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Ligand-Promoted Asymmetric Imino-Reformatsky Reaction of Ethyl Dibromofluoroacetate

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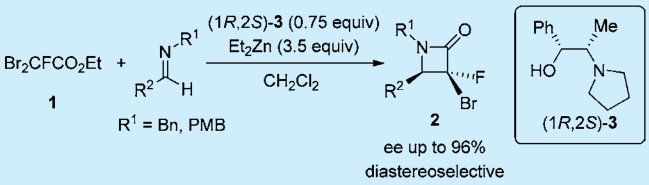
Supporting Information

ABSTRACT: An enantioselective Reformatsky reaction has been developed for the reaction of ethyl dibromofluoroacetate (**1**) with an imine. This method represents the first ligand-promoted imino-Reformatsky approach to use a halofluoroacetate. The use of an amino alcohol ligand allowed for the preparation of enantioenriched α-bromo-α-fluoro-β-lactams in good yields with enantioselectivities up to 96% ee. This process also provided access to β-lactam rings bearing two stereogenic centers.

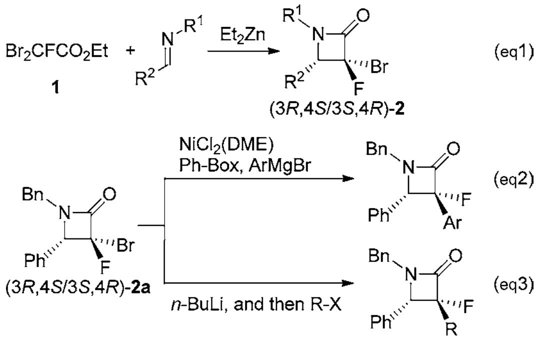


The incorporation of fluorine into an organic compound often leads to dramatic changes in the physical, chemical, and biological properties of the parent compound, and fluorine has been used in this way to alter the properties of compounds in the pharmaceutical, agrochemical, and material fields.[1] Although a broad range of methods have been reported for the regioselective introduction of fluorine substituents, asymmetric approaches toward highly enantioenriched fluorine compounds remain scarce.[2]

The Reformatsky reaction is a robust and reliable transformation for the formation of C−C bonds and has been used extensively for the synthesis of a wide range of different compounds,[3] such as bioactive natural products.[4] A variety of enantioselective approaches have been reported during the past decade for the Reformatsky reaction of α-halogenated esters (nonfluorinated), including imino-Reformatsky reactions, as well as reactions involving Schiff bases,[5] BINOL derivatives,[6] and amino alcohol ligands.[7−9] These Reformatsky reactions have been applied to the asymmetric synthesis of β-hydroxy-α,α-difluoroesters using bromodifluoroacetate but provided low levels of enantioselectivity.[10] Of the different reaction conditions available, good stereocontrol was achieved by Knochel et al.[10c] in their synthesis of β-hydroxy-α,α-difluoroesters, although this transformation did require the addition of a stoichiometric amount of a chiral amino alcohol ligand. More recently, high levels of enantioselectivity have been achieved through the reaction of ethyl iododifluoroacetate or ethyl iodofluoroacetate with ketones in the presence of a stoichiometric amount of chiral ligand.[11,12] Unfortunately, despite providing access to the desired products in high yields and high enantioselectivities, these approaches have been limited by the poor chemical stability of the iodoacetate reagents. Compared with carbonyl electrophiles, there have been no reports in the literature pertaining to the asymmetric imino-Reformatsky reaction of a fluorinated haloacetate with an imine in the presence of a chiral ligand.

Ethyl dibromofluoroacetate (**1**) has been used extensively as a reagent in the Reformatsky reaction, where it has been used to provide efficient access to a range of interesting compounds, including α-bromo-α-fluoro-β-hydroxyesters, α-bromo-α-fluoro-β-hydroxyamides, and α-bromo-α-fluoro-β-lactams **2**.[13−15] Furthermore, reagent **1** is useful as a research object due to the commercial availability and chemical stability. We recently reported the imino-Reformatsky reaction of **1** using diethylzinc to give racemic **2** (Scheme 1, eq 1).[15] The reaction featured the highly diastereoselective addition of the Reformatsky reagent, which was prepared from the reaction of **1** with diethylzinc, to a series of imine substrates. We also demonstrated that **2** could be functionalized at the α-carbon using a nickel-catalyzed cross-

