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Catalytic Generation of Activated Carboxylates: Direct, Stereoselective Synthesis of β-Hydroxyesters from Epoxyaldehydes

Kenneth Yu-Kin Chow and Jeffrey W. Bode*

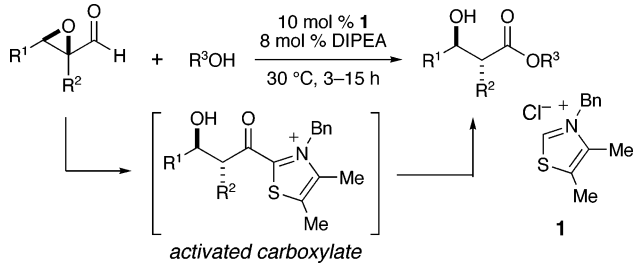
Department of Chemistry and Biochemistry, University of California, Santa Barbara, California 93106-9510

Received May 3, 2004; E-mail: bode@chem.ucsb.edu

Synthetic methods for the preparation of carboxylic acid derivatives typically rely on the stoichiometric preparation of an activated carboxylate followed by reaction with an appropriate nucleophile.[1] While these protocols have found widespread utility for the synthesis of esters and related compounds, they suffer from disadvantages including the need to employ significant molar excesses of the coupling reagents and the formation of large amounts of byproducts. To overcome these limitations, chemists have sought catalytic methods for effecting esterifications and amidations. Although some success has been found through the use of Lewis[2] or Brønsted[3] acids at high temperature, there remains a great need for truly catalytic methods under mild reaction conditions.[4]

As part of a program aimed at developing new approaches to stereoselective, atom-economical esterifications and amidations, we now document the catalytic, diastereoselective synthesis of β-hydroxy esters from α,β-epoxy aldehydes. In addition to providing a new method for the preparation of these important structural motifs from readily available starting materials, this chemistry unveils a mechanistically viable solution to the catalytic generation of activated carboxylates (Scheme 1).

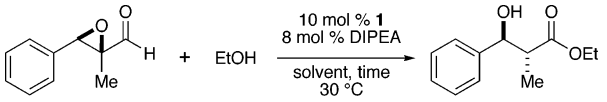
Scheme 1



The inspiration for our catalytic, diastereoselective esterification is the facility of thiazolium−aldehyde adducts to undergo oxidation to 2-acyl thiazolium species, which are efficient and well-known acyl donors, i.e., activated carboxylates.[5] While previous studies have utilized stoichometric oxidants[6] or electrochemical conditions,[7] we reasoned that incorporation of a reducible functionality into the aldehyde substrate could set the stage for a catalyst-induced intramolecular redox reaction. This, in turn, leads to the generation of the key acyl thiazolium species, poised for reaction with nucleophiles.[8]

For initial studies we selected 2,3-epoxyaldehydes, such as **2**, as suitable substrates for reaction development (eq 1). In addition to the widespread availability of these structures in enantiopure form,[9] the expected β-hydroxyester products are synthetically valuable building blocks for the construction of natural products and pharmaceuticals. Preliminary trials employing commercially available thiazolium salts led to formation of the desired product (Table 1, entry 1); however, the chemical yield was less than optimal. A screen of alternative catalysts and reaction conditions led to our selection of readily prepared thiazolium precatalyst **1**[10] and operationally convenient reaction parameters: 30 °C, 0.5 M, 10 mol % **1**, and 8 mol % DIPEA (entry 2). The reaction was accelerated by increased amounts of base (entry 3) or the use of DBU (entry 4), albeit with slightly diminished chemical yields. Of interest was the solvent-dependent, and notably high, diastereoselectivity of catalytic carboxylate generation: catalytic reactions in CH_2Cl_2 (entries 2−4) or CH_3CN (entry 7) reliably formed the *anti*-β-hydroxy ester in >12:1 diastereoselectivity.[11,12]

Table 1. Optimization of Reaction Conditions for the Synthesis of *anti*-β-Hydroxyesters from Epoxyaldehydes[a]



(1)

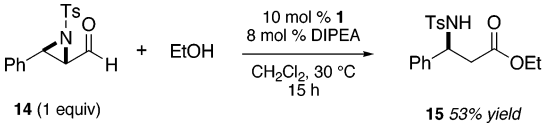
2 (1 equiv) **3** (3 equiv) **4**-*anti*

entry	solvent	time/h	yield[b] **4**/%	dr **4** (*anti*:*syn*)[c]
1[d]	CH_2Cl_2	15	48	8:1
2	CH_2Cl_2	15	89	13:1
3[e]	CH_2Cl_2	4	77	12:1
4[f]	CH_2Cl_2	4	72	12:1
5	DMF	15	88	3.5:1
6	EtOH	15	68	7:1
7	CH_3CN	15	75	12:1
8	none	15	76	8:1

[a] All reactions were performed on a 0.5 mmol scale at 0.5 M. DIPEA = diisopropylethylamine; DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene. [b] Isolated yield following chromatography. [c] Determined by GC analysis of unpurified reaction mixtures. [d] 3-Benzyl-5-(2-hydroxyethyl)-4-methyl thiazolium chloride (10 mol %) was used as catalyst. [e] 20 mol % DIPEA. [f] 8 mol % DBU.

