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# A Cu-BOX catalysed enantioselective Mukaiyama-aldol reaction with difluorinated silyl enol ethers and acylpyridine *N*-oxides†‡

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A Cu(II)/BOX complex catalyses the enantioselective addition of difluorinated silyl enol ethers to acylpyridine *N*-oxides. The reaction provides difluorinated chiral tertiary alcohols of great interest in medicinal chemistry. These compounds are obtained in moderate to excellent yields and with high enantioselectivities. The stereochemical outcome of the reaction has been explained by DFT calculations.

## Introduction

The introduction of fluoroalkyl substituents in organic molecules has an important effect on their physical and chemical properties, including those relevant to biomedical applications such as biodisponibility and metabolic stability.[1] The importance of these properties in pharmacological and agrochemical applications has inspired the organic chemistry community during the last few decades and a huge effort has been dedicated to the development of synthetic methods for organofluorine compounds,[2] even in an enantioselective fashion.[3] From the synthetic point of view, the synthesis of carbonyl compounds decorated with fluoroalkyl substituents is especially appealing, as they allow for further modification in virtually every functional group. Specifically, the synthesis of difluorinated carbonyl compounds has attracted attention due to the oxygen bioisosteric properties of the $-CF_2-$ group[4] and the biological activity of some of these compounds (Fig. 1).[5] α,α-Difluorocarbonyl compounds can also serve as versatile building blocks for the synthesis of other fluorinated moieties.[6] On the other hand, the difluoromethylene group attached to a stereogenic centre can be found as a structural motif in drugs and bioactive compounds (Fig. 1).[7] However, the enantioselective synthesis of chiral compounds bearing such a structural motif is not a trivial task as the presence of the fluorine atoms may alter the reactivity of the involved functional groups or the interaction of the substrates with the chiral catalyst, hampering the enantiomeric control.[8] Thus, while the electronegativity of fluorinated substituents has facilitated their use as electrophilic starting materials,[9] the enantioselective introduction of fluorine-containing scaffolds as nucleophiles is a more challenging task that requires the use of special reagents.[10]

In this context, the employment of difluoroenoxysilanes[11] as nucleophiles has been demonstrated to be an efficient tool for the synthesis of difluoromethyl-containing compounds. However, the number of examples involving the nucleophilic addition of difluoroenoxysilanes in an enantioselective fashion is scarce and almost limited to nucleophilic addition to

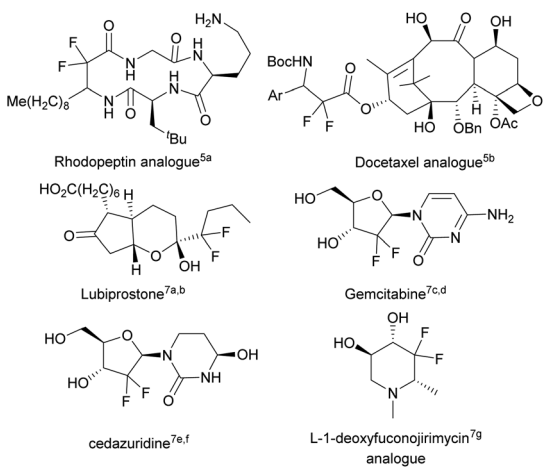


**Fig. 1** Some examples of bioactive compounds bearing an α,α-difluorocarbonyl moiety or a $CF_2$ attached to a stereogenic centre.

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†Dedicated to Professor Joan Bosch, Universitat de Barcelona, on the occasion of his 75th birthday.

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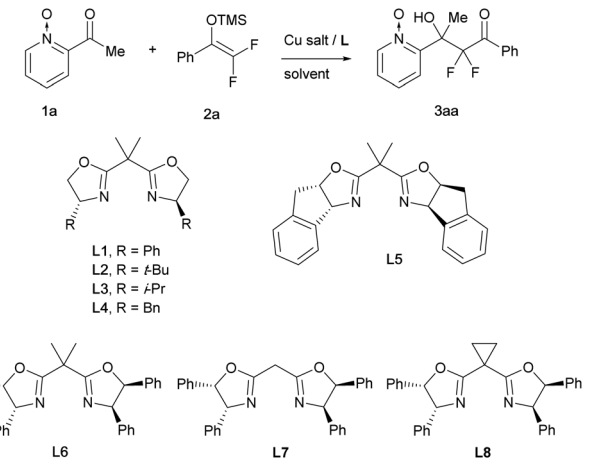
imines,[12,13] while the Mukaiyama aldol-type reaction[14] remains almost unexplored and only two organocatalytic examples involving reactive α-keto esters[15] or isatins[16] have been reported by Zhou, to the best of our knowledge (Scheme 1).

