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Aminohalogenation of Electron-Deficient Olefins Promoted by Hypervalent Iodine Compounds

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An efficient and practical procedure for the aminohalogenation of electron-deficient olefins promoted by hypervalent iodine compounds has been demonstrated. The catalytic efficiency of various hypervalent iodine compounds with different carboxylic and sulfonic ligands has also been investigated and of these (diacetoxyiodo)benzene exhibited the highest activity. A series of substrates, including α,β-unsaturated ketones, cinnamates, and cinnamides, were tolerable under the conditions employed and were aminochlorinated/-brominated in good yields and with excellent diastereoselectivities.

Introduction

The synthesis of vicinal haloamines is an important goal in modern organic chemistry because of their use as key intermediates in the synthesis of biologically and pharmaceutically important molecules.[1] By replacement of the halogen atom with multifarious nucleophiles, these compounds can be easily transformed into various products. Typically, the vicinal haloamino functionalities are installed by aminohalogenation of the unsaturated carbon–carbon bond, which has been known for several decades.[2–5] Early research in this field employed various reagent systems such as *N*,*N*-dihalosulfonamides,[2] *N*,*N*-dihalocarbamates,[3a–3d] *N*-halocarbamates,[4] and cyanamide/NBS.[5] Li[6] and co-workers developed the first catalytic aminohalogenation reaction of electron-deficient olefins, including α,β-unsaturated esters,[6a–6e] ketones,[6g,6h] amides,[6f,6j] and nitriles,[6i] to produce various vicinal haloamino carbonyl compounds, which are prevalent architectures in organic synthesis.[7,8] By employment of several different nitrogen/chlorine sources, such as 4-$TsNCl_2$,[6a,6c,6e–6j] 2-NsNNaCl,[6d] or a combination of 2-$NsNCl_2$ and 2-NsNHNa,[6b,6h] the aminochlorination reaction can be carried out in good yield and with excellent regio- and diastereoselectivity with copper[6a,6b,6d–6i] and palladium[6c,6j] as catalysts. More recently, Li and co-workers also successfully achieved the aminochlorination of nitrostyrenes.[9] Raghavan et al. employed *S*,*S*-dimethyl-*N*-(*p*-toluenesulfonyl)sulfilimine and NBS to synthesize bromoamines.[10] Sudalai and co-workers reported a procedure for the aminobromination of a broad range of olefins with $TsNH_2$ and NBS catalyzed by metal salts.[11] Corey and co-workers also demonstrated a versatile methodology for the aminobromination of olefins that involved *N*-bromoacetamide and a Lewis acid in acetonitrile.[12] The aminohalogenation of methylenecyclopropanes was also realized by Li and Huang and their co-workers.[13] First achieved by a transition-metal-catalyzed process,[14] the intramolecular version of this transformation was recently accomplished by a $PhI(OAc)_2$-induced highly efficient oxidative bromocyclization of homoallylic sulfonamides without a metal catalyst.[15]

The use of metal catalysts has one common drawback, that is, the complete elimination of a metal impurity in the final product is always troublesome. Thus, reactions using efficient, selective, and high-yielding methods under metal-free conditions are one of the most important challenges in modern organic synthesis. Fortunately, Li and co-workers reported a metal-free aminochlorination reaction of chalcones with 2-$NsNCl_2$ in an ionic liquid in which the substrate range was relatively narrow.[16] Very recently, we demonstrated an unprecedented Brønsted acid promoted aminochlorination process in water.[17] The feasibility of performing this kind of reaction in pure water makes this protocol more practical and attractive. Furthermore, we also found that in the presence of (diacetoxyiodo)benzene [$PhI(OAc)_2$], various electron-deficient olefins could be aminohalogenated efficiently and regio- and diastereoselectively (Scheme 1).[18]

Hypervalent iodine compounds such as $PhI(OAc)_2$ are usually used as clean and efficient oxidants in various organic transformations.[19] In the protocol that we developed, surprisingly, $PhI(OAc)_2$ could be used with substoichiometric loading,[18] however, an uncommon device (a ball mill) was required. Intrigued by the unusual role of

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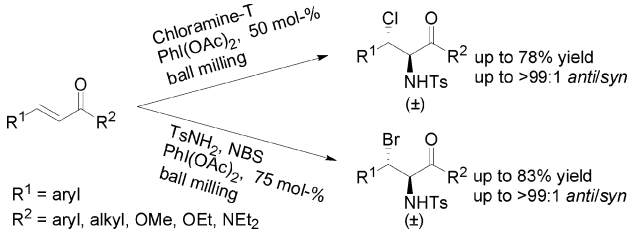


Scheme 1. $PhI(OAc)_2$-promoted aminohalogenation of electron-deficient olefins in a ball mill.

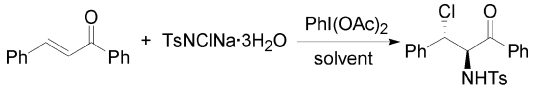
$PhI(OAc)_2$ in the aminohalogenation reactions, in this article we would like to describe the aminohalogenation of electron-deficient olefins in organic solvent as an extension of this chemistry and show that the aminobromination process can be applied to a gram-scale synthesis.

