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Enantioselective alkynylation of aromatic aldehydes catalyzed by new chiral amino alcohol-based ligands

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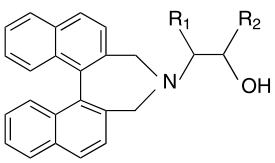
Abstract—A series of binaphthyl-derived amino alcohols were synthesized and used as catalytic ligands in the asymmetric alkynylation of aromatic aldehydes in the presence of a dialkylzinc reagent. The alkynylation of a variety of aromatic aldehydes gave the corresponding chiral propargylic alcohols in 61–93% e.e. © 2001 Published by Elsevier Science Ltd.

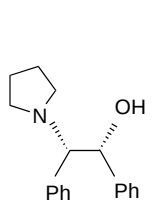
1. Introduction

Numerous binaphthyl-derived ligands have been employed as chiral auxiliaries in catalytic reactions. The easy preparation of binaphtho-azepines from readily available 2,2′-bis(bromomethyl)-1,1′-binaphthyl precursors and their successful applications in asymmetric transformations[1,2] revealed an excellent opportunity for the study of the asymmetric catalytic properties of binaphtho-azepino alcohol ligands in the alkynylation reactions of aromatic aldehydes. In order to study the relationship between ligand structure and the enantioselectivity and catalytic activity, we prepared ligands **1**–**4** by reacting the appropriate chiral amino alcohols with (*R*)- and (*S*)-bis(bromomethyl) binaphthyl and investigated the catalytic alkynylation of aromatic aldehydes utilizing these ligands.

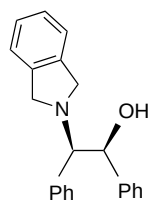


(1*R*,2*S*,3*R*)-1 R_1=Ph R_2=Ph
(1*R*,2*R*,3*S*)-2 R_1=Ph R_2=Ph
(1*S*,2*S*,3*R*)-3 R_1=Ph R_2=Ph
(1*R*,2*R*,3*S*)-4 R_1=CH_3 R_2=Ph

Chiral propargylic alcohols are useful building blocks for enantioselective syntheses.[3,4] Direct approaches to the synthesis of these compounds involve the asymmetric reduction of α,β-ynones via asymmetric hydroboration[5] or catalytic transfer hydrogenation.[6] However, good yields and enantioselectivities have been achieved only in the case of acetylenic alkyl ketones. The asymmetric addition of alkynes to aromatic aldehydes have also been reported, but the systems with good enantioselectivity required the use of large quantities of chiral auxiliary.[7,8] Other problems included the formation of considerable amounts of side products and only moderate enantioselectivity for the desired products.[9] Recently, Li et al.[10] reported the use of amino alcohols **5** and **6** and their derivatives to catalyze the reaction of terminal alkynes with aromatic aldehydes to afford alkynols with e.e. of up to 85%.



(1*R*,2*S*)-5



(1*S*,2*R*)-6

Herein, we report the application of a binaphthyl amino alcohol system in this interesting reaction. The bulky chiral binaphthyl group is expected to affect the catalytic center and thus may provide higher enantioselectivity in this reaction.

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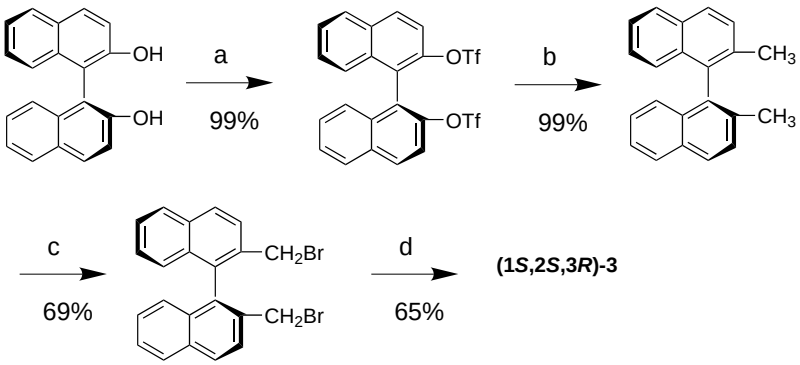
2. Results and discussion

Commercially available (*R*)- or (*S*)-binaphthol were used in the synthesis of ligands **1**–**4** according to the common method established in the synthesis of azepine,[11] as depicted in Scheme 1.

