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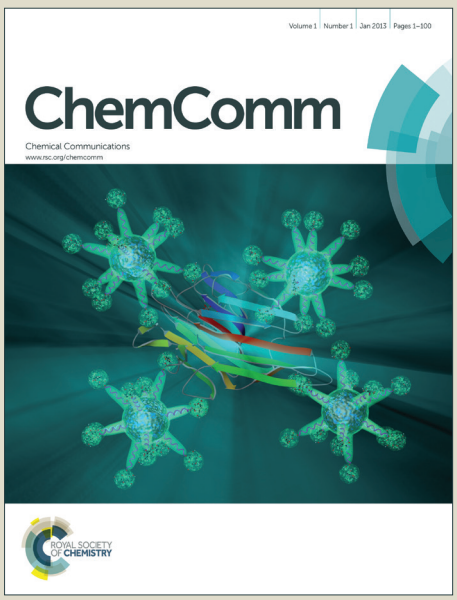





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Cite this: DOI: 10.1039/c0xx00000x

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ARTICLE TYPE

# Catalytic asymmetric conjugate addition of terminal alkynes to β-trifluoromethyl α,β-enones†

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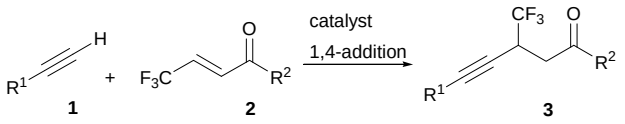
***Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX***

**DOI: 10.1039/b000000x**

**The first enantioselective conjugate alkynylation of β-trifluoromethyl α,β-enones using terminal alkynes and a taniaphos-Cu(I) complex as catalyst is described. Ketones bearing a trifluoromethylated propargylic chiral centre in the β-position were obtained with good yields and high enantiomeric excesses (up to 99%).**

In recent years the stereoselective introduction of perfluoroalkyl substituents[1] into organic molecules has attracted great attention in the field of medicinal, agricultural and material chemistry, mainly due to the significant changes in the physical, chemical, and biological properties that the introduction of fluorine atoms causes in the parent molecules.[2] In this context, molecules containing chiral centres bearing a trifluoromethyl substituent[3] have raised a special interest due to the increasing occurrence of this motif in biologically active compounds,[4] but also in chiral reagents[5] or in materials for optoelectronic devices.[6] This kind of chiral centres have been constructed by following two general approaches: (i) the direct trifluoromethylation of prochiral carbons and (ii) the functionalization of trifluoromethylated prochiral carbons. Although straightforward, there are few enantioselective examples using the first approach[7] and the second one has been more often preferred for the construction of chiral centres bearing a trifluoromethyl group in an enantioselective fashion.[3,8] On the other hand, chiral trifluoromethylated propargylic carbons are present in a number of bioactive compounds such as the HIV reverse transcriptase inhibitor efavirenz and its analogues.[9] Recently some enantioselective procedures for the synthesis of trifluoromethylated propargylic carbons having an heteroatom by trifluoromethylation of ynones,[10] and alkynylation of ketones[11] or imines[12] have been reported in the literature. However, a catalytic procedure for the enantioselective synthesis of trifluoromethylated propargylic carbons without heteroatoms has not been reported yet, to the best of our knowledge. By following strategy (ii) we envisioned that this kind of chiral centres may be created by asymmetric conjugate alkynylation of β-trifluoromethyl α,β-unsaturated carbonyl compounds, i.e. enones (Scheme 1).

The enantioselective conjugate alkynylation of α,β-unsaturated carbonyl compounds has been carried out by using pre-formed metal alkynylides,[13] or, more conveniently, by direct alkynylation with terminal alkynes using Cu,[14] Rh,[15] Co,[16] Zn,[17] Ru (one example with 82% *ee*)[18] and Pd (two examples with 39% and 38% *ee*)[19] catalysts. However, none of these procedures has been applied with fluorinated substrates.




