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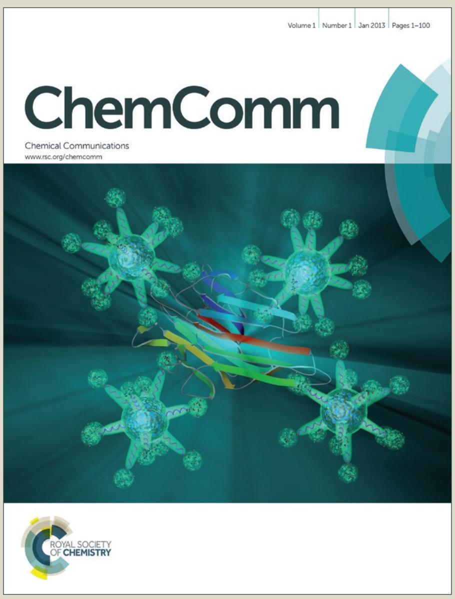

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Cite this: DOI: 10.1039/x0xx00000x

Highly Enantioselective Copper(I)-Catalyzed Conjugate Addition of 1,3-Diynes to α,β-Unsaturated Trifluoromethyl Ketones†

Received 00th January 2012,
Accepted 00th January 2012

DOI: 10.1039/x0xx00000x

www.rsc.org/

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The conjugate diynylation of α,β-unsaturated trifluoromethyl ketones is carried out in the presence of a low catalytic load (2.5 mol %) of a copper(I)-MeOBIPHEP complex, triethylamine and a terminal 1,3-diyne. Pre-metalation of the terminal 1,3-diyne with stoichiometric or higher amounts of dialkylzinc reagent is not required. The corresponding internal diynes bearing a propargylic stereogenic center are obtained with good yields and excellent enantioselectivities.

The 1,3-diyne moiety is present in a large number of natural and artificial molecules.[1] Naturally occurring diynes are found as metabolites in a variety of fungi, higher plants and marine organisms, and many of them have important biological and pharmacological properties ranging from antifungal to anticancer activities.[2] Diynes and oligoynes also have interest a as probes of extended π-conjugation and can serve as active components in optoelectronic devices.[3] Furthermore, conjugate diynes are intriguing building blocks due to the unique behavior of alkynes, especially in transition metal-catalyzed processes.[4]

In recent years the nucleophilic addition of terminal alkynes to prochiral electrophiles has emerged as one of the most efficient procedures for the synthesis of internal alkynes bearing a propargylic stereogenic center. Thus considerable success has been obtained in the enantioselective alkynylation of carbonyl compounds[5] and imines,[6] and, more recently, in the conjugate alkynylation of electrophilic double bonds.[7] However, studies on enantioselective additions of 1,3-diynes are more limited, and all the examples reported in the literature involve the activation of terminal 1,3-diynes as diynylzinc reagents, which requires in most of the cases the use of stoichiometric or larger amounts of expensive dialkylzinc reagents. Thus, after the pioneering work by Carreira in 2003,[8] on the use of 4 equivalents of $Zn(OTf)_2$/*N*-methylephedrine to achieve the addition of a terminal 1,3-diyne to an aliphatic aldehyde, Trost[9] reported in 2010 a catalytic enantioselective addition of 1,3-diynes to aldehydes using a dinuclear ProPhenol/zinc catalyst. Later on, Pu,[10] Tykwinski[11] and Wang[12] developed their own versions of the asymmetric zinc-catalyzed addition of 1,3 diynes to aldehydes by using combinations of dialkylzinc with amino alcohol[11,12] or binaphthol-type[10] ligands. In 2011, Ma described the enantioselective addition of 1,3-diynylzinc reagents, generated in situ from Me_2Zn and terminal diynes, to aromatic ketones in the presence of a Cu(II)-hydroxycamphor-sulfonamide complex and Me_2Zn.[13] On the other hand, the diynylation of different kind of aldimines[14] and fluorinated ketimines[15] has been reported by the same group using terminal diynes, Me_2Zn and binaphthol-type ligands. However, a procedure for the enantioselective addition of 1,3-diynes to electrophilic C-C double bonds, i.e. enones, has not been reported so far.

