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Enantioselective *N*-Heterocyclic Carbene-Catalyzed Annulation Reactions with Imidazolidinones

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The development of efficient strategies for the stereoselective construction of privileged heterocyclic systems is an important objective in chemical synthesis and pharmaceutical sciences. Over the last decade, *N*-heterocyclic carbene (NHC) catalysis has provided opportunities for the development of new transformations based on polarity reversal or *Umpolung* reactivity.^[1] The exploration of these unconventional reactivity patterns with new electrophilic coupling partners facilitates advances in synthesis and provides access to bioactive natural products and unique, drug-like scaffolds.^[2] Substituted imidazoles are a privileged structural motif that is prevalent in pharmaceutical small molecules with diverse biological activities, including inflammation,^[3] HIV,^[4] depression,^[5] and various other disease areas.^[6]

There are several methods for the synthesis of substituted imidazoles and one main approach involves the conversion of readily accessible imidazolidinones to the related imidazoles through functional group transformations.^[4b, 7] However, unlike the related oxazolones, new asymmetric methods involving imidazolidinones are scarce in the literature. There have been several recent reports involving the use of alkylidene oxazolones in enantioselective processes,^[8] likely due the ability to access unnatural amino acids from these readily available precursors.^[9] While the related imidazolidinones can also be cleaved to reveal the corresponding amino acids,^[10] their more robust nature has resulted in intense exploration of these compounds for a variety of medicinal chemistry applications.^[11] We envisioned that the investigation of Michael acceptors with this heterocyclic framework combined with α,β -unsaturated aldehydes under carbene catalysis conditions could provide access to novel chiral imidazoles through a formal [4+2] annulation (Figure 1). While this NHC-enolate pathway has been explored previously,^{[12],[13]} the use of such electron rich conjugate acceptors has not been investigated.^[14] There are several challenges associated with the development of this reaction- *the two most critical being the ability to engage these much less reactive acceptors in a Michael reaction and control over the mode of NHC reactivity (homoenolate, enolate, acyl anion).*

Herein, we report the NHC-catalyzed combination of α,β -unsaturated aldehydes with alkylidene imidazolidinones to afford enantioenriched bicyclic lactones through a formal

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[4+2] annulation. The subsequent treatment of the lactone products with dilute acid followed by acylation affords a second class of 5-oxyimidazoles. This convergent, stereoselective and modular approach to these two unique classes of imidazoles allows for incorporation of a wide range of functionality through appropriate choice of the imidazolidinone and aldehyde coupling partners.

We began our studies by combining phenyl substituted imidazolidinone **4a** with cinnamaldehyde in the presence of triethylamine and azolium **A**. Under these conditions, we observed a modest 33% conversion of the imidazolidinone to lactone **5a** (Table 1). Encouraged by this lead, different aryl-substituted imidazolidinones were prepared and explored in this NHC-catalyzed annulation. Due to the limited solubility of imidazolidinone **4a** in typical organic solvents, we initially hypothesized that this physical characteristic was responsible for the low conversion. Initial exploration of imidazolidinones **4b–d**, bearing a substituent at the 4-position, provided no improvement in solubility or conversion relative to **4a**. The synthesis of imidazolidinones **4e–h** with *ortho*-substitution on the aromatic ring provided more interesting results. We were interested to find that while the *ortho*-substituent increased solubility, resulting in a homogeneous reaction mixture for substrates **4e–h**, higher levels of conversion were observed in the presence of electron-withdrawing (**4g–h**) compared to electron-donating groups (**4e–f**). Prompted by these results, a number of 2-aryl imidazolidinones bearing additional electron withdrawing substituents, specifically a difluoroaryl group, were evaluated. We were pleased to find that with imidazolidinones **4i–k** >80% conversion was achieved. Unfortunately, the high rates of conversion were accompanied by the formation of another alkylidene imidazolidinone+cinnamaldehyde product based on mass spectrometry analysis (see below).

At this point, 2,5-difluorophenyl substituted imidazolidinone **4j** was selected for further investigation of the reaction conditions. With 15 mol % azolium **A** and triethylamine as the base, the reaction between imidazolidinone **4j** and cinnamaldehyde afforded lactone **5j** as the major product, but also gave rise to a significant amount of spirocycle **6j** as a 1:1 mixture of diastereomers (Table 2, entry 1). The formation of spirocycle **6j** results from a formal [3+2] annulation between the imidazolidinone and cinnamaldehyde.^[15]

The use of chiral triazolium precatalyst **B**^[12a, 16] did not significantly improve the ratio of **5j:6j**, but the lactone (**5j**) was generated with excellent enantioselectivity (95:5 er). Similar results were obtained with our 2,6-diethylphenyl substituted triazolium **C**,^[17] and due to a reproducible increase in enantioselectivity (98:2 er), this catalyst was employed in further optimization endeavors (entry 3). Interestingly, the homoenolate driven process that generates spirocycle **6j** proceeds with significantly lower enantioselectivity (70:30 er, results not shown). Given the excellent selectivity for the formal [4+2] process, and the opportunity to access various classes of substituted 2-aryl imidazoles through opening of the lactone, we decided to focus our efforts on improving the selectivity for lactone **5j**.