Results and Discussion

Aminochlorination with Chloramine-T

Chloramine-T, a readily available, convenient-to-handle, stable crystalline solid, has been extensively utilized as a nitrene transfer reagent to synthesize aziridines from alkenes.[20] Only a few examples of the aminochlorination of alkenes with Chloramine-T have been reported.[21,22] In our previous report, we described the aminochlorination of chalcone **1a** with 1.0 equiv. of $PhI(OAc)_2$ and 2.0 equiv. of Chloramine-T trihydrate (**2**) in CH_2Cl_2 at room temperature, which gave the product **3a** in 53% yield (Table 1, entry 1).[18a] We then screened the reaction conditions systematically to optimize this preliminary result. The details are listed in Table 1. Decreasing the loading of $PhI(OAc)_2$ was clearly harmful and the reaction yield dropped dramatically (entry 2). Fortunately, when we raised the reaction temperature to reflux, the desired chloramine **3a** was isolated in 77% yield and with excellent diastereoselectivity in the presence of 0.5 equiv. of $PhI(OAc)_2$ within 4 h (entry 3), which was comparable with the result obtained in the solid state.[18a] However, decreasing the loading of $PhI(OAc)_2$ to 25 mol-% was deleterious, affording only a moderate yield even with a prolonged reaction time (entry 4). A further experiment indicated that a one-fold excess of Chloramine-T was essential to achieve a high yield (entry 5). The reaction performed in 1,2-dichloroethane (DCE) was sluggish; the product was obtained in only 37% yield (entry 6). CH_3CN, which is used as a privileged solvent in aminohalogenation reactions,[6] furnished **3a** in 31% yield (entry 7). Other protonic and aprotic solvents of different polarities were also examined, however, no or only trace amounts of products were observed in all cases (entries 8–13). When 1,4-dioxane and toluene were employed, the reactions did proceed, albeit with low yields (8 and 7%, respectively, entries 14 and 15, Table 1). We also noticed that the product could be isolated in 34% yield when acetone was used as the reaction medium (entry 16).

Table 1. Aminochlorination of chalcone **1a** with Chloramine-T promoted by $PhI(OAc)_2$ in various solvents.[a]



Entry	Solvent	*T* [°C]	Time [h]	Yield [%][b]	*dr* (*anti*/*syn*)[c]
1[d]	CH_2Cl_2	25	10	53	92:8
2	CH_2Cl_2	25	12	35	92:8
3	CH_2Cl_2	reflux	4	77	92:8
4[e]	CH_2Cl_2	reflux	12	45	92:8
5[f]	CH_2Cl_2	reflux	12	61	92:8
6	DCE	reflux	10	37	92:8
7	CH_3CN	reflux	12	31	92:8
8	DMF	100	12	0	–
9	DMSO	100	12	0	–
10	THF	reflux	12	trace	n.d.[g]
11	hexane	reflux	12	0	–
12	Et_2O	reflux	12	trace	n.d.[g]
13	EtOH	reflux	12	trace	n.d.[g]
14	dioxane	reflux	12	8	91:9
15	PhMe	reflux	12	7	92:8
16	acetone	reflux	12	34	91:9

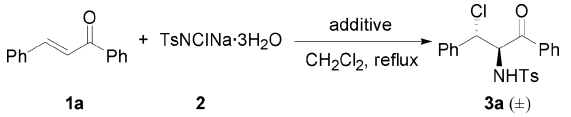
[a] Unless otherwise specified, all reactions were performed with chalcone **1a** (0.5 mmol), Chloramine-T (1.0 mmol), and $PhI(OAc)_2$ (0.25 mmol) in the solvent indicated. [b] Isolated yields were determined by flash column chromatography. [c] Determined by ^1H NMR spectroscopy. [d] 0.5 mmol of $PhI(OAc)_2$ was employed. [e] 0.125 mmol of $PhI(OAc)_2$ was employed. [f] 0.75 mmol of Chloramine-T was employed. [g] Not determined.

Having found the most efficient reaction medium, we next investigated the catalytic efficiency of various hypervalent iodine compounds with different carboxylic and sulfonic ligands. The results are summarized in Table 2. When [bis(trifluoroacetoxy)]iodobenzene was employed to promote the reaction, the yield decreased dramatically (entry 2). The use of iodosylbenzene, a compound with no carboxylic group, led to a sluggish reaction, giving the final product in a very low yield (entry 3). Three hypervalent iodine compounds with sulfonic ligands (Koser's reagent) were synthesized[23] and applied to effect this transformation. Each of these ligands delivered the product in a moderate yield, ranging from 50 to 58% (entries 4–6). A large variety of phenyliodine(III) dicarboxylates can be prepared from $PhI(OAc)_2$ by a ligand-exchange reaction.[24] The aminochlorination of chalcone **1a** promoted by these compounds with various benzoate ligands required longer reaction times and proceeded with moderate-to-good yields (entries 7–11). The hypervalent iodines derived from these aliphatic carboxylic acids gave results similar to $PhI(OAc)_2$, and of these, $PhI[CH_3(CH_2)_2CO_2]_2$ exhibited the highest activity (entries 12–15).

On the basis of both the efficiency and availability of these hypervalent iodine compounds, we concluded that $PhI(OAc)_2$ was the best promoter for this reaction.

