Organocatalysis

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N-Heterocyclic Carbene Catalyzed C–C Bond Cleavage in Redox Esterifications of Chiral Formylcyclopropanes**

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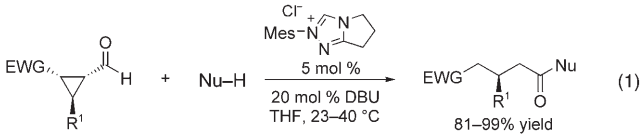
Dedicated to Professor Michael P. Doyle

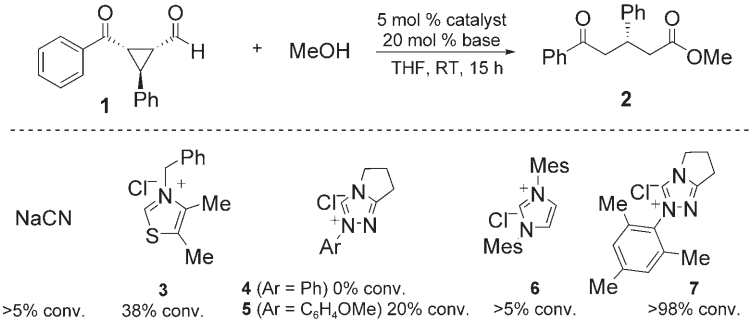
Ring-opening reactions of small, strained molecules translate the high degree of stereoselectivity inherent in the synthesis of diverse cyclic structures into the establishment of absolute stereochemistry in acyclic systems.[1] A disadvantage of many ring-opening processes, which are formally reduction reactions, is the necessity of stoichiometric reagents that are often expensive or toxic metals. To address this limitation, we recently developed an organocatalytic redox opening of α,β-epoxyaldehydes with concomitant oxidation of the aldehyde and subsequent esterification.[2,3] This efficient process transforms widely available, enantioenriched epoxides into a variety of value-added products, including *anti*-propionate aldol adducts under mild, practical conditions.

In seeking to extend the concept of catalytic cyclic-to-acyclic stereochemical translation of readily prepared, enantiopure starting materials, we were attracted to the recent advances made by Kunz and MacMillan on the direct, highly enantioselective synthesis of formylcyclopropanes with the commercially available organocatalyst (2*S*)-indoline-2-carboxylic acid.[4] We reasoned that an efficient method for redox esterifications that involves opening the cyclopropane unit would result in a concise approach to enantioenriched β-substituted carboxylic acid derivatives, an attractive class of chiral building blocks with few methods for their general, asymmetric preparation.[5] To achieve this transformation, however, we required the cleavage of a carbon–-carbon bond lacking heteroatom functionalities,[6] a process that normally requires strong reducing agents and vigorous conditions even in highly strained systems.[7] We now report the successful development of C–C-bond-cleaving ring-openings of formylcyclopropanes mediated by an N-heterocyclic carbene (NHC) organocatalyst, thus leading to esters and thioesters via the intermediacy of catalytically generated activated carboxylates [Eq. (1); DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, electron-withdrawing group (EWG) = ketone, ester, amide, or nitro].



(1)

At the onset of our studies, it was unclear if the stabilized acyl anion equivalents expected to be formed by addition of an NHC catalyst to a formylcyclopropane would lead to ring-opening reactions in preference to benzoin dimerizations,[8] especially under the protic conditions mandated by redox esterification processes. We selected readily prepared, enantiomerically enriched formylcyclopropane **1** as a model substrate for reaction development. Initial efforts confirmed our trepidation that simple thiazolium- and triazolium-derived NHCs would prove inefficient or prefer competing pathways (Scheme 1). However, we were pleased to find that our mesityl-substituted triazolium salt **7**,[3b] which deters



Scheme 1. The influence of NHC precatalysts on catalytic redox esterifications of formylcyclopropane **1**. The starting aldehyde was recovered in reactions with lower conversion. Mes = 2,4,6-trimethylphenyl.

nucleophilic reactions of the catalytically generated acyl anion equivalent, serves as a highly active precatalyst for ring-opening esterifications of formylcyclopropanes in excellent yield. A screen of solvents, bases, reaction temperatures, and catalyst loadings revealed the optimal conditions. Weaker bases (NEt_3, Hünig's base) proved less efficient at ambient temperature but worked well at 60 °C. We selected THF as the optimal solvent, but comparable conversions and rates were observed in EtOAc, CH_2Cl_2, and toluene. Careful studies using GC and HPLC with chiral columns confirmed the preservation of the stereochemistry at the β-position.

