Asymmetric Catalysis

DOI: 10.1002/anie.201201643

An N-Heterocyclic Carbene/Lewis Acid Strategy for the Stereoselective Synthesis of Spirooxindole Lactones**

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The development of efficient strategies for the stereoselective construction of privileged heterocyclic systems is an ongoing objective in chemical synthesis. Over the last decade, the development of powerful NHC-catalyzed (NHC = N-heterocyclic carbene) homoenolate equivalents has allowed access to a wide range of hetero- and carbocyclic structural motifs.[1] Despite significant advancements in this NHC–homoenolate field, with additions to activated C=X systems by the groups of Glorius, Bode, Nair, and others, as well as ourselves,[2] the combination of these interesting and unconventional nucleophilic species with less active electrophiles, such as ketones, remains challenging.[3] Furthermore, rendering these carbonyl addition processes enantioselective remains an important goal, as these annulation reactions provide an efficient method for accessing bioactive γ-butyrolactones. We have been investigating cooperative carbene catalysis strategies to explore new opportunities with NHCs as Lewis base catalysts.[4] In select cases, the use of a Lewis acid in conjunction with an NHC has: 1) enhanced yield and enantioselectivity, 2) reversed diastereoselectivity, and 3) enabled new reactions between enals and carbonyl reaction partners.[5,6] Although strong Lewis acids presumably inhibit carbene catalysis through NHC–Lewis acid complexation, milder Lewis acids, such as $Mg(OtBu)_2$ and $Ti(OiPr)_4$, can be essential additives for new NHC–homoenolate reactions.[7] However, the use of alkali metal salts in NHC reactions is surprisingly underexplored given that these salts play critical roles in a variety of carbon–carbon bond forming reactions.[8] The impact of alkali metal salt effects on carbene-catalyzed reactions has been observed by our group,[9a] as well as the groups of Lupton[9b] and You,[9c] and we sought to explore the potential of these metal salts in the context of NHC–homoenolate additions to ketones. Herein, we report the highly enantioselective NHC-catalyzed addition of α,β-unsaturated aldehydes to isatins activated by lithium cations (Figure 1). In this formal [3+2] annulation, the alkali salt significantly enhances the level of enantioselectivity in the resultant spirooxindole products.

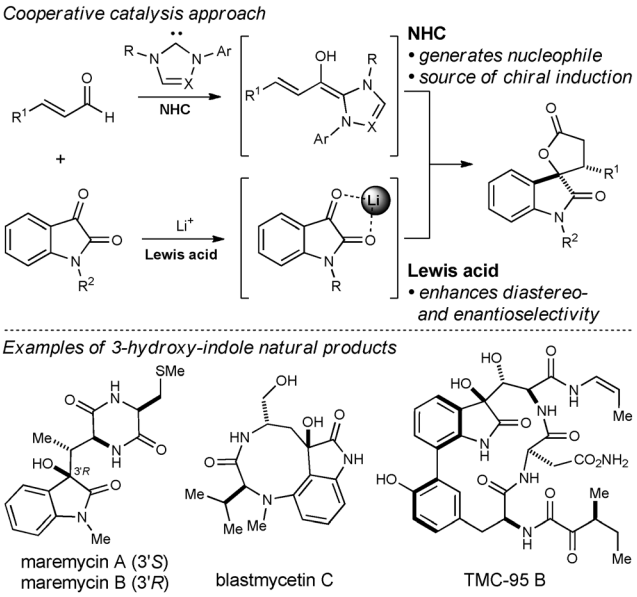

Figure 1. Cooperative catalysis approach to spirooxindoles.

In 2006, Nair et al. reported an interesting NHC-catalyzed annulation of 1,2-diketones with enals to generate racemic spirocyclic lactone products as a 1:1 mixture of diastereomers.[3b,10] Recently, You et al. reported a related enantioselective annulation that relies on a hydrogen-bonding NHC catalyst.[11] Our group has been interested in the preparation of spirooxindoles[12] because of the prevalence of this structural motif in a number of architecturally complex and biologically relevant natural products (Figure 1).[13] Given our strong interest in the synthesis of these compounds and carbene catalysis, we sought to develop an NHC-catalyzed method for accessing these privileged structures in a diastereo- and enantioselective manner.

