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Tetrahedron Letters
Tetrahedron Letters 46 (2005) 863–865

Enantioselective alkynylation of aromatic aldehydes catalyzed by new chiral oxazolidine ligands

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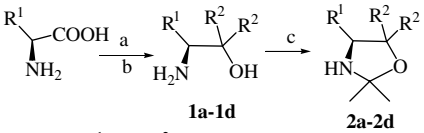
Received 3 September 2004; revised 18 November 2004; accepted 24 November 2004
Available online 18 December 2004

Abstract—New chiral oxazolidines were conveniently synthesized from natural amino acids in three simple steps with good yields. The use of chiral oxazolidine ligands for the enantioselective alkynylation of aldehydes provides a simple, practical and inexpensive method to generate chiral propargyl alcohols with 85–99% ee.

The enantioselective alkynylzinc addition to ketones[1] or aldehydes[2] is a very useful method for the synthesis of chiral propargyl alcohols, which are important versatile building blocks of many biologically active compounds and natural products.[3] Since Ishizaki and Hoshino reported the first addition of alkynylzinc reagents to aldehydes in 1994,[4] some chiral ligands, such as *N*-methyl ephedrine,[5] sulfonamide alcohol,[6] BINOL and its derivatives,[7] have successfully been applied in this reaction in recent years. Other chiral compounds, such as disulfide-oxazolidine,[8] have also been used, but in low enantioselectivity (36–60% ee). Herein we report the discovery of a new chiral oxazolidine ligand for the asymmetric addition of terminal acetylenes to aromatic aldehydes with high ee values under mild and convenient condition.

The oxazoline ligands derived from the natural amino acids have become a series of important molecules in asymmetric catalysis because of its easy availability and low cost. 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 the Diels–Alder reactions,[9] the oxidation reactions,[10] the cyclopropanation reactions,[11] the Mukaiyama-aldol reactions,[12] the carbonyl-ene reactions[13] and others.[14] Based on the results of our recent report on catalytic asymmetric addition of alkynylzinc to aldehydes,[6,15] we think that the chiral oxazolidine ligands can also catalyze the asymmetric addition of alkynylzinc to aldehydes.

From commercially available cheaper starting materials, oxazolidine ligands **2a**–**d** were prepared in three simple steps (Scheme 1).[14a,c,16,17] After the typical methyl esteration of amino acids, the amino methylesters were treated with excess amount of phenylmagnesium bromide or ethylmagnesium bromide to give the corresponding amino alcohols **1a**–**d**. Compounds **1a**–**d** were treated with excess amount of acetone and 4 Å MS to afford the corresponding oxazolidines **2a**–**d** in 52–66% overall yields.



1a-1d **2a-2d**

2a: R^1=*i*Pr, R^2=phenyl, yield : 62%
2b: R^1=*i*Bu, R^2=phenyl, yield : 52%
2c: R^1=Bn, R^2=ethyl, yield : 60%
2d: R^1=Bn, R^2=phenyl, yield : 66%

Scheme 1. Preparation of oxazolidine from amino acids. Reagents and conditions: (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.

Keywords: Aldehydes; Alkynes; Oxazolidines; Addition; Asymmetric catalysis.
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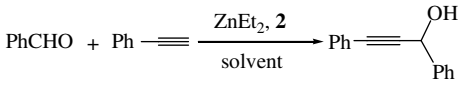
doi:10.1016/j.tetlet.2004.11.165



Scheme 2. Asymmetric addition phenylacetylene to benzaldehyde.

Ligands **2a–d** were tested in the asymmetric addition of phenylacetylene to benzaldehyde in the presence of Et_2Zn (Scheme 2, Table 1, entries 1–4) initially. The results showed that ligand **2d** gave the highest enantioselectivity among the four ligands. The oxazolidine ligands containing a bulkier benzyl substituent on the chiral carbon atom were found to be more effective than those containing isopropyl or isobutyl substituents. The replacement of the diphenyl groups on the 5,5-positions of **2d** with diethyl groups also gave low enantioselectivity.

The catalytic properties of ligand **2d** in asymmetric alkynylation were explored in the reaction of phenylacetylene with benzaldehyde in the presence of diethylzinc (Table 1, entries 4–13). We found that enantioselectivity of this reaction was strongly solvent dependent. Very low ee values was obtained in toluene (entry 5), toluene–THF (entry 7) and toluene–CH_2Cl_2 (entry 8). However, there was a dramatic enhancement in enantioselectivity when ether or toluene–ether were used as the solvent (entries 4 and 6). So toluene–ether was the best solvent. We then examined the effect of the amount of $ZnEt_2$ on this reaction, and found decreasing the amount of $ZnEt_2$ from 300 to 140 mol % gave higher ee, but further decreasing the amount of $ZnEt_2$ to 120 mol % lead to a decrease in ee values. So the appropriate amount of $ZnEt_2$ was 140 mol % (entries 4, 9–11). We also varied the reaction temperature in order to optimize the reaction condition. But, only decreased ee values were observed at either higher or lower temperatures (entries 10, 12–13). Thus, the 0 °C condition seems most suitable for this reaction.

