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Asymmetric NHC-catalyzed synthesis of α -fluoroamides from readily accessible α -fluoroenals

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Abstract

The scope of the NHC-redox amidation has been expanded to include a variety of α,β -unsaturated aldehydes, including α -fluoro α,β -unsaturated aldehydes which give rise to enantioenriched α -fluoroamides in good to excellent yield and enantioselectivity (up to 97% ee). Enantioenriched amines may be elaborated to either diastereomer of the product in high diastereoselectivity (up to 99:1). Functionalization of the amide products to amines and fluorohydrins is also demonstrated with retention of enantioenrichment at the fluorine stereocenter.

Amide bonds are ubiquitous in both nature and medicine.¹ As a result, the area of peptide synthesis is highly developed, and a vast array of methods to form amide bonds is known.² Most of these methods use some form of stoichiometric reagent to activate a carboxylic acid for attack of an amine nucleophile. While effective, these stoichiometric methods are not optimal in terms of atom efficiency,³ and catalytic methods for the generation of amide products have been pursued by a number of groups.⁴

In 2007, we reported the catalytic generation of amides from α -reducible aldehydes using an N-heterocyclic carbene (NHC)-catalyzed redox process (eq 1).^{5,6,7} We believe this type of reaction proceeds by a co-catalytic process in which the NHC generated from **1a** first attacks the aldehyde and undergoes proton transfer to form Breslow intermediate **I** (Scheme 1).⁸ The α -leaving group is then eliminated to generate enol **II**, which can tautomerize to acyl triazolium **III**. This species is an acylating reagent; however, it does not acylate amines efficiently.⁹ Therefore, the co-catalyst **2** intercepts acyl triazolium **III** to generate activated ester **IV**, a commonly used intermediate in peptide couplings. Displacement of **IV** with the amine gives the observed amide products.

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(1)

Our substrate scope included α,α -dichloroaldehydes, α,β -epoxy and aziridinyl aldehydes, and α,β -unsaturated aldehydes. Among these, α,β -unsaturated aldehydes are the least exotic and the most attractive as starting materials. However, only two examples of amide bond formation using this type of substrate were demonstrated in our seminal paper. Furthermore, we felt the method described was not optimal in terms of procedural convenience. The propensity of amines to condense directly on the aldehyde substrates necessitated slow addition of the amine over several hours for an efficient amidation reaction to occur.¹⁰

In our 2007 report, a single asymmetric reaction was demonstrated generating α -chloroamide **5a** in 80% ee with chiral triazolium **4a** as the catalyst (eq 2).

(2)

We hypothesized that this modest selectivity was due to the tautomerization of **II** and **III** catalyzed by base (Scheme 1), leading to epimerization of the newly installed stereocenter. This hypothesis was confirmed by experiments using deuterated α -chloroaldehyde **6** as starting material (eq 3). Under identical reaction conditions, the deuterium label is completely washed out, indicating an epimerization process.¹¹

(3)

In 2010, we reported a related reaction providing α -fluorocarboxylic acids **9** from α -fluoroenals **8** in good yield and excellent enantioselectivity.¹² To overcome the problem of epimerization, we employed buffered, biphasic aqueous conditions and achieved high selectivity (eq 4).

(4)

The inherent reactivity of acyl triazolium **III** and activated ester **IV** with water precludes the use of a biphasic aqueous reaction medium as a solution for amidation (*vide infra*).

Therefore, a distinct approach was necessary that would tolerate inherently basic partners but would insulate the stereocenter. We hypothesized that under the hydration conditions the epimerization is attenuated by low effective concentration of base in the organic layer, and we thought that if we could accomplish the same in the presence of an amine nucleophile under anhydrous conditions, we could prepare enantioenriched amides with greater selectivity.

Among the possible substrates for our planned enantioselective NHC-redox amidation, α -fluoroenals offer a rare opportunity to generate a stereogenic fluorine in the amide product. Fluorine is a unique and highly valuable element to chemists in many fields. Its high electronegativity and small size make it capable of strong polar interactions that can dramatically influence the physical and chemical properties of organic molecules.¹³ Substitution of fluorine for hydrogen can modulate bioavailability, lipophilicity, conformation, and metabolic stability of a drug candidate.¹⁴ However, practical access to fluorinated compounds is limited, and considerable effort has been invested in the development of mild reactions capable of selective installation of fluorine substituents, particularly in enantioselective fashion.¹⁵ Furthermore, very few asymmetric methods are known to generate fluorinated amides directly.^{16,17} The successful application of our amidation reaction to α -fluoroenals **8** would open the door to valuable enantioenriched α -fluoroamides **10** from readily available materials¹⁸ in a single, organocatalytic step (eq 5).

(5)

With the goal of eventually applying our method to the asymmetric synthesis of fluorinated amides, we started by exploring the achiral NHC-redox amidation using amine hydrochloride salts as the nucleophiles. We speculated that an appropriate base could both generate the NHC from the triazolium precatalyst and slowly freebase the hydrochloride into solution, thereby creating the buffered conditions that would minimize epimerization.

In the event, adding a superstoichiometric amount of diisopropylethylamine to a slurry of glycine methyl ester hydrochloride and cinnamaldehyde **11a** with achiral triazolium catalyst **1a** and HOAt gave the known amide **7b**, albeit in low yield (32%, Table 1, entry 1). It was noted that the entirety of the aldehyde was consumed, with the majority of the mass balance made up of hydrocinnamic acid **12** resulting from hydrolysis of the acyl azolium. Heating the reaction to 70 °C led to slightly higher yields of the amide with catalyst **1b**; however, a significant amount of **12** was still formed. To inhibit acid formation, 4 Å molecular sieves were added to the reaction, which effectively precluded hydration and gave excellent yield of the amide (entry 13).