We began our studies by combining *N*-methyl isatin (**1**) with cinnamaldehyde (**2**) in the presence of triazolium precatalyst **A** (15 mol%) and DBU (30 mol%). Under these conditions, lactone **3** was obtained as a 1:1.1 mixture of diastereomers in 34% *ee* (Table 1, entry 1). With this baseline established for comparison, we turned our attention toward the use of Lewis acid additives to improve both the

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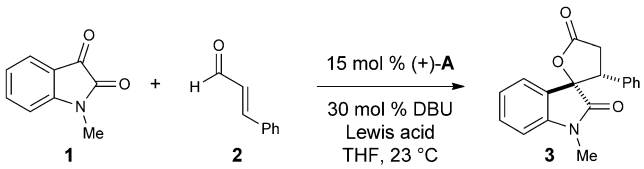
[**] Financial support has been generously provided by the NIH (NIGMS RO1-GM073072). T.B.H.S. was supported by a 2011 Northwestern Summer Undergraduate Research Grant. D.T.C thanks the ACS Division of Organic Chemistry for a 2011-12 Graduate Fellowship (sponsored by Organic Synthesis/Organic Reactions). We thank Michael Katz (NU) and John M. Roberts (NU) for assistance with X-ray crystallography.

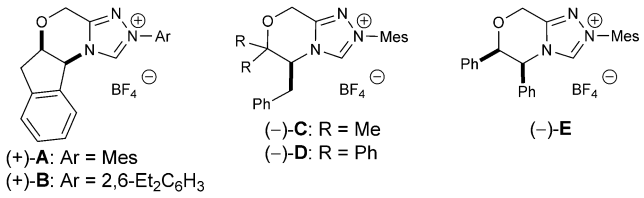
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201201643.

Table 1: Optimization of the reaction conditions.



Entry	Variation of the standard conditions	Conv. [%][a]	d.r.[a]	*ee* [%][b]
1	no Lewis acid	99	1.1:1	34
2	$Mg(OtBu)_2$ (50 mol%)	99	1.5:1	35
3	$Ti(OiPr)_4$ (50 mol%)	99	1:1	52
4	LiCl (50 mol%)	99	1.8:1	70
5	LiCl (1 equiv)	99	2:1	77
6	LiCl (2 equiv)	99	2.5:1	90
7	LiCl (2 equiv), [12]crown-4 (4 equiv)	99	1.2:1	35
8	NaCl (2 equiv)	99	1.2:1	53
9	KCl (2 equiv)	99	1:1	47
10	$LiBF_4$ (2 equiv)	99	1:1	62
11	LiOTf (2 equiv)	99	3.7:1	39
12	(+)-**B**, LiCl (2 equiv)	99	2.8:1	92
13	(−)-**C**, LiCl (2 equiv)	66	1.1:1	38
14	(−)-**D**, LiCl (2 equiv)	99	1.7:1	32
15	(−)-**E**, LiCl (2 equiv)	99	1.4:1	50
16	5 mol% (+)-**B**, 10 mol% DBU, LiCl (2 equiv)	99	2.4:1	96

[a] Determined by ^{1}H NMR spectroscopy (500 MHz) of the unpurified reaction. [b] Enantiomeric excess determined by HPLC analysis. DBU = diazabicycloundecene, Mes = 2,4,6-$Me_3C_6H_2$.