Following our research interest in the conjugate alkynylation reaction,[7d,e,I,j] we report in this communication our results on the enantioselective copper-catalyzed conjugate addition of terminal 1,3-diynes to enones, a reaction without any precedent in the literature. In our study, we have chosen α,β-unsaturated trifluoromethyl ketones (Scheme 1) as electrophiles because of the significance of fluorinated compounds in medicinal chemistry.[15] Trifluoromethyl enones[16,17] are a particularly challenging class of substrates for conjugate asymmetric transformations since the presence of the strongly electron-withdrawing trifluoromethyl group not only activates the alkene but also renders the ketone functionality highly reactive making the control over regioselectivity difficult. In fact, only two examples of alkynylation of trifluoromethyl enones have been reported so far, both taking place regioselectively on the carbonyl group.[17a,18]

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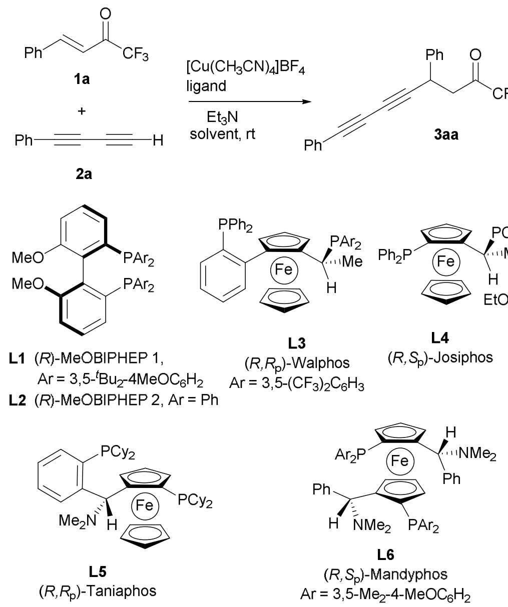


Scheme 1. Conjugate diynylation of α,β-unsaturated trifluoromethyl ketones and ligands used in this study.

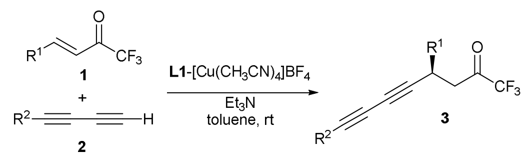
Table 1. Conjugate addition of phenylbuta-1,3-diyne (**1a**) to enone **2a**. Screening of ligands and reaction conditions.

Entry	L	L-Cu (mol %)	1a (equiv)	Et_3N (equiv)	solvent	t (h)	Yield [%]	ee (%)[a]
1	**L1**	20	7.4	1.0	toluene	18	82	93
2	**L1**	10	5	1.0	toluene	18	70	93
3	**L1**	5	3	1.0	toluene	18	73	93
4	**L1**	5	3	0.1	toluene	18	75	93
5	**L1**	2.5	1.3	0.1	toluene	18	73	93
6	**L1**	2.5	1.3	0	toluene	18	n.r.	-
7	**L2**	2.5	1.3	0.1	toluene	18	n.r.	-
8	**L3**	2.5	1.3	0.1	toluene	18	n.r.	-
9	**L4**	2.5	1.3	0.1	toluene	18	n.r.	-
10	**L5**	2.5	1.3	0.1	toluene	18	trace	-
11	**L6**	2.5	1.3	0.1	toluene	18	trace	-
12[b]	**L1**	2.5	1.3	0.1	toluene	18	65	93
13	**L1**	2.5	1.3	0.1	THF	48	34	94
14	**L1**	2.5	1.3	0.1	CH_2Cl_2	48	17	90
15	**L1**	2.5	1.3	0.1	Et_2O	48	58	90
16	**L1**	2.5	1.3	0.1[c]	toluene	18	65	91

[a] Determined by HPLC using chiral stationary phases. [b] CuOTf·0.5 Tol was used instead of $[Cu(CH_3CN)_4]BF_4$. [c] DIPEA was used instead of Et_3N.

