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Asymmetric Iodoamination of Chalcones and 4-Aryl-4-oxobutenoates Catalyzed by a Complex Based on Scandium(III) and a *N,N′*-Dioxide Ligand

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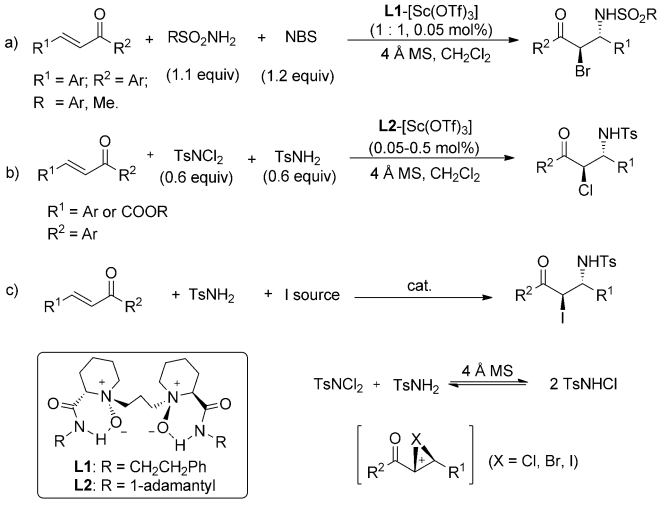
Abstract: Highly diastereo- and enantioselective iodoamination of chalcones, 4-aryl-4-oxobutenoates, and a trifluoro-substituted enone has been accomplished in the presence of a chiral *N,N′*-dioxide/[$Sc(OTf)_3$] complex (0.5–2 mol%), delivering the desired vicinal *anti*-α-iodo-β-amino carbonyl compounds regioselectively in high yields (up to 97%) and with excellent diastereoselectivities (>99:1 d.r.) and enantioselectivities (up to 99% *ee*). Enantiopure *syn*-α-iodo-β-amino products could also be obtained from the isomerization of particular iodo compounds. TsNHX species (X = Cl, Br, I), generated from the reactions between the halo sources and $TsNH_2$, were further confirmed as the active species in the haloamination reactions involved in the formation of the key halonium ion intermediates. A typical haloamination dependency was observed, with reactivity decreasing in the order NBS > NIS ≫ NCS.

Keywords: asymmetric catalysis · dioxides · iodoamination · iodonium ions · scandium

The intermolecular reactions between olefins and sources of N^- and X^+ (X = F, Cl, Br, I)—haloamination or aminohalogenation reactions—are powerful methods for the preparation of vicinal haloamines, which are among the most versatile building blocks in organic synthesis.[1–4] Diastereoselective variants of these reactions for the synthesis of *anti*-chloroamines and *anti*-bromoamines have been well documented in the last decades.[5–7] A series of transition metal salts, as well as their complexes, such as CuOTf, CuI, $CuCl_2{\cdot}2H_2O$, CuCN, $Cu(OAc)_2$, V_2O_5, $MnSO_4$, Mn^{III}/salen, $FeCl_3$, $FeCl_3/PPh_3$, $Co(OAc)_2{\cdot}4H_2O$, $NiCl_2{\cdot}6H_2O$, $ZnCl_2$, $LPdCl_2$ (L = 1,10-phenanthroline), Pd/C, $[(C_3F_7CO_2)_2Rh]_2$, and $K_2OsO_2(OH)_4/(DHQ)_2PHAL$, have been employed as catalysts in these reactions.[5,7] Very recently, through the employment of only 0.05 mol% of a C_2-symmetric *N,N′*-dioxide/Sc^{III} complex as the catalyst, we were able to report the first example of enantioselective bromoamination of chalcones to deliver *anti*-α-bromo-β-amino carbonyl compounds with reversed regioselectivity in relation to the products in the previous reports (Scheme 1a).[8a]

This catalytic system was subsequently successfully applied to chloroamination by use of $TsNCl_2$ and $TsNH_2$ as the chlorine/nitrogen sources (Scheme 1b).[8b] In continuation of our studies on reactions of this kind, involving onium ion intermediates, we turn our attention to iodoamination.



Scheme 1. Catalytic asymmetric haloamination reactions.