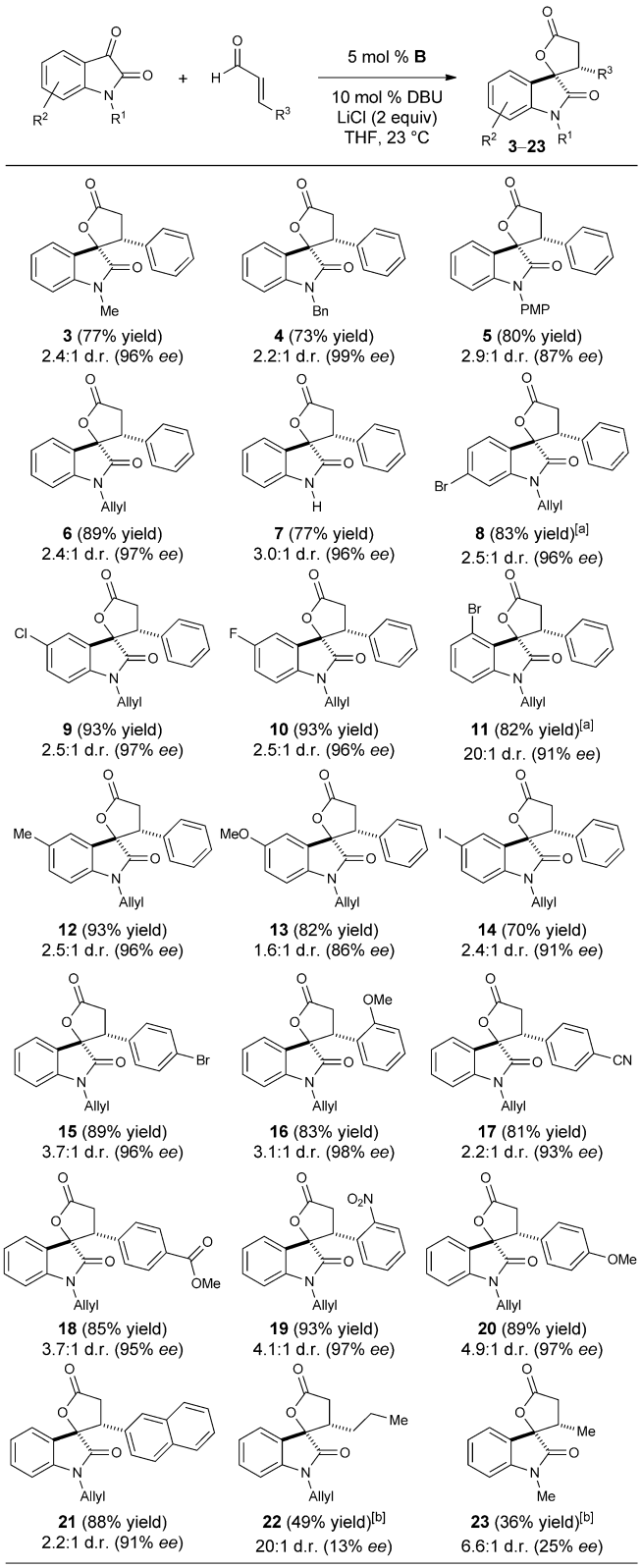
diastereo- and enantioselectivity. Unfortunately, in the presence of 50 mol% of either $Mg(OtBu)_2$ or $Ti(OiPr)_4$, lactone **3** was obtained with only a modest increase in diastereoselectivity or enantioselectivity, respectively (entries 2 and 3). No significant improvement in stereoselectivity was observed upon extensive variation of the reaction components, including stoichiometry, temperature, solvent, and the nature of the Lewis acid. We next turned our attention toward the use of lithium chloride as a potential mild Lewis acid additive.[9] Gratifyingly, the addition of 50 mol% lithium chloride provided lactone **3** as an approximate 2:1 mixture of diastereomers; more importantly, this result was associated with an increase in enantioselectivity to 70% *ee* (entry 4). A significant difference in both diastereo- and enantioselectivity was observed by increasing the amount of lithium chloride (entries 4–6). Two equivalents of LiCl proved optimal, and lactone **3** was obtained in 2.5:1 d.r. and 90% *ee* (entry 6).

