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Highly Enantioselective Catalytic Alkynylation of Ketones – A Convenient Approach to Optically Active Propargylic Alcohols

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Abstract: The development of highly enantioselective catalysts involving $Cu(OTf)_2$ and chiral camphorsulfonamides for the alkynylation of ketone is described. The influences of Lewis acids, reaction conditions and chiral ligands on the outcome of the reaction are discussed. The best enantioselectivity (up to 97% *ee*) was obtained in the alkynylation of 2′-chloroacetophenone. The scope of the reaction is also examined.

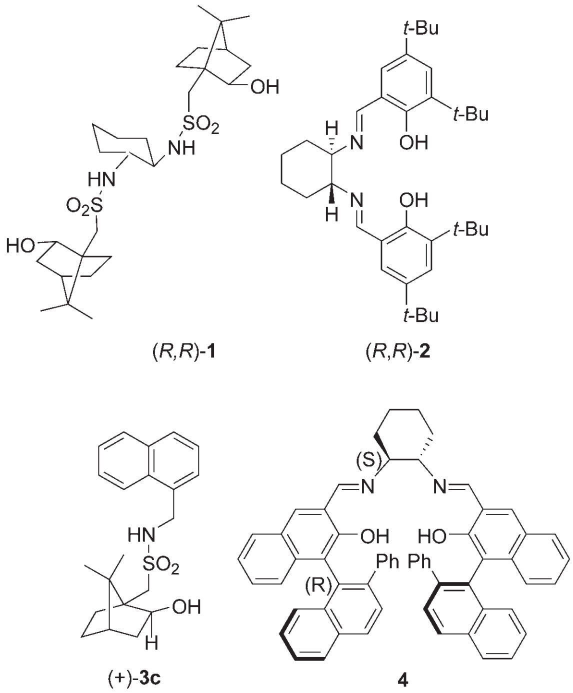
Keywords: alkynylation; asymmetric catalysis; camphorsulfonamides; organozinc compounds

Introduction

Chiral tertiary alcohols are important building blocks for organic synthesis, and the construction of such stereogenic carbon centers continues to be a considerable challenge in organic synthesis.[1] Among the different strategies, the nucleophilic addition of organometallics (especially mild organozinc reagents) to carbonyl compounds is perhaps the most straightforward and useful method to achieve this goal.

Recently, significant improvements have been made in the asymmetric alkylation of ketones.[2] Walsh et al. developed a bis(sulfonamide)diol ligand **1** (Scheme 1) which gave excellent results for the catalytic addition of dialkylzinc to ketones.[3a] Later this catalyst was found to be highly efficient for a broad range of substrates including aliphatic ketones, aromatic ketones and conjugated enones,[3b–g] and the organozinc reagents can be either alkylzinc, arylzinc[3h,i] or vinylzinc[3j–l] compounds. Several examples of enantioselective addition of alkylzinc to α-keto esters have also been reported.[4–8]

The enantioselective addition of alkynylzinc to ketones has been less studied despite the fact that chiral tertiary propargylic alcohols are important pharmaceutical intermediates and are normally difficult to generate with high enantioselectivity using other methodologies.[9] Tan and co-workers reported the first stoichiometric asymmetric alkynylzinc (which was prepared *in situ* from an alkynyllithium or a Grignard reagent) addition to some highly activated ketones with up to 98% *ee* for the product, which was an intermediate for efavirenz, an anti HIV drug.[10] Cozzi used chiral zinc-**2** complex (Scheme 1) to catalyze the asymmetric alkynylation of unactivated ke-

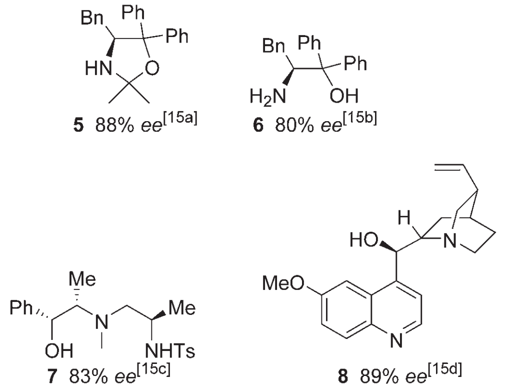


Scheme 1.

tones in up to 81% *ee*.[11] In a preliminary communication we also reported the asymmetric addition of alkynylzinc to aromatic ketones using catalytic amount of the chiral $Cu(OTf)_2$-**3c** complex (Scheme 1) as catalyst, and the corresponding tertiary propargylic alcohols were obtained in high yields and up to 97% *ee*.[12] To the best of our knowledge, that was among the highest ee's for the enantioselective addition of alkynylzinc reagents to ketones.