To the best of our knowledge, direct synthesis of vicinal iodoamines through iodoamination or aminoiodination reactions has not previously been reported. We postulated that the main issues were as follows. Firstly, the iodinating agents—*N*-iodosuccinimide (NIS), for example—are simple and inexpensive, although unlike *N*-chloro and *N*-bromo compounds, *N*-iodo compounds of this kind immediately hydrolyze on contact with water.[9] Because of its large size, iodine forms relatively weak bonds with most elements. Additionally, chiral α-iodinated products are prone to racemization.[10] Here we describe highly efficient catalytic diastereo- and enantioselective iodoaminations of enones and 4-aryl-4-oxobutenoates (Scheme 1c).

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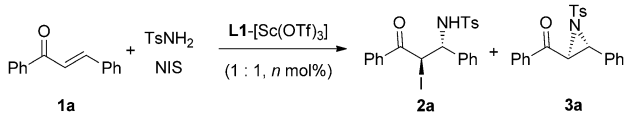
Results and Discussion

Initially, iodoamination of chalcone (**1a**, Table 1) with NIS/$TsNH_2$ was selected as a model reaction for the catalyst screening. A broad investigation of potential *N*,*N*′-dioxide/

Table 1. Optimization of the reaction conditions in the catalytic asymmetric iodoamination of chalcone (**1a**) with $TsNH_2$ and NIS.[a]



Entry	*n* [mol%]	Additive	Yield [%][b]	*t* [h]	*ee* [%][c]	d.r.[d]
1	5	–	48 (4)	20	96	>99:1
2	5	–	62 (4)	20	96	>99:1
3	5	–	79 (7)	48	96	>99:1
4	5	I_2	73 (4)	20	96	97:3
5	5	H_2O	22 (3)	20	91	>99:1
6	5	succinimide	50 (3)	20	96	>99:1
7	5	MS (4 Å)	97 (3)	12	96	>99:1
8[e]	5	MS (4 Å)	91 (8)	72	98	>99:1
9[f]	0.5	MS (4 Å)	45 (5)	20	96	>99:1
10[g]	0.5	MS (4 Å)	96 (4)	20	96	>99:1

[a] Unless otherwise noted, all reactions were performed with **L1**/[Sc(OTf)$_3$] (1:1), additive (0.1 mmol) or MS (4 Å, 30 mg), **1a** (0.1 mmol), $TsNH_2$ (0.12 mmol), NIS (0.11 mmol, purified with CH_2Cl_2 and Et_2O before use) in CH_2Cl_2 (0.5 mL) under N_2 at 23 °C for the indicated time. [b] Yields of isolated product **2a**. The data in parentheses are isolated yields of **3a**. [c] Determined by HPLC analysis on a chiral stationary phase with a Chiralcel AD-H column. [d] Determined by HPLC and ^{1}H NMR analysis. [e] The reaction was carried out at 0 °C. [f] Commercially available NIS was used without purification. [g] The reaction was performed with exclusion of light with freshly activated MS (4 Å, dried at 500 °C for 5 h).

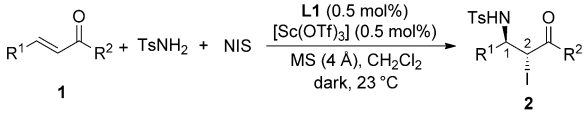
Sc^{III} complexes[11] (see the Supporting Information for details) showed that the scandium complex of the *N*,*N*′-dioxide **L1** (Scheme 1), derived from (*S*)-pipecolic acid, could produce the *trans*-α-iodo-β-amino product **2a** with 96% *ee* and a diastereomeric ratio (d.r.) of over 99:1, but only in 48% yield (Table 1, entry 1). At the same time, the corresponding aziridine **3a** was generated in 4% yield and with the same stereoselectivity as that of **2a**, and these transformations were also accompanied by the decomposition of NIS to generate I_2. With use of NIS that had previously been purified with CH_2Cl_2 and Et_2O, the yield increased to 62% (Table 1, entry 2). Prolonging the reaction time was not appropriate for improvement of the yield of **2a** because of increased amounts of side product (Table 1, entry 3).

