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Catalytic enantioselective addition of terminal 1,3-diynes to aromatic ketones: facile access to chiral nonracemic tertiary alcohols†

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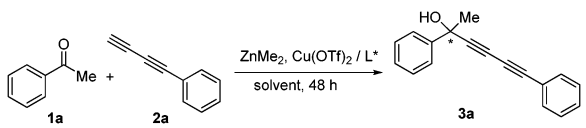
An efficient, catalytic, and enantioselective 1,2-addition of terminal 1,3-diynes to aromatic ketones was realized in the presence of 10 mol% of a Cu(OTf)$_2$-hydroxycamphor-sulfonamide complex, affording chiral tertiary alcohols in up to 94% yield and 90% ee.

Chiral nonracemic tertiary alcohols are important structural subunits that can be found in a large number of natural products, pharmaceuticals, and biologically active compounds.[1] The catalytic enantioselective addition of carbon nucleophiles to prochiral ketones, which can simultaneously construct a carbon skeleton and tetrasubstituted stereogenic center, represents the most convergent and efficient approach to the synthesis of optically active tertiary alcohols.[2] Although ketones are challenging substrates because of their low reactivity and because of the difficulty in controlling facial stereoselectivity, many effective methods have been developed for the catalytic enantioselective C–C bond-forming reactions with ketones. In this context, the catalytic enantioselective addition of organozinc to ketones has been extensively studied in the past decade.[3] A great effort has been devoted to the development of highly selective and efficient catalytic systems, and the utilization of various organozinc reagents including alkyl-,[4] aryl-,[5] alkenyl-,[6] and alkynylzinc[7] in this synthetically useful addition transformation. Despite significant progress made in this area, the use of terminal 1,3-diynes as carbon nucleophiles in this 1,2-addition reaction to ketones has been much less investigated.[8] Mikami and coworkers developed an enantioselective palladium-catalyzed diynylation of ethyl trifluoropyruvate with diynylsilanes.[9] Although the yields as well as the enantioselectivities are good to high, the main drawback is the use of the limited ketone substrate. As a result of efforts toward the development of new catalytic reactions with challenging substrates, herein we report the first general, facile, and effective method for the catalytic enantioselective addition of terminal 1,3-diynes to aromatic ketones. Such studies would be of immense benefit for expanding the scope of application of this addition reaction in organic synthesis.

We recently developed a catalytic enantioselective alkynylation of trifluoromethyl ketones by a combination of Ti(OPr^i)$_4$, BaF$_2$, and readily available cinchona alkaloids.[10] In our initial attempt to extend this methodology, low reactivity and low enantioselectivity were observed in the addition of diyne **2a** to acetophenone **1a**. Subsequently, the addition of diynylzinc to acetophenone **1a** in the presence of various aminoalcohols also failed to produce the desired adduct. In comparison with aldehydes, the attenuated reactivity of ketones means that strong activators are necessary for reasonable reaction rates. Next, we decided to employ the Cu-complexes (Chan's catalyst system)[11] to enhance the reactivity of ketones toward the attack of diynylzinc (Table 1). We were delighted to find that the Cu(OTf)$_2$-hydroxycamphorsulfonamide complex was the most promising catalyst for the test reaction (Table 1, entries 1–5), whereas the other Cu-complexes tested resulted in lower yields or enantioselectivities. A series of chiral hydroxycamphor-sulfonamide derivatives (Fig. 1, **I–VI**) were screened for the Cu-catalyzed diynylation of **1a**. Ligand **II** with an *endo*-hydroxy group gave a

Table 1 Optimizing of conditions for the addition of **2a** to **1a** to give **3a**[a]



Entry	Catalyst (mol%)	Solvent	Temp/°C	Yield[b] (%)	ee[c] (%)
1	Cu(OTf)$_2$/**I** (10)	DCM	25	94	70
2	CuF$_2$/**I** (10)	DCM	25	67	14
3	CuOTf/**I** (10)	DCM	25	90	68
4	CuI/**I** (10)	DCM	25	10	—
5	CuBr/**I** (10)	DCM	25	73	20
6	Cu(OTf)$_2$/**II** (10)	DCM	25	52	10
7	Cu(OTf)$_2$/**III** (10)	DCM	25	95	75
8	Cu(OTf)$_2$/**IV** (10)	DCM	25	90	50
9	Cu(OTf)$_2$/**V** (10)	DCM	25	82	22
10	Cu(OTf)$_2$/**VI** (10)	DCM	25	45	13
11[d]	Cu(OTf)$_2$/**III** (10)	DCE	25	90	75
12	Cu(OTf)$_2$/**III** (10)	$CHCl_3$	25	20	15
13	Cu(OTf)$_2$/**III** (10)	Toluene	25	90	60
14	Cu(OTf)$_2$/**III** (10)	Benzene	25	92	57
15	Cu(OTf)$_2$/**III** (10)	Et_2O	25	0	0
16	Cu(OTf)$_2$/**III** (10)	THF	25	0	0
17	Cu(OTf)$_2$/**III** (10)	DCM	10	94	77
18	Cu(OTf)$_2$/**III** (10)	DCM	0	88	77
19	Cu(OTf)$_2$/**III** (15)	DCM	10	95	75
20	Cu(OTf)$_2$/**III** (5)	DCM	10	60	60

