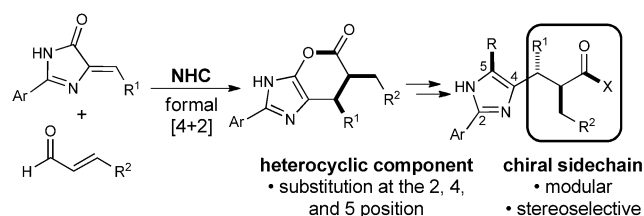


Enantioselective N-Heterocyclic Carbene Catalyzed Annulation Reactions with Imidazolidinones**

Elizabeth O'Bryan McCusker and Karl A. Scheidt*

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 that are 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 small molecules with biological activities against inflammation,^[3] HIV,^[4] depression,^[5] and various other diseases.^[6]

There are several methods for the synthesis of substituted imidazoles; one main approach involves the conversion of readily accessible imidazolidinones into the related imidazoles through functional-group transformations.^[4b,7] However, unlike for the related oxazolones, new asymmetric methods involving imidazolidinones are rarely reported. Recently, there have been several reports that involve the use of alkylidene oxazolones in enantioselective processes,^[8] which is likely due to the ability to access unnatural amino acids from these readily available precursors.^[9] Whereas 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 applications in medicinal chemistry.^[11] We envisioned that the investigation of Michael acceptors with this heterocyclic framework in combination with α,β -unsaturated aldehydes under carbene catalysis conditions could provide access to novel chiral imidazoles through a formal [4+2] annulation (Figure 1). Although 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



Examples of biologically active chiral imidazoles:

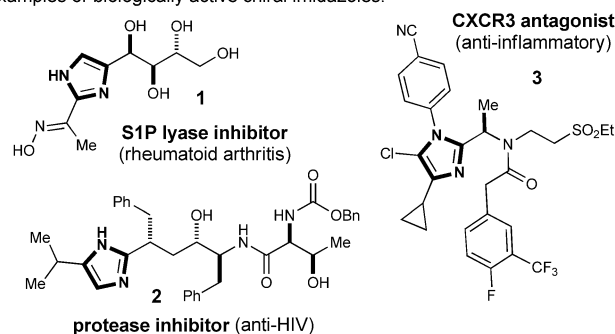


Figure 1. Access to substituted imidazoles through NHC catalysis.

ability to engage these much less reactive acceptors in a Michael reaction and the control over the mode of NHC reactivity (homoenolate vs. enolate vs. acyl-anion reactivity).

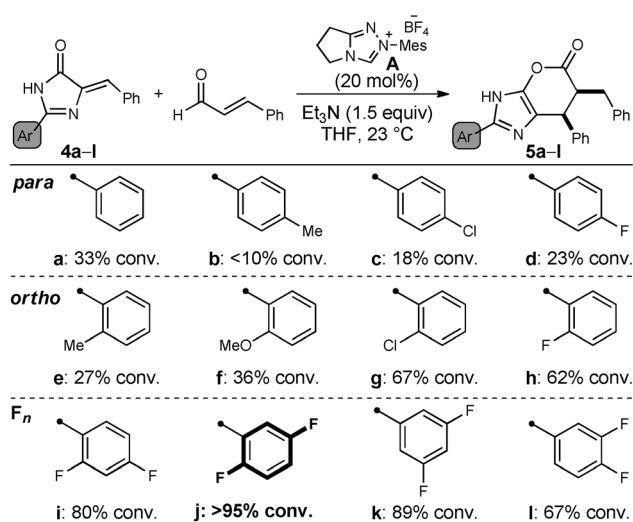
Herein, we report the NHC-catalyzed transformation of α,β -unsaturated aldehydes with alkylidene imidazolidinones to afford enantioenriched bicyclic lactones through a formal [4+2] annulation. Subsequent treatment of the lactone products with dilute acid followed by acylation affords a second class of 5-oxyimidazoles. This convergent, stereoselective, and modular approach to these two classes of imidazoles allows the incorporation of a wide range of functional groups through the 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 modest 33 % conversion of the imidazolidinone into lactone **5a** (Scheme 1). Encouraged by this lead, different aryl-substituted imidazolidinones were prepared and explored in this NHC-catalyzed annulation. Because of 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**, which bear a substituent at the 4 position, provided no improvement in solubility or conversion relative to **4a**. The use of imidazolidinones **4e–h** with substituents at the *ortho* position of the aromatic ring provided more interesting results.