Subsequently, Katsuki and Saito demonstrated that chiral salen ligand **4** bearing a 2′-substituted binaphthyl unit (Scheme 1) can serve as more efficient catalyst than **2** for the asymmetric alkynylation of aliphatic ketones (up to 91% *ee*).[13]

Recently Wang et al. used (*S*)-BINOL and $Ti(O\text{-}i\text{-}Pr)_4$ as the chiral catalyst for the catalytic asymmetric addition of alkynylzinc to simple ketones, good enantioselectivities (92% *ee*) were obtained.[14] Some other chiral ligands **5–8** were also developed for enantioselective phenylacetylene addition to ketones (Scheme 2).[15]



5 88% *ee*[15a]

6 80% *ee*[15b]

7 83% *ee*[15c]

8 89% *ee*[15d]

Scheme 2.

In this paper we report the full account of our studies on the development of more efficient catalyst systems in the alkynylation of various ketone substrates. The scope of the reaction is also examined.

Results and Discussions

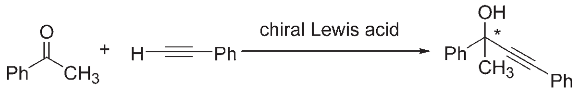
Reaction Optimization

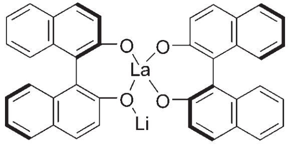
Effect of Lewis Acids

Our first attempts to apply the chiral $Ti(O\text{-}i\text{-}Pr)_4$-BINOL catalyst[16] (Table 1 entry 1) and a chiral heterobimetallic multifunctional catalyst[17] (entry 2) for the asymmetric alkynylation of ketones were unsuccessful, and no reaction was observed. The use of Carreira's catalyst system[18] (entry 3) also failed to produce the desired products. The reason might lie in the low activity of ketones towards the nucleophile under these reaction conditions.[19] With the expectation that the reactivity of ketones might be improved by a stronger Lewis acid, we used $Cu(OTf)_2$ as promoter and obtained a considerable amount of the tertiary propargylic alcohol.

Further study revealed that $Cu(OTf)_2$-camphorsulfonamide (**3c**) was a promising catalyst for this reac-

Table 1. Alkynylation of acetophenone using different chiral Lewis acids.[a]



Entry	Chiral Lewis acid	Catalyst [mol%]	Yield [%][b]	*ee* [%][c]	Remarks
1	(*R*)-BINOL + $Ti(O\text{-}i\text{-}Pr)_4$	20	NR	-	[21]
2[d]		10	NR	-	
3[d]	**3c** + $Zn(OTf)_2$ + Et_3N	120	-	-	by-product
4	**3c** + $Cu(OTf)_2$	10	92	88 (+)	
5	**3c** + $[Cu(OTf)]_2$·toluene	10	84	89 (+)	
6	**3c** + CuI	10	NR	-	
7	**3c** + $Sc(OTf)_3$	10	-	-	by-product
8	**3c** + CuBr	10	10	-	

[a] Acetophenone:phenylacetylene:Me_2Zn = 0.4:1.04:1.2 (molar ratio), 0°C for 48 h.

[b] Isolated yield of the corresponding products.

[c] The enantiomeric excess was determined by HPLC analysis of the alcohol or its derivative using a Chiralcel OD or OD-H column.

