JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

COMMUNICATION

pubs.acs.org/JACS

Catalytic Asymmetric Chloroamination Reaction of α,β-Unsaturated γ-Keto Esters and Chalcones

Yunfei Cai, Xiaohua Liu, Jun Jiang, Weiliang Chen, Lili Lin, and Xiaoming Feng*

Key Laboratory of Green Chemistry & Technology, Ministry of Education, College of Chemistry, Sichuan University, Chengdu 610064, P. R. China

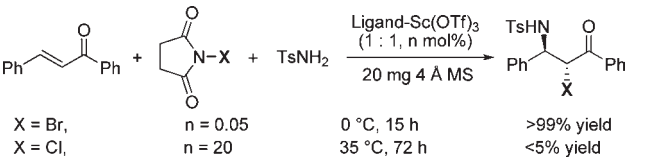
Supporting Information

ABSTRACT: Highly efficient catalytic chloroamination reaction of α,β-unsaturated γ-keto esters and chalcones has been developed via a chloronium-based mechanism to deliver *anti*-regioselective vicinal chloroamines instead of the aziridinium intermediates delivered aminochlorides. The combination of $TsNCl_2$ and $TsNH_2$ as reagents made the transformation highly efficient, delivering the γ-carbonyl-β-chloro-α-amino acid derivatives and α-chloro-β-amino-ketone derivatives in nearly quantitative yields with up to 99% ee and 99:1 dr under 0.05−0.5 mol % catalyst loading. TsNHCl was demonstrated to act as the key reactive species to form a bridged chloronium ion intermediate in the presence of a chiral scandium complex. The method might provide useful information for further realization of other haloamination reactions.

The functionalization of olefins with halogen and amine groups remains an intriguing challenge in modern organic synthesis.[1] Moreover, the resulting vicinal haloamine derivatives represent very useful structure moieties in medicinal chemistry[2] and can also serve as key intermediates for further manipulations.[3] In the past decades, considerable progress has been made in developing efficient synthetic approaches to this functionality.[4] However, asymmetric synthesis of these haloamines through direct aminohalogenation or haloamination reaction remains quite limited and only two examples reported by Li group gave vicinal chloroamines with moderate diastereoselectivities via a chiral substrate-directed process.[5] Recently, our group reported the efficient catalytic asymmetric bromoamination of chalcones to synthesize vicinal bromoamines using NBS/$TsNH_2$ as bromine and nitrogen sources.[6] Unfortunately, the attempt to employ NCS/$TsNH_2$ as chlorine and nitrogen sources in the chloroamination of chalcones, even under 20 mol % catalyst loading at 35 °C, seemed unsuccessful (Scheme 1).

We postulated that the main issues were as follows: (1) the low reactivity of NCS or chalcones in the chloroamination reaction led to the sluggish formation of the bridged chloronium ion intermediate; (2) the bridged chloronium ion was more unstable than the bromonium ion due to its smaller atomic radius and higher electronegativity. Thus, searching for more reactive substrates or reagents, which could form and capture the chloronium ion intermediate, is essential to solve this challenging objective.

Scheme 1. Contrast between Chloroamination Reaction and Bromoamination Reaction of Chalcone



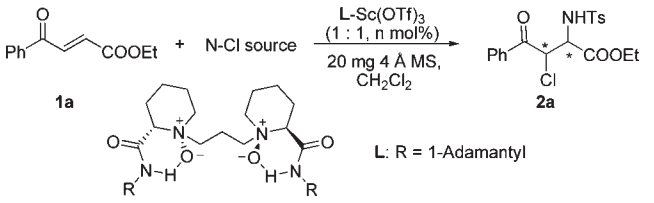
Herein, we address this issue and report the first highly enantioselective chloroamination reaction to afford enantiomerically enriched γ-carbonyl-β-chloro-α-amino acid derivatives and α-chloro-β-amino-ketone derivatives in excellent outcomes.