The structure of (1*R*,2*S*,3*R*)-**1** was determined by single-crystal X-ray diffraction analysis (Fig. 1).

The catalytic properties of ligands **1**–**4** in asymmetric alkynylation were explored in the reaction of 2-chlorobenzaldehyde with phenylacetylene at 0°C in the presence of dimethylzinc. Ligand **1** was very effective and provided promising results (Table 1). The configuration of the product was influenced mainly by the chirality of the amino alcohol moiety of the ligand. Amino alcohol ligands containing phenyl substituents on the 1,2-positions were found to be more effective than those containing methyl substituents.



Scheme 1. (a) Tf_2O, Py, CH_2Cl_2; (b) MeMgBr or MeMgI, $NiCl_2$(dppp), Et_2O; (c) NBS, benzoyl peroxide, CCl_4; (d) (1*R*,2*S*)-(+)-2-amino-1,2-diphenylethanol, acetonitrile.

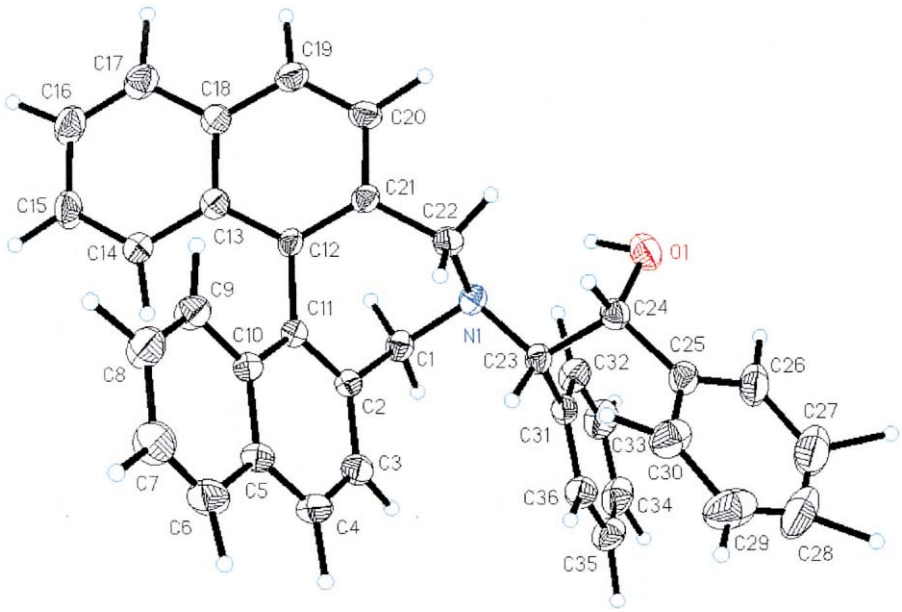
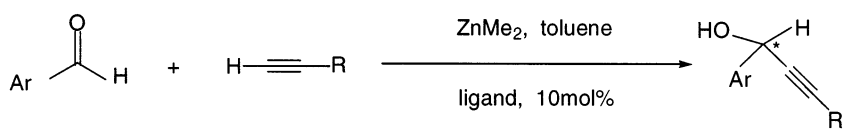


Figure 1. X-Ray structure of (1*R*,2*S*,3*R*)-**1**.

Table 1. Alkynylation of 2-chlorobenzaldehyde with phenylacetylene in the presence of ligands **1**–**4**



Ligand	(1*R*,2*S*,3*R*)-**1**	(1*R*,2*R*,3*S*)-**2**	(1*S*,2*S*,3*R*)-**3**	(1*R*,2*R*,3*S*)-**4**
Conv. (%)	>95	>95	>95	>95
e.e. (%)	85 (+)	35 (−)	26 (+)	24 (−)

While the mechanism of the reaction is still not clear and we do not pretend to have a definite answer, it may be helpful to explain the influence of the binaphthyl moiety by speculating possible transition states of the alkynyl transfer step. As shown in Fig. 2, for (1*R*,2*S*,3*R*)-**1**, the large steric hindrance of the chiral (*R*)-binaphthyl moiety (with the relevant naphthyl ring tilting down) forces the aryl ring of the coordinated chlorobenzaldehyde to take a position away from the binaphthyl group, consequently the alkynyl transfer provides (*S*)-product in high e.e.[12,13] As for (1*S*,2*S*,3*R*)-**3**, the relevant naphthyl ring tilts up and the steric effect of this moiety is not as significant as that in (*R*)-binaphthyl. Consequently, in addition to the possible stereo-arrangement of the chlorobenzaldehyde as in the case of (1*R*,2*S*,3*R*)-**1**, another possible arrangement with the aryl ring of the aldehyde in a position near the binaphthyl group occurs. This lowers the e.e. of the product to 26%. It must be emphasized that this speculation is only for the explanation of the results and a much more in-depth study is needed to elucidate the actual mechanism of the reaction.