With the optimized conditions in hand, we next investigated the substrate scope of this reaction (Table 3). Various chalcones, with substituents of different electronic proper-

Table 2. Aminochlorination of chalcone **1a** with Chloramine-T promoted by various hypervalent iodine compounds.[a]



1a **2** **3a** (±)

Entry	Additive[b]	Time [h]	Yield [%][c]	*dr* (*anti*/*syn*)[d]
1	$PhI(OAc)_2$	4	78	93:7
2	$PhI(CF_3CO_2)_2$	4	36	91:9
3	PhI=O	12	10	91:9
4	PhI(OH)OTs	5	50	92:8
5	PhI(OH)OMs	10	58	88:12
6	PhI(OH)OCs	5	53	91:9
7	$PhI(C_6H_5CO_2)_2$	5	71	93:7
8	$PhI(4\text{-}MeOC_6H_4CO_2)_2$	12	51	92:8
9	$PhI(4\text{-}NO_2C_6H_4CO_2)_2$	20	57	94:6
10	$PhI(4\text{-}MeC_6H_4CO_2)_2$	12	60	94:6
11	$PhI(4\text{-}ClC_6H_4CO_2)_2$	12	51	93:7
12	$PhI(CH_3CH_2CO_2)_2$	4	76	93:7
13	$PhI[CH_3(CH_2)_2CO_2]_2$	4	78	93:7
14	$PhI[(CH_3)_2CHCO_2]_2$	6	71	93:7
15	$PhI[CH_3(CH_2)_4CO_2]_2$	6	63	94:6

[a] All reactions were performed with chalcone **1a** (0.5 mmol), Chloramine-T (1.0 mmol), and additive (0.25 mmol) in refluxing CH_2Cl_2. [b] Ts = 4-Me-$C_6H_4SO_2$; Ms = $MeSO_2$; Cs = (1*R*)-10-camphorylsulfonyl. [c] Isolated yields were determined by flash column chromatography. [d] Determined by ^1H NMR spectroscopy.

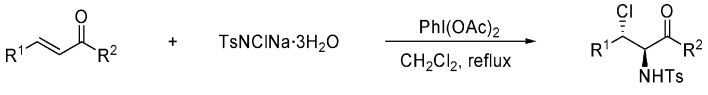
ties on the phenyl rings, were aminochlorinated smoothly giving the products in moderate-to-good yields and with excellent diastereoselectivities (entries 1–9). The use of an enone with an alkyl group also produced the corresponding chloramine in good yield (entry 10). The aminochlorination reactions of cinnamates and cinnamides were successful and afforded the final products in moderate yields exclusively with the *anti* configuration (entries 11–15).

Aminobromination

We have also reported previously the aminobromination reaction of various olefins under mechanical milling conditions.[18b] However, this reaction could only be performed on a relatively small scale; when it was scaled up, a dramatic decrease in yield was observed. To overcome this limitation, we performed this reaction in organic solvent (Table 4). The reaction of chalcone **1a** with 2.0 equiv. of $TsNH_2$ and 1.5 equiv. of NBS in the presence of 0.75 equiv. of $PhI(OAc)_2$ was clean and efficient, proceeding in 78% yield within 4 h at 25 °C (entry 1). Note that the reaction could be carried out on the 0.5 mmol scale. Raising the reaction temperature was not beneficial, giving a slightly reduced yield (entry 2). In contrast, the reaction became sluggish at reduced temperature (entry 3). Effort focused on the reduction of $PhI(OAc)_2$ loading proved unsuccessful; the product yield dropped noticeably when 25 mol-% of $PhI(OAc)_2$ was employed (entry 5). Further investigation suggested that the loading of $TsNH_2$ could be reduced to 1.5 equiv. without compromising the reaction yield (entry 6). Whereas the reaction performed in DCE only afforded a moderate yield of the product, with acetonitrile, toluene, and acetone as solvents extremely low yields of the products were isolated (entries 7–10). Other common organic solvents were also screened. However, none of them showed any activity in this reaction (entries 11–17). As a result, CH_2Cl_2 is the preferred and privileged medium for this aminohalogenation reaction in our protocol.

Various hypervalent iodine compounds were also examined to effect this transformation. The results are listed in Table 5. The reaction yield was lowered dramatically by utilizing [bis(trifluoroacetoxy)]iodobenzene (entry 2). Iodosylbenzene gave the product in good yield, which shows a

Table 3. Aminochlorination of electron-deficient olefins promoted by $PhI(OAc)_2$ in refluxing CH_2Cl_2.[a]

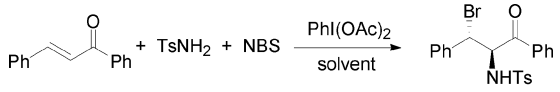


1 **2** **3** (±)

Entry	R^1	R^2	Time [h]	Product	Yield [%][b]	*dr* (*anti*/*syn*)[c]
1	Ph	Ph	4	**3a**	77	92:8
2	$4\text{-}ClC_6H_4$	Ph	5	**3b**	73	94:6
3	$2\text{-}ClC_6H_4$	Ph	5	**3c**	66	99:1
4	$3,4\text{-}Cl_2C_6H_3$	Ph	7	**3d**	71	>99:1
5[d,e]	$4\text{-}NO_2C_6H_4$	Ph	12	**3e**	58	>99:1
6	Ph	$4\text{-}MeOC_6H_4$	8	**3f**	73	91:9
7	$4\text{-}ClC_6H_4$	$4\text{-}MeOC_6H_4$	10	**3g**	72	88:12
8	Ph	$4\text{-}ClC_6H_4$	6	**3h**	67	93:7
9[e]	$4\text{-}ClC_6H_4$	$4\text{-}ClC_6H_4$	10	**3i**	71	>99:1
10	Ph	Me	8	**3j**	51	94:6
11	Ph	OMe	8	**3k**	59	>99:1
12	$4\text{-}ClC_6H_4$	OMe	12	**3l**	41	>99:1
13[d]	$4\text{-}ClC_6H_4$	OEt	12	**3m**	36	>99:1
14	Ph	NEt_2	9	**3n**	51	>99:1
15[e]	$4\text{-}ClC_6H_4$	NEt_2	8	**3o**	67	>99:1

[a] All reactions were performed with olefin **1** (0.5 mmol), Chloramine-T (1.0 mmol), and $PhI(OAc)_2$ (0.25 mmol) in refluxing CH_2Cl_2. [b] Isolated yields were determined by flash column chromatography. [c] Determined by ^1H NMR spectroscopy. [d] 0.5 mmol of $PhI(OAc)_2$ was employed. [e] 1.5 mmol of Chloramine-T was employed.

