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# Chiral β-iodoamines by urea-catalysed iodocyclization of trichloroacetimidates†

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Highly enantioselective vicinal iodoamination of olefins is accomplished through the iodocyclization of alkenyl trichloroacetimidates catalysed by a new chiral Schiff-base urea derivative. The resulting products are converted readily to a variety of polyfunctional amine-containing chiral building blocks.



## Introduction

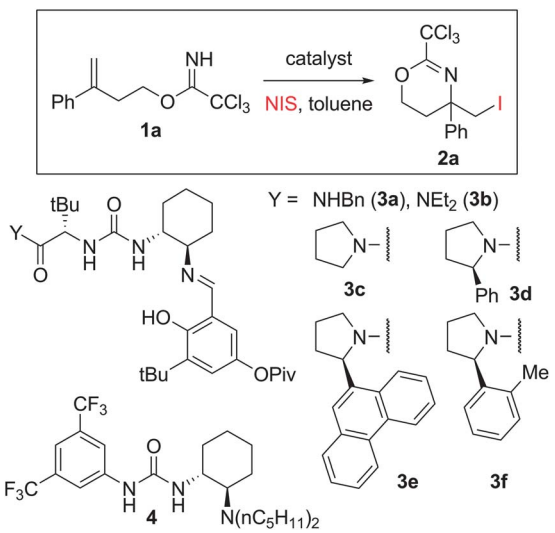
Alkene halocyclizations provide a powerful pathway for the preparation of sterically congested and stereochemically defined heterocycles.[1] Several recent studies have documented catalytic asymmetric halolactonizations for the construction of chiral lactones.[2] Vicinal haloaminations, by comparison, represent an underdeveloped class of alkene oxidations in asymmetric catalysis,[3,4] and this type of transformation could provide useful access to valuable nitrogen-containing chiral intermediates.[5] Drawing on the recently demonstrated ability of chiral ureas to promote stereoselective transformations of iodonium intermediates,[2g] we describe here the intramolecular vicinal iodoamination of alkenes catalysed with high enantioselectivity by new Schiff-base urea derivatives.

Our selection of a target reaction for the development of enantioselective iodoamination catalysts was guided by the goal of accessing products that could serve as versatile chiral building blocks. We chose alkene **1a** (Table 1) as a model substrate because the trichloroacetimidate group would be delivered to the alkene in an iodoamination reaction through a readily cleavable tether.[6,7] The resulting product **2a** is a synthetic equivalent of a β-iodo-1,3-aminoalcohol with the nitrogen residing on a newly formed tertiary stereogenic center.

## Results and discussion

Evaluation of a broad series of chiral H-bond donors as potential catalysts[8] led to promising lead results with the known Schiff-base urea derivatives **3a** and **3b** (Table 1, entries 1 and 2).[9] Commercially available *N*-iodosuccinimide (NIS) was identified as the optimal source of electrophilic iodine, and the presence of trace amounts of water, light, radical scavengers, or catalytic $I_2$ was found to have little effect on either the observed enantioselectivity or efficiency of the reaction. The tertiary aminourea **4**, which was the optimal catalyst in previously reported

**Table 1** Catalyst optimization for intramolecular iodoamination of **2a**[a]




| Entry | Catalyst | Temp. (°C) | Time (d) | Yield[b] (%) | ee (%) |
|---|---|---|---|---|---|
| 1[c] | **3a** | −20 | 9 | 56 | 27 |
| 2[d] | **3b** | −20 | 1.5 | 33 | 74 |
| 3[d] | **3c** | −20 | 1.5 | 31 | 74 |
| 4[d] | **3d** | −20 | 1.5 | 44 | 79 |
| 5[d] | **3e** | −20 | 1.5 | 84 | 82 |
| 6[d] | **3e** | −30 | 3 | 87 | 88 |
| 7[d] | **3f** | −20 | 1.5 | 100 | 79 |
| 8[d] | **3f** | −40 | 1.5 | 100 | 90 |
| 9[c] | **4** | −20 | 9 | 91 | −15 |

[a] Conditions: 10 mol% catalyst, [**2a**] = 0.05 M. [b] Crude yields based on $^1$H NMR integration against an internal quantitative standard. [c] 1.1 eq. NIS. [d] 5 eq. NIS.