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Scheme 1. Role of the aryl substituent at the 2-position. Conversions were determined by ¹H NMR analysis (500 MHz) of the unpurified reaction mixture.

Whereas the *ortho* substituent increased solubility, which resulted in a homogeneous reaction mixture for substrates **4e–h**, higher levels of conversion were observed in the presence of electron-withdrawing substituents (**4g**, **4h**) compared to electron-donating groups (**4e**, **4f**). Prompted by these results, a number of 2-aryl imidazolidinones that bear additional electron-withdrawing substituents, specifically a difluorophenyl group, were evaluated. We were pleased to find that with imidazolidinones **4i–k**, a conversion of > 80% was achieved. Unfortunately, the high rates of conversion were accompanied by the formation of another product from the reaction of the alkylidene imidazolidinone and cinnamaldehyde, as determined by mass spectrometry (see below).

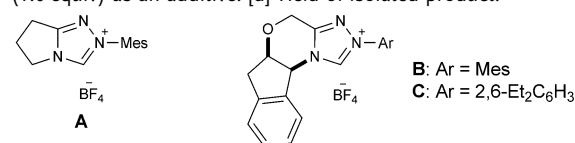
At this point, 2,5-difluorophenyl-substituted imidazolidinone **4j** was selected for further investigation of the reaction conditions. With azolium **A** (15 mol%) and triethylamine as the base, the reaction between imidazolidinone **4j** and cinnamaldehyde afforded lactone **5j** as the major product, but also gave rise to a significant amount of spirocycle **6j** as a 1:1 mixture of diastereomers (Table 1, 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 e.r.). Similar results were obtained with our 2,6-diethylphenyl-substituted triazolium salt **C**^[17] because of a reproducible increase in enantioselectivity (98:2 e.r.), 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 e.r., 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**.

Table 1: Optimization of the reaction conditions.

Entry	NHC	Base (equiv)	Conv. ^[a]	5/6 ^[a]	d.r. (5j) ^[a]	e.r. ^[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	<i>n</i> Bu ₄ NOAc (0.3)	94	82:18	6:1	98:2
9 ^[c]	C	<i>n</i> Bu ₄ NOAc (0.3)	96 (73) ^[d]	91:9	6:1	98:2

[a] Determined by ¹H NMR analysis (500 MHz) of the unpurified reaction mixture. [b] Determined by HPLC analysis. [c] Acetic acid (1.0 equiv) as an additive. [d] Yield of isolated product.

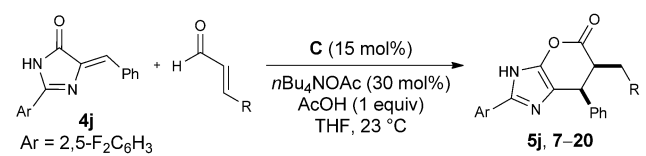


We hypothesized that an increase in the rate of the initial β -protonation would increase the product ratio to favor lactone **5j**. Inspired by recent reports, a Brønsted acid additive was employed to explore possible selectivity between the formal [4+2] and [3+2] processes.^[12f,18] These studies indicated that acetic acid indeed improved the ratio of **5/6** in favor of lactone **5j** while maintaining high levels of enantioselectivity (entry 4). Based on this result, the use of acetate bases with various 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 (82:18 for **5j/6j**, 6:1 d.r., 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**; lactone **5j** was isolated in 73% yield and an enantiomeric ratio of 98:2 (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, and the corresponding lactones were afforded in good yield and diastereoselectivity and excellent enantioselectivity (Table 2, entry 2–5). Aldehydes that bear electron-withdrawing groups were also explored (entry 6–9); the lactones **11–14** were formed in moderate to good yield and selectivities.^[19] Enals with various other aromatic substituents, including 2-naphthyl and 2-furyl groups, 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 and

Table 2: Variation of the aldehyde.^[a]



