferri, L.; Tiecco, M.; Tingoli, M.; Chianelli, D.; Montanucci, M. The Reactions of Unactivated Aryl Halides with Sodium Methoxide in HMPA. *Tetrahedron* **1983**, *39*, 193–197.
71. Zhou, C.-Y.; Li, J.; Peddibhotla, S.; Romo, D. Mild Arming and Derivatization of Natural Products via an In(OTf)₃-Catalyzed Arene Iodination. *Org. Lett.* **2010**, *12*, 2104–2107.
72. Gavara, L.; Boisse, T.; Rigo, B.; Hénichart, J.-P. A new method of bromination of aromatic rings by an iso-amyl nitrite/HBr system. *Tetrahedron* **2008**, *64*, 4999–5004.
73. O’Connell, J.L.; Simpson, J.S.; Dumanski, P.G.; Simpson, G.W.; Easton, C.J. Aromatic chlorination of α-phenylalkylamines and α-phenylalkylamides in carbon tetrachloride and α,α,α-trifluorotoluene. *Org. Biomol. Chem.* **2006**, *4*, 2716–2723.
74. Reich, H.J.; Whipple, W.L. Mechanism of the lithium–iodine exchange in an iodothiophene. *Can. J. Chem.* **2005**, *83*, 1577–1587.

*Sample Availability*: Samples of all the compounds except 16, 17, 20, 23, 28, 38a–c, 39a–c and 41 are available from the authors.

© 2013 by the authors; licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution license (http://creativecommons.org/licenses/by/3.0/).