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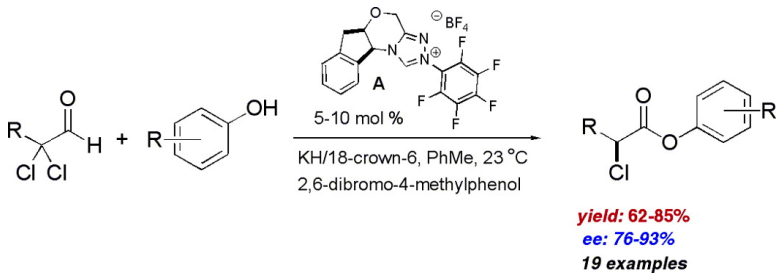

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Enantioselective Protonation of Catalytically Generated Chiral Enolates as an Approach to the Synthesis of α-Chloroesters

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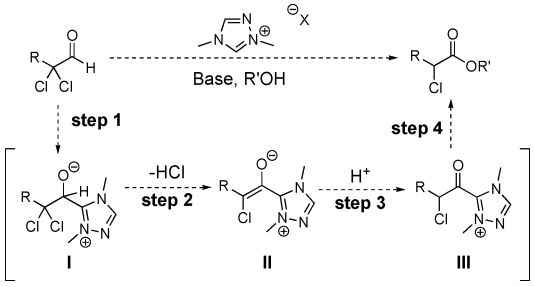
The control of stereochemistry α to carbonyls is a long-standing problem in organic chemistry with a host of solutions based on chiral auxiliary chemistry.[1] More recently, a number of catalytic asymmetric methods have appeared taking advantage of in situ generated nucleophiles for direct aldol,[2] Mannich,[3] halogenation,[4] and protonation reactions.[5,6] In connection with our work on nucleophilic carbene-catalyzed *umpolung* reactions,[7] we considered that our catalytically generated nucleophile complexed enolate may participate in a range of electrophile trapping/acylation sequences that would result in chiral α-substituted esters. Herein we disclose that 2,2-dichloroaldehydes react with phenols in the presence of chiral triazolinylidene carbenes to form α-chloroesters in good yield and enantioselectivity.

In our proposed mechanism (Scheme 1), the carbene, generated upon deprotonation of the azolium salt by base, adds to the α-haloaldehyde to form **I**, which subsequently undergoes an elimination of HCl to provide azolium enolate. Protonation of this intermediate[8] produces an acyl azolium species (**III**, Scheme 1), which performs an acylation to provide catalyst turnover. The use of a chiral azolium salt thus provides entry into a chiral enolate (**II** in Scheme 1), and we hypothesized that it should be possible to identify a set of conditions wherein protonation of **II** would afford **III** with the stereocenter defined. The subsequent acylation event would close the catalytic cycle and afford enantioenriched α-substituted esters.

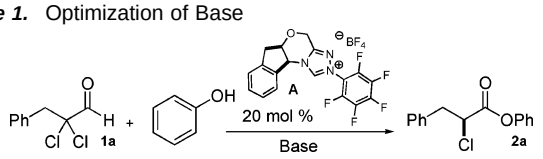
Scheme 1. Proposed Synthesis of α-Chloroesters



At the outset of our investigation, we realized the need for three different reagents in this reaction: (1) a base to sequester the generated HCl (step 2, Scheme 1), (2) a proton source (step 3, Scheme 1), and (3) an alcohol to undergo acylation, providing the α-haloester and regenerating the catalyst (step 4, Scheme 1). Previous successful asymmetric enolate protonations[5] have used phenol as a proton source, and phenol has proven to be a competent nucleophile in our acyl azolium chemistry.[7f] Therefore, we began our investigations by studying the conversion of **1a** to its phenyl ester **2a**.

