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# Synthesis of α,α-difluoro-β-amino amides using aldimines and bromodifluoroacetamides *via* the Reformatsky reaction†

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α,α-Difluoro-β-amino amides are attractive building blocks of biologically active compounds such as fluorinated pharmaceutical mimics and oligopeptides. Herein, we describe the zinc-promoted Reformatsky reaction of aldimines using bromodifluoroacetamides which provides a direct synthetic approach to α,α-difluoro-β-amino amides. This method gave various *N*-PMP protected α,α-difluoro-β-amino-β-aryl amides in 64–95% yields. Furthermore, these amides were efficiently converted into 2,2-difluoropropane-1,3-diamines under reductive conditions using a combination of $NaBH_4$ and $BF_3$.

## Introduction

Fluorine atoms are nearly the same size as hydrogen atoms and are often used as isosteres of hydrogen in medicinal chemistry.[1] For example, C–F bond containing molecules are less likely to undergo oxidative metabolism than fluorine-free molecules, and in some cases exhibit superior metabolic stability.[2] Since β-amino amides are attractive scaffolds for various bioactive molecules such as andrimid, sitagliptin and L-carnosine,[3] fluorinated β-amino amides such as α,α-difluoro-β-amino amides are also expected to be a scaffold that can be used to design novel biologically active compounds.[4] As fluorinated analogues of natural products and pharmaceuticals with a β-amino amide moiety, antifungal tetrapeptides, renin inhibitory peptides and selective TAF1(2) bromodomain inhibitors have already been reported (Fig. 1).[5]

In general, α,α-difluoro-β-amino amides have been synthesized by a condensation reaction between an amine and α,α-difluoro-β-amino acids (Fig. 2a)[6] or α,α-difluoro-β-lactams (Fig. 2b),[7] but their synthesis requires several steps from readily available substrates such as imines and halodifluoroacetic acid esters. In recent years, the Mannich-type reaction of imines using α,α-difluoro-α-trimethylsilylacetoamide (Fig. 2c),[8] the three-component reaction of (bromodifluoromethyl)trimethylsilane, imines, and isocyanides (Fig. 2d),[9] and the Reformatsky-type reaction of amides and bromodifluoroacetamides using an iridium catalyst (Fig. 2e)[10] have been developed as direct synthesis methods for α,α-difluoro-β-amino amides. Herein, we report the zinc-promoted Reformatsky reaction of bromodifluoroacetamides with aldimines as a simpler synthetic method to directly access α,α-difluoro-β-amino amides (Fig. 2f).

## Results and discussion

At first, we examined and optimized a zinc-mediated Reformatsky reaction of *N*-(4-methoxybenzylidene)aniline **1a** and bromodifluoroacetamide **2a** (Table 1). The reaction was carried out using 0.8 equivalents of trimethylsilyl chloride[11] as an activator of zinc powder in THF to give α,α-difluoro-β-amino amide **3a** in 95% yield (entry 1). The yield decreased to 86% on reducing the amount of trimethylsilyl chloride to 0.4 equivalents, and the yield decreased drastically to 44% in the absence of trimethylsilyl chloride (entries 2 and 3). The use of

