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Greatly enhanced enantioselectivity by an apparently remote steric effect in the 1,1′-binaphthyl-catalyzed alkynylzinc addition to aldehydes

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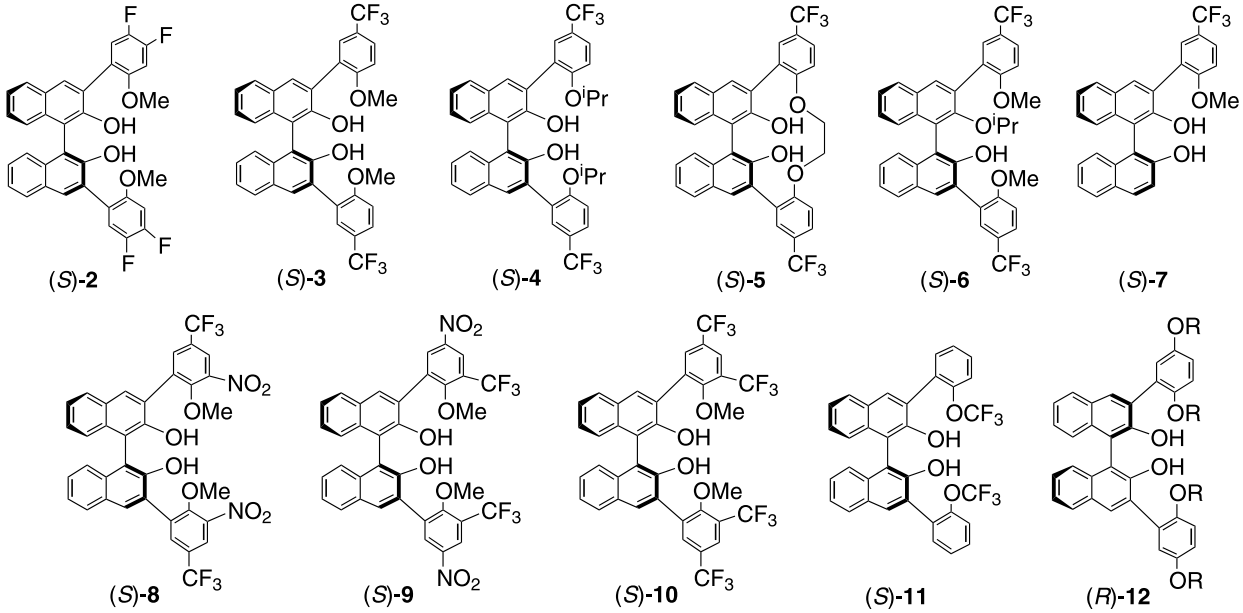
Abstract—An unusual steric effect in the binaphthyl-catalyzed asymmetric alkynylzinc addition to aldehydes is observed. Increasing the steric bulkiness at the *para*-position of the 3,3′-anisyl groups of the 1,1′-binaphthyl ligands, though apparently remote from the Lewis acid coordination sites, has greatly enhanced the enantioselectivity as well as catalytic activity. Propargyl alcohols with ees up to 92% have been produced from the reaction of a terminal alkyne with aromatic aldehydes by using the binaphthyl catalysts.

Optically active propargyl alcohols are versatile precursors to many chiral organic compounds.[1–7] Recently, significant progress has been made in the asymmetric alkynylzinc addition to aldehydes for the synthesis of chiral propargyl alcohols (**1**) (Scheme 1).[8–16] Among the catalysts developed, those based on ephedrine[11] and 1,1′-bi-2-naphthol[12,13] have shown the most general enantioselectivity.

In 2000, we reported that the binaphthyl compound (*S*)-**2** was highly enantioselective for the diphenylzinc addition to aldehydes.[17] It is believed that all the four oxygen atoms in (*S*)-**2** participate in the coordination with the Lewis acidic zinc centers to catalyze the reaction. In order to develop enantioselective catalysts for the alkynylzinc addition, we prepared a series of analogous binaphthyl compounds (*S*)-**2**-(*S*)-**11** that



Keywords: alkynylzinc; 1,1′-binaphthyl; enantioselective; propargyl alcohols; aldehydes.

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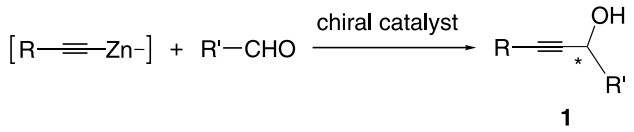


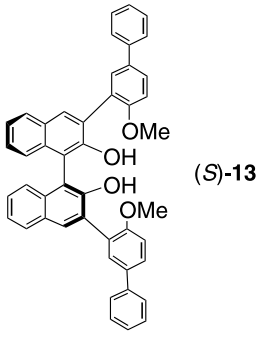
Scheme 1. Asymmetric alkynylzinc addition to aldehydes for the synthesis of propargyl alcohols.

contain 3,3′-anisyl groups with a variety of electron-withdrawing substituents.[18] However, all of these compounds showed low enantioselectivity for the reaction of phenylacetylene with benzaldehyde in the presence of diethylzinc with or without $Ti(O^iPr)_4$. The ee of the resulting propargyl alcohol product was observed in the range of 0–67%. Ligand (*R*)-**12** that contains the electron-donating alkoxy groups at the 3,3′-anisyls, although highly enantioselective for the alkylzinc addition to aldehydes,[19] was found not good for the alkynylzinc addition.

