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Asymmetric alkynylzinc additions to aldehydes and ketones

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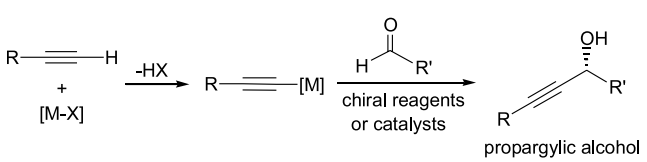
Contents

1. Introduction

The acidity of a terminal alkynyl proton makes it easy to prepare alkynyl-metal reagents as good functional carbon nucleophiles. Among the nucleophilic reactions of alkynyl-metal reagents, the addition to aldehydes is particularly useful because the resulting propargylic alcohols are versatile precursors to many organic molecules including natural products and pharmaceutical compounds (Scheme 1).[1–5] This nucleophilic addition produces a C–C bond and a chiral alcohol center simultaneously. The acetylene and hydroxyl functions of the propargylic alcohol products can be used to construct very diverse molecular structures.



Scheme 1. Nucleophilc additions of alkynylmetal reagents to aldehydes.

Stoichiometric amounts of chiral reagents have been developed to control the stereoselectivity of this reaction. The asymmetric addition of lithium-acetylides to benzaldehyde was reported by Mukaiyama et al. who used 4 equiv. of a chiral diamino alcohol at −123°C to produce propargylic alcohols with up to 92% ee.[6] Corey's laboratory developed a catalytic process by using an oxazaborolidine to catalyze the reaction of alkynylboranes with aldehydes.[7] They demonstrated excellent enantioselectivity (>90% ee) and good yields (>70%) for a fairly large range of alkynes and aldehydes. In this method, preparation of alkynylstannanes was required which were then needed to be converted to the alkynylboranes before the asymmetric addition to aldehydes.

Among the asymmetric alkyne additions to aldehydes, using zinc acetylides is the most studied. This is because zinc acetylides can be conveniently prepared in situ from the reaction of terminal alkynes with the easily available alkylzincs or Zn(OTf)$_2$. In addition, unlike the lithium acetylides, the zinc acetylides can tolerate many functional groups such as esters, amides, nitro groups and nitriles. In this article, the asymmetric alkynylzinc additions to aldehydes using both stochiometric chiral reagents and chiral catalysts are reviewed. Results for most of the reactions with over 90% ee are tabulated. The much less reported asymmetric alkynylzinc additions to ketones are

Keywords: asymmetric; alkynylzinc additions; aldehydes; ketones; propargylic alcohols; amino alcohols; BINOL; 1,1′-binaphthyl.

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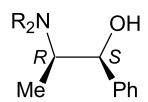
also discussed in this paper. For earlier comprehensive reviews on asymmetric organozinc additions to carbonyl compounds, see Ref. 8a,b.

2. Asymmetric alkynylzinc additions to aldehydes using nitrogen-containing ligands

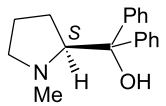
In the asymmetric alkynylzinc additions to aldehydes, chiral amino alcohols are the most investigated ligands. These compounds can be easily prepared from chiral amino acids or other sources. The active chiral catalysts or reagents in the alkynylzinc additions are often generated in situ from the reaction of the chiral ligands with the metal precursors. Highly enantioselective catalytic as well as stoichiometric amino alcohols have been developed for these additions. Cinchonidine and pyridyl ligands containing a hydroxyl group have also shown promising results. Amine or pyridyl ligands without a hydroxyl group cannot provide good stereocontrol for the alkynylzinc additions.

2.1. Amino alcohol and amine ligands

In 1990, Soai et al. reported the first example of a catalytic asymmetric addition of an alkynylzinc reagent to an aldehyde by using the enantiomerically pure amino alcohols and amines **1**–**3**.[9] In their experiments, the alkynylzinc reagent was prepared by heating an alkyne with Et_2Zn in an organic solvent.[10] Compound **1c** (5 mol%) was used to catalyze the reaction of benzaldehyde with the alkynylzinc derived from phenylacetylene and Et_2Zn. At room temperature in various solvents, the ee's of the resulting propargylic alcohol were all less than 34%, though the yields were high. The highest ee (43%) was observed when the amount of **1c** was increased to 20 mol%, but further increasing the amount of **1c** reduced the ee. All the other ligands **1**, **2** and **3** gave either a comparable or even much lower enantioselectivity than **1c**. Pretreatment of **1c** with Et_2Zn before adding the alkyne and aldehyde reduced the ee of the product. The reactions of other alkynes and aldehydes in the presence of **1c** and Et_2Zn also gave low enantioselectivity (<25% ee).



