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Iodoamination

Organocatalytic Stereoselective Iodoamination of Alkenes

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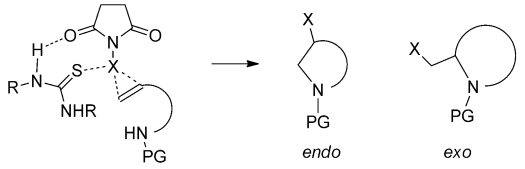
Abstract: A new chiral thiohydantoin catalyst is used for the stereoselective iodoamination of alkenes. *N*-iodosuccinimide as the source of the electrophilic iodine is activated by catalytic amounts of different additives which also influence the regioselectivity of some cyclizations.



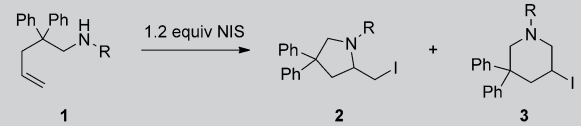
Scheme 1. Regioselectivity in thiourea-directed halocyclizations.

Haloaminations of alkenes are important organic transformations as they provide an effective approach to introduce two heteroatoms onto non-activated C–C double bonds.[1] Vicinal amino halides serve as versatile synthetic intermediates which have received considerable attention from chemists, and significant progress has been made in their application in drug discovery and combinatorial chemistry.[2] Various methods for reagent-controlled enantioselective halogenations of alkenes have been developed by using either chiral Lewis acids, chiral amines, or chiral sulfides.[3] Enantioselective halogenations of alkenes have received wide attention in recent years. Organocatalytic methods for enantioselective halolactonizations, bromoaminocylizations as well as transition metal-catalyzed aminohalogenations of alkenes have been reported.[4] A few metal-catalyzed stereoselective reactions of this type are known,[5] but the enantioselectivites for organocatalyzed reaction are fairly moderate and only a limited insight into the regioselectivity of such reactions has been provided.

We report here a catalytic method for the enantioselective iodoamination of alkenes using a novel chiral organocatalyst. Additional investigations have been performed to control the regioselectivity of such iodoaminations. Earlier studies have shown that *N*-bromosuccinimide-mediated bromoaminations presumably proceed through a halogen bonding interaction between the Lewis acidic catalyst and the bromine atom.[6] A thiourea-based catalyst should also be able to interact via halogen bonding between the Lewis-basic sulfur center and the electrophilic iodine atom. This might be pivotal for electrophilic halogen-induced alkene heterodifunctionalization. The iodonium intermediate can undergo 5-*exo* or 6-*endo* intramolecular cyclization as shown in Scheme 1. According to Baldwin's rules of cyclization,[7] both the 5-*exo* and 6-*endo* products are feasible, however, the 5-*exo* product is the main product in most haloaminations.

The iodoamination of *N*-protected 2,2-disubstituted-pent-4-enylamines **1** using *N*-iodosuccinimide (NIS) as the electrophilic iodine source was used as the model reaction to investigate optimal reaction conditions. The efficient uncatalyzed reaction was the first hurdle to overcome as the reaction takes place at room temperature within 6 h to give a good yield of the product. The rate of the reaction was much slower at −78 °C leading to 18% yield after 24 h (Table 1, entry 4), hence indicating that the background reaction can be suppressed at low temperatures. As studies have shown that additives can improve the yield as well as the enantioselectivity of such reactions, additives such as I_2, KI, KBr (Table 1, entries 7–9) were used and the yield of the reaction was determined. The background reaction was found to be influenced dramatically and the reac-

Table 1. Optimization of reaction conditions.