The requisite dichloroaldehydes are bench-stable compounds, easily accessed by treatment of various aldehydes with *tert*-butylamine and NCS.[9] Initial experiments revealed that at least 1 equiv of base was required. In general, amine bases gave lower enantioselectivities but good yields (entry 1, Table 1). Carbonate bases provide product, but suffered from low yield or enantiomeric excess

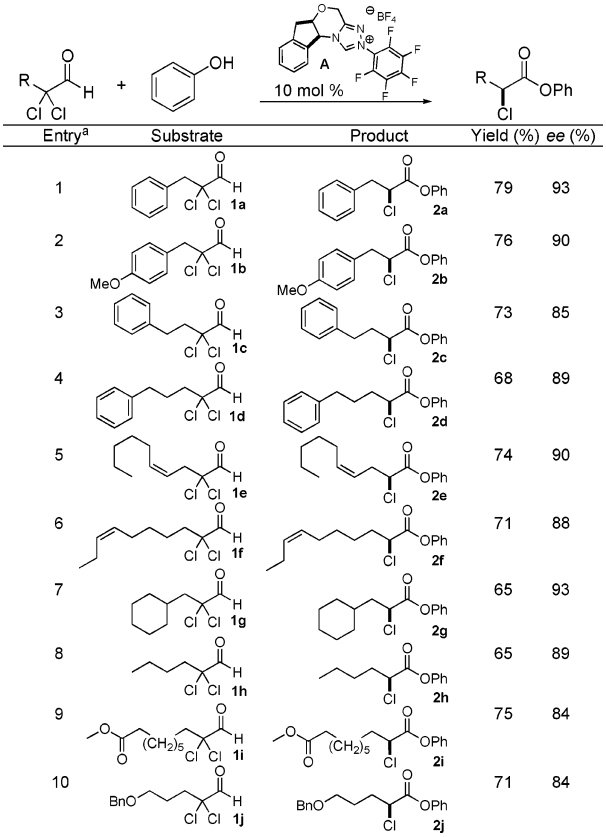
Table 1. Optimization of Base



entry[a]	base	equiv of base	yield (%)	ee (%)
1	$^{i}Pr_2NEt$	1.20	88	74
2	$NaHCO_3$	1.00[b]	61	88
3	K_2CO_3	1.20	84	44
4	KH	1.15	75	84
5	KH	1.15[c]	75	81
6	KH + **3**	1.00[d]	80	92

[a] All reactions conducted at 0.12 M in PhMe at 23 °C. [b] With 0.18 equiv of triethylamine. [c] With 1.15 equiv of 18-crown-6. [d] With 1.00 equiv of 18-crown-6 and 1.20 equiv of 2,6-dibromo-4-methylphenol (**3**).

Table 2. Synthesis of α-Haloesters: Substrate Scope



[a] All reactions conducted at 0.06 M in substrate with 10 equiv of PhOH, 1.2 equiv of **3**, 1 equiv of KH, and 0.5 equiv of 18-crown-6 in PhMe at 23 °C for 19 h.

(entries 2 and 3, Table 1). We ultimately chose potassium phenoxide, generated in situ from potassium hydride and phenol, for development as it provided the best combination of yield and enantiomeric excess (entry 4, Table 1). Thus, the phenol/phenoxide com-

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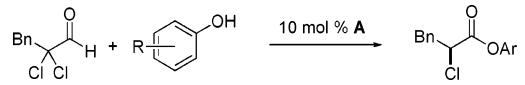
Table 3. Reactions of **1a** with Substituted Phenols



entry[a]	R	yield (%)	ee (%)	entry[a]	R	yield (%)	ee (%)
1	H	79	93	6	2-chloro	75	91
2	4-methyl	71	89	7	2,6-dichloro	65	82
3	4-methoxy	71	91	8	2,6-dibromo-4-methyl	85	76
4	4-chloro	75	83	9	2,4,6-trimethyl	0	na
5	2-methyl	62	90	10	3,4-dimethyl	80	89

[a] See footnote in Table 2.

