Enantioselective Alkynylation of Aromatic Ketones Catalyzed by New Chiral Oxazolidine Ligands

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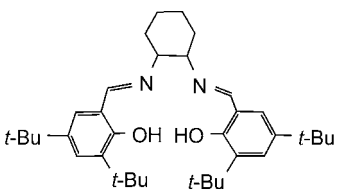
Received: September 2, 2004; Accepted: December 12, 2004

Abstract: New chiral oxazolidine ligands have been derived conveniently from natural amino acids in good yields. Their use in the enantioselective addition of phenylacetylene to aromatic ketones has been tested with the best ee being up to 88%. We provide a simple, practical and inexpensive method to generate chiral tertiary propargylic alcohols.

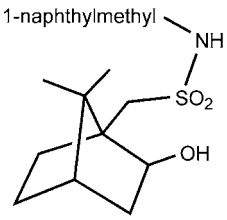
Keywords: addition to ketones; alkynes; asymmetric catalysis; C–C bond formation; oxazolidines; propargylic alcohols

Chiral tertiary propargylic alcohols are important pharmaceutical intermediates, and the simplest approach for the preparation of chiral tertiary alcohols is the enantioselective addition of organometallic reagents to ketones,[1] but there are still great challenges in this area of asymmetric catalysis. Unlike the enantioselective addition of alkynylzinc to aldehydes,[2] much less work on the enantioselective addition of alkynylzinc to ketones has been reported. This is mostly due to the much lower reactivity of ketones and the difficulty in controlling facial stereoselectivity. To overcome the low reactivity of ketones, some activated ketones are used. For example, Tan and co-workers[3] reported a stoichiometric asymmetric addition of alkynylzinc to activated ketones for the synthesis of Efavirenz, a drug for AIDS treatment. Ketones were activated with the strongly electron-withdrawing trifluoromethyl group. The other case is the asymmetric addition of alkynes to α-keto esters by Jiang and co-workers.[4] The reaction works only for highly electrophilic ketones such as α-keto esters, providing, in general, excellent results.

A catalytic asymmetric alkynylzinc addition to unactivated ketones has been developed recently, but there have been only two reports of this reaction. One was by Cozzi,[5] who used acetylene derivatives, excess dimethylzinc, and the Zn(salen) bifunctional catalyst **A** (Figure 1). In this case, the chiral salen catalyst was deprotonated to form the corresponding diphenolate-zinc system, which was acidic enough to chelate and activate the ketone effectively, so that moderate enantioselectivities (32–81% ee) and yields (40–89%) were obtained. Another excellent example was reported by Chan,[6] who used phenylacetylene, excess dimethylzinc, $Cu(OTf)_2$, and the chiral camphorsulfonamide ligand **B** (Figure 1). $Cu(OTf)_2$ was used as a promoter in this reaction because of its stronger Lewis acidity and high enantioselectivities (up to 71–97% ee) were obtained. Although excellent results have been achieved by Chan, the design and development of easily accessible and economical chiral ligands are still a worthwhile project. From both fundamental and practical standpoints, there is a growing need to find a cheap, practical and novel catalyst which can catalyze the asymmetric addition of terminal acetylenes to ketones with high ees under mild and convenient condition.



A

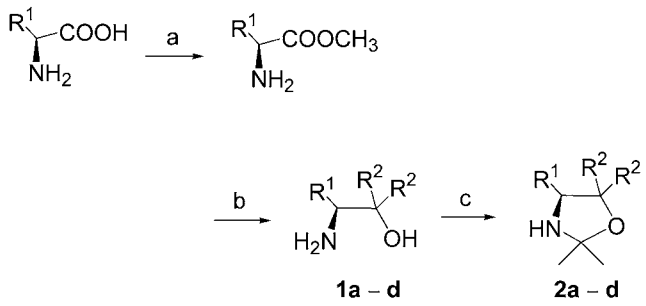


B

Figure 1. Ligands **A** and **B**.

Oxazoline ligands derived from the natural amino acids have become a series of important molecules in asymmetric catalysis because of their easy availability and cheapness. The direct use of the oxazoline ligands in combination with metal salts in asymmetric catalysis has resulted in a series of exciting discoveries. Among these there are Diels–Alder reactions,[7] oxidation reactions,[8] cyclopropanation reactions,[9] Mukaiyama-aldol reactions,[10] carbonyl-ene reactions,[11] and others.[12] But to the best of our knowledge, the use of chiral oxazolidine ligands in the enantioselective alkynylation of

 DOI: 10.1002/adsc.200404278



1, 2	a	b	c	d
R^1	*i*-Pr	*i*-Bu	Bn	Bn
R^2	phenyl	phenyl	ethyl	phenyl

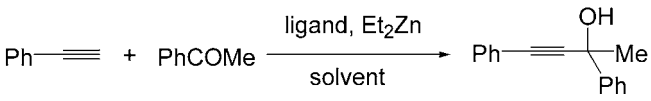
a) MeOH, $SOCl_2$, –30 °C,to rt, then reflux for 2 h
b) PhMgBr or EtMgBr, THF, rt, 24 h
c) acetone, 4 Å MS, rt, 24 h

Scheme 1. Preparation of oxazolidine ligands from amino acids.

ketones has not yet been reported. The results of our investigation on the enantioselective addition of alkynylzinc to ketones catalyzed by chiral oxazolidine ligands are presented here.