Initially, activated α,β-unsaturated γ-keto ester **1a** was chosen as a model substrate to optimize the reaction conditions which could afford useful β-chloro-α-amino acid derivative **2a**. With *N*-chlorosuccinimide (NCS) and *p*-toluenesulfonamide ($TsNH_2$) as chlorine and nitrogen sources, an investigation on a series of ligands and central metals (see Supporting Information for details) showed that (*S*)-pipecolic acid derived *N*,*N*′-dioxide **L**-Sc(OTf)$_3$ could produce **2a** exclusively with 96% ee and 97:3 dr but in 45% yield (Table 1, entry 1). The low yield prompted us to examine other active chlorine and nitrogen sources. *N*,*N*-Dichloro-4-methylbenzene-sulfonamide ($TsNCl_2$) was widely used as both a chlorine and nitrogen source in amino-chloronation reactions.[4e] When it was employed in the reaction, pleasingly, the yield of **2a** increased from 45% to 72% without the formation of an aminochlorinated product (Table 1, entry 2). However, the source of where the hydrogen on the nitrogen of the product **2a** came from intrigued us. We speculated that it most probably came from a trace amount of water in the system. Thus, the combination of additives which contain an active proton might further accelerate the reaction. Meanwhile, $TsNH_2$ can serve as not only an additive to meet the above prerequisite but also a reagent to participate in the reaction. When $TsNH_2$ was combined with $TsNCl_2$, the transformation became highly efficient, and complete conversion was accomplished in less than 2 h without any loss of stereoselectivity even under 0.05 mol % catalyst loading (>95% yield, 94% ee, 96:4 dr; Table 1, entries 3−4). Furthermore, use of 0.6 equiv of $TsNH_2$/$TsNCl_2$ (1:1) still gave complete conversion with higher ee (98% yield, 97% ee, Table 1, entry 5). It was noteworthy that the absence of 4 Å MS led to a sharply decreased yield (61% yield, Table 1, entry 6 vs entry 4).

Received: November 28, 2010
Published: March 28, 2011

dx.doi.org/10.1021/ja110668c | *J. Am. Chem. Soc.* 2011, 133, 5636–5639

Table 1. Optimization of the Reaction Conditions[a]



entry	N−Cl source	*n* (mol %)	time (h)	ee (%), dr[b]	yield (%)[c]
1	$NCS/TsNH_2$	5	48	96, 97:3	45
2	$TsNCl_2$	5	48	94, 96:4	72
3	$TsNCl_2/TsNH_2$	5	0.5	94, 96:4	>95[d]
4[e]	$TsNCl_2/TsNH_2$	0.05	2	94, 96:4	98
5[e,f]	$TsNCl_2/TsNH_2$	0.05	6	97, 96:4	98
6[f,g]	$TsNCl_2/TsNH_2$	5	24	97, 96:4	61

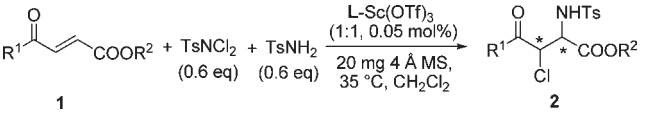
[a] Unless otherwise noted, all reactions were performed with **L**-Sc(OTf)$_3$ (1:1), new activated 4 Å MS (20 mg), **1a** (0.1 mmol), N−Cl source (1:1, 0.12 mmol) in CH_2Cl_2 (0.5 mL) under N_2 at 35 °C for the indicated time. [b] Determined by chiral HPLC. [c] Isolated yield. [d] Total conversion, less than 5% yield of byproducts. [e] Using 0.05 mol % catalyst (8 μL, 0.006 M **L**-Sc(OTf)$_3$ in THF). [f] Using 0.6 equiv of $TsNCl_2$/$TsNH_2$ (1:1). [g] Without 4 Å MS.

