Enantioselective Alkynylation of Aromatic Aldehydes: Pyridyl Phenylene Terpeneol Catalysts with Flexible Biaryl Axes

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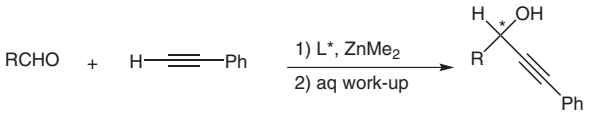
Dedicated to Prof. Dr. Dieter Enders on the occasion of his 65th birthday

Abstract: Free rotating biaryl axes of pyridyl phenylene terpenols are fixed by zinc cations to give conformationally pure zinc complexes. These zinc alkoxide catalysts provide yields up to 99% and ee values up to 86% in the enantioselective addition of phenylacetylene to aromatic aldehydes.

Key words: enantioselectivity, biaryls, organometallic reagents, zinc, alkynes

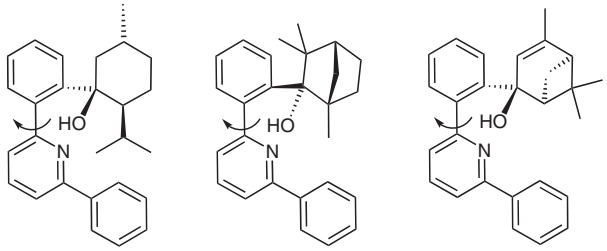
The enantioselective addition of terminal alkynes to aldehydes is of great preparative interest for the generation of enantiomerically enriched propargylic alcohols.[1] Optically active secondary propargylic alcohols are valuable building blocks in many pharmaceutical and natural product syntheses.[1] Addition reactions with organozinc reagents are useful for the synthesis of various propargylic alcohols because the reactions can be carried out under mild conditions and many functional groups are tolerated without inconvenient side reactions.[2]



Scheme 1 Zinc-catalyzed addition of terminal alkynes to aldehydes with organozinc reagents (L* are pyridyl phenylene terpenols)

There are many chiral catalysts that enable the asymmetric alkynylation of carbonylic components, for example, ephedrines,[3] BINOLs,[4] terpene-derived amino and pyridyl alcohols,[5] and bisprolinols developed by Trost,[6] and other catalysts have been used for the asymmetric alkynylation of aldehydes.[7] Enantiopure atropisomeric biaryl systems with flexible chiral axes such as BINOL or BINAP are known to provide excellent results in various types of catalytic asymmetric reactions.[8]

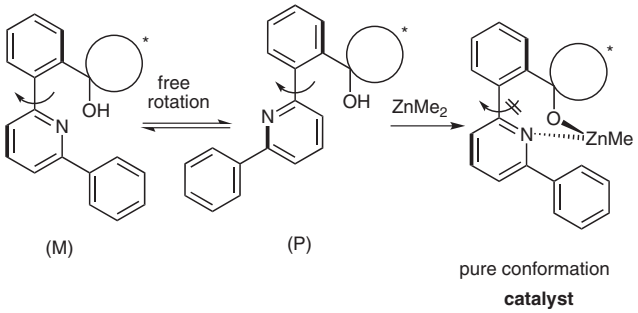
We report herein the use of catalysts with flexible biaryl axes that are only fixed by a metal ion, to control enantioselectivity. Enantiopure pyridylterpenols give yields up to 99% and up to 95% ee when employed as ligands in the addition of dialkylzincs (i.e., $ZnMe_2$, $ZnEt_2$) to benzaldehyde.[9]



1 2 3

Figure 1 Diphenylpyridine-based terpenols **1**–**3** (the flexible chiral biaryl axes are marked by arrows)

These pyridylacohols contain flexible phenylpyridyl moieties with fast (P)/(M) biaryl equilibrium.[9] This conformational equilibrium is found to be eliminated by complexation of zinc cations (Scheme 2) and complexes with conformationally pure biaryl axes are formed.[9] The conformations of the biaryl axes were identified as being the origin of enantioselectivity in catalyzed additions of zinc dialkyls to benzaldehyde.[9]



Scheme 2 Observed elimination of the conformational equilibrium during the formation of the catalytically active zinc alkoxide

The precatalysts **1**–**3** were employed for the asymmetric alkynylation of aromatic aldehydes with phenylacetylene as a model system for acetylenes of further synthetic interest.