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† Electronic supplementary information (ESI) available: Experimental procedures, characterization data, additional discussion on catalyst optimization and substrate scope, and crystallographic information (CIF) for compounds **2i**, **2l**, **5c** and **7a**. CCDC 924031–924034. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c3sc50410g

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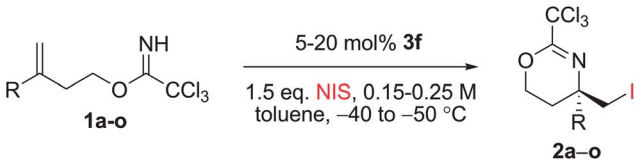
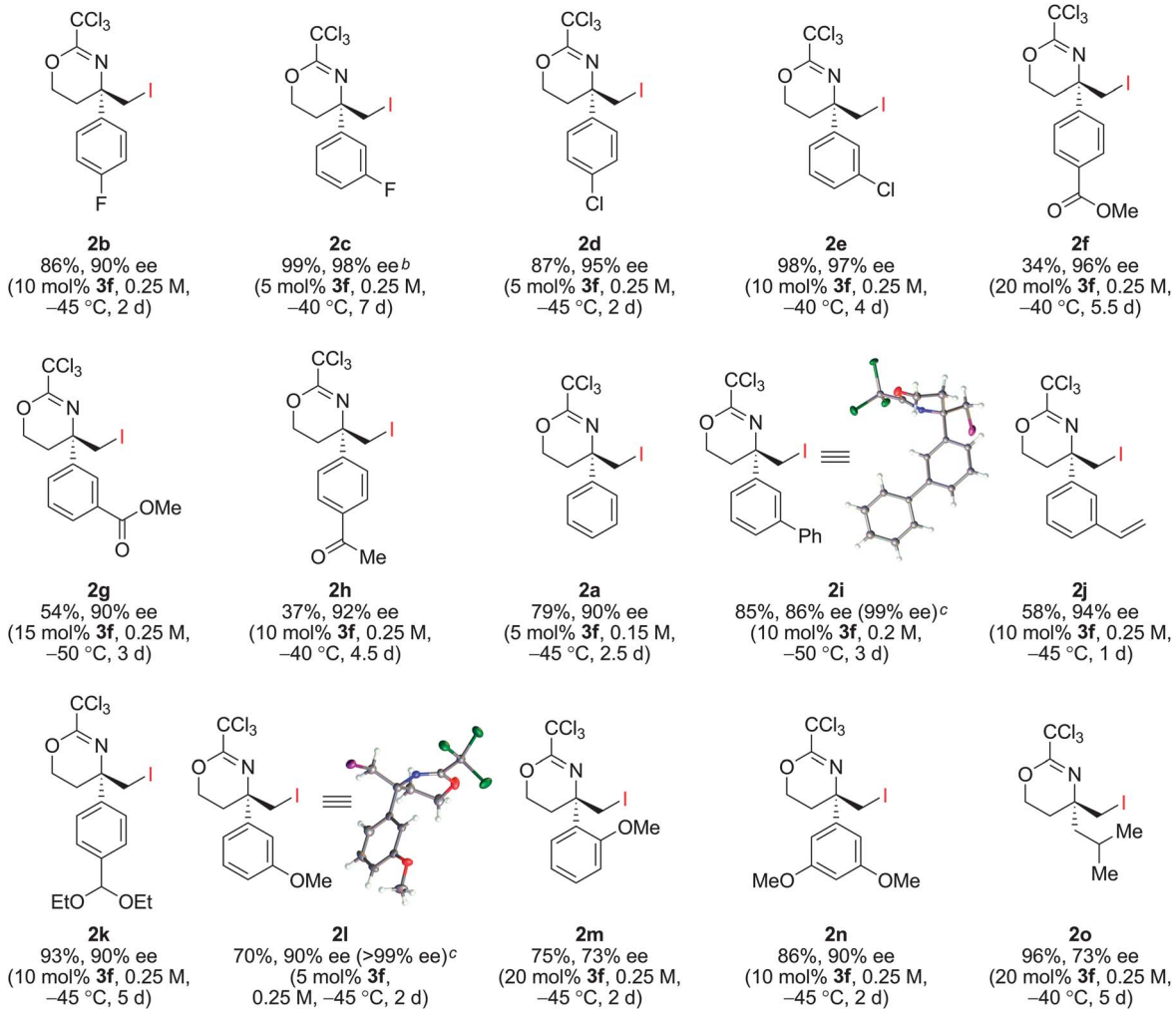
iodolactonization reactions,[2g] induced iodocyclization of **1a** with very poor enantioselectivity (entry 9). Other urea derivatives lacking the salicylaldimine functionality were ineffective in promoting iodoamination. Based on catalyst structure–enantioselectivity relationship studies,[8] we identified the 3-(*tert*-butyl)-5-formyl-4-hydroxyphenyl pivalate as the optimal Schiff-base substituent; replacing the OH group with either a H or OMe afforded less selective catalysts. Even minor variations of the electronic properties of the aromatic substituent led to diminished enantioselectivities. Thus, it is likely that the phenolic hydroxyl group plays a direct role in the iodoamination reaction mechanism, not only by restricting the catalyst conformation through an intramolecular H-bond, but perhaps also through interaction with the basic imidate during the cyclization.

