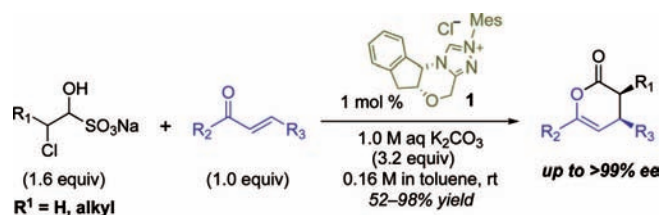


Chiral NHC-Catalyzed Oxodiene
Diels–Alder Reactions with
 α -Chloroaldehyde Bisulfite SaltsMing He, Brendan J. Beahm, and Jeffrey W. Bode^{*,†}Department of Chemistry and Biochemistry, University of California, Santa Barbara,
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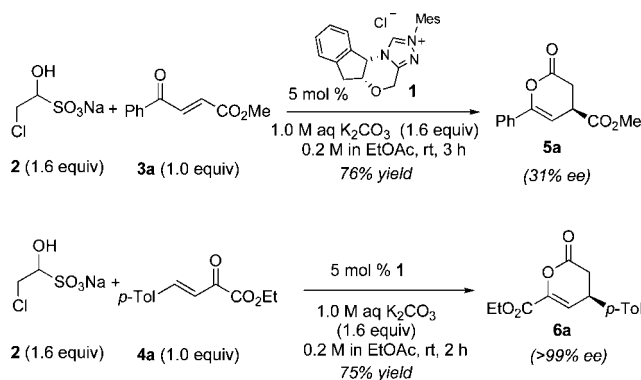
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ABSTRACT



α -Chloroaldehyde bisulfite adducts were successfully employed in chiral NHC-catalyzed hetero-Diels–Alder reactions with various oxodienes under biphasic reaction conditions with high levels of enantioselectivity. This new protocol makes possible enantioselective additions from commercially available chloroacetaldehyde sodium bisulfite and demonstrates that this unique class of catalysts readily tolerates aqueous conditions.

Enantioselective hetero-Diels–Alder reactions provide a versatile and convergent approach to the construction of chiral heterocycles.¹ In recent years, significant progress has been achieved in the development of efficient chiral metal and organic catalysts for enantioselective hetero-Diels–Alder reactions.^{2,3} Their great synthetic utility

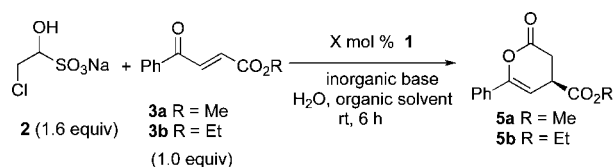
Scheme 1. NHC-Catalyzed Hetero-Diels–Alder Reactions with Chloroaldehyde Sodium Bisulfite **2**

continues to drive further interest in improved protocols and expanded substrate scope. Of particular need are reactions in which the starting materials are readily accessible, and

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Table 1. Effect of Inorganic Bases and Organic Solvents on Epimerization^a

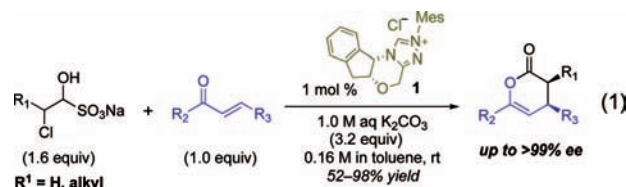
entry	X	R	aqueous base	organic solvent	time/h	yield/% ^b	ee/% ^c
1	5	Me	1.6 equiv of 1.0 M K ₂ CO ₃	0.2 M EtOAc	2.5	76	31
2	5	Me	1.6 equiv of 1.0 M NaHCO ₃	0.2 M EtOAc	23.0	78	65
3	5	Me	1.6 equiv of 1.5 M NaHCO ₃	0.2 M toluene	23.0	48	75
4	5	Me	1.6 equiv of 1.0 M K ₂ CO ₃	0.2 M toluene	2.5	40	99
5	5	Me	1.6 equiv of 1.0 M K ₂ CO ₃	0.2 M toluene	4.0	55	93
6	5	Me	1.6 equiv of 1.0 M K ₂ CO ₃	0.2 M toluene	6.0	62	86
7	1	Et	3.2 equiv of 1.0 M K ₂ CO ₃	0.16 M toluene	6.0	84	90

^a All reactions were performed with 1.6 equiv of **2** and 1.0 equiv of oxodiene. ^b Isolated yield after chromatography. ^c Determined by HPLC analysis.

low catalyst loadings can be employed while still maintaining high levels of enantioselectivity.