2-Acylpyridine *N*-oxides are interesting substrates for asymmetric catalysis. Their capacity to form a chelate with a chiral metal complex makes them ideal electrophilic substrates for stereoselective transformations, providing pyridine derivatives with chiral pendants. Taking advantage of these properties, these compounds have been widely used in enantioselective transformations. Jørgensen and co-workers described in 2006 the Cu-BOX catalysed addition of ketene silyl–enol ethers to the *N*-oxides of formylpyridine.[17] Since then, a variety of transformations have been reported with these substrates by our group[18] and others,[19] giving access to enantioenriched compounds containing a widely spread pyridine moiety. Herein, we report our results on the copper-catalysed Mukaiyama aldol reaction of difluoroenoxysilanes and 2-acylpyridine *N*-oxides (Scheme 1c).

## Results and discussion

### Optimisation of the reaction conditions

At the onset of our investigation, we chose 2-acetylpyridine *N*-oxide (**1a**) and difluoroenoxysilane **2a** as reaction partners for the optimization process. Taking into account the precedent reported by our research group,[18] we envisioned that Cu(II)/BOX could serve as an effective catalytic system. Therefore, we screened a series of BOX chiral ligands with different substitution patterns, using $Cu(OTf)_2$ as the metal source (Scheme 2 and Table 1). Despite the modest reactivity of the system, promising levels of enantioinduction were obtained with **L8** (Table 1, entry 8). Further optimization of the copper(II) source revealed an improvement in enantioselectivity when $Cu(BF_4)_2$ was used, albeit still with modest reactivity (Table 1, entry 10). An increase in the equivalents of nucleophile **2a** led to the expected improvement in yield, although with a moderate decrease in the enantioselectivity (Table 1, entry 11).§ We next studied the effect of the solvent, observing a further improvement in yield when using THF, keeping the good levels of enantioselectivity (Table 1, entry 14). Finally, we performed the reaction at different temperatures. The reaction virtually shuts down at −20 °C, while an increase to 50 °C has a detrimental effect on the enantioinduction (Table 1, entries 16 and 17). Therefore, we established BOX ligand **L8** in combination with $Cu(BF_4)_2$ to be our optimal catalytic system, while

