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Sulfamide-amine alcohol catalyzed enantioselective alkynylation of aromatic ketones

Jincheng Mao, Boshun Wan*, Fan Wu, Shiwei Lu*

Dalian Institute of Chemical Physics, Chinese Academy of Sciences, Zhongshan Road 457, Dalian 116023, PR China

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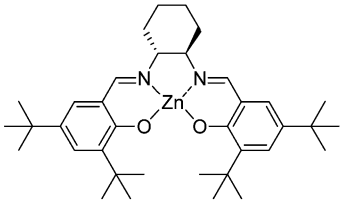
Abstract

The new readily available sulfamide-amine alcohol **11** was found to be effective in catalyzing the enantioselective phenylacetylene addition to aromatic ketones without using another central metal, providing the chiral tertiary propargylic alcohols in good yields (up to 83%) and enantioselectivities (up to 83% e.e.). The conditions of this catalytic process are both mild and simple.

Keywords: Sulfamide-amine alcohol; Enantioselective alkynlyzinc addition; Propargylic alcohol; Ketones

1. Introduction



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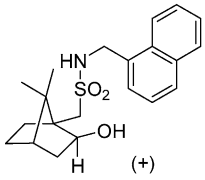

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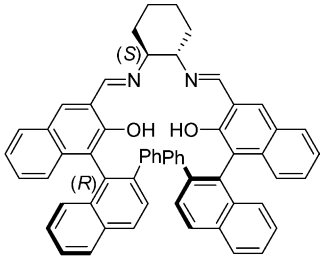

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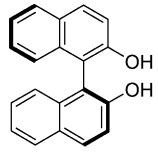

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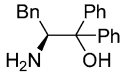

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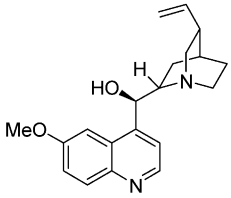

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Asymmetric addition of terminal phenylacetylene to aldehydes has been studied extensively [1,2]. Comparatively, asymmetric addition of phenylacetylene to ketones is much more complicated because of inertness of ketones and controlled facial stereoselectivity [1,3]. Moreover, using the unactivated ketones as electrophilic substrates is considered to be more challenging [3a–3h]. Cozzi reported the first

* Corresponding authors. Fax: +86 411 84379260.
E-mail address: bswan@dicp.ac.cn (B. Wan).

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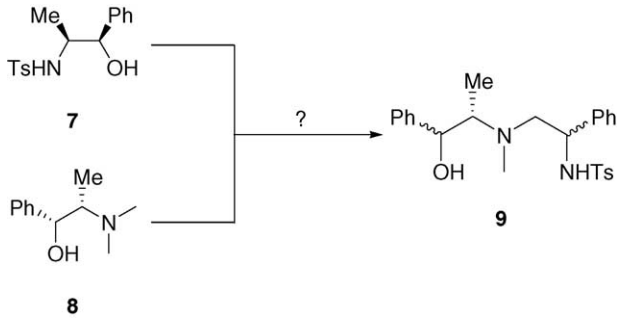


Scheme 1. Structurally converting ligand **7** and **8** to ligand **9**.

example of such a reaction catalyzed by Zn-salen bifunctional complexes **1** [3a]. However, this protocol was proved be more effective to aliphatic ketones. Differently, Chan showed an easily available chiral camphorsulfonamide **2** with $Cu(OTf)_2$ as a promoter for asymmetric addition of phenylacetylene to aromatic ketones, providing the products in high yields and enantioselectivities [3b]. Subsequently, Katsuki and Saito described another chiral salen ligand **3** for the aliphatic ketones to give better results (up to 91% e.e.) than salen ligand **1** did [3c]. Using commercially available BINOL **4** as ligand, Cozzi developed a practical protocol for the synthesis of chiral tertiary propargyl alcohols without using pyrophoric or expensive reagents [3d]. At the same time, Wang and co-workers described an efficient enantioselective alkynylation in the presence of suitable proportion of $Ti(O^iPr)_4$ to **4** [3e] and also demonstrated the addition of alkynylzinc reagent to aromatic ketones, promoted by readily available (*S*)-phenylalanine-derived β-amino alcohol **5** to give a maximum e.e. value of 80% [3f]. Very recently, Wang and co-workers also reported another efficient enantioselective alkynylation of ketones, based on Cinchona alkaloid **6** using Et_3Al as Lewis acid [3g]. Although such chiral ligands have been developed for highly enantioselective phenylacetylene addition to ketones, stable, easily accessible, operationally simple ligands are still desirable.