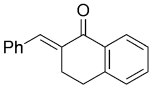
The factors potentially disadvantageous to the yield and enantiomeric purity of the iodoaminated product were then investigated. When stoichiometric amounts of I_2 were added, the yield of **2a** increased from 62 to 73% but the diastereoselectivity decreased a little (Table 1, entry 4 vs. entry 2). It is worth pointing out that in the presence of I_2, the diastereomerization of the major product *anti*-**2a** at the carbon atom adjacent to the iodo group was accelerated, leading to the formation of the corresponding *syn*-**2a**.[12] Both H_2O and succinimide had considerable negative effects on the yield (Table 1, entry 5 and entry 6). Meanwhile, the decomposition of NIS became even more obvious in the presence of H_2O and thus greatly suppressed the reaction, with a decreased *ee* value (Table 1, entry 5 vs. entry 2).[9] In these cases the amounts of by-product **3a** did not increase, which was consisted with transformation of **2a** into **3a** being at a relatively sluggish rate.[13] To reduce the disadvantages of residual H_2O in the catalytic system, molecular sieves (MS, 4 Å) were used as an additive. Pleasingly, the catalytic efficiency was significantly improved and quantitative conversion of the chalcone (**1a**) was observed. The desired product **2a** was obtained in 97% yield, with 96% *ee* and over 99:1 d.r., with only a 3% yield of **3a** (Table 1, entry 7). Investigation of the effect of reaction temperature revealed that the enantioselectivity was increased to 98% *ee* at 0 °C, but that more aziridine **3a** was formed during the course of the prolonged process (Table 1, entry 8). Unfortunately, simply decreasing the catalyst loading to 0.5 mol% led to a dramatically decreased yield (Table 1, entry 9). However, when the reaction was performed under strictly anhydrous conditions with exclusion of light, the yield and stereoselectivity could be maintained in the presence of 0.5 mol% of **L1**/Sc(OTf)$_3$ complex and freshly dried MS (4 Å) (96% yield, 96% *ee*, and >99:1 d.r.; Table 1, entry 10).[14]

With the optimized reaction conditions in hand (Table 1, entry 10), the substrate scope of chalcone derivatives was examined and the results are listed in Table 2. In all cases, diastereomeric ratios of over 95:5 were obtained and less than 5% yields of *syn* products were detected for all evaluated substrates. Excellent yields (85–97%) and enantioselectivities (93–99% *ee*) were obtained, regardless of the electronic natures or positions of the substituents on the phenyl ring (Table 2, entries 1–8 and 12–15). Moreover, fused-ring chalcones as well as cinnamyl-, heteroaromatic-, and multisubstituted ones were also suitable substrates for the reaction (90–95% yields, 98% *ee*, >95:5 d.r.; Table 2, entries 9 and 16–19). Remarkably, (*E*)-1-phenylbut-2-enone and 1-phenylprop-2-enone were also usable with this catalytic system and delivered the corresponding products in 86% yield with 94% *ee* and in 90% yield with 90% *ee*, respectively (Table 2, entries 10 and 11). Notably, a chalcone derivative with a *para*-methoxy substituent on the β-phenyl group was also shown to be a competent candidate in this reaction (95% *ee*, >95:5 d.r.; Table 2, entry 7), which implied that no racemization of the iodonium ion intermediate was in evidence, unlike in the cases of bromonium and chloronium ions.[15] The absolute configuration of the product **2h** (1*R*,2*R*) was determined by X-ray crystallography (Figure 1),[16] which also confirmed the *anti* configuration and the stereostructure assignment.

Encouraged by the successful iodoaminations of chalcones, we also investigated the substrate scope of 4-aryl-4-oxobutenoates **4**, which deliver the useful β-iodo-α-amino acid derivatives **5**. As shown in Table 3, the *ee* values (93–98% *ee*) were excellent and the yields (88–97%) were as well, except in the cases of the substrates with bulky groups

Table 2. Substrate scope in the catalytic asymmetric iodoamination of enones with $TsNH_2$ and NIS.[a]



Entry[a]	R^1	R^2	t [h]	Yield [%][b]	ee [%][c]	d.r.[d]
1	Ph	Ph	20	96 (**2a**)	96	>99:1
2[e,f]	2-$CH_3C_6H_4$	Ph	48	95 (**2b**)	98	>99:1
3	3-$CH_3C_6H_4$	Ph	20	96 (**2c**)	98	>99:1
4[f]	4-$CH_3C_6H_4$	Ph	48	86 (**2d**)	98	>99:1
5	4-FC_6H_4	Ph	20	85 (**2e**)	97	>99:1
6[e,f]	4-ClC_6H_4	Ph	48	95 (**2f**)	98	>99:1
7[e,f]	4-$MeOC_6H_4$	Ph	72	90 (**2g**)	95	>95:5
8	3-$NO_2C_6H_4$	Ph	24	92 (**2h**)	98[g]	>99:1
9[e,f]	3,4-$Cl_2C_6H_3$	Ph	48	90 (**2i**)	98	>99:1
10[e,f]	H	Ph	12	90 (**2j**)	90	–
11[e]	Me	Ph	12	86 (**2k**)	94	>99:1
12[e,f]	Ph	4-$CH_3C_6H_4$	72	93 (**2l**)	97	>99:1
13[f]	Ph	4-FC_6H_4	48	97 (**2m**)	97	>99:1
14[e,f]	Ph	4-ClC_6H_4	48	96 (**2n**)	98	>99:1
15[e,f]	Ph	4-$MeOC_6H_4$	72	91 (**2o**)	98	>99:1
16[e,f]	Ph	2-naphthyl	48	92 (**2p**)	98[h]	>99:1
17[e,f]	Ph	2-furyl	24	90 (**2q**)	98	>99:1
18[e,i]	Ph	PhCHCH−	10	93 (**2r**)	98	>99:1
19[e]			20	95 (**2s**)	99	96:4