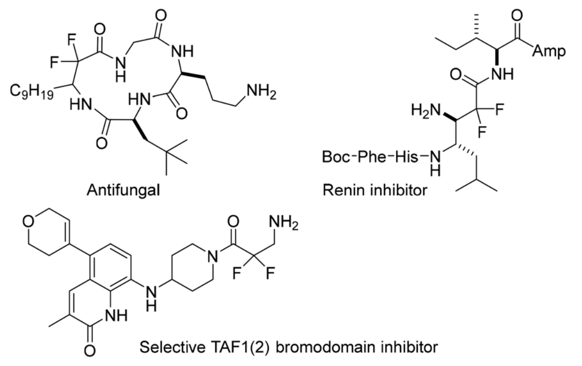

**Fig. 1** Examples of biologically active α,α-difluoro-β-amino amides.

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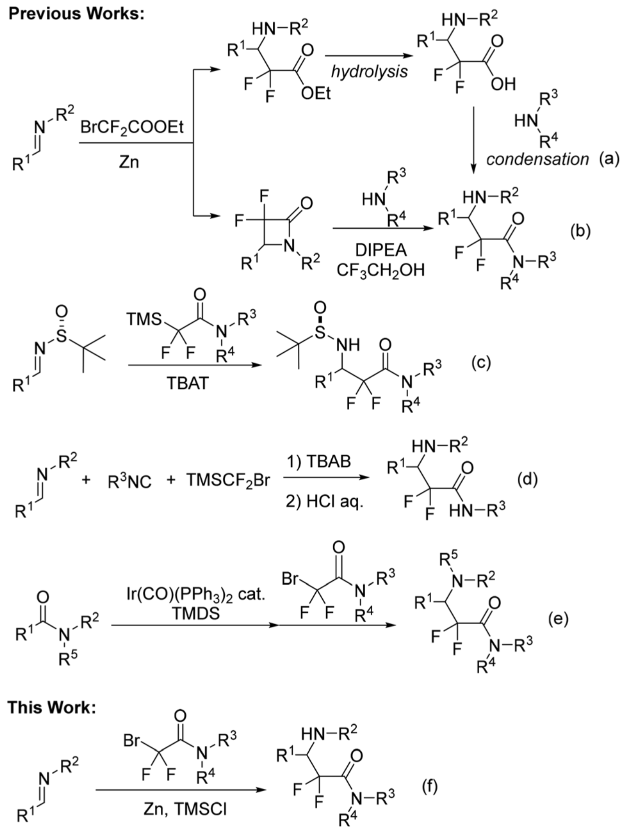
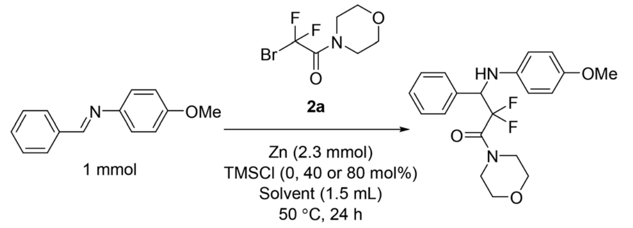


**Fig. 2** Previous methods and our approach for the synthesis of α,α-difluoro-β-amino amides.

**Table 1** Optimization of reaction conditions for the Reformatsky reaction with *N*-(4-methoxybenzylidene)aniline **1a** and bromodifluoroacetamide **2a**



**1a** **2a** **3a**

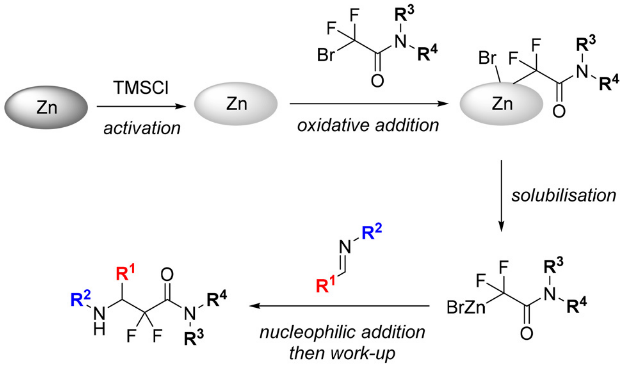
| Entry | TMSCl (mol%) | Solvent | Yield (%) |
|---|---|---|---|
| 1 | 80 | THF | 95[a] |
| 2 | 40 | THF | 86[a] |
| 3 | 0 | THF | 44[b] |
| 4 | 80 | 2-Me-THF | 63[a] |
| 5 | 80 | 1,4-Dioxane | 38[b] |
| 6 | 80 | Acetonitrile | 16[b] |
| 7 | 80 | DMF | 8[b] |
| 8 | 80 | DMSO | 45[b] |
| 9 | 80 | Toluene | 11[b] |
| 10 | 80 | Hexane | 13[b] |

[a] Isolated yield. [b] Determined by $^1$H NMR using triphenylmethane as an internal standard.

other ether solvents such as 2-Me-THF and 1,4-dioxane reduced the yields to 63% and 38% respectively (entries 4 and 5). DMSO promoted the reaction moderately, but other highly polar solvents such as acetonitrile and DMF were not suitable for the reaction (entries 6–8). Less polar solvents such as toluene and hexane were also ineffective in this reaction (entries 9 and 10).

