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COMMUNICATION

Copper-Catalysed Enantioselective Michael Addition of Malonic Esters to β-Trifluoromethyl-α,β-Unsaturated Imines†‡

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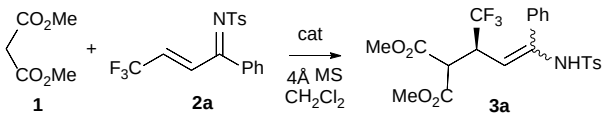
Copper triflate-BOX complexes catalyse the enantioselective conjugate addition of methyl malonate to β-trifluoromethyl-α,β-unsaturated imines to give the corresponding enamines bearing a trifluoromethylated stereogenic centre with good yields, diastereo- and enantioselectivity. The usefulness of the method has been shown with the synthesis of optically active β-trifluoromethyl δ-amino esters and optically active trifluoromethyl piperidones.

The interest in the chemistry of chiral organofluorine compounds has experienced a tremendous growth in the last years due to their wide range of applications in medicinal and agricultural chemistry, as well as in material science.[1] Among organofluorinated compounds, those having a trifluoromethyl group[2] attached to a stereogenic centre deserve special attention due to the occurrence of this structural motif in bioactive compounds[3] and chiral reagents.[4] These stereocentres are most frequently prepared by nucleophilic addition reactions to trifluoromethylated prostereogenic groups such as trifluoromethylketones[5] and trifluoromethylimines.[6] In this context, several carbon nucleophiles have been also reported to undergo enantioselective Michael-type reactions[7] with β-trifluoromethyl α,β-unsaturated carbonyl compounds[8] or with nitroalkenes[9] to obtain compounds with a trifluoromethylated sterogenic centre not connected to heteroatom.

In the last years, α,β-unsaturated imines (1-aza-butadienes) have emerged as interesting Michael acceptors[10,11] that have been used in several enantioselective conjugate addition reactions providing chiral nitrogenated compounds.[12,13] Following our interest in the chemistry of 1-aza-butadienes[12d,e,13b] and considering the importance of fluorine-containing amino acids in medicinal chemistry,[14] we report in this communication the first example of enantioselective conjugate addition of malonate esters to β-trifluoromethyl α,β-unsaturated *N*-tosyl imines as an efficient procedure to access to chiral β-trifluoromethyl-δ-amino acid derivatives, a reaction that has no precedent in the literature.



Scheme 1. Conjugate addition of dimethyl malonate (**1**) to imine **2a**

Our group has previously reported the enantioselective conjugate addition of dimethyl malonate to unsaturated *N*-tosyl imines derived from chalcone, using La(OTf)$_3$-pyBOX complexes in the presence of 4Å molecular sieves (MS), with good yields and stereoselectivity.[12d,e] When this catalytic system was applied to the reaction (Scheme 1) between dimethyl malonate (**1**) and (*E,E*)-*N*-tosyl-4,4,4-trifluoro-1-phenylbut-2-en-1-imine (**2a**),[§] the expected Michael reaction product **3a** was obtained with good yields but low enantioselectivities with different La(OTf)$_3$-pyBOX complexes (see Supplementary Information). Other pyBOX complexes with trivalent metal triflates such as Yb(OTf)$_3$, Sc(OTf)$_3$ or In(OTf)$_3$ performed similarly or worse than La(OTf)$_3$. Due to the low stereocontrol obtained with trivalent metals-pyBOX, we proceeded to test the reaction in the presence of Cu(OTf)$_2$-BOX complexes (Figure 1, Table 1).[15]

The reaction requires the presence of 4Å molecular sieves (MS) to proceed (Table 1, entries 1 and 2). 4Å MS probably works as an effective proton scavenger favouring the generation of the dimethyl malonate enolate in sufficient concentration.[16] Under these reaction conditions, several BOX ligands were tested (Table 1, entries 2-11). All BOX ligands with the exception of **BOX8** favoured the formation of the *E*-enamine. Indene-derived bisoxazoline (**BOX7**) lead to the best results in terms of yield and stereoselectivity providing enamine **3a** in 93% yield, as a ca. 90:10 mixture of *E/Z*-diastereomers and 95% ee for the