Table 4. Aminobromination of chalcone **1a** with $TsNH_2$ and NBS promoted by $PhI(OAc)_2$ in various solvents.[a]

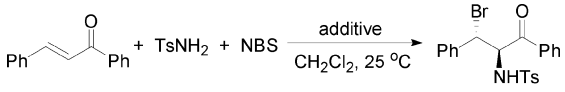


1a **4** **5** **6a** (±)

Entry	Solvent	*T* [°C]	Time [h]	Yield [%][b]	*dr* (*anti*/*syn*)[c]
1[d]	CH_2Cl_2	25	4	78	95:5
2[d]	CH_2Cl_2	reflux	3	74	95:5
3[d]	CH_2Cl_2	10	6	63	95:5
4[e]	CH_2Cl_2	25	4	70	96:4
5[f]	CH_2Cl_2	25	4	54	96:4
6	CH_2Cl_2	25	4	77	96:4
7	DCE	25	10	38	94:6
8	CH_3CN	25	12	7	95:5
9	PhMe	25	12	6	94:6
10	acetone	25	12	6	95:5
11	DMF	25	12	0	–
12	DMSO	25	12	0	–
13	THF	25	12	0	–
14	dioxane	25	12	trace	n.d.[g]
15	hexane	25	12	0	–
16	Et_2O	25	12	trace	n.d.[g]
17	EtOH	25	12	trace	n.d.[g]

[a] Unless otherwise specified, all reactions were performed with chalcone **1a** (0.5 mmol), $TsNH_2$ (0.75 mmol), NBS (0.75 mmol), and $PhI(OAc)_2$ (0.375 mmol) in the solvent indicated. [b] Isolated yields were determined by flash column chromatography. [c] Determined by ^1H NMR spectroscopy. [d] 1.0 mmol of $TsNH_2$ was employed. [e] 0.25 mmol of $PhI(OAc)_2$ was employed. [f] 0.125 mmol of $PhI(OAc)_2$ was employed. [g] Not determined.

Table 5. Aminobromination of chalcone **1a** with $TsNH_2$ and NBS promoted by various hypervalent iodine compounds.[a]



1a **4** **5** **6a** (±)

Entry	Additive	Time [h]	Yield [%][b]	*dr* (*anti*/*syn*)[c]
1	$PhI(OAc)_2$	4	77	96:4
2	$PhI(CF_3CO_2)_2$	24	7	93:7
3	PhI=O	6	67	94:6
4	PhI(OH)OTs	12	29	95:5
5	PhI(OH)OMs	12	33	93:7
6	PhI(OH)OCs	8	66	95:5
7	$PhI(C_6H_5CO_2)_2$	6	59	95:5
8	$PhI(4\text{-}MeOC_6H_4CO_2)_2$	8	58	94:6
9	$PhI(4\text{-}NO_2C_6H_4CO_2)_2$	12	43	95:5
10	$PhI(4\text{-}MeC_6H_4CO_2)_2$	12	39	95:5
11	$PhI(4\text{-}ClC_6H_4CO_2)_2$	5	69	94:6
12	$PhI(CH_3CH_2CO_2)_2$	4	78	94:6
13	$PhI[CH_3(CH_2)_2CO_2]_2$	4	71	95:5
14	$PhI[(CH_3)_2CHCO_2]_2$	5	71	94:6
15	$PhI[CH_3(CH_2)_4CO_2]_2$	6	75	95:5

[a] All reactions were performed with chalcone **1a** (0.5 mmol), $TsNH_2$ (0.75 mmol), NBS (0.75 mmol), and additive (0.375 mmol) in CH_2Cl_2 at 25 °C. [b] Isolated yields were determined by flash column chromatography. [c] Determined by ^1H NMR spectroscopy.

different property compared with the aminochlorination process (entry 3). When Koser's reagents were employed, the desired products were obtained in moderate-to-good yields (entries 4–6). Inferior results were obtained when the reactions were promoted by phenyliodine(III) dibenzoates (entries 7–11). Good results were observed with iodosobenzene additives derived from aliphatic carboxylic acids (entries 12–15). In particular, phenyliodine(III) dipropanoate was demonstrated to be the most efficient, providing about the same yield as $PhI(OAc)_2$ (entry 12). Overall, $PhI(OAc)_2$ was found to be the best choice for this transformation on the basis of its easy availability.

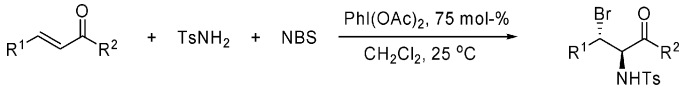
To demonstrate the generality of this method, the scope of the reaction was investigated under the optimized conditions and the results are summarized in Table 6. We found that the optimized conditions proved to be suitable for a range of enones, cinnamates, and cinnamides, and these reactions usually went to completion within 10 h. In all cases, none or only small amounts of *syn* diastereoisomers were detected. For reactions of chalcones with $TsNH_2$ and NBS, both electron-rich and -poor chalcones, which are suitable reaction partners in this process, afforded similar yields (entries 1–9). 4-Phenylbut-3-en-2-one, an enone with an alkyl group on the carbonyl moiety, also provided the corresponding chloramine in good yield (entry 10). Three cinnamates were aminobrominated to give the products in moderate-to-good yields and with slightly decreased diastereoselectivities (entries 11–13). Similarly, two cinnamides reacted smoothly with $TsNH_2$ and NBS to give the expected products in 67 and 41% yields, respectively, exclusively as the *anti* diastereoisomers (entries 14 and 15). Unfortunately, the olefins in which R^1 was an alkyl group are not suitable substrates under the current conditions.