By modifying the tertiary amide component in our Schiff-base urea catalysts, significant improvements in enantioselectivity were obtained (entries 2–8). Although product ee was only weakly responsive to the structure of the tertiary amide, reactivity could be enhanced through the introduction of appropriate arylpyrrolidine derivatives.[10] The *o*-tolylpyrrolidino

**Table 2** Substrate scope of intramolecular iodoamination[a]



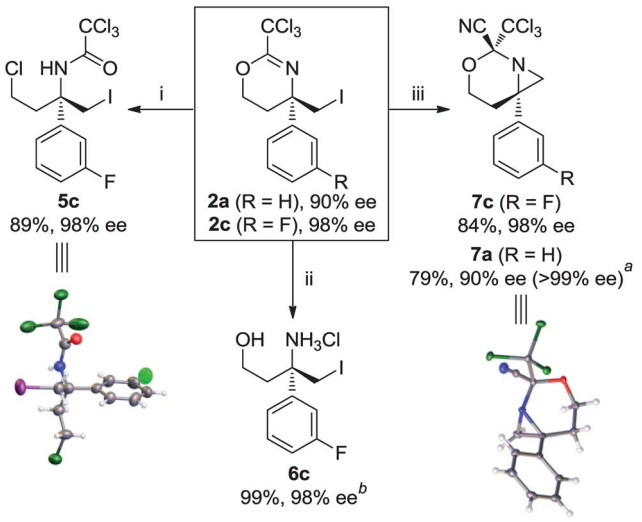

[a] Reactions were performed on a 0.1 mmol scale unless otherwise indicated. Yields are of isolated product following purification. Enantiomeric excesses (ee) were determined by HPLC analysis on commercial chiral columns. The absolute configuration of (*S*)-**2i** and (*S*)-**2l** was determined by obtaining molecular structures by X-ray crystallography. The absolute configuration of (*S*)-**2a** and (*S*)-**2c** was determined by derivatization (see Scheme 1). All other products are assigned by analogy. See ESI for full details.[8] [b] Reaction was conducted on a 1 mmol scale (432 mg **2c** was isolated). [c] ee following a single recrystallization from hexanes.

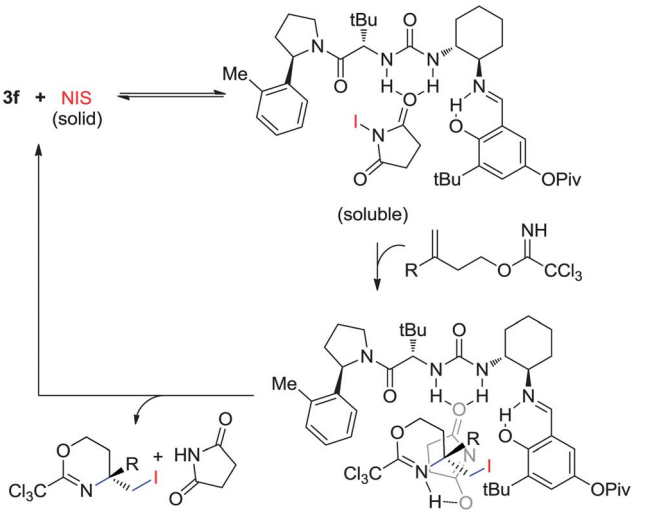
derivative **3f** was found to be optimal in this regard, allowing the reaction to be carried out with improved enantioselectivity and high yield at reduced temperatures (entry 8).