NHC-catalyzed ring-opening reactions of trisubstituted formylcyclopropanes proceeded with a wide range of substitution patterns in the presence of 5 mol % **7** and 20 mol % DBU (Table 1). The necessary substrates were available in a single, convenient step from the corresponding sulfur ylides,

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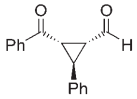
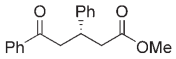
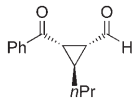
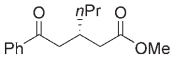
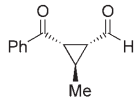
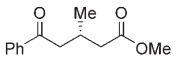
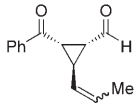
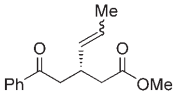
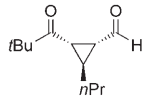
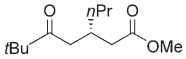
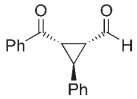
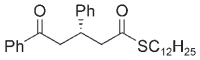
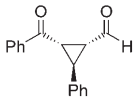
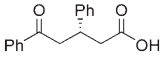
Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

Table 1: NHC-catalyzed redox esterifications of chiral, enantiomerically enriched formylcyclopropanes.[a]

Entry	RCHO	NuH	Product	*T* [°C]	*ee* [%]	Yield [%][b]
1		MeOH		23	89[c]	90
					89[d]	
2		MeOH		40	93[c]	87
					90[d]	
3[d]		MeOH		40	83[c]	84
					77[d,e]	
4		MeOH		40	83[c]	96
					81[d]	
5		MeOH		40	93[c,e]	95
6		$C_{12}H_{25}SH$		23	88[c]	99
					88[d]	
7[f]		H_2O		23	88[c]	92
					87[d]	

[a] Unless otherwise indicated, all reactions were performed on a 0.2–0.8-mmol scale at 0.5 M in THF with 5 mol% **7** and 20 mol% DBU for 15 h. [b] Yields of the isolated products following chromatography. [c] The *ee* values were assessed by chiral GC or HPLC analysis of the major diastereomer of the starting cyclopropane. [d] The *ee* values were assessed by chiral HPLC or GC analysis of the product ester. [e] Minor cyclopropane diastereomer (≈10%) was present in the starting aldehyde. [f] DBU = 1.2 equiv.

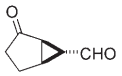
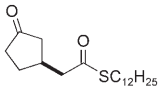
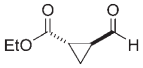
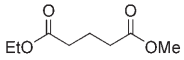
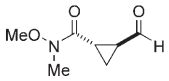
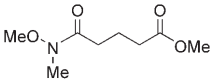
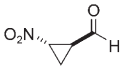
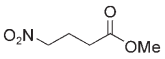
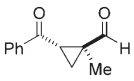
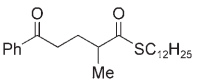
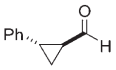
unsaturated aldehydes, and a commercially available amino acid catalyst, thus rendering the two-step MacMillan cyclopropanation/redox ring-opening reaction a highly efficient method for the preparation of acyclic, enantiomerically enriched β-substituted carboxylic acid derivatives. Importantly, this strategy is amenable to a full range of substituent types, including aromatic, aliphatic, and unsaturated moieties. Although we have focused on alcohol nucleophiles, thiols also proved to be highly reactive, thus leading to synthetically useful thioesters poised for further transformation (Table 1, entry 6).[9] Water, in conjunction with 1.2 equivalents of DBU, made possible the direct preparation of the corresponding acid (Table 1, entry 7). At the present stage of development, attempts to use primary or secondary amine nucleophiles led to complex reaction mixtures.