In the onset of our investigation we studied the addition of phenyl-1,3-butadiyne (1a, R^1=Ph) to enone **2a** (R^2=Ph) catalyzed by 20 mol % of $[Cu(CH_3CN)_4]BF_4$ and (*R*)-MeOBIPHEP 2 (**L1**) in toluene (Scheme 1, Table 1, entry 1). Pleasantly, compound **3aa** was obtained in 82% yield and 93% ee under these reaction conditions. No products arising from 1,2-addition to the carbonyl group were observed. Further studies with this catalytic system (Table 1, entries 2-6) showed that the catalyst load could be reduced as low as 2.5 mol % and the amount of base decreased to sub-stoichiometric 0.1 equiv without a significant effect on the reaction outcome. Furthermore, the amount of diyne was also reduced to only 1.3 equivalents with respect to enone. Other phosphine ligands **L2**-**L6** were also tested (Table 1, entries 7-11). Surprisingly, from all the studied ligands, only biarylphosphine **L1** provided a catalytic complex sufficiently active to promote the reaction with this low catalytic load. The use of copper(I) triflate (Table 1, entry 12) provided similar results as $[Cu(CH_3CN)_4]BF_4$, whereas other solvents such as THF or CH_2Cl_2 decreased the reaction rate, compound **3aa** being obtained in lower yields than in toluene, although still with good enantioselectivities (Table 1, entries 13,14). Diethyl ether performed better than THF, but with lower yield and ee than toluene (Table 1, entry 15). The use of other bases such as DIPEA did not improve the results obtained with Et_3N (Table 1, entry 16).

Table 2. Enantioselective conjugate addition of terminal 1,3-diynes **2** to enones **1**. Scope of the reaction.[a]



Entry	1	R^1	2	R^2	3	Yield (%)	ee (%)[b]
1	**1a**	Ph	**2a**	Ph	**3aa**	73	93
2	**1b**	2-MeC_6H_4	**2a**	Ph	**3ba**	94	94
3	**1c**	3-MeC_6H_4	**2a**	Ph	**3ca**	55	93
4	**1d**	4-MeC_6H_4	**2a**	Ph	**3da**	56	92
5	**1e**	2-BrC_6H_4	**2a**	Ph	**3ea**	76	94
6	**1f**	4- BrC_6H_4	**2a**	Ph	**3fa**	55	92
7	**1g**	2-$MeOC_6H_4$	**2a**	Ph	**3ga**	69	94
8	**1h**	4-$MeOC_6H_4$	**2a**	Ph	**3ha**	41	92
9	**1i**	2-naphthyl	**2a**	Ph	**3ia**	59	92
10[c]	**1j**	$PhCH_2CH_2$	**2a**	Ph	**3ja**	50	84
11[c]	**1k**	$CH_3(CH_2)_3$	**2a**	Ph	**3ka**	53	87
12[c]	**1l**	$(CH_3)_2CHCH_2$	**2a**	Ph	**3la**	50	88
13	**1a**	Ph	**2b**	3-FC_6H_4	**3ab**	50	90
14	**1a**	Ph	**2c**	4-FC_6H_4	**3ac**	68	92
15	**1a**	Ph	**2d**	2-$MeOC_6H_4$	**3ad**	89	92
16	**1a**	Ph	**2e**	4-$MeOC_6H_4$	**3ae**	65	91
17	**1a**	Ph	**2f**	3-thienyl	**3af**	72	94
18	**1a**	Ph	**2g**	$PhCH_2CH_2$	**3ag**	41	93
19	**1b**	2-MeC_6H_4	**2g**	$PhCH_2CH_2$	**3bg**	50	95
20	**1a**	Ph	**2h**	6-ClC_4H_8	**3ah**	61	93
21	**1a**	Ph	**2i**	TIPS	**3ai**	50	85
22[d]	**1a**	Ph	**2a**	Ph	**3aa**	62	92

[a] **1** (0.14 mmol), **2** (1.3 equiv), Et_3N (0.1 equiv), $[Cu(CH_3CN)_4]BF_4$ (2.5 mol %), **L6** (2.5 mol %), toluene, rt. [b] Determined by HPLC using chiral stationary phases. [c] Reaction carried out with 10 mol % of catalyst. [d] Reaction carried out with 0.6 mmol of **1a**.

