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Highly enantioselective alkynylation of aldehydes catalyzed by a readily available chiral amino alcohol-based ligand

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A new inexpensive chiral amino alcohol-based ligand, (1*S*,2*S*)-2-*N*,*N*-dimethylamino-1-(*p*-nitrophenyl)-3-(*t*-butyldimethylsilyloxy)propane-1-ol, was developed for the asymmetric alkynylation of aliphatic and aromatic aldehydes, to prepare the corresponding propargylic alcohols in high yields with up to 99% ee.

The catalytic asymmetric nucleophilic alkynylation of carbonyl compounds has considerable synthetic and industrial importance.[1] Great progress has been made in the enantioselective alkylation of aldehydes using chiral amino alcohols as ligands.[2] In contrast, there has been very limited success with the enantioselective nucleophilic alkynylation of aldehydes. Up to now, ligands (such as ephedrine derivatives) which have been successfully applied to catalyze the alkynylation of aldehydes with highly ee are relatively rare.[3–6] We report here the preparation of secondary chiral propargylic alcohols involving the highly enantioselective addition of alkynes to aldehydes in the presence of a new economical chiral ligand, (1*S*,2*S*)-2-amino-3-(*p*-nitrophenyl)propane-1,3-diol derivative.† Inexpensive (1*S*,2*S*)-2-amino-3-(*p*-nitrophenyl)propane-1,3-diol (**1**), which is obtained from chloramphenicol synthesis (its (1*R*,2*R*)-enantiomer can be obtained from the same source), is commercially available, and has been used in the resolution of racemic chrysanthemic acid on an industrial scale.[7] However, it has never been used in a catalytic asymmetric reaction.

To study the enantioselective alkynylation of the aldehyde with zinc alkynylide using (1*S*,2*S*)-2-amino-3-(*p*-nitrophenyl) propane-1,3-diol (**1**) as a ligand, the amino group in (1*S*, 2*S*)-**1** was converted to *N*,*N*-dimethyl derivative (1*S*,2*S*)-**2** in quantitative yield by reacting (1*S*,2*S*)-**1** with formaldehyde and formic acid.[8] A preliminary study was performed to determine the feasibility of enantioselective alkynylation using (1*S*, 2*S*)-**2** as a chiral auxiliary. We found that the nucleophilic addition of phenylacetylene with isobutyraldehyde proceeded in toluene with 1.1 equiv. of $Zn(OTf)_2$, 1.1 equiv. of triethylamine and 1.2 equiv. of ligand (1*S*, 2*S*)-**2**. An enantiomeric excess of 88% was obtained, but with poor chemical yield (21%). Attempts to improve the chemical yield by using different solvents such as THF, CH_2Cl_2 or toluene/CH_2Cl_2 (1 : 1) and by the addition of TMSCl or 4 Å sieves were fruitless, whereas the optical purity was increased to 97% ee in THF. When 2.0 equiv. $Zn(OTf)_2$ was added, the yield was slightly increased. It is rather interesting that the ee value significantly increased from 91% to 97% ee in THF instead of toluene since in the well-studied addition of dialkylzinc reagents to aldehydes the product enantioselectivity is adversely affected in THF[5a] (Table 1).

When alkyne was added to the mixture of $Zn(OTf)_2$, Et_3N and (1*S*,2*S*)-**2** in toluene, an oily product was formed on the glass wall. The oily product was unstable in air and sensitive to moisture. It has been proposed that a zinc alkynylide-ligand complex was formed in the catalytic enantioselective alkynylation reaction.[1c,6b] The yield of this reaction may be affected by the solubility of the zinc alkynylide-ligand intermediate. We thought that improvement of the lipid-solubility of the ligand might increase the chemical yield of the reaction. Therefore, (1*S*,2*S*)-**2** was transformed into the more lipid-soluble silyl ether (1*S*,2*S*)-**3** in 95% yield by selectively masking the terminal hydroxy group in (1*S*,2*S*)-**2** with *tert*-butyldimethylsilyl chloride in the presence of the imidazole and a catalytic amount of DMAP at 0 °C.[9] Interesting results were obtained with (1*S*,2*S*)-**3** as a chiral ligand in the enantioselective alkynylation reaction. The reaction was completed within 2 h and a secondary propargylic alcohol was obtained with 98% ee and in almost quantitative yield (Table **2**, entry 1). Further optimization of the amount of zinc triflate was studied. The best results were obtained in toluene with 1.1 equiv. of $Zn(OTf)_2$, 1.1 equiv. of Et_3N and 1.2 equiv. of (1*S*,2*S*)-**3**. The results using various aliphatic or aromatic aldehydes with alkynes under similar conditions are summarized in Table 2. As shown, all of the propargylic alcohols were obtained with excellent enantiomeric excess (up to 99%) and in high chemical yield (up to 99%). The reactions of aliphatic aldehydes were finished in 2 h while those of aromatic aldehydes were completed in 12 h.

