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Enantioselective Organocatalytic Amine-Isocyanate Capture-Cyclization: Regioselective Alkene Iodoamination for the Synthesis of Chiral Cyclic Ureas

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Abstract

Ureas of chiral diamines are prominent features of therapeutics, chiral auxiliaries, and intermediates in complex molecule synthesis. Although many methods for diamine synthesis are available, metal-free enantioselective alkene functionalizations to make protected 1,2- and 1,3-diamines from simple achiral starting materials are rare, and a single reagent that accesses a cross-section of each congener with high enantiomeric excess is not available. We describe a method to synthesize enantioenriched cyclic 5- and 6-membered ureas from allylic amines and an isocyanate using a C2-symmetric BisAmidine (BAM) catalyst that delivers N-selectivity from an ambident sulfonyl imide intermediate, overcoming electronic and steric deactivation at nitrogen. The geometry of 1,2-disubstituted alkenes is correlated to 5-exo and 6-endo cyclizations without altering alkene face selectivity, which is unexpectedly opposite that observed with O-nucleophiles. Straightforward product manipulations to diamine and imidazolidinone derivatives are underscored by the synthesis of an NK1 antagonist.

Graphical Abstract

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ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI:

Complete experimental details (SI1, PDF)

NMR and HPLC trace data (SI2, PDF)

Notes

No competing financial interests have been declared.

Keywords

Bifunctional catalysis; Brønsted acid-base catalysis; alkene diamination; enantioselective; cyclic urea

Chiral ureas are used widely as molecular building blocks in the fields of organic and inorganic chemistry. Natural products,¹ small molecule therapeutics,² ligands,³ organocatalysts,⁴ and chiral auxiliaries⁵ are among the applications wherein ureas and urea derivatives (i.e. of chiral diamines) find utility. Examples of well-studied therapeutics include cisplatin derivatives,⁶ HIV protease inhibitors,⁷ and NK₁-antagonists,⁸ all containing a 1,2-diamino (*vic*-diamine) functionality where the chirality at carbon of C-N is essential to activity.⁹ In addition, there are many instances where 1,3-imidazolidinone and tetrahydro-2-pyrimidone ureas are useful precursors for the synthesis of chiral imidazolines, guanidines, hydantoins, and amins.¹⁰

Enantiopure diamine precursors to cyclic ureas are often resolved from racemates¹¹ leaving half of the material to waste, or prepared by enantioselective desymmetrization of *meso*-diamines.¹² Preparations through stereospecific rearrangements from enantioenriched starting materials are available as well.¹³ The main enantioselective reactions to prepare diamines from alkenes include direct diamination,^{14,15} C-H activation,¹⁶ and metal-mediated cyclization.¹⁷ Although access to chiral 1,2- and 1,3-diamines can follow numerous paths, no examples of organocatalyzed methods have been reported for the preparation of these privileged scaffolds using an enantioselective carbon-nitrogen bond forming reaction.¹⁸

C₂-Symmetric chiral bis(amidine) [BAM] catalysts have been used exclusively in enantioselective oxygen cyclizations,¹⁹ but we required an alkene haloamination²⁰ that would enable the concise synthesis of cyclic ureas. Using easily accessible allylic amines, inexpensive *p*-toluenesulfonyl isocyanate (\$0.04–0.15/mmol), and an electrophilic halogen source, the aim was to develop a bifunctional BAM catalyst capable of catalyzing the enantioselective isocyanate capture/aminocyclization of allylic amines in one pot (Scheme 1).²¹

In addition to the need to establish alkene facial selectivity, the relative rate of nitrogen-carbon versus oxygen-carbon bond formation in the catalyst-controlled capture/cyclization was an anticipated challenge (Scheme 1).

Similar attempts using halo-functionalization²² have been demonstrated by the enantioselective cyclization of sulfonamides and cyclizations of sulfonyl imides, but they are generally restricted to pyrrolidine and piperidine formation.^{23,24} Control of ambident nucleophiles underlies many successful methodologies and has prompted research to develop design principles for substrate and catalyst control.²⁵ While there are many examples that use amide donors, the oxygen is frequently the donor atom.²⁶ It is rare to achieve high selectivity with an ambident nucleophile leading to *N*-cyclization of a urea controlled by an organocatalyst, particularly among enantioselective transformations.

Initial results using a benzyl-protected allylic amine 1 and (*R,R*)-StilbPBAM (free base 4a)²⁷ yielded good selectivity for carbon-nitrogen bond formation but moderate enantioselection (57% ee) (Table 1, entry 1). LiAlH₄ reduction of the major product (Scheme 2) afforded diamine 3, establishing the major product as a urea and not an imidate (c.f. Scheme 1).²⁸ Among other catalysts explored, the more electron-rich bis(amidine)s 4b and 4c were examined. These revealed improved selectivity (Table 1, entries 2–3). Use of the cyclohexane diamine-derived bis(amidine), one that is also less electron-rich, led to lower enantioselection (Table 1, entry 4). No detectable product formation was observed under these conditions in the absence of catalyst. At higher temperatures, complex mixtures formed (catalyst-free). Addition of an achiral base at room temperature provided the desired urea, albeit with lower N:O selectivity (Table 1, entry 5).