We hypothesized that an increase in the rate of the initial β -protonation would increase the product ratio to favor lactone **5j**. Inspired by recent reports, the use of a Brønsted acid additive was employed to explore this possible modulation between the formal [4+2] and [3+2] manifolds.^[12f, 18] These studies indicated that acetic acid indeed improved the ratio of **5:6** in favor of lactone **5j** while maintaining the high levels of enantioselectivity (entry 4). Based on this result, the use of acetate bases with varying counterions was investigated (entry 5–8). Different acetate bases produced lactone **5j** with varying levels of selectivity, with tetra-*n*-butylammonium acetate providing the highest levels of conversion and selectivity (82:12 for **5j/6j**, 6:1 dr, entry 8). Finally, the use of acetic acid in conjunction with tetra-*n*-butylammonium acetate further improved the level of selectivity for lactone **5j**.

over spirocycle **6j**, with lactone **5j** isolated in 73% yield and 98:2 enantiomeric ratio (entry 9).

With the optimized reaction conditions established, we explored the scope of this NHC-enolate driven formal annulation with various α,β -unsaturated aldehydes. Electron-donating substituents were well tolerated at all positions of the aromatic ring, affording the lactone products in good yield and diastereoselectivity and excellent enantioselectivity (Table 2, entry 2–5). Aldehydes bearing electron withdrawing groups were also explored (entry 6–9), with lactones **11–14** formed in moderate to good yield and selectivities.^[19] Various other aromatic substituents, including 2-naphthyl and 2-furyl, also performed well in the reaction.

Importantly, β -alkyl substituted enals were competent substrates in this transformation. With 2-hexenal and crotonaldehyde, the reaction proceeded to full conversion to afford lactones **17** and **18** in 90% and 80% yield, respectively, and with superb diastereo- and enantioselectivity (entry 12–13). Despite the fact that the reactions involving the cyclohexyl-substituted enal and the highly reactive parent aldehyde, acrolein, did not reach full conversion (>60% over 48 h), lactones **19** and **20** were nevertheless obtained in moderate yield and excellent selectivity (entry 14–15).

Structural modification of the aryl and alkylidene components of the imidazolidinone was also explored (Table 3). Several of the previously examined imidazolidinones were employed in the annulation reaction under the optimized reaction conditions. With chiral triazolium **C**, imidazolidinones **4h** and **4i** displayed sluggish reactivity, but were converted to the corresponding lactones in good yield and selectivity over prolonged reaction times (>70% conversion over 48 h). In addition, the 3,5-trifluoromethyl substrate also performed well in this reaction. Variation of the alkylidene substituent revealed that several aromatic groups were tolerated at this position, including those with electron withdrawing and donating substituents. In addition, the incorporation of an alkyl group was achieved and enabled the preparation of various alkyl substituted lactones with excellent diastereo- and enantioselectivity. Of particular interest is the synthesis of bis-alkyl substituted lactone **26** in 59% yield and >99:1 enantiomeric ratio.

Our current understanding of this annulation is that the lactone products can be obtained through either a stepwise or concerted [4+2] process,^[20] while the observed spirocycle (**6**) arises from a divergent formal [3+2] annulation pathway (Scheme 1). Based on previous computational reports by Verma,^[21] Domingo,^[22a] and Lupton^[22b] as well as our own observations, we favor a stepwise process for this specific reaction. The proposed catalytic cycle for both the lactone and spirocycle products begins with addition of the NHC to cinnamaldehyde to generate the extended Breslow intermediate (**I**). At this point, the NHC-bound homoenolate can undergo either β -protonation to generate catalytic enol intermediate **IV**, or conjugate addition to the imidazolidinone to arrive at an alternate catalytic enol (**VII**). We propose that in the presence of an acid source, the rate of β -protonation is increased to favor formation of the formal [4+2] annulation product. In this case, the generation of enol **II** then promotes approach of the imidazolidinone from the back face and subsequent coordination through a hydrogen bonding interaction, resulting in an organized transition state (**III**). Following carbon-carbon bond formation, azolium **IV** undergoes *O*-acylation to release the NHC catalyst and furnish the lactone product (**5**). Further studies to probe these mechanistic aspects are underway.

Alternatively, if β -protonation is slow, a mixture of products is obtained due to a competing [3+2] annulation pathway. In this case, it is proposed that the imidazolidinone can approach in either a synclinal (**VI**) or antiperiplanar fashion (not shown), and the lack of differentiation between these two transition states results in the poor diastereoselectivity

(1:1) observed. Following carbon-carbon bond formation to generate hydroxy imidazole-terminated enol **VII**, tautomerization occurs to give rise to acyl azolium **VIII**, which then presumably undergoes atypical C-acylation vs. O-acylation to afford **6**. This represents one of the few examples in which a cyclopentanone has been prepared using NHC-catalysis: the much more commonly observed pathway for ejecting the NHC catalyst from an acyl azolium intermediate involves O-acylation.^[15, 23]