The scope of the enantioselective iodoamination reaction was explored with the optimal catalyst **3f** (Table 2). Most α-styrenyl derivatives examined bearing homoallylic trichloroacetimidate groups were found to be suitable substrates, undergoing iodocyclization to products **2b–n** with enantioselectivities exceeding 90% in most cases.[11] The transformation is compatible with a variety of functional groups including esters (**2f–g**), ketones (**2h**), acetals (**2k**), and bystander alkenes (**2j**). In general, the cyclization products are obtained cleanly: unreacted homoallylic trichloroacetimidate is observed and can be recovered in cases where modest yields were obtained. Substrates bearing electron-rich aromatic substituents underwent cyclization with lower enantioselectivity, and most of those bearing *ortho* substituents (with the exception of **1m**) did not provide iodoamination products.[12] Aliphatic homoallylic trichloroacetimidates were also found to undergo iodocyclization, albeit with reduced enantioselectivity (*e.g.*, **2o**).

The utility of the chiral vicinal iodotrichloroacetimidates produced in this reaction is readily demonstrated in a variety of simple transformations (Scheme 1). Full deprotection of the trichloroacetimidate could be induced by treatment of **2c** with acid in the presence of water to generate **6c**. Under anhydrous conditions, 4-chloro-1-iodo-2-trichloroacetamide **5c** was formed *via* selective cleavage of the C–O bond and generation of a new C–Cl bond, leaving the trichloroacetamide group intact. Reaction of **2a** and **2c** with cyanide resulted in smooth conversion to products **7a** and **7c**, respectively. Instead of direct $S_N2$ displacement of the highly congested iodide, cyanide addition to the trichloroacetimidate occurred with subsequent iodide displacement to afford the unusual aziridine *N*,*O*-acetals diastereoselectively.[13,14] The absolute and relative stereochemistry of aziridine **7a** was established unambiguously by X-ray crystallography.




**Scheme 1** Transformations of chiral iodotrichloroacetimidates. (i) 4 M HCl (dioxane), $CH_2Cl_2$, 12 h, 89%, 98% ee; (ii) 2 M HCl (aq.), MeOH, 13 h, 99%; (iii) NaCN, DMF, 50 °C, 12 h, 84%, 98% ee (**7a**), 16 h, 79%, 90% ee (**7c**). [a] ee following a single recrystallization from hexanes/$Et_2O$. [b] ee determined *via* derivatization. See ESI for full details.†




**Scheme 2** Proposed role of **3f** as a phase transfer catalyst. For spectroscopic evidence and potential conformations for a related NIS·**3b** complex, see ESI.†

The electrophilic iodinating agent, *N*-iodosuccinimide (NIS), has no detectable solubility in the reaction medium used for the catalytic iodoamination reaction (toluene, −40 °C to −50 °C). However, a soluble complex is generated in the presence of the urea catalyst, as evidenced by $^1$H NMR spectral shifts of the catalyst's urea N–H protons observed upon addition of one equivalent of NIS (Scheme 2). Complexation is presumably reversible since the active catalyst can be reisolated following a reductive quench of the reaction mixture. Preliminary computational studies on substrate complexation reveal that the salicylaldimine group is in close proximity to the bound molecule of NIS.[8] This suggests a basis for the high sensitivity of enantioinduction on the substituents on the salicyaldimine. We propose that the urea Schiff-base catalysts promote the iodocyclization reaction by acting as a neutral phase transfer agent. This pathway is reminiscent of the chiral phosphate anion phase transfer catalysis that has recently been implicated in related halocyclizations,[15] although the solubilization mechanism is clearly quite different in the present case.

## Conclusions

We have achieved the enantioselective synthesis of chiral iodoamines by a urea-catalysed iodocyclization of easily accessed alkenyl trichloroacetimidates. This approach to enantioselective iodoamination represents a potentially general platform for electrophilic alkene functionalizations that may be readily extended to other onium ions.

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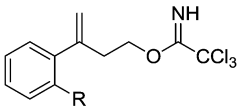
12 Substrates bearing *ortho*-substitution (with the exception of **2m**) do not provide iodoamination products and instead undergo elimination of the trichloroacetamide functionality to afford 1,3-butadiene byproducts.

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