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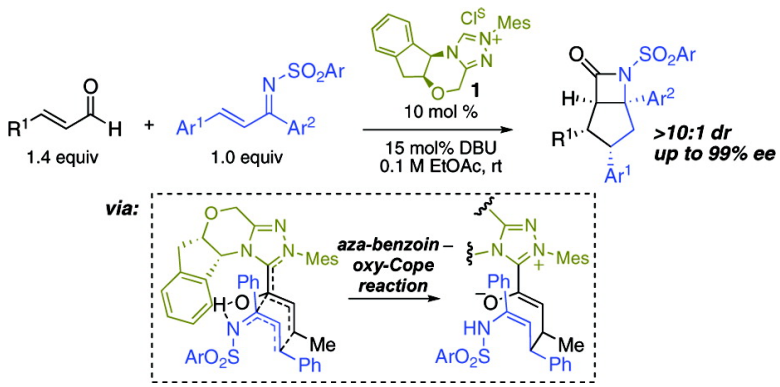

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Enantioselective, NHC-Catalyzed Bicyclo-*β*-Lactam Formation via Direct Annulations of Enals and Unsaturated *N*-Sulfonyl Ketimines

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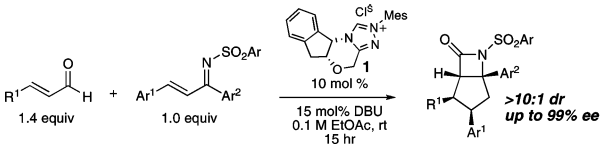
The synthesis and properties of *β*-lactams maintain a rarefied place in the history of organic reactions, structure, and therapeutic applications.[1] It is therefore no surprise that chemical methods leading to the direct and facile synthesis of *β*-lactams, particularly, catalytic enantioselective methods, remain among the most prized targets for reaction development.[2] To this end, important advances have emerged from Doyle,[3a] Lectka,[3b] Fu,[3c,d] and others.[2]

We have recently pioneered N-heterocyclic carbene (NHC)-promoted annulations of enals via the catalytic generation of reactive species.[4,5] As part of these studies, we demonstrated that NHC-catalyzed reactions of enals and certain α,*β*-unsaturated ketones afford enantioenriched cyclopentenes via a cascade process featuring a crossed-benzoin/oxy-Cope rearrangement.[6,7] The mechanistic postulate intrinsic to these annulations anticipates a method that could lead to the formation of a stable *β*-lactone or *β*-lactam annulation product. We now document a successful, highly enantio- and diastereoselective synthesis of enantiomerically pure bicyclic *β*-lactams via a remarkable annulation process of 3-alkyl or 3-aryl enals and chalcone-derived imines[8] (eq 1).

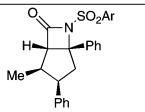
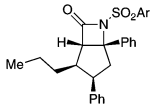
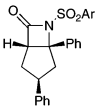
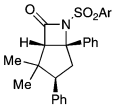
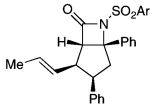
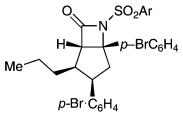
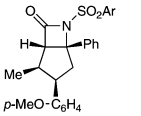
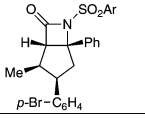


(1)

We initially dismissed enantioselective *β*-lactam formation as unviable due to the high probability of competing enal dimerization or aza-Diels−Alder reaction, as we have previously reported highly enantioselective triazolium-catalyzed annulations between unsaturated *N*-sulfonyl *aldimines* and *electron-deficient* enals.[9] Our studies, however, noted that the reaction outcomes of similar or even identical substrate pairs can be modulated by judicious choices of precatalyst (triazolium vs imidazolium),[9] amine base (DBU vs NEt_3),[10] and substrates (electron-deficient versus 3-alkyl or 3-aryl enals). Our initial forays identified a new reaction of *trans*-2-butenal and the *N*-*para*-methoxybenzene sulfonyl imine of chalcone,[11] DBU, and chiral *N*-mesityl-substituted triazolium precatalyst **1** (Table 1, entry 1).[12] The relative and absolute stereochemistry was established by X-ray analyses as a bicyclo[3.2.0]lactam wherein all of the substituent groups are situated on the same face. Optimization of the conditions selected, for 3-alkyl enals, EtOAc as the preferred solvent. Notably, prior studies had shown that 3-alkyl enals were either poor substrates or inert to NHC-catalyzed C−C bond-forming reactions under mild conditions. Even acrolein was a viable substrate, albeit in diminished yield due to a competing Diels−Alder reaction (entry 3).

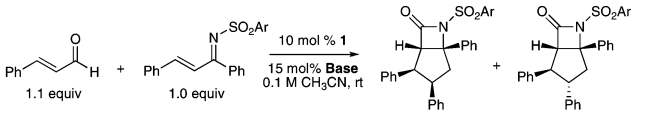
Cinnamaldehyde derivatives were also viable substrates under the conditions shown in Table 1 but led to the lactam products as mixtures of diastereomers (Scheme 1). We discovered a pronounced effect of the catalytic base on the diastereoselectivity. When the reactions were performed in CH_3CN using DMAP as the catalytic base,[13] a slower but cleaner reaction resulted, leading to formation of the desired product in 9:1 dr. A slight modification of these conditions improved the dr and was directly applicable to both