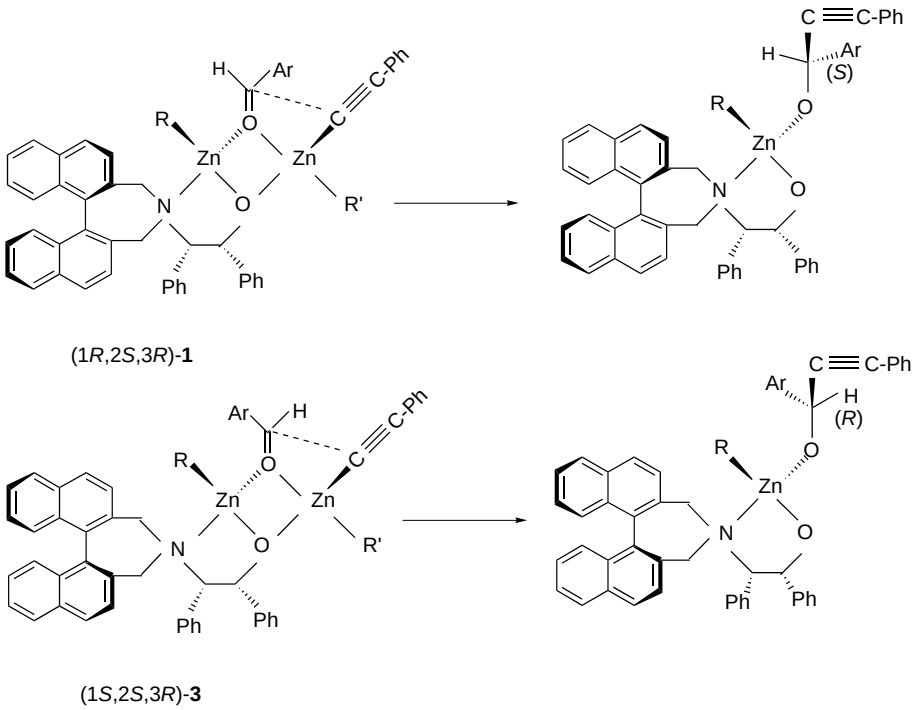
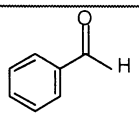
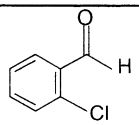


Figure 2. The possible transition state of the alkynylation.

Table 2. Effects of temperature and catalyst concentration on the alkynylation of aldehydes in the presence of (1*R*,2*S*,3*R*)-**1**

Entry	Aldehyde	T (°C)	Catalyst/substrate	Reaction time	Conv. (%)	e.e. (%)
1		0	0.10	24 h.	>95	70 (-) (*S*)[a]
2		-20	0.10	48 h.	>95	79 (-) (*S*)
3		0	0.01	24 h.	20	3 (+)
4		0	0.05	24 h.	45	12 (+)
5		0	0.10	6 h.	>95	85 (+)
6		0	0.20	6 h.	>95	88 (+)
7		-20	0.10	24 h.	>95	89 (+)
8		-20	0.20	12 h.	>95	93 (+)

[a]The absolute configuration is based on measurement of the optical rotation and comparison with the literature values.[10]

The effects of reaction temperature and the ratio of (1*R*,2*S*,3*R*)-**1** to aldehyde were studied and the results are summarized in Table 2.

In most cases complete conversions and good enantioselectivities were obtained. Under the optimized conditions, the methyl addition was essentially suppressed and no other by-product was observed. The use of 0.2 equiv. of (1*R*,2*S*,3*R*)-**1** increased the enantioselectivity from 85 to 88% (entry 5 versus entry 6). When less than 0.1 equiv. of (1*R*,2*S*,3*R*)-**1** was used, both the conversion and enantioselectivity decreased (entries 3 and 4). Higher enantioselectivity was obtained at ca. −20°C; however, at this temperature the rate of reaction was substantially slower than that at 0°C. At −30°C, the reaction became very slow.

