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Highly Enantioselective Azadiene Diels−Alder Reactions Catalyzed by Chiral N-Heterocyclic Carbenes

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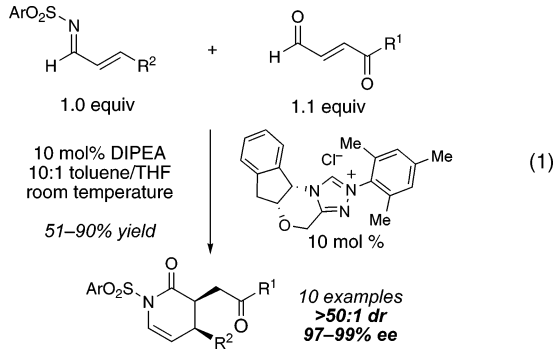
Carbon−carbon bond forming processes mediated by N-heterocyclic carbene (NHC) organocatalysts have witnessed recent, impressive progress in the discovery of new reaction manifolds and the development of asymmetric processes.[1,2] Notable advances include new chiral triazolium catalysts for enantioselective intermolecular homodimerization of aryl aldehydes,[3] intramolecular aldehyde−ketone benzoin cyclizations,[4] and intramolecular Stetter reactions.[5] Our own efforts have focused on extending the mechanistic pathways available to the key "Breslow intermediate" formed by the nucleophilic addition of NHC catalysts to aldehydes,[6] and we have reported the application of this strategy to the catalytic generation of activated carboxylates[7,8] and to novel carbon−carbon bond forming processes that proceed via a formal homoenolate intermediate.[9]

In the context of these studies, we recognized that protonation or trapping of a conjugated Breslow-type intermediate **i** should lead to the formation of a catalyst-bound enol or enolate poised for carbon−carbon bond formation (Scheme 1).[10,11] We now report the first example of such a strategy, namely, the NHC-catalyzed generation of a highly reactive dienophile that participates in $LUMO_{diene}$-controlled Diels−Alder cyclizations with α,β-unsaturated imines under unprecedentedly mild conditions.[12] Furthermore, we have developed a new triazolium precatalyst that affords the dihydropyridinone products in >99% ee for a wide range of substrates (eq 1).



(1)

An obstacle to the successful implementation of this approach to the catalytic generation of reactive enolates was the unexpected reluctance of the postulated Breslow intermediate, or its homoenolate resonance structure, to undergo protonation. When imidazolium-derived NHC catalysts were employed, no protonation at the β-position occurred even in protic solvents at elevated temperatures.[7b] To address this, triazolium precatalyst **7** was designed and, in conjunction with a weak tertiary amine base, found to promote the desired protonation reaction, presumably leading to enol **iii** or enolate **iv** (Scheme 1). Efforts to trap these species, however, were frustrated by high temperatures and the tendency of the nucleophilic carbenes to react with an added electrophile in preference to the enal.[9c]

Scheme 1. Proposed NHC-Mediated Enolate Generation

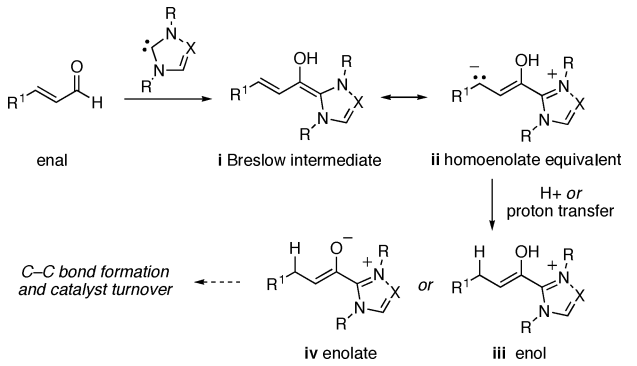
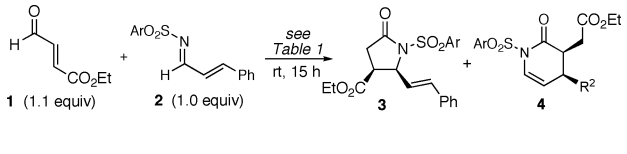
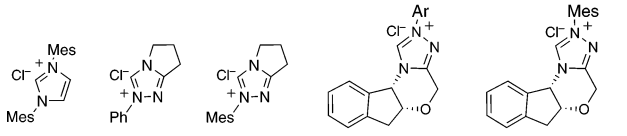