As known, chiral sulfonamide alcohol **7** had been proved to be a poor catalyst in the asymmetric alkynylation of ketones [3b]. With the expectation that the known Carreira's ligand **8** showed excellent enantioselectivities in the asymmetric addition of phenylacetylene to aliphatic aldehydes [4], we employed it in the asymmetric alkynylation of ketones. Surprisingly, we found that it only gave poor result of 10% e.e. and 10% yield. Recognizing that our developed sulfamide-amine alcohol **9**, which includes structures of both **7** and **8** (Scheme 1) bears with the additional weakly coordinative site, nitrogen atom from the sulfonamide [5], we expected it show better results in the same reaction. Therefore, in this paper we reported sulfamide-amine alcohol catalyzed asymmetric alkynylation of aromatic ketones under very mild conditions in the hope of obtaining some meaningful results without using additional central metal (other than zinc itself).

2. Experimental

All reactions were carried out under an argon atmosphere condition and monitored by thin layer chromatography (TLC). Column chromatography purifications were performed using silica gel. All solvents were dried and degassed by standard methods and all aldehydes and organozinc reagents were purchased from Aldrich. Phenylacetylene was purchased from Acros. NMR spectra were measured in $CDCl_3$ on a Bruker DRX-400 NMR spectrometer (400 MHz) with TMS as an internal reference. Optical rotations were measured with a HORIBA SEPA-200 high sensitive polarimeter. Enantiomeric excess (ee) determination was carried out using HPLC with a Daicel Chiralcel OD-H column on an Agilent HP-1100 HPLC instrument; solvent, 95:5 hexane/isopropanol; flow rate 1 mL min^{-1}; 254 nm UV detection.

2.1. Synthesis of ligand (*14*)

(*S*,*S*)-**14** was synthesized by (*S*)-(+)-2-phenylglycinol with (*S*)-2-phenyl-1-tosylaziridine in refluxing acetonitrile for 40 h. The pure ligand was obtained by simple recrystallization as white solid with 40% yield. m.p. 133–134 °C; $[\alpha]_D^{10} = +117.53$ (*c* 0.24, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 2.00 (br, 1H), 2.35 (s, 3H), 2.61–2.71 (m, 2H), 3.50–3.53 (m, 1H), 3.64–3.67 (m, 2H), 4.37–4.39 (s, 1H), 7.01–7.31 (m, 12H), 7.60 (d, $J = 8.0$ Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 21.7, 52.4, 57.2, 63.9, 67.1, 126.8, 127.3, 127.4, 127.7, 128.0, 128.6, 128.9, 129.6, 137.4, 139.1, 139.8, 143.4; HRMS (APCI) calcd for $C_{23}H_{27}N_2O_3S$ ($M + H^+$): 411.1737, found: 411.1697.