Because the flexible biaryl systems were found to depend strongly on the reaction conditions, four procedures were tested to determine the most promising menthyl ligand in

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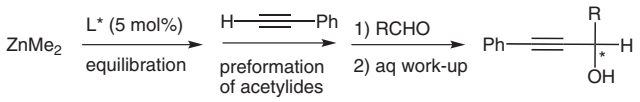
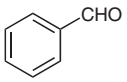
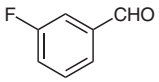
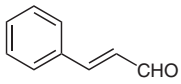
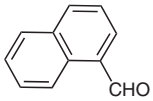
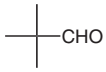
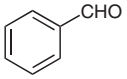
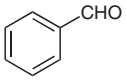
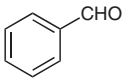
order to find an optimum for a general procedure (Table 1). The most important parameter affecting the yield and ee was found to be the in situ preformation of the alkynylzinc species. The test catalytic reactions were all carried out with 5 mol% precatalyst and all yields were isolated (Table 1).



Scheme 3 Stages of the zinc-catalyzed addition of phenylacetylene to aldehydes with organozinc reagents (L* are pyridyl phenylene terpenols **1**–**3**)

Table 1 Alkynylation of Aromatic Aldehydes with Phenyl-acetylene in the Presence of Dimethyl Zinc and the Precatalyst **1** (Scheme 1)

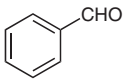
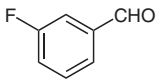
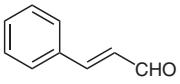
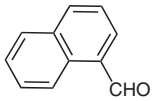
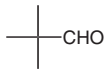
Aldehyde	Yield (%)[a]	ee (%)[a]	Enantiomer	Procedure[b]
	61	66	R	A
	88	53	n.d.	A
	99	52	R	A
	99	82	R	A
	86	8	R	A
	31	86	R	B
	39	83	R	C
	49	69	R	D

[a] All Yields are isolated and the ee was determined by chiral HPLC.
[b] Procedure A: Precatalyst and dimethyl zinc were stirred at r.t. for 30 min in toluene. Phenylacetylene was added subsequently and the mixture was stirred at 0 °C for 45 min before aldehyde was added. Procedure B: See procedure A with stirring catalyst, dimethyl zinc and phenylacetylene for 5 min. Procedure C: See procedure B with toluene–*n*-Hexane (1:1) as solvent. Procedure D: See procedure A, precatalyst (0.5 mmol) was stirred with dimethyl zinc (0.6 mmol) in toluene for 45 min and, separately, a mixture of dimethyl zinc and phenylacetylene was stirred in toluene for 30 min then added at 0 °C to the catalyst complex.

In procedure A, the precatalyst and dimethyl zinc were combined and equilibrated. Phenylacetylene was added and allowed to react with the zinc species for 45 minutes, before the aldehydes were added (Scheme 3). Procedures B and C were carried out analogously except that the reaction time for the preformation of the phenylacetylide was 5 minutes; Procedure C employed a 1:1 mixture of toluene and *n*-hexane as solvent. Procedure D avoided direct reactions of the preformed catalysts with phenylacetylene; thus, alkynylzinc and zinc alkoxide were generated separately and combined before aldehydes were added.

A comparison of the procedures shown in Table 1 reveals that the yields depend strongly on the duration of the preformation of the alkynylzinc. The longer phenylacetylene is allowed to react with dimethyl zinc and the precatalyst, the higher the yields. The ee value decreases from 86 to 66% with longer equilibration of phenylacetylene among the zinc species before the aldehydes are added (see procedures B and A). The type of aldehyde employed was also significant. 1-Naphthaldehyde gave the highest ee and yield (up to 99% yield and 82% ee) whereas the propargylic alcohol formed from trimethylacetaldehyde was almost completely racemic (8% ee). Because the best results were achieved by applying procedure A, precatalysts **2** and **3** were tested according to procedure A.

Table 2 Alkynylation of Aromatic Aldehydes with Phenylacetylene in the Presence of Dimethyl Zinc and Precatalyst **2** (Scheme 1)[a]

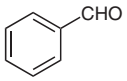
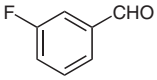
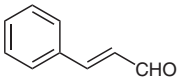
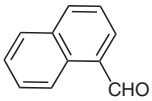
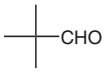
Aldehyde	Yield (%)[b]	ee (%)[b]	Enantiomer
	54	57	*S*
	88	55	n.d.
	87	16	*S*
	99	19	*S*
	99	0	

[a] Procedure A was used in all cases (Table 1).
[b] All Yields are isolated and the ee values were determined by chiral HPLC.

These results presented in Table 2 suggest that the menthone-based ligand **1** performs much better in this type of reaction than the fenchol ligand **2**. The results for benzaldehyde and 3-fluorobenzaldehyde are similar (cf. Table 1 and Table 2), but 1-naphthaldehyde, cinnamic aldehyde and trimethylacetaldehyde gave poor ee values (up to 52%), although the yields were high (up to 99%). The verbenone based ligand **3** also gave moderate ee values (up to 42%) and yields up to 99% (Table 3).