Scheme 1. Imino-Reformatsky Reaction of Dibromofluoroacetate and the Application of the α-Bromo-α-fluoro-β-lactam to Further Reactions



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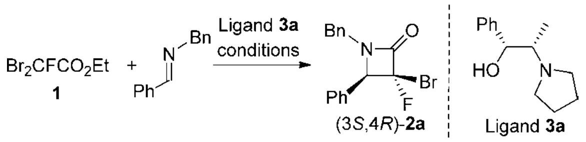
coupling reaction or lithiation chemistry (Scheme 1, eqs 2 and 3).[16] During the course of these experiments, we succeeded in achieving the enantioselective imino-Reformatsky reaction of **1** using a chiral amino alcohol catalyst to provide optically active **2** in good yield. Although there are already known reactions with a carbonyl substrate, this is the first example of the asymmetric reaction with an imine substrate. In this paper, we report the first enantioselective imino-Reformatsky reaction of **1** with a variety of different imines.

The imino-Reformatsky reaction was initially carried out in the presence of a stoichiometric amount of (1*R*,2*S*)-1-phenyl-2-(1-pyrrolidinyl)-propan-1-ol (**3a**) to determine whether this material would affect the asymmetric induction of the reaction (Table 1, entry 1). The reaction proceeded smoothly to afford the desired product **2a** in 78% yield and 15% ee. Encouraged by this result, we screened a variety of different reaction conditions to determine the optimal conditions for the transformation.[17] Solvent optimization experiments revealed that dichloromethane was the best solvent for this particular transformation. Lowering the reaction temperature to −40 °C led to considerable improvements in both the ee value and the chemical yield (Table 1, entry 2). Furthermore, decreasing the ligand loading of **3a** to 0.75 equiv led to a small improvement in the asymmetric induction (Table 1, entry 3). Moreover, another promoter was investigated toward the true catalytic system. In the reported catalytic asymmetric Reformatsky reactions, the combination of dimethyl zinc with air[6,7d,g,8b] or dimethyl zinc with Ni salts[7f,8a] has been used as a promoter. When dimethyl zinc, which is less reactive than diethyl zinc,[5a,b,6a,7d] and air were used as promoters, the desired product was not obtained and **1** was recovered from the reaction mixture (Table 1, entry 4). Ni salts were also not effective, recovering **1** as well as entry 4 (Table 1, entries 5 and 6). These reagents were not able to promote this reaction. In all cases, the product was obtained diastereoselectively as a single diastereomer with the 3*S*,4*R* configuration. This result was significantly different from those reported for the reaction of ethyl iodofluoroacetate with ketones, which showed no diastereoselectivity.[12] In contrast to our previous reports, no aziridine byproduct was obtained during the screening of reaction conditions.[15,18]

Table 1. Initial Investigation of Stereoselective Imino-Reformatsky Reaction of 1



entry	condition	ligand 3 (equiv)	solvent	temp (°C)	yield (%)[a]	ee (%)[b]
1	Et_2Zn	1.0	THF	0	78	15
2	Et_2Zn	1.0	CH_2Cl_2	−40	82	91
3	Et_2Zn	0.75	CH_2Cl_2	−40	83	92
4	Me_2Zn under air[c]	0.75	CH_2Cl_2	−40	0	
5	Me_2Zn with 8 mol % of $NiCl_2(PPh_3)$	0.75	CH_2Cl_2	−40	trace	
6	Me_2Zn with 10 mol % of $NiBr_2$	0.75	CH_2Cl_2	−40	0	

[a] Isolated yields. [b] Determined by HPLC. [c] Air was introduced in the reaction mixture through a $CaCl_2$ drying tube after the addition of Me_2Zn.

Having optimized the reaction solvent, temperature, and catalyst loading, we investigated a variety of different chiral ligands, as shown in Figure 1. The substitution pattern on the nitrogen atom affected the chemical yield of products in the cases of ligand **3b**−**d**. These ligands led to significant improvements in the enantioselectivity of imino-Reformatsky reaction with 84, 87, and 80% ee, respectively, although the chemical yields of these reactions were lower than that achieved with **3a**. The prolinol-based chiral ligands **3e** and **3f** also led to lower yield of the desired product, with **3f** providing a particularly low enantioselectivity. The similar tendency was observed in other amino alcohol ligands **3g** and **3h**. Introduction of a phenyl group next to the hydroxyl group was effective for the stereoselectivity of this reaction. The low yield of aziridine was obtained as a racemate in the screening of ligands except for **3a**.[19] Based on these results, most effective and easy available **3a** was selected as the optimal chiral ligand for the transformation in dichloromethane at −40 °C.