2.2. Typical procedure for asymmetric alkynylation reactions

Phenylacetylene (0.60 mmol) was added into a 10 mL two-neck round bottom flask containing 2 mL dry diethyl ether at room temperature under dry argon atmosphere. The stirred mixture was then cooled to 0 °C for 5 min, followed by the addition of a 1.0 M solution of diethylzinc in hexane (0.55 mmol). The resulting solution was brought to RT and stirred for 2 h, and then ligand (0.025 mmol, 10 mol%) was added. The homogenous solution was stirred at RT for 30 min and then ketone (0.25 mmol) was added via syringe. The resulting mixture was stirred at RT for 48 h. When the reaction was complete, it was quenched by adding sat. NH_4Cl (2 mL) at 0 °C. The aqueous phase was extracted with diethyl ether (3 × 5 mL). The combined organic phase was washed with little brine and dried over anhydrous Na_2SO_4. Purification of the crude product by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 18:1) afforded pure product. The enantiomeric excess was determined by HPLC analysis using a Chiralcel OD-H column. The configuration was assigned by comparison with the sign of specific rotation of the known compounds.

2.3. Characterization of the tertiary propargylic alcohols

2.3.1. 2,4-Diphenyl-but-3-yn-2-ol

Sixty-six percent yield isolated after 48 h, 78% e.e. determined by HPLC analysis (Chiralcel OD-H column, 5% IPA in hexane, 254 nm). Retention time: t_{minor} = 8.96 min and t_{major} = 10.94 min. ^{1}H NMR ($CDCl_3$) δ 1.87 (s, 3H), 2.52 (br, 1H), 7.32 (d, J = 4.0 Hz, 4H), 7.37–7.40 (m, 2H), 7.47–7.49 (m, 2H), 7.73 (d, J = 7.6 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 33.5, 70.6, 85.1, 92.6, 122.7, 125.2, 126.3, 127.9, 128.5, 128.7, 131.9, 145.8.

2.3.2. 2-(2-Chloro-phenyl)-4-phenyl-but-3-yn-2-ol

Eighty-three percent yield, 65% e.e. determined by HPLC analysis (Chiralcel OD-H column, 5% IPA in hexane, 254 nm). Retention time: t_{minor} = 10.61 min and t_{major} = 11.72 min. ^{1}H NMR ($CDCl_3$) δ 2.01 (s, 3H), 3.23 (br, 1H), 7.22–7.29 (m, 5H), 7.39–7.41 (m, 1H), 7.43–7.45 (m, 2H), 7.81–7.83 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 29.8, 69.3, 84.6, 91.7, 122.7, 126.8, 127.1, 128.4, 128.6, 129.1, 131.5, 131.8, 132.1, 141.6.

2.3.3. 2-(2-Fluoro-phenyl)-4-phenyl-but-3-yn-2-ol

Forty percent yield, 53% e.e. determined by HPLC analysis (Chiralcel OD-H column, 5% IPA in hexane, 254 nm). Retention time: t_{minor} = 9.38 min and t_{major} = 11.92 min. ^{1}H NMR ($CDCl_3$) δ 1.97 (s, 3H), 2.90 (br, 1H), 7.07–7.10 (m, 1H), 7.15 (d, J = 7.6 Hz, 1H), 7.29–7.30 (m, 4H), 7.44–7.46 (m, 2H), 7.71 (d, J = 8.0 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 30.7, 68.2, 84.5, 91.6, 116.4, 116.6, 122.6, 124.1, 126.9, 128.4, 128.6, 129.7, 129.8, 131.9, 132.1, 132.2, 159.1, 161.6.

2.3.4. 4-Phenyl-2-o-tolyl-but-3-yn-2-ol

Thirty-three percent yield, 67% e.e. determined by HPLC analysis (Chiralcel OD-H column, 5% IPA in hexane, 254 nm). Retention time: t_{minor} = 10.79 min and t_{major} = 11.55 min. ^{1}H NMR ($CDCl_3$) δ 1.92 (s, 3H), 2.67 (s, 3H), 7.19–7.21 (m, 3H), 7.27 (d, J = 3.6 Hz, 3H), 7.40–7.42 (m, 2H), 7.73–7.75 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 21.5, 31.2, 70.1, 84.7, 93.0, 122.8, 125.1, 126.0, 126.9, 127.9, 128.5, 128.6, 128.8, 129.2, 131.7, 132.5, 135.9, 142.5.

