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Bisoxazolidine-Catalyzed Enantioselective Alkynylation of Aldehydes

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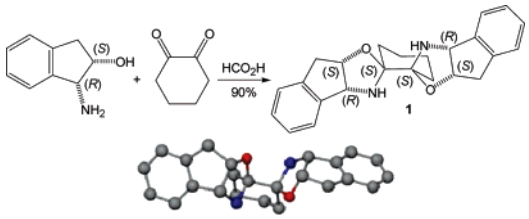
The ever-increasing industrial and academic demand for enantiopure chemicals has been accompanied by the development of numerous asymmetric synthetic methods utilizing highly efficient chiral catalysts and auxiliaries.[1] Ideally, a practical asymmetric catalyst is inexpensive, readily available in both enantiopure forms, and provides high yields and enantioselectivities for a wide range of substrates in various reactions. Among the many chiral catalysts reported to date, a relatively small number derived from rigid C_2-symmetric ligands including BINOL, BOX, salen, DIOP, DUPHOS, and TADDOL have proved to be exceptionally versatile and effective. Despite the structural similarity to bisoxazoline ligands which have been applied very successfully in catalytic asymmetric Diels−Alder and ene reactions,[2] Mukaiyama aldol reactions,[3] cyclopropanations,[4] and aziridinations,[5] to the best of our knowledge there have been no reports of asymmetric catalysts derived from C_2-symmetric bisoxazolidines. In analogy to chiral bisoxazolines which are easily synthesized from readily available amino alcohols and malonyl dichloride or derivatives thereof, we expected that bisoxazolidines could be prepared in a single step by replacing the diacyl halide with a 1,2-diketone. Herein, we provide the first example of a chiral bisoxazolidine and describe its use for catalytic asymmetric carbon−carbon bond formation.

Employing (1*R*,2*S*)-*cis*-1-amino-2-indanol in the acid-promoted reaction with 1,2-cyclohexanedione we obtained bisoxazolidine **1** in 90% yield and 99% de while other amino alcohols gave complex isomeric mixtures (Scheme 1). However, **1** was produced with excellent diastereoselectivity and exclusive formation of the (*S*,*S*)-*N*,*O*-diketal was confirmed by crystallographic analysis.[6] The ligand possesses a C_2-symmetric structure and an averaged separation of 2.35 Å between the nitrogen and oxygen atoms which should facilitate bidentate binding to metal ions and organometallic compounds. We therefore envisioned that **1** is a useful Lewis basic catalyst for asymmetric reactions with organozinc reagents.

Since chiral secondary alcohols have been identified as versatile building blocks for asymmetric synthesis,[7] the enantioselective addition of organozinc reagents to aldehydes has emerged as one of the most important carbon−carbon bond forming reactions. To date, asymmetric alkynylation of aldehydes has been realized using stoichiometric amounts of chiral ligands[8] and several catalytic procedures have been reported.[9] Many of these protocols focus on the addition of phenylacetylene to aromatic aldehydes,[10] while few address the need to utilize nonaromatic substrates.[11] It is therefore desirable to further extend this reaction to both aliphatic aldehydes and aliphatic alkynes. General drawbacks of currently existing methods include the need for freshly distilled solvents and purified reagents in addition to laborious and time-consuming procedures requiring stepwise premixing of chiral ligand, organozinc reagent, and acetylene in a certain order and stirring for extensive times, in some cases several hours, prior to the addition of the aldehyde.

Initial studies using various amounts of diethylzinc, phenylacetylene, and benzaldehyde in the presence of 10 mol % of **1** revealed that superior results can be obtained with nonpolar solvents such as hexanes and toluene while both yields and ee's dropped when

Scheme 1. Synthesis and Single Crystal Structure of Ligand 1



tetrahydrofuran, diethyl ether, or dichloromethane were used as solvent. We then varied the amount and ratio of both phenylacetylene and organozinc reagent and explored the use of diisopropyl- and dimethylzinc. To our delight, we found that the latter effectively impedes the competing alkylation reaction favoring alkynylation when equimolar amounts of dimethylzinc and phenylacetylene were employed in nonpolar solvents. Temperature and solvent composition proved to have a distinctive effect on yields and ee's and were carefully optimized. Best results were obtained using 10 mol % of **1** in a heptane−toluene mixture (5.6:1 v/v) at −4 °C (see Supporting Information).