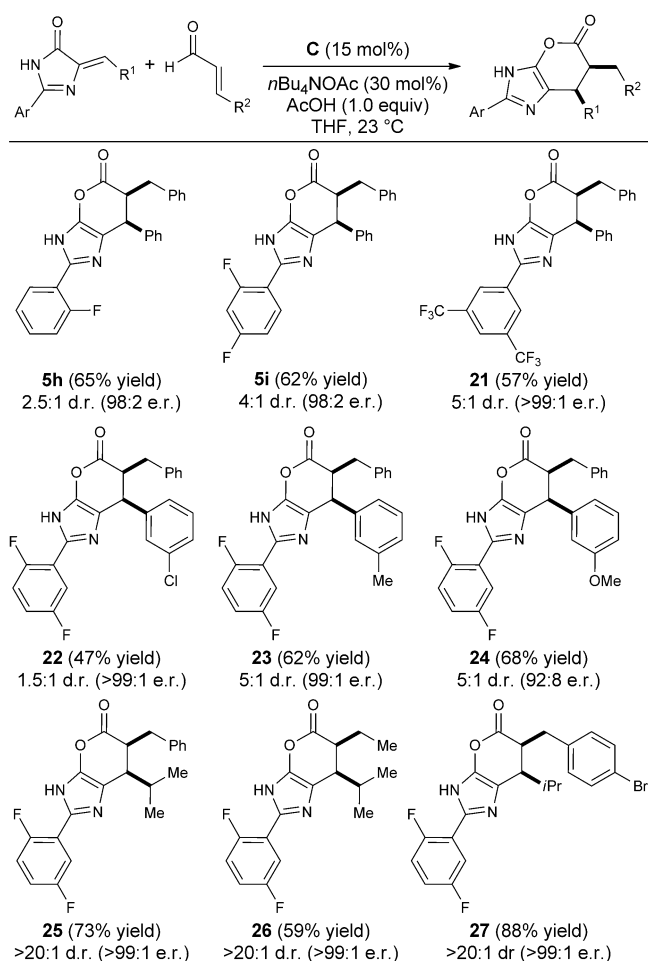
Entry	R	Yield ^[b] [%]	d.r. ^[c]	e.r. ^[d]
1	Ph (5j)	73	6:1	98:2
2	4-MeC ₆ H ₄ (7)	82	6:1	99:1
3	3-MeC ₆ H ₄ (8)	61	2:1	97:3
4 ^[c]	4-OMeC ₆ H ₄ (9)	76	7:1	99:1
5	2-OMeC ₆ H ₄ (10)	61	7:1	96:4
6	4-BrC ₆ H ₄ (11)	64	2:1	96:4
7	4-ClC ₆ H ₄ (12)	58	7:1	98:2
8	3-ClC ₆ H ₄ (13)	46	2:1	> 99:1
9 ^[c]	2-ClC 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 the Supporting Information for details. [b] Yields of isolated products after chromatography. [c] Determined by ¹H NMR (500 MHz) or ¹⁹F NMR (376 MHz) spectroscopy. [d] For the major diastereomer, determined by HPLC analysis.

afforded lactones **17** and **18** in 90% and 80% yield, respectively, and with outstanding diastereo- and enantioselectivity (entry 12 and 13). Despite the fact that the reactions of the cyclohexyl-substituted enal and highly reactive 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 and 15).

Structural modification of the aryl and alkylidene components of the imidazolidinone was also explored (Scheme 2). Several of the previously examined imidazolidinones were employed in the annulation reaction under the optimized reaction conditions. With chiral triazolium salt **C**, imidazolidinones **4h** and **4i** displayed sluggish reactivity, but were converted into the corresponding lactones in good yield and selectivity over prolonged reaction times (> 70% conversion over 48 h). Furthermore, the 3,5-trifluoromethyl-substituted 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. Furthermore, the incorporation of an alkyl group 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 an enantiomeric ratio of > 99:1.

