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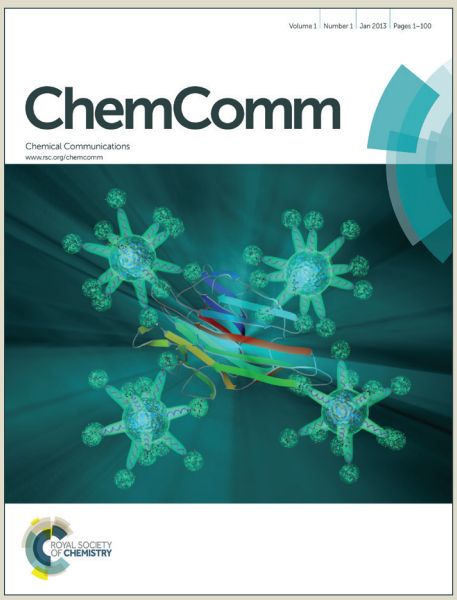

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ARTICLE TYPE

Stereoselective Synthesis of ε-Lactones or Spiro-Heterocycles through NHC-Catalyzed Annulation: Divergent Reactivity by Catalyst Control

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Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX

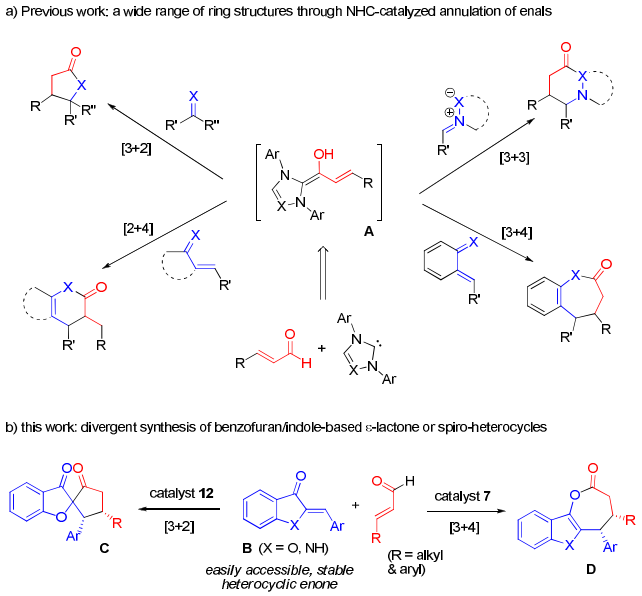
DOI: 10.1039/b000000x

NHC-catalyzed divergent annulations of enals with heterocyclic enones were developed to produce benzofuran/indole-containing ε-lactones or spiro-heterocycles in a highly diastereo- and enantioselective fashion. The chemo-selectivity controlled by the chiral catalyst backbone is particularly noteworthy.

Introduction

The efficient generation of complexity and diversity in molecular structures such as privileged carbo- and heterocycles is an important goal in organic synthesis and chemical biology.[1] Among various synthetic strategies, the utilization of a common reactive intermediate that is capable of undergoing cyclization with multiple reaction partners in an intermolecular fashion has proven highly valuable and versatile. Over the past decade, *N*-heterocyclic carbene (NHC) catalysis has been developed into a powerful tool to promote a wide range of annulation reactions (Scheme 1a).[2] The intermediate **A** that is generated from the reaction of NHC with functionalized aldehydes may serve as either enolate or homoenolate to engage different polarized π-systems. The [3+2] annulation of enals with aldehydes and imines has been extensively developed by many groups following the pioneering work from the Bode group and the Glorius group in 2004.[3] The [3+3] annulation of enals with azomethines or nitrones was demonstrated by the Scheidt group in 2007, followed by other examples of formal [3+3] annulations.[4] For the reaction with α,β-unsaturated carbonyls and imines, NHC-catalyzed [2+4] annulation was also shown to be versatile for the preparation of δ-lactones and δ-lactams.[5-7] Very recently, the difficult-to-access ε-lactones were also prepared through a formal [3+4] annulation of enals with *o*-quinone methides, in which aromatization was exploited as a driving force to induce 7-member-ring formation.[8] While the Ye group utilized electron-rich and stable 1,3-benzodioxole-derived *o*-quinone methides,[8a] the Scheidt group introduced a dual Lewis base activation strategy that enabled the use of unstable, transient ones.[8b] In contrast to all the previous systems that generate lactones or lactams, it is noteworthy that the generation of carbocycles involving attack of the acyl azolium intermediate by a carbon-based nucleophile remains a challenge in NHC catalysis.[9]