The formal [4+2] annulation products can be readily converted to a second class of 5-oxyimidazoles through acid-catalyzed opening of the lactone followed by acylation. In this manner, imidazole **28** was generated in 66% yield over the two-step sequence (Scheme 2). It is envisioned that a wide range of acylating agents could be employed to access various 5-acylimidazoles.^[24]

In conclusion, a highly selective NHC-catalyzed formal [4+2] annulation of α,β -unsaturated aldehydes with imidazolidinones has been developed. An electron-withdrawing 2-aryl substituent on the imidazolidinone was necessary to activate the new, yet sluggish, conjugate acceptor and achieve high conversion. In addition, a Brønsted acid is an essential additive to achieve chemoselectivity for the formal [4+2] annulation product. This enhancement of a desired reaction pathway with acid underscores the subtle balance that proton exchange plays in all carbene-catalyzed processes and opens additional opportunities to create distinct molecular topologies and scaffolds from a common set of starting materials. This new enantioselective methodology provides a distinct approach to substituted imidazoles, wherein the incorporation of various substituents can be achieved through judicious choice of the imidazolidinone and aldehyde starting materials. Continuing investigations of new processes involving carbene-catalyzed homoenolate and enolate equivalents and the factors involved in controlling these versatile and selective [4+2] vs. [3+2] manifolds are ongoing.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Examples of biologically active chiral imidazoles

Figure 1.
NHC-Catalysis approach to substituted imidazoles.

Scheme 1.
Proposed Reaction Pathway.

Scheme 2. Representative Ring Opening^[a]

^[a] See Supporting Information for details. *Reagents and conditions:* (a) 5% formic acid in MeOH, 65 °C, 70% (b) Et₃N, 4-chlorobenzoyl chloride, THF, 23 °C, 94%

Table 1

Role of the 2-aryl substituent.^[a]

para			
a:	33% conv	b:	<10% conv
c:	18% conv	d:	23% conv
ortho			
e:	27% conv	f:	36% conv
g:	67% conv	h:	62% conv
F_n			
i:	80% conv	j:	>95% conv
k:	89% conv	l:	67% conv

^[a] Determined by ¹H NMR spectroscopy (500 MHz) of the unpurified reaction.

Table 2

Optimization of reaction conditions.

entry	NHC	base (equiv)	conv ^[a]	5 ^[a]	dr major ^[a] er ^[b]
1	A	Et ₃ N(1.5)	85	55:45	10:1 --
2	B	Et ₃ N(1.5)	84	63:37	10:1 95:5
3	C	Et ₃ N(1.5)	75	66:34	10:1 98:2
4 ^[c]	C	Et ₃ N(1.5)	81	82:18	11:1 98:2
5	C	NaOAc (0.3)	68	69:31	10:1 98:2
6	C	KOAc (0.3)	44	76:24	10:1 98:2
7	C	CsOAc (0.3)	96	71:29	1.5:1 96:4
8	C	ⁿ Bu ₄ NOAc (0.3)	94	82:18	6:1 98:2
9 ^[c]	C	ⁿ Bu ₄ NOAc (0.3)	96(73) ^[d]	91:9	6:1 98:2

A

B: Ar = Mes

C: Ar = 2,6-Et₂Ph

^[a] Determined by ¹H NMR spectroscopy (500 MHz) of the unpurified reaction.

^[b] Enantiomeric excess determined by HPLC.

^[c] 1.0 equiv acetic acid as an additive.

^[d] Isolated yield.

Table 3

Aldehyde reaction scope.^[a]

entry	R	yield (%) ^[b]	dr ^[c]	er (major) ^[d]
1	Ph (5j)	73	6:1	98:2
2	4-Me-C ₆ H ₄ (7)	82	6:1	99:1
3	3-Me-C ₆ H ₄ (8)	61	2:1	97:3
4	4-OMe-C ₆ H ₄ (9)	76	7:1	99:1
5	2-OMe-C ₆ H ₄ (10)	61	7:1	96:4
6	4-Br-C ₆ H ₄ (11)	64	2:1	96:4
7	4-Cl-C ₆ H ₄ (12)	58	7:1	98:2
8	3-Cl-C ₆ H ₄ (13)	46	2:1	>99:1
9	2-Cl-C ₆ H ₄ (14)	48	2.5:1	92:8
10	2-naphthyl (15)	71	2:1	96:4
11	2-furyl (16)	66	3:1	98:2
12	<i>n</i> -propyl (17)	90	>20:1	>99:1
13	Me (18)	80	>20:1	>99:1
14	cyclohexyl (19)	56	>20:1	98:2
15	H (20)	42	>20:1	>99:1

^[a] See Supporting Information for details.^[b] Isolated yield after chromatography.^[c] Determined by ¹H NMR (500 MHz) or ¹⁹F NMR (376 MHz) spectroscopy.^[d] Enantiomeric ratio determined by HPLC.

Table 4

Imidazolidinone Reaction Scope.^[a]

^[a] See Supporting Information for details. Yield of isolated product after chromatography. Diastereomeric ratios determined by ¹H NMR (500 MHz) of ¹⁹F NMR (376 MHz) spectroscopy. Enantiomeric ratio determined by HPLC.