We have recently reported the first chiral N-heterocyclic carbene (NHC) catalyzed hetero-Diels–Alder reaction, via the catalytic generation of chiral enolates that serve as dienophiles.^{4,5} We have also extended the dienophile precursors from electron-deficient enals to α -chloroaldehydes,⁶ which can be readily prepared from the corresponding aldehydes.⁷ However, α -chloroaldehydes are sensitive to moisture and oxygen,^{8a} and their preparation and storage require precautions. Furthermore, α -chloroacetaldehyde, which would provide entry into challenging but synthetically important enantioselective acetate additions,⁹ is difficult and unsafe to obtain in pure form.^{8b} In this communication, we document efficient solutions to both of these challenges through the use of α -chloroaldehyde bisulfite salts under

biphasic conditions (eq 1). This new protocol both extends the scope and operational simplicity of NHC-catalyzed enantioselective hetero-Diels–Alder reactions and demonstrates that this unique class of catalysts readily tolerates aqueous conditions.¹⁰



At the outset of our studies, we investigated a number of α -chloroaldehyde surrogates, including hemiacetals, bromopyruvic acid, and the α -chloroaldehyde bisulfite adducts. Among these starting materials, the α -chloroaldehyde bisulfite adducts were particularly attractive as they were bench-stable solids that could be readily prepared by the addition of aqueous sodium bisulfite to a solution of the appropriate aldehydes.^{11b} Their use as substrates, however, would necessitate the use of aqueous conditions to decompose the bisulfite adducts to the corresponding aldehydes in the presence of the NHC catalyst.^{11,12}