Table 1. Development and Optimization of NHC-Catalyzed Azadiene Diels−Alder Reactions (Ar = $MeOC_6H_4$)





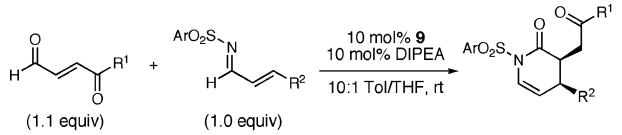
entry	cat. (%)	conditions	3:4[a]	% conv.[b]
1	**5** (15)	10 mol % of DBU, 0.1 M THF	>10:1	36 (7:1 dr)
2	**5** (15)	10 mol % of DIPEA, 0.1 M THF	>10:1	13 (2:1 dr)
3	**6** (15)	10 mol % of DBU, 0.1 M THF		nr
4	**7** (15)	10 mol % of DBU, 0.1 M THF	1:8	47
5	**7** (15)	10 mol % of DBU, 0.1 M EtOAc	1:5	38
6	**7** (15)	10 mol % of DBU, 0.1 M toluene	1:10	44
7	**7** (15)	10 mol % of DIPEA, 0.1 M toluene	>1:20[c]	44
8	**7** (10)	10 mol % of DIPEA, 23 h 0.05 M 10:1 toluene:THF	>1:20[c]	63
9	**8** (10)	10 mol % of DIPEA, 23 h 0.05 M 10:1 toluene:THF		nr
10	**9** (10)	10 mol % of DIPEA, 23 h 0.05 M 10:1 toluene:THF	>1:20[c]	90% yield[d] 99.5% ee

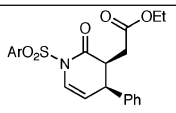
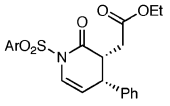
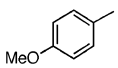
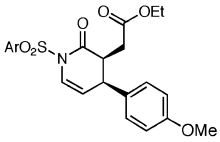
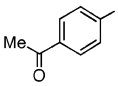
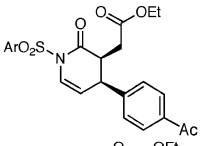
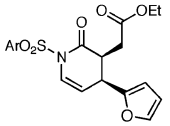
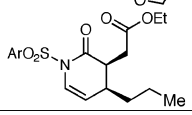
[a] Product ratios and diastereoselectivities determined by ^1H NMR analysis of unpurified reaction mixtures. [b] Ratio of lactam products relative to starting imine. [c] Lactam **3** was not detected. [d] Yield of isolated product. DIPEA = *N*,*N*-diisopropylethylamine.

To increase the electrophilicity of the enal, we selected inexpensive, commercially available ethyl *trans*-4-oxo-2-butenoate[13] **1** as a substrate for NHC-promoted reactions with *N*-sulfonyl imines. The reaction of imidazolium-derived carbenes with **1** was fast, but did not result in protonation at the β-position. Instead, γ-lactams were formed (Table 1, entries 1 and 2).[9c] In contrast, hindered triazolium catalyst **7** led to the formation of a new product. Structure

10.1021/ja062707c CCC: $33.50

Table 2. Catalytic, Enantioselective Diels−Alder Reactions[a]



entry	R^1	R^2	product	% yield[b]	% ee[d]
1	OEt	Ph		90	99 (*S*,*S*)
2[c]	OEt	Ph		90	99 (*R*,*R*)
3	OEt			81	99 (*S*,*S*)
4	OEt			55	99 (*S*,*S*)
5	OEt			71	99 (*S*,*S*)
6	OEt	*n*-Pr		58	99 (*S*,*S*)

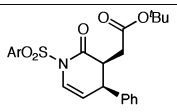
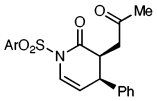
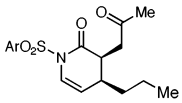
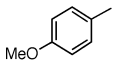
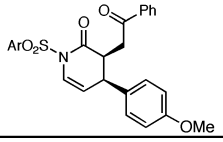
[a] Ar = 4-$MeOC_6H_4$. All reactions were performed at 0.05 M for 23−48 h. In all cases, only a single diastereomer was detected in unpurified reaction mixtures by ^{1}H NMR or HPLC analysis. [b] Yields of isolated products. [c] 10 mol % of *ent*-**9** was used as the catalyst. [d] Determined by HPLC analysis on Chiralpak AS (entries 1−3, 6), OD (entry 4), or AD (entry 5) columns. All enantiomeric ratios were >200:1 based on integration of the minor enantiomer or baseline.

elucidation by single-crystal X-ray analysis revealed this product to be dihydropyridinone **4**, apparently formed by a Diels−Alder-type reaction of imine **2** and a catalytically generated dienophile. A screen of solvents and bases optimized the product ratio and conversion (entries 4−7). Remarkably, the reaction occurs readily at lower temperatures (−20 °C), although these conditions offered no significant advantages to catalytic couplings at ambient temperature.