Although investigations modifying the sulfonyl substituent failed to improve selectivity, use of a *para*-methoxy phenyl (PMP) protecting group at nitrogen, combined with the more Brønsted basic catalyst (^{6,7}(MeO)₂StilbPBAM (4c)) ultimately afforded the product with high yields and high selectivity for *N*-cyclized product and 91% ee (Table 2, entry 1).²⁸ Key aspects of the optimized conditions included a reaction time to ensure high conversions, use of *N*-iodopyrrolidone (NIP), and a workup using 15% powdered Na₂S₂O₄ in silica.²⁹ NIP exhibited favorable solubility under the reaction conditions. The product is formed with complete *N*-selectivity, but unexpectedly, *the major enantiomer of the nitrogen cyclization is opposite in configuration compared to the previously reported selectivities for oxygen cyclizations with (R,R)-BAM catalysts*.^{19,30}

(*R,R*)-BAM-Catalyzed (4c) 5-*exo* cyclizations of nitrogen in Table 2 exhibit *opposite* alkene facial selectivity when compared to 5- and 6-*exo* cyclizations of oxygen nucleophiles (carboxylic acid,^{19a} phosphoramidic acid^{19b}). Of the two, the phosphoramidic acid cyclization is most closely analogous as they share both stereoelectronic (5-*exo*) and alkene features (allylic amine).³⁰ The nature of the nucleophilic atom, oxygen vs. nitrogen, appears to be the decisive feature, perhaps due to the larger sulfonimide size relative to carboxylic or phosphoramidic acid oxygen. Notably, the addition of a strong acid to the catalyst has little effect on the outcome of nitrogen cyclizations reported here,²⁷ unlike BAM-catalyzed cyclizations of unsymmetrical alkenes.

An inspection of substrate scope revealed some generality (Table 2). This included the often troublesome electron-rich styrene 5h³¹ which cyclized in 80% yield and 90% ee (Table 2, entry 8). The hindered 5d exhibited diminished reactivity (15% yield), but the product isolated showed some enantiomeric enrichment at 49% ee (Table 2, entry 4). Another highlight was the observation that heteroaromatic substrate 5i, prone to electrophilic aromatic substitution, was tolerated with 93% yield and 88% ee (Table 2, entry 9). Alkenes substituted with alkyl groups provided moderate to good yield, but lower ee, regardless of size (Table 2, entries 10–12). In cases where low to moderate enantioselectivity is observed, it is still encouraging that high isolated yields indicate effective catalyst-controlled selectivity for nitrogen cyclization.

Catalytic enantioselective halocyclization of a *Z*-alkene exhibits good regioselectivity favoring the 5-*exo* product.³² Cyclizations of *E*-alkenes with high enantio- and

regioselectivity, however, are sparse.³³ Attempts to overcome the bias for low regioselectivity have been reported³⁴ but are not enantioselective. The Borhan group achieved a highly enantioselective 6-*endo* chloro cyclization of amides using *E*-alkenes but *Z*-alkenes were unreactive.^{26c}

We sought a procedure that could provide both 5-*exo* and 6-*endo* halocyclization of 1,2-disubstituted alkenes with high enantioselection using a single reagent, which redirected our attention to 1,2-disubstituted *E*- and *Z*-alkenes (Table 3). Catalyst 4c was found to be effective for both geometric isomers. In the case of *Z*-allylic amines, 5-*exo* cyclization regioselectivity was favored, delivering cyclic ureas such as 9 in excellent yield (93%) for a single diastereomer and high enantioselection (93% ee) (Table 3, entry 1). This cyclization highlights the preference for 5-*exo* cyclization despite the benzylic nature of the carbon that would lead to 6-*endo* cyclization. For cyclizations of *E*-1,2-disubstituted allylic amines, however, the *endo* pathway was favored. For example, allylic amine 7a undergoes isocyanate capture/cyclization to produce the six-membered urea 8a (Table 3, entry 2) in 60% yield and 94% ee. Enantioselection remained high for conjugated alkene substrates 7b and 7c (Table 3, entries 3 and 4). Increasing the sterics by employing a trisubstituted alkene furnishes 8d and 8e in more modest 86 and 63% ee respectively (Table 3, entries 5 and 6).

Catalyst 4c is unusually versatile and effective for regio- and stereoselective cyclizations involving nitrogen nucleophiles in alkene halofunctionalizations across 1,1- and 1,2-disubstituted alkenes. Unified access to cyclic ureas of tertiary and secondary amines in enantioenriched form has great potential as a tool for therapeutic development. The transformations in Scheme 3 illustrate both reductive (10, 13) and homologative (12) conversions of the primary iodide. Additionally, oxidative conversion of the urea methylene provides a hydantoin (11) which can serve as a protected α -amino amide bearing phenyl and iodomethylene side chains. In a final demonstration, the NK₁ antagonist 16 (Schering-Plough) was prepared (Scheme 4).⁸ The key cyclization proceeds well using the *para*-fluoro derivative 5f and can be scaled to 1 gram without significant loss of yield or enantioselection. Subsequent radical-mediated oxygenation³⁵ delivers a key alcohol that can be alkylated to deliver ether 15. Double deprotection then furnished the desired target 16.⁹