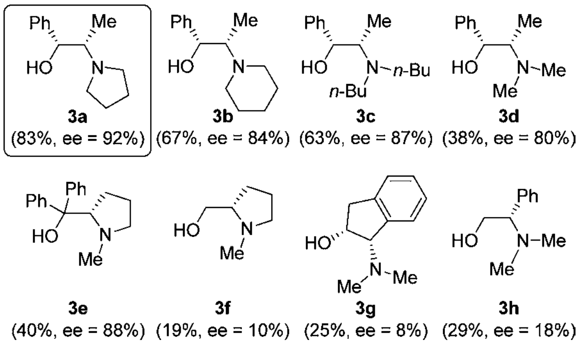
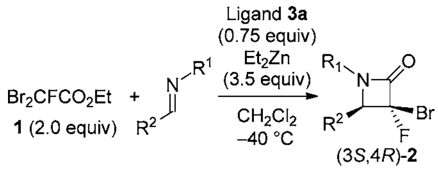


Figure 1. Screening of chiral amino alcohol ligand **3**.

With the optimal reaction conditions in hand, we explored the scope and limitations of this stereoselective imino-Reformatsky reaction using a variety of different imines. The results of these scoping experiments are summarized in Table 2. Although the chemical yields of the reactions were dependent on the electronic nature of the substituents on the aromatic ring, the enantiomeric purities of the products were high with the (3*S*,4*R*)-isomers being obtained enantioselectively in all cases. The reaction of aromatic imines bearing an electron-withdrawing group gave compounds **2d**−**i** with high enantioselectivity (Table 2, entries 4−9). The substitution pattern of the aromatic compounds did not have a discernible impact on the outcome of the reaction, with *ortho*-, *meta*-, and *para*-substituted imines providing similar levels of enantioselectivity. A relatively low yield of the product was obtained, however, in the case of *ortho*-substituted imine, likely because of steric hindrance from the *ortho* substituent (Table 2, entry 7). Electron-donating substituents such as Me and MeO had an adverse impact on the reaction, with the corresponding products **2j** and **2k** being formed in moderate yields (Table 2, entries 10 and 11). The poor performance of these substrates was attributed to the weakening of the electrophilicity of the imines as a consequence of the electron-donating groups. It is noteworthy that the ee values of the products could be increased to be almost enantiopure form by the recrystallization of the solid products. We also conducted the reaction on a larger scale, using up to 1.95 g of the imine to afford **2a** in 71% yield and 92% ee after recrystallization (Table 2, entry 12). The opposite enantiomer of the ligand could also be used under the

Table 2. Scope and Limitations of the Enantioselective Imino-Reformatsky Reaction of 1



entry	R^1	R^2	product	time (h)	yield (%)[a]	ee (%)[b]	
1	Bn	Ph	**2a**	1	83	92	(94)[c]
2	PMB[d]	Ph	**2b**	2	78	91	
3	Bn	2-naphthyl	**2c**	3	79	93	
4	Bn	4-CF$_3$-C$_6$H$_4$	**2d**	2	76	96	(>99)[c]
5	Bn	4-Cl-C$_6$H$_4$	**2e**	2	82	93	(98)[c]
6	Bn	3-Cl-C$_6$H$_4$	**2f**	2	90	95	
7	Bn	2-Cl-C$_6$H$_4$	**2g**	20	55	91	(>99)[c]
8	Bn	4-MeOCO-C$_6$H$_4$	**2h**	2	90	96	(>99)[c]
9	Bn	4-CN-C$_6$H$_4$	**2i**	2	89	91	(>99)[c]
10	Bn	4-Me-C$_6$H$_4$	**2j**	14	64	91	(>99)[c]
11[e]	Bn	4-MeO-C$_6$H$_4$	**2k**	6	53	85	
12	Bn	Ph	**2a**	4	71[f]	92[f]	
13[g]	Bn	Ph	**2a**	1	70	−90	