From commercially available cheaper starting materials, oxazolidine ligands **2a**–**d** were prepared in three simple steps according the Scheme 1.[12c,13] After the typical methyl esterification of amino acids, the amino esters were treated with an excess amount of phenylmagnesium bromide or ethylmagnesium bromide to give the corresponding amino alcohols **1a**–**d**. Compounds **1a**–**d** were treated with an excess amount of acetone and 4 Å MS to afford the corresponding oxazolidines **2a**–**d** in 52–66% overall yields.

We studied the application of oxazolidine ligands **2a**–**d** in the reaction of phenylacetylene with acetophenone in the presence of Et_2Zn (Scheme 2). There are several methods to prepare alkynylzinc reagents. One is the treatment of a terminal alkyne with diethylzinc in refluxing organic solvent described by Pu[2k,2l] and Hoshino[2u] in the asymmetric addition of terminal alkynes to aldehydes, but our attempt to apply this method in the asymmetric addition of terminal alkynes to ketones was unsuccessful. In another method alkynylzinc reagents are generated *in situ* from phenylacetylene with diethylzinc at room temperature and this was successfully used in this asymmetric alkynylation of ketones, thus avoiding the steps of separate preparation and metallation. In addition, there are no additional metal centers as a promoter in this asymmetric addition reaction. A typical addition procedure involves the coordination of oxazolidine ligands with diethylzinc in toluene-ether at room temperature, then phenylacetylene is added, finally



Scheme 2. The addition of phenylacetylene to acetophenone.

the reaction is cooled to 0 °C and treated with acetophenone. This procedure gives an easy and efficient methodology for the enantioselective addition of alkynylzinc to ketones.

A preliminary study was conducted with the aim of determining the best of the chiral ligands, and the results summarized in Table 1 (entries 1–4) show that ligand **2d** gave the highest enantioselectivity among the four ligands. The oxazolidine ligands containing the bulkier benzyl substituent on the chiral carbon atom were found to be more effective than those containing isopropyl or isobutyl substituents. Replacement of the diphenyl groups on the 5,5-positions of **2d** with diethyl groups also gave low enantioselectivity.

We then explored the conditions for the use of ligand **2d** in the reaction of phenylacetylene with acetophenone (Table 1, entries 4–13). Various conditions were explored in this asymmetric reaction. We varied the type of solvent on this reaction in the first place and found that very low ee values were obtained in THF (entry 6), CH_2Cl_2 (entry 8). Toluene and hexane and ether improved respectively the ee values to 64% (entry 5) and 68% (entry 4) and 60% (entry 7). So hexane was the best solvent. Increasing the amount of ligand led to higher enantioselectivity (entry 9). We then examined the effect of the amount of $ZnEt_2$ on this reaction, and found that increasing the amount of $ZnEt_2$ gave a slightly enhanced ee, but further increasing the amount of $ZnEt_2$ to 4 equivs. did not lead to a further increase in ee (entries 10–12). We examined the effect of temperature on this reaction, but found only decreased ee values at higher temperatures (entry 13).

Under the optimized reaction conditions of entry 12 in Table 1, ligand **2d** was employed to catalyze the enantioselective addition of phenylacetylene to a variety of aromatic ketones (Table 2). Good enantioselectivity has been achieved for the addition of phenylacetylene to aromatic ketones and the ee value was up to 88%. Under the same conditions, we also used ligand **2d** in the addition of phenylacetylene to the aliphatic ketone: 4-methyl-2-pentanone. The enantioselectivity were found to be 59% ee (yield 82%).

In summary, we have successfully developed a third catalyst for the enantioselective addition of phenylacetylene to aromatic ketones under very mild conditions, namely a new chiral oxazolidine ligand, which can be prepared conveniently from natural amino acids in three simple steps with good yields. Ligand **2d** exhibits good catalytic activity for this asymmetric reaction, and we provide a simple, practical and inexpensive method to

Table 1. Asymmetric addition phenylacetylene to acetophenone using **2** as ligands.

