Enantioselective Alkynylation

Enantioselective Alkynylation of Aromatic Ketones Catalyzed by Chiral Camphorsulfonamide Ligands**

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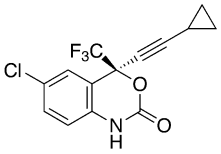
Chiral tertiary propargylic alcohols are important pharmaceutical intermediates. The synthesis of these compounds by the catalytic asymmetric addition of carbon nucleophiles to ketones has met with only very limited success, although methods to promote the alkynylation of aldehydes are well-studied.[1–6] Grabowski and co-workers[7–10] and Jiang and Feng[11] realized the addition of lithium cyclopropylacetylide to a *p*-methoxybenzyl-protected ketoaniline in 98–99% *ee*. The reaction is a key step in the manufacturing of efavirenz (DMP 266), a drug used in the treatment of AIDS.[12]



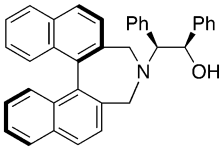
Efavirenz

However, large amounts of catalysts and the protection/deprotection of the aniline moiety are necessary. Grabowski and co-workers reported the direct alkynylation of ketoanilines (up to 99% *ee*) by alkynyl lithium or alkynyl magnesium reagents with *stoichiometric* amounts of chiral amino-alcohol and dialkyl zinc reagents.[13]

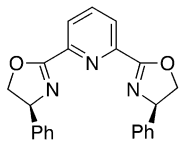
Carreira and co-workers developed a practical method for the synthesis of optically active secondary propargylic alcohols from terminal alkynes and aldehydes in the presence of $Zn(OTf)_2$ and Et_3N.[14–16] This method was applied to the alkynylation of ketoesters,[17] which exhibited reactivities between those of aldehydes and ketones. Kozlowski and DiMauro demonstrated the addition of diethylzinc reagents to α-ketoesters with chiral salen catalysts to give moderate enantiomeric excess.[18]

Organozinc reagents are also highly selective in nucleophilic addition to carbonyl compounds.[1–2] They can tolerate the presence of many functional groups that are reactive towards organolithium and -magnesium reagents, therefore may offer a useful alternative to these highly reactive nucleophiles. However, the low reactivities of organozinc species have limited their synthetic utility. Although three systems for the asymmetric addition of alkyl zinc reagents to ketones have been reported,[19–22] to the best of our knowledge, there was only one report of the catalytic, enantioselective addition of alkynyl zinc reagents to ketones.[23] From both fundamental and practical standpoints, it is highly desirable to develop new methods for the nucleophilic alkynylation of ketones with good stereocontrol.

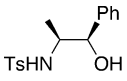
Our attempts to apply chiral binaphthol, titanium tetraisopropoxide, and alkynyl zinc reagents (which are known to be effective catalyst systems for the addition of alkynyl groups to aldehydes[3–6]) to the asymmetric alkynylation of ketones were unsuccessful, and no reaction was observed. The difficulty was mainly due to the inertness of ketones towards this reaction. With the expectation that the reactivity of ketones might be improved by using a stronger Lewis acid, we found that a considerable amount of tertiary propargylic alcohol was obtained by using $Cu(OTf)_2$ as a promoter in the reaction. In a preliminary screening study, we found that when chiral binaphthol, amino alcohol **1**, pybox **2**, and sulfonamide **3** were used as ligands, either poor enantioselectivity or undesired side products were obtained. On the other hand, the use of camphorsulfonamide ligand **4a** gave



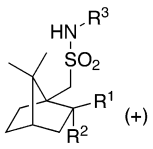
(*R,S,R*)-**1**



(*R,R*)-**2**



(*R,S*)-**3**



4a R^1= OH, R^2= H, R^3= benzyl (90% yield, 82% *ee*)
4b R^1= H, R^2= OH, R^3= benzyl (49% yield, 13% *ee*)
4c R^1= OH, R^2= H, R^3= 1-naphthylmethyl (92% yield, 88% *ee*)
4d R^1= OH, R^2= H, R^3= phenyl (32% yield, 61% *ee*)
4e R^1= OH, R^2= H, R^3= 1-naphthyl (51% yield, 65% *ee*)

90% yield of the product with 82% *ee*. This interesting result prompted us to examine the use of camphor derivatives in the enantioselective reaction. It was found that a sterically hindered ligand such as **4c** gave better yields, whereas ligand **4b** with the hydroxy group in the *endo* position gave very poor *ee*.

The asymmetric alkynylation of acetophenone in the presence of chiral ligand **4a** (**4c** in entries 8–11) in different solvents and with different copper salt/substrate ratios was examined (Table 1). The results revealed that CH_2Cl_2 was the best solvent and the optimum ratio of copper salt to acetophenone was 0.10.