1a: R = Et
1b: R = ^{n}C$_3$H$_7$
1c: R = ^{n}C$_4$H$_9$
1d: R = ^{n}C$_5$H$_{11}$
1e: R = ^{n}C$_6$H$_{13}$
1f: RR = -[CH$_2$]$_4$-
1g: R = CH$_2$=CHCH$_2$-



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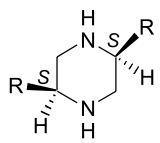
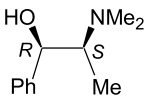


3a: R = PhCH$_2$
3b: R = Me$_2$CH

Tombo and co-workers used stoichiometric amounts of the enantiomerically pure amino alcohol **4** as well as its lithium salt **5**, made from the reaction of **4** with ^{n}BuLi, to carry out alkynylzinc additions to aldehydes.[11] They prepared PhC≡CZnEt (**6**) by reaction of EtZnI with PhC≡CLi. Another alkynylzinc reagent PhC≡CZnBr (**7**) was prepared from the reaction of PhC≡CBr with activated Zn. In the presence of 1 equiv. of **4**, the reaction of 2 equiv. of **6** with the aldehyde **8** gave the corresponding propargylic alcohol product of only 42% ee. However, when the amino alcohol was replaced with its lithium salt **5** and the alknylzinc reagent **6** was replaced with **7**, the product ee was greatly increased to 88% (80% yield). This reaction was conducted at 0–5°C in toluene. Under the same conditions, benzaldehyde afforded the adduct of 80% ee and aliphatic aldehydes gave products of much lower ee's (19–67%).



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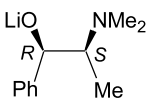

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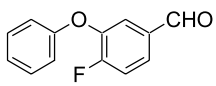

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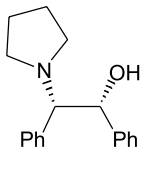
The amino alcohols **9** and **10** were found by Li et al. to catalyze the reaction of terminal alkynes with aromatic aldehydes with up to 85% ee and 94% yield.[12] These reactions were conducted in the presence of 10 mol% of the ligand and 1.2 equiv. of Me_2Zn at −20 to −30°C. Without using a ligand, no reaction was observed between phenylacetylene and Me_2Zn at room temperature. Reaction of the amino alcohol with Me_2Zn both generates a chiral zinc complex and catalyzes the formation of an alkynylzinc reagent for the subsequent asymmetric addition to aldehydes. Almost no methyl addition to aldehydes was observed. Other ligands including **11**–**13** were tested for the alkynylzinc addition to an aryl aldehyde but showed much lower ee's (2–57%). The amine ligand **13** without a hydroxyl group had the lowest enantioselectivity.



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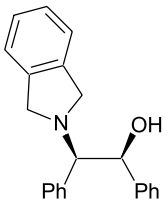

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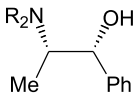
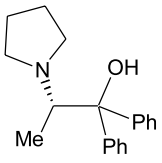


11a: R = ^{n}Bu
11b: -RR- = -(CH$_2$)$_4$-



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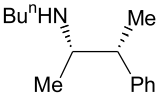

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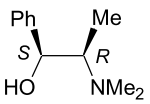
Highly enantioselective alkynylzinc additions to aldehydes were achieved by Carreira and co-workers. They used a stoichiometric amount of a chiral amino alcohol, *N*-methylephedrine (**14**), to control the stereoselective reaction of terminal alkynes with aldehydes.[13] In the presence of **14**, $Zn(OTf)_2$ and Et_3N, propargylic alcohols were produced with up to 99% ee at room temperature from alkyne additions to a broad range of aldehydes. In these reactions, the alkynylzinc reagents were generated from the reaction of the terminal alkynes with $Zn(OTf)_2$ in the presence of the amine base. After the reaction, the amino alcohol was recovered by acid wash and extraction of the aqueous solution under basic condition. In a typical experiment, a toluene solution of an aldehyde and an alkyne was treated with 1 equiv. of $Zn(OTf)_2$, 1.2 equiv. of Et_3N and 1.2 equiv.