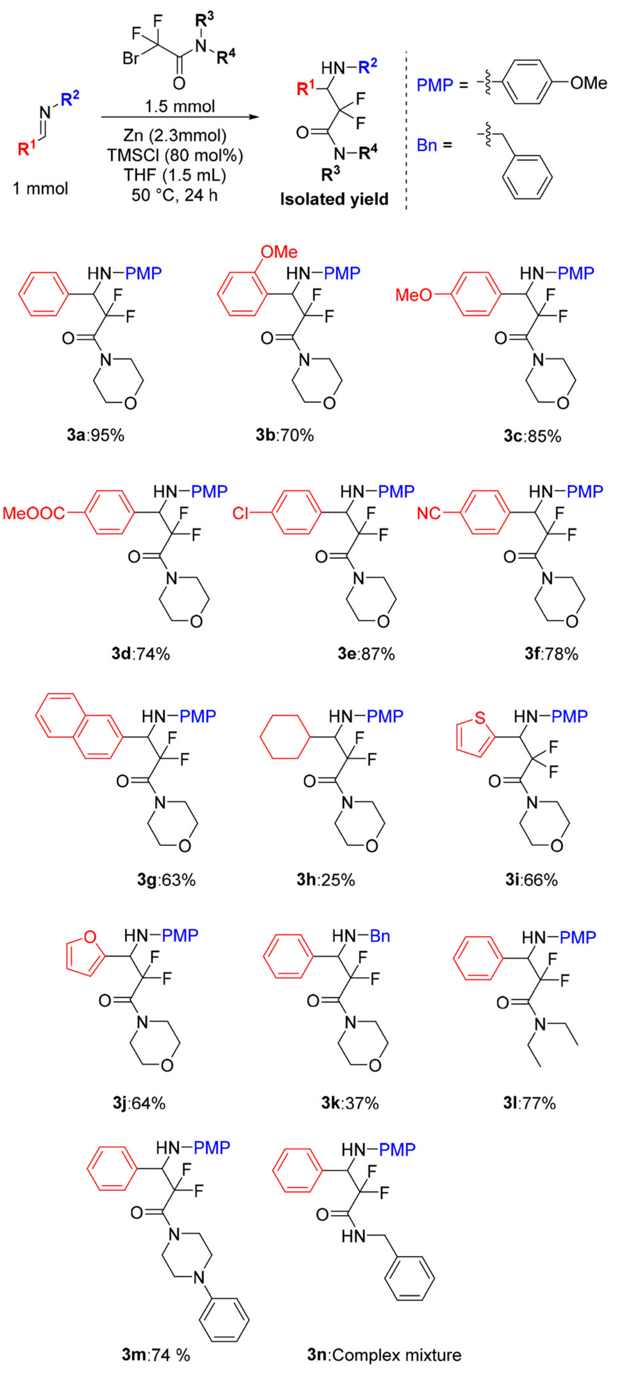
Recently, Blum reported that trimethylsilyl chloride aids to solubilise organozinc intermediates from zinc(0) metal after oxidative addition, and that this solubilisation can be sufficiently maintained with a catalytic amount of trimethylsilyl chloride.[12] Based on Blum's report, we propose a plausible mechanism for this type of imino-Reformatsky reaction in Scheme 1. As trimethylsilyl chloride facilitates the oxidative addition of bromodifluoroacetamide to zinc(0) and the solubilisation of zinc enolates on the metal zinc surface, the nucleophilic addition of enolates to imines proceeded smoothly.