[a] Acetophenone : buta-1,3-diynylbenzene : Me_2Zn = 1 : 2.6 : 3 (equivalent ratio) for 48 h. [b] Isolated yield. [c] Enantiomeric excess was determined by chiral HPLC analysis. [d] DCE: dichloroethane.

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† Electronic supplementary information (ESI) available. CCDC 830329. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c1cc15968b

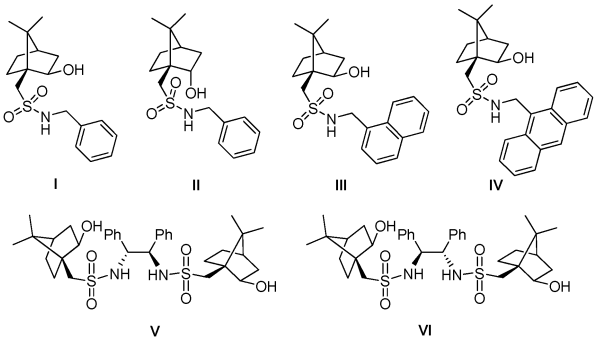


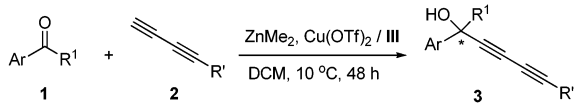
Fig. 1 Chiral ligands tested in the addition reaction of diynes to ketones.

very poor ee (entry 6). The modification of the methylamine moiety with bulky aryl groups gave rise to the fluctuation in enantioselectivity (entries 7–10), with 10 mol% of ligand **III** giving the best performance in terms of both the yield and the enantioselectivity (entry 7). A comparison of the results obtained in different solvents showed that this asymmetric transformation is highly sensitive to the solvent used (entries 11–16). No reaction occurred in the coordinating solvents, and dichloromethane (DCM) was found to be the best solvent for this reaction. Further optimization by changing the temperature and the catalyst loading (entries 17–20) led to the discovery that the best results were obtained when 10 mol% of the $Cu(OTf)_2$-**III** complex was used at 10 °C (94% yield, 77% ee, entry 17).

With the optimized reaction conditions in hand, we explored the scope of this diynylation reaction by varying the aromatic ketones and the terminal 1,3-diynes. The results are summarized in Table 2. Most of the tertiary diynols were obtained in good chemical yields, yet the ee values were dependent on the nucleophilic property of the diyne and the steric hindrance of the ketone substrate. For all aromatic ketones studied that bear substituents in the 2-, 3-, or 4-position, the enantiomeric excess of the tertiary diynols **3a–k** was in the range of 65–90% (entries 1–11). Aromatic ketones that contain an electron-donating group reacted slowly with terminal 1,3-diyne. For example, 2′- and 4′-methylacetophenones gave the desired products in the yield of 60% and 67%, respectively (entries 5 and 6). Additionally, the reaction worked well with 1-(naphthalen-2-yl)ethanone to afford the 1,2-adduct **3l** in good yield and enantioselectivity (entry 12). Propiophenone gave the corresponding product **3m** in 95% yield with 62% ee (entry 13). Further exploration of the substrate scope focused on the nucleophilic diynes. It appeared that electron-donating and electron-withdrawing substituents on the aromatic ring can be tolerated, and good stereocontrol (62–80% ee) was observed for the products **3n–r** (entries 14–18). Alicyclic diyne also gave the diynylation adduct **3s** in good yield and enantioselectivity (entry 19). Triisopropylsilyl-substituted 1,3-diyne is also a viable substrate, affording the desired product **3t** in 70% yield with 72% ee (entry 20). In addition, we investigated the addition reaction with 2-butanone, 3,3-dimethyl-2-butanone, and (4-chlorophenyl)(phenyl)methanone. These substrates were found to be unsuitable for this asymmetric transformation and poor enantioselectivity (<15%) was observed.