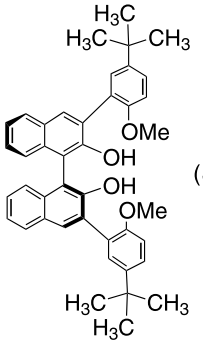
We then synthesized the binaphthyl compound (*S*)-**13** that contains *para*-phenyl-substituted 3,3′-anisyl groups.[18,20] This compound was used to catalyze the reaction of phenylacetylene with benzaldehyde. In the presence of diethylzinc (2.0 equiv.) and $Ti(O^iPr)_4$ (1.0 equiv.), (*S*)-**13** (20 mol%) catalyzed the reaction in THF at room temperature with 80% ee. Since both electron-donating and electron-withdrawing groups at the 3,3′-anisyls of the binaphthyl ligands gave relatively poor results, we suspected that the significantly improved enantioselectivity of (*S*)-**13** over ligands (*S*)-**2**-(*R*)-**12** might be due to an unusual steric effect at the remote *para*-position of the 3,3′-anisyls. Therefore, we introduced the more bulky tertiary butyl groups to make compound (*S*)-**14**.[18,21] When this compound (10 mol%) was used to catalyze the reaction of phenylacetylene (2.1 equiv.) with benzaldehyde in the presence of $Ti(O^iPr)_4$ (20 mol%) and diethylzinc (2.0 equiv.) in THF, very good enantioselectivity (85% ee) was observed as shown in entry 1 of Table 1. Other solvents were not as effective as THF (entries 2–4). Reducing the temperature to 0°C increased the ee to 88% but decreased the yield (entry 5). In all these reactions, a solution of diethylzinc (2.0 equiv.) and phenylacetylene (2.1 equiv.) was heated at reflux under nitrogen for 5 h before the addition of (*S*)-**14**, $Ti(O^iPr)_4$, and benzaldehyde.

We also found that the reflux step could be avoided by stirring a solution of (*S*)-**14**, phenylacetylene and diethylzinc at room temperature for 12 h followed by the addition of $Ti(O^iPr)_4$ and benzaldehyde. Apparently, the zinc complex generated from the reaction of (*S*)-**14** with diethylzinc catalyzed the formation of an alkynylzinc reagent from phenylacetylene and diethylzinc. Table 2 summarizes the results obtained from this procedure. The temperature and reaction time in Table 2 are for the step involving $Ti(O^iPr)_4$ and benzaldehyde. As shown in entry 2, up to 92% ee was observed for the reaction at room temperature. Entry 3 indicates that there was a slight reduction in ee as the reaction proceeded to 83% yield. At 0°C, the reaction became much slower and the longer reaction time also led to reduction in ee (entries 4–6). This suggests that racemization of the propargyl alkoxide could take place, though slow, under the reaction condition.

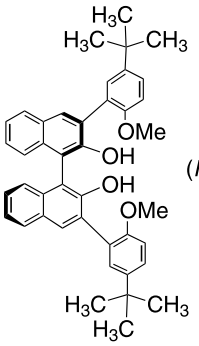
The enantiomer of (*S*)-**14**, (*R*)-**14**, was prepared. Compound (*R*)-**14** was used to catalyze the reaction of phenylacetylene with benzaldehyde in the presence of diethylzinc and $Ti(O^iPr)_4$. The following gives the optimized procedure for the reaction catalyzed by (*R*)-**14**.



(*S*)-**13**



(*S*)-**14**



(*R*)-**14**

Table 1. Reaction of phenylacetylene with benzaldehyde catalyzed by (*S*)-**14** in the presence of $Ti(O^iPr)_4$ and diethylzinc

Entry	Solvent	Temperature	Isolated yield (%)	ee (%)	*t* (h)
1	THF	r.t.	~70	85	12
2	CH_2Cl_2	r.t.	~70	83	12
3	Toluene	r.t.	~70	40	12
4	Ether	r.t.	~70	40	12
5	THF	0°C	50	88	35

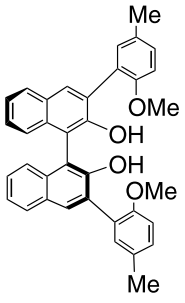
Table 2. Reaction catalyzed by (*S*)-**14** without refluxing phenylacetylene with diethylzinc

Entry	Temperature	Time (h)	Yield (%)[a]	ee (%)
1	r.t.	0.5	53	88
2	r.t.	1.0	66	92
3	r.t.	2.0	83	89
4	0°C	2.3	12	89
5	0°C	7.5	27	87
6	0°C	22.0	58	84

[a] Measured by ^{1}H NMR.