[a] Unless specified, the reactions were performed with **1** (0.1 mmol), **L1**/[$Sc(OTf)_3$] (0.5 mol%, 1:1) and MS (4 Å, 30 mg), $TsNH_2$ (0.12 mmol), and NIS (0.11 mmol) in CH_2Cl_2 (0.5 mL) at 23 °C for the indicated time. [b] Yields of isolated products. [c] Determined by HPLC analysis (see the Supporting Information for details). [d] Determined by HPLC and ^1H NMR analysis. [e] 2.0 mol% of catalyst was used. [f] Reaction was carried out at 0 °C. [g] The absolute configuration of **2h** (1*R*,2*R*) was determined by X-ray crystallography. [h] Determined by HPLC after transformation into the corresponding aziridine product. [i] Further prolonging of the reaction time led to the transformation of *anti*-**2r** into *syn*-**2r** after the complete conversion of **1r**.

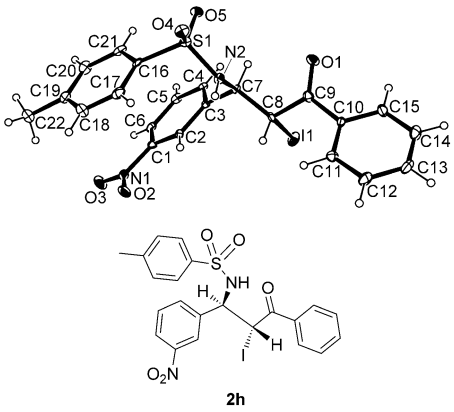


Figure 1. X-ray crystallographic structure of **2h**.

on the ester moiety (73–85% yields, Table 3, entries 4 and 5). The steric hindrance of ester moieties and the electronic properties of the substituents on the aromatic ring had little influence on the diastereoselectivities (>95:5 d.r.; Table 3).[17]

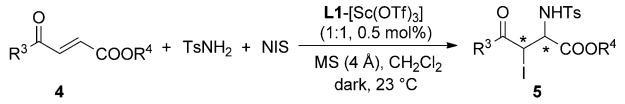
Haloamination of the trifluoro-substituted enone **6** (Scheme 2) was also explored. With judicious choice of nitrogen and halogen sources (X = I, Br, Cl), the desired haloaminated products **7** were obtained in excellent yields, with 93 to 98% *ee* and over 95:5 d.r..[18]

To show the synthetic utility of the catalyst system, the iodoamination of chalcone (**1a**) was expanded to a gram scale. As shown in Scheme 3a, the desired *anti*-iodoamine **2a** was obtained in 96% yield with 97% *ee*, with the use of only 0.5 mol% of **L1**/[$Sc(OTf)_3$] catalyst. Unexpectedly, in the presence of I_2 the *anti*-**2a** could be gradually transformed into *syn*-**2a**, which could be obtained exclusively in 85% yield and with 99% *ee* through spontaneous racemization and crystallization-induced resolution (Scheme 3b).[19] Compound *cis*-**3a** could then be obtained from the resulting *syn*-**2a**.