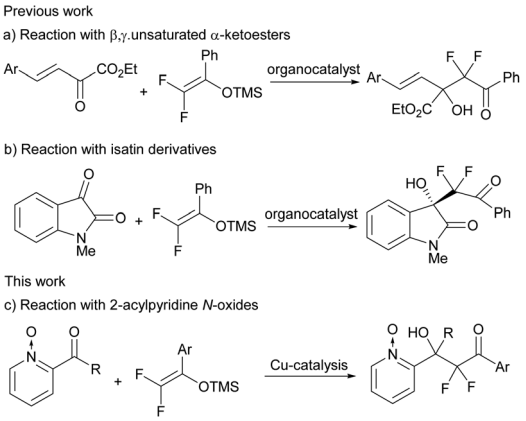



**Scheme 2** Enantioselective reaction between **1a** and **2a** and BOX ligands used in this study.

**Table 1** Copper-catalysed enantioselective reaction of **1a** and **2a**. Optimization of the reaction conditions[a]

| Entry | Cu salt | L | Solvent | Yield[b] (%) | ee[c] (%) |
|---|---|---|---|---|---|
| 1[d] | $Cu(OTf)_2$ | **L1** | $CH_2Cl_2$ | 37 | −15 |
| 2[d] | $Cu(OTf)_2$ | **L2** | $CH_2Cl_2$ | 43 | 48 |
| 3[d] | $Cu(OTf)_2$ | **L3** | $CH_2Cl_2$ | 40 | 10 |
| 4[d] | $Cu(OTf)_2$ | **L4** | $CH_2Cl_2$ | 27 | 55 |
| 5[d] | $Cu(OTf)_2$ | **L5** | $CH_2Cl_2$ | 24 | 41 |
| 6[d] | $Cu(OTf)_2$ | **L6** | $CH_2Cl_2$ | 42 | 67 |
| 7[d] | $Cu(OTf)_2$ | **L7** | $CH_2Cl_2$ | 20 | 0 |
| 8[d] | $Cu(OTf)_2$ | **L8** | $CH_2Cl_2$ | 32 | 83 |
| 9[d] | $CuBr_2$ | **L8** | $CH_2Cl_2$ | 30 | 81 |
| 10[d] | $Cu(BF_4)_2$ | **L8** | $CH_2Cl_2$ | 24 | 91 |
| 11[e] | $Cu(BF_4)_2$ | **L8** | $CH_2Cl_2$ | 70 | 85 |
| 12[e] | $Cu(BF_4)_2$ | **L8** | DCE | 38 | 80 |
| 13[e] | $Cu(BF_4)_2$ | **L8** | $CHCl_3$ | 48 | 84 |
| 14[e] | $Cu(BF_4)_2$ | **L8** | THF | 90 | 87 |
| 15[e] | $Cu(BF_4)_2$ | **L8** | Toluene | 42 | 66 |
| 16[e,f] | $Cu(BF_4)_2$ | **L8** | THF | 9 | — |
| 17[e,g] | $Cu(BF_4)_2$ | **L8** | THF | 87 | 73 |

[a] **1a** (0.1 mmol), **2a** (0.12 or 0.5 mmol), Cu salt (0.01 mmol), **L** (0.01 mmol), room temperature, **4d**. [b] Isolated yields. [c] Determined by chiral HPLC analysis. [d] **2a** (0.12 mmol. [e] **2a** (0. 5 mmol). [f] Reaction performed at −20 °C. [g] Reaction performed at 50 °C.




**Scheme 1** Enantioselective Mukaiyama aldol reaction with difluoroenoxysilanes.

§ The use of 2 equivalents of **2a** led to just a modest increase of yield (35%). On the other hand, the triethylsilyl protected difluoroenoxysilane (TES instead of TMS) was not reactive.

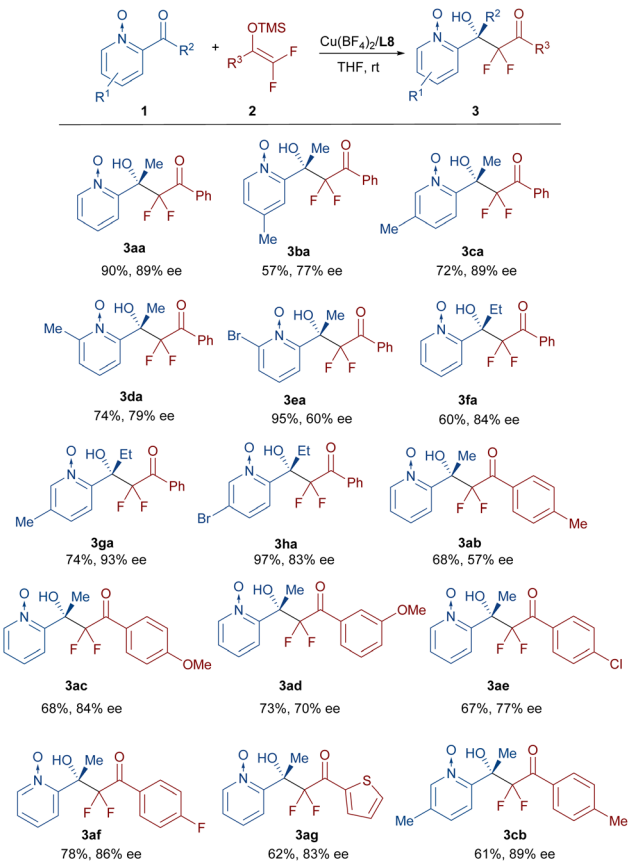
performing the reaction in THF as the solvent at room temperature.