Under the optimized conditions, we synthesized various functionalized α,α-difluoro-β-amino amides **3** and clarified the scope and limitations of aldimines **1** and bromodifluoroacetamides **2** (Table 2). Benzaldimines bearing sterically hindered *o*-methoxyphenyl and 2-naphthyl groups were converted into the corresponding aminoamides **3b** and **3g** in moderate yields of 70% and 63%, respectively. The substituents at the positions distant from the imino group of benzaldimines did not have a significant effect on the reaction, whether they were electron-donating groups such as the *p*-methoxy group or electron-withdrawing groups such as *p*-methoxycarbonyl, *p*-chloro and *p*-cyano groups, and the desired aminoamides **3c–f** were obtained in high yields. An aliphatic imine such as 1-cyclohexyl-*N*-(4-methoxyphenyl)methanimine was not suitable for this reaction, and the product **3h** was afforded in only 25% yield. Other aliphatic aldimines derived from acetaldehyde and pivalaldehyde were difficult to purify and handle, so we were unable to use them in this reaction. Heteroaryl imines from 2-thiophenecarboxaldehyde or furfural reacted smoothly and afforded the desired products **3i** and **3j** in good yields. Replacing the PMP group of aldimine **1a** with a benzyl group dramatically reduced its reactivity and the corresponding amine **3k** was obtained in a poor yield. The tertiary amides



**Scheme 1** Plausible mechanism of the imino-Reformatsky reaction.

**Table 2** Scope and limitations of the zinc-mediated Reformatsky reaction with aldimines **1** and bromodifluoroacetamides **2**



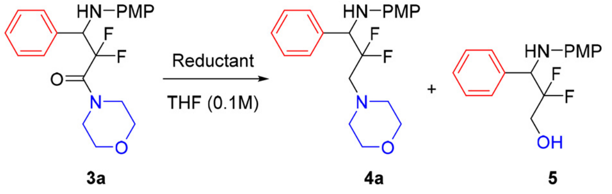
gave the desired products **3l** and **3m** regardless of whether the alkyl group on the nitrogen had a linear or cyclic structure, but when a secondary amide was used as the substrate, a complex mixture **3n** was obtained.

In general, amide groups can be easily converted into aminomethylene groups using hydride reducing agents such as $LiAlH_4$, $BH_3$ and others.[13] Hence, one application of fluorinated β-amino amides would be their conversion into fluorinated 1,3-diamines, which are used as building blocks for a wide range of biologically active compounds such as antisense agents,[14] selective TAF1(2) bromodomain inhibitors,[5c] and adenosine monophosphate-activated kinase activators.[15]

Table 3 shows the results of the reduction of α,α-difluoro-β-amino amide **3a** using conventional hydride reagents. As reported by Leclerc,[8] the use of $NaBH_4$ resulted in negligible formation of 1,3-diamine **4a** and gave γ-amino alcohol **5** in a moderate yield (entry 1). $LiAlH_4$ is a typical reductant for amides, but like $NaBH_4$ it gave γ-amino alcohol **5** instead of 1,3-diamine **4a** (entry 2). Staas *et al.* reported that $BH_3{\cdot}Me_2S$ was effective in the reduction of α,α-difluoro-β-amino amides, but under their conditions, the reaction time was long and the yield was moderate.[6b] $BH_3{\cdot}Me_2S$ was suitable for the reduction of amides, but it also produced γ-amino alcohol **5** along with 1,3-diamine **4a** (entry 3). Interestingly, when $BH_3$ produced by the combination of $NaBH_4$ and $BF_3{\cdot}Et_2O$ was used for the reduction,[16] the yield of **4a** was improved to 69%, and the by-product γ-amino alcohol **5** was suppressed (entry 4). Furthermore, when the reaction using $NaBH_4/BF_3$ was carried out for 1 hour at room temperature and then for 2 hours at 75 °C, the yield increased to 94% (entry 5). The yields of the reduction gradually decreased as the equivalent amount of $NaBH_4$ was reduced (entries 6 and 7).

Next, we demonstrated the applicability of the $NaBH_4/BF_3$ reduction system for several α,α-difluoro-β-amino amides **3** (Table 4). Amide **3d** with a methoxycarbonyl group, which is readily reduced by $BH_3$, gave the corresponding amine **4b** in a yield of 63% when reacted at room temperature. Additionally, a complex mixture of by-products was also formed under these conditions. The reduction of amides containing chlorine or heteroaromatic rings, such as thiophene and furan, proceeded smoothly and the desired amines **4c–e** were obtained in excel-