Under the best reaction conditions available (Table 1, entry 5) we studied the scope of the reaction with various enones **1** and diynes **2**.‡ First, we conducted the addition of diyne **2a** with several trifluoromethyl enones bearing different substituents at the β position of the double bond. The results are gathered in Table 2. Good results were obtained with a variety of enones bearing a substituted aromatic ring at this position. Good enantiomeric excesses were obtained for enones bearing an aromatic ring substituted at either the *ortho*, *metha* or *para* positions (Table 2, entries 2-4). Aromatic rings bearing electron-withdrawing (Table 2, entries 5, 6) or electron-donating (Table 2, entries 7, 8) substituents were also tolerated yielding the expected products with enantiomeric excesses

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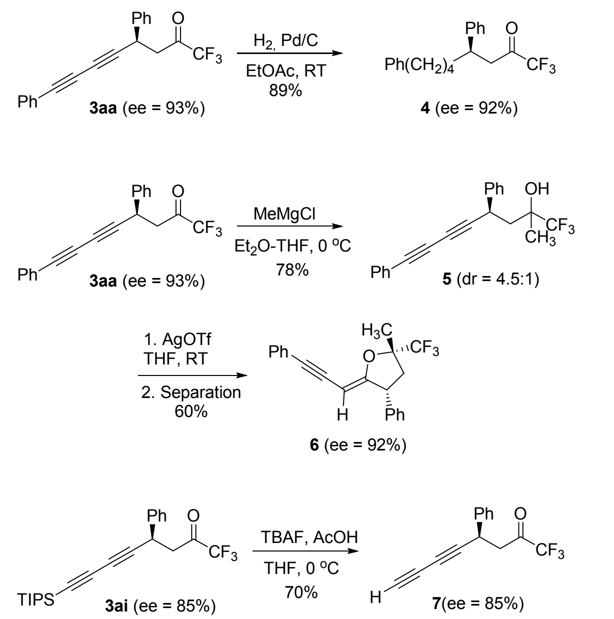
above 90%. Enone **1i** bearing a bulky 2-naphthyl group also reacted under the optimized conditions to give the diynylated product **3ia** with good yield and high ee. Remarkably, the reaction could also be carried out with enones, featuring aliphatic groups on the β-carbon, providing the corresponding products **3ja-3la** with moderated yields but high enantiomeric excesses (84-88%, Table 2, entries 10-12), although a higher catalytic load (10 mol %) was required in these cases.

Next, we tested the diyne scope (Table 2, entries 13-21). Substituted phenyl-1,3-butadiynes bearing electron-donating (MeO) or electron-withdrawing groups (F) on the phenyl group reacted with compound **1a** with variable yields but excellent enantioselectivities (Table 2, entries 13-16). The heterocyclic 3-thienyl-1,3-butadiyne (**2f**) reacted with **1a** to give compound **3af** with 72% yield and 94% ee (Table 2, entry 17). Next, we examined the reaction with aliphatic diynes, which reacted similarly to aromatic diynes. 6-Phenyl-1,3-hexadiyne reacted with enones **1a** and **1b** to give the corresponding chiral diynes **3ag** and **3bg**, respectively, with moderate yield but high enantioselectivity (Table 2, entries 18-19). 8-Chloro-1,3-octadiyne (**2h**) reacted in a similar way to give compound **3ah** in 61% yield and 93% ee (Table 2, entry 20). These results contrast with those observed in the copper-catalyzed conjugate alkynylation of β-trifluoromethyl enones with terminal monoynes where aliphatic alkynes reacted with lower yields and enantioselectivities than aromatic and heteroaromatic ones.[7d] Finally, silyldiyne **2i**, which is an equivalent of 1,3-butadiyne, could be reacted with enone **1a** to give the diynylated product **3ai** with 85% ee (Table 2, entry 21), showing the broad scope of the reaction regarding the diyne nucleophile. The reaction between enone **1a** and diyne **2a** was also carried out at a fourfold scale with a small decrease of yield but without noticeable effect on the enantioselectivity (Table 2, entry 22).