## Study of the reaction scope

With the optimized reaction conditions in hand (Table 1, entry 14), we explored the scope of our methodology by reacting enol ether **2a** with different 2-acylpyridine *N*-oxides **1** (Scheme 3). Alkyl substituents are well tolerated at different positions of the pyridine ring of **1**. Substrate **1b**, bearing a methyl group at position 4 ($R^1$ = 4-Me), delivered the desired product **3ba** in fair yield and enantioselectivity (57%, 77% ee). Better results were obtained when using substrate **3c** substituted at position 5 ($R^1$ = 5-Me) that provided **3ca** in 72% yield and 89% ee. Interestingly, *N*-oxides **1d** ($R^1$ = 6-Me) and **1e** ($R^1$ = 6-Br), which have potentially problematic substituents at position 6 of the pyridine ring near the *N*-oxide coordination site, reacted satisfactorily to provide **3da** and **3ea** in high yields and still remarkable enantioselectivities (79% and 60% ee, respectively). At this point, we explored other ketones **1f–h** bearing a larger ethyl group attached to the carbonyl group. These reacted with **2a** to give compounds **3fa**, **3ga** and **3ha** in good yields and with high enantioselectivities (84%, 93% and 83% ee, respectively).

Next, the substitution in the difluorosilyl enol ether moiety was evaluated, albeit with diverse success. Unexpectedly, switching from phenyl to the 4-methylphenyl substituent in **2b** had a detrimental effect on enantioinduction (**3ab**, 68% yield, 57% ee). Interestingly, the excellent selectivity was re-established when **2b** was reacted with **1c**, which afforded compound **3cb** in moderate yield but with excellent enantioselectivity (61%, 89% ee). Moreover, phenyl rings substituted at different positions with electron-donating groups **2c** ($R^3$ = 4-$MeOC_6H_4$), **2d** ($R^3$ = 3-$MeOC_6H_4$), or halogens **2e** ($R^3$ = 4-$ClC_6H_4$) and **2f** ($R^3$ = 4-$FC_6H_4$) were tolerated, giving the expected products **3ac–3af** with fair to good enantiomeric excesses. Finally, enol ether **2g** bearing a heterocyclic ring ($R^3$ = 2-thienyl) could be employed, yielding aldol **3ag** in moderate yield and good enantiomeric excess (83%). Unfortunately, difluoroenoxysilanes **2** bearing an alkyl $R^3$ group (Bn) did not react under the optimised conditions.

At this point, we performed a control experiment to establish the importance of the *N*-oxide moiety in our method. Upon subjecting 2-acetylpyridine (**4**) to the optimized reaction conditions with **2a**, the corresponding aldol was obtained in less than 10% yield (Scheme 4). This result showcases the importance of the *N*-oxide scaffold, especially in order to achieve the required coordination of the electrophilic reaction partner with the metal catalyst. Reduction of the *N*-oxide functional group was achieved by Pd-catalysed hydrogenolysis with concomitant ketone reduction, affording **6aa** without a noticeable erosion of enantiomeric excess. On the other hand, treatment of compound **3ac** with *m*-CPBA yielded the corresponding Baeyer–Villiger product **7ac** regioselectively. Noticeably, the Baeyer–Villiger reaction did not proceed with compound **3aa** and required an electron-richer substituent attached to the carbonyl group. Finally, addition of MeMgBr to the ketone in **3ha** allowed us to obtain the corresponding tertiary alcohol **8ha** in good yield and with modest diastereoselectivity.



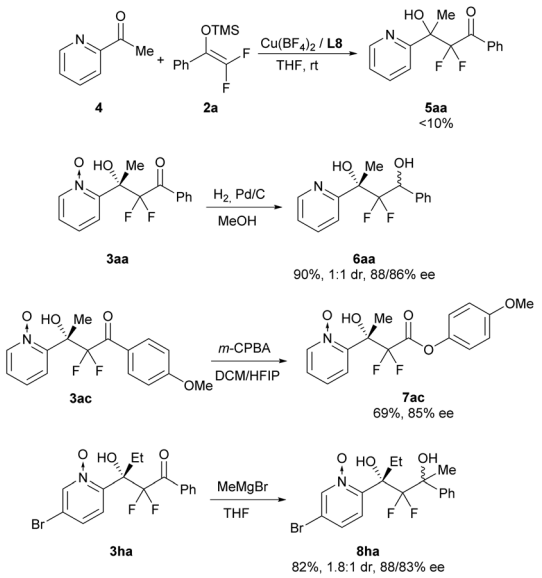

**Scheme 3** Enantioselective Mukaiyama-aldol reaction of acylpyridine *N*-oxides **1** and difluoroenoxysilanes **2**. Reaction conditions: **1** (0.2 mmol), **2** (1 mmol), $Cu(BF_4)_2$ (0.02 mmol), **L8** (0.02 mmol), THF (2 mL), room temperature, 4 days. Isolated yields. Ee determined by chiral HPLC analysis.