In conclusion, a new organocatalytic enantioselective reaction forming a chiral carbon-nitrogen has been developed. High control of nitrogen cyclization over oxygen cyclization has been achieved using a C₂-symmetric BisAmidine catalyst. Three of the most common alkene classes were examined in allyl amine substrates, each delivering urea products with a high degree of regioselectivity. While 1,1- and *Z*-1,2-disubstituted alkenes favored 5-*exo* cyclization, *E*-1,2-disubstituted alkenes delivered 6-*endo* products instead, still with high enantioselection. Unexpectedly, the facial selectivity in these iodoaminations are opposite those for oxygen nucleophiles. Investigations into this behavior will be reported in due course, but we speculate that the unique steric and electronic demands of sulfonyl imides underlie this phenomenon. The enantioenriched 5- and 6-membered ureas are easily derivatized, leading to diamines, hydantoins, and fully deprotected imidazolidinones. The value of reagent-controlled alkene iodoamination was illustrated by a synthesis of an imidazolidinone NK₁ antagonist using entirely enantioselective methods.

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Scheme 1.

Cyclic Urea Synthesis Goal: Alkene Halofunctionalization Using a Nitrogen Nucleophile

Scheme 2. Conversion of Iodocyclization Product **2** to Diamine **3** to Confirm N-C Bond Formation

Scheme 3.
Transformations of Chiral Iodomethyl-substituted Cyclic Ureas

Scheme 4. Enantioselective Synthesis of an NK_1 Antagonist (**16**)

Table 1.

Enantioselective Alkene Iodoamination by Isocyanate Capture by 1,1-Disubstituted Allylic Amines^a

entry	catalyst	N:O	yield ^b (%)	ee (N, %) ^c
1	4a	87:13	99	57
2	4b	95:5	quant	71
3	4c	87:13	88	91
4	4d	85:15	quant	24
5	tetramethylguanidine	73:27	64	na

^aReactions at 0.05 mmol scale, 0.04 M in toluene for 16 h, except entry 5 (6 min, 25 °C). See SI for complete experimental details.^bYield measured by ¹H NMR using CH₂Br₂ as an internal standard.^cEnantiomeric excess (ee) determined by HPLC using a chiral stationary phase.

Table 2.

Enantioselective Alkene Iodoamination by Isocyanate Capture by 1,1-Disubstituted Allylic Amines^a

entry	R ₁	5/6	time (h)	yield ^b (%)	ee (%) ^c
1 ^d	C ₆ H ₅	a	36	82	91
2	<i>p</i> -MeC ₆ H ₄	b	36	97	92
3	<i>m</i> -MeC ₆ H ₄	c	36	88	91
4	<i>o</i> -MeC ₆ H ₄	d	96	15	49
5	<i>p</i> -BrC ₆ H ₄	e	36	90	88
6 ^e	<i>p</i> -FC ₆ H ₄	f	36	90	89
7	<i>p</i> -CF ₃ C ₆ H ₄	g	48	75	90
8	<i>p</i> -MeOC ₆ H ₄	h	36	80	90
9	3-thiophene	i	36	93	88
10	Bn	j	36	75	49
11	Me	k	36	93	29
12	H	l	36	70	38

^aReactions at 0.1 mmol scale, 0.05 M in toluene for 36 h, except entries 4 (96 h) and 7 (48 h). See SI for complete experimental details.^bIsolated yields.^cEnantiomeric excess (ee) determined by HPLC using a chiral stationary phase. Absolute configuration for **6e** assigned by X-ray analysis, remaining examples assigned by analogy.^d1.0 mmol of starting material used.^eWhen 3.1 mmol of starting material was used, the yield was 83% (89% ee).

Table 3.

Enantioselective Alkene Iodoamination by Isocyanate Capture: Behaviors of Di- and Trisubstituted Allylic Amines^a

entry	R ₁	R ₂	product	time (h)	yield (%) ^b	ee (%) ^c
1	H	C ₆ H ₅	9	36	93	93
2	C ₆ H ₅	H	8a	84	60	94
3 ^d	<i>E</i> -C ₆ H ₅ CH=CH	H	8b	36	74	93
4	<i>E</i> -CH ₃ CH=CH	H	8c	36	40	94
5 ^e	C ₆ H ₅	CH ₃	8d	72	31	86
6	CH ₃	CH ₃	8e	36	75	63

^aReactions at 0.1 mmol scale, 0.05 M in toluene. See SI for complete experimental details.

^bIsolated yields of 6-*endo* product are listed (except entry 1).

^cEnantiomeric excess (ee) determined by HPLC using a chiral stationary phase. Absolute configuration for **8b** assigned using X-ray analysis. Absolute configuration for **9** assigned by chemical correlation using *L*-Phe: see SI for details. Remaining examples assigned by analogy.

^d1.0 mmol of starting material used.

^eStarting allylic amine 19:1 *E:Z*.