Table 1. Asymmetric addition phenylacetylene to benzaldehyde using 10 mol % **2** as ligands

Entry	Ligands	Et_2Zn (mol %)	Solvent	Temp (°C)	ee[a] (%)
1	**2a**	200	Tol[b]–ether	0	28
2	**2b**	200	Tol–ether	0	68
3	**2c**	200	Tol–ether	0	5
4	**2d**	200	Tol–ether	0	76
5	**2d**	200	Tol	0	29
6	**2d**	200	Ether	0	66
7	**2d**	200	Tol–THF	0	32
8	**2d**	200	Tol–CH_2Cl_2	0	15
9	**2d**	120	Tol–ether	0	82
10	**2d**	140	Tol–ether	0	93
11	**2d**	300	Tol–ether	0	73
12	**2d**	140	Tol–ether	Rt[c]	78
13	**2d**	140	Tol–ether	−10	80

[a] The enantiomeric excess was determined by HPLC analysis of the corresponding products on a Chiralcel OD column.
[b] Tol = toluene.
[c] Rt = room temperature.

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

Aldehydes	Time (h)	Isolated yield (%)	ee[c] (%)
Benzaldehyde	24	75	93/*R*[d]
3-Tolualdehyde	48	66	87
4-Tolualdehyde	48	68	86
3-Anisaldehyde	48	70	86
4-Anisaldehyde	48	74	85
3-Nitrobenzaldehyde	24	60	99
3-Bromobenzaldehyde	24	77	90
4-Bromobenzaldehyde	24	74	91
2-Chlorobenzaldehyde	24	70	85
4-Chlorobenzaldehyde	24	76	88
4-Fluorobenzaldehyde	24	78	93
β-Naphthaldehyde	48	71	85

[a] In all of the entries: Et_2Zn:phehylacetylene:aldehyde:**2d** = 1.4:1.4:1.0:0.1.
[b] All the reactions were processed under argon and at 0 °C.
[c] The ee values were determined by chiral HPLC with Chiracel OD column.
[d] The absolute configuration is based on measurement of the optical rotation and comparison with the literature values.[8,20]

Under such optimized reaction conditions of entry 10 in Table 1, ligand **2d** was employed to induce the enantioselective addition of phenylacetylene to a family of aromatic aldehydes.[18,19] All propargyl alcohol derivatives was obtained with high enantioselectivity and the ee value was up to 99% (Table 2).

In conclusion, new chiral oxazolidines were conveniently synthesized from natural amino acids in three simple steps with good yields. We have demonstrated that new chiral oxazolidine ligand **2d** is an effective catalyst for the enantioselective alkynylation of aldehydes under mild conditions to give 85–99% ee. We provide a simple, practical and inexpensive method to generate chiral propargyl alcohols.

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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17. Selected characterization of **2d**: White crystals, yield 66%; mp 94–96 °C; $[\alpha]_{20}^{D}$ −128 (*c* 2.3, $CH_3CO_2C_2H_5$); ^{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): ν 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.
18. Typical procedure for the asymmetric addition of phenylacetylene to aldehydes: Under argon, to a solution of the ligand **2d** (0.05 mmol, 17.2 mg) in ether (4 mL), was added a solution of Et_2Zn (0.7 mmol, 1.0 M in toluene, 0.7 mL) at room temperature. After the mixture was stirred at the room temperature for 2 h, phenylacetylene(0.7 mmol, 76 μL) was added and the stirring continued for another 2 h. The solution was cooled to 0 °C and treated with aldehyde (0.5 mmol, 50 μL), then the resultant mixture was stirred for 24–48 h at 0 °C. Optically active propargyl alcohol was obtained after acid workup and purification by silica gel TLC.
19. Under the same conditions, we also used ligand **2d** in the addition of phenylacetylene to two aliphatic aldehydes: isobutylaldehyde and cyclohexanecarboxaldehyde. The enantioselectivities were determined by chiral HPLC on a Chiracel OD column and were found to be 75% (yield 60%) and 62% (yield 56%) ee, respectively.
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