[d] Without using dimethylzinc.

tion. Other Lewis acids such as CuI or CuBr did not catalyze the reaction at all, while $[Cu(OTf)]_2$·toluene provided a similarly high selectivity as $Cu(OTf)_2$.[20]

Effect of Reaction Conditions

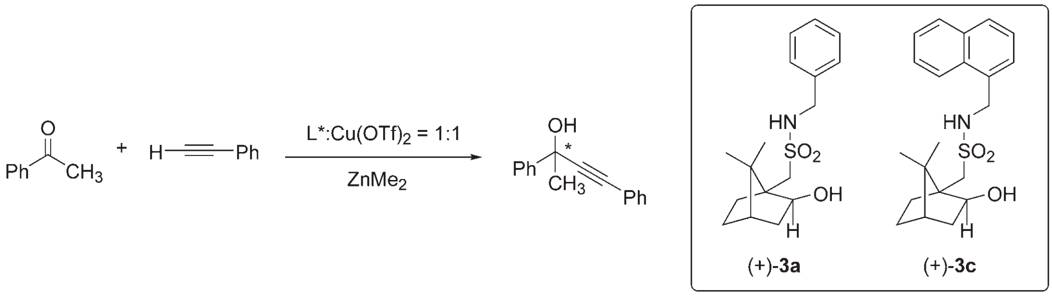
Thorough screening experiments were performed to find the best reaction conditions for the catalytic enantioselective alkynylation of ketones. Acetophenone and phenylacetylene were chosen as standard substrates, and some common factors such as the choice of solvent, substrate-to-catalyst ratio, etc. were examined (Table 2). The enantioselectivities were found to be quite sensitive to the solvents used. When the reaction was carried out at 0 °C in toluene, THF, CH_3OH, hexane, Et_2O and CH_2Cl_2, the results ranged from no reaction to high yield and high *ee*. CH_2Cl_2 was found to be the best solvent for this reaction. The product *ee* increased with the increase of catalyst loading and reached a plateau when the catalyst loading reached 10 mol%. Higher catalyst loadings were not useful because of the poor solubility of the copper salt (in CH_2Cl_2).

Effect of Chiral Ligands

While chiral ligands such as binaphthol, amino alcohol **9**, pybox **10** and sulfonamide **11** gave either poor enantioselectivities or undesired by-products in the asymmetric alkynylation of ketones, the camphorsulfonamide ligand **3a** gave the desired product in 90% yield and 82% *ee* (Table 3 entry 5). This preliminary success prompted us to examine other camphorsulfonamide derivatives in this enantioselective reaction. It was found that a sterically hindered ligand such as **3c** gave higher yields than the corresponding less hindered ligands, and ligand **3b** with an *endo*-hydroxy group gave a very poor *ee* (entry 6). Similar effects had been observed in the titanium complex-catalyzed alkylation of ketones.

Sulfonamides **3f** and **3g**, prepared through the reaction of D-(+)-camphorsulfonyl chloride with (*R*)-α-methylbenzylamine and (*S*)-α-methylbenzylamine, respectively, were also tested but no desired product was obtained. This may be due to the extra steric hindrance of the imines caused by the adjacent extra stereocenters. Ligands **3a** and **3c** were superior to **3d** and **3e**, possibly due to the presence of a flexible CH_2 group adjacent to the imine, which may help to fix the pro-chiral face of the substrate in the transition state and therefore result in better selectivity. The bisulfonamide ligand **1** failed to give a good result in this reaction although it performed well in the alkylation of ketones. Among all the ligands tested, ligand **3c** was found to give the best results.

Table 2. Alkynylation of acetophenone under different reaction conditions.[a]



Entry	Ligand (mol%)	Solvent	Yield [%][b]	*ee* [%][c]
1	**3a** (10)	tetrahydrofuran	0	-
2	**3a** (10)	toluene	87	36 (+)
3	**3a** (10)	methanol	0	-
4	**3a** (10)	hexane	39	13 (+)
5	**3a** (10)	ether	0	-
6	**3a** (10)	dichloromethane	90	82 (+)
7	**3c** (20[d])	dichloromethane	80	85 (+)
8	**3c** (10)	dichloromethane	92	88 (+)
9	**3c** (5)	dichloromethane	88	86 (+)
10	**3c** (1)	dichloromethane	48	36 (+)