The absolute sterochemistry of compound **3af** (Table 2, entry 15) was elucidated by X-ray crystallographic analysis (see Figure S2 in the SI),[19] and for the rest of the products it was assigned on the assumption of a uniform reaction mechanism.

Some synthetic modifications of diynes **3** are presented in Scheme 2. Thus, full hydrogenation of both triple bonds in **3aa** could be carried out over 10% Pd/C in ethyl acetate to give trifluoromethyl ketone without any loss of optical purity. On the other hand, a chiral tetrahydrofuran bearing a trifluoromethylated quaternary stereocenter could be obtained after diastereoselective addition of methylmagnesium chloride to compound **3aa** followed by silver-catalyzed cyclization. We have also performed the desilylation of compound **3ai** (70% yield) to give the chiral terminal diyne **7** upon treatment with TBAF and acetic acid in THF.

In summary, we have reported the first example of enantioselective conjugate diynylation of enones. The reaction requires only a small excess (1.3 equiv) of a terminal diyne and is carried out in the presence of a low catalytic load of a copper(I)-biphosphine complex (0.025 equiv) and an amine (0.1 equiv) to provide the corresponding internal diynes bearing a propargylic stereogenic center with excellent enantioselectivities. The reaction is broad in scope for a wide range of trifluoromethyl ketones[19] allowing variation of substituents on the enone β-carbon as well as on the diyne. It should be remarked that, unlike in other enantioselective diynylations of carbonyl compounds and imines previously reported in the literature, pre-metalation of the terminal diyne with stoichiometric amounts of a dialkylzinc reagent is not required. Our results show that the transient diynyl-copper species formed from the terminal diyne and the copper(I) complex in the presence of an amine are sufficiently nucleophilic to react even with weak electrophiles. This may anticipate the possibility of other enantioselective diynylation reactions not requiring pre-metalation of terminal diynes with stoichiometric amounts of organometallic reagents in the future.



Scheme 2. Examples of chemical transformations carried out on diynes **3**.

Financial support from the Ministerio de Economía y Competitividad (MINECO-Gobierno de España) and FEDER (EU) (CTQ2013-47494-P), and from Generalitat Valenciana (ISIC2012/001) is gratefully acknowledged. A. S.-M. thanks the MINECO for a predoctoral grant (FPI program). Access to NMR and MS facilities from the Servei Central de Suport a la Investigació Experimental (SCSIE)-UV is also acknowledged.

Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental procedures and characterization data for new compounds. X-ray data and ortep plot for compound **3af**. See DOI: 10.1039/c000000x/

‡ **General procedure for the enantioselective conjugate diynylation reaction:** $[Cu(CH_3CN)_4]BF_4$ (1.1 mg, 0.0034 mmol) and (*R*)-**L1** (4.1 mg, 0.0034 mmol) were added to a dried round bottom flask which was purged with nitrogen. Toluene (0.2 mL) was added via syringe and the

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mixture was stirred for 1.5 h at room temperature under nitrogen atmosphere. Then, a solution of α,β-unsaturated trifluoromethyl ketone **1** (0.144 mmol) in toluene (1.0 mL) was added via syringe, followed of triethylamine (2 μL, 0.0144 mmol). The solution was stirred for 10 min at room temperature. Then a solution of 1,3-diyne **2** (0.188 mmol) in toluene (1.0 mL) was added via syringe and the solution was stirred at room temperature 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 x 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:ethyl acetate mixtures afforded compound **3**.

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19 CCDC-1046444 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

20 Other non-fluorinated enones such as 2-cyclohexenone, chalcone or 4-phenyl-3-buten-2-one did not react under the optimized conditions.