A surprising result of this study was the strong influence of the applied reaction times. The significant effect of the reaction protocol on the yields can be explained by the

Table 3 Alkynylation of Aromatic Aldehydes with Phenylacetylene in the Pesence of Dimethyl Zinc and Precatalyst **3** (Scheme 1)[a]

Aldehyde	Yield(%)[b]	ee (%)	Enantiomer
	51	22	S
	99	25	n.d.
	91	9	S
	65	42	S
	83	3	S

[a] Procedure A was used in all cases (Table 1).
[b] All Yields are isolated and the ee values were determined by chiral HPLC.

formation of aryl or alkyl ethanols as side products by reaction with residual dimethyl zinc.[5a]

The enantioselectivities of the employed catalysts depend on the duration of zinc acetylide preformation. When the catalyst reacted with phenyl acetylene over a period of 45 minutes prior to addition of the aldehyde (benzaldehyde, procedure A, Table 1) 69% ee was found. However, the enantiomeric excess was increased to 86% when the reaction with phenyl acetylene was restricted to only 5 minutes in an equivalent procedure (Table 1).

Therefore, it is clear that the catalytically active zinc alkoxide is modified in the presence of phenyl acetylene or the corresponding alkynyl zinc species. According to NMR experiments, the catalytically active methyl zinc alkoxide, based on ligand **1**, was almost completely transformed into species without methyl zinc groups under the catalytic conditions.

According to NOE experiments, the conformation of the chiral biaryl axis is not retained for longer reaction times. The conformational purity of the chiral biaryl axis could only be determined for the initial unimpaired methyl zinc complex. Enantioselectivities, however, are known to depend nearly entirely on the conformations of the chiral biaryl axes.[9] Hence, the substitution of alkyl for alkynyl groups at the zinc, and a conformational equilibration in the employed catalyst system, explain why longer reaction times result in decreased enantioselectivities in aldehyde alkynylations.[10]

Acknowledgment

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(10) All reactions were carried out under an argon atmosphere using Schlenk techniques. Solvents used in chemical conversions were dried by standard methods and distilled under argon prior to use. The enantiomeric excesses of the chiral propargylic alcohols were determined by chiral HPLC. A La Chrome elite unit from Hitachi was employed together with a 25 cm Chiracel OD-H chiral column (flow: 0.8 mL/min; pressure: 32 bar; detection λ = 240 nm; eluent: 90% *n*-hexanes and 10% *i*-propanol). The enantiomers of the alcohols were identified by comparison to reference spectra.[11]

NMR spectroscopy. Deuterated solvents where purchased from Acros Organics. Toluene-d_8 was stored over sodium-lead alloy. NMR spectra for characterization of compounds where recorded with a Bruker DPX 300 spectrometer (^{1}H frequency 300.13 MHz). 2D NMR and one-dimensional high resolution spectra for analysis of the catalytically active system were recorded with a Bruker AVANCE II 600 spectrometer (^{1}H frequency 600.20 MHz) using a triple resonance Z gradient probe and processed using TopSpin 2.1 software (Bruker inc.). The temperature was calibrated with a 100% MeOH sample. 600 MHz 1D and 2D NMR experiments were carried out according to the following procedures.

Characterization of the methyl zinc alkoxide based on ligand 1: Ligand **1** (0.026 mmol, 10 mg) was charged into a NMR tube and degassed in vacuo for 10 min. absolute toluene-d_8 (0.30 mL) was added prior to addition of dimethyl zinc (2 M in toluene, 0.8 mL, 0.156 mmol). The constitution of the formed methyl zinc complex was confirmed by H,C-HMQC, H,N-HMQC and H,H-NOESY spectroscopic analysis at a temperature of 295 K. The conformation of the chiral biaryl axis was determined by characteristic NOE contacts.

In situ study of the reaction of the methyl zinc alkoxide based on 1 with phenylacetylene: A sample was prepared as described above. The mixture was equilibrated over a period of 30 min and phenylacetylene (0.02 mL, 0.156 mmol) was added. The mixture was equilibrated for 1 h prior to use for measurements. The methylzinc alkoxide derivative of **1** was shown to be almost completely converted into a new species, which was analyzed by H,C-HMQC, H,C-HMBC, H,N-HMQC, and H,H-NOESY spectroscopy at a temperature of 295 K.