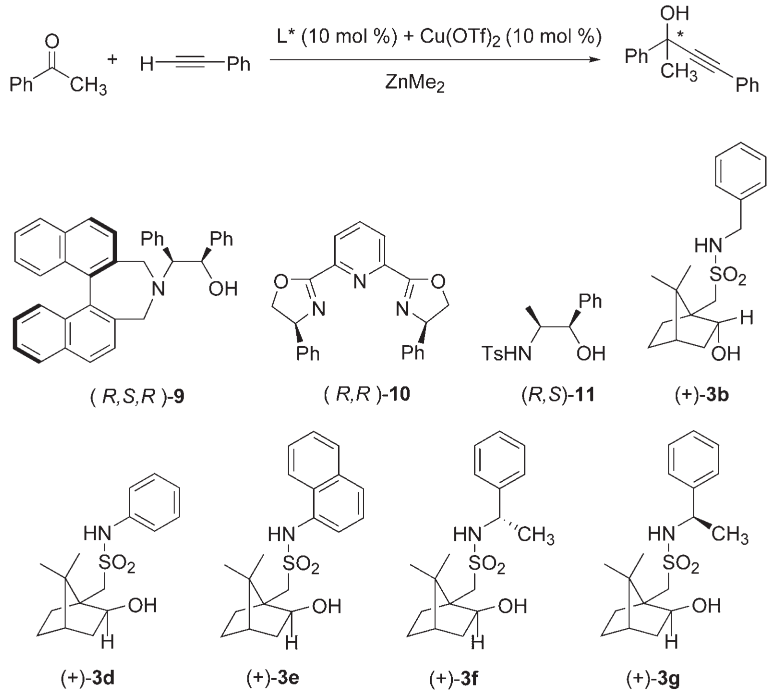
[a] Acetophenone:phenylacetylene:Me_2Zn = 0.4:1.04:1.2 (molar ratio); 0 °C for 48 h.

[b] Isolated yield of the corresponding product.

[c] The *ee* was determined by HPLC analysis of the alcohol or its derivative using a Chiralcel OD or OD-H column.

[d] A large amount of CH_2Cl_2 (4 mL) was used to dissolve the $Cu(OTf)_2$.

Table 3. Alkynylation of acetophenone using different chiral ligands.[a]



Entry	Ligand	Yield [%][b]	*ee* [%][c]
1	(*R*)-BINOL	ND	8
2	(*R*,*S*,*R*)-**9**	ND	3
3	(*R*,*R*)-**10**	29	racemic product
4	(*R*,*S*)-**11**	-	-
5	**3a**	90	82
6	**3b**	49	13
7	**3c**	92	88
8	**3d**	32	61
9	**3e**	51	65
10	**3f**	-	-
11	**3g**	-	-
12	(*R*,*R*)-**1**	50	13

[a] Acetophenone:phenylacetylene:Me$_2$Zn = 0.4:1.04:1.2 (molar ratio), 0 °C for 48 h.

[b] Isolated yield of the corresponding product.

[c] The *ee* was determined by HPLC analysis of the alcohol or its derivative using a Chiralcel OD or OD-H column.

Scope of Substrates

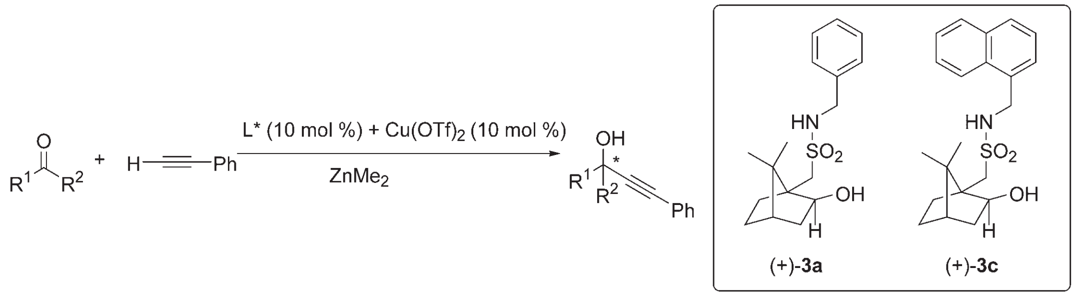
Aromatic Ketones

The alkynylation of different aromatic ketones was studied using Cu(OTf)$_2$ and ligand **3c** as catalyst. Without exception, all substrates presented in Table 4 were alkynylated to the corresponding tertiary propargylic alcohols with good to excellent enantioselectivities.

