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Facile and practical enantioselective synthesis of propargylic alcohols by direct addition of alkynes to aldehydes catalyzed by chiral disulfide–oxazolidine ligands

Antonio L. Braga,[a,*] Helmoz R. Appelt,[a] Claudio C. Silveira,[a] Ludger A. Wessjohann[b] and Paulo H. Schneider[a]

[a]*Departamento de Química, Universidade Federal de Santa Maria, CEP-97105-900 Santa Maria, RS, Brazil*
[b]*Leibniz-Institute of Plant Biochemistry, Weinberg 3, D-06120 Halle (Saale), Germany*

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Abstract—The enantioselective alkynylation reaction of aldehydes with alkynes and diethylzinc, catalyzed by chiral disulfide–oxazolidine ligands, provides a simple, practical and inexpensive method to access chiral propargylic alcohols in good yields and satisfactory ee's.

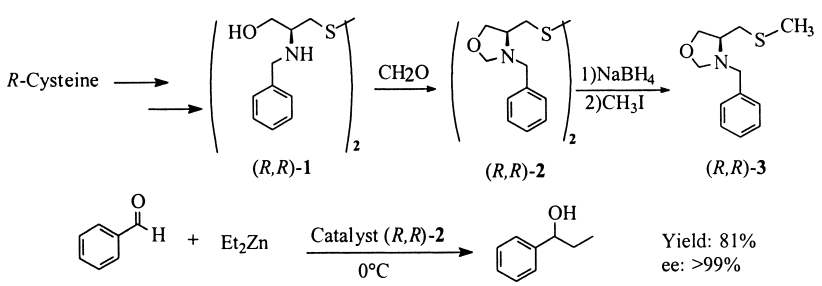
1. Introduction

A survey of the recent chemical literature reveals an explosion of interest in the development and design of chiral auxiliaries and catalysts to access pure or enriched chiral compounds.[1] Development of new or improved methods for the asymmetric preparation of chiral propargylic alcohols has gained considerable significance during the past years because they are useful building blocks for the synthesis of various biologically active and structurally interesting compounds.[2] Compounds of this important class had been prepared by stoichiometric,[3] enzymatic or catalytic[4] reduction of acetylenic ketones or by enantioselective alkynylation of aldehydes using stoichiometric[5] or catalytic amounts of ligands.[6]

As part of our broader program to explore the preparation and use of chiral organochalcogen compounds in asymmetric catalysis especially ligands binding via sulfur or selenium, we describe in this article our studies on the alkynylation of aldehydes. We have demonstrated previously that oxazolidine disulfides are appropriate ligands for an enantioselective diethylzinc addition to aldehydes[7] (Scheme 1).

Now, we wish to communicate that this kind of catalyst promotes the direct enantioselective reaction of terminal alkynes with aldehydes to afford propargylic alcohols in good yields and satisfactory enantioselectivity (Scheme 2, Tables 1 and 2).

Alkynyl zinc reagents are generated in situ by reaction of terminal alkynes and diethylzinc, thus avoiding separate preparative metalation steps. Thus, treatment of a solution of an alkyne at −20 to −30°C in THF with diethylzinc and 5–10 mol% of a catalyst (**1**–**3**), followed by the aldehyde,



Scheme 1.

Keywords: sulfide; asymmetric alkynylation; amino alcohol; diethylzinc; propargylic alcohol.
* Corresponding author. Fax: +55-55-220-8031; e-mail: albraga@quimica.ufsm.br

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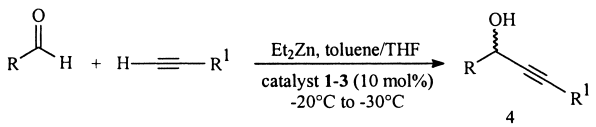


Scheme 2.

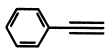
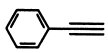
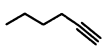
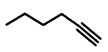
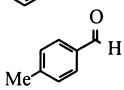
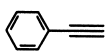
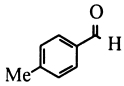
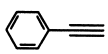
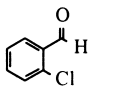
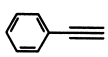
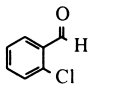
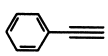
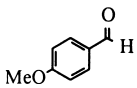
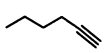
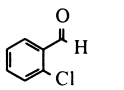
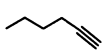
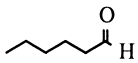
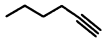
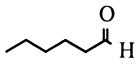
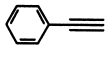
furnishes the desired adducts in moderate to satisfactory yields and up to 60% ee, after 48 h of reaction. For each of the propargylic adducts, GC analysis permitted the enantiomeric purity of the products to be determined.