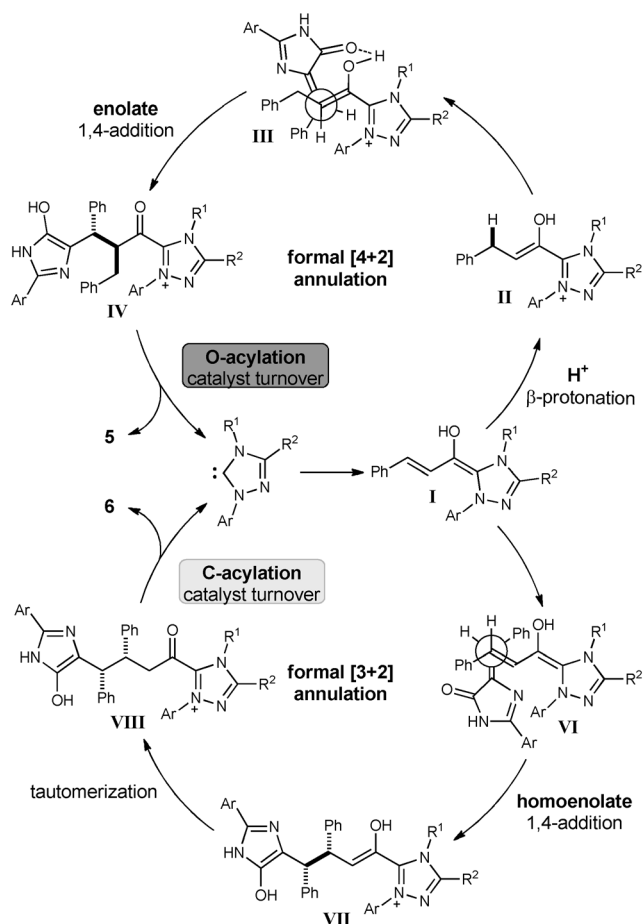
Our current understanding of this annulation is that the lactone products can be obtained through either a stepwise or a concerted [4+2] process,^[20] whereas the observed spirocycle **6** arises from a divergent formal [3+2] annulation pathway (Scheme 3). Based on previous computational reports by the groups of Verma,^[21] Domingo,^[22a] and Lupton^[22b] as well as our own observations, we favor a stepwise



Scheme 2. Variation of the imidazolidinone. See the Supporting Information for details. Yields of isolated products after chromatography are given. Diastereomeric ratios were determined by ¹H NMR (500 MHz) or ¹⁹F NMR (376 MHz) spectroscopy. Enantiomeric ratios were determined by HPLC analysis.

process for this specific reaction. The proposed catalytic cycles for both the lactone and the spirocyclic products begin 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 a different catalytic enol **VII**. We propose that in the presence of acid, 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** promotes approach of the imidazolidinone from the back face and subsequent coordination through a hydrogen-bonding interaction, which results in an organized transition state **III**. Following carbon-carbon bond formation, azolium **IV** undergoes O-acylation to release the NHC catalyst and to 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 because of a competing [3+2] annulation pathway. In this case, it is proposed that the imidazolidinone

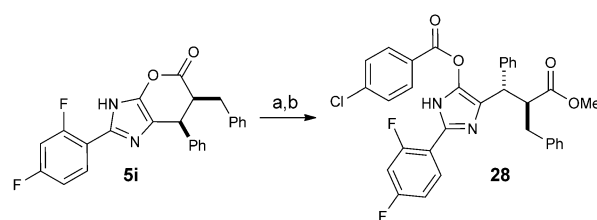


Scheme 3. Proposed reaction pathway.

can approach in either a synclinal (**VI**) or antiperiplanar fashion (not shown); 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 rather than O-acylation to afford **6**. This is one of the few examples of the preparation of a cyclopentanone through 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 into a second class of 5-oximidazoles 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 4). 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 aryl substituent at the 2-position of the imidazolidinone was necessary to activate the new, yet sluggish, conjugate acceptor and achieve high conversion. Furthermore, a Brønsted acid is an essential additive to achieve high chemoselectivity for the



Scheme 4. Representative ring opening. See the Supporting Information for details. Reagents and conditions: a) formic acid (5 % in MeOH), 65 °C, 70 %; b) Et₃N, 4-chlorobenzoyl chloride, THF, 23 °C, 94 %.

formal [4+2] annulation product. This enhancement of a desired reaction pathway with acid emphasizes the subtle, yet important role 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 method 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 that involve the carbene-catalyzed generation of homoenolate and enolate equivalents and studies on the factors that control these versatile and selective [4+2] or [3+2] annulation reactions are ongoing.

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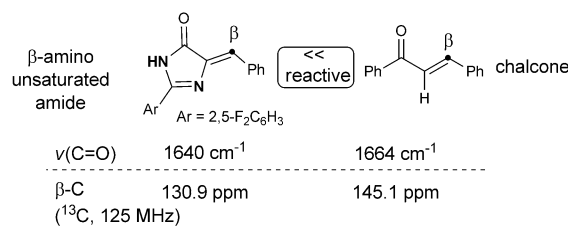
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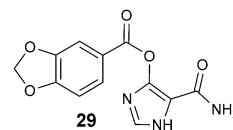
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