(1*S*, 2*S*)-2-*N*,*N*-Dimethylamino-1-phenyl-3-(*tert*-butyldimethyl silyloxy)propane-1-ol (**4**)[10] as ligand also was tested in the

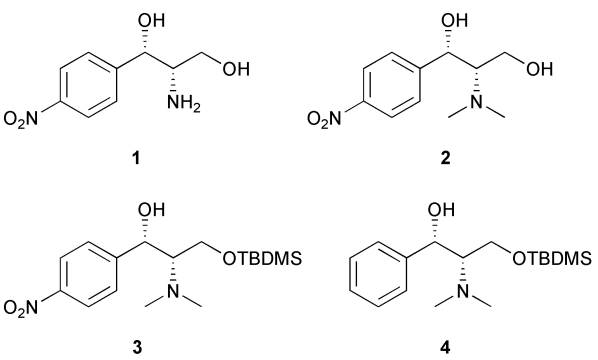
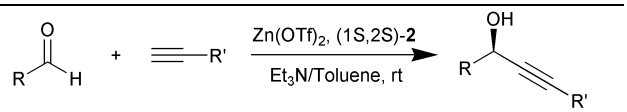


Table 1 The effect of reaction conditions on the enantioselectivity of the alkynylation of cyclohexane carboxaldehydes[a]



5 **6** **7**

Entry	Solvent	$Zn(OTf)_2$	Additive	Yield (%)[b]	Ee %[c]	Config.[d]
1	Toluene	1 equiv.		21	91	(+)-(*R*)
2	DCM	1 equiv.		8	91	(+)-(*R*)
3	THF	1 equiv.		28	97	(+)-(*R*)
4	Toluene/ DCM(1 : 1)	1 equiv.		16	93	(+)-(*R*)
5	Toluene	2 equiv.		33	93	(+)-(*R*)
6	Toluene	1 equiv.	TMSCl	No react.		
7	Toluene	1 equiv.	4 Å sieves	25	91	(+)-(*R*)

[a] Reactions carried out with addition of 1.1 equiv. of (1*S*, 2*S*)-**2** and 1.1 equiv. of Et_3N (2 mL) at 25 °C for 24 h; R = cyclohexyl, R′ = Ph. [b] Isolated yield. [c] Enantiomeric excess was determined by HPLC analysis of the alcohol or its derivatives. [d] Absolute configuration is based on the comparison with the literature.[6]

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Table 2 Asymmetric alkynylation of aldehydes with terminal alkynes catalyzed by (1*S*, 2*S*)-**3** and $Zn(OTf)_2$[a]

Entry	Alkyne (R′C≡CH)	Aldehyde (RCHO)	Yield of **7** (%)[b]	Ee (%)[c]	Rotat. Sign/Config.[d]
1	PhC≡CH	$(CH_3)_2CHCHO$	99	98	(+)-(*R*)[d]
2	$PhCH_2CH_2C{\equiv}CH$	$(CH_3)_2CHCHO$	99	> 99	(+)-(*R*)[d]
3	PhC≡CH	*n*-$C_6H_{13}CHO$	94	96.5	(−)
4	PhC≡CH	*n*-$C_6H_{13}CHO$	92	96[e]	(−)
5	$PhCH_2CH_2C{\equiv}CH$	*n*-$C_6H_{13}CHO$	94	99	(+)
6	PhC≡CH	*c*-$C_6H_{11}CHO$	99	96.5	(−)-(*R*)[d]
7	$PhCH_2CH_2C{\equiv}CH$	*c*-$C_6H_{11}CHO$	97	99	(−)-(*R*)[d]
8	PhC≡CH	$(Et)_2CHCHO$	99	97	(−)
9	$PhCH_2CH_2C{\equiv}CH$	$(Et)_2CHCHO$	99	98	(−)
10	PhC≡CH	*c*-C_3H_5CHO	93	93.5	(−)
11	PhC≡CH	PhCHO[f]	85	97	(+)-(*R*)[d]
12	$PhCH_2CH_2C{\equiv}CH$	PhCHO[f]	73	94	(+)-(*R*)[d]
13	*n*-$C_4H_9C{\equiv}CH$	*c*-$C_6H_{11}CHO$	82	95[g]	(−)
14	$TMSC{\equiv}CH$	*c*-$C_6H_{11}CHO$	83	96[g]	(−)-(*R*)[d]
15	$(CH_3)_3CC{\equiv}CH$	*c*-$C_6H_{11}CHO$	93	96[g]	(−)
16	*c*-$C_3H_5C{\equiv}CH$	*c*-$C_6H_{11}CHO$	98	97[g]	(−)
17	$TBDMSOCH_2C{\equiv}CH$	*c*-$C_6H_{11}CHO$	94	99[g]	(−)-(*R*)[d]
18	PhC≡CH	$(CH_3)_2CHCHO$	98	92[h]	(+)-(*R*)[d]
19	PhC≡CH	*n*-$C_6H_{13}CHO$	91	93[h]	(−)
20	PhC≡CH	*c*-$C_6H_{11}CHO$	85	93[h]	(−)-(*R*)[d]
21	PhC≡CH	*c*-C_3H_5CHO	89	85[h]	(−)
22	PhC≡CH	$(Et)_2CHCHO$	95	93[h]	(−)