Table 1. Enantioselective, NHC-Catalyzed *β*-Lactam Formation with 3-Alkyl Enals (see eq 1 for reaction scheme)[a]

entry	R^1 =	Ar^1 =	Ar^2 =	product	% yield[b]	% ee[c]
1	Me	Ph	Ph		94	>99
2	*n*-Pr	Ph	Ph		81	99
3	H	Ph	Ph		45	99
4	[d]	Ph	Ph		50	87
5		Ph	Ph		76[e]	99 (5:1)[f]
6	*n*-Pr	*p*-Br–C_6H_4	*p*-Br–C_6H_4		77	99
7	*n*-Pr	*p*-MeO–C_6H_4	Ph		63	99
8	Me	*p*-Br–C_6H_4	Ph		75	99

[a] Ar = 4-$MeOC_6H_4$. All reactions were performed at 0.1 M for 15 h. Except in entry 5, only a single diastereomer was detected in unpurified reaction mixtures. [b] Isolated yield after chromatography. [c] Determined by HPLC or SFC. [d] With 3-methyl-2-butenal. [e] Under the conditions employed in Table 2: 78% yield, 99% ee, 5:1 dr. [f] Diastereomeric ratio.

Scheme 1. Effect of Catalytic Base on Lactam Stereochemistry



Base:	DBU	NEt_3	$^iPr_2NEt$	TMEDA	(−)-sparteine	DMAP
dr:	2.6:1	3.3:1	4.0:1	3.5:1	3.9:1	9:1

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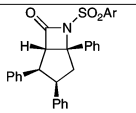
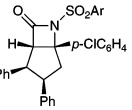
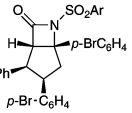
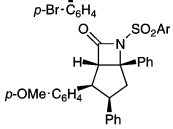
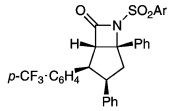
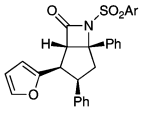
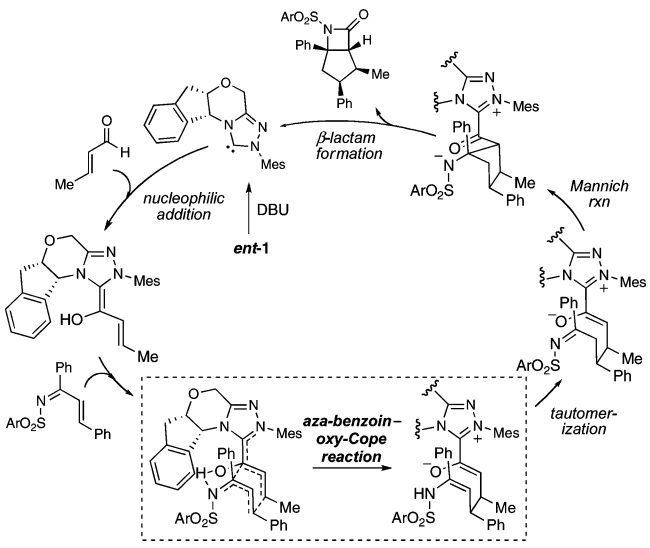
Table 2. Enantioselective, NHC-Catalyzed β-Lactam Formation with 3-Aryl Enals (see eq 1 and Scheme 1 for conditions)[a]

entry	R^1 =	Ar^1 =	Ar^2 =	product	% yield[b]	% ee[c] (dr)[d]
1	Ph	Ph	Ph		80	99 (10:1)
2	Ph	Ph	*p*-Cl-C_6H_4		72	>99 (20:1)
3	Ph	*p*-Br-C_6H_4	*p*-Br-C_6H_4		67	99 (10:1)
4	*p*-MeO-C_6H_4	Ph	Ph		62	>99 (10:1)
5	*p*-CF_3-C_6H_4	Ph	Ph		72	88 (>20:1)
6	1-furyl	Ph	Ph		71	98 (>20:1)

[a] Ar = 4-$MeOC_6H_4$. All reactions were performed at 0.1 M with 1.4 equiv of enal, 1.0 equiv of imine, 10 mol % of **1**, and 30 mol % of DMAP for 24−36 h. [b] Isolated yield after chromatography. [c] Determined by HPLC or SFC analysis. [d] The ratio of diastereomers was determined by ^{1}H NMR analyses of unpurified reaction mixtures.

Scheme 2. Postulated Catalytic Cycle (*ent*-**1** is shown as the NHC)



electron-deficient and electron-rich cinnamaldehyde and chalcone−imine derivatives (Table 2).[14]

The stereochemical outcome provides further support for a tandem, or possibly concerted, crossed-benzoin/oxy-Cope reaction as the key bond-forming step (Scheme 2).[6] The *cis*-relative configuration of the cyclopentane substituents would arise from a boat oxy-Cope transition state that maximizes secondary orbital overlap between the Breslow intermediate and the unsaturated imine. The remaining stereocenter is established by a reversible intramolecular Mannich reaction, wherein only one stereochemical outcome allows subsequent lactamization to form the β-lactam and release the catalyst. The *trans* isomer from cinnamaldehyde substrates may be produced via an alternative mechanism featuring conjugate additions of catalytically generated homoenolates, which Nair demonstrated to prefer the *trans* products in a cyclopentene-forming annulation.[7] The high preference for this process, rather than NHC-catalyzed Diels−Alder reaction, arises from the use of nonactivated enals which are slow to undergo protonation at the β-position.[10]

In summary, we have documented a highly enantio- and diastereoselective direct annulation of enals, including 3-alkyl enals, and chalcone-derived imines that takes advantage of a powerful benzoin/oxy-Cope strategy. This process allows direct access to cyclopentyl-fused β-lactams in an operationally simple process that establishes four contiguous stereocenters.

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Supporting Information Available: Experimental procedures and characterization data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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