Entry	Ligand [mol%]	Solvent	Et_2Zn [mol%]	T [°C]	ee[a] [%]
1	**2a**(10)	Hexane	200	0	58
2	**2b**(10)	Hexane	200	0	37
3	**2c**(10)	Hexane	200	0	19
4	**2d**(10)	Hexane	200	0	68
5	**2d**(10)	Toluene	200	0	64
6	**2d**(10)	THF	200	0	20
7	**2d**(10)	Ether	200	0	60
8	**2d**(10)	CH_2Cl_2	200	0	32
9	**2d**(20)	Hexane	200	0	70
10	**2d**(20)	Hexane	140	0	69
11	**2d**(20)	Hexane	300	0	71
12	**2d(20)**	**Hexane**	**400**	**0**	**72**
13	**2d**(20)	Hexane	400	rt	67

[a] The enantiomeric excess was determined by HPLC analysis of the corresponding products on a Chiralcel OD column.

Table 2. Asymmetric addition phenylacetylene to aromatic ketones promoted by ligand **2d**.[a, b]

Entry	Ketone	Time [h]	Yield [%]	ee[c] [%]
1	Acetophenone	24	70	72
2	2′-Fluoroacetophenone	30	85	83
3	2′-Methoxyacetophenone	48	69	78
4	3′-Methylacetophenone	36	71	76
5	3′-Bromoacetophenone	30	80	68
6	4′-Methylacetophenone	30	70	73
7	4′-Fluoroacetophenone	30	68	70
8	4′-Chloroacetophenone	30	68	71
9	4′-Methoxyacetophenone	36	77	78
10	2′-Naphthacetophenone	30	75	86
11	1′-Naphthacetophenone	48	57	88

[a] In all of the entries: Et_2Zn:phehylacetylene:ketone:**2d** = 4 : 4.2 : 1.0 : 0.2.
[b] All the reactions were run under argon and at 0 °C.
[c] The enantiomeric excess was determined by HPLC analysis of the corresponding products on a Chiralcel OD column.

generate chiral propargylic alcohols by this asymmetric reaction.

Experimental Section

General Remarks

All reactions were carried out under an argon atmosphere and solvents were dried according to established procedures. Reactions were monitored by thin layer chromatography (TLC), Column chromatography purifications were carried out using silica gel. All ketones and amino acids were purchased from Acros or Fluka. Diethylzinc was prepared from EtI and Zn and then was diluted with hexane to 1.0 M. Melting points are uncorrected and were recorded on an X-4 melting point apparatus. ^{1}H NMR spectra were measured on a DRX-200 MHz spectrometers (in $CDCl_3$ with TMS as an internal standard). IR spectra were obtained on a Nicolet NEXUS 670 FT-IR. Optical rotations were recorded on a Perkin-Elmer 341 polarimeter. HR-MS were measured with an APEX II 47e mass spectrometer and the ESI-MS were recorded on a Mariner® biospectrometer. The ee value determination was carried out using chiral HPLC with a Daicel Chiracel® OD column on Waters® system with a 996 UV-detector.

Amino alcohols **1a–d** and oxazolidine **2a** were prepared as described in the literature.[12c,13]

General Procedure for the Synthesis of Oxazolidines 2b–d

The respective amino alcohol (2 mmol) and acetone (10 mL) were stirred with 4 Å MS at room temperature for 12–24 h. The products were isolated by filtration after the reaction was complete as checked by TLC. Evaporation of excess acetone provided the oxazolidine. The crude oxazolidine can be stored and used conveniently as a 0.1 M solution in toluene. The pure products were obtained by recrystallization from hexane or short column chromatography.

(*S*)-2,2-Dimethyl-5,5-diphenyl-4-isobutyl-1,3-oxazolidine (2b): Following the general procedure, from **1b** (538 mg,

2 mmol), **2b** was obtained; yield: 587 mg (95%); yellow oil; $[\alpha]_D^{21}$: −135 (*c* 1.21, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$, TMS): δ = 7.48–7.15 (m, 10H, Ph-H), 4.17 (d, *J* = 11.2 Hz, 1H, CHN), 1.76 [m, 2H, $CH_2CH(CH_3)_2$], 1.751 (s, 3H, CH_3), 1.235 (s, 3H, CH_3), 1.02 (d, *J* = 6.4 Hz, 3H, CH_3), 0.84 (d, *J* = 6.6 Hz, 3H, CH_3), 0.63 [m, 1H, $CH(CH_3)_2$]; ^{13}C NMR (50 MHz, $CDCl_3$, TMS): δ = 21.50, 24.04, 26.55, 26.88, 27.60, 42.64, 65.31, 87.93, 94.97, 126.58, 126.83, 127.04, 127.54, 127.99, 144.30, 147.68; IR (KBr): $\tilde{\nu}$ = 3059, 3027, 2955, 2869, 1599, 1491, 1448, 1379, 1264, 1154, 1015, 883, 834, 802, 753, 700 cm^{-1}; MS (ESI): *m/z* = 310 $[M+H]^+$; anal. calcd. for $C_{21}H_{27}NO$: C 81.85, H 8.79, N 4.53; found: C 81.87, H 8.64, N 4.55.