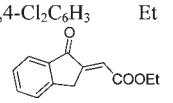
Under the optimized conditions (Table 1, entry 5), the substrate scope was investigated. As shown in Table 2, in all cases, the ee values of the products **2** were excellent (93−99% ee, Table 2) and the yields were as well (Table 2, entries 1−2, 5−17) except for substrates with a bulky group on the ester moiety (Table 2, entries 3 and 4). The diastereoselectivity was influenced a little by the electronic property of the substituents at the aromatic ring. Generally, the substrates with an electron-donating group gave the desired products with a high dr (Table 2, entries 7−8), while the electron-withdrawing substituents on the phenyl group reduced the stability of the chloronium intermediate which resulted in a relatively lower diastereoselectivity (Table 2, entries 9−13). Notably, fused-ring esters as well as multisubstituted and heteroaromatic-substituted ones were tolerated under the current system (Table 2, entries 14−17).[7]

Encouraged by the extremely high reactivity of $TsNCl_2$/$TsNH_2$, we then returned to realize the chloroamination reaction of chalcones **3**. As shown in Table 3, the desired α-chloro-β-amino-ketone derivatives **4** were obtained in good to excellent yield with excellent diastereoselectivities (>99:1 dr) and excellent enantioselectivities (96−99% ee) under a 0.05−0.5 mol % catalyst loading. Remarkably, fused-ring chalcones as well as cinnamyl-, heteroaromatic-, and multisubstituted ones were also suitable substrates for the reaction (Table 3, entries 10−12, 23−26). Distinctively, for a chalcone derivative with a *para*-methoxy substituent on the β-phenyl group, a poor ee value (Table 3, entry 27) was obtained which was in accord with that in the bromoamination reaction. It implied that a similar bridged chloronium ion intermediate was possible and an electron-rich chloronium ion might be easier to racemize through the bimolecular olefin-to-olefin transfer pathway.[6,8]

Additionally, the stereostructures of the chloroaminated products **2** and **4** were assigned on the basis of HRMS analysis, which showed the prominent peaks corresponding to the $[TsNHCHCOOR]^+$ or $[ArCHNHTs]^+$ ion fragment. The

Table 2. Substrate Scope for the Catalytic Asymmetric Chloroamination Reaction of α,β-Unsaturated γ-Keto Esters[a]



entry	R^1	R^2	**2**	yield (%)[b]	ee (%)[c]	dr[d]
1	Ph	Et	**2a**	98	97	96:4
2	Ph	Me	**2b**	98	96	95:5
3[e]	Ph	*i*-Pr	**2c**	80	95	98:2
4[e]	Ph	*t*-Bu	**2d**	65	96	97:3
5[e]	Ph	Bn	**2e**	98	>95	>96:4
6[e]	Ph	Ph	**2f**	93	97	96:4
7	4-$MeOC_6H_4$	Et	**2g**	97	99	98:2
8	4-MeC_6H_4	Et	**2h**	99	97	98:2
9	4-FC_6H_4	Et	**2i**	99	97	92:8
10	4-ClC_6H_4	Et	**2j**	96	98	93:7
11	4-BrC_6H_4	Et	**2k**	95	93	87:13
12	4-$NO_2C_6H_4$	Et	**2l**	95	93	83:17
13	3-$NO_2C_6H_4$	Et	**2m**	93	94	93:7
14	2-naphthyl	Et	**2n**	96	97	>95:5
15[e,f]	2-furyl	Et	**2o**	95	98	>99:1
16	3,4-$Cl_2C_6H_3$	Et	**2p**	96	96	87:13
17[e]			**2q**	95	98	>99:1

[a] Unless otherwise noted, all reactions were carried out with 0.05 mol % **L**/Sc(OTf)$_3$ (1/1), **1** (0.1 mmol), $TsNCl_2$ (0.06 mmol), $TsNH_2$ (0.06 mmol), new activated 4 Å MS (20.0 mg) in 0.5 mL of CH_2Cl_2 at 35 °C (for details, see Supporting Information). [b] Isolated yield. [c] Determined by chiral HPLC. [d] Determined by chiral HPLC or ^1H NMR analysis. [e] Using 0.2 mol % catalyst. [f] Reaction was performed at 20 °C for 40 h.

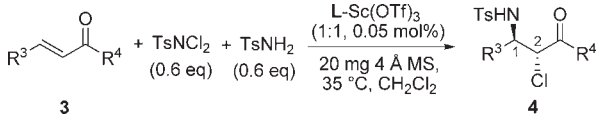
absolute configuration (1*R*,2*R*) was determined by X-ray crystallography of product **4u**,[9] which also confirmed the *anti*-configuration and stereostructure assignment.