ortho-Substituted aromatic ketones were found to give a higher enantioselectivity. For example, 2′-methyl-, 2′-fluoro-, 2′-chloro-, and 2′-bromoacetophenone all gave excellent *ee*s (Table 4, entries 3–7). The best enantioselectivity (97%) was obtained in the alkynylation of 2′-chloroacetophenone (entry 5). It is possible that the steric hindrance of the *ortho*-substituent restricted the orientation of the substrate and thus resulted in higher enantioselectivities for the alkynylation of such ketones. Increasing the size of the substituent at the *ortho*-position of the substrate led to lower yields, for example, 65% for 2′-bromoacetophenone (entry 4), 94% for 2′-chloroacetophenone (entry 5) and 49% for 2′-methylacetophenone (entry 7).

The alkynylation product of 4′-ferrocenylacetophenone was isolated in high yield and up to 90% *ee* (Table 4 entry 17), whereas the alkynylation of acetylferrocene gave an unidentified by-product(s). This can be explained by the strong electron-withdrawing

Table 4. Enantioselective addition of phenylacetylene to various aromatic ketones.[a]



(+)-**3a** (+)-**3c**

Entry	R^1/R^2	Ligand	Yield [%][b]	*ee* [%][c]
1	Ph/Me	**3a**	90	82 (+)
2	Ph/Me	**3c**	92	88 (+)
3	2-BrC_6H_4/Me	**3a**	39	87 (−)
4	2-BrC_6H_4/Me	**3c**	65	96 (−)
5	2-ClC_6H_4/Me	**3c**	94	97 (−)
6	2-FC_6H_4/Me	**3c**	91	96 (−)
7	2-MeC_6H_4/Me	**3c**	49	96 (−)
8	3-BrC_6H_4/Me	**3c**	80	82 (+)
9	4-BrC_6H_4/Me	**3c**	75	91 (+)
10	4-ClC_6H_4/Me	**3c**	72	71 (+)
11	3-MeC_6H_4/Me	**3c**	83	86 (+)
12	3-$CF_3C_6H_4$/Me	**3c**	91	70 (−)
13	4-MeC_6H_4/Me	**3c**	77	92 (+)
14	4-$CF_3C_6H_4$/Me	**3c**	82	93 (+)
15	2-Naphthyl/Me	**3c**	75	85 (+)
16	Ph/Et	**3c**	57	71 (+)
17	4-FerrocenylC_6H_4/Me	**3c**	62	90 (+)

[a] **3a** or **3c** as chiral ligand; ketone:ligand:$Cu(OTf)_2$:Me_2Zn = 0.4:0.04:0.04:1.2 (molar ratio), CH_2Cl_2 as solvent; 0 °C for 48 h.

[b] Isolated yield of the corresponding product.

[c] Enantiomeric excess was determined by HPLC analysis of the alcohol or its derivative using a Chiralcel OD or OD-H column.

properties of the ferrocenyl groups, which strongly activate the acetylferrocene substrate and therefore caused other side reactions.

Aliphatic Ketones or Alkynes

Table 5 summarizes some typical results of the alkynylation of various aliphatic or aromatic ketones with different terminal alkynes. Most of the tertiary propargylic alcohols were obtained in good chemical yields, yet the *ee*s were strongly dependent on the nucleophilic property of the alkyne and the steric hindrance of the ketone substrate.