1 2 3

Entry	Substrate	R	Solvent	Additive (2 mol%)	Time [h]	Temperature [°C]	**2**: Yield [%]
1	**1a**	Ts	MeCN	–	7	20	34
2	**1a**	Ts	CH_2Cl_2	–	7	20	87
3	**1a**	Ts	CH_2Cl_2	–	7	0	56
4	**1a**	Ts	CH_2Cl_2	–	24	−78	18
5	**1b**	Boc	CH_2Cl_2	–	7	20	0
6	**1c**	Cbz	CH_2Cl_2	–	7	20	0
7	**1b**	Boc	CH_2Cl_2	I_2	1	−78	53
8	**1b**	Boc	CH_2Cl_2	KI	1	−78	83
9	**1c**	Cbz	CH_2Cl_2	KBr	1	−78	67[a]

[a] Additionally compound **3c** (R = Cbz) is formed in 5% yield.

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tion proceeded even at −78 °C when 2 mol% of an additive were used. A recent study by Sakakura and Ishihara et al. has also highlighted that the combination of NIS and iodine generates a more reactive iodinating species.[8] While their study indicates that stoichiometric amounts of NIS or the cheaper oxidant *N*-chlorophthalimide are necessary, we observe a catalytic activation of NIS with different additives. These results show that a combination of NIS with an additive can generate highly reactive species which are able to perform iodocyclizations at very low reaction temperatures. This is shown by the high reaction yields (53–83%) at −78 °C when either iodine, KBr, or KI are used as an additive to stoichiometric amounts of NIS (Table 1, entries 7–9). The nature of the protecting group in the substrate **1** also has a large effect, it was observed that with a tosyl (Ts) protecting group (**1**, R = Ts) the reaction took place easily while this was not the case when the protecting group was *tert*-butyloxycarbonyl (Boc) or carboxybenzoyl (Cbz) (Table 1, entries 5 and 6). This also indicates that the nucleophilicity of the nitrogen atom has a major impact on the overall reaction.

Initially, the commercially available BOX ligand **4** (Figure 1) was used in the reaction which led to very low selectivity in

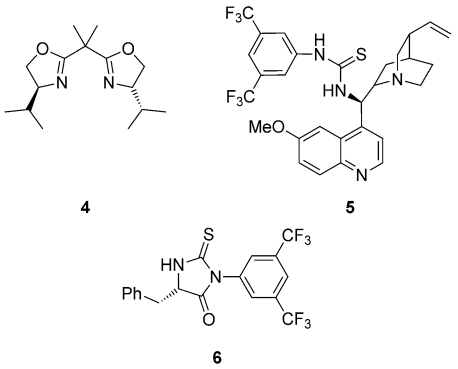
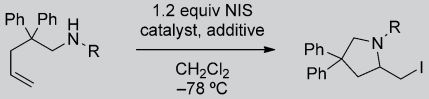


Figure 1. Chiral catalysts for iodoaminations.

product **2** (Table 2, entries 1 and 2). Similar low selectivities were observed with catalyst **5**, which was reported to be highly efficient in Michael additions and aldol reactions (Table 2, entries 3 and 4).[9] Based on the reasoning that one should be able to control the stereoselectivity of the reaction by halogen bonding interaction, we prepared a novel cyclic thiourea catalyst **6** in 87% yield by reacting optically pure phenylalanine ethyl ester hydrochloride with 5-isothiocyanato-1,3-bis(trifluoromethyl) benzene. Recently, similar thiohydantoin derivatives were reported to be efficient catalysts for asymmetric Michael additions.[10]

To understand the interaction of the additives with the catalyst, variable temperature NMR experiments were carried out. It was observed that the additive KBr influences the interaction between the catalyst **6** and the substrate **1a**. This is evident as the chemical shifts values move downfield when KBr is added to a mixture of **1a** and the catalyst **6** at −50 °C. No such interaction is observed with only the substrate and KBr or between

Table 2. Stereoseelctive iodoaminations using catalysts **4**–**6**. Reaction conditions: 1.2 equiv NIS, CH_2Cl_2, −78 °C.

