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Chiral N-Heterocyclic Carbene Catalyzed, Enantioselective Oxodiene Diels−Alder Reactions with Low Catalyst Loadings

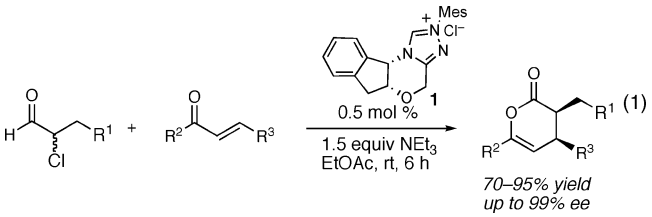
Ming He, Gerson J. Uc, and Jeffrey W. Bode*

Department of Chemistry and Biochemistry, University of California at Santa Barbara, Santa Barbara, California 93106−9510

Received September 3, 2006; E-mail: bode@chem.ucsb.edu

We recently reported chiral N-heterocyclic carbene (NHC) catalyzed 1-azadiene Diels−Alder reactions of enals and α,β-unsaturated, *N*-sulfonylimines.[1] These highly enantio- and diastereoselective processes proceeded via the catalytic generation of a chiral enolate that served as a remarkably reactive dienophile, leading to *cis*-3,4-dihydropyridinone products under mild conditions. Key to the success of this approach was our finding that *N*-mesitylsubstituted azolium salts are exceptionally effective in NHC-catalyzed redox reactions.[2,3] Preliminary efforts to extend these conditions to other processes were complicated by the tendency of the enals to undergo dimerization via a variety of pathways. Therefore, we considered alternative starting materials for generating chiral enolates via NHC-catalyzed intramolecular redox reactions[4] of α,β-epoxyaldehydes,[5] α-haloaldehydes,[6] and formylcyclopropanes.[7]

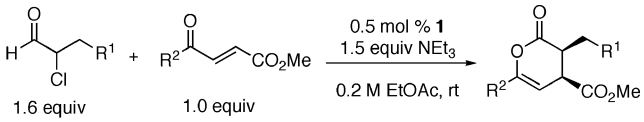
We now document chiral NHC-catalyzed, highly enantioselective 1-oxodiene Diels−Alder reactions[8,9] of a broad range of enones, using *racemic* α-chloroaldehydes as the dienophile precursors. This process affords a diverse set of nonracemic, 3,4,6-trisubstituted dihydropyran-2-ones from readily available starting materials under mild, simple conditions (room temperature, 1.5 equiv NEt_3, 6 h). Significantly, when the NHC-catalyzed oxo-diene Diels−Alder reactions are performed in EtOAc, the loading of the chiral organocatalyst can be reduced to 0.5 mol % without compromising the reaction rate, enantioselectivity, or chemical yield. This is an unparalleled example of a highly enantioselective, intermolecular C−C bond-forming reaction catalyzed by less than 1 mol % of a small organic molecule.[10,11]

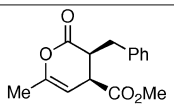
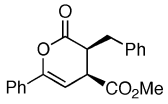
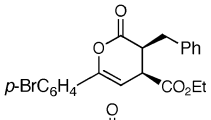
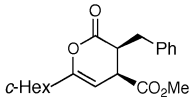
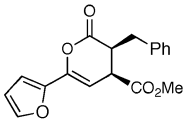
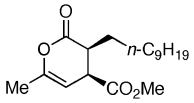
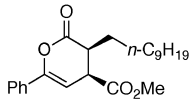
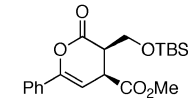


Although we had previously anticipated that *racemic a*-chloroaldehydes could serve as dienophile precursors in hetero- Diels−Alder reactions catalyzed by *achiral* NHCs, the stereochemical course of annulations employing an enantiomerically pure NHC catalyst with *racemic* chloroaldehydes was unclear. Furthermore, the viability of oxodienes, which are less reactive than their *N*-sulfonyl counterparts, was unknown. To investigate these aspects in the context of the previously undocumented NHC-catalyzed oxodiene Diels−Alder reactions, we selected readily prepared *rac*-α-chlorohydrocinnamaldehyde and (*E*)-methyl-4-oxo-pent-2-enoate for initial studies. Using our recently reported chiral triazolium salt **1** as a precatalyst,[12] we screened an assortment of bases, solvents, and reaction stoichiometries. The reaction proceeded cleanly under a number of conditions, although annulations performed in ethyl acetate with NEt_3 were notably faster and higher yielding, possibly because of the attendant precipitation of $Et_3N{\cdot}HCl$ from the reaction mixture. Significantly, this finding allowed us to identify optimized conditions (1.6 equiv aldehyde, 1.5 equiv NEt_3, 0.2 M EtOAc, room temperature) for oxodiene Diels−Alder reactions employing only 0.5 mol % of chiral organocatalyst **1**. A preparative scale reaction using only 44 mg (0.5 mol %, 2 h) **1** afforded 5.3 g product (>99% ee, >50:1 dr) after a single crystallization of the reaction mixture (Table 1, entry 3).