## Computational studies

Compound **3ag** could be crystallized and subjected to X-ray analysis that allowed us to determine the configuration of the stereogenic centre to be *S* (Fig. 2).¶

The stereochemistry of all compounds **3** was assigned by analogy, assuming a common stereochemical pathway. The observed stereochemistry indicates a preferential attack of the silyl enol ether to the *Re* face of the carbonyl group. To explain this stereochemical outcome, DFT calculations were performed with the UB3LYP-D3 functional,[20] as implemented in Gaussian 09,[21] with **1a** and **2a** as model substrates (Fig. 3). Geometries were optimized using the 6-31G(d,p) basis set for H, C, N, O, F, and Si, while the LANL2DZ pseudopotential was employed for Cu.[22] Based on these geometries, single-point

¶CCDC 2190657 contains the supplementary crystallographic data for compound **3ag**.




**Scheme 4** Control experiments and synthetic transformations of compounds **3**.

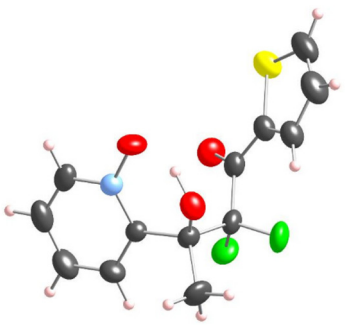


**Fig. 2** ORTEP plot for the X-ray structure of compound **3ag** with thermal ellipsoids drawn at the 50% probability level. Flack parameter 0.01(3).

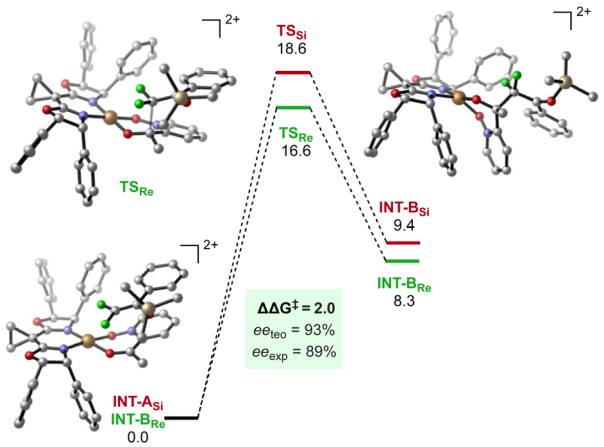



**Fig. 3** DFT calculations for the enantioinduction step. Free energy values are at the ωB97XD/LANL2TZ(Cu)/6-311+G(d,p)//UB3LYP-D3 (SMD-tetrahydrofurane)/LANL2DZ (Cu)/6-31G(d,p) level of theory. Hydrogens omitted for clarity.

calculations were performed using functional ωB97XD at the 6-311+G(d,p) level of theory for H, C, N, O, F, and Si and LANL2TZ for Cu.[23] As expected, our studies showed that distorted square-planar complexes, with **1a** chelating the copper centre with both oxygens, are energetically favoured. Subsequent nucleophilic attack of the silyl enol ether **2a** is sterically controlled by the position of the phenyl rings in the ligand, which blocks more efficiently the attack from the *Si*-face by interaction with the fluorine atoms in **2a**. The *Re*-face approach (TS-*Re*) presents a barrier of 16.6 kcal $mol^{-1}$, while the one leading to the attack from the *Si* face goes up to 18.6 kcal $mol^{-1}$. This $\Delta\Delta G^{\ddagger}$ = 2 kcal $mol^{-1}$ is in good agreement with our experimental results. Finally, the corresponding **INT-B** will lead to the observed product by TMS-group transfer.

## Conclusions

In conclusion, in this communication we present the first enantioselective addition of difluorinated silyl enol ethers to acylpyridine *N*-oxides, using a Cu(II)/BOX catalytic system. Moderate to excellent yields and high enantioselectivities are usually obtained for a variety of substitution patterns. This methodology provides an innovative access to novel difluorinated chiral tertiary alcohols, which are of great interest in fields such as medicinal chemistry. Finally, we proved the importance of the *N*-oxide moiety in the success of the method, and we also demonstrated its removal by Pd-catalysed hydrogenolysis.

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

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