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Aminochlorination in Water: First Brønsted Acid-Promoted Synthesis of Vicinal Chloramines

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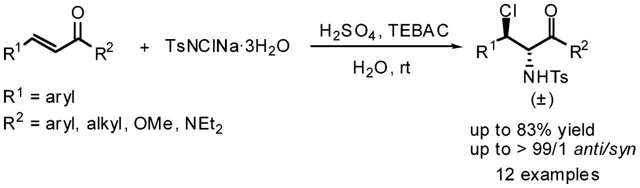

A practical and scaleable route for the regio- and diastereoselective synthesis of vicinal chloramines from electron-deficient olefins and Chloramine-T promoted by Brønsted acids in water has been realized for the first time. This novel protocol is efficient, mild, ecofriendly, and broadly applicable for the aminochlorination of various electron-deficient olefins including α,*β*-unsaturated ketones, cinnamate, and cinnamide. Water represents as a privileged solvent for the aminochlorination reaction in our system.

Vicinal haloamines obtained from the aminohalogenation of unsaturated carbon−carbon bonds are an important class of compounds that serve as useful intermediates of various pharmacologically active compounds by replacement of the halogen atom with multifarious nucleophiles.[1] Although the aminohalogenation reaction has been known for about 40 years, the preparation of vicinal haloamine derivatives still confronts significant limitations.[2] Recently, various procedures for the aminohalogenation of electron-deficient olefins have been successfully established by Li[3] and others.[4] A series of α,*β*-unsaturated ketones,[3g] esters,[3a−e] and nitriles[3j] have been aminochlorinated with good yield and excellent diastereoselectivity by the use of several different nitrogen/chlorine sources such as 4-TsNCl$_2$,[3a,c,e−h,j] 2-NsNNaCl,[3d] or the combination of 2-NsNCl$_2$ and 2-NsNHNa[3b,i] in the presence of metal catalysts.[5] However, most of these systems involve toxic solvents and transition metal catalysts. The use of more readily available and nontoxic catalysts instead of expensive and sensitive catalysts as well as non-organic solvents is highly desirable.

A metal-free aminochlorination reaction of chalcones with 2-NsNCl$_2$ in ionic liquid was reported very recently.[6] But the reaction was performed in a dried and heated system, and a large quantity of ionic liquid and other additives was employed to achieve high selectivity and yield. We[7] also reported the aminochlorination of electron-deficient olefins using commercially available inexpensive Chloramine-T[8] as a nitrogen and chlorine source promoted by (diacetoxyiodo)benzene under our mechanical milling conditions.[9] This methodology was very convenient and easy to handle; however, the relatively expensive hypervalent iodine reagent was used in 50 mol %, and therefore greatly restricted its application. Thus, we were triggered to develop more economical and environmentally friendly systems for this transformation.

On the other hand, performing organic reactions in more environmentally benign ways is an important goal from an ecological point of view.[10] Utilizing water as the reaction media has attracted many synthetic organic chemists because it is one of the best ways to avoid many environmental problems that can occur with industrial organic synthesis.[11] In our previous work, we disclosed that various Lewis acids could promote the aminochlorination of electron-deficient olefins.[7] We envisioned that Brønsted acids, which are cheaper and more readily available, may facilitate this transformation. In continuation of

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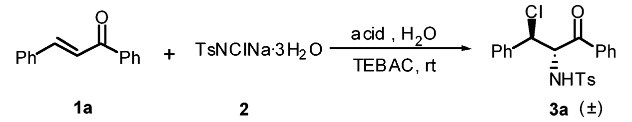
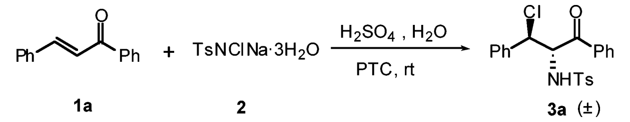
TABLE 1. Aminochlorination of Chalcone 1a Promoted by Various Brønsted Acids in Water[a]



entry	acid	time (h)	yield[b] (%)	dr[c] (*anti*/*syn*)
1		10	0	/
2	HCl	7	67	91/9
3	H_2SO_4	5	80	91/9
4	H_3PO_4	10	70	91/9
5	TsOH	5	79	92/8
6	MsOH	8	69	90/10
7[d]	L-proline	10	0	/
8[d]	HOAc	10	69	90/10
9[d]	$PhCO_2H$	6	64	90/10
10	TFA	6	66	92/8
11	TfOH	6	60	93/7
12[e]	H_2SO_4	5	78	90/10
13[f]	H_2SO_4	8	61	91/9
14[g]	H_2SO_4	10	58	92/8
15[h]	H_2SO_4	3	75	91/9

[a] Unless otherwise specified, all reactions were performed with chalcone **1a** (0.2 mmol), Chloramine-T (0.3 mmol), acid (0.24 mmol), and TEBAC (0.04 mmol) in water (2.0 mL) as solvent. [b] Isolated yields by flash column chromatography. [c] Determined by the analysis of ^{1}H NMR. [d] 2.0 equiv of the acid was used. [e] 0.2 mmol of H_2SO_4 was employed. [f] 0.1 mmol of H_2SO_4 was employed. [g] 0.2 mmol of Chloramine-T was employed. [h] Reaction was performed at 50 °C. TEBAC = triethylbenzylammonium chloride.