A range of enones bearing an electron-withdrawing group were viable reaction partners (Table 1). Our studies focused on the use of either aromatic or aliphatic substituted 4-oxo-enoates, which in

Table 1. Catalytic, Asymmetric Oxodiene Diels−Alder Reactions[a]



entry	R^1 =	R^2 =	product	d.r.	% yield[b]	% ee[c]
1	Ph	Me		>20:1[d]	88	99 (*S*,*S*)
2	Ph	Ph		8:1	91	99 (*S*,*S*)
3[e]	Ph	Ph		15:1	98(70)[f]	99 (*S*,*S*)
4	Ph	*p*-Br-C_6H_4		6:1	80	99 (*S*,*S*)
5[g]	Ph	*c*-Hex		>20:1[d]	76	86 (*S*,*S*)
6	Ph	Furyl		8:1[d]	94	99 (*S*,*S*)
7	*n*-C_9H_{19}	Me		>20:1[d]	71	99 (*S*,*S*)
8	*n*-C_9H_{19}	Ph		>20:1[d]	90	99 (*S*,*S*)
9	OTBS	Ph		3:1	80	97 (*R*,*S*)

[a] All reactions were performed on a 0.5 mmol scale for 2−8 h. [b] Yield of diastereomeric mixtures after chromatography. [c] Determined by HPLC analysis on Chiralpak columns (see Supporting Information). [d] A single diastereomer was detected by ^1H NMR of unpurified reaction mixtures. [e] 24 mmol scale, 2 h; [f] Isolated yield of >50:1 dr material obtained by crystallization of the unpurified product. [g] 24 h.

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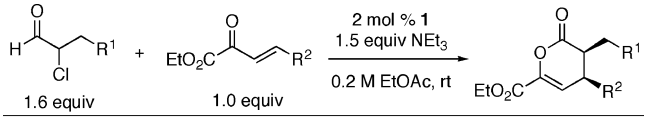
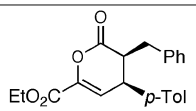
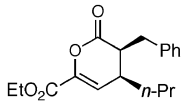
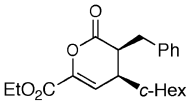
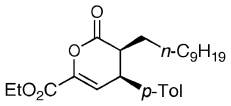
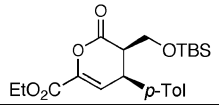
Table 2. NHC-Catalyzed Reactions of Unsaturated α-Ketoesters[a]



entry	R^1 =	R^2 =	product	% yield[b]	% ee[c]
1	Ph	*p*-Tol		74	97 (*S*,*S*)
2	Ph	*n*-Pr		84	98 (*S*,*S*)
3	Ph	*c*-Hex		85	95 (*S*,*S*)
4	n-C_9H_{19}	*p*-Tol		70	99 (*S*,*S*)
5	OTBS	*p*-Tol		83	95 (*R*,*S*)

[a] All reactions were performed on a 0.2 mmol scale for 6−8 h. In all cases, only a single diastereomer was detected in unpurified reaction mixtures. [b] Isolated yield after chromatography. [c] Determined by HPLC analysis on Chiralpak columns.

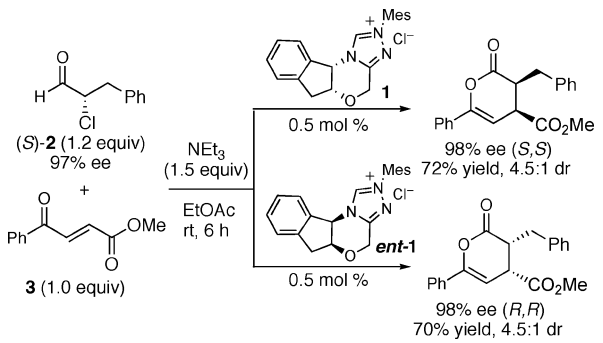
all cases tested afforded the desired product in good yield and with outstanding enantioselectivity. A sole exception was a hindered ketone, which required a longer reaction time and gave the product in lower than usual enantioselectivity (entry 5). The lower diastereoselectivities observed with the aryl ketone derivatives (entries 2, 4, 6, 9) appear to result from epimerization of the initially formed *cis*-annulation products.[13] A variety of α-chloroaldehydes were efficient precursors (entries 7−9).

Alternatively, β,γ-unsaturated, α-ketoesters proved to be highly reactive substrates and afforded synthetically valuable products in excellent yields and stereoselectivities (Table 2).[14] These reactions could proceed with less than 1 mol % catalyst, but the 2 mol % loading proved optimal in chemical yield and enantioselectivitiy. This variant also tolerated a wide scope of enones, including both aromatic and aliphatic substitution.

We have postulated that the very high *cis*-diastereoselectivities observed in the NHC-catalyzed Diels−Alder reactions arose from the stereoselective formation of a (*Z*)-enolate in the redox reaction of enals in conjunction with a high preference for an *endo* cycloaddition.[1] The enolates generated from α-chloroaldehydes arise by elimination of HCl from diastereomeric catalyst−aldehyde adducts, and the stereochemistry of the α-chloro center may play a role in the stereochemical outcome. To test this hypothesis, we prepared enantioenriched chloroaldehyde **2**[15] and explored its reaction with both enantiomers of precatalyst **1**. Each reaction proceeded with similar reaction rates and afforded the annulation product in identical yield, diasteromeric ratio, and enantiopurity; the sole difference in the reaction outcomes were the absolute configurations of the products. Stopping either of the experiments shown in Scheme 1 prior to completion (1.5 h) revealed complete epimerization of the α-chloroaldehyde.

The use of readily prepared racemic *a*-chloroaldehydes as enolate precursors greatly expands the scope of enantioselective N-heterocyclic carbene-catalyzed Diels−Alder reactions. It also makes possible, for the first time, asymmetric annulations with exceptional

Scheme 1



enantioselectivities under reliable conditions with less than 1 mol % of a chiral NHC-catalyst.

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

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