Intrigued by the prospect of developing an enantioselective entry to these attractive products, we screened known chiral triazolium salts as catalysts. Disappointingly, the aminoindanol-derived precatalyst **8** described by Rovis was completely inactive in the reaction.[14] A brief survey of triazolium salts possessing more sterically demanding aryl groups identified mesityl-substituted salt **9** as a highly active catalyst, affording the dihydropyridinone product in >99% ee, >50:1 *cis*-diastereoselectivity, and without forming γ-lactam product **3**. The absolute configuration was determined by X-ray analysis of the product arising from a *para*-bromocinnamaldehyde imine (see Supporting Information). Other protecting groups on the imine nitrogen were viable; the *para*-methoxybenzenesulfonyl derivative provided the highest rates and yields of isolated products by diminishing electrophilic inhibition of the nucleophilic NHC catalyst.[9c]

In the optimized protocol, enantiopure dihydropyridinones were obtained simply by mixing near equimolar amounts of enal and an

Table 3. Variation of the Enal Substrate[a]

entry	R^1	R^2	product	% yield[b]	% ee[c]
1	O^{t}Bu	Ph		70	97 (*S*,*S*)
2[b]	Me	Ph		51	99 (*S*,*S*)
3	Me	*n*-Pr		71	98 (*S*,*S*)
4	Ph			52	99 (*S*,*S*)

[a] See Table 2 for reaction conditions and notes. [b] An additional 1.0 equiv portion of the enal was added after 15 h. [c] Determined by HPLC analysis on Chiralpak AD (entry 2) and AS (entries 1, 3, 4) columns.

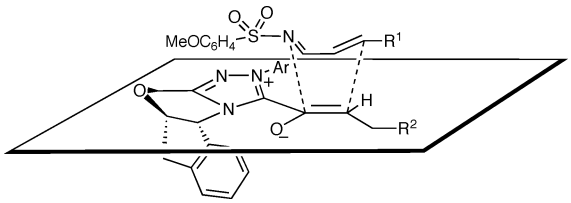


Figure 1. Stereochemical model for *endo*-Diels−Alder cycloaddition.

α,β-unsaturated imine in the presence of 10 mol % of **9** and 10 mol % of DIPEA at ambient temperature for 23−48 h followed by removal of the solvent and purification by chromatography. The only detectable side products were those arising from imine decomposition (5−25%) and small amounts of enal dimerization (>5%). No byproducts are formed in the reaction, obviating the need for an aqueous workup. This process tolerated a full range of unsaturated imine substrates (Table 2), including both electron-rich and electron-deficient cinnamaldehyde derivatives, as well as heterocyclic and aliphatic examples. In all cases, the enantiomeric excesses were >99%.

Variation in the enal reactant was also possible, and the necessary substrates were prepared in a single step from the corresponding phosphonate esters and dimethylglyoxaldehyde acetal.[15] The synthetically attractive *tert*-butyl ester substrate participated in good yield and enantioselectivity (Table 3, entry 1). Methyl or phenyl ketones also gave the desired product in >98% ee (entries 2−4).

The formation of dihydropyridinones bears the hallmark of a $LUMO_{diene}$-controlled inverse electron demand Diels−Alder cycloaddition.[12] Related, uncatalyzed processes have been described in detail by Boger,[16] Fowler,[17] and Hsung.[18] In these studies, however, the reaction of unactivated imines, such as **2**, with electron-rich dienophiles required high pressure (12 kbar) or high temperatures, while the NHC−carbene-catalyzed aza-Diels−Alder reaction proceeds readily at ambient conditions. The exceptional diastereoselectivity is rationalized by the high preference for an *endo* transition state, and in the NHC-catalyzed system, this reaction mode is reinforced by the presence of the bulky triazolium moiety in the active dienophile (Figure 1). The *cis*-stereoselectivity would arise from a (*Z*)-enolate reacting as the dienophile. We have postulated that protonation of the Breslow intermediate can occur only in a fully conjugated, extended arrangement that necessarily leads to the (*Z*)-enolate or enol structure.[7b] The model shown in