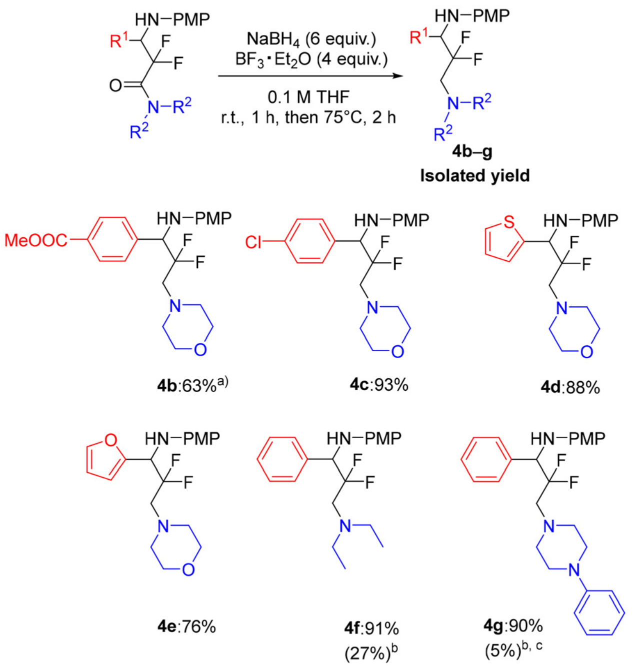
**Table 3** Optimization of reduction with α,α-difluoro-β-amino amide **3a**



| Entry | Reductant (equiv.) | Reaction temp. and time | 4a[a] (%) | 5[a] (%) |
|---|---|---|---|---|
| 1 | $NaBH_4$ (6) | r.t., 2 h | Trace[b] | 49 |
| 2 | $LiAlH_4$ (6) | r.t., 2 h | Trace[b] | 47 |
| 3 | $BH_3{\cdot}Me_2S$ (6) | r.t., 2 h | 51 | 16 |
| 4 | $NaBH_4$ (6) and $BF_3{\cdot}Et_2O$ (4) | r.t., 2 h | 69 | Trace[b] |
| 5 | $NaBH_4$ (6) and $BF_3{\cdot}Et_2O$ (4) | r.t., 1 h, then 75 °C, 2 h | 94 | Trace[b] |
| 6 | $NaBH_4$ (4) and $BF_3{\cdot}Et_2O$ (4) | r.t., 1 h, then 75 °C, 2 h | 91 | Trace[b] |
| 7 | $NaBH_4$ (2) and $BF_3{\cdot}Et_2O$ (2) | r.t., 1 h, then 75 °C, 2 h | 83 | Trace[b] |

[a] Isolated yield. [b] Determined by $^{19}F$ NMR of a crude mixture.

**Table 4** Reduction of α,α-difluoro-β-amino amides **3** using $NaBH_4/BF_3$



[a] The reaction was carried out at r.t. for 2 h. [b] $LiAlH_4$ was used instead of $NaBH_4/BF_3{\cdot}Et_2O$. [c] The yield was determined by $^{19}F$ NMR using benzotrifluoride as an internal standard.

lent yields. Even when the morpholine moiety of the amide was replaced with diethylamine or 1-phenylpiperazine, the amines **4f** and **4g** were still provided in satisfactory yields of 91% and 90%, respectively. The reduction of amides **3l** and **3m** with $LiAlH_4$ instead of $NaBH_4/BF_3$ gave a complex mixture containing unidentified products and the corresponding 1,3-diamines **4f** and **4g** were obtained in low yields. In addition, γ-amino alcohol **5** was not detected in either of these crude products by $^{19}F$ NMR.

## Conclusions

In conclusion, we have achieved a one-step synthesis of α,α-difluoro-β-amino amides from aldimines and bromodifluoroacetamides *via* the Reformatsky reaction using zinc and trimethylsilyl chloride as a zinc activator under mild conditions. The α,α-difluoro-β-amino amides were converted into 2,2-difluoropropane-1,3-diamines with high selectivity and excellent yields using the combination of $NaBH_4$ and $BF_3$ as reducing agents.

## Author contributions

T. Y. conceived and directed the project. R. O. performed the experiments and prepared the ESI.† T. Y. and R. O. wrote the manuscript, discussed the results, and commented on the manuscript.

## Data availability

The data supporting this article have been included in the ESI.†

## Conflicts of interest

There are no conflicts to declare.

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