To evaluate this catalytic system on a large-scale, 3 mmol of substrate **1c** was used to perform the diynylation addition

Table 2 Scope of the catalytic enantioselective 1,2-addition of terminal 1,3-diynes to aromatic ketones to afford product **3**[a]



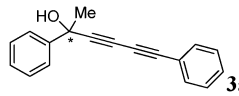
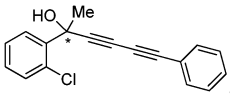
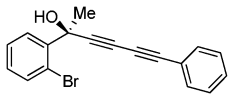
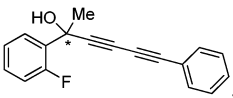
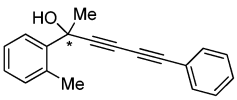
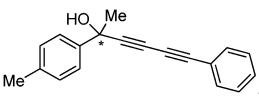
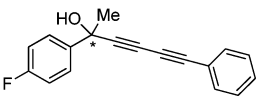
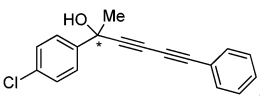
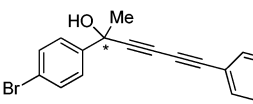
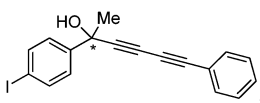
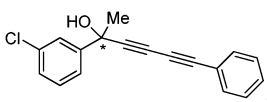
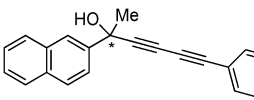
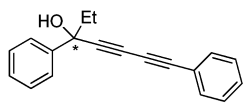
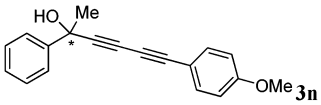
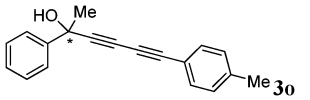
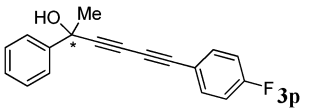
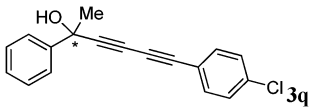
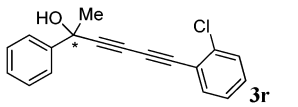
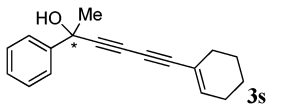
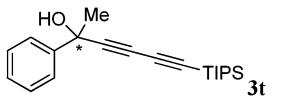
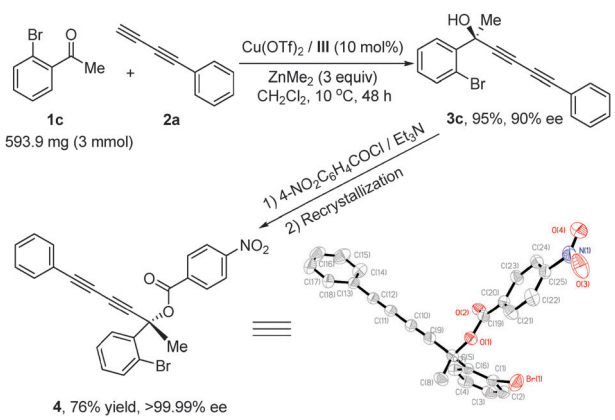
Entry	Product	Yield[b] (%)	ee[c] (%)
1	 **3a**	94	77
2	 **3b**	92	90
3	 **3c**	91	90
4	 **3d**	88	79
5	 **3e**	60	71
6	 **3f**	67	71
7	 **3g**	83	71
8	 **3h**	86	72
9	 **3i**	80	65
10	 **3j**	95	81
11	 **3k**	92	70
12	 **3l**	71	68
13	 **3m**	91	62

Table 2 (*continued*)

Entry	Product	Yield[b] (%)	ee[c] (%)
14	 **3n**	90	80
15	 **3o**	82	70
16	 **3p**	77	62
17	 **3q**	79	66
18	 **3r**	85	67
19	 **3s**	85	79
20	 **3t**	71	72

[a] The reaction was run with 10 mol% $Cu(OTf)_2$/**III** at 10 °C for 48 h. [b] Isolated yield. [c] ee was determined by HPLC analysis using a chiral stationary phase.

and the product **3c** was obtained in 95% yield and 90% ee. Further transformation of the adduct **3c** furnished the crystalline derivative **4** whose absolute stereochemistry was determined to be *S* from single-crystal X-ray structural analysis (Scheme 1).[12] Thus, we established that the absolute configuration of the major enantiomer **3c** is *S*. These results show that



Scheme 1 Scaled-up version of the addition reaction, further transformation, and X-ray structure for the determination of the absolute configuration.

the Si-face of the ketone was predominantly approached by the nucleophilic diyne.

In summary, we have successfully developed the first catalytic enantioselective addition of terminal 1,3-diynes to aromatic ketones. In the presence of chiral hydroxycamphorsulfonamide, the reaction proceeded smoothly to afford a series of chiral tertiary alcohols in 60–94% yield with 62–90% ee. Further mechanistic investigation, extension of the reaction scope, and additional improvement on the enantioselectivity are ongoing in our laboratory.

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12 The absolute configuration of **4** was confirmed by X-ray crystal structure analysis. See ESI† for further details. Crystallographic data for **4**: CCDC 830329.