Our group has been interested in the use of heterocyclic enones such as **B** (Scheme 1b) in stereoselective annulation reactions as they are easily accessible and stable, and more importantly they may provide divergent reactivity stemming from the relatively electron-rich enone that in the same time possesses enol/enamine character.[10] In conjunction with our interest in NHC catalysis,[11] we decided to examine the reaction of **B** with enals catalyzed by NHC, with the hope that different valuable spirocyclic (such as **C**) or medium-sized lactone products (such as **D**) could be accessible from this reaction under different conditions. Both structures are challenging targets in stereoselective synthesis and the topic of current interest with NHC catalysis.[8,12,13] We report here an interesting catalyst-controlled divergent reaction leading to the formation of either benzofuran/indole-fused ε-lactones **D** or spiro heterocycles **C** in good to excellent stereoselectivity.

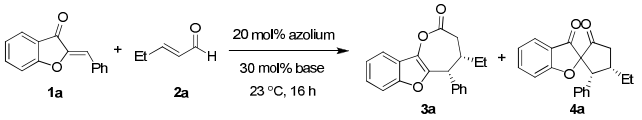


Scheme 1 Structural diversity from NHC-catalyzed annulations.

We initiated our studies by examining the reaction of heterocyclic enone **1a** and enal **2a** under NHC catalysis (Table 1). While the use of various azolium salts including **5** and **6** with DBU as the base led to low conversion (entries 1-2), to our delight, the desired annulation reaction proceeded smoothly in the presence of triazolium salt **7** to afford the formal [3+4] annulation product ε-lactone **3a** as the major product (>20:1 dr) together with spirocycle **4a** (formal [3+2] annulation product; entry 3) in a

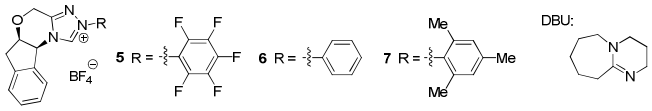
ratio of 3:1. The screening of a wide range of organic and inorganic bases proved DBU to be the optimal choice (entries 4-5; see supporting information for more details). Solvent screening then identified toluene as the optimal choice in terms of chemo- and stereoselectivity, albeit with low reactivity (entry 6; see SI for more details).

Table 1 Optimization of [4+3] annulation of **1a** and **2a**.[a]



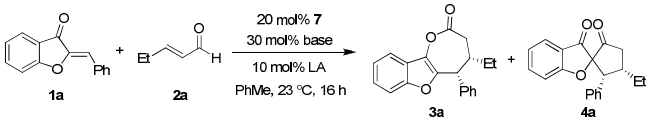
Entry	Azolium	Base	Solvent	**3a** : **4a**[b]	d.r. (**3a**)[b]	Yield[c]	ee$_{3a}$[d]
1	**5**	DBU	DCM	/	/	<5	/
2	**6**	DBU	DCM	/	/	<5	/
3	**7**	DBU	DCM	3:1	> 20:1	80	89
4	**7**	Et_3N	DCM	1.5:1	> 20:1	72	79
5	**7**	KOAc	DCM	2.5:1	> 20:1	26	83
6	**7**	DBU	PhMe	**18:1**	> 20:1	25	**91**

[a] Reaction conditions: **1a** (0.1 mmol), **2a** (0.2 mmol), 20 mol% of triazolium salt, 30 mol% of base in solvent (1.0 mL) at 23 °C for 16 h, unless noted otherwise. [b] Determined by ^{1}H NMR analysis (500 MHz) of the unpurified reaction mixture. [c] Isolated yield. [d] Determined by HPLC.