An array of aromatic aldehydes were employed for the enantioselectivity study using (1*R*,2*S*,3*R*)-**1** under the optimum conditions derived from the above study, and the results are summarized in Table 3.

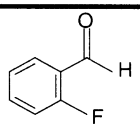
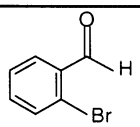
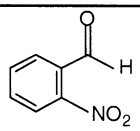
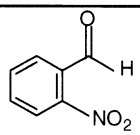
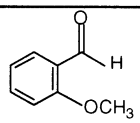
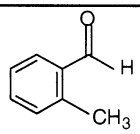
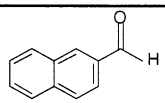
All of the substituted benzaldehydes studied gave better enantioselectivity as compared to benzaldehyde. The results from entries 3 and 4 demonstrated that this catalyst is applicable to both aromatic and aliphatic acetylenes in the alkynylation of aromatic aldehydes.

The reactions of terminal alkynes with aliphatic aldehydes were found to give low enantioselectivities (36% e.e. for the alkynylation of cyclohexanecarboxaldehyde).

3. Conclusion

A series of new binaphthyl amino alcohol ligands were synthesized, and one of these ligands, (1*R*,2*S*,3*R*)-**1**,

Table 3. Asymmetric alkynylation of aromatic aldehydes[a]

Entry	Aldehyde	Alkyne	T (°C)	Reaction time	Conv. (%)	e.e. (%)[b]
1		Ph	0	12 h.	>95	87(+)
2		Ph	0	12 h.	>95	90(+)
3		Ph	0	24 h.	>95	87(+)
4		C_3H_7	0	24 h.	>95	85(+)
5		Ph	0	6 h.	>95	71(+)
6		Ph	0	24 h.	>95	71(+)
7		Ph	0	24 h.	>95	61(+)

[a] Conditions: aldehyde : alkyne : **1** : Me_2Zn = 1 : 2.4 : 0.1 : 2.2; 0°C; 6~24 h.; toluene as solvent.

[b] The e.e. values were determined by HPLC analysis. The sign of rotation of the predominant enantiomer is indicated in parentheses.

was found to be highly effective in the asymmetric alkynylation of aldehydes. In the presence of 10 mol% (1*R*,2*S*,3*R*)-**1**, a variety of aromatic aldehydes were converted to the corresponding chiral propargylic alcohols with good enantioselectivities and high conversions. The results compared favorably with other known amino alcohol ligands in similar reactions. The design of other new binaphthyl amino alcohol ligands and their applications in catalytic asymmetric alkynylation are in progress.

4. Experimental

4.1. General methods

All reactions were performed using oven-dried glassware under an atmosphere of dry nitrogen. All solvents were distilled and dried before use. Reagents were purchased from either Acros or Aldrich chemical companies and were used without further purification, except for the aldehydes which were redistilled before use.

Optical rotations were measured with a Perkin–Elmer Model 341 polarimeter at 20°C. NMR spectra were recorded on a Varian-500 spectrometer. Mass spectra were obtained on a Finnigan Model Mat 95 ST mass spectrometer. HPLC analyses (Chiralcel OD or OD-H column from Daicel, IPA-hexane as eluent) were performed using a Hewlett–Packard model HP 1050 LC interfaced to an HP 1050 Series computer workstation.

4.2. A general procedure for the syntheses of amino alcohol ligands

A solution of (*R*)-2,2′-dibromomethyl-1,1′-binaphthyl[11] (0.11 g, 0.25 mmol), containing Et_3N (0.07 mL, 0.5 mmol) in toluene (2 mL) was treated by dropwise addition of a solution of (1*R*,2*S*)-(+)-2-amino-1,2-diphenylethanol (0.053 g, 0.25 mmol) in CH_3CN (15 mL). The mixture was stirred under reflux for 24 h and the solvent was removed. The residue obtained was dissolved in CH_2Cl_2 (4 mL) and the undissolved solid was removed by filtration. The filtrate was evaporated and the crude product obtained was purified via column chromatography (silica gel, hexane:ethyl acetate = 4:1) to afford a white solid of (1*R*,2*S*,3*R*)-**1**, (*R*)-*N*-[(1*S*,2*R*)-1,2-diphenyl-2-hydroxyethyl]-3,5-dihydro-4*H*-dinaphtho[2,1-*c*:1′,2′-*e*]-azepine (0.80 g, 65%). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.31 (d, J = 12 Hz, 2H, CH_2), 3.47 (d, J = 3 Hz, 1H, CH-N), 4.07 (d, J = 12.5 Hz, 2H, CH_2), 5.30 (d, J = 3.5 Hz, 1H, CH-O), 6.78–6.80 (m, 2H, ArH), 7.05–7.07 (m, 4H, ArH), 7.17–7.31 (m, 8H, ArH), 7.39–7.41 (m, 2H, ArH), 7.48–7.53 (m, 3H, ArH), 7.94–7.98 (m, 3H, ArH). MS (30 eV): m/z 492 (M^++1).