When chalcone **7** with a 4-methoxyphenyl on the double bond was employed, the aminobrominated product was isolated in high yield as the reverse regioisomer (Scheme 2). This result is consistent with the electronic nature of the substrate and was also observed in the solid-state reaction.[18b]

Other sulfonamides employed as the nitrogen source for the aminobromination reaction of chalcone **1a** with NBS were also investigated (Table 7). Comparable yields were obtained when benzenesulfonamide and 4-chlorobenzenesulfonamide were utilized (entries 1–3). However, the activity of sulfonamide could be dramatically reduced by strong electron-withdrawing groups. The reaction only proceeded in 39% yield when 4-nitrobenzenesulfonamide was used as the nitrogen source (entry 4). The sterically encumbered 2,4,6-triisopropylbenzenesulfonamide failed to give any desired product even when the reaction time was prolonged (entry 5). Methylsulfonamide gave tolerable results, affording the corresponding chloramine in good yield (entry 6).

Other halogen sources were also employed in this transformation. The results are listed in Table 8. NCS was much less reactive than NBS, and a lower yield was obtained at 25 °C (entry 1). Raising the temperature increased the yield, but the product was still only isolated in moderate yield along with a lot of unreacted chalcone **1a** (entry 2). The

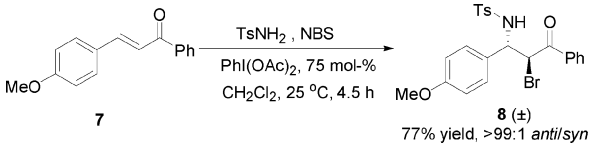
Table 6. Aminobromination of electron-deficient olefins promoted by $PhI(OAc)_2$.[a]



1 4 5 6 (±)

Entry	R^1	R^2	Time [h]	Product	Yield [%][b]	*dr* (*anti*/*syn*)[c]
1	Ph	Ph	4	**6a**	77	96:4
2	4-ClC_6H_4	Ph	4	**6b**	71	94:6
3	2-ClC_6H_4	Ph	4	**6c**	77	98:2
4	3,4-$Cl_2C_6H_3$	Ph	4	**6d**	75	96:4
5[d,e]	4-$NO_2C_6H_4$	Ph	7	**6e**	72	95:5
6	Ph	4-$MeOC_6H_4$	5	**6f**	78	96:4
7	4-ClC_6H_4	4-$MeOC_6H_4$	6.5	**6g**	76	93:7
8	Ph	4-ClC_6H_4	5	**6h**	73	95:5
9[f]	4-ClC_6H_4	4-ClC_6H_4	4	**6i**	71	96:4
10	Ph	Me	8	**6j**	65	88:12
11	Ph	OMe	8	**6k**	68	88:12
12[e,f]	4-ClC_6H_4	OMe	10	**6l**	45	91:9
13	4-ClC_6H_4	OEt	6	**6m**	62	87:13
14	Ph	NEt_2	8	**6n**	67	>99:1
15[e]	4-ClC_6H_4	NEt_2	8	**6o**	41	>99:1

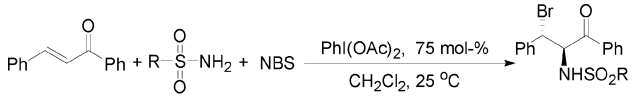
[a] Unless otherwise specified, all reactions were performed with olefin **1** (0.5 mmol), $TsNH_2$ (0.75 mmol), NBS (0.75 mmol), and $PhI(OAc)_2$ (0.375 mmol) in CH_2Cl_2 at 25 °C. [b] Isolated yields were determined by flash column chromatography. [c] Determined by ^1H NMR spectroscopy. [d] 0.6 mmol of $PhI(OAc)_2$ was employed. [e] 2.0 mmol of $TsNH_2$ was employed. [f] 0.5 mmol of $PhI(OAc)_2$ was employed.



7 8 (±)
77% yield, >99:1 *anti*/*syn*

Scheme 2. Reversed regioselectivity in the aminobromination of chalcone **7**.

Table 7. Aminobromination of chalcone **1a** with various sulfonamides.[a]

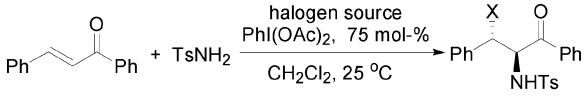


1a 9 5 10

Entry	R	Time [h]	Product	Yield [%][b]	*dr* (*anti*/*syn*)[c]
1	4-$CH_3C_6H_4$	4	**6a**	77	96:4
2	C_6H_5	4	**10a**	80	98:2
3	4-ClC_6H_4	5	**10b**	72	90:10
4[d]	4-$NO_2C_6H_4$	16	**10c**	39	94:6
5	2,4,6-(iPr)$_3C_6H_2$	24	**10d**	0	–
6	CH_3	10	**10e**	67	87:13

[a] Unless otherwise specified, all reactions were performed with chalcone **1a** (0.5 mmol), sulfonamide (0.75 mmol), NBS (0.75 mmol), and $PhI(OAc)_2$ (0.375 mmol) in CH_2Cl_2 at 25 °C. [b] Isolated yields were determined by flash column chromatography. [c] Determined by ^1H NMR spectroscopy. [d] 1.5 mmol of sulfonamide and 1.0 mmol of NBS were employed.