In an effort to enhance the efficiency of the catalytic system, we decided to examine the cooperative catalysis by NHC and Lewis acid that was pioneered by the Scheidt group and later adopted by many other groups.[14] As illustrated in Table 2, the addition of a few different Lewis acids all led to increased conversion, although at the cost of reduced chemo-selectivity. Ti(O^{i}Pr)$_4$ proved optimal to yield **3a** in 72% yield with 91% ee.

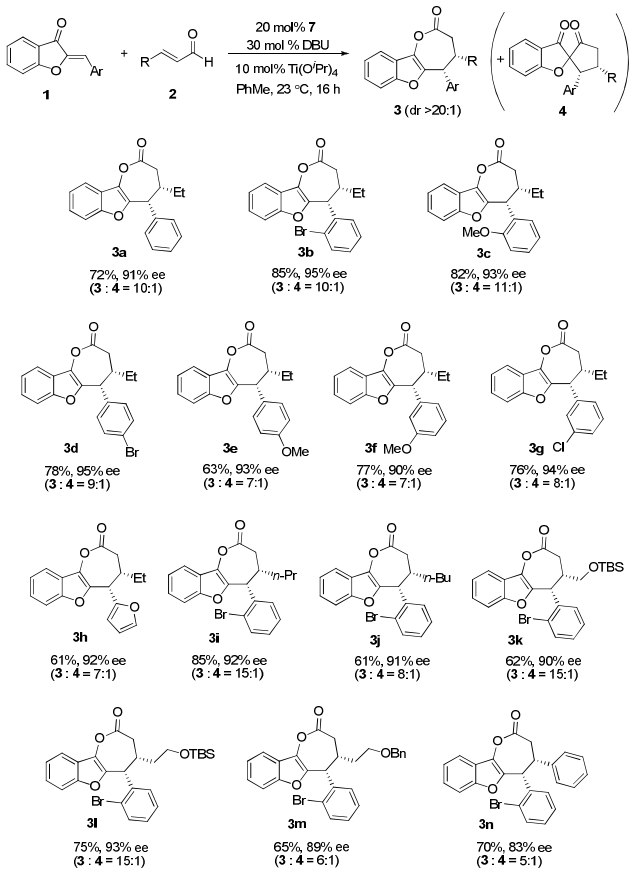
Table 2 Cooperative effect of Lewis acid and NHC.[a]



Entry	Lewis acid	**3a** : **4a**[b]	d.r. (**3a**)[b]	Yield[c]	ee$_{3a}$[d]
1	None	18 : 1	> 20:1	25	91
2	Mg(O^{t}Bu)$_2$	4: 1	> 20:1	52	91
3	Ti(O^{i}Pr)$_4$	10 : 1	> 20:1	**72**	**91**
4	Sc(OTf)$_3$	8 : 1	> 20:1	65	91

[a-d] See Table 1.

The substrate scope of this catalytic system turned out to be remarkably broad. The same set of reaction conditions could be used for the successful annulation of a wide range of **1** and **2** (Scheme 2). The easily accessible coumaranone derivatives **1** bearing ortho-, meta- or para-substituents of both electron-rich and poor characters as well as heterocycles could be well-tolerated to yield the corresponding product **3** in high chemo-, diastereo- and enantioselectivity (**3a-3h**). In addition, various enals **2** bearing simple alkyl or ether-containing substituents participated in the reaction similarly well (**3i-3m**). Cinnamaldehyde was also tested and the desired product **3n** could be obtained in good yield and slightly diminished chemo- and stereoselectivity. It is noteworthy that ε-lactone **3** was obtained as a single *syn*-diastereomer in all cases except for **3n** (5:1 dr), which is presumably due to steric repulsion of the two aryl rings.