Based on the control experiments (see Supporting Information for details) as well as the full transformation using 0.6 equiv of $TsNH_2/TsNCl_2$ (1:1) as reagents and the observation of two N-protected products employing 0.6 equiv of $MeSO_2NH_2/TsNCl_2$ (1:1) as reagents,[7] TsNHCl was demonstrated to be an extremely active species in the chloroamination reaction. It was also notable that 4 Å MS played a crucial role in accelerating the formation of TsNHCl from the mixture of $TsNCl_2$ and $TsNH_2$, which was unambiguously monitored by ^1H NMR analysis (see Supporting Information for details). Although $TsNCl_2$ could also work as a chlorine/nitrogen reagent, the directly functionalized product **B** (Scheme 2) could not be transformed into the product **A** under the current catalytic conditions which indicated that $TsNCl_2$ was not the reagent to form the chlorinum ion intermediate and further confirmed that TsNHCl from the reaction of $TsNCl_2$ with a trace amount of H_2O should be the real reactant.

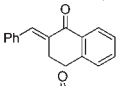
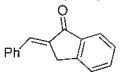
In light of the *anti*-configuration, a bridged chloronium ion intermediate should be conceivable (Scheme 2). The same absolute configuration of the chloroamination products[10] as that of bromoaminated ones[6] brought around an onium intermediate. Therefore, a possible mechanism was that the highly reactive species TsNHCl was generated upon the promotion of the 4 Å MS initially. Then, a *N*,*N*′-dioxide-Sc(III) complex mediated the formation of the chiral chloronium ion intermediate following instantly nucleophilic attack of negative nitrogen to deliver the

dx.doi.org/10.1021/ja110668c | *J. Am. Chem. Soc.* 2011, 133, 5636–5639

Table 3. Substrate Scope for the Catalytic Asymmetric Chloroamination Reaction of Chalcones[a]



3 4

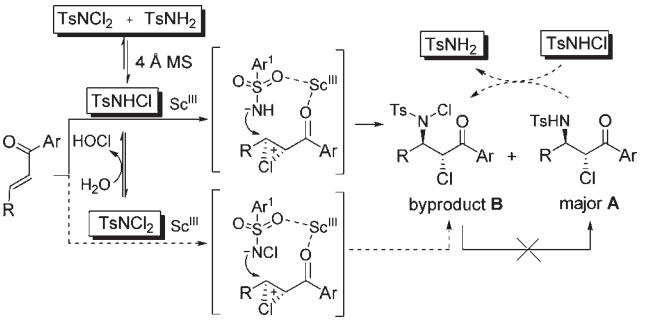
entry	R^3, R^4	4	yield (%)[b]	ee (%)[c]	dr[d]
1	Ph, Ph	**4a**	99	98	>99:1
2	Ph, 4-MeC_6H_4	**4b**	99	98	>99:1
3	Ph, 3-MeC_6H_4	**4c**	99	96	>99:1
4	Ph, 4-FC_6H_4	**4d**	99	97	>99:1
5	Ph, 4-ClC_6H_4	**4e**	96	98	>99:1
6	Ph, 4-BrC_6H_4	**4f**	95	98	>99:1
7	Ph, 4-$MeOC_6H_4$	**4g**	92	98	>99:1
8	Ph, 4-$NO_2C_6H_4$	**4h**	91	97	95:5
9	Ph,3-$NO_2C_6H_4$	**4i**	96	95	>99:1
10	Ph, 2-naphthyl	**4j**	99	98	>99:1
11	Ph, 3,4-$Cl_2C_6H_3$	**4k**	96	98	>99:1
12[e,f]	Ph, 2-furyl	**4l**	99	99	>99:1
13	2-MeC_6H_4, Ph	**4m**	96	97	98:2
14	3-MeC_6H_4, Ph	**4n**	99	97	97:3
15	4-MeC_6H_4, Ph	**4o**	97	97	98:2
16	4-FC_6H_4, Ph	**4p**	99	98	>99:1
17	4-ClC_6H_4, Ph	**4q**	98	98	>99:1
18	4-BrC_6H_4, Ph	**4r**	94	98	>99:1
19	3-$MeOC_6H_4$, Ph	**4s**	98	96	>99:1
20	4-PhC_6H_4, Ph	**4t**	88	97	>99:1
21	3-$NO_2C_6H_4$, Ph	**4u**	90	99 (1*R*, 2*R*)[g]	>99:1
22	3,4-$Cl_2C_6H_3$, Ph	**4v**	98	97	>99:1
23	2-naphthyl, Ph	**4w**	96	98	>99:1
24	PhCH=CH-, Ph	**4x**	95	98	97:3
25[e]		**4y**	85	97	>99:1
26[e]		**4z**	75	96	>99:1
27	Ph, 4-$MeOC_6H_4$	**4ba**	61	21	>99:1