TABLE 2. H_2SO_4-Promoted Aminochlorination of Chalcone 1a Assisted by Various Phase-Transfer Catalysts (PTC)[a]



entry	PTC	time (h)	yield[b] (%)	dr[c] (*anti*/*syn*)
1		8	63	89/11
2	SDS	10	54	89/11
3	TMAB	10	45	92/8
4	TBAI	10	57	91/9
5	CTAB	10	47	89/11
6	TBAB	5	61	91/9
7	TEBAC	5	80	91/9
8[d]	TEBAC	5	79	91/9
9[f]	TEBAC	7	71	92/8

[a] Unless otherwise specified, all reactions were performed with chalcone **1a** (0.2 mmol), Chloramine-T (0.3 mmol), H_2SO_4 (0.24 mmol), and PTC (0.04 mmol) in water (2.0 mL) as solvent. [b] Isolated yields by flash column chromatography. [c] Determined by the analysis of ^{1}H NMR. [d] 0.06 mmol of TEBAC was employed. [f] 0.02 mmol of TEBAC was employed. SDS = sodium dodecyl sulfate, TMAB = tetramethylammonium bromide, TBAI = tetrabutylammonium iodide, TBAB = tetrabutylammonium bromide, CTAB = cetyltriethylammonium bromide.

our interest in organic reactions in water,[12] herein we report the first Brønsted acid-promoted aminochlorination of electron-deficient olefins with Chloramine-T in water.

In our initial study, we examined the inherent property of various Brønsted acids for the aminochlorination reaction of electron-deficient olefins in water with chalcone **1a** as model substrate. Because the reaction would generate hydroxide ion,[3,7] stoichiometric acid was necessary to achieve high conversion. Phase-transfer catalyst (PTC) was believed to accelerate this heterogeneous reaction because of the ionic character of Chloramine-T. The results are listed in Table 1 with triethylbenzylammonium chloride as the PTC agent. It should be emphasized that all of the reactions were performed in pure water in open air without any additive. The reaction was totally inert without an acid mediator (entry 1). However, we were pleased to find that the reaction promoted by common inorganic acids provided the desired chloramine **3a** in good yields and excellent diastereoselectivities at room temperature (entries 2−4). Among these examined acids, H_2SO_4 afforded the best result. TsOH gave a similar result as H_2SO_4, while MsOH provided a decreased yield (entries 5−6). Unfortunately, amino acid failed to give any product (entry 7). To our surprise, weak organic acids such as acetic acid and benzoic acid afforded moderate yields by increasing the acid loading (entries 8−9). However, fluorinated strong acids resulted in decreased yields (entries 10−11).

Although TsOH and H_2SO_4 exhibited similar activities, we chose the latter to promote this reaction because H_2SO_4 was more readily available and cheaper than TsOH. When we reduced the H_2SO_4 loading to 1.0 equiv, only a slightly decreased yield was observed (entry 12). Further reducing the H_2SO_4 loading to 0.5 equiv compromised the yield obviously even though the reaction time was prolonged (entry 13). When the loading of Chloramine-T was reduced to 1.0 equiv, the yield was decreased rapidly with lots of unreacted chalcone **1a** (entry 14). Elevated temperature was not necessary and resulted in a slightly decreased yield (entry 15). This H_2SO_4-promoted process exhibited as the most convenient and clean procedure to realize the highly efficient aminochlorination of chalcone **1a**.

Various solvent systems were explored for the aminochloriantion reaction of chalcone **1a** mediated by H_2SO_4. Organic solvents including hexane, toluene, THF, CH_2Cl_2, ethanol, and dioxane failed to produce any product. In CH_3CN, chloramine **3a** was isolated in 6% yield at room temperature. Aqueous media such as EtOH/H_2O = 1:1 and THF/H_2O = 1:1 were also screened; however, only trace products were observed. It is none but water could facilitate this acid-promoted aminochlorination reaction. Water represented as a unique reaction medium here.