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major *E*-diastereomer, after 96 hours (Table 1, entry 8). Addition of a catalytic amount of triethylamine in an attempt to speed up the reaction brought about a decrease in the yield due to hydrolysis of the imine, as well as an erosion in the stereoselectivity, which could not be avoided even in the presence of MS (Table 1, entries 12 and 13). Addition of 1 equivalent of triethylamine produced an inversion in diastereoselectivity, the *Z*-isomer being obtained as the major one in almost racemic form (Table 1, entry 14).

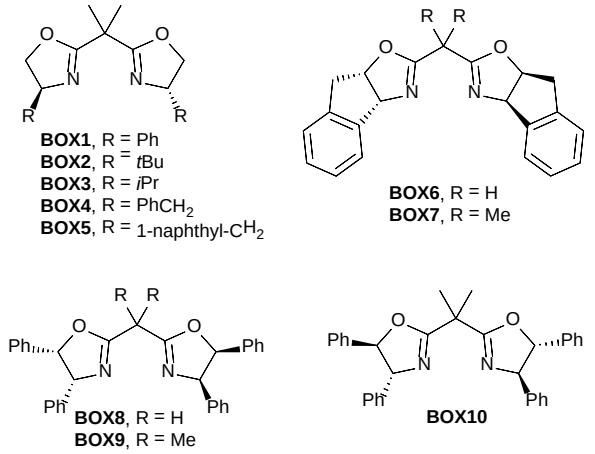


Figure 1. BOX ligands used in this study

Table 1. Enantioselective conjugate addition of dimethyl malonate (**1**) to imine **2a** according to scheme 1. Screening of catalysts.[a]

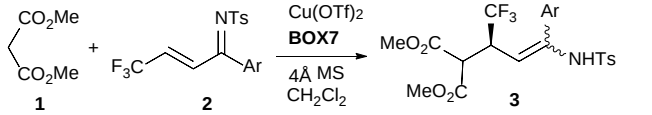
Entry	M	**BOX**	*t* (h)	Yield (%)[b]	dr (*E*:*Z*)[c]	ee (%) (*E*:*Z*)[d]
1[e]	Cu	**BOX1**	24	-[f]	-	-
2	Cu	**BOX1**	96	60	80:20	-33/35
3	Cu	**BOX2**	96	-[f]	-	-
4	Cu	**BOX3**	96	85	66:34	-85/71
5	Cu	**BOX4**	72	77	80:20	67/-41
6	Cu	**BOX5**	96	31	70:30	-55/54
7	Cu	**BOX6**	96	-[f]	-	-
8	Cu	**BOX7**	72	93	90:10	95/-75
9	Cu	**BOX8**	96	58	36:64	30/-70
10	Cu	**BOX9**	96	92	72:28	-2/-7
11	Cu	**BOX10**	96	47	80:20	-32/25
12[e,g]	Cu	**BOX7**	96	-[h]	-	-
13[g]	Cu	**BOX7**	72	36	47:53	76/-65
14[i]	Cu	**BOX7**	24	23	38:62	4/7
15	Zn	**BOX7**	96	36	92:8	57/-43
16	Ca	**BOX7**	96	81	84:16	69/-49

[a] Reaction conditions: **1** (0.3 mmol), **2a** (0.125 mmol), **BOX** (0.0125 mmol, $M(OTf)_2$ (0.0125 mmol), 4Å MS (110 mg), CH_2Cl_2 (1.1 mL). [b] Yield of isolated product. [c] Determined by ^1H NMR. [d] Determined by HPLC with chiral stationary phases; opposite sign within a same diastereomer indicates opposite enantiomers. [e] MS was not used. [f] Little advance of the reaction was observed after the indicated time. [g] Et_3N (0.016 mmol). [h] Hydrolysis of the imine was observed. [i] Et_3N (0.3 mmol).