Similarly, amino alcohol ligands **2**–**4** were prepared.

4.2.1. (*R*)-*N*-[(1*R*,2*S*)-1,2-Diphenyl-2-hydroxyethyl]-3,5-dihydro-4*H*-dinaphtho[2,1-*c*:1′,2′-*e*]-azepine, (1*R*,2*R*,3*S*)-2. Yield: 70%; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.21 (d, J = 13 Hz, 2H, CH_2), 3.64 (d, J = 3.5 Hz, 1H, CH-N), 4.03 (d, J = 12.5 Hz, 2H, CH_2), 5.83 (d, J = 3.5 Hz, 1H, CH-O), 7.00–7.16 (m, 10H, ArH), 7.26–7.31 (m, 2H, ArH), 7.49–7.54 (m, 4H, ArH), 7.63–7.65 (m, 2H, ArH), 7.99–8.04 (m, 4H, ArH).

4.2.2. (*S*)-*N*-[(1*S*,2*R*)-1,2-Diphenyl-2-hydroxyethyl]-3,5-dihydro-4*H*-dinaphtho[2,1-*c*:1′,2′-*e*]-azepine, (1*S*,2*S*,3*R*)-3. Yield: 68%; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.20 (d, J = 12.5 Hz, 2H, CH_2), 3.63 (d, J = 3.5 Hz, 1H, CH-N), 4.03 (d, J = 12.5 Hz, 2H, CH_2), 5.83 (d, J = 3.5 Hz, 1H, CH-O), 6.99–7.14 (m, 10H, ArH), 7.26–7.30 (m, 2H, ArH), 7.48–7.52 (m, 4H, ArH), 7.62–7.64 (m, 2H, ArH), 7.98–8.03 (m, 4H, ArH).

4.2.3. (*R*)-*N*-[(1*R*,2*S*)-1-Methyl-2-phenyl-2-hydroxyethyl]-3,5-dihydro-4*H*-dinaphtho[2,1-*c*:1′,2′-*e*]-azepine, (1*R*,2*R*,3*S*)-4. Yield: 64%; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.82 (d, J = 7 Hz, 3H, CH_3), 3.11 (m, 1H, CH-N), 3.36 (d, J = 12 Hz, 2H, CH_2), 3.91 (d, J = 12 Hz, 2H, CH_2), 5.22 (d, J = 3.5 Hz, 1H, CH-O), 7.26–7.31 (m, 3H, ArH), 7.39–7.53 (m, 8H, ArH), 7.60–7.62 (m, 2H, ArH), 7.97–8.01 (m, 4H, ArH).

4.3. General procedure for the nucleophilic addition of alkynes to aldehydes[10]

To a solution of phenylacetylene (52.7 μL, 0.48 mmol) in toluene (1 mL), was added a solution of dimethylzinc (2 M, 0.22 mL, 0.44 mmol) in toluene. The mixture was stirred at 0°C for 30 min. A solution of (1*R*,2*S*,3*R*)-**1** (9.82 mg, 0.02 mmol) in toluene (1 mL) was added. After stirring the mixture for 30 min, the aldehyde (0.2 mmol) was added in one portion with a syringe. The mixture was stirred at 0°C for 6–24 h, and the reaction was then quenched with an aqueous HCl solution (5%, 2 mL). The mixture was extracted with diethyl ether (3×2 mL). The organic layer was separated and concentrated at reduced pressure, and was purified using flash chromatography and afforded the chiral alcohol. The e.e. (%) value of the product was determined by HPLC analysis.

Acknowledgements

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