This method was then applied to an assortment of amine hydrochloride nucleophiles, giving amide products in good to excellent yields (Chart 1). Several amino acid esters are competent (**7b–e**), including *N*-acetyl lysine methyl ester (**7g**), as are secondary amines giving tertiary amides. A variety of α,β -unsaturated aldehydes are also competent in this reaction, including aliphatic substrates (**7o–q**).

We then turned to examining conditions to couple glycine methyl ester hydrochloride with fluorinated enal substrate **8a**. Early screens indicated **4d** as the optimal precatalyst for enantioselectivity (Scheme 2). Less hindered amine bases, such as triethylamine, give higher yield but decreased selectivity, while weaker acetate bases give consistently higher yield and good enantioselectivity. Sodium pivalate and sodium benzoate gave the best yield and enantioselectivity, respectively. The increased yield with weak bases may be attributed to acceleration of homoenolate protonation in relation to other possible reaction pathways,^{19,20} while the high selectivity may be explained by slower epimerization. The observed increase in selectivity with more hindered bases suggests that the conjugate acid plays a role in delivering the proton in the enantiodetermining tautomerization step (Scheme 2).

Subjecting a variety of amine hydrochloride salts to these conditions with α -fluorocinnamaldehyde gives a number of secondary and tertiary α -fluorinated amides in

good yield and excellent enantioselectivity (Chart 2, **10b–g**).²¹ A variety of Weinreb amides²² can be made from both aromatic and aliphatic α -fluoroenals (**10g–l**). Electron withdrawing and electron releasing substituents on substituted fluorocinnamaldehydes are tolerated, as are silyl ether (**10l**) and carbamate (**10d**) protecting groups.

Chiral amines participate readily in this reaction to give excellent diastereoselectivity (**10m**). Access to either diastereomer of an α -fluoroamide product could be envisioned, with the selected antipode of chiral catalyst exerting control over selectivity. Indeed, when L-phenylalanine methyl ester hydrochloride is used as the nucleophile, the *anti* diastereomer of α -fluoroamide **10n** can be prepared in 68% yield and 99:1 dr using triazolium **4d**. Substituting **ent-4d** gives the *syn* diastereomer in nearly identical yield and selectivity (Scheme 3). Either enantiomer of phenethylamine hydrochloride can be treated under the reaction conditions with triazolium **4d** to give both the *syn* and *anti* diastereomers of α -fluoroamide **10o** in similar fashion (96:4 and 95:5 dr, respectively).

We were interested to see what impact the fluorine stereocenter might have on further synthetic transformations. Recently, Woerpel reported high selectivity in the addition of a Grignard reagent to α -fluorocyclohexanone.^{23,24} To probe this effect in an acyclic system, we performed a double alkylation of Weinreb amide **10g** (eq 6). Tertiary alcohol **14** can be prepared in 67% 2-step yield, 9:1 dr, and retaining 95% ee. As observed by Myers,²⁵ the diastereomer opposite of that predicted by the Ahn-Eisenstein model is favored.²⁶

(6)

α -Fluoroamides are also suitable precursors to enantioenriched, fluorinated amines. Using lithium aluminum hydride, fluoroamide **10c** was reduced to the corresponding amine without epimerization of the fluorine stereocenter to give fluorinated amine **15** in 73% yield, retaining 90% ee (eq 7).

(7)

Conclusions

We have developed an efficient and highly selective method for the preparation of enantioenriched α -fluoroamides from readily available α -fluoroenals. These reactions are conducted under mild conditions and are tolerant of functional groups such as esters, silyl ethers, and carbamates. Furthermore, these products can be elaborated to ketones, alcohols, and amines bearing a fluorine stereocenter. This method is highly applicable to the synthesis of new fluorinated therapeutic agents, biological probes, and other compounds of interest.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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26. The major diastereomer was assigned by converting the fluorohydrin to the corresponding epoxide; see SI for details.

Scheme 1.
Mechanism of NHC-redox amidation

Yields in parentheses determined by HPLC assay.

Scheme 2.

Catalyst optimization

Yields in parentheses determined by HPLC assay.

Scheme 3. Access to diastereomeric α -fluoroamides by catalyst control

Chart 1.
Amine hydrochloride scope

Chart 2.

Scope of asymmetric α -fluoroamide synthesis

General Conditions: 20 mol % triazolium, 20 mol % HOAt, 1.5 equiv NaOPiv, 1.5 equiv fluoroenal, 0.05M in toluene, 12–16h at 23 °C; a) NaOBz was used in place of NaOPiv. b) HOBt was used in place of HOAt. c) 2.0 equiv of fluoroenal was used as ca. 1:1 mixture of olefin isomers. d) Conducted on 500 mg scale.

Table 1

Entry	Catalyst	Solvent	Yield of 7a (%)
1	1a	PhMe	32
2	1b	PhMe	31
3	1c	PhMe	0
4	1d	PhMe	0
5	1e	PhMe	0
6	1a	THF	<20
7	1a	CH ₂ Cl ₂	<20
8	1a	CH ₃ CN	0
9	1a	Et ₂ O	0
10	1a	dioxane	0
11	1a	PhMe	24 ^a
12	1b	PhMe	50 ^a
13	1b	PhMe	93 ^b

1b: Ar = 2,4,6-trichlorophenyl; **1c**: Ar = phenyl; **1d**: Ar = 3,5-bistrifluoromethyl; **1e**: Ar = 4-methoxyphenyl.

^aRun at 70 °C.

^bRun at 70 °C with 4 Å MS.