A preliminary study was conducted with the aim of determining the best of the available chiral ligands and solvent conditions (Table 1). We explored the catalyzed alkynylation of benzaldehyde with phenylacetylene at −20 to −30°C for 48 h. The best results were obtained with the ligand (*R*,*R*)-**2**. With this ligand, the corresponding propargylic alcohol was obtained in 67% yield and 56% ee.

In all cases studied, the desired propargylic alcohols were slightly contaminated by the corresponding alkyl alcohols, α-ethylaryl alcohol, resulting from the transfer of the ethyl group of diethyl zinc to aldehydes, as previously reported.[6a,8] It was observed also that the decrease of the catalyst concentration from 10 to 5 mol% does not result in a decrease of enantiomeric excess of the product, but the yield was reduced (Table 1; entry 4). In this case, the by-product, α-ethylaryl alcohol, was obtained in 41%. When the ligand *R*,*R*-**1** was used as catalyst, an average yield was obtained, but racemic product was formed.

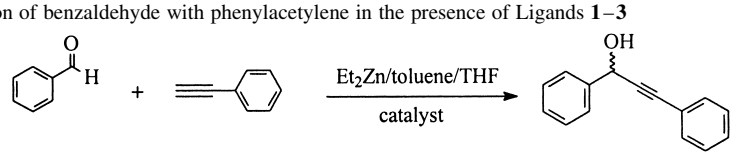
With the ligand (*R*,*R*)-**3** as catalyst, the best yield was obtained, but the ee was very low. Interestingly, variation of the solvent has a profound influence on the yields of this reaction. The use of toluene or different mixtures of toluene/THF resulted in the same level of optical purity of the propargylic alcohols, but the yields were diminished, specially by using toluene only, which resulted in a 7% yield (Table 1; entry 5). This observation is in contrast to that of Carreira[5] who obtained the best result in pure toluene. Also in contrast to this method, no amine base is required and the reaction conditions can be considered almost neutral.

Table 2. Asymmetric alkynylation of aldehydes catalyzed by chiral disulfide (*R*,*R*)-**2**

Entry	Aldehyde	Acetylene	Reaction	*t* (h)	Yield (%)	ee (%)[a]
1			4a	24	50	60(−)(*S*)[b]
2			4a	48	67	56(−)(*S*)
3			4b	24	51	41(−)(*S*)
4			4b	48	55	36(−)(*S*)
5			4c	24	54	60(−)(*S*)
6			4c	48	76	58(−)(*S*)
7			4d	24	61	53(+)(*S*)
8			4d	48	80	50(+)(*S*)
9			4e	48	81	52(−)(*S*)
10			4f	48	72	58(+)(*S*)
11			4g	48	73	43(−)(*S*)
12			4h	48	82	51(+)(*S*)

Reactions were carried out at −20 to −30°C with 10 mol% ligand **2** following the general procedure.
[a] The enantioselectivities was determined by GC analysis using chiral columns.
[b] The absolute configuration of the products was established by correlation with known compounds or by analogy.[3d,e,4a,6]

Table 1. Ligand study: alkynylation of benzaldehyde with phenylacetylene in the presence of Ligands **1**–**3**



Entry	Catalyst	Catalyst (mol%)	Solvent	Yield (%)	ee (%)[a]
1	(*R*,*R*)-**1**	10	$PhCH_3$/THF 2.75:1	65	–
2	(*R*,*R*)-**2**	10	$PhCH_3$/THF 2.75:1	67	56[b]
3	(*R*,*R*)-**3**	10	$PhCH_3$/THF 2.75:1	69	18
4	(*R*,*R*)-**2**	5	$PhCH_3$/THF 2.75:1	23	60
5	(*R*,*R*)-**2**	10	$PhCH_3$	7	61
6	(*R*,*R*)-**2**	10	$PhCH_3$/THF 5.5:1	45	60
7	(*R*,*R*)-**2**	10	$PhCH_3$/THF 1:1	60	55

Reactions were carried out at −20 to −30°C with 5 or 10 mol% ligand following the general procedure described in Section 3.
[a] Determined by GC analysis of crude reaction mixture using 2,6-Me,3-Pe-β-CD column (155°C).
[b] With (*S*,*S*)-**2** the opposite enantiomer was isolated in comparable yield and ee.

In a second set of experiments, the influence of various aldehydes, alkynes and the reaction time, on yield and enantioselectivity were tested, using the best catalyst (*R*,*R*-**2**). Most of the substituted aryl aldehydes underwent the addition reaction with similar levels of enantioselectivity compared with the parent benzaldehyde. Comparison of several examples suggests that this chemistry is applicable to both aromatic and aliphatic acetylenes.