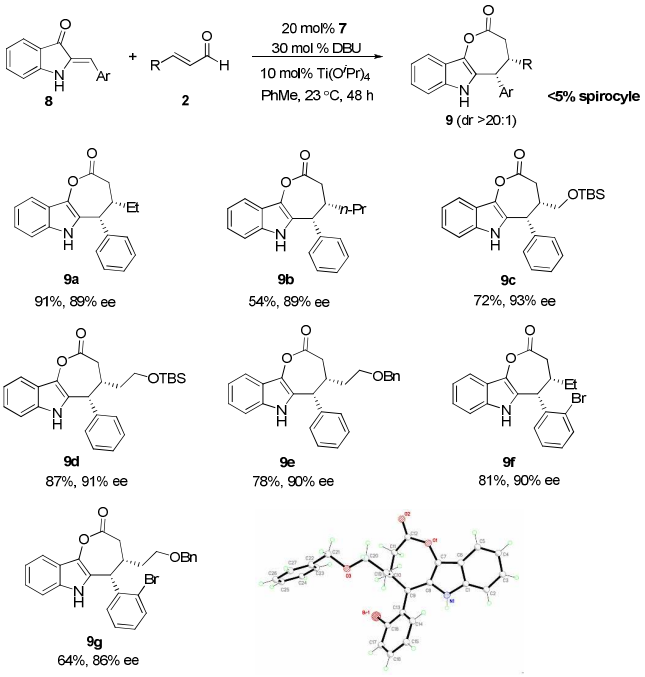


Unless otherwise noted, the reactions of **1** (0.2 mmol) and **2** (0.4 mmol) in the presence of 20 mol% of **7**, 30 mol% of DBU and 10 mol% Ti(O^{i}Pr)$_4$ were carried out in toluene (2.0 mL) at 23 °C for 16 h. **3** were isolated as a single diastereomer (>20:1 dr) in all cases except **3n** (dr = 5:1).

Scheme 2 Scope of benzofuran-fused ε-lactones.

To our delight, indole-fused ε-lactone could also be obtained by our catalytic system, thus dramatically expanding the scope of this catalytic system (Scheme 3). Interestingly, only ε-lactone products were produced for this series, and in all cases a single diastereomer was formed. Again, a wide range of substituents on the aryl ring in **8** and the substituents in enal **2** could be well-tolerated (**9a-9g**).

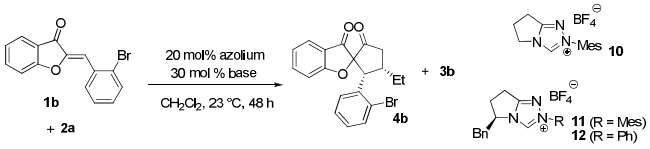
The relative and absolute configuration of **9g** (98% ee after one recrystalization) was unambiguously assigned by single-crystal X-ray diffraction analysis. Considering similar reaction mechanism is operative for the formation of **3** and **9** that share the same NMR characters, all the other ε-lactones were assigned to have the same absolute configuration as **9g**.



Scheme 3 Scope of indole-fused ε-lactones.

An interesting discovery was made during the preparation of the racemic sample of **3** and **4** using the achiral azolium salt **10**, which yielded spirocycle **4b** as the major product instead of **3b** (entry 1, Table 3). This led us to speculate that the backbone of the azolium might have a dramatic effect on the chemo-selectivity of the annulation. When we examined the closely related chiral catalyst **11** and **12**, we were happy to observe the formation of **4b** as the major product with a promising level of diastereo- and enantioselectivity (entries 2-3). Reaction condition optimization was then carried out, which identified DABCO as the best choice of base (entry 5 vs. entries 3 & 4). The optimized conditions could be extended to yield a few representative spiro heterocycles **4b**, **4c** and **4k** in moderate to good yield with good enantioselectivity (Scheme 4).

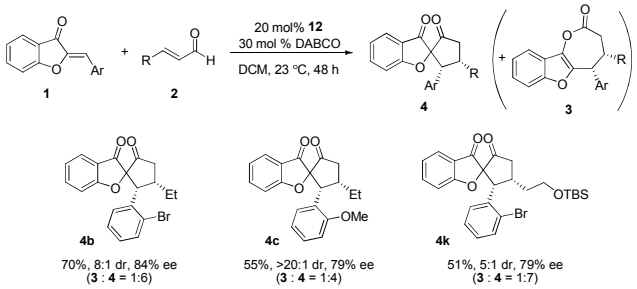
Table 3 Optimization of [2+3] annulation of **1a** and **2a**.[a]



Entry	azolium	base	**3** : **4**[b]	d.r. (**4**)[b]	Yield$_4$[c]	ee$_4$[d]
1	**10**	DBU	1:3	13:1	56	/
2	**11**	DBU	1:2	11:1	49	82
3	**12**	DBU	1:4	15:1	51	78
4	**12**	DIPEA	1:5	7:1	60	81
5	**12**	DABCO	1:6	8:1	70	84

[a-d] See Table 1.