Cyclohexyl phenyl ketone was converted to the corresponding tertiary propargylic alcohol in low yield (20%) and low enantioselectivity (nearly racemic). Cyclopropyl phenyl ketone failed to react. The alky-

Table 5. Reaction of various ketones with alkynes under optimized reaction conditions.[a]

Entry	Ketone	Alkyne	Yield [%][b]	*ee* [%][c]
1	c-$C_3H_5COCH_3$	Ph-C≡C-H	93	5
2	$(CH_3)_2CHCOCH_3$	Ph-C≡C-H	90	**88**
3	$PhCH_2CH_2COCH_3$	Ph-C≡C-H	89	35
4	$PhCOCH_3$	c-C_3H_5-C≡C-H	81	60
5	$PhCOCH_3$	$(CH_3)_3Si$-C≡C-H	76	54

[a] **3c** as chiral ligand; ketone:ligand:$Cu(OTf)_2$:Me_2Zn = 0.4:0.04:0.04:1.2 (molar ratio), CH_2Cl_2 as solvent; 0 °C for 48 h.

[b] Isolated yield of the corresponding products.

[c] Enantiomeric excess was determined by HPLC analysis of the alcohol or its derivative using a Chiralcel OD or OD-H column.

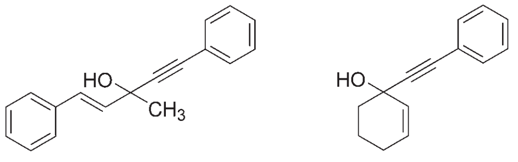
nylation of 2-tetralone also gave a racemic product. These results might be due to the large steric hindrance of these substrates.

The reactions of aliphatic terminal alkynes with acetophenone gave a low enantioselectivity (54% *ee* for trimethylsilylacetylene and 60% *ee* when cyclopropyl acetylene was used, Table 5 entries 4 and 5), possibly due to the different electronic properties of the aliphatic alkynes. Aliphatic ketones were generally less selective although results comparable to those of the aryl ketones had been obtained for the reaction of 3-methyl-2-butanone (Table 5 entry 2), which might be partially related with the suitable hindrance and orientation of the isopropyl group.

Heteroaromatic Ketones

When **3c** was used to catalyze the alkynylzinc addition to 3-acetylpyridine, the product was obtained with good yield (81%) but with no enantioselectivity. To improve the enantioselectivity of the reaction, other chiral catalysts were also tested. The study showed that BINOL and (*R,S,R*)-**9** gave less than 30% enantiomeric excess, while (*R,R*)-**10**, (*R,R*)-**12** and (*R*)-**13** gave either racemic product or even no reaction at all (Scheme 3). The poor enantioselectivity might be due to the strong coordination of the nitrogen atom in the substrate to Cu(OTf)$_2$ or the organozinc reagent (or both).

To further explore the scope of the substrates, we also investigated the effectiveness of catalyst **3c** in the asymmetric alkynylation of unsaturated ketones. It was found that the catalyst system Cu(OTf)$_2$/**3c** tends to catalyze the alkynylation of the C=O double bond preferentially over the coexisting C=C bond (Scheme 4). The results revealed that high yields were obtained for 1,2-addition reactions of both cyclic and acyclic α,β-unsaturated ketones, and the enantioselectivity for the alkynylation of acyclic unsaturated ketones, such as *trans*-4-phenyl-3-buten-2-one was substantially higher (**3a** as catalyst: 93% yield, 59% *ee*; **3c** as catalyst: 95% yield, 85% *ee*) than that for the cyclic unsaturated ketones such as 2-cyclohexenone (**3c** as catalyst: 92% yield, 15% *ee*).



3a 93% yield, 59% *ee*
3c 95% yield, 85% *ee*

3c 92% yield, 15% *ee*

Scheme 4.

Our preliminary study indicates that the mechanism of the camphorsulfonamide-mediated reaction is quite similar to that proposed by Noyori et al. in the sulfonamide-catalyzed asymmetric conjugate addition of enones.[20] Further experimental results are needed, however, before a mechanistic model can be proposed with any certainty.