Phase-transfer catalyst (PTC) was supposed to accelerate the reaction. We then screened the effects of various PTCs on the H_2SO_4-promoted aminochlorination reaction of chalcone **1a** (Table 2). Chloramine **3a** was obtained in 63% yield after 8 h without any PTC (entry 1). SDS, TMAB, TBAI, and CTAB were detrimental to the reaction (entries 2−6). It was only TEBAC that could facilitate this aminochlorination process. The exact reason for the unique accelerating property of TEBAC is unknown right now. With 20 mol % of TEBAC, the reaction afforded **3a** in 80% yield and excellent diastereoselectivity (entry 7). When we increased its loading, the yield did not rise (entry 8). However, reducing the loading caused an obvious decrease in both yield and reaction rate (entry 9).

With the optimized conditions in hand, the scope of this efficient reaction was explored with various electron-deficient olefins. The results are summarized in Table 3. Our method was successfully applied to a wide range of chalcones **3a**-**3i**, allowing preparation of aminochlorinated ketones in good yields

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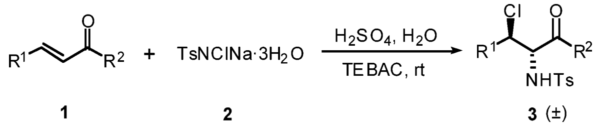
TABLE 3. H_2SO_4-Promoted Aminochlorination of Electron-Deficient Olefins in Water[a]



entry	R^1	R^2	product	time (h)	yield[b] (%)	dr[c] (*anti*/*syn*)
1	Ph	Ph	**3a**	6	83	91/9
2	4-Cl-C_6H_4	Ph	**3b**	6	77	94/6
3	2-Cl-C_6H_4	Ph	**3c**	8	71	96/4
4	3,4-Cl_2-C_6H_4	Ph	**3d**	12	69	>99/1
5[d,e]	4-NO_2-C_6H_4	Ph	**3e**	20	40	>99/1
6[d]	Ph	4-MeO-C_6H_4	**3f**	8	73	93/7
7[d]	4-Cl-C_6H_4	4-MeO-C_6H_4	**3g**	10	75	92/8
8	Ph	4-Cl-C_6H_4	**3h**	10	74	95/5
9[d,e]	4-Cl-C_6H_4	4-Cl-C_6H_4	**3i**	12	70	>99/1
10	Ph	Me	**3j**	15	41	95/5
11	Et	Ph	**3k**	10	0	/
12[d]	Ph	OMe	**3l**	15	71	>99/1
13[d]	Ph	NEt_2	**3m**	12	65	>99/1

[a] Unless otherwise specified, all reactions were performed with chalcone (0.5 mmol), Chloramine-T (0.75 mmol), H_2SO_4 (0.6 mmol), and TEBAC (0.1 mmol) in water (3 mL) as solvent. [b] Isolated yields by flash column chromatography. [c] Determined by the analysis of ^1H NMR. [d] 1.0 mmol of Chloramine-T was employed. [e] Reaction was performed at 50 °C.

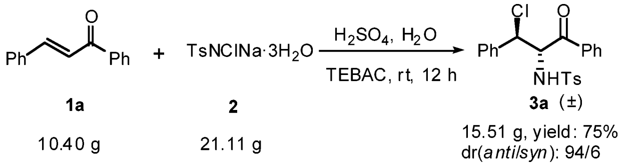
and diastereoselectivities except for **3e** (entries 1−9). The substrate with a strong electron-withdrawing NO_2 group only afforded the product in moderate yield (entry 5).

The superiority of our methodology could be successfully extended to an enone with R^2 as an alkyl group, which led to a moderate yield that was comparable with the (diacetoxyiodo)-benzene system[7] (entry 10). However the reaction failed when R^1 was an alkyl group probably due to its electronic factors (entry 11). The enones where R^1 = H or Me could be successfully aminochlorinated by using $TsNCl_2$ and CuOTf.[3g] Our unsuccess in aminochlorination of enones with R^1 as an alkyl group might ascribe to the different activities of $TsNCl_2$ and Chloramine-T.

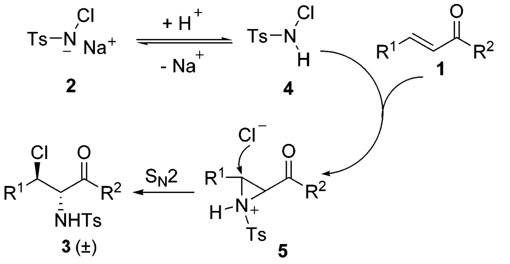
Representative cinnamate **3l** and cinnamide **3m** were also examined to show the scope. Much to our delight, both cinnamate and cinnamide could be aminochlorinated smoothly with good yields and excellent diastereoselectivities (entries 12 and 13).