We prepared a range of formylcyclopropanes bearing electron-deficient functional groups to probe the requirements for an electron sink in the cyclopropane substrates (Table 2). These findings suggest a wide scope for interfacing this process with emerging methods for the catalytic, enantioselective synthesis of chiral formylcyclopropanes.[10–12]

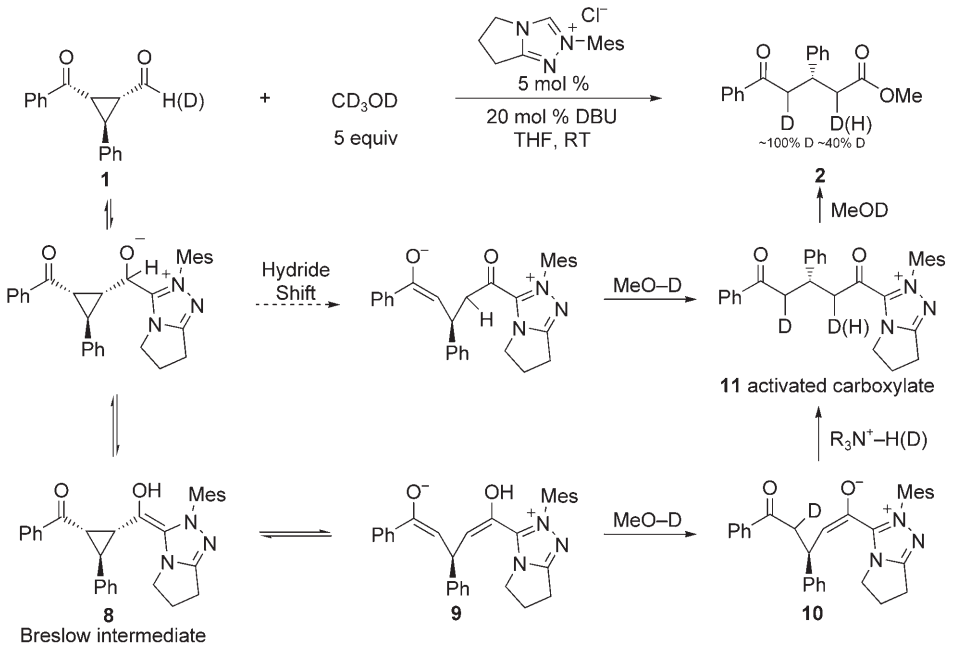
The NHC-catalyzed ring-opening reaction leads to the formation of enolate **9**.[13] Under our present conditions, this species is most likely quenched by rapid proton transfer to lead to a more stabilized, catalyst-bound enolate **10** (or its corresponding enol), which undergoes protonation and tautomerization to form acyl triazolium activated carboxylate **11** (Scheme 2). A reaction performed with five equivalents of MeOD resulted in the quantitative incorporation of a single deuterium atom, as a mixture of diastereomers, adjacent to the ketone moiety. Quenching the reaction at partial conversion leads to the recovery of the starting aldehyde deuterated at the acyl carbon atom, thus demonstrating that the NHC catalyst can react reversibly with the formylcyclopropane. These observations would be consistent with a hydride-shift mechanism; however, an experiment in which an enantioenriched substrate gave a racemic product currently disfavors this pathway, at least for the substitution pattern examined.[14]

In summary, we have described the first NHC-organocatalyzed C–C bond-cleavage reaction that is useful for the synthesis of enantiomerically enriched esters and thioesters

Table 2: Further scope of NHC-catalyzed redox esterifications of formylcyclopropanes.[a]

Entry	RCHO	NuH	Product	*T* [°C]	Yield[b] [%]
1		$C_{12}H_{25}SH$		40	81
2		MeOH		23	95
3[d]		MeOH		23	98
4		MeOH		23	90
5		$C_{12}H_{25}SH$		23	95
6		MeOH	[c]	60	–

[a] Unless otherwise indicated, all reactions were performed on a 0.2–0.8-mmol scale at 0.5 M in THF with 5 mol% **7** and 20 mol% DBU for 15 h. All the starting aldehydes shown in this table were used as racemic mixtures. [b] Yield of the isolated products following chromatography. [c] Only the starting material and benzoin dimer were observed.



Scheme 2. Reaction pathways for NHC-catalyzed redox reactions of formylcyclopropanes.

from readily available chiral formylcyclopropanes. The overall two-step process for the synthesis of enantioenriched carboxylic acid derivatives is notable for proceeding from simple starting materials under mild, nearly neutral conditions without reagents or reaction by-products.

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[14] The enantiomerically enriched substrate was prepared by a chiral NHC-catalyzed kinetic resolution of a racemic mixture of formylcyclopropanes; further studies on the use of chiral NHCs for the enantioselective transformation of formylcyclopropanes will be reported in due course.