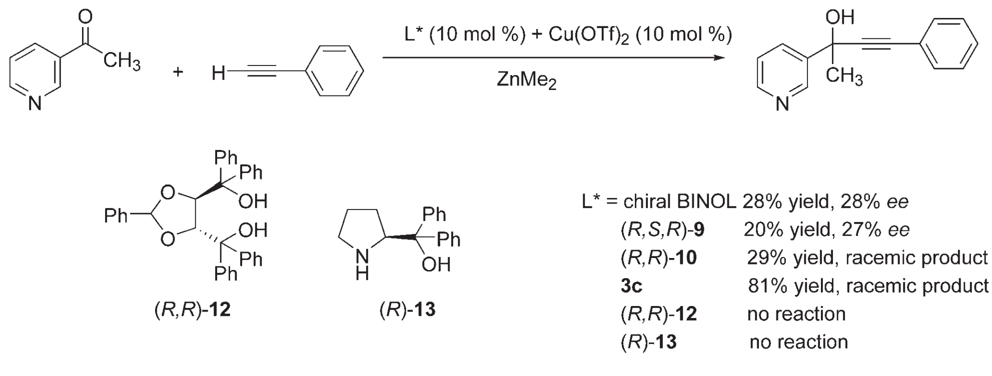
Conclusions

In conclusion, we have demonstrated that Cu(OTf)$_2$ and commercially available camphorsulfonamide ligands catalyzed the alkynylation of ketones with high yields and excellent enantioselectivities. The influence of Lewis acids, the reaction conditions and the chiral ligands on these reactions have been discussed, the scope of the reaction has also been examined.

Experimental Section

General Considerations

All experiments were carried out under a nitrogen atmosphere. Unless otherwise stated, commercial reagents purchased from either Acros or Aldrich chemical companies were used without further purification. The reactions were carried out in solvents distilled from standard drying agents. Phenylacetylene and ketones were freshly distilled under



L* = chiral BINOL 28% yield, 28% *ee*
(*R,S,R*)-**9** 20% yield, 27% *ee*
(*R,R*)-**10** 29% yield, racemic product
3c 81% yield, racemic product
(*R,R*)-**12** no reaction
(*R*)-**13** no reaction

Scheme 3.

normal or reduced pressure before use. ^{1}H NMR spectra were recorded on a Varian (500 MHz) spectrometer and the spectra were referenced internally to the residual proton resonance in $CDCl_3$ ($\delta = 7.26$), or with tetramethylsilane (TMS, $\delta = 0.00$) as the internal standard. Chemical shifts were reported as parts per million (ppm) in the δ scale downfield from TMS. ^{13}C NMR spectra were recorded on a Varian 500 spectrometer and referenced to $CDCl_3$ ($\delta = 77.0$). Thin layer chromatography was performed on Merck precoated silica gel 60 F_{254} plates. Silica gel (Merck, 230–400 mesh) was used for flash column chromatography. HPLC analyses were conducted on a Waters 600 instrument using Chiralcel columns (0.46 cm diameter × 25 cm length) columns. The absolute configurations of products were determined based on the comparison of HPLC traces and/or the direction of optical rotation with known compounds.

General Procedure for the Nucleophilic Addition of Alkynes to Ketones Catalyzed by Copper-Camphorsulfonamide Catalyst

A CH_2Cl_2 solution (2.0 mL) of sulfonamide ligand **3c** (14.92 mg, 0.04 mmol) and copper(II) triflate (14.79 mg, 0.04 mmol) was stirred at room temperature for 30 min to prepare the copper complex. Phenylacetylene (114 μL, 1.04 mmol) and a 2.0 M solution of dimethylzinc in toluene (0.6 mL, 1.2 mmol), were added to a dry flask at 0 °C under N_2 with stirring for 15 min. The copper complex was added to the flask containing $ZnMe_2$ and phenylacetylene *via* a syringe and the homogeneous solution was stirred at 0 °C for 30 min before acetophenone (46.8 μL, 0.4 mmol) was added. The mixture was allowed to stir at 0 °C for 48 h. The reaction was quenched with 2.0 mL of 5% HCl solution. The product was extracted with ethyl acetate (3×2 mL) and dried with Na_2SO_4. The compound was purified *via* flash chromatography (silica gel) using 10% ethyl acetate in hexane as eluent. The enantiomeric excess was determined by HPLC analysis on a Chiralcel OD or OD-H column.

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