We also tested the reaction in the presence of the **BOX7** complexes with Zn(II) and Ca(II) triflates, without improving the results obtained with Cu(II). The reaction with the Zn(II) complex proceeded sluggishly, while in the presence of the Ca(II) complex compound **3a** was obtained with good yield but fair diastereo- and enantioselectivity (Entries 15, 16).

The conditions established in Table 1, entry 8, were applied to a number of β-trifluoromethyl-α,β-unsaturated *N*-tosylimines **2** having an aromatic ring attached to the imine carbon. The results are gathered in Table 2.[§§]

Table 2. Enantioselective conjugate addition of dimethyl malonate (**1**) to β-trifluoromethyl-α,β-unsaturated *N*-tosylimines **2**.[a]



Entry	**2**	Ar	t(h)	**3**	Yield (%)[b]	dr (*E*:*Z*)[c]	ee (%) (*E*/*Z*)[d]
1	**2a**	Ph	68	**3a**	93	90:10	95/75
2	**2b**	*p*-MeC_6H_4	89	**3b**	86	89:11	94/40
3	**2c**	*p*-ClC_6H_4	112	**3c**	82	87:13	97/32
4	**2d**	*p*-BrC_6H_4	89	**3d**	75	89:11	95/43
5	**2e**	*p*-$NO_2C_6H_4$	89	**3e**	86	74:26	90/54
6	**2f**	*p*-$MeOC_6H_4$	112	**3f**	34	84:16	94/56
7	**2g**	*m*-MeC_6H_4	136	**3g**	97	87:13	94/41
8	**2h**	*m*-ClC_6H_4	89	**3h**	86	82:18	91/49
9	**2i**	*m*-$NO_2C_6H_4$	64	**3i**	94	60:40	83/58
10	**2j**	*m*-$MeOC_6H_4$	89	**3j**	87	83:17	87/82
11	**2k**	*o*-$MeOC_6H_4$	112	**3k**	23	72:28	89/17
12	**2l**	2-naphthyl	112	**3l**	60	87:13	93/27

[a] **1** (0.3 mmol), **2** (0.125 mmol), **BOX7** (0.0125 mmol), $Cu(OTf)_2$ (0.0125 mmol), 4Å MS (110 mg), CH_2Cl_2 (1.1 mL). [b] Yield of isolated product. [c] Determined by ^1H NMR. [d] Determined by HPLC with chiral stationary phases.

The reaction can be carried out with imines bearing an aromatic ring attached to the imine carbon substituted with either electron-donating or electron-withdrawing substituents. Good to excellent yields of compounds **3** were obtained in almost all the cases except when the phenyl group is substituted with a strong electron donating group (MeO) at the *ortho* or *para* positions (Table 2, entries 6 and 11). However, this drawback is not found when this group is in *meta* position (Table 2, entry 10). (entries 1-8). A naphthyl group attached to the imine carbon was also tolerated (Table 2, entry 12). Compounds **3a-l** were obtained with fair to good diastereoselectivities (from 60:40 to 90:10) favouring the *E*-diastereomer and with high enantiomeric excesses (from 83% to 97% ee for the major *E*-diastereomer) regardless of the electronic character of the substituent on the aromatic ring, although *para*-substituted rings gave slightly higher enantioselectivities (Table 2, entries 2-6). The study with unsaturated imines **2** having an aliphatic (Me) group attached to the imine carbon was not possible because of enolisation of the *N*-sulfonyl imine during the preparation of the starting materials.

Compound **3a** (Table 2, entry 1) could be crystallised and subjected to X-ray analysis, what allowed to establish the configuration of the stereogenic centre as *S*, and confirmed the *E*-geometry of the enamine double bond in the major diastereomer (Figure 2).[§§§] The absolute stereochemistry of all compounds **3** was assigned by analogy upon the assumption of a uniform stereochemical pathway.