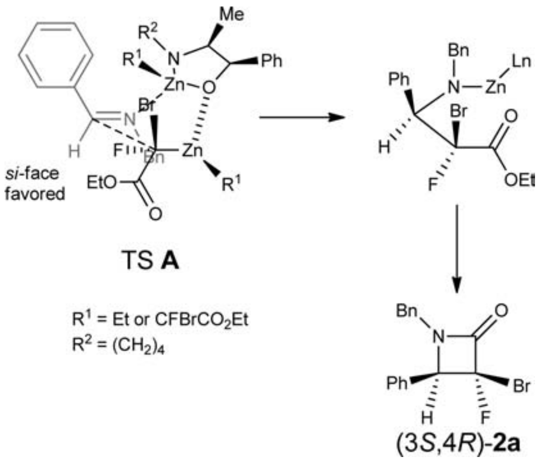
[a] Isolated yields. [b] Determined by HPLC. [c] The values in parentheses indicate the ee after recrystallization of the products. [d] *p*-Methoxybenzyl. [e] Ligand **3a** (1.0 equiv) was used. [f] The yield and ee were obtained after a recrystallization step. [g] (1*S*,2*R*)-Ligand was used instead of (1*R*,2*S*)-ligand.

optimized conditions to give the (3*R*,4*S*) product **2a** in 70% yield and 90% ee (Table 2, entry 13). Unfortunately, the reaction of **1** with aliphatic imine gave the complex mixture, and the desired product was not detected from the crude reaction mixture in the ^{19}F NMR spectrum. The absolute configuration of **2h** was determined by X-ray analysis to be the 3*S*,4*R* configuration. The stereochemistries of the other products were assumed to be the same based on a comparison of the order of their elution by chiral HPLC analysis, the sign of their optical rotation, and their NMR spectra.

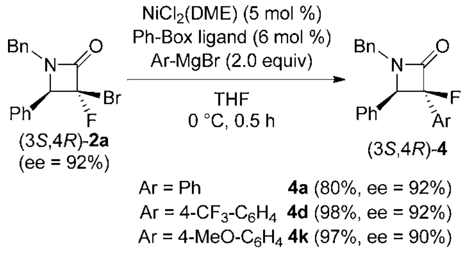
Although the precise mechanism of this reaction remains unclear, we have proposed a possible catalytic cycle based on the absolute configuration products **2**. The stereoselectivity of this Reformatsky reaction can be explained using Noyori's representative transition model (Scheme 2).[20] The transition state was also applied to the reaction of alkylzinc and aldehyde using *N*,*N*-dialkylnorephedrines as chiral catalyst.[21] Transition model **A** could be used to explain the outcome of the reaction based on the formation of a coordination network involving the imine nitrogen, zinc ion, ligand, and Reformatsky reagent, which would allow for the successful formation of multiple chiral inductions. Transition model **A** would therefore provide the correct product with the desired stereochemistry, which would be the opposite to that formed from ethyl iododifluoroacetate[11] and ethyl iodoacetate.[6,7a−e]

To demonstrate the utility of the chiral *α*-bromo-*α*-fluoro-*β*-lactam **2**, chiral product **2** was applied to a recently reported Ni-catalyzed cross-coupling reaction.[16a] Treatment of (3*S*,4*R*)-**2a** with aryl Grignard reagents in the presence of NiCl$_2$(DME) and the Ph-Box ligand afforded the corresponding *α*-arylated coupling products **4a**, **4d**, and **4k** diastereoselectively without any reduction in their enantiopurities (Scheme 3). Diastereoselective insertion of the aryl groups was also observed in all of the other cases tested, with the (3*S*,4*R*)-isomers being formed as sole products in excellent yields.

Scheme 2. Proposed Stereochemical Model



Scheme 3. Synthetic Utility of Product 2a



In summary, we have developed an enantioselective imino-Reformatsky reaction of ethyl dibromofluoroacetate (**1**) using a substoichiometric amount of (1*R*,2*S*)-1-phenyl-2-(1-pyrrolidinyl)-propan-1-ol (**3a**) as a chiral ligand. The imino-Reformatsky reaction of **1** proceeded enantioselectively to give **2** with the 3*S*,4*R* configuration in good yields, allowing for the construction of multiple stereogenic centers in a single step. Furthermore, compound **2** was successfully functionalized to give a diverse range of *α*-aryl-*α*-fluoro-*β*-lactams without any reduction in the optical purity. Efforts to further expand the scope of this reaction and elucidate the mechanism are currently underway.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and spectroscopic data of products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(17) Solvents, reaction temperature, and the amounts of chiral ligand were examined. See Supporting Information.

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