2.3.5. 2-(3-Chloro-phenyl)-4-phenyl-but-3-yn-2-ol

Seventy-five percent yield, 70% e.e. determined by HPLC analysis (Chiralcel OD-H column, 5% IPA in hexane, 254 nm). Retention time: t_{minor} = 8.42 min and t_{major} = 10.75 min. ^{1}H NMR ($CDCl_3$) δ 1.83 (s, 3H), 2.62 (br, 1H), 7.20–7.32 (m, 5H), 7.45–7.57 (m, 2H), 7.58 (d, J = 6.8 Hz, 1H), 7.71 (s, 1H).

2.3.6. 1-Naphthalen-2-yl-4-phenyl-but-3-yn-2-ol

Fifty percent yield, 55% e.e. determined by HPLC analysis (Chiralcel OD-H column, 5% IPA in hexane, 254 nm). Retention time: t_{minor} = 13.11 min and t_{major} = 16.34 min. ^{1}H NMR ($CDCl_3$) δ 2.11 (s, 3H), 2.97 (br, 1H), 7.22 (d, J = 5.2 Hz, 3H), 7.37–7.51 (m, 5H), 7.76 (d, J = 8.4 Hz, 1H), 7.82 (d, J = 8.0 Hz, 1H), 7.93 (d, J = 7.2 Hz, 1H), 8.85 (d, J = 8.8 Hz, 1H).

2.3.7. 2-Naphthalen-2-yl-4-phenyl-but-3-yn-2-ol

Eighty-three percent yield, 83% e.e. determined by HPLC analysis (Chiralcel OD-H column, 5% IPA in hexane, 254 nm). Retention time: t_{minor} = 12.82 min and t_{major} = 17.83 min. ^{1}H NMR ($CDCl_3$) δ 1.94 (s, 3H), 2.73 (br, 1H), 7.21–7.32 (m, 3H), 7.46–7.51 (m, 4H), 7.79–7.87 (m, 4H), 8.18 (s, 1H).

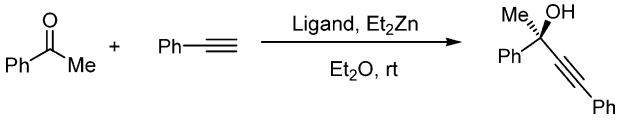
2.3.8. 3,4,4-trimethyl-1-phenylpent-1-yn-3-ol

Thirty-five percent yield, 18% e.e. determined by HPLC analysis (Chiralcel OD-H column, 5% IPA in hexane, 254 nm). Retention time: t_{minor} = 5.60 min and t_{major} = 9.58 min. ^{1}H NMR ($CDCl_3$) δ 1.11 (s, 9H), 1.53 (s, 3H), 2.15 (br, 1H), 7.26–7.28 (m, 3H), 7.41 (s, 2H). ^{13}C NMR ($CDCl_3$) δ 24.9, 25.3, 26.9, 29.8, 74.4, 84.0, 93.1, 123.1, 126.8, 128.2, 128.3, 131.7.