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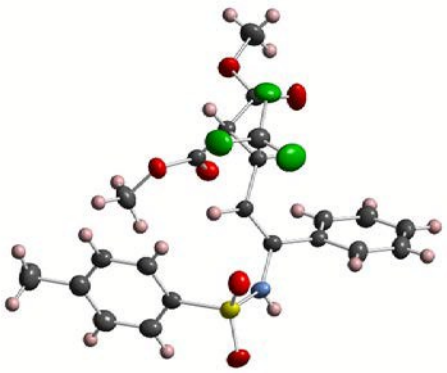
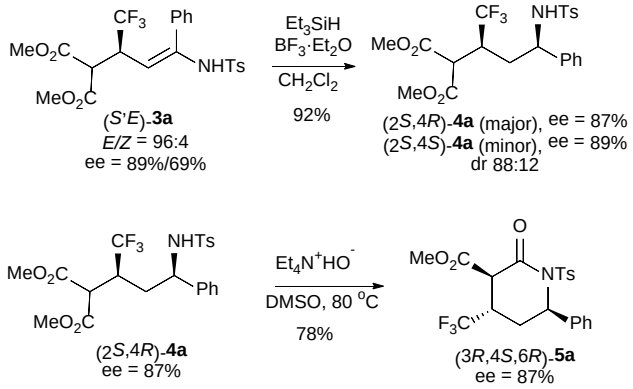


Figure 2. Ortep plot for the X-ray structure of compound **3a**. The thermal ellipsoids are drawn at the 50% probability level.

Scheme 2 shows some transformations on compound **3a** that show the potential application of enamines **3** in the synthesis of optically active trifluoromethyl-containing nitrogenated compounds. Thus, reduction of compound **3a** can be efficiently achieved by treatment with triethylsilane in the presence of boron trifluoride to give δ-amino ester **4a** in 92% yield with good diastereoselectivity (dr 88:12) and without noticeable erosion in the ee. On the other hand, treatment of compound **4a** with tetraethylammonium hydroxide in DMSO gave the trifluoromethylated piperidone **5a** with good yield.

Studies addressed to extend this methodology to other 1,3-dicarbonyl compounds are currently ongoing in our laboratory.



Scheme 2. Synthetic modification of compound **3a**

Conclusions

In summary, we have reported the first enantioselective conjugate addition of dimethyl malonate[§§§§] to β-trifluoromethyl α,β-unsaturated *N*-tosylimines to give the corresponding γ-dehydro-δ-amino esters bearing a trifluoromethylated stereogenic centre at the allylic position, which is catalysed by Cu(II)-BOX complexes. The reaction provides the *E*-enamine as the major diastereomer with good yields, fair to good diastereoselectivities and good enantioselectivities. The enamino esters are effective synthons for the preparation of optically active β-trifluoromethyl δ-amino esters and optically active trifluoromethyl piperidones.

Notes and references

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§ The *E,E* geometry for the C-C and C-N double bonds in compound **2a** has been determined by X-ray analysis. See SI. CCDC-1535016 contains the supplementary crystallographic data for this compound. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

§§ $Cu(OTf)_2$ (4.5 mg, 0.0125 mmol) was dried in a Schlenk tube under vacuum. **BOX7** (4.5 mg, 0.0125 mmol) was added and the tube was filled with nitrogen. CH_2Cl_2 (0.55 mL) was added via syringe and the mixture was stirred for 30 min. A solution of imine **2** (0.125 mmol) dissolved in dry CH_2Cl_2 (0.5 mL), was added via syringe, followed by 4 Å MS (110 mg) and dimethyl malonate (34 μL, 0.3 mmol). The mixture was stirred at room temperature for the indicated time and chromatographed on silica gel eluting with hexane/EtOAc mixtures to give compounds **3**.

§§§ CCDC-1535017

§§§§ Other active methylene compounds were also tested: Dibenzoylmethane reacted slowly with **2a** to give the corresponding Michael addition product in 40% yield, with good diastereoselectivity (E/Z = 96:4) but almost racemic (11% ee); malononitrile gave a complex reaction mixture while bis(phenylsulfonyl)methane did not react with **2a** under our reaction conditions.

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