Based on our chemo-divergent and stereochemical outcome as well as the related previous studies from the Scheidt and Ye groups, we propose a stepwise mechanism shown in Figure 1 (with catalyst **7**). The homoenolate intermediate **I** generated from the enal and carbene catalyst attacks the heterocyclic enone to produce enolate **III**, in which the configuration of the newly formed stereogenic centers are established under the control of the chiral catalyst (as illustrated in transition state model **II**). The level of enantioselectivity was essentially the same for the ε-lactone and spirocycle, implying that the two series go through the same intermediate. For the enals possessing linear aliphatic substituent R, >20:1 dr was obtained for the product; when R equals a more bulky aromatic group (as in **3n**), the steric repulsion among R, Ar and the heterocyclic backbone may force alternative conformation leading to lower diastereoselectivity. In the final step, the chemo-selectivity is determined by the O- or C-alkylation of enolate **B**. The observation of divergent reactivity from two catalysts is an intriguing showcase of the subtle catalyst control in NHC-catalysis.[15] To better understand the origin of this divergent selectivity, current efforts are focused on mechanistic studies (especially use of the Eyring approach) as well as computation, which will be reported in due course.



Scheme 4 Scope of spiro-heterocycles.

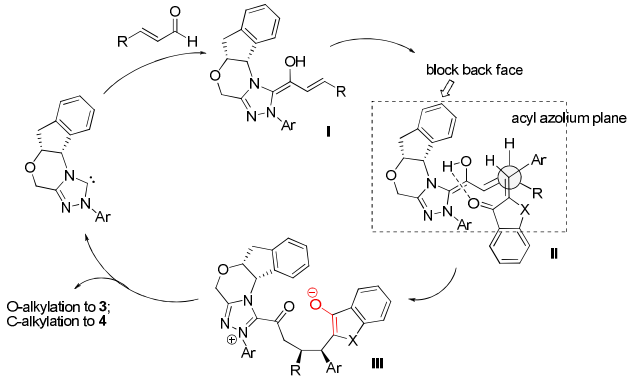


Fig. 1 Proposed catalytic cycle.

In conclusion, NHC-catalyzed divergent annulations of enals with heterocyclic enones were developed to produce benzofuran/indole-containing ε-lactones or spiro-heterocycles in a highly diastereo- and enantioselective fashion. The understanding of the catalyst-controlled chemoselectivity in this process and the development of other NHC-catalyzed annulations are currently under investigation in our laboratories.

We are grateful for the generous financial support from Singapore National Research Foundation (NRF Fellowship) and National University of Singapore.

Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental details, characterization data, and NMR spectral charts. See DOI: 10.1039/b000000x/

‡ These authors contributed equally.

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12 In their report of δ-lactone formation (ref 5j), the Scheidt group described the formation of imidazolidinone-based spirocycle as the side product with moderate enantioselectivity. The reaction pathways leading to both products were also elegantly proposed.

13 In the process of the preparation of this manuscript, the Glorius group reported an elegant NHC-catalyzed stereoselective spiro-heterocycle formation using closely related *N*-protected **8**. The complimentary chemoselectivity (spirocycle formation instead of ε-lactone in our case) further showcased the subtlety of substrate control in NHC catalysis. See: C. Guo, M. Schedler, C. G. Daniliuc, F. Glorius, *Angew. Chem. Int. Ed*., 2014, **53**, 10232–10236.

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15 For a recent excellent review, see: J. Mahatthananchai, A. M. Dumas, and J. W. Bode, *Angew. Chem. Int. Ed.*, 2012, **51**, 10954–10990.