With these initial results, we next investigated this ion effect on enantioselectivity.[14] The sequestration of the lithium cation from the reaction mixture by addition of an excess of [12]crown-4 delivered lactone **3** with diminished diastereo- and enantioselectivity, which is similar to what was observed when the reaction was run without a Lewis acid (Table 1, entry 7). Other alkali metal chloride salts, such as NaCl and KCl, afforded lactone **3** with lower enantioselectivity than with LiCl (entries 8 and 9), providing further evidence that this effect was particular to lithium. However, lithium tetrafluoroborate and lithium triflate did not produce lactone **3** with levels of stereoinduction as high as those achieved with lithium chloride (entries 10 and 11).[15] The data currently support the need for both ions to obtain high levels of enantioselectivity and that there is not an observable increase in overall rate vs. reaction without Li^+ (for example, Table 1, entry 1 vs. entry 6). Further investigation of this phenomenon is underway. Having established that lithium chloride was the optimal Lewis acid additive, various chiral NHCs were examined to enhance the diastereo- and enantioselectivity of the reaction. Employing chiral azolium catalysts **B**–**E** resulted in a wide range of diastereo- and enantioselectivities, with the 2,6-diethylphenyl substituted triazolium precatalyst **B** being the catalyst of choice (entries 12–15). We discovered that with only 5 mol% catalyst **B** similar levels of conversion and selectivity were obtained (entry 16).

With the optimized reaction conditions, we surveyed the synthesis of lactones from isatins with varying nitrogen protecting groups and substitution around the aromatic ring (Scheme 1, **3**–**14**). Both electron-withdrawing and electron-donating substituents on the aromatic ring were well accommodated, providing the lactone products in 1.6–3.0:1 d.r. and 86–99% *ee*. Notably, the isatin bearing an unsubstituted N−H group provides the desired product **7** in high *ee* and yield. A slight decrease in enantioselectivity was observed in the case of products derived from either an isatin bearing a *p*-methoxyphenyl protecting group (**5**) or a 5-methoxy isatin (**13**), which gave 87% and 86% *ee*, respectively. Interestingly, the 6-bromo isatin delivered lactone **11** with exquisite diastereoselectivity (20:1) and high enantioselectivity (90%).

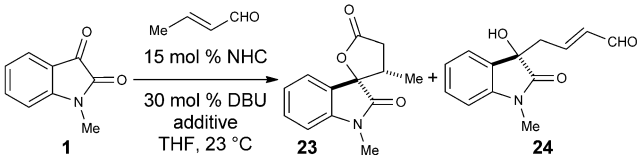
Structural modification of the cinnamaldehyde component was also explored (Scheme 1, **15**–**21**). Both electron-withdrawing and electron-donating groups were tolerated, furnishing the desired lactones in good yields (81–93%) and high enantioselectivities (91–98%). With enals bearing a β-alkyl substituent, both the yields and the level of enantioinduction decreased significantly, as is typical with many NHC–homoenolate reactions.[2] With 2-hexenal and crotonaldehyde, lactones **22** and **23** were obtained with good diastereoselectivity, but in modest yield (49% and 39%, respectively), and low enantioselectivity (13% and 25% *ee*, respectively). As a number of 3-hydroxy indole natural products contain alkyl substituents, for example the maremycins (Figure 1), it was necessary to re-examine conditions for the β-alkyl enals.

With the previously optimized conditions, lactone **23** was obtained in 36% yield and 25% *ee* (Table 2, entry 1). The low yield could be partially attributed to the unexpected formation of enal **24** through a γ-alkylation pathway. An extensive screen of solvents and Lewis base additives yielded no improvement in efficiency, enantioselectivity, or suppression of enal **24** (results not shown). Interestingly, when the annulation reaction was carried out with catalyst **A** in the absence of lithium chloride, lactone **23** was obtained in 76% yield, with no observable amounts of **24**, albeit with diminished levels of enantioselectivity. The increase in yield



Scheme 1. Isatin and enal reaction scope. All reactions performed on a 0.3 mmol scale. Yield of isolated product after chromatography. Diastereomeric ratios determined by ^{1}H NMR spectroscopy (500 MHz). Enantiomeric excesses determined by HPLC analysis. [a] Structure confirmed by X-ray crystallography, see the Supporting Information. [b] Catalyst **B** (20 mol%) and DBU (40 mol%). Bn = benzyl, DBU = diazabicycloundecene, PMP = 4-MeOC$_6$H$_4$.