Increased reaction times (24–48 h) have only a small influence on the reaction, giving slightly improved yields but decreased ee's (Table 2; entries 1–8).

2. Conclusions

In summary, the chiral oxazolidine disulfide derived from commercial (*R*)-cysteine was found to promote the enantioselective alkynylation of aldehydes to afford the chiral propargylic alcohols in good yields and satisfactory enantiomeric excess under non-basic conditions. Although this first generation of new, sulfur based catalyst is not yet as optimized as the more traditional aminoalcohols,[5] we are confident that they will prove to be a useful alternative to existing methods as was already shown in other organozinc reactions,[7,9] especially the case of preparation from cheap cysteine is intriguing. Further studies dealing with their improvement and application in organic synthesis are in progress.

3. Experimental

Reagents were used as received unless otherwise stated. All manipulations were carried out under an inert atmosphere of Ar. The glassware was oven dried prior to use for the alkynylation reactions. Optical rotations were measured on a Perkin–Elmer 341 polarimeter. The ^{1}H and ^{13}C NMR spectra were register on a Bruker DPX 200 spectrometer using TMS as an internal standard. Elemental analyses (C, H, N) were performed on a Vario El and Perkin–Elmer CHN 2400 analyzer. Gas chromatography (GC) was performed using a Varian 3400 gas chromatograph with (2,6-Me-3-Pe)-β-cyclodextrin column as chiral stationary phase for ee determination of the propargylic alcohols obtained.

3.1. Asymmetric alkynylation reactions. Typical procedure

Acetylene (2.6 mmol) was added into a 15 mL two-neck round bottom flask containing 0,85 mL dry THF at rt under N_2. The stirred mixture was then cooled to −20°C for 5 min, followed by the addition of a 1.1 M solution of diethylzinc in toluene (2.4 mmol). The resulting solution was stirred at −20°C for 15 min, and ligand (0.2 mmol, 10 mol%) was added. The homogenous solution was stirred at −20°C for 15 min, and then aldehyde (2.0 mmol) was added via syringe. The resulting mixture was stirred at −20 to −30°C for 48 h. When the reaction was complete, it was quenched by the addition of MeOH (1 mL) at −20°C, and as it warmed to 0°C, sat. NH_4Cl (2 mL) was added. EtOAc (50 mL) and sat. NH_4Cl (10 mL) were then added and the layers were separated. The aqueous layer was extracted with EtOAc (2×20 mL). The combined organic phase was washed with brine and dried ($MgSO_4$). After filtration, the solvent was removed under reduced pressure. The crude product was purified by column chromatography (silica gel, 10/1 hexane/EtOAc) to afford pure product. The enantiomeric excess was determined by GC analysis of reaction mixture on a 2,6-Me-3-Pe,β-CD column.

3.1.1. (−)-1,3-Diphenylprop-2-yn-1-ol (4a).[6] The typical procedure was followed. The compound was purified by flash chromatography (silica gel) by elution with 10% EtOAc/hexane. The enantiomeric excess was determined by GC analysis on a 2,6-Me-3-Pe,β-CD column (155°C). ^{1}H NMR ($CDCl_3$, 200 MHz): δ=7.66–7.58 (m, 2H, ArH), 7.52–7.48 (m, 2H, ArH), 7.46–7.32 (m, 6H, ArH), 5.71 (m, 1H), 2.50 (d, J=6.2 Hz, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ=140.7, 131.8, 128.6, 128.5, 128.4, 126.8, 122.5, 88.8, 86.7, 65.2.

3.1.2. (−) 1-Phenylhept-2-yn-1-ol (4b). The typical procedure was followed. The compound was purified by flash chromatography (silica gel) by elution with 9% EtOAc/hexane. The enantiomeric excess was determined by GC on a 2,6-Me-3-Pe, β-CD column (50–155°C, 3°C/min). ^{1}H NMR ($CDCl_3$, 200 MHz): δ=7.22–7.18 (m, 2H), 7.09–6.97 (m, 3H), 5.05 (m, 1H), 2.33 (s, 1H), 2.04–1.96 (m, 2H), 1.36–1.19 (m, 4H), 0.70 (t, J=6.94 Hz, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ=142.5, 129.4, 128.5, 127.9, 127.4, 87.4, 81.8, 65.1, 31.6, 22.9, 19.4, 14.6.