Having optimized the bisoxazolidine-catalyzed alkynylation of benzaldehyde with phenylacetylene, we decided to screen a series of aromatic and aliphatic aldehydes and acetylenes to evaluate the scope of this reaction (Table 1). We were pleased to find that alkynylation of electron-rich and electron-deficient aromatic aldehydes with phenylacetylene in the presence of 10 mol % of **1** gave the corresponding propargylic alcohols in excellent yield and ee's (Table 1, entries 1−9). Importantly, our method is also suitable to both linear and branched aliphatic alkynes (entries 10−14). For example, alkynylation of benzaldehyde with cyclohexylacetylene and 1-hexyne proceeded with 87−96% yield and 92% ee. Excellent results were also observed with 1-ethynylcyclohexene and cyclopropylacetylene (entries 12 and 14) which compare favorably to the 74−77% yield and 83−89% ee obtained with 10 mol % of an In(III)/BINOL catalyst.[11a] Similarly, alkynylation of aliphatic aldehydes gave the corresponding propargylic alcohols in high yields and enantioselectivities (entries 15 and 16). The catalyst has been recovered after asymmetric alkynylation of benzaldehyde with phenylacetylene and successfully recycled (Table 1, entry 1).

Catalyst **1** was also employed in the asymmetric addition of silylacetylenes to aldehydes under the same conditions (Figure 1). The corresponding 3-silylpropargylic alcohols were obtained in up to 88% yield and 99% ee. The efficient asymmetric synthesis of these compounds is important because of the versatile use of desilylated derivatives in alkylations and Sonogashira couplings.

Noteworthy, our procedure eliminates the need for commonly used additives such as HMPA or titanium tetraisopropoxide while premixing and stirring of the ligand and the organozinc reagent or acetylene prior to addition of the aldehyde is not required. It should be noted, however, that various other procedures avoid cumbersome premixing and require only small amounts of inexpensive amine additives.[9a,11a,12]

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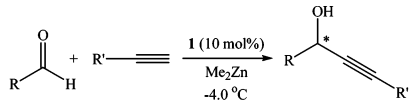
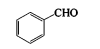
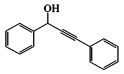
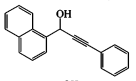
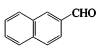
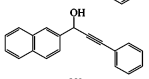
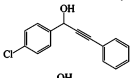
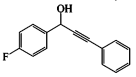
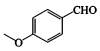
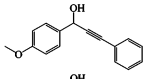
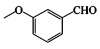
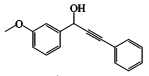
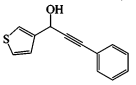
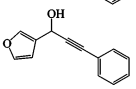
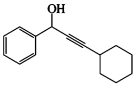
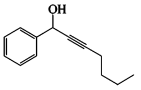
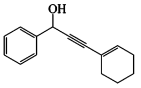
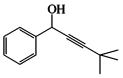
Table 1. Bisoxazolidine-Catalyzed Asymmetric Alkynylation of Aldehydes



entry	aldehyde	acetylene	propargylic alcohol	yield[a] (%)	ee[b] (%)
1				90 (88)[d]	93 (91)[d]
2				91	94
3				88	91
4				86	94
5				92	94
6				95	93
7				88	94
8				90	89
9				94	78
10				87	92
11				96	92
12				91	90
13				71	95
14				81	89
15				95	77
16				99[c]	83

[a] Isolated yields. [b] Determined by HPLC on Chiralcel OD. [c] Temperature = −15 °C. [d] Obtained with recycled catalyst.

Figure 1. Structures of 3-silylpropargylic alcohols.

Although monooxazolidines have been used for alkylation and alkynylation of aldehydes,[13] the C_2-symmetry of bisoxazolidine **1** provides superior results and appears to be crucial for both catalytic activity and asymmetric induction. For comparison, we prepared

Scheme 2. Oxazolidine-Catalyzed Alkynylation

(1*R*,2*S*)-*cis*-1-amino-2-indanol-derived oxazolidine **2** using cyclohexanone instead of cyclohexanedione and tested its catalytic performance under the same reaction conditions. Alkynylation of benzaldehyde with phenylacetylene in the presence of 10 mol % of **2** gave the corresponding alcohol in only 76% yield and 17% ee (Scheme 2).

In conclusion, we have prepared the first bisoxazolidine ligand and showed its usefulness for asymmetric catalysis. Ligand **1** was synthesized in high yields in a single step from inexpensive aminoindanol which is available in both enantiomeric forms. The bisoxazolidine ligand was successfully applied in the catalytic enantioselective alkynylation of a range of aromatic and aliphatic aldehydes generating chiral propargylic alcohols in high yields and enantioselectivities. The rigid, C_2-symmetric structure and the simplicity of the preparation of enantiopure **1** make this an attractive new chiral ligand that may find multiple applications in asymmetric catalysis.

Supporting Information Available: Experimental procedures and full characterization of **1** and all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(6) Careful evaporation of a solution of **1** in chloroform gave a single-crystal suitable for crystallographic analysis (CDCC602445). Crystal structure data: $C_{24}H_{26}N_2O_2$, monoclinic, space group *P*21, a = 16.9199(16) Å, b = 5.5487(5) Å, c = 23.585(2) Å, α = 90.00°, β = 108.5190(10)°, γ = 90.00°, V = 2099.6(3) Å3, Z = 4, ρ_{calcd} = 1.367 g cm^{-3}, T = 173 K.

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