Table 2: Optimization of conditions with crotonaldeyde.



Entry	NHC	Additive	Conv. [%][a] (yield [%])[b]	**23**/**24**[a]	d.r.[a]	*ee* [%][c]
1	(+)-**A**	LiCl (2 equiv)	99 (36)	4:1	6.6:1	25
2	(+)-**A**	none	99 (76)	>20:1	8:1	<10
3	(+)-**B**	none	99	>20:1	6.2:1	<10
4	(−)-**C**	none	99	>20:1	7.4:1	19
5	(−)-**D**	none	99	>20:1	6.8:1	30
6[d]	(+)-**E**	none	99 (76)	>20:1	5:1	−78[e]

[a] Determined by ^{1}H NMR spectroscopy (500 MHz). [b] Yield of isolated product after chromatography. [c] Enantiomeric excess determined by HPLC analysis. [d] Catalyst (+)-**E** (5 mol%) and DBU (10 mol%). [e] 99% enantiomeric excess after recrystallization in hexanes/EtOAc (44% overall yield of 99% *ee* lactone **23**). DBU = diazabicycloundecene.

prompted us to re-examine azolium catalysts **B**–**E** with crotonaldehyde in the absence of lithium chloride. Although most of the catalysts provided unsatisfactory results, with catalyst **E** lactone **23** was obtained in 76% yield, 5:1 d.r., and 78% *ee* (entry 6). The target lactone **23** could then be accessed in 99% *ee* after recrystallization. The modified reaction conditions produced a similar outcome for the reaction with 2-hexenal, as now lactone **22** could be isolated in 91% yield, 7:1 d.r., and 79% *ee*.

For β-aryl-substituted enals, we propose that the high levels of enantioselectivity result from lithium cations generating an organized transition state through coordination of the enol oxygen atom of the NHC-bound homoenolate and the 1,2-dicarbonyl of the isatin (Figure 2). The indene subunit

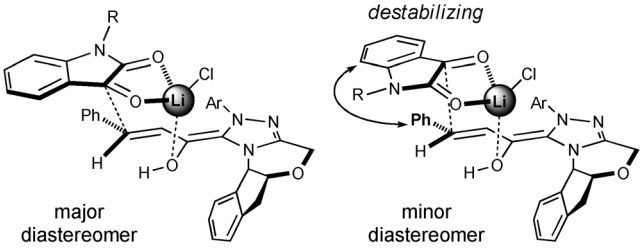
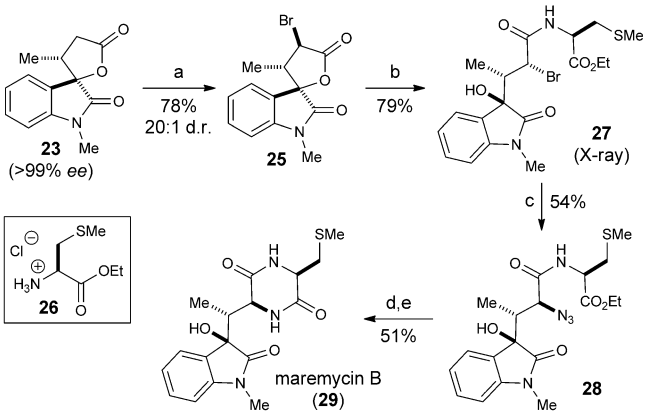


Figure 2. Model for stereoinduction with β-aryl enals.

on the NHC controls the facial bias of the homoenolate equivalent and the major diastereomer results from avoiding a destabilizing interaction between the β-aryl group and isatin ring. The trends in enantioselectivity observed upon variation of the alkali metal and counterion are presumably because of the oxophilicity and coordination states of lithium compared to sodium or potassium and fine-tuning of the Lewis acidity upon variation of the lithium counterion. For β-alkyl-substituted enals, initial modeling suggests that the NHC–homoenolate may adopt a conformation leading to opposite

facial accessibility, as NHC **E** has the bis-phenyl directing groups in a stacked orientation (vs. flat for NHC **A**).