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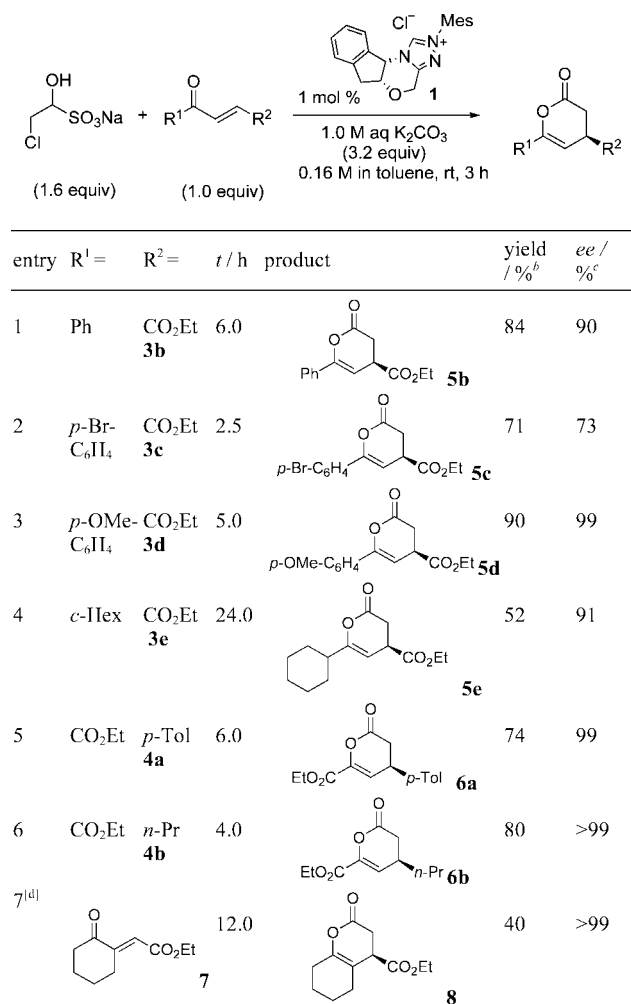
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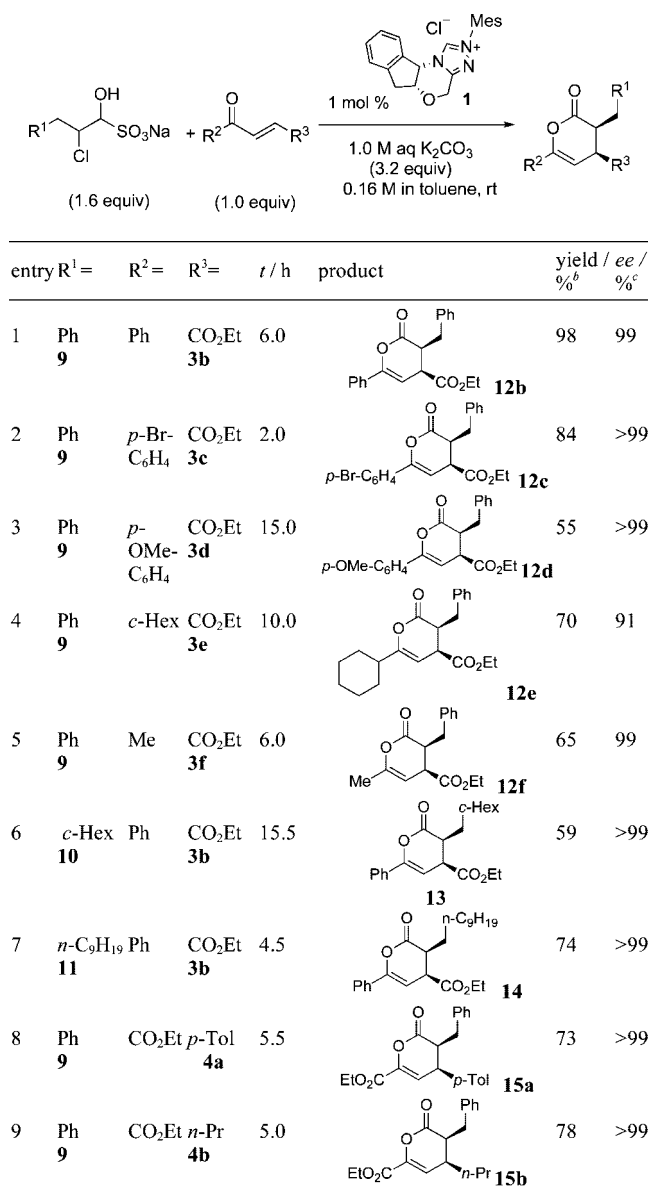
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Table 2. NHC-Catalyzed Biphasic Diels–Alder Reactions of **2** with Different Oxodienes^a

^a All reactions were performed at 0.16 M in toluene with 1.6 equiv of chloroacetaldehyde sodium bisulfite **2**, 1.0 equiv of oxodiene, 1 mol % of **1**, and 3.2 equiv of 1.0 M aq K₂CO₃. ^b Isolated yield after chromatography. ^c Determined by HPLC or SFC analysis. ^d 5 mol % of **1** was employed.

To test the feasibility of our approach, we selected inexpensive, commercially available chloroacetaldehyde sodium bisulfite **2** as a precursor of chloroacetaldehyde for the NHC-promoted reactions with two representative oxodienes: 4-oxoenoate **3a** and β,γ -unsaturated α -ketoester **4a** (Scheme 1). We screened a number of reaction conditions before selecting biphasic conditions employing 1.0 M K₂CO₃ as the inorganic base and EtOAc as the organic solvent for further development. These studies established the feasibility of using the bisulfite adducts as starting materials but confirmed our fears of epimerization. The use of **3a** as the oxodiene provided product **5a** only in 31% ee, while the use of **4a** afforded adduct **6a** in >99% ee.^{4b}

We reasoned from these results that the low enantioselectivity observed for **5a** was due to epimerization of the annulation product. Notably, this product contains a readily epimerizable stereocenter by virtue of the β,γ -unsaturated ester and lacks adjacent substitution, which

Table 3. NHC-Catalyzed Biphasic Diels–Alder Reactions of Chloroaldehyde Bisulfite Salts^a

^a All reactions were performed at 0.16 M in toluene with 1.6 equiv of chloroaldehyde bisulfite adduct, 1.0 equiv of oxodiene, 1 mol % of **1**, and 3.2 equiv of 1.0 M aq K₂CO₃. In all cases, only one diastereomer was detected in unpurified reaction mixtures. ^b Isolated yield after chromatography. ^c Determined by HPLC or SFC analysis.