3. Results and discussions

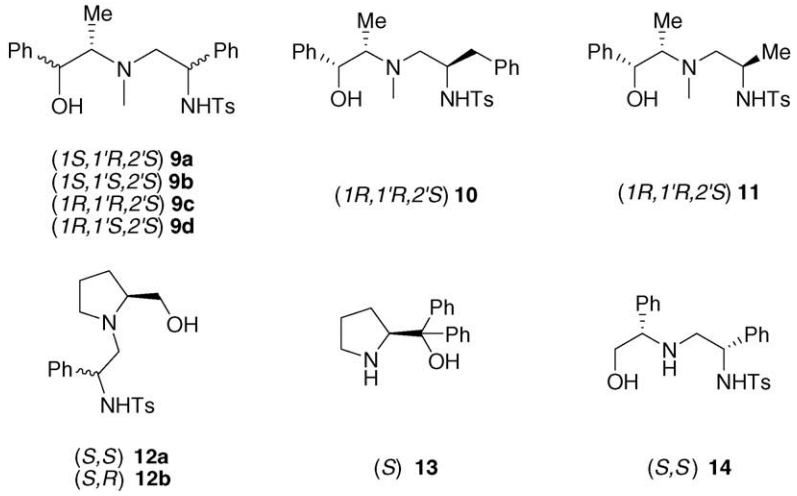
Very recently, we have reported our finding of a highly enantioselective diethylzinc addition to aldehydes catalyzed by a set of stable and practical sulfamide-amine alcohol ligands (**9–12**), which were easily synthesized from readily available and inexpensive starting materials via a simple, efficient method [5]. Accordingly, the catalytic properties of these ligands in asymmetric alkynylation of acetophenone were tested (Scheme 2). The results were summarized in Table 1. Ligands **9a**–**9d** derived from natural (−)-ephedrine

Table 1
Asymmetric addition of phenylacetylene to acetophenone using **9**–**14** as ligands[a]



Entry	Ligand	Yield (%)[b]	e.e. (%)[c]
1	**9a**	0	–
2	**9b**	0	–
3	**9c**	38	8
4	**9d**	25	1
5	**10**	33	49
6	**11**	48	62
7	**12a**	0	–
8	**12b**	0	–
9	**13**	26	45
10	**14**	17	7

[a] Phenylacetylene/Et_2Zn/ketone/ligand = 2.4:2.2:1:0.1, RT, 48 h.
[b] Isolated yield.
[c] The enantiomeric excess was determined by HPLC analysis of the corresponding products on a Chiralcel OD-H column.



Scheme 2. The evaluated ligands in the paper.

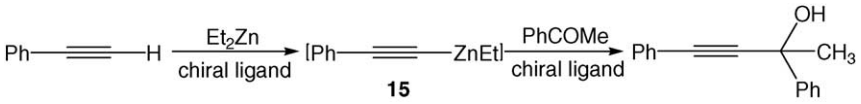
and (+)-pseudoephedrine hardly could catalyze the reaction except that ligand **9c** gave 8% e.e. (entries 1–4). Although the enantioselectivity was not high temporarily, ligand **10** and **11** amazingly afforded promising results only by changing the substituents (entries 5–6). Apparently, steric effect was observed. However, surprisingly, another type of chiral sulfamide-amine alcohols (**12a** and **12b**) based on L-prolinol was also ineffective for alkynylzinc addition (entries 7–8). Subsequently, chiral aminoalcohol **13** [6] and another chiral sulfamide-amine alcohol **14** were used in the addition reaction. To our disappointment, more satisfactory results were not obtained (entries 9–10).

With the above-mentioned optimal result, the conditions for the use of ligand **11** in the reaction of phenylacetylene

Table 2
Conditions for asymmetric addition of phenylacetylene to acetophenone using **11**[a]

Entry	**11** (mmol%)	Solvent	PhC≡CH/Et_2Zn	Yield (%)[b]	e.e. (%)[c]
1	12	Et_2O	240/220	47	61
2	12	Hex	240/220	43	70
3	12	THF	240/220	0	–
4	12	Tol	240/220	36	26
5	12	DCM	240/220	0	–
6	12	Hex	300/300	67	70
7	12	Hex	150/150	66	78
8	6	Hex	150/150	45	70
9	18	Hex	150/150	55	74
10[d]	12	Hex	150/150	34	74
11[d,e]	12	Hex	150/150	16	70
12[f]	12	Hex	150/150	34	78
13[d,f]	12	Hex	300/300	32	69
14[g]	12	Hex	150/150	33	78
15[h]	12	Hex	150/150	20	80
16[i]	12	Hex	150/150	14	23
17[j]	12	Hex	150/150	27	52
18[k]	12	Hex	150/150	48	75
19[l]	12	Hex	150/150	46	74

[a] The reaction was performed at RT for 48 h.
[b] Isolated yield.
[c] The enantiomeric excess was determined by HPLC analysis of the corresponding products on a Chiralcel OD-H column.
[d] Dimethylzinc instead of diethylzinc.
[e] DIMPEG (2.5 mmol%) as additive.
[f] DIMPEG (1 mmol%) as additive.
[g] 0 °C.
[h] −10 °C.
[i] TMSCl (1 equiv.) as additive.
[j] 4A MS (50 mg) as additive.
[k] Reaction time was 72 h.
[l] Reaction time was 96 h.