We have found this reaction to be general for a variety of epoxyaldehydes and alcohols. Thus BnOH, ^{i}PrOH, and CD_3OD reacted with **2** to give the anti-β-hydroxyesters in good yield and diastereoselectivity (Table 2, entries 1−3). Substrates lacking an α-alkyl group gave the corresponding acetate−aldol adduct (entry 4). An aliphatic example provided the expected products in good yields and stereoselectivity (entries 5). This chemistry also offers a valuable approach to enantiomerically pure β-alkyl-β-hydroxyesters, which are difficult to obtain via other methods (entry 6).[13]

The catalytic generation of activated carboxylates is not limited to epoxide substrates. For example, α,β-aziridinylaldehyde **14** gave the desired *N*-tosyl-β-aminoester **15** in 53% yield under standard conditions. This result points to a potentially broader scope for catalytic carboxylate activation and offers an attractive approach to β-amino acids.[14]

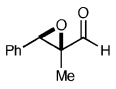
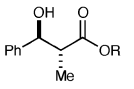
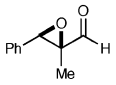
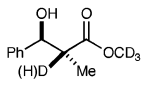
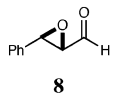
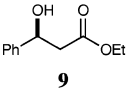
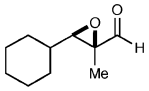
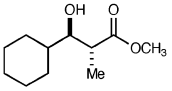
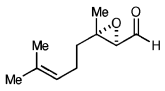
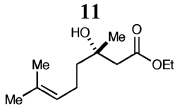


(2)

14 (1 equiv) **15** *53% yield*

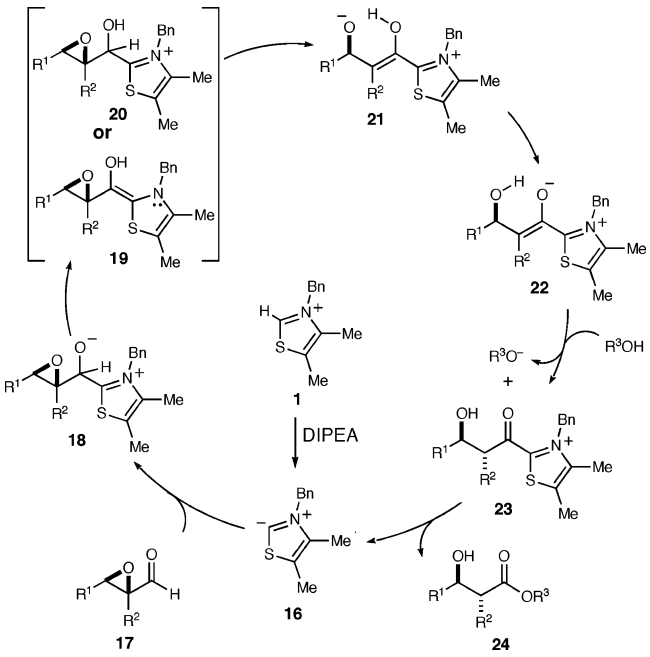
10.1021/ja047407e CCC: $27.50

Table 2. Catalytic Esterifications of Epoxyaldehydes[a]

entry	epoxy-aldehyde	nu	product	dr[b]	yield / %[c]
1		BnOH		>10:1[d]	89
2	**2**	^{i}PrOH	**5** (R = Bn) **6** (R = ^{i}Pr)	>10:1[d]	79
3	 **2**	CD_3OD	 **7**	9:1	81[e]
4	 **8**	EtOH	 **9**	—	84
5	 **10**	CH_3OH	 **11**	7:1	82[f]
6[g]	 **12**	EtOH	 **13**	—	85

[a] Unless otherwise indicated, all reactions were performed on racemic epoxides at 0.5 M in CH_2Cl_2 at 30 °C for 15 h using 10 mol % **1**, 8 mol % DIPEA, and 3 equiv of the nucleophile. [b] Determined by GC analysis of unpurified reaction mixtures. [c] Isolated yield following chromatography. [d] Determined by ^{1}H NMR analysis of unpurified reaction mixtures. [e] Reaction time was 3 h; longer reaction times gave identical results. [f] 8 mol % DBU was employed. [g] Enantiomerically enriched (94% ee) epoxide was used.

Scheme 2



Despite the similarity of the reaction conditions to those typically used for benzoin reactions, we have yet to observe any trace of the corresponding acyloin dimers; the only detectable byproducts were small amounts (~2% each) of the α,β-unsaturated esters and oligomeric esters. The reactivity of 2,3-epoxyaldehydes under these conditions appears to be related to the transformation of trichloroacetaldehyde to dichloroacetic acid in the presence of cyanide, reported by Wallach in 1873.[15] An apparently similar process, mediated by a thiamine-dependent enzyme, has also been postulated for the biosynthesis of clavulanic acid.[16] These reports, coupled with experimental observations, support the catalytic cycle shown in Scheme 2. Of particular significance is the epoxide-opening step, which could occur either via a concerted elimination to give **21** from **20** or in a stepwise manner via stabilized anion **19**. Reactions performed in the presence of CD_3OD, and quenched at 50% completion, reveal no deuterium incorporation into recovered **17**, suggesting either a concerted process or a rate-determining deprotonation step. Likewise, the stereochemical outcome and additional isotopic labeling experiments, which produce deuterium incorporation at the α-position (~50% incorporation), disfavor a Favorskii-like or hydride-shift mechanism from intermediate **18** or a hemiacetal (Table 2, entry 3).

In summary, we have developed a truly catalytic method for the generation of activated carboxylates from epoxyaldehydes and its application to a unique esterification process. This mechanistic prototype invites further applications to stereoselective, waste-free syntheses of other important carboxylic acid derivatives.

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

References

(1) The term activated carboxylate is taken to encompass any acyl species that reacts irreversibly with nucelophiles to give stable carboxylic acid derivates. Examples include acyl halides, acyl cyanides, and activated esters.
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