had been present in all of the examples from our prior work. To improve the enantiomeric excess of the product **5a**, we investigated the effect of reaction conditions including inorganic bases and organic solvents (Table 1). Although the use of either a weaker base (NaHCO₃, entries 1 and 2) or a nonpolar solvent (entry 3) suppressed epimerization, the combination of NaHCO₃ and toluene afforded the product only in 75% ee. In contrast, those of 1.0 M K₂CO₃ and toluene minimized the epimerization (entries 4 and 5) at the expense of diminished yields. Some of the product loss was traced to hydrolysis, and improved yields could be obtained simply by employing the more

stable ethyl ester (entries 6 and 7). *Notably, these conditions also allowed us to lower the catalyst loading to 1 mol % of chiral triazolium precatalyst 1.*

The scope of these conditions for NHC-catalyzed Diels–Alder reactions with chloroacetaldehyde bisulfite salt **2** with various oxodiene substrates is shown in Table 2. This survey demonstrated that this biphasic process accommodated various substrates **3b–e** (entries 1–4) including aromatic and aliphatic substitution. Except for entry 2, all of the substrates screened afforded the desired 4,6-disubstituted dihydropyran-2-ones with good enantioselectivity, albeit slightly diminished by epimerization. As expected, the β,γ -unsaturated α -ketoesters **4a** and **4b** furnished the corresponding products in good yields and with excellent enantioselectivity. The absolute configuration of the products was determined by single-crystal X-ray analysis of the product (*R*)-ethyl 6-(4-bromophenyl)-2-oxo-3,4-dihydro-2*H*-pyran-4-carboxylate (Table 2, entry 2).¹³ Interestingly, the sterically hindered 4-oxoenolate **7**, which did not react with any α -chloroaldehydes in our previous investigations, afforded bicyclic product **8** with excellent enantioselectivity when catalyzed by 5 mol % of **1**.

In addition to allowing direct use of the commercially available chloroacetaldehyde bisulfite adduct, we also sought to utilize these conditions to simplify the preparation, handling, and reactions of substituted α -chloroaldehydes. After some experimentation, we identified reliable conditions for the conversion of common α -chloroaldehydes to the bench-stable, solid bisulfite adducts (see Supporting Information).^{11b} We were pleased to find that the reaction conditions optimized for the chloroacetaldehyde bisulfite salt were directly applicable to these substrates. Biphasic reactions with either substituted 4-oxoenolates (entries 1–7) or β,γ -unsaturated α -ketoesters (entry 8 and 9) provided the Diels–Alder products in good chemical yields and excellent enantioselectivity.¹⁴

In all cases, only 1 mol % of chiral triazolium precatalyst **1** was employed. The absolute configuration was determined

(13) A sample with 93% ee was prepared for the X-ray analysis, although in low yield. CCDC 689207 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

by X-ray analysis of an enantiomerically pure sample of (3*S*,4*S*)-ethyl 3-benzyl-6-(4-bromophenyl)-2-oxo-3,4-dihydro-2*H*-pyran-4-carboxylate (Table 3, entry 2, see Supporting Information).¹⁵

In summary, we have developed a catalytic enantioselective method for hetero-Diels–Alder reactions that employs easily available, bench-stable α -chloroaldehyde bisulfite salts as starting materials. This enantioselective, biphasic hetero-Diels–Alder reaction represents the first enantioselective NHC-catalyzed reaction that is demonstrably water-tolerant. It provides an innovative solution to enantioselective additions of acetate equivalents using the inexpensive, commercially available bisulfite adduct of chloroacetaldehyde, thereby interfacing with ongoing efforts to employ commodity chemicals in lieu of preactivated or protected reactants.¹⁶ This approach also extends the scope of enantioselective NHC-catalysis and provides a more convenient and operationally simple protocol for NHC-catalyzed Diels–Alder reactions.

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Supporting Information Available: Full experimental procedures and characterization data and X-ray crystallographic data for **5c**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(14) These conditions eliminated epimerization and gave diastereoselectivities superior to the conditions in ref 4b.

(15) CCDC 689208 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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