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Chiral β -Iodoamines by Urea-Catalyzed Iodocyclization of Trichloroacetimidates

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Abstract

Highly enantioselective vicinal iodoamination of olefins is accomplished through the iodocyclization of alkenyl trichloroacetimidates catalyzed 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,^{2h} we describe here the intramolecular vicinal iodoamination of alkenes catalyzed 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 catalysts⁸ led to promising lead results with the known Schiff-base urea derivatives **3a–b** (Table 1, entries 1–2).^{9,10} 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

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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** (CCDC 924031), **2l** (CCDC 924032), **5c** (CCDC 924033), and **7a** (CCDC 924034). See DOI: 10.1039/b000000x/

catalytic I₂ 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 iodolactonization reactions,^{2h} induced iodocyclization of **1a** with very poor enantioselectivity (entry 9). However, significant improvements in enantioselectivity with the Schiff-base urea catalysts were obtained by incorporating a tertiary amide component (entries 2–8). Although product ee was only weakly responsive to the structure of the tertiary amide of the catalyst, reactivity could be improved significantly through the introduction of appropriate arylpyrrolidine derivatives.¹¹ The *o*-tolylpyrrolidino 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. The transformation is compatible with a variety of functional groups including esters (**2f–g**), ketones (**2h**), acetals (**2k**), and bystander alkenes (**2j**). 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.⁸ 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 (Figure 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.

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 ¹H NMR spectral shifts of the catalyst's urea N–H protons observed upon addition of one equivalent of NIS (Figure 2). 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-catalyzed 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Scheme 1.

Transformations of chiral iodotrichloroacetimidates. (i) 4M HCl (dioxane), CH₂Cl₂, 12 h, 89%, 98% ee; (ii) 2M HCl (aq.), MeOH, 13 h, 99%, ee not determined; (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/Et₂O. ^b ee determined via derivatization. See ESI for full details.⁸

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.

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 ¹H NMR integration against an internal quantitative standard.

d_5 eq. NIS.
 $c_{1.1}$ eq. NIS.

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Table 2

Substrate scope of intramolecular iodoamination.^a

^aReactions 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 Figure 1). All other products are assigned by analogy. See ESI for full details.⁸

^bReaction was conducted on a 1 mmol scale (432 mg **2c** was isolated).

^cEe following a single recrystallization from hexanes.