To examine the possible nitrogen/iodine sources in the iodoamination reactions, other *N*-iodo reactants were examined. No reactivity was found with use of I_2 directly, which established that I_2 generated from the decomposition of NIS was not the active species involved in formation of the key iodonium ion intermediate (Scheme 4, (1) vs. Table 1, entry 10). With the employment of 1,3-diiodo-5,5-dimethylhydantoin (DIH, either 1.1 equiv or 0.6 equiv), containing two activated iodo groups, **2a** could be obtained in nearly quantitative yields with the same stereoselectivities as in the case of NIS, which indicated that the same active species—TsNHI produced by I-transfer—might be involved in this iodoamination reaction (Scheme 4, (2)).[20] The combination of $TsNH_2$ and *N*-iodosaccharin (NISC) produced a mixture of iodoaminated products **2a** and **8a**, with no enantioselectivity being observed in either case (Scheme 4, (3)). The amount of product **8a** exceeded that of **2a** more than twofold. Moreover, NISC itself could be used as the iodoamination reagent, affording racemic **8a** in 92% yield (Scheme 4, (4)). It would thus appear that the TsNHI species (generated from $TsNH_2$/NIS) or the NISC species might be the real active reactants involved in formation of the iodonium intermediates.[21] Accordingly, TsNHBr (generated from $TsNH_2$/NBS) might be the active species in the bromoamination reaction.[8b] Additionally, ^1H NMR analysis of mixtures of NIS and $TsNH_2$ or of NBS and $TsNH_2$ confirmed the existence of TsNHI (see the Supporting Information) or TsNHBr.[5g]

A proposed possible reaction process for the haloamination reaction, based on the above results and on previous mechanistic studies on the chloroamination and bromoamination reactions,[8] is shown in Scheme 5. Initially, TsNHX (X = I, Br, Cl) could be generated through the reaction of $TsNH_2$ and the halo source, such as DIH, NIS, NBS, or $TsNCl_2$. Then, in the presence of the chiral *N*,*N*′-dioxide/Sc^{III} complex, TsNHX could stereoselectively attack the enones

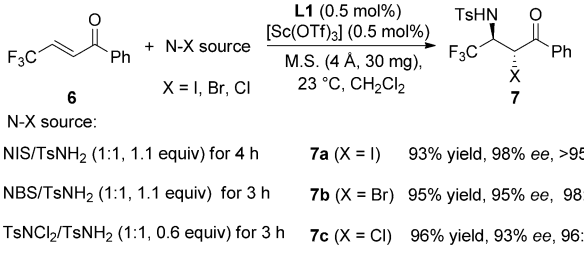
Table 3. Substrate scope in the catalytic asymmetric iodoamination of 4-aryl-4-oxobutenoates with $TsNH_2$ and NIS.[a]



4 5

Entry[a]	R^3	R^4	t [h]	Yield [%][b]	ee [%][c]	d.r.[d]
1	Ph	Me	8	96 (**6a**)	96	98:2
2	Ph	Et	8	96 (**6b**)	98	99:1
3	Ph	*i*Pr	20	83 (**6c**)	96	99:1
4	Ph	*t*Bu	20	75 (**6d**)	97	>99:1
5	Ph	Ph	16	90 (**6e**)	97	>95:5
6	Ph	Bn	12	94 (**6f**)	97	98:2
7	4-$MeOC_6H_4$	Et	20	92 (**6g**)	95	97:3
8	4-MeC_6H_4	Et	20	89 (**6h**)	96	98:2
9	4-FC_6H_4	Et	6	97 (**6i**)	97	98:2
10	4-ClC_6H_4	Et	6	95 (**6j**)	96	97:3
11	4-BrC_6H_4	Et	8	88 (**6k**)	97	98:2
12	3-$MeOC_6H_4$	Et	8	90 (**6l**)	98	>95:5
13	3,4-$Cl_2C_6H_3$	Et	8	92 (**6m**)	97	98:2

[a] Unless specified, the reactions were performed with **4** (0.1 mmol) , **L1**/[Sc(OTf)$_3$] (0.5 mol%, 1:1) and MS (4 Å, 30 mg), $TsNH_2$ (0.12 mmol), and NIS (0.11 mmol) in CH_2Cl_2 (0.5 mL) under N_2 at 23 °C for the indicated time (see the Supporting Information for details). [b] Yields of isolated products. [c] Determined by HPLC analysis (see the Supporting Information). [d] Determined by ^{1}H NMR spectroscopy and HPLC with a chiral stationary phase.