[a] Unless otherwise noted, all reactions were carried out with 0.05 mol % **L**/$Sc(OTf)_3$ (1/1), **3** (0.1 mmol), $TsNCl_2$ (0.06 mmol), $TsNH_2$ (0.06 mmol), new activated 4 Å MS (20.0 mg) in 0.5 mL of CH_2Cl_2 at 35 °C (See Supporting Information for details). [b] Isolated yield. [c] Determined by chiral HPLC. [d] Determined by chiral HPLC or ^1H NMR analysis. [e] Using 0.5 mol % catalyst. [f] Reaction was performed at 0 °C with preactivated reagents. [g] Determined by X-ray crystallography.

final product **A**, and a trace amount of byproduct **B**[10] could be formed by the reaction of product **A** with TsNHCl.[11]

In summary, we have developed a highly efficient catalytic enantioselective chloroamination reaction. Remarkably, with 0.05−0.5 mol % chiral *N*,*N*′-dioxide-Sc(III) complex, the reaction was performed well over a series of (*E*)-α,*β*-unsaturated *γ*-keto esters and chalcones,[12] giving the desired products regioselectively in excellent yields (up to 99%) with excellent diastereoselectivities (>99:1) and enantioselectivities (up to 99% ee) under mild conditions. The demonstration that TsNHCl performed as the key reactive species to form the chloronium ion intermediate might provide a new entry for further realization of other haloamination reactions. Further efforts will be dedicated to explore the application to simple olefins and other α,*β*-unsaturated compounds as well as the protection group of the *N*-source to make the reaction more useful.

Scheme 2. Possible Mechanism of the Chloroamination Reaction



■ ASSOCIATED CONTENT

Supporting Information. Experimental details and analytic data (NMR, HPLC, and ESI-HRMS). This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author
xmfeng@scu.edu.cn

■ ACKNOWLEDGMENT

We appreciate the National Natural Science Foundation of China (Nos. 20732003 and 21021001) and National Basic Research Program of China (973 program: No. 2010CB833300) for financial support. We also thank Sichuan University Analytical & Testing Center for NMR analysis and X-ray analysis.

■ REFERENCES

(1) Kemp, J. E. G. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 3, pp 469−513 and reference therein.

(2) Thomas, G. *Medicinal Chemistry: An Introduction*; John Wiley & Sons: New York, 2000.

(3) De Kimpe, N.; Verhé, R. *The Chemistry of α-Haloketones, α-Haloaldehydes, and α-Haloimines*; John Wiley & Sons: New York, 1988.