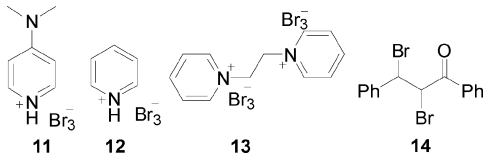
Table 8. Aminohalogenation of chalcone **1a** with various halogen sources.[a]



1a 4 3a (±) or 6a (±)

Entry	Source	X	Time [h]	Yield [%][b]	*dr* (*anti*/*syn*)[c]
1	NCS	Cl	8	21	95:5
2[d]	NCS	Cl	6	43	95:5
3	**11**	Br	12	0	–
4	**12**	Br	12	0	–
5	**13**	Br	12	0	–

[a] Unless otherwise specified, all reactions were performed with chalcone **1a** (0.5 mmol), $TsNH_2$ (0.75 mmol), the halogen source (0.75 mmol), and $PhI(OAc)_2$ (0.375 mmol) in CH_2Cl_2 at 25 °C. [b] Isolated yields were determined by flash column chromatography. [c] Determined by ^1H NMR spectroscopy. [d] The reaction was performed in refluxing CH_2Cl_2.

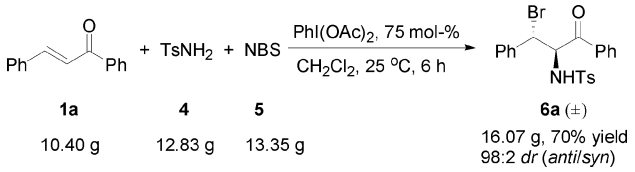


11 12 13 14

Figure 1. Other halogen sources employed in the aminohalogenation reaction and compound **14**.

other bromine sources shown in Figure 1 were examined, however, they all failed to give any of the desired products. Instead, the dibrominated compound **14** was isolated as the single product (entries 3–5).

Our methodology could be further highlighted by a gram-scale synthesis of bromoamine **6a** (Scheme 3). The reaction proceeded with great efficiency, giving the final product in good yield within 6 h on a laboratory scale.



Scheme 3. Gram-scale synthesis of vicinal bromoamine **6a**.

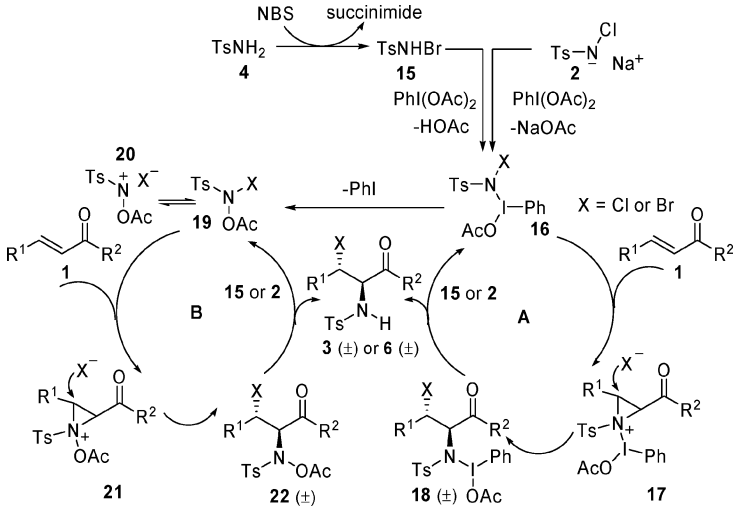
The exact mechanism of this aminohalogenation process is still unknown and the role of hypervalent iodine compounds remains to be clarified. However, based on Li and co-workers' proposition[6] and the results of our reaction, a tentative pathway can be proposed (Scheme 4). Chloramine-T may react with $PhI(OAc)_2$ to produce, after releasing NaOAc, intermediate **16a** (X = Cl) by ligand exchange. Similarly, NBS may react with $TsNH_2$ to generate *N*-bromo-*p*-toluenesulfonamide (**15**), which would be oxidized by $PhI(OAc)_2$ to yield intermediate **16b** (X = Br). Compound **16** may act as an active species to mediate the reaction (cycle A). The halogen anion may dissociate from **16** and the thus formed nitrenium intermediate could react with the double bond of **1** immediately to generate aziridinium **17**. Intermediate **17** is unstable and was attacked by the nearby halogen anion to yield compound **18** stereoselectively.[6,8] Finally, intermediate **18** reacted with TsNHBr (**15**) or Chloramine-T trihydrate to furnish the final haloamine product and regenerated intermediate **16**. However, in the aziridination of olefins with $PhI(OAc)_2$, it was believed that $PhI(OAc)_2$ oxidized *N*-aminophthalimide to produce intermediate PhI(OAc)(PhthNH) and the phenyl iodide group dissociated quickly to generate PhthNH(OAc) as a reactive intermediate.[25] Thus, we envisioned that the N–I bond of intermediate **16** might not be stable enough to survive the reaction process. The phenyl iodide group dissociated from **16** with the formation of *N*-acetoxy-*N*-halo-*p*-toluenesulfonamide **19**, which could be the active intermediate (cycle B). Species **19** forms an equilibrium with intermediate **20** by dissociation of the bromine anion because the nitrenium ion formed can be stabilized by the neighboring lone-pair on the oxygen atom of the acetoxy group.[26] The unstable nitrenium cation reacted with olefin **1** to afford aziridinium intermediate **21**. S_N2 nucleophilic attack on the aziridinium cation by the nearby halide anion produced intermediate **22** with high regio- and diastereoselectivity.[8] Finally, the *N*-acetoxyamine **22** reacted with TsNHBr (**15**) or Chloramine-T trihydrate to give the final product and regenerated intermediate **19**.[18]

Although we envisioned that cycle B was more reliable, we do not have any direct evidence to prove this hypothesis at this stage and the possibility of intermediate **16** as the reaction intermediate (cycle A) cannot be ruled out.