Procedure A: Pyridyl phenylene terpenol (0.074 mmol; 5 mol%; **1**: 28 mg; **2**: 29 mg; **3**: 28 mg) was degassed in vacuum for 10 min, then dissolved in toluene (6 mL) and a solution of dimethyl zinc (2.0 M in toluene, 1.80 mL 3.6 mmol) was added at 0 °C. The ice bath was removed and the catalyst was equilibrated for 30 min at r.t. Phenylacetylene (3 mmol, 0.33 mL) was added at r.t. and the mixture was further stirred for 45 min. The mixture was cooled on the ice bath again and aldehyde (1.0 mmol) was added. The colorless solution was kept at 0 °C for 3 days and the reaction was subsequently quenched with saturated $NaHSO_4$ (5 mL). The organic phase was separated, the aqueous phase was extracted with MTBE (3 × 5 mL), and the combined organic phases were evaporated. The resulting oil was purified by column chromatography (*n*-hexanes–ethyl acetate, 4:1; 70 g SiO_2) to give the pure product.

Procedure B: See procedure A, with 5 min reaction time after adding phenylacetylene.

Procedure C: See procedure A, with 5 min reaction time after adding phenylacetylene and the solvent was replaced by a mixture of toluene and *n*-hexanes (1:1).

Procedure D: See procedure A, the precatalyst was stirred with dimethyl zinc (0.6 mmol) in toluene (3 mL) for 45 min and, separately, a mixture of dimethyl zinc (3.0 mmol) and phenylacetylene (3.0 mmol) in toluene (3 mL) was stirred for 30 min, then added to the catalyst complex at 0 °C.

1,3-Diphenylprop-2-yn-1-ol:[11b] ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.36 (s, 1 H), 5.72 (s, 1 H), 7.34–7.64 (m, 10 H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 42.0, 118.1, 123.0, 128.9, 140.0. HPLC [Daicel Chiracel OD-H; λ = 254 nm; hexane–IPA = 90:10; 0.8 mL/min]: t_R = 10.7 (*R*), 17.4 (*S*) min.

1-(3-Fluorophenyl)-3-phenylprop-2-yn-1-ol:[11c] ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.28 (s, 1 H), 5.71 (s, 1 H), 7.28–7.50 (m, 9 H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 64.3, 86.6, 88.2, 113.7, 115.3, 122.0, 122.0, 122.3, 128.4, 128.8, 130.2, 131.8, 143.2, 164.5. HPLC [Daicel Chiracel OD-H; λ = 254 nm; hexane–IPA = 90:10; 0.8 mL/min]: t_R = 9.4, 21.8 min.

(*E*)-1,5-Diphenylpent-1-en-4-yn-3-ol:[11a] ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.31 (t, *J* = 6.0 Hz, 1 H), 6.38 (m, 1 H), 6.90 (d, 1 H), 7.28–7.49 (m, 10 H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 63.5, 86.5, 87.9, 122.4, 126.8, 128.1, 128.2, 128.4, 128.7, 131.9, 132.1, 136.0. HPLC [Daicel Chiracel OD-H; λ = 254 nm; hexane–IPA = 90:10; 0.8 mL/min]: t_R = 14.1 (*R*), 39.8 (*S*) min.

1-(Naphthalen-1-yl)-3-phenylprop-2-yn-1-ol:[11a] ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.40 (d, *J* = 6.0 Hz, 1 H), 6.38 (d, *J* = 5.9 Hz, 1 H), 7.40–7.80 (m, 8 H), 7.95 (d, *J* = 10.1 Hz, 1 H), 8.12 (d, *J* = 8.2 Hz, 1 H), 8.43 (d, *J* = 8.4 Hz, 1 H), 9.27 (d, *J* = 8.5 Hz, 1 H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 63.3, 87.2, 89.0, 122.4, 124.9, 127.0, 128.4, 128.8, 130.7, 131.3, 131.8, 134.1, 135.4, 135.5, 138.0. HPLC [Daicel Chiracel OD-H; λ = 254 nm; hexane–IPA = 90:10; 0.8 mL/min]: t_R = 15.2 (*R*), 28.6 (*S*) min.

4,4-Dimethyl-1-phenylpent-1-yn-3-ol:[11d] ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.09 (s, 9 H), 1.95 (1 H), 4.26 (d, *J* = 5.9 Hz, 1 H), 7.28–7.46 (m, 5 H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 25.4, 36.0, 71.9, 85.7, 89.0, 122.8, 128.3, 128.6, 131.7. HPLC [Daicel Chiracel OD-H; λ = 254 nm; hexane–IPA = 90:10; 0.8 mL/min]: t_R = 8.0 (*R*), 10.7 (*S*) min.

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