Scheme 2. Postulated Catalytic Cycle

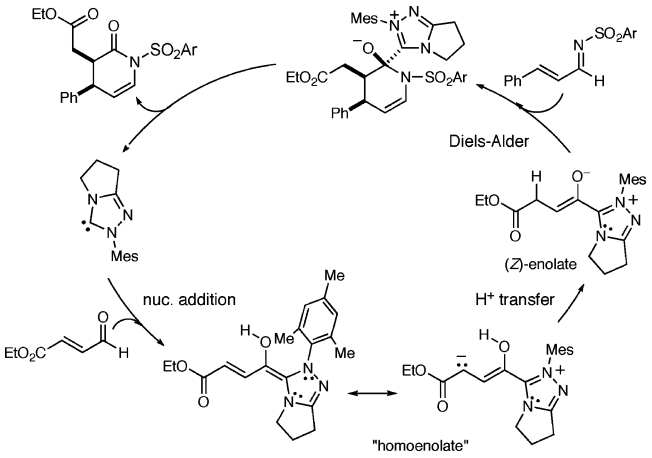
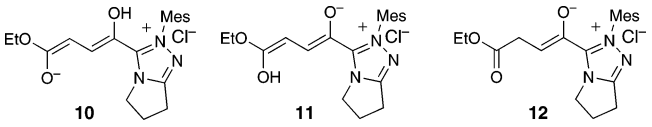
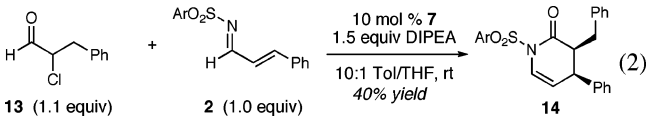


Figure 1 also rationalizes the observed absolute stereochemistry of the products. The conformation of the enol−triazolium bond is a key determinate of the stereochemical outcome, and the origin of this preference is not immediately clear. Further experimental and computational investigations are underway and will lead to an improved understanding of the mechanism and stereochemical outcome.

At present, we attribute the need for enals bearing electron-withdrawing groups only to the increased electrophilicity of these substrates, which enhances the rate of their reaction with the nucleophilic catalysts.[19] There does not appear to be a mechanistic limitation requiring extended conjugation in the catalytically generated dienophile as would be found in enolate **10**, a resonance structure of the Breslow intermediate, or **11**, a tautomeric form.



To test this hypothesis, we briefly explored the generation of dienophiles from α-chloro aldehyde **13**, which is known to undergo related NHC-catalyzed redox reactions,[8] leading to enols or enolates. In the presence of 10 mol % of **7** and 1.5 equiv of DIPEA, **13** afforded dihydropyridinone product **14** in 40% yield. Thus, although we cannot conclusively exclude a role for **10** or **11** in NHC-catalyzed reactions of **1**, we currently favor prior protonation of the homoenolate to generate **12**.



The ability of nucleophilic carbenes to add reversibly to unsaturated esters and ketones was recently demonstrated by Fu, suggesting an alternative Morita−Baylis−Hillman-like generation of the enolate.[20] Attempts to employ fumarates or other electron-deficient substrates lacking the aldehyde functionality have so far been unproductive, disfavoring this mechanistic pathway. A stepwise conjugate addition−lactamization sequence featuring an intermediate activated carboxylate would require exclusive reaction of the *s-cis*-imine conformer, rendering this mechanism less likely. Taken together, these considerations, along with our previous investigations of NHC-catalyzed transformations, support the catalytic cycle shown in Scheme 2.

In summary, we have described a new manifold for asymmetric organocatalysis through the first NHC-catalyzed Diels−Alder reaction. In addition to the potential of this powerful approach to the catalytic generation of an exceptionally reactive dienophile, it is a rare example of a highly enantioselective intermolecular cross-coupling reaction catalyzed by an NHC organocatalyst.[21] The operationally friendly reaction conditions do not require heating, cooling, workup, or additional reagents. The chiral dihydropyridinone products, which are obtained in good yield and with remarkable enantioselectivities, are valuable structures for the synthesis of biologically active molecules.

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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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