**Scheme 1** Conjugate alkynylation of β-trifluoromethyl enones

In this communication we describe the first example of enantioselective alkynylation of β-trifluoromethyl α,β-unsaturated ketones with terminal alkynes, using copper(I)-complexes as catalysts. Although convenient from the economic and environmental point of view, the use of copper catalysis in conjugate alkynylation is hampered by the low nucleophilicity of the intermediate copper alkynylides. In fact, the copper(I)-catalyzed conjugated alkynylation of α,β-unsaturated carbonyl compounds has been only possible with highly activated substrates, i.e. Meldrum's acid derivatives[14a] with two carbonyl groups on the double bond α-carbon, or by the use of unsaturated thioamides specially designed to simultaneously activating the alkyne and the double bond via a soft Lewis acid/hard Brønsted base cooperative catalysis.[14b-d] Despite these limitations, we believed that the presence of the strongly electron-withdrawing trifluoromethyl group should increase the electrophilicity of the double bond by lowering the LUMO energy level,[20] thus allowing the reaction to take place.

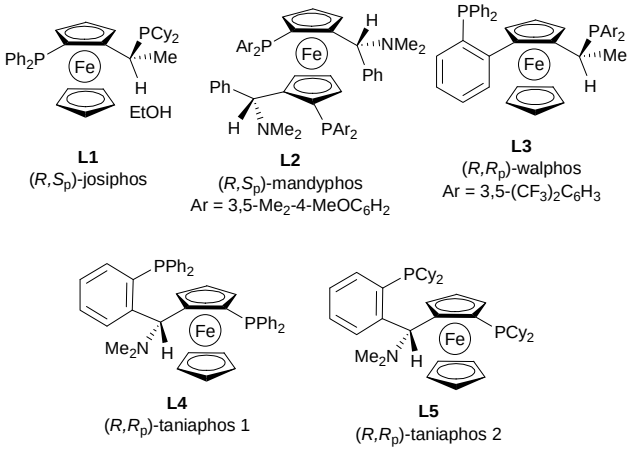



**Fig. 1** Ligands tested in the addition of phenylacetylene (**1a**, $R^1$=Ph, to trifluoromethyl enone **2a** ($R^2$=Ph)

In the onset of our investigation we studied the addition of phenylacetylene (**1a**, $R^1$=Ph) to enone **2a** ($R^2$=Ph) in the presence of $[Cu(CH_3CN)_4]BF_4$, a variety of ferrocene-based phosphane ligands (Figure 1) and triethylamine in toluene at 60 °C (Table 1, entries 1-5).‡ The best result was obtained with ligand **L4** (taniaphos 1) that provided compound **3aa** ($R^1$=$R^2$=Ph) in 64% yield and 78% *ee*. The use of $[(CuOTf)_2Tol]$ instead of $[Cu(CH_3CN)_4]BF_4$ produced a decrease of the reaction yield (entry 4 *vs* entry 6). Changing the base to diisopropylamine decreased both the yield and enantioselectivity (entry 4 *vs* entry 9). Next, we examined the effect of the temperature. When the reaction was carried out at 40 °C a slight increase of the *ee* was obtained (entry 7). However, further decrease of the temperature to rt was detrimental for the yield without improving the enantioselectivity (entry 8). Finally, we tested several solvents. The best results were observed in THF, which allowed obtaining compound **3aa** in 70% yield and 85% *ee* (entry 13).

**Table 1** Enantioselective conjugate addition of phenylacetylene (**1a**, $R^1$=Ph) to trifluoromethyl enone **2a** ($R^2$=Ph). Screening of ligands and conditions.[a]