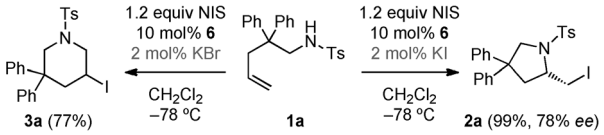


1 **2**

Entry	Substrate	R	Catalyst (10 mol%)	Additive (2 mol%)	Time [h]	**2**: Yield [%]	**2**: *ee* [%]
1	**1a**	Ts	**4**	–	1	73	6 (*S*)
2	**1a**	Ts	**4**	I_2	1	76	10 (*S*)
3	**1a**	Ts	**5**	–	1	78	11 (*S*)
4	**1a**	Ts	**5**	I_2	1	82	20 (*S*)
5	**1a**	Ts	**6**	–	1	90	17 (*S*)
6	**1a**	Ts	**6**	I_2	3	90	81 (*S*)
7	**1c**	Cbz	**6**	I_2	1	80	79 (*S*)
8	**1a**	Ts	**6**	KI	1	99	78 (*S*)
9	**1a**	Ts	**6**	KF	1	93	63 (*S*)
10	**1a**	Ts	**6**	KCl	4	17	n.d.[a]
11	**1a**	Ts	**6**	KBr	4	77[b]	n.d.[c]
12	**1a**	Ts	**6**	K_2CO_3	4	–	–
13	**1b**	Boc	**6**	KBr	4	–	–
14	**1c**	Cbz	**6**	KBr	4	–	–

[a] n.d.: Not determined. [b] Compound **3a** is formed exclusively in 77% yield. [c] n.d.: Not determined as **3a** is unstable and undergoes elimination to a 1,4-dihydropyridine derivative.

the only catalyst and KBr. Similar behavior is found also at higher temperatures up to 20 °C (see the Supporting Information). The direct manifestation of this interaction is expressed in the completely reversed regioselectivity of the iodoamination. The reaction with 2 mol% KBr as additive leads exclusively to the tetrahydropyridine compound **3a** (Table 2, entry 11). This compound is unstable under HPLC conditions and the enantiomeric excess could not be determined. The reaction with 2 mol% KI as additive produces only the five-membered product **2a** in 99% yield (Table 2, entry 8) as illustrated in Scheme 2.

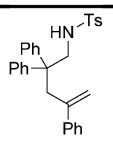
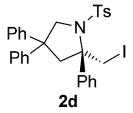
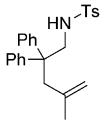
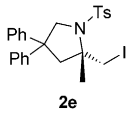
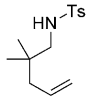
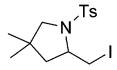


Scheme 2. Change in regioselectivity with different additives.

Using the optimized reaction conditions, we explored the substrate scope for the organocatalytic iodoamination. An alkyl substitution in *N*-protected 2,2-disubstituted-pent-4-enylamine had a large effect on the iodocyclization. Similar to our recently reported diamination reaction of alkenes,[11] no reaction was observed here when *N*-protected 2,2-dimethyl-pent-4-enylamine was used as a substrate with or without additives (Table 3, entry 3). Good selectivities and yields were obtained in the synthesis of tetrasubstituted chiral centers in the products **2d** and **2e** (Table 3, entries 1 and 2).

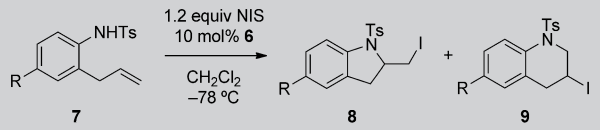
The protocol of the stereoselective iodoamination was further extended to 2-allylaniline derivatives of type **7**. With these

Table 3. Cyclization of homoallylic tosylamine derivatives.

Entry	Substrate	Additive	Product	Yield [%]	*ee* [%]
1	 **1d**	I_2 or KBr	 **2d**	87	90
2	 **1e**	I_2 or KBr	 **2e**	89	85
3	 **1f**	–	 **2f**	0[a]	–

[a] Also no reaction with iodine as additive.

Table 4. Cyclization of 2-allyl aniline derivatives **6**.