6 7

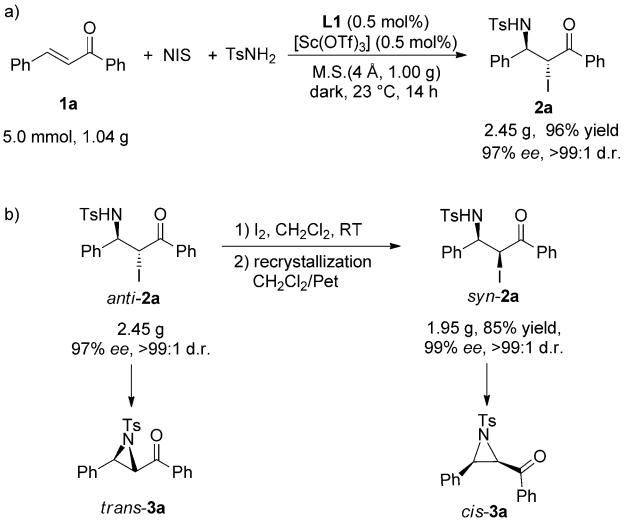
N-X source:

NIS/$TsNH_2$ (1:1, 1.1 equiv) for 4 h	**7a** (X = I)	93% yield, 98% *ee*, >95:5 d.r.
NBS/$TsNH_2$ (1:1, 1.1 equiv) for 3 h	**7b** (X = Br)	95% yield, 95% *ee*, 98:2 d.r.
$TsNCl_2$/$TsNH_2$ (1:1, 0.6 equiv) for 3 h	**7c** (X = Cl)	96% yield, 93% *ee*, 96:4 d.r.

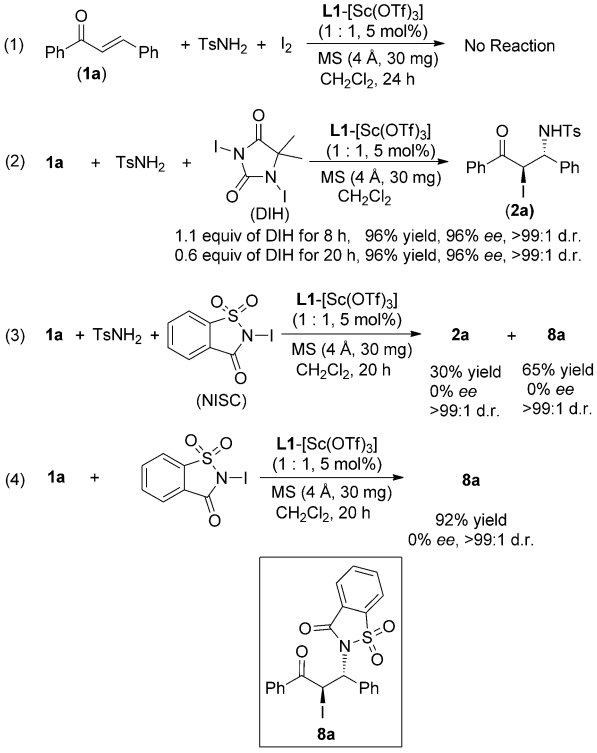
Scheme 2. Haloamination of the trifluoro-substituted enone **6**.

to form chiral halonium ion intermediates,[22] followed instantly by nucleophilic attack of negative nitrogen to deliver the final enantiomerically enriched product. With the use of NISC (which could act as an active species itself in the iodoamination reaction) as the reactant, the disparity of enantioselectivity might be a consequence of its steric hindrance.

To compare the relative activities of haloamination reactions, reactions of chalcone (**1a**) with $TsNH_2$ and NXS (X = C, B, I) under the same reaction conditions were carried out (Scheme 6). No reaction took place with $TsNH_2$/NCS as reactants, which indicated that chloroamination exhibited the lowest reactivity. With the combined use of $TsNH_2$ (1.0 equiv), NIS (0.5 equiv), and NBS (0.5 equiv) as reagents, the amount of the bromoaminated product **2aa** exceeded that of the iodoaminated product **2a** by more than threefold after 16 h.[23] Typical haloamination dependency is therefore, observed with reactivity decreasing in the order NBS > NIS ≫ NCS.



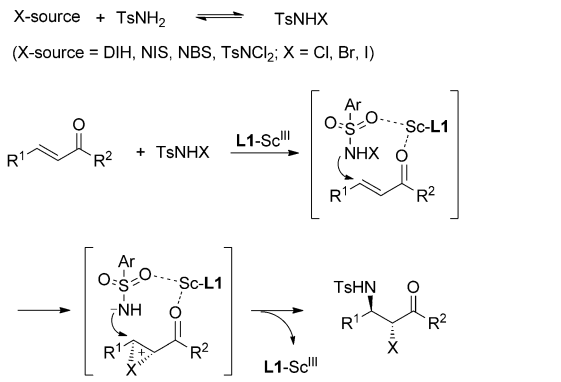
Scheme 3. The synthetic utility of the catalytic reactions. a) Asymmetric iodoamination of chalcone on a gram scale. b) Unexpected transformation of *anti* product to *syn* product.