To further demonstrate the advantage of our methodology, a gram-scale synthesis of chloramine **3a** was performed (Scheme 1). Again, the product was obtained in fairly good yield (75%) and high diastereoselectivity (94/6 *anti*/*syn*) after simple work-ups. It offered a robust access to gram quantities of aminochlorinated carbonyl compounds that exhibited a possibility for industrial application of our methodology.

SCHEME 1. Gram-Scale Synthesis of 3a



SCHEME 2. Possible Pathway of Brønsted Acid-Promoted Aminochlorination with Chloramine-T



Chloramine-T has recently been used for the aziridination of olefins catalyzed by metal salts[13] or halogenated compounds.[14] Some of these reactions were even performed in aqueous media.[13e,14e,f] However, the aziridinated products were not observed under our conditions. Based on the results, we proposed a possible pathway of our aminochlorination reaction (Scheme 2). In acidic medium, Chloramine-T was transformed into chloramine **4**, which could react with olefin **1** to yield aziridium **5** by elimination of Cl^-.[3,7] Intermediate **5** was immediately attacked by the nearby Cl^- to afford the final product **3**. The highly regio- and stereoselectivity of the reaction perfectly supported this S_N2 process.

In summary, we have demonstrated a Brønsted acid-promoted regio- and diastereoselective aminochlorination of electron-deficient olefins in water with Chloramines-T as nitrogen as well as chlorine source. The use of water as a green reaction medium proved critical to achieve high yield and selectivity. This unprecedented method has several synthetically attractive features: environmental benign reaction medium, operational simplicity, totally metal free, minimal byproducts, and suitable for large-scale synthesis. To the best of our knowledge, this is the most convenient and practical methodology so far.

Experimental Section

General Procedure for the Aminochlorination of Chalcone 1a Promoted by Various Brønsted Acids in Water. To a mixture of chalcone **1a** (41.6 mg, 0.2 mmol), Chloramine-T trihydrate (84.3 mg, 0.3 mmol), and TEBAC (9.1 mg, 0.04 mmol) in a 25 mL round-bottom flask was added a chosen Brønsted acid (0.24 mmol) in H_2O (2.0 mL). This mixture was allowed to stir vigorously at room temperature for the indicated time. The reaction was stopped, and ethyl acetate (2 mL × 2) was added to extract the product. The organic layer was dried with $MgSO_4$ and then evaporated to dryness in vacuo. The residual was separated on a silica gel column with petroleum ether/ethyl acetate 7:1 as the eluent to get the desired product **3a**:[3g] ^1H NMR (300 MHz, $CDCl_3$) δ 7.71 (d, J = 7.8 Hz, 2H), 7.58 (t, J = 7.3 Hz, 1H), 7.52 (d, J = 8.1 Hz, 2H), 7.40 (t, J = 7.3 Hz, 2H), 7.27−7.19 (m, 5H), 7.03 (d, J = 8.1 Hz, 2H), 5.54 (d, J = 9.6 Hz, 1H), 5.40 (dd, J= 9.6, 6.3 Hz, 1H), 5.11 (d, J = 6.3 Hz, 1H), 2.27 (s, 3H).

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General Procedure for the Aminochlorination of Electron-Deficient Olefins 1a−m in Water. To a mixture of electron-deficient olefins **1a** (**1b−m**, 0.50 mmol), Chloramine-T trihydrate (211.0 mg, 0.75 mmol), and TEBAC (22.8 mg, 0.10 mmol) was added H_2SO_4 (58.8 mg, 0.60 mmol) in H_2O (3.0 mL). This mixture was allowed to stir vigorously at room temperature for the indicated time. The same workup procedure afforded product **3a** (**3b−m**).

Gram-Scale Synthesis of Chloramine 3a. To a mixture of chalcone **1a** (10.40 g, 50 mmol), Chloramine-T trihydrate (21.10 g, 75 mmol), and TEBAC (0.91 g, 4 mmol) in a 250 mL round-bottom flask was added H_2SO_4 (4.90 g, 50 mmol) in H_2O (100 mL). This mixture was allowed to stir vigorously at room temperature for 12 h. The reaction was stopped, and ethyl acetate (50 mL × 2) was added to extract the product. The organic layer was dried with $MgSO_4$ and then evaporated to dryness in vacuo. The resulting pale yellow solid was washed with petroleum ether (50 mL) and was then recrystallized from petroleum ether/EtOAc 5/1 to afford 15.51 g (75%) of product **3a**.

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Supporting Information Available: Detailed experimental procedures, ^{1}H NMR spectral data and spectra of **3a−j**,**l**,**m**. This material is available free of charge via the Internet at http://pubs.acs.org.

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