(4) (a) Li, G.; Wei, H.-X.; Kim, S. H.; Neighbors, M. *Org. Lett.* **1999**, *1*, 395–397. (b) Li, G.; Wei, H.-X.; Kim, S. K. *Org. Lett.* **2000**, *2*, 2249–2252. (c) Chen, D.; Timmons, C.; Chao, S.; Li, G. *Eur. J. Org. Chem.* **2004**, 3097–3101. (d) Yeung, Y.-Y.; Gao, X.; Corey, E. J. *J. Am. Chem. Soc.* **2006**, *128*, 9644–9645. (e) Li, G.; Kotti, S. S. R. S.; Timmons, C. *Eur. J. Org. Chem.* **2007**, 2745–2758. (f) Wu, X.-L.; Xia, J.-J.; Wang, G.-W. *Org. Biomol. Chem.* **2008**, *6*, 548–553. (g) Wu, X.-L.; Wang, G.-W. *Eur. J. Org. Chem.* **2008**, 6239–6246. (h) Chen, Z.-G.; Wei, J.-F.; Li, R.-T.; Shi, X.-Y.; Zhao, P.-F. *J. Org. Chem.* **2009**, *74*, 1371–1372. (i) Chen, Z.-G.; Wei, J.-F.; Wang, M.-Z.; Zhou, L.-Y.; Zhang, C.-J.; Shi, X.-Y. *Adv. Synth. Catal.* **2009**, *351*, 2358–2368. (j) Wei, J.-F.; Chen, Z.-G.; Lei, W.; Zhang, L.-H.; Wang, M.-Z.; Shi, X.-Y.; Li, R.-T. *Org. Lett.* **2009**, *11*, 4216–4219. (k) Zhi, S.-J.; Sun, H.; Zhang, G.; Li, G.; Pan, Y. *Org. Biomol. Chem.* **2010**, *8*, 628–631.

(5) (a) Xu, X.; Kotti, S. S. R. S.; Liu, J.; Cannon, J. F.; Headley, A. D.; Li, G. *Org. Lett.* **2004**, *6*, 4881–4884. (b) Wang, Y.-N.; Kattuboina, A.; Ai, T.; Banerjee, D.; Li, G. *Tetrahedron lett.* **2007**, *48*, 7894–7898.

(6) Cai, Y. F.; Liu, X. H.; Hui, Y. H; Jiang, J.; Wang, W. T.; Chen, W. L.; Lin, L. L.; Feng, X. M. *Angew. Chem., Int. Ed.* **2010**, *49*, 6160–6164.

(7) In this catalytic system the sulfonyl group seemed very important to the activity. We tested other RNH_2 donors combined with $TsNCl_2$,

such as $PhNH_2$, $PhCONH_2$, and CH_3CONH_2, but no corresponding products were observed. The combination of $MsNH_2$ and $TsNCl_2$ provided the TsNH and MsNH products together with compatible stereoselectivity (97% ee, 96:4 dr for TsNH product and 96% ee, 98:2 dr for MsNH product **2r**). The yield of the latter increased from 51% to 76% when the amount of $MsNH_2$ increased from 0.6 to 5 equiv which implied that MsNHCl or TsNHCl might be the active chloride/nitrogen species. The products of **1a** with $PhSO_2NH_2$ and $TsNCl_2$ could not be separated, but the amount of sulfonamide had a similar influence on the yield (from 43% to 51% determined by ^1H NMR).

(8) (a) Brown, R. S. *Acc. Chem. Res.* **1997**, *30*, 131–137. (b) Denmark, S. E.; Burk, M. T.; Hoover, A. J. *J. Am. Chem. Soc.* **2010**, *132*, 1232–1233.

(9) CCDC 798271 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambrige Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.

(10) Trace amounts of byproduct **B** were observed for the substrates surveyed. Substrate **1m** gave the corresponding byproduct **5m** in 6% yield (see Supporting Information).

(11) (a) Banerji, K. K.; Jayaram, B; Mahadevappa, D. S. *J. Sci. Ind. Res.* **1987**, *46*, 65. (b) Puttaswamy; Jagadeesh, R. V. *Appl. Catal. A: Gen.* **2005**, *292*, 259–271. (c) Puttaswamy; Suresha, N. *Indian J. Chem., Sect. A: Inorg., Bio-inorg., Phys., Theor. Anal. Chem.* **2008**, 1649–1655.

(12) Under the current catalyst system, the investigation of other olefins such as styrene, cinnamone, and nitroalkene indicated that the benzoyl group on the enones had direct influences on the reactivity as well as regio- and stereoselectivity. When styrene was used, racemic products with poor regioselectivity (1:3) and moderate yield (50%) were obtained. For cinnamone as the substrate, moderate yield and stereoselectivity (70% ee, 87:13 dr) were obtained with the problem that byproducts from the α-chloriantion reaction were generated. Complicated products were obtained with nitroalkene as the substrate (see Supporting Information for details).