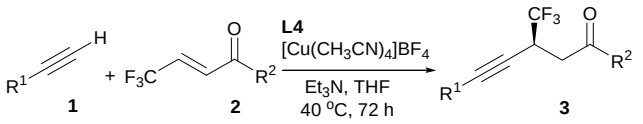
| Entry | Ligand | T (°C) | Solvent | time (h) | yield (%) | *ee* (%)[b] |
|---|---|---|---|---|---|---|
| 1 | **L1** | 60 | toluene | 72 | 26 | 14 |
| 2 | **L2** | 60 | toluene | 72 | 45 | 10 |
| 3 | **L3** | 60 | toluene | 48 | 93 | 42 |
| 4 | **L4** | 60 | toluene | 72 | 64 | 78 |
| 5 | **L5** | 60 | toluene | 72 | 47 | 75 |
| 6[c] | **L4** | 60 | toluene | 72 | 30 | 78 |
| 7 | **L4** | 40 | toluene | 72 | 64 | 80 |
| 8 | **L4** | rt | toluene | 96 | 53 | 80 |
| 9[d] | **L4** | 40 | toluene | 96 | 40 | 76 |
| 10 | **L4** | 40 | $PhNO_2$ | 96 | 40 | 73 |
| 11 | **L4** | 40 | anisole | 96 | 56 | 81 |
| 12 | **L4** | 40 | TBME | 96 | 20 | 79 |
| 13 | **L4** | 40 | THF | 72 | 70 | 85 |
| 14 | **L4** | 40 | dioxane | 96 | 26 | 81 |

[a] **1a** (7.5 equiv), **2a** (1.0 equiv), $Et_3N$ (1.0 equiv), $[Cu(CH_3CN)_4]BF_4$ (0.2 equiv), ligand (0.2 equiv), unless if otherwise stated. [b] Determined by HPLC. [c] $[(CuOTf)_2Tol]$ instead of $[Cu(CH_3CN)_4]BF_4$. [d] $^iPr_2NH$ instead of $Et_3N$.

Under the optimal reaction conditions‡‡ (Table 1, entry 13) various β-trifluoromethyl aryl enones **2** and alkynes **1** were screened (Table 2). Noteworthy, the electronic nature of the substituent at the phenyl ring of the enones **2** had little influence on the enantioselectivity of the reaction (entries 1-4), although the presence of a very strong electron-withdrawing nitro group brought about an appreciable decrease of both reactivity and enantioselectivity (entry 5). Moreover, fused ring and heteroaromatic ring substrates were also applicable, giving the expected products with good results (entries 6-7). Remarkably, the presence of the thienyl ring enhanced both the reactivity and enantioselectivity, product **3ag** being obtained quantitatively with 90% *ee* (entry 7). The reaction also allowed variation on the alkyne. Substituted phenylacetylenes bearing electron-donating or electron-withdrawing groups at different positions (entries 8-16) reacted with enones **2a** and **2g** to give the alkynylation products with good yields and enantioselectivities, with near 100% *ee* for the addition of 2-methoxyphenylacetylene and 3-fluorophenylacetylene (entries 14 and 15, respectively). Again the 2-thienyl derived enones showed higher enantioselectivity with respect to the phenyl enone. The reaction could be carried out also with heterocyclic alkynes, such as 3-ethynylthiophene (**1h**) that reacted with enone **2g** to give compound **3hg** with good yield and excellent enantioselectivity (entry 17). Finally, the reaction also worked with aliphatic alkynes such as 4-phenyl-1-butyne (**1i**), although in this case the reaction was slow and the alkynylation product **3ig** (entry 18) was obtained in moderate yield after 72 h but with excellent enantioselectivity (92% *ee*).

Enones bearing an aliphatic group $R^2$ attached to the carbonyl group were also tested, which were less reactive than the aromatic ones. Thus, enone **2h** ($R^2$ = $PhCH_2CH_2$) reacted slowly with phenylacetylene (**1a**) and *p*-methoxyphenylacetylene (**1b**) to give the corresponding products **3ah** and **3bh** with low yields, although good enantioselectivities (entries 19 and 20), after 90 h. However, the reaction of phenylacetylene (**1a**) with enone **2i** ($R^2$ = *n*-Bu) did not show any appreciable advance after a similar time (entry 21)

