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N-Heterocyclic Carbene Catalyzed Asymmetric Hydration: Direct Synthesis of α-Protio and α-Deuterio α-Chloro and α-Fluoro Carboxylic Acids

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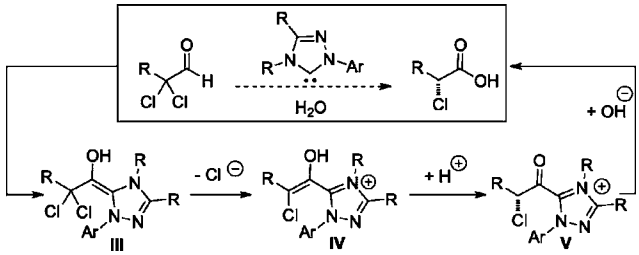
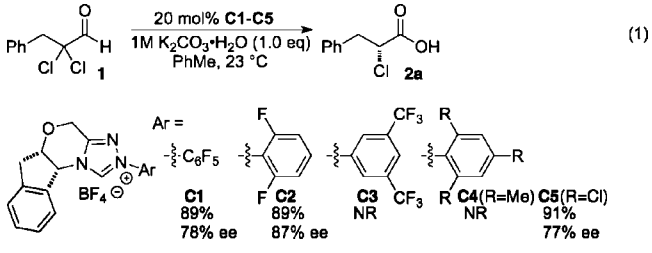
The catalytic asymmetric synthesis of α-halo carbonyl derivatives has received considerable attention in recent years.[1] Approaches to accessing these valuable synthons currently rely on the asymmetric generation of the α-halo aldehyde[2] or ester[3] and their subsequent manipulation. We have previously shown that α,α-dichloro aldehydes in the presence of a chiral N-heterocyclic carbene (NHC)[4] and phenol can yield the respective α-chloro aryl ester in good yields and ee's.[5−7] In an effort to maximize both atom and step economy in these processes, we envisioned that water would be the ideal nucleophile to generate the α-halo acids directly, the redox[8] hydration of the α-reducible aldehyde (Scheme 1).[9] Herein, we report the asymmetric synthesis of α-chloro and α-fluoro carboxylic acids through a mild biphasic redox process. The versatility of the developed reaction also lends itself to the incorporation of a deuterium by simply using D_2O.

Scheme 1. Mechanism of the NHC Redox Process



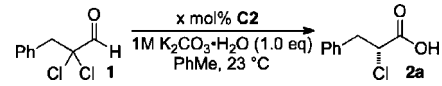
Carbonate bases were identified as being optimal in an initial screen. Investigations into the catalyst revealed that **C1**, previously demonstrated as the optimal precatalyst in our asymmetric synthesis of α-chloro esters, affords the α-chloro acid **2a** in 89% yield and 78% ee (eq 1). Efforts to determine the effect of the carbene on the reaction showed that a sufficiently electron withdrawing 2,6-difluorophenyl group, **C2**,[10] was necessary to facilitate reactivity (87% yield) with an increase in the enantioselectivity to 87%. The electron-deficient 3,5-bis(trifluoromethyl)phenyl species **C3**[10] and sterically hindered mesityl derivative **C4** led to no reaction. In order to obtain the reactivity observed with **C1** while mimicking the sterics of precatalyst **C4**, we synthesized **C5**, which generates the desired product in 91% yield and 77% ee.



(1)

In an effort to improve efficiency, we conducted a catalyst loading study. While lower catalyst loading results in diminished enantioselectivities (entry 1, Table 1), surprisingly improved ee is obtained at higher catalyst loadings (entries 2−4, Table 1).[11] We suggest that there is more than one agent capable of delivering the proton to enol **IV**, the presumed stereoselectivity-determining event. At higher catalyst loading, conditions where we observe improved selectivities, it stands to reason that the more stereoselective pathway involves more than one molecule of catalyst.

Table 1. Effect of Catalyst on Selectivity and Reactivity

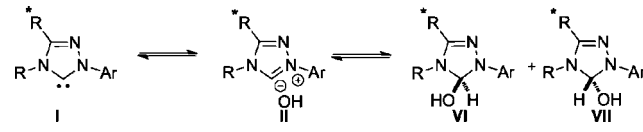


entry[a]	mol%	additive	yield (%)	ee (%)[b]	entry[a]	mol%	additive	yield (%)	ee (%)[b]
1	10	-	50	80	5	10	brine	60	87
2	20	-	89	87	6	10	Bu_4NI	85	87
3	30	-	90	90	***7***	***10***	***brine/Bu_4NI***	***89***	***88***
4	40	-	90	92					

[a] All reactions conducted in PhMe (0.02 M) at 23 °C. [b] ee's determined on the derived methyl ester by HPLC analysis on a chiral stationary phase.

One might envision several modes by which the carbene may interact with water (Scheme 2). Protonation of the carbene with water may lead to azolium hydroxide **II**, which can act as a phase-transfer agent supplying hydroxide into the organic phase. Additionally, diastereomeric hemiaminals **VI** and **VII** may form, the hydrate of carbene **I**.[12] Speculating that residual water in the organic phase may serve as the proton source for **IV**, we introduced brine as an additive and observed an increase in both yield and ee (entry 5, Table 1). In an attempt to probe the role of the azolium as a phase transfer agent, we also added 10 mol % tetrabutylammonium iodide (Bu_4NI) and found improved reactivity and selectivity (entry 6, Table 2). The use of both brine and Bu_4NI proved to be optimal (entry 7, Table 1).