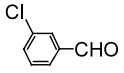
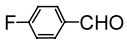
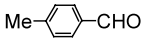
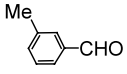
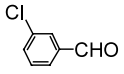
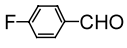
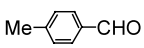
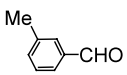
Under nitrogen, (*R*)-**14** (0.05 mmol, 30 mg), phenylacetylene (1.1 mmol,121 μL) and diethylzinc (1.0 mmol, 102 μL) were added to a 10 mL flask containing THF (5 mL, dried over sodium). This solution was stirred at room temperature for 12 h. Then, Ti(O^{i}Pr)$_4$ (0.25 mmol, 74 μL) was added. After stirred for an hour, benzaldehyde (0.5 mmol, 50 μL) was added, and the reaction mixture was stirred at room temperature for additional 3 h. Concentrated ammonium chloride was added to quench the reaction. The mixture was extracted with methylene chloride and dried with sodium sulfate. After column chromatographic purification on silica gel eluted with 2–10% ethyl acetate in hexanes, the propargyl alcohol product 1,3-diphenyl-prop-2-yn-1-ol was isolated in 80% yield. No side product was observed in this reaction. The enantiomeric purity of the product was determined to be 89% ee by using HPLC-ChiralDiacel OD column.

We prepared another ligand (*S*)-**15** that has a smaller methyl group at the *para*-position of the 3,3′-anisyl substituents of the binaphthyl.[18] Its catalytic properties are compared with those of (*R*)-**14** by using the optimized procedure and the results are summarized in Table 3. The reactions catalyzed by (*R*)-**14** proceeded with much higher enantioselectivity than (*S*)-**15**. The speed of the reactions catalyzed by (*R*)-**14** was also much faster than that by (*S*)-**15**. For example, ^{1}H NMR study showed 83% yield in 2 h for the reaction using (*R*)-**14**, but only 45% yield for using (*S*)-**15** under the same condition.



(*S*)-**15**

Table 3. Asymmetric addition of phenylacetylene to aromatic aldehydes catalyzed by (*R*)-**14** and (*S*)-**15**

Entry[a]	Aldehyde	Catalyst	ee (%)	Configuration
1		(*R*)-**14**	84	*R*
2		(*R*)-**14**	84	*R*
3		(*R*)-**14**	85	*R*
4		(*R*)-**14**	89	*R*
5		(*S*)-**15**	56	*S*
6		(*S*)-**15**	73	*S*
7		(*S*)-**15**	81	*S*
8		(*S*)-**15**	83	*S*

[a] Reactions carried out at room temperature with 10% catalyst, 25% Ti(O^{i}Pr)$_4$, 2 equiv. $ZnEt_2$, and 2.1 equiv. phenylacetylene in 5 mL THF at room temperature.

In summary, we have observed an unusual steric effect in the binaphthyl-catalyzed asymmetric alkynylzinc addition to aldehydes. Increasing the steric bulkiness at the *para*-position of the 3,3′-anisyl groups of the 1,1′-binaphthyl ligands, though apparently remote from the Lewis acid coordination sites, has greatly enhanced the enantioselectivity as well as catalytic activity. Propargyl alcohols with ee's up to 92% have been produced from the reaction of a terminal alkyne with aromatic aldehydes by using the binaphthyl catalysts.

Acknowledgements

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19. Huang, W.-S.; Hu, Q.-S.; Pu, L. *J. Org. Chem.* **1998**, *63*, 1364–1365.
20. Characterization of (*S*)-**13**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (s, 2H), 7.92–7.89 (m, 2H), 7.78 (d, 2H, $J=2.31$ Hz), 7.67-7.62 (m, 6 H), 7.47–7.31 (m, 12H), 7.11 (d, 2H, $J=8.47$ Hz), 5.80 (s, 2H), 3.88 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.48, 150.77, 140.69, 134.64, 133.65, 131.70, 131.09, 129.48, 128.98, 128.67, 128.51, 128.18, 127.73, 127.08, 125.00, 124.09, 114.73, 111.82, 56.37. HRMS (DEI) calcd for $C_{46}H_{34}O_4$: 650.2457; found: 650.2442.
21. Characterization of (*S*)-**14**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93–7.88 (m, 4H), 7.53 (d, 2H, $J=2.69$ Hz), 7.44–7.40 (m, 2H), 7.38–7.29 (m, 6H), 6.964 (d, 2H, $J=8.47$ Hz), 5.93 (s, 2H), 3.81 (s, 6H), 1.37 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.30, 150.39, 144.18, 133.43, 131.15, 129.49, 129.24, 129.19, 129.21, 126.50, 126.16, 124.94, 123.68, 115.35, 110.88, 56.10, 31.57. Anal. calcd for $C_{42}H_{40}O_4$: C, 82.59; H, 6.93. Found: C, 82.31; H, 7.38. HRMS (DEI) calcd for $C_{42}H_{42}O_4$: 610.3083; found: 610.3096.