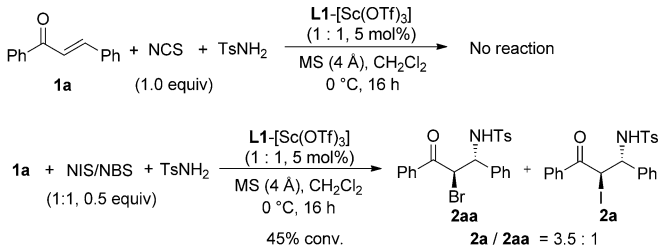
Scheme 4. Iodoamination of chalcone (**1a**) with use of other I sources.

Conclusion

In summary, we have developed highly efficient enantioselective iodoamination reactions of chalcones and 4-aryl-4-oxobutenoates, as well as of a trifluoro-substituted enone. In the presence of the chiral Sc^{III}/*N*,*N*′-dioxide complex (0.5–2 mol%), the reactions performed well over a series of sub-



Scheme 5. Proposed mechanism of the haloamination reaction.



Scheme 6. Contrast in the reactivities of haloamination reactions.

strates, delivering the desired vicinal *anti*-α-iodo-β-amino products regioselectively in excellent yields (up to 97%), and with excellent diastereoselectivities (>99:1) and enantioselectivities (up to 99% *ee*s). Enantiopure *syn*-α-iodo-β-amino products could also be obtained from the isomerization of particular iodo compounds. TsNHX generated from the reactions between the halo sources and $TsNH_2$ was further confirmed as the active species involved in the formation of the key halonium ion intermediates. Additionally, a typical haloamination dependency was observed, with reactivity decreasing in the order NBS > NIS ≫ NCS. Further development of catalytic asymmetric fluoroamination reactions and application of these haloamination reactions are underway.

Experimental Section

Preparation of the catalyst: CH_2Cl_2 (5.0 mL) was added under N_2 to a 10 mL flask charged with **L1** (0.01 mmol, 5.4 mg), $[Sc(OTf)_3]$ (0.01 mmol, 4.9 mg), and freshly activated MS (4 Å, 600 mg, dried at 500 °C for 5 h before use). The mixture was stirred under N_2 at 35 °C for 1 h. The solvent was then removed in vacuo to afford the catalyst as a white solid. The catalyst was stored under N_2 at room temperature and used for asymmetric reactions.

General procedure for the reaction with 0.5 mol% catalyst loading: A dry reaction tube was charged with the prepared catalyst (30.0 mg, 0.5 mol%), a substrate **1**, **4**, or **6** (0.1 mmol), *para*-toluenesulfonamide ($TsNH_2$, 20.5 mg, 0.12 mmol), and *N*-iodosuccinimide (NIS, 24.7 mg, 0.11 mmol, purified with CH_2Cl_2 and Et_2O before use to remove trace amounts of I_2 and H_2O) under N_2 and with exclusion of light. CH_2Cl_2 (0.5 mL) was then added at 0 °C or 23 °C. The reaction mixture was kept stirring at 0 °C or 23 °C for the indicated time. The residue was purified by flash chromatography on silica gel to afford the desired product. The enantiomeric excess (*ee*) was determined by high-performance liquid chromatography (HPLC) with Chiralcel AD-H, Chiralcel IA, Chiralcel OD-H, or Chiralcel IB. The diastereomeric ratio (d.r.) was determined by ^1H NMR spectroscopy and HPLC analysis.

General procedure for the reaction with 2 mol% catalyst loading: CH_2Cl_2 (0.3 mL) was added under N_2 to a dry reaction tube charged with **L1** (0.002 mmol, 1.1 mg) and $[Sc(OTf)_3]$ (0.002 mmol, 1.0 mg). The mixture was stirred under N_2 at 35 °C for 0.5 h. The solvent was then removed in vacuo. The substrate **1** or **4** (0.1 mmol), *para*-toluenesulfonamide ($TsNH_2$, 20.5 mg, 0.12 mmol), and *N*-iodosuccinimide (NIS, 24.7 mg, 0.11 mmol, purified with CH_2Cl_2 and Et_2O before use to remove trace amounts of I_2 and H_2O) was weighed into this tube, followed by addition of CH_2Cl_2 (0.5 mL). Under N_2 and with exclusion of light, the reaction mixture was stirred at 0 °C or 23 °C for the indicated time. The residue was purified by flash chromatography on silica gel to afford the desired product. The *ee* value was determined by high-performance liquid chromatography (HPLC) with Chiralcel AD-H, Chiralcel IA, Chiralcel OD-H, or Chiralcel IB. The d.r. was determined by ^1H NMR spectroscopy and HPLC analysis.