**Table 2** Enantioselective conjugate alkynylation of enones **2** with alkynes **1**. Scope of the reaction.[a]



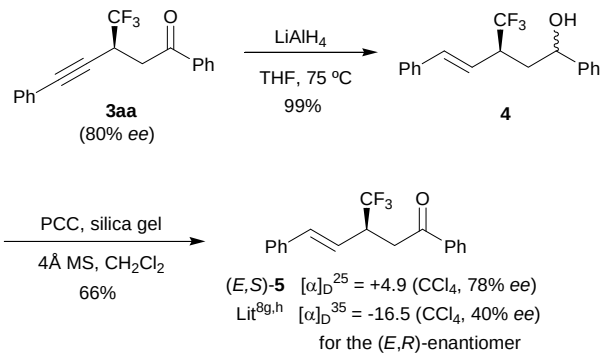

| Entry | **1** | $R^1$ | **2** | $R^2$ | **3** | yield (%) | *ee* (%) |
|---|---|---|---|---|---|---|---|
| 1 | **1a** | Ph | **2a** | Ph | **3aa** | 70 | 85 |
| 2 | **1a** | Ph | **2b** | 4-$MeC_6H_4$ | **3ab** | 66 | 80 |
| 3 | **1a** | Ph | **2c** | 4-$MeOC_6H_4$ | **3ac** | 64 | 80 |
| 4 | **1a** | Ph | **2d** | 4-$ClC_6H_4$ | **3ad** | 94 | 80 |
| 5 | **1a** | Ph | **2e** | 4-$NO_2C_6H_4$ | **3ae** | 54 | 70 |
| 6 | **1a** | Ph | **2f** | 2-naphthyl | **3af** | 87 | 84 |
| 7 | **1a** | Ph | **2g** | 2-thienyl | **3ag** | 99 | 90 |
| 8 | **1b** | 4-$MeOC_6H_4$ | **2a** | Ph | **3ba** | 90 | 83 |
| 9 | **1c** | 4-$FC_6H_4$ | **2a** | Ph | **3ca** | 77 | 80 |
| 10 | **1d** | 4-$ClC_6H_4$ | **2a** | Ph | **3da** | 60 | 77 |
| 11 | **1b** | 4-$MeOC_6H_4$ | **2g** | 2-thienyl | **3bg** | 96 | 93 |
| 12 | **1c** | 4-$FC_6H_4$ | **2g** | 2-thienyl | **3cg** | 99 | 90 |
| 13 | **1d** | 4-$ClC_6H_4$ | **2g** | 2-thienyl | **3dg** | 81 | 84 |
| 14 | **1e** | 2-$MeOC_6H_4$ | **2g** | 2-thienyl | **3eg** | 86 | 98 |
| 15 | **1f** | 3-$FC_6H_4$ | **2g** | 2-thienyl | **3fg** | 97 | 99 |
| 16 | **1g** | 3,5-$(MeO)_2C_6H_3$ | **2g** | 2-thienyl | **3gg** | 68 | 86 |
| 17 | **1h** | 3-thienyl | **2g** | 2-thienyl | **3hg** | 80 | 88 |
| 18 | **1i** | $PhCH_2CH_2$ | **2g** | 2-thienyl | **3ig** | 51[c] | 92 |
| 19[d] | **1a** | Ph | **2h** | $PhCH_2CH_2$ | **3ah** | 30[e] | 79 |
| 20[d] | **1b** | 4-$MeOC_6H_4$ | **2h** | $PhCH_2CH_2$ | **3bh** | 28[f] | 82 |
| 21[d] | **1a** | Ph | **2i** | *n*-Bu | **3ai** | - | - |

[a] **1** (7.5 equiv), **2** (1.0 equiv), $Et_3N$ (1.0 equiv), $[Cu(CH_3CN)_4]BF_4$ (0.2 equiv), **L4** (0.2 equiv), THF, 40 °C, 72 h. [b] Determined by HPLC. [c] Starting material **2g** (17%) was recovered. [d] Reaction carried out for 90 h. [e] Starting material **2h** (51%) was recovered. [f] Starting material **2h** (50%) was recovered.