[a] Unless otherwise stated the reactions were carried out with addition of 1.1 equiv. of (1*S*, 2*S*)-**3** and 1.05 equiv. of $Zn(OTf)_2$ and 1.1 equiv. of Et_3N in toluene (2 mL) at 25 °C for 2 h. [b] Isolated yield. [c] Enantiomeric excess was determined by HPLC analysis of the alcohol or its derivatives. [d] Absolute configuration is based on the comparison with the literature.[6c,7] [e] 1.2 equiv. of (1*S*,2*S*)-**4** as ligand. [f] Reaction time was 12 h. [g] Enantiomeric excess was determined by ^{19}F NMR of the corresponding (*R*)-MTPA ester, [h] 0.22 equiv. of (1*S*, 2*S*)-**3** and 0.2 equiv. of $Zn(OTf)_2$ and 0.5 equiv of Et_3N.

reaction, and gave a result similar to (1*S*,2*S*)-**3** (Table 2, entry 4).

Further study found that another catalytic condition, 0.22 equiv. ligand (1*S*,2*S*)-**3** and 0.2 equiv. $Zn(OTf)_2$ as additive,[6c] was effective for this reaction too, although the enantiomeric excess was slightly decreased (Entries 18–22, Table 2).

In conclusion, (1*S*,2*S*)-2-*N*,*N*-dimethylamino-1-(*p*-nitrophenyl)-3-(*tert*-butyldimethylsilyloxy)propane-1-ol (**3**) was conveniently prepared in two steps and in high yields from inexpensive commercially available (1*S*,2*S*)-2-amino-3-(*p*-nitrophenyl)propane-1,3-diol. This is the first time that this chiral compound has been used as ligand in the asymmetric reaction for the preparation of optically active propargylic alcohols in high yields with up to 99% ee. The reaction was carried out in a homogenous phase using various aldehydes and alkynes in the presence of ligand **3** and zinc triflate. We found that a different catalytic condition (0.22 equiv. ligand (1*S*,2*S*)-**3** and 0.2 equiv. $Zn(OTf)_2$ as additive) was also effective for this reaction, but with slightly decreased ee. A more detailed study using this new ligand to catalyze asymmetric alkynylation of carbonyl compounds is underway.

Notes and references

† A typical procedure for the asymmetric alkynylation reaction is as follows: To a solution of $Zn(OTf)_2$ and chiral ligand (1.2 equiv.) in toluene was added triethylamine (1.1 equiv.) under a nitrogen atmosphere at ambient temperature. Alkyne (1.2 equiv.) was then added to the mixture. After 15 min, the aldehyde (1.0 equiv.) was introduced by syringe. The reaction mixture was then stirred for 2–12 h at 25 °C. After the reaction was completed, the propargylic alcohol was separated from the ligand by washing with acid. The ligand was recovered in 98% yield by extracting the oily substance obtained by neutralizing the acidified aqueous solution. The crude product was purified through a short flash chromatography column to give the corresponding propargylic alcohols.

The catalytic condition is as follows: To a solution of $Zn(OTf)_2$ (0.2 equiv.) and chiral ligand (0.22 equiv.) in toluene was added triethylamine (0.5 equiv.) under a nitrogen atmosphere at ambient temperature. Alkyne (1.2 equiv.) was then added to the mixture. After 15 min, the aldehyde (1 equiv.) was introduced by syringe. The reaction mixture was then stirred for 4–6 h at 50 °C. then work up as usual to give the corresponding propargylic alcohols and recycle the ligand.

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