Scheme 2. Hemiaminal Formation



A variety of α,α-dichloro aldehydes participate in this reaction to yield the respective α-chloro acids in good yields and high enantioselectivities. Substitution of D_2O in place of H_2O leads to an asymmetric deuteration reaction affording enantioenriched isotopically labeled chloroacids, of potential interest as drug analogues.[13] *o*-Methoxy and *p*-N-Boc-amino groups are each tolerated on the aromatic ring (**2b**,**c**, Chart 1), yielding the respective products in 78−80% and 78−95% ee.[14] It is interesting to note that presence of an additional proton donor in **2c** significantly reduces the ee, presumably due to

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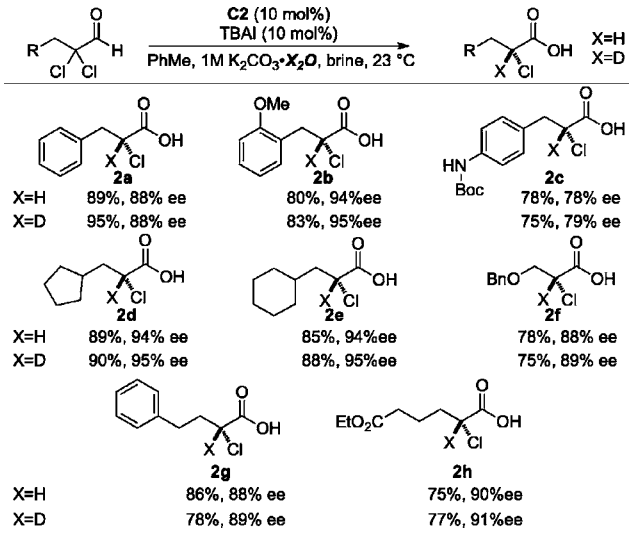
Chart 1. Scope of α-Chloro Carboxylic Acids[a]

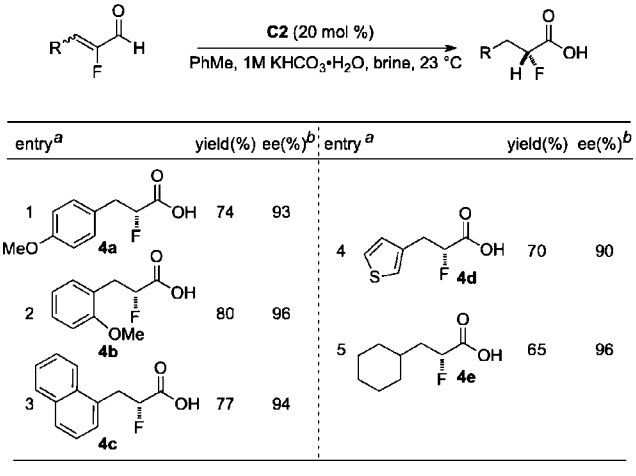


[a] See footnotes *a* and *b* in Table 1.

competitive protonation. Analogues bearing aliphatic groups, **2d**,**e** (Chart 1), and functional groups, **2f**−**h** (Chart 1), all give the acid in good yield (75−86%) and 89−91% ee.[15]

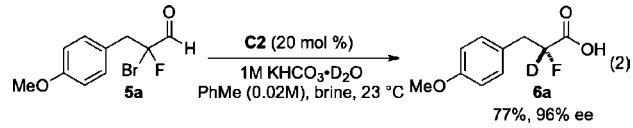
α-Fluoro carboxylic acids are attractive products for the pharmaceutical industry, as fluorine is an isostere for hydrogen.[16] α-Fluoroenals were chosen as the redox partner for this mild catalytic process, and we were pleased to observe that mixtures of olefin isomers are tolerated.[17] Several points are worthy of note: the use of TBAI leads to enal decomposition, and we observe higher yields using $KHCO_3$ in place of K_2CO_3. Subjection of the aldehyde to the optimized conditions yields the respective α-fluoro carboxylic acids in excellent yields and enantioselectivities.[18,19] The aromatic and heteroaromatic fluoroenals **4a**−**d** (entries 1−4, Table 2) yield the α-fluoro carboxylic acids in 70−80% yield and 90−96% ee. Aliphatic enals are also suitable substrates, with **4e** formed in 65% yield and 96% ee (entry 5, Table 2). To access the enantioenriched α-deuterio α-fluoro carboxylic acid, we subjected α-bromo α-fluoro aldehyde **5a** to the optimized conditions, forming acid **6a** in 77% yield and 96% ee (eq 2).

Table 2. Scope of α-Fluoro Carboxylic Acids



[a] See footnote *a* in Table 1.

We have thus shown that enantioenriched α-chloro and α-fluoro carboxylic acids can be accessed in a catalytic asymmetric manner.



The versatility of the developed reaction also lends itself to a mild and inexpensive method for the incorporation of an α-deuteron in an asymmetric fashion using D_2O.

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

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(11) With 5 mol % catalyst, we observe no conversion after 12 h.

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(14) Absolute stereochemistry has been assigned by chemical correlation to adducts obtained from phenol addition to the haloaldehydes; see the Supporting Information.

(15) A large-scale (1.5 g of cyclopentylmethyldichloroacetaldehyde) reaction affords **2d** in 84% yield and 95% ee.

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(17) (*Z*)-α-Fluoro-*p*-methoxyphenylacrylaldehyde provides **4a** in 93% ee and 84% yield, while the *E* substrate provides **4a** in 93% ee and 42% yield under identical conditions.

(18) Aldehyde purity plays an integral role in the enantioselectivities observed.

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