The results of the addition of phenylacetylene to a variety of aromatic ketones catalyzed by chiral camphorsulfonamide **4a** and **4c** are summarized in Table 2. It appeared that electron-donating and electron-withdrawing substituents have little effect on the *ee* of the product. For example, 3′-methyl and 3′-bromoacetophenone gave products with 86 and 82% *ee*, respectively (Table 2, entries 8 and 10). 4′-Methyl- and 4′-bromoacetophenone also showed a similar trend (Table 2 entries 9 and 11).

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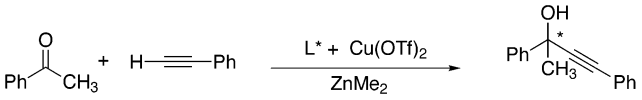
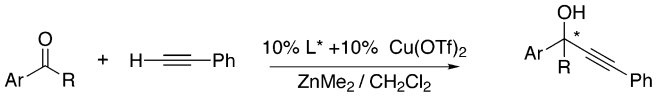
Table 1: The effect of reaction conditions on the enantioselectivity of the alkynylation of acetophenone.[a]



Entry	Solvent	Ligand	Copper triflate/substrate	Yield [%][b]	*ee* [%][c]
1	THF	**4a**	0.10	0	–
2	toluene	**4a**	0.10	87	36 (+)
3	CH_3OH	**4a**	0.10	0	–
4	acetone	**4a**	0.10	0	–
5	hexane	**4a**	0.10	39	13 (+)
6	Et_2O	**4a**	0.10	0	–
7	CH_2Cl_2	**4a**	0.10	90	82 (+)
8	CH_2Cl_2	**4c**	0.20[d]	80	85 (+)
9	CH_2Cl_2	**4c**	0.10	92	88 (+)
10	CH_2Cl_2	**4c**	0.05	88	86 (+)
11	CH_2Cl_2	**4c**	0.01	48	36 (+)

[a] **4a** or **4c** as chiral ligand, acetophenone/phenylacetylene/Me_2Zn = 0.4:1.04:1.2 (molar ratio), 0 °C, 2 mL solvent, 48 h. [b] Yields of isolated products. [c] The enantiomeric excess was determined by HPLC analysis of the alcohols. The sign of rotation of the predominant enantiomer is indicated in parentheses. [d] A large amount of CH_2Cl_2 (4 mL) was used to dissolve the $Cu(OTf)_2$.

Table 2: Enantioselective additions of phenylacetylene to aromatic ketones.[a]



Entry	Substrate	Ligand	Yield [%][b]	*ee* [%][c]
1	acetophenone	**4a**	90	82 (+)
2	acetophenone	**4c**	92	88 (+)
3	2′-bromoacetophenone	**4a**	39	87 (−)
4	2′-bromoacetophenone	**4c**	65	96 (−)
5	2′-chloroacetophenone	**4c**	94	97 (−)
6	2′-fluoroacetophenone	**4c**	91	96 (−)
7	2′-methylacetophenone	**4c**	49	96 (−)
8	3′-bromoacetophenone	**4c**	80	82 (+)
9	4′-bromoacetophenone	**4c**	75	91 (+)
10	3′-methylacetophenone	**4c**	83	86 (+)
11	4′-methylacetophenone	**4c**	77	92 (+)
12	2′-naphthacetophenone	**4c**	75	85 (+)
13	propiophenone	**4c**	57	71 (+)

[a] **4a** or **4c** 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, 48 h. [b] Yields of isolated products. [c] The enantiomeric excess was determined by HPLC analysis of the alcohols. The sign of rotation of the predominant enantiomer is indicated in parentheses.

Substituents at the *ortho* position of the substrate had a favorable effect on the enantioselectivity. Both 2′-methyl, 2′-fluoro, 2′-chloro, and 2′-bromoacetophenone gave excellent enantioselectivities (Table 2, entries 4–7). The best enantioselectivity (97% *ee*) was obtained in the alkynylation of 2′-chloroacetophenone in the presence of chiral ligand **4c**. It is possible that the proper steric hindrance of the *ortho* substituents restricts the orientation of the substrates and thus results in higher enantioselectivities for the alkynylation of such ketones.

For the alkynylation of α,β-unsaturated ketones, such as *trans*-4-phenyl-3-buten-2-one, moderate selectivity (85% yield, 73% *ee*) was obtained. The reactions of aliphatic terminal alkynes with acetophenone gave low enantioselectivity (54% *ee* when using trimethylsilylacetylene).

In conclusion, camphorsulfonamides are effective chiral catalysts for the production of tertiary propargylic alcohols with good to excellent enantioselectivities. This work represents a highly enantioselective catalytic addition of alkynyl zinc reagents to simple ketones. Further studies on the scope and mechanism of this reaction are underway.

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Keywords: alkynylation · asymmetric catalysis · enantioselectivity · ketones · nucleophilic addition

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