3.1.3. (−)-1-(4-Methylphenyl)-3-phenylprop-2-yn-1-ol (4c). The typical procedure was followed. The compound was purified by flash chromatography (silica gel) by elution with 9% EtOAc/hexane. The enantiomeric excess was determined by GC on a 2,6-Me-3-Pe,β-CD column (155°C). ^{1}H NMR ($CDCl_3$, 200 MHz): δ=7.48–7.42 (m, 4H, ArH), 7.28–7.26 (m, 3H, ArH), 7.18–7.14 (m, 2H, ArH), 5.60 (m, 1H), 2.64 (s, 1H), 2.33 (s, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ=138.0, 137.7, 131.6, 129.2, 128.4, 128.1, 126.6, 122.4, 88.9, 86.3, 64.7, 21.0.

3.1.4. (+)-1-(2-Chlorophenyl)-3-phenylprop-2-yn-1-ol (4d).[6] The typical procedure was followed. The compound was purified by flash chromatography (silica gel) by elution with 9% EtOAc/hexane. The enantiomeric excess was determined by GC analysis of his (methyl) ether derivate on a 2,6-Me-3-Pe,β-CD column (50–155°C, 4°C/min). ^{1}H NMR ($CDCl_3$, 200 MHz): δ=7.85 (d, J=7.3 Hz, 1H, ArH), 7.48 (m, 2H, ArH), 7.43–7.27 (m, 6H, ArH), 6.06 (m, 1H), 2.70 (s, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ=137.9, 132.9, 131.8, 129.8, 129.7, 128.7, 128.5, 128.4, 127.3, 122.3, 87.6, 86.7, 63.5.

3.1.5. (−)-1-(4-Methoxyphenyl)hept-2-yn-1-ol (4e). The typical procedure was followed. The compound was purified by flash chromatography (silica gel) by elution with 7% EtOAc/hexane. The enantiomeric excess was determined by GC on a 2,6-Me-3-Pe,β-CD column (50–155°C, 2°C/min). ^{1}H NMR ($CDCl_3$, 200 MHz): δ=7.48–7.39 (m, 2H), 6.95–6.81 (m, 2H), 5.35 (m, 1H), 3.72 (s, 3H), 3.04 (s, 1H), 2.29–2.20 (m, 2H), 1.51–1.41 (m, 4H), 0.89 (t, J=6.84 Hz, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ=159.0,

133.6, 128.8, 128.6, 113.4, 113.3, 76.7, 80.1, 63.8, 54.8, 30.4, 21.6, 13.2.

3.1.6. (+)-1-(2-Chlorophenyl)-hept-2-yn-1-ol (4f). The typical procedure was followed. The compound was purified by flash chromatography (silica gel) by elution with 10% EtOAc/hexane. The enantiomeric excess was determined by GC on a 2,6-Me-3-Pe,β-CD column (50–155°C, 3°C/min). ^{1}H NMR ($CDCl_3$, 200 MHz): δ=7.73 (d, J=7.3 Hz, 1H, ArH), 7.33–7.14 (m, 4H, ArH), 5.76 (m, 1H), 3.05 (s, 1H), 2.25–2.18 (m, 2H), 1.55–1.28 (m, 4H), 0.88 (t, J=6.9 Hz, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ=138.4, 132.4, 129.3, 129.0, 128.0, 126.8, 87.2, 78.8, 61.6, 30.3, 21.7, 18.2, 13.3.

3.1.7. (−)-Dodec-7-yn-6-ol (4g). The typical procedure was followed. The compound was purified by flash chromatography (silica gel) by elution with 8% EtOAc/hexane. The enantiomeric excess was determined by GC on a 2,6-Me-3-Pe,β-CD column (50–155°C, 3°C/min). ^{1}H NMR ($CDCl_3$, 200 MHz): δ=4.45 (m, 1H), 2.15–2.12 (m, 2H), 1.58–1.40 (m, 4H), 1.36–1.23 (m, 8H), 0.86–0.80 (m, 6H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ=85.1, 81.3, 62.5, 38.0, 33.9, 30.6, 25.9, 22.9, 22.8, 18.2, 14.7, 13.8.

3.1.8. (+)-1-Phenylnon-1-yn-3-ol (4h). The typical procedure was followed. The compound was purified by flash chromatography (silica gel) by elution with 10% EtOAc/hexane. The enantiomeric excess was determined by GC on a 2,6-Me-3-Pe,β-CD column (50–155°C, 3°C/min). ^{1}H NMR ($CDCl_3$, 200 MHz): δ=7.33–7.31 (m, 2H), 7.15–7.14 (m, 2H), 4.48 (m, 1H), 2.93 (s, 1H), 1.66–1.63 (m, 4H), 1.38–1.17 (m, 6H), 0.77 (t, J=6.89 Hz, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ=131.5, 128.7, 128.0, 122.7, 90.3, 84.5, 62.6, 37.7, 32.0, 28.8, 25.1, 22.4, 13.8.

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