(*S*)-2,2-Dimethyl-5,5-diethyl-4-benzyl-1,3-oxazolidine (2c): Following the general procedure, from **1c** (414 mg, 2 mmol), **2c** was obtained; yield: 469 mg (95%); yellow oil; $[\alpha]_D^{20}$: −7 (*c* 1.07, $CH_3CO_2C_2H_5$); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 0.87(t, *J* = 7.2 Hz, 3H, CH_3), 0.96 (t, *J* = 7.6 Hz, 3H, CH_3), 1.29 (s, 3H, CH_3), 1.43 (s, 3H, CH_3), 1.34–1.50 (m, 2H, CH_2 Me), 1.64–1.70 (m, 2H, CH_2Me), 2.01 (s, 1H, NH), 2.63–2.78 (m, 2H, $PhCH_2$), 3.52 (dd, *J* = 5.2 Hz, *J* = 8.8 Hz, 1H, CHN), 7.20–7.32 (m, 5H, Ph); IR (KBr): $\tilde{\nu}$ = 3027, 2973, 2932, 2880, 1603, 1578, 1495, 1456, 1423, 1375, 1290, 1254, 1172, 1115, 1035, 1001, 951, 889, 835, 753, 724, 698 cm^{-1}; MS (ESI): *m/z* = 248 $[M+H]^+$; anal. calcd. for $C_{16}H_{25}NO$: C 77.68, H 10.19, N 5.66; found: C 77.28, H 10.10, N 5.99.

(*S*)-2,2-Dimethyl-5,5-diphenyl-4-benzyl-1,3-oxazolidine (2d): Following the general procedure, from **1d** (606 mg, 2 mmol), **2d** was obtained; yield: 652 mg (95%); white crystals; mp 94–96 °C; $[\alpha]_D^{20}$: −128 (*c* 2.29, $CH_3CO_2C_2H_5$); ^{1}H NMR (200 MHz, $CDCl_3$, TMS): δ = 1.21 (s, 3H, CH_3), 1.79 (s, 3H, CH_3), 1.96 (dd, *J* = 10.8 Hz, *J* = 14.6 Hz, 1H, $PhCH_A$), 1.88 (dd, *J* = 11.2 Hz, *J* = 15 Hz, 1H, $PhCH_B$), 2.89 (d, *J* = 14.8 Hz, 1H, HN), 4.43 (d, *J* = 11.2 Hz, 1H, CHN), 7.23–7.59(m, 15H, 3Ph); ^{13}C NMR (50 MHz, $CDCl_3$, TMS): δ = 147.2, 144.1, 139.4, 128.5, 128.4, 128.1, 127.7, 127.0, 126.8, 126.6, 126.3, 95.2, 88.0, 68.4, 39.8, 27.8, 26.8; IR(KBr): $\tilde{\nu}$ = 3059, 3027, 2981, 2928, 2852, 1600, 1492, 1447, 1378, 1318, 1289, 1263, 1210, 1186, 1151, 1082, 1014, 929, 889, 839, 798, 753, 726, 699 cm^{-1}; MS (ESI): *m/z* = 344 $[M+H]^+$; anal. calcd. for $C_{24}H_{25}NO$: C 83.93, H 7.34, N 4.08; found: C 84.03, H 7.24, N 4.01.

General Procedure for the Addition of Phenylacetylene to Ketones

Under argon, to a solution of the ligand **2d** (0.05 mmol, 17.2 mg) in hexane (2 mL) was added a solution of Et_2Zn (1 mmol, 1.0 M in hexane, 1 mL) at room temperature. After the mixture had been stirred at the room temperature for 90 min, phenylacetylene (1.05 mmol, 125 μL) was added and stirring continued for another 90 min. The solution was cooled to 0 °C and treated with acetophenone (0.25 mmol, 29 μL), then the resultant mixture was stirred at 0 °C for 24–48 h. After the reaction was complete as checked by TLC, it was quenched by 2% aqueous HCl at 0 °C. The mixture was extracted with ether. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under vacuum. The residue was purified by flash column chromatography (silica gel, 12.5% EtOAc in hexane) to give the product.

Acknowledgements

We are grateful to the National Natural Science Foundation of China (Nos.20372028, 20472026), the Ministry of Science and Technology of China, the Teaching and Research Award Program for Outstanding Young Teachers, and the Specialized Research Fund for the Doctoral Program in Higher Education Institutions of the Ministry of Education of China.

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