However, this catalytic cycle seems not to be so efficient. In most cases, 50 and 75 mol-% $PhI(OAc)_2$ were necessary for the aminochlorination and -bromination reactions, respectively, to achieve high yields. Decreasing the loading of $PhI(OAc)_2$ was harmful to the reaction yield. However, with 25 mol-% $PhI(OAc)_2$ as the catalyst, the bromoamine product could still be obtained in 54% yield (entry 5, Table 4). This result indicates that the catalytic effect of $PhI(OAc)_2$ actually exists, but the turnover number of this reaction is very small. Our continuing work on aminohalogenation reactions catalyzed by hypervalent iodine compounds will focus on improving catalytic efficiency.

Conclusions

We have demonstrated a practical and efficient methodology for the aminohalogenation of electron-deficient olefins with hypervalent iodine compounds as remarkable promoters in CH_2Cl_2 solution. A wide range of olefins were readily aminohalogenated in good yields and with excellent diastereoselectivities. Furthermore, the aminobromination reaction even proceeded on a multi-gram preparative scale, which shows it has great potential for application in both laboratory and industry. This protocol performed in CH_2Cl_2 affords a complementary alternative to the ball-



Scheme 4. Possible pathway for the hypervalent iodine-promoted aminohalogenation reaction.

milling reaction. Further studies focusing on aminohalogenation reactions promoted by hypervalent iodine compounds are underway.

Experimental Section

General Remarks: All reagents were obtained from commercial sources and used without further purification. Koser's reagent[23] and phenyliodine(III) dicarboxylates[24] were synthesized according to the reported methods. Chromatographic purification of products was accomplished using flash column chromatography on silica gel. All melting points were reported uncorrected. Nuclear magnetic resonance (NMR) spectra were acquired on a Bruker AV300 spectrometer operating at 300 and 75 MHz for ^1H and ^{13}C, respectively, and chemical shifts (δ) were reported in parts per million relative to tetramethylsilane. Infrared spectra were recorded on a VECTOR-12 infrared spectrometer in KBr pellet and reported in cm^{-1}. High-resolution mass spectra (HRMS) were recorded on a BRUKER VPEXII spectrometer with EI mode. Elemental analysis was performed on an Elementar Vario-III CHN analyzer.

General Procedure for the Aminochlorination of Electron-Deficient Olefins 1a–o with Chloramine-T: Chloramine-T trihydrate (281.7 mg, 1.0 mmol) and $PhI(OAc)_2$ (80.6 mg, 0.25 mmol) were added to a solution of chalcone **1a** (**1b**–**o**, 0.5 mmol) in CH_2Cl_2 (5 mL). This mixture was stirred at reflux for the appropriate time and monitored by TLC. Upon completion, the mixture was filtered to remove the insoluble material which was washed with CH_2Cl_2 (5 mL). The resulting solution was condensed under reduced pressure. The residual was separated on a silica gel column with petroleum ether/ethyl acetate (5:1) as the eluent to give the desired product **3a** (**3b**–**o**).

General Procedure for the Aminobromination of Electron-Deficient Olefins 1a–o with $TsNH_2$ and NBS: $TsNH_2$ (128.3 mg, 0.75 mmol), NBS (133.5 mg, 0.75 mmol), and $PhI(OAc)_2$ (120.9 mg, 0.375 mmol) were added to a solution of chalcone **1a** (**1b**–**o**, 0.5 mmol) in CH_2Cl_2 (5 mL). This mixture was stirred at 25 °C for the appropriate time and monitored by TLC. Upon completion, the mixture was directly separated on a silica gel column, without condensation, with petroleum ether/ethyl acetate (5:1) as eluent to give the desired product **6a** (**6b**–**o**).

Procedure for the Aminobromination of Chalcone 7 with $TsNH_2$ and NBS: $TsNH_2$ (128.3 mg, 0.75 mmol), NBS (133.5 mg, 0.75 mmol), and $PhI(OAc)_2$ (120.9 mg, 0.375 mmol) were added to a solution of chalcone **7** (119.0 mg, 0.5 mmol) in CH_2Cl_2 (5 mL). This mixture was stirred at 25 °C for 4.5 h. Upon completion, the mixture was directly separated on a silica gel column, without condensation, with petroleum ether/ethyl acetate (3:1) as eluent to give the desired product **8**.

General Procedure for the Aminobromination of Chalcone 1a with Sulfonamides and NBS: The relevant sulfonamide (0.75 mmol), NBS (133.5 mg, 0.75 mmol), and $PhI(OAc)_2$ (120.9 mg, 0.375 mmol) were added to a solution of chalcone **1a** (104.0 mg, 0.5 mmol) in CH_2Cl_2 (5 mL). This mixture was stirred at 25 °C for the appropriate time and monitored by TLC. Upon completion, the mixture was directly separated on a silica gel column, without condensation, with petroleum ether/ethyl acetate (5:1) as eluent to give the desired product **6a** (**10a**–**c** and **10e**).

General Procedure for the Aminohalogenation of Chalcone 1a with $TsNH_2$ and Various Halogen Sources: $TsNH_2$ (128.3 mg, 0.75 mmol), the relevant halogen source (0.75 mmol), and $PhI(OAc)_2$ (120.9 mg, 0.375 mmol) were added to a solution of chalcone **1a** (104.0 mg, 0.5 mmol) in CH_2Cl_2 (5 mL). This mixture was stirred at 25 °C for the appropriate time and monitored by TLC. Upon completion, the mixture was directly separated on a silica gel column, without condensation, with petroleum ether/ethyl acetate (5:1) as eluent to give the desired product.