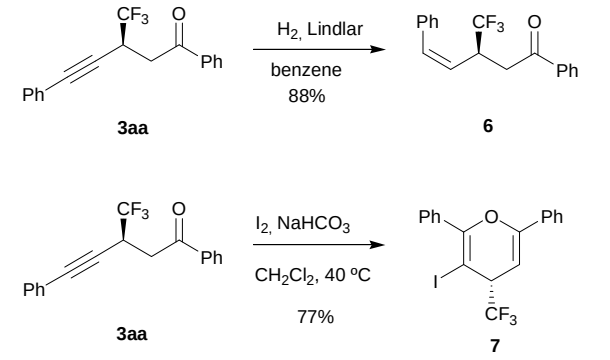
The determination of the absolute stereochemistry of compound **3aa** was carried out by chemical correlation with compound **5** of known stereochemistry (Scheme 2). Hydroalumination of the triple bond of a 80% *ee* sample of compound **3aa** with $LiAlH_4$ under THF reflux took place with concomitant reduction of the ketone to give, after hydrolysis, a mixture of two epimeric *E*-allylic alcohols **4**, which were oxidized with pyridinium chlorochromate (PCC) to the *E*-enone **5**.[8g,h] Compound **5** prepared in this way showed opposite optical rotation sign and elution times in chiral HPLC (Chiralpak AD-H) to (*E,R*)-**5**,‡‡‡ indicating that our compound **5** and, therefore, compound **3aa**

were both of *S*-configuration at the stereogenic centre. For the rest of compounds **3**, the stereochemistry was assigned upon the assumption of a common stereogenic mechanism.

Some synthetic modifications of compound **3aa** that show the synthetic potential of the β-alkynyl-β-trifluoromethyl ketones are presented in Scheme 3. Thus, further to the *trans* hydrogenation of the triple bond shown in Scheme 1, hydrogenation over Lindlar catalyst yields compound **6**, having a trifluoromethylated allylic carbon with the *Z*-double bond. More interestingly, iodine in basic medium promotes the cyclisation of compound **3aa** to give the highly substituted chiral 4-trifluoromethyl-4*H*-pyran **7** without any lost of optical purity.




**Scheme 2** Determination of the absolute stereochemistry of compound **3aa**




**Scheme 3** Synthetic modifications of compound **3aa**

In summary, we have described the first enantioselective conjugate alkynylation of β-trifluoromethyl α,β-enones. The reaction is carried out in a catalytic fashion by using terminal alkynes in the presence of a Cu(I)-taniaphos complex to give ketones having a trifluoromethylated propargylic stereogenic centre in β to the carbonyl group with good yields and high enantiomeric excesses. These compounds have been shown to be building blocks for the synthesis of chiral trifluoromethylated heterocycles such as 4-trifluoromethyl-4*H*-pyrans upon iodocyclisation. Research toward the extension of this procedure to other perhalogenated substrates and new applications of the resulting products are underway in our laboratory.

Financial support from the Ministerio de Economía y Competitividad (Gobierno de España) and FEDER (European Union) (CTQ2009-13083) and from Generalitat Valenciana (ACOMP2012-212 and ISIC2012/001) is acknowledged. A. S-M. thanks the MEC for a pre-doctoral grant (FPI). We thank the Solvias Company for the donation of a university ligand kit.

## Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental procedures and characterization of all new compounds. See DOI: 10.1039/b000000x/

‡ We also tested some catalysts based on pyBOX-Cu(I) complexes which were inactive.

‡‡ **Typical procedure for the enantioselective alkynylation:** $[Cu(CH_3CN)_4]BF_4$ (5.7 mg, 0.018 mmol) and **L4** (12.4 mg, 0.018 mmol) were placed in a dry round bottom flask which was purged with nitrogen. THF (0.2 mL) was added and the mixture was stirred for 1.5 h at room temperature. Then, a solution of β-trifluoromethyl-α,β-enone **2** (0.090 mmol) in dry THF (1.0 mL) was added via syringe, followed of triethylamine (12.5 μL, 0.090 mmol). The solution was placed in a bath at 40 °C. After 10 min, the alkyne **1** (0.675mmol) was added and the solution was stirred at 40 °C under nitrogen until the reaction was complete (TLC). The reaction mixture was quenched with 20% aqueous $NH_4Cl$ (1.0 mL), extracted with $CH_2Cl_2$ (2 × 15 mL), washed with brine (15 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography on silica gel eluting with hexane:diethyl ether mixtures afforded compound **3**.

‡‡‡ We thank Professor Tsutomu Konno, Kyoto Institute of Technology, for sending us complete characterization data of compound (*E,R*)-**5**.

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