With the ability to engage a wide range of α,β-unsaturated aldehydes in this enantioselective annulation reaction, we sought to apply this method to the synthesis of maremycin B (**29**), given its interesting 3-hydroxy indole core architecture and anticancer activity.[16] We envisioned accessing maremycin B through functionalization of previously prepared β-alkyl-substituted lactone **23**. To begin, lactone **23** (99% *ee* after recrystallization) was treated with LiHMDS followed by the addition of bromine to generate α-bromo lactone **25** in 78% yield with 20:1 diastereoselectivity (Scheme 2).



Scheme 2. Total synthesis of maremycin B (**29**). Reagents and conditions: a) LiHMDS, −78 °C to 0 °C, THF; then Br_2, −78 °C; 78% yield (20:1 d.r.). b) $AlMe_3$, **26**, THF; 79% yield. c) $TMSN_3$, TBAT, THF; 54% yield. d) PMe_3, THF; then H_2O, 60 °C. e) Imidazole, MeOH, 60 °C; 51% yield (2 steps). See the Supporting Information for further details. LiHMDS = lithium hexamethyldisilazide, TBAT = tetrabutylammonium difluorotriphenylsilicate, TMS = trimethylsilyl.

Attempts to displace the bromide with a variety of nitrogen nucleophiles were unsuccessful at this stage. Instead, the introduction of the cysteine side chain was pursued prior to displacement of the bromide. Toward this end, α-bromo lactone **25** was converted to α-bromo amide **27** in the presence of (*S*)-methyl cysteine ethyl ester hydrochloride (**26**) and trimethylaluminum in 79% yield, without compromising the sensitive α-bromo carbonyl functionality.[17] The subsequent displacement of the halogen was achieved by modifying the Deshong–Smith method with tetrabutylammonium difluorotriphenylsilicate (TBAT) and trimethylsilylazide.[18] A Staudinger reduction of **28** with trimethylphosphine to the amine,[19] followed by treatment with imidazole in methanol furnished maremycin B (**29**) in 51% yield over the two steps.[20] The ^1H and ^{13}C NMR spectral data for maremycin B matched the literature, and the absolute configuration was confirmed by optical rotation ($[\alpha]_D^{20} = +9.0$ ($c = 0.11$ in MeOH); Lit. $[\alpha]_D^{20} = +2.9$ ($c = 0.21$ in MeOH)).[15] This cooperative carbene catalysis approach to the maremycins highlights the efficiency of this formal [3+2] reaction as compared to recent synthetic studies on these compounds: this is the first enantioselective total synthesis of maremycin B in five steps from lactone **23** (only six steps from commercial materials) without the use of protecting groups and in 17% overall yield.

In conclusion, an enantioselective NHC/Lewis acid catalyzed homoenolate annulation of enals with isatins has been developed. This approach is one of the few general methods of enantioselective addition of NHC-generated homoenolate equivalents to ketones and opens up the possibility to include new, less reactive electrophilic partners with NHC–homoenolates using cooperative catalysis. The addition of lithium chloride as a Lewis acid with β-aryl substituted enals generates lactone products with high levels of enantioselectivity (>90%). Interestingly, with enals bearing β-alkyl substituents, lithium chloride was detrimental, owing to the promotion of a competing pathway. In the absence of lithium chloride, a different triazolium precatalyst was employed to generate the alkyl-substituted lactones in good yield and enantioselectivity. The utility of this highly selective formal [3+2] annulation method was highlighted by a concise total synthesis of maremycin B. Our investigations into defining a clear model for stereoinduction in this reaction and integrating NHC catalysis with other modes of activation (including Lewis acid and transition metal catalysis) are continuing and will be reported in due course.

Received: February 29, 2012
Published online: April 4, 2012

Keywords: asymmetric synthesis · homoenolates · homogeneous catalysis · Lewis acids · total synthesis

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