Gram-Scale Synthesis of Bromoamine 6a: $PhI(OAc)_2$ (12.09 g, 37.5 mmol) was added to a mixture of chalcone **1a** (10.40 g, 50 mmol), $TsNH_2$ (12.83 g, 75 mmol), and NBS (13.35 g, 75 mmol) in CH_2Cl_2 (100 mL) in a 250 mL round-bottomed flask. This mixture was stirred vigorously at 25 °C for 6 h. The reaction was stopped and the solvent was evaporated to one-third of its volume. The residual was separated on a silica gel column with petroleum ether/ethyl acetate (5:1) as the eluent to give the crude product. This crude product was further purified by recrystallization from petroleum ether/ethyl acetate (5:1) to afford 16.07 g (70%) of bromoamine **6a**.

Products **3a**–**l**,[6g,18a] **3n**,[18a] **6a**–**o**,[11,18b] **8**,[11] **10a**,[18b] **10c**,[18b] and **10e**[18b] have previously been isolated and fully characterized and were characterized by comparison with their reported data. The physical and spectroscopic data of the newly synthesized compounds are given below.

Ethyl 3-Chloro-3-(4-chlorophenyl)-2-(tosylamino)propionate (3m): Yield 74.9 mg (36%); white solid, m.p. 99–101 °C. IR (KBr): $\tilde{\nu}$ = 3283, 2996, 1714, 1597, 1493, 1443, 1372, 1348, 1330, 1233, 1166, 1090, 1012, 908, 816, 763, 665, 552, 529 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.62 (d, J = 8.1 Hz, 2 H), 7.25–7.24 (m, 6 H), 5.22 (d, J = 9.6 Hz, 1 H), 5.08 (d, J = 6.0 Hz, 1 H), 4.36 (dd, J = 9.6, 6.0 Hz, 1 H), 4.04–3.92 (m, 2 H), 2.42 (s, 3 H), 1.11 (t, J = 6.9 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, all 1 C unless indicated otherwise): δ = 168.6, 144.1, 136.7, 135.1, 134.8, 129.8 (2 C), 129.2 (2 C), 128.8 (2 C), 127.3 (2 C), 62.5, 62.1, 61.3, 21.7, 13.9 ppm. HRMS (EI–TOF): calcd. for $C_{18}H_{18}NO_4S^{35}Cl$ [M – HCl]$^+$ 379.0645; found 379.0651. $C_{18}H_{19}Cl_2NO_4S$ (416.32): calcd. C 51.93, H 4.60, N 3.36; found C 51.79, H 4.66, N 3.28.

3-Chloro-3-(4-chlorophenyl)-*N*,*N*-diethyl-2-(tosylamino)propionamide (3o): Yield 148.3 mg (67%); white solid, m.p. 138–140 °C. IR (KBr): $\tilde{\nu}$ = 3184, 2927, 1627, 1492, 1339, 1160, 1093, 930, 812, 663, 545, 527 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.35 (d, J = 8.1 Hz, 2 H), 7.20–7.10 (m, 6 H), 5.90 (d, J = 9.3 Hz, 1 H), 4.90 (d, J = 9.3 Hz, 1 H), 4.68 (t, J = 9.3 Hz, 1 H), 3.50–3.44 (m, 3 H), 3.26–3.19 (m, 1 H), 2.40 (s, 3 H), 1.26 (t, J = 6.9 Hz, 3 H), 1.08 (t, J = 6.9 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, all 1 C unless indicated otherwise): δ = 169.0, 143.2, 137.8, 136.0, 134.8, 129.7 (2 C), 129.4 (2 C), 128.6 (2 C), 126.6 (2 C), 61.2, 57.5, 42.8, 41.2, 21.6, 14.1, 12.4 ppm. HRMS (EI–TOF): calcd. for $C_{20}H_{23}N_2O_3S^{35}Cl$ [M – HCl]$^+$ 406.1118; found 406.1111. $C_{20}H_{24}Cl_2N_2O_3S$ (443.39): calcd. C 54.18, H 5.46, N 6.32; found C 54.31, H 5.54, N 6.21.

3-Bromo-2-(4-chlorophenylsulfonylamino)-1,3-diphenylpropan-1-one (10b): Yield 172.1 mg (72%); white solid, m.p. 40–42 °C. IR (KBr): $\tilde{\nu}$ = 3274, 2925, 1681, 1594, 1450, 1341, 1163, 1089, 755, 698, 621, 522 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.83 (d, J = 7.8 Hz, 2 H), 7.66–7.61 (m, 1 H), 7.51–7.45 (m, 4 H), 7.25–7.17 (m, 7 H), 5.58–5.53 (m, 2 H), 5.11 (d, J = 6.0 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, all 1 C unless indicated otherwise): δ = 196.6, 139.3, 138.4, 136.5, 135.2, 134.5 (2 C), 129.2 (2 C), 129.0 (4 C), 128.8 (2 C), 128.6 (2 C), 128.5 (2 C), 60.8, 51.3 ppm. HRMS (EI–TOF): calcd. for $C_{21}H_{16}NO_3S^{35}Cl$ [M – HBr]$^+$ 397.0539; found 397.0540. $C_{21}H_{17}BrClNO_3S$ (478.79): calcd. C 52.68, H 3.58, N 2.93; found C 52.80, H 3.65, N 2.86.

Acknowledgments

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