7 **8** **9**

Entry	Substrate	R	Additive (2 mol%)	**8**: Yield [%]	**8**: *ee* [%]	**9**: Yield [%]
1	**7a**	H	–	57	87 (*S*)	0
2	**7a**	H	I_2	89	80 (*S*)	0
3	**7b**	OMe	–	23	83[a] (*R*)	0
4	**7c**	Cl	–	86	88 (*R*)	0
5	**7a**	H	KBr	58	87 (*S*)	14
6	**7b**	OMe	KBr	33	19[a] (*R*)	0
7	**7c**	Cl	KBr	14	89 (*R*)	10

[a] This enantiomeric excess was determined by optical rotation as the enantiomers were not separable with the available HPLC columns.

substrates it was also observed that KBr as additive can influence the regiochemistry of the cyclization. But also the electronic properties of the aromatic ring have a major effect on the regioselectivity. In the presence of electron-donating substituents such as a methoxy group in compound **7b** (Table 4, entries 3 and 6), the *exo*-cyclization compound **8b** was the only product obtained, albeit in much lower yields. However, in the presence of an electron-withdrawing group such as chlorine, both the *exo*- and the *endo*-product were obtained and this observation is similar to the reaction in the absence of a substitution on the aromatic ring (**7a**, R = H) (Table 4, entry 5), thereby confirming the hypothesis that the additive influences the halogen bonding interaction between the thiourea catalyst, the substrate, and the electrophilic iodine species. Since the electron density of the substrate plays a pivotal role, any change would influence the regioselectivity. Substrates **7a** and **7c** also lead to good enantioselectivities in the observed dihydroindol products **8a** and **8c** (up to 89% *ee*). Interestingly, the absolute configuration for **8a** is opposite to that of **8b** and **8c** for unknown reasons. The enantioselectivities for the *endo*-products **9a** and **9c** (Table 4, entries 5 and 7) could not be determined as the molecule underwent de-iodination when dissolved in 2-propanol or even $CDCl_3$ in certain cases, to obtain 1-tosyl-1,4-dihydroquinoline products and hence lost its chirality. Their optical rotation, however, shows that the compounds **9a** and **9c** are not racemic.

In conclusion, we have developed a highly stereoselective organocatalytic method for iodoaminations of substituted pentenylamines and 2-allylanilines. A control of the regioselectivity is possible with the help of additives.

Experimental Section

Procedure for cyclization: *N*-Iodosuccinimide (18 mg, 0.08 mmol) was dissolved in dry CH_2Cl_2 (2 mL) under argon and cooled to −78 °C. After 15 min, a solution of the catalyst **6** (2.8 mg, 6.6 μmol) in dry CH_2Cl_2 (2 mL) was added. The mixture was stirred for another 15 min before the additive (1.3 μmol) [KI: 2.2 mg; KBr: 1.6 mg; I_2: 3.3 mg], dissolved in dry CH_2Cl_2 (2 mL), was added. After 15 min at −78 °C a solution of the substrate (66.5 μmol) in CH_2Cl_2 (2 mL) was added. The reaction was monitored by TLC. Upon completion, the reaction was quenched by adding saturated aqueous $Na_2S_2O_3$ solution (3 mL) at −78 °C. The aqueous layer was extracted with CH_2Cl_2 (3×5 mL) and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel using ethyl acetate/hexane (1:9).

All synthetic methods including spectroscopic and analytical data are included in the Supporting Information.

Acknowledgements

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Keywords: cyclization · diamination · hypervalent iodine · organocatalysis · stereoselective synthesis

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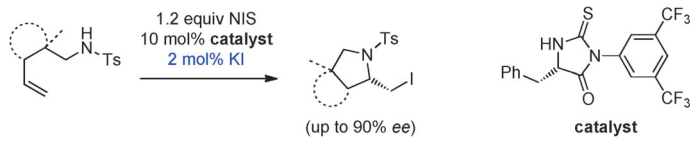

An unexplored class of chiral thiohydantoins can be used as efficient catalysts for iodoaminations while additives effect the regiochemistry. Also quaternary stereocenters can be easily generated with this metal-free, organocatalytic protocol.

Iodoamination

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Organocatalytic Stereoselective Iodoamination of Alkenes