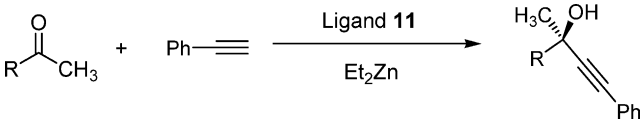


Scheme 3. Asymmetric reaction of phenylacetylene with acetophenone.

with acetophenone were explored. Table 2 summarized these experiments. In entries 1–5, various solvents were tested, among which hexane was found to be the best. Decreasing the amount of phenylacetylene versus Et_2Zn led to increase in enantioselectivity (entries 6–7). This indicated that the excessive phenylethynyl ethylzinc intermediate **15** was not favorable in the addition to ketone (Scheme 3). Changing the amount of ligand did not lead to further enhanced e.e. (entries 8–9). Surprisingly, dimethylzinc instead of diethylzinc or adding DIMPEG ($M = 2000$) [7] as additive gave depressed enantioselecitivities (entries 10–12). Additionally, as the amount of PhC≡CH/Me_2Zn was increased, no effect on enantioselectivity was observed (entry 13). Reducing the reaction temperature led to enhanced e.e. (up to 80%) but reduced yield (entries 14–15). Addition of TMSCl or 4A MS as additive made the enantioselectivity drop rapidly (entries 16–17). Prolongation of the reaction time did not improve e.e. (entries 18–19), which showed that the reaction had already finished in 48 h.

With this final protocol in hand, we examined the scope of this reaction using a variety of aromatic ketone substrates. Most of ketones afforded high yields (up to 83%) and the e.e. values were up to 83% (Table 3). The reactions of the phenylacetylene addition to aliphatic ketones, such as 3,3-dimethyl-2-butanone, were also observed, but only 18% e.e. was obtained with 35% yield. Thus, from the aromatic ketones as raw materials we could easily get various chiral tertiary propargylic alcohols, which were considered as useful precursors of many important pharmaceuticals.

Table 3
Asymmetric addition of phenylacetylene to aromatic ketones using **11**[a]



Entry	Substrate	Yield (%)[b]	e.e. (%)[c]
1	Acetophenone	66	78
2	2′-Chloroacetophenone	83	65
3	2′-Fluororoacetophenone	40	53
4	2′-Methylacetophenone	33	67
5	3′-Chloroacetophenone	75	70
6	1′-Naphthacetophenone	50	55
7	2′-Naphthacetophenone	83	83

[a] Phenylacetylene/Et_2Zn/ketone/ligand = 1.5:1.5:1:0.12, RT, 48 h.
[b] Isolated yield.
[c] The enantiomeric excess was determined by HPLC analysis of the corresponding products on a Chiralcel OD-H column.

4. Conclusion

In summary, we have demonstrated that the readily available sulfamide-amine alcohol **11** is an effective catalyst for the catalytic asymmetric addition of alkynylzinc to unactivated simple ketones, providing the products in good yields (up to 83%) and enantioselectivities (up to 83% e.e.). The conditions of this catalytic process are both mild and simple. The new type of ligand in this reaction is stable, easily accessible, operationally simple and low-cost. These favorable characteristics represent an advance toward the discovery of simplified catalyst systems for eventual availability. Further work is in progress in this laboratory with the aim of examining the scope of this catalyst.

Acknowledgement

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