Typical procedure for the scale-up reaction: CH_2Cl_2 (5.0 mL) was added under N_2 to a 25 mL flask charged with **L1** (0.025 mmol, 13.5 mg), $[Sc(OTf)_3]$ (0.025 mmol, 12.2 mg), and freshly activated MS (4 Å, 1.0 g, dried at 500 °C for 5 h before use). The mixture was stirred under N_2 at 35 °C for 1 h. The solvent was then removed in vacuo. The substrate **1a** (1.04 g, 5 mmol), *para*-toluenesulfonamide ($TsNH_2$, 1.03 g, 6 mmol), and *N*-iodosuccinimide (NIS, 1.23 g, 5.5 mmol, purified with CH_2Cl_2 and Et_2O before use to remove trace amounts of I_2 and H_2O) was weighed into this flask, followed by addition of CH_2Cl_2 (12.5 mL). Under N_2 and with exclusion of light, the reaction mixture was stirred at 23 °C for 12 h. The residue was purified by flash chromatography on silica gel (ethyl acetate/petroleum ether, 1:4) to afford the desired product **2a** as a white solid (2.45 g, 96% yield, 97% *ee*, and >99:1 d.r.).

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[12] The control experiments showed that i) 8% yield of *syn*-**2a** was obtained after stirring of *anti*-**2a** (0.1 mmol) in CH_2Cl_2 (0.5 mL) for 24 h under 1.0 equiv of I_2; ii) 32% yield *anti*-**2a** was obtained after stirring of *syn*-**2a** (0.1 mmol) in CH_2Cl_2 (0.5 mL) for 24 h under 1.0 equiv of I_2. Notably, catalytic amount of I_2 which was easily introduced to the solid product due to unavoidable decomposition of NIS could also enhance this isomerization.

[13] The azirine adduct **3a** was obtained in 4% yield after stirring of *anti*-**2a** (0.1 mmol) in CH_2Cl_2 (0.5 mL) for 24 h.

[14] Under low catalyst loading, the catalyst system is extremely sensitive to water. The mositure contained in the reaction system sharply decreased the yield and diastereoselectivity of the reaction due to easy decomposition of NIS. Pretreatment of NIS and use of the optimized experimental procedure (see the Experimental Section for details) are also needed.

[15] *Ee* of the corresponding bromoaminated and chloroaminated product was only 0 and 21% *ee*, respectively. For the racemization of possible bromonium and chloronium ion intermediates, see: a) R. S. Brown, *Acc. Chem. Res.* **1997**, *30*, 131–137; b) D. C. Braddock, S. A. Hermitage, L. Kwok, R. Pouwer, J. M. Redmond, A. J. P. White, *Chem. Commun.* **2009**, 1082–1084; c) S. E. Denmark, M. T. Burk, A. J. Hoover, *J. Am. Chem. Soc.* **2010**, *132*, 1232–1233.

[16] CCDC-831428 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[17] The diastereoselectivity of iodoamination was always higher than that of chloroamination. In our previous study about chloroamination reaction (Ref. [8b]), only 87:13 to 93:7 d.r. were obtained for 4-aryl-4-oxobutenoates **5** with electron-withdrawing group.

[18] Diastereomerization of the iodoaminated product **8a** was more obvious in the existence of I_2. Strictly controlling the reaction time was needed.

[19] The poor solubility of *syn*-**2a** in CH_2Cl_2 accelerated its generation from the *anti*-**2a**. Thus, this transformation cannot be applied to all products. For spontaneous racemization and crystallization-induced dynamic resolution of *a*-halo compounds, see: H. Xu, Q. Wang, J. Zhu, J. Deng, L. Cun, X. Cui, J. Wu, X. Xu, Y. Wu, *Org. Biomol. Chem.* **2005**, *3*, 4227–4232.

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[21] NBS was proposed as active species to form the key bromonium ion intermediate in our previous reported bromoamination reaction (Ref. [8a]). Based on our further studies in this work as well as previous reported chloroamination reaction (Ref. [8b]), TsNHBr generated from the mixture of NBS and $TsNH_2$ is more possible to act as the active species to form the key bromonium ion intermediate in the bromoamination reaction.

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[23] The ratio between **2a** and **2aa** was determined by ^{1}H NMR analysis on the isolated mixture of the products (for details, see the Supporting Information).

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