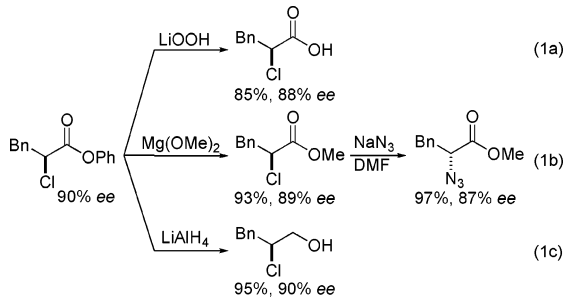
bination fulfills the unique role of base, proton source, and nucleophile.

Due to the poor solubility of potassium phenoxide in toluene, we added 18-crown-6, which provided a homogeneous reaction medium, resulting in similar yield, but a slight decrease in enantioselectivity (entry 5, Table 1). However, we found that enantioselectivity varied slightly from run to run, and we speculated that a modest level of background epimerization was responsible. To alleviate this problem, we considered buffering the solution by adding a bulkier, more acidic phenol which would form the base reservoir. To our gratification, we discovered that the use of 1.2 equiv of 2,6-dibromo-4-methylphenol (**3**) afforded **2a** in 92% ee.

Under optimized conditions (1.0 equiv of potassium hydride, 0.5 equiv of 18-crown-6, 1.2 equiv of **3**, 10 equiv of phenol, 10 mol % of catalyst **A**, 0.06 M), we obtained **2a** in 79% yield and 93% ee (entry 1, Table 2). The transformation is general with regards to the participating aldehydes, with enantioselectivities ranging from 84 to 93%, and tolerant of diverse functionality including olefins, ethers, and esters (Table 2). The reaction is currently limited to aldehydes lacking β-branching,[10] making it complementary to previously developed ketene methods.[11]

A distinct advantage of the current approach is the ability to incorporate a variety of aryl esters into the product (Table 3). The reaction is fairly independent of phenol pK_a (entries 1−4, Table 3). Orthosubstituted phenols participate well only in the presence of **3** (entries 5−8, Table 3). In the absence of **3**, 2-methylphenol affords the corresponding ester in only 15% yield and 42% ee (achiral catalyst **B**,[12] however, provides the product in 83% yield). These results suggest that steric[13] and electronic[14] factors prevent 2-methylphenol from functioning efficiently as a base or proton source, a crucial role that is played by **3**. Bisorthosubstituted 2,4,6-trimethylphenol (**4**) did not afford any of the desired ester (entry 9, Table 3); instead, a 56% yield of the ester derived from **3** was recovered in 65% ee. Control experiments revealed that **4** is not a competent nucleophile in the presence of catalyst **A**, while catalyst **B** provides a 30% yield of acylated **4**.

The α-chloro phenyl ester products may be hydrolyzed to the acid or reduced with $LiAlH_4$, in both cases with nearly complete retention of enantioselectivity (eqs 1a and 1c). Alternatively, transesterification may be achieved with $Mg(OMe)_2$, followed by azide[15] displacement with inversion to provide the corresponding α-azidoester (eq 1b).



In conclusion, we have demonstrated a unique synthesis of α-chloroesters based on an enantioselective protonation of in situ generated chiral α-haloenolates. The reaction is robust[16] and an excellent complement to the literature, allowing for the synthesis of a wide range of phenolic esters. Studies investigating the reaction of other electrophiles with our catalytically generated enolates are currently underway.

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Supporting Information Available: Complete experimental procedures and characterization of novel compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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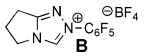
(12) Achiral catalyst:



B

(13) *A* values: Br = 0.7; Me = 1.6−1.8. van der Waals radii: Br = 1.95; Me = 2.0. C−X bond lengths: Br = 1.94; Me = 1.54. See: Eliel, E. R.; Haber, R. G. *J. Am. Chem. Soc.* **1959**, *81*, 1249−1254.
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(16) Under the reported conditions, using 5 mol % of **A** (1.42 g) and **1a** (60 mmol) provided 8.67 g of **2a** (55% yield) with 90% ee (62% recovery of excess PhOH).

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