Table 1. Alkynylzinc additions to aldehydes using **14**-Zn(OTf)$_2$-Et$_3$N

Entry	Alkyne	Aldehyde	*t* (h)	Yield (%)	ee (%)
1	PhC≡CH	^{c}C$_6$H$_{11}$CHO	1	99	96
2	Ph(CH$_2$)$_2$C≡CH	^{c}C$_6$H$_{11}$CHO	4	98	99
3	Ph(CH$_2$)$_2$C≡CH	Me$_2$CHCHO	2	90	99
4	PhC≡CH	Me$_2$CHCHO	2	95	90
5	Ph(CH$_2$)$_2$C≡CH	*trans*-PhCH=CHCHO	20	39	80
6	Ph(CH$_2$)$_2$C≡CH	Me$_3$CCHO	2	84	99
7	PhC≡CH	Me$_3$CCHO	2	99	94
8	Ph(CH$_2$)$_2$C≡CH	PhCHO	20	52	96
9	PhC≡CH	PhCHO	20	53	94
10	Me$_3$SiC≡CH	^{c}C$_6$H$_{11}$CHO	2	93	98
11	Ph(CH$_2$)$_2$C≡CH	Me$_3$CCH$_2$CHO	2	72	99
12	PhC≡CH	Me$_3$CCH$_2$CHO	2	90	97
13	Me$_3$SiCH$_2$C≡CH	^{c}C$_6$H$_{11}$CHO	4	84	98
14	TBDMSOCH$_2$C≡CH	^{c}C$_6$H$_{11}$CHO	5	83	98
15	(EtO)$_2$CHC≡CH	^{c}C$_6$H$_{11}$CHO	8	90	98
16	CH$_2$=C(Me)C≡CH	^{c}C$_6$H$_{11}$CHO	3	94	98
17	Me$_2$C(OH)C≡CH	Me$_2$CHCHO	4	97	98

of **14**. The reactions took 2–20 h at 23°C to complete. The results for the use of **14** are summarized in Table 1. High enantioselectivities were observed for the reactions of alkynes with both aliphatic aldehydes and benzaldehyde. The yield and ee for the reaction of an α,β-unsaturated aldehyde were significantly lower (entry 5). These alkynylzinc additions were able to be conducted in air using reagent grade toluene solvent without pre-drying,[13,14] which made this method very convenient and practical.



14

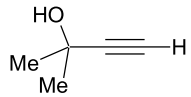
2-Methyl-3-butyn-2-ol (**15**) is an inexpensive commodity chemical. Its additions to aldehydes were studied.[15] In the presence of 1.1–1.2 equiv. of the amino alcohol **14**, Zn(OTf)$_2$ and Et$_3$N at room temperature, the reactions of **15** with various aldehydes exhibited very high enantioselectivities (Table 2).[15] The propargylic alcohol products from these reactions were converted to terminal alkynes by protecting the secondary alcohol with benzoyl or triisopropylsilyl groups followed by refluxing in toluene in the presence of 18-crown-6 and K_2CO_3 (Scheme 2). The propargylic alcohols with a terminal alkyne function are very useful in further chemical derivatization. The addition of another functional alkyne, propargyl acetate (**16**), to various aldehydes in the presence of 1.1–1.2 equiv. of **14**, Zn(OTf)$_2$ and Et$_3$N also showed high enantioselectivity (Table 3).[16] The products from these reactions were converted to γ-hydroxy α,β-unsaturated aldehydes which are highly functionalized synthetic intermediates.

Table 2. Reactions of **15** with aldehydes using **14**-Zn(OTf)$_2$-Et$_3$N

Entry	Aldehyde	Yield (%)	ee (%)
1	^{i}C$_3$H$_7$CHO	97	98
2	^{c}C$_6$H$_{11}$CHO	89	99
3	Me$_3$CCHO	82	98
4	^{n}C$_5$H$_{11}$CHO	81	51
5	^{n}C$_5$H$_{11}$CHO (2.1 equiv. **14**)	81	98
6	^{n}C$_3$H$_7$CHO (2.1 equiv. **14**)	77	99
7	PhCHO	96	98
8	*trans*-PhCH=CHCHO	47	75
9	*trans*-PhCH=CHCHO (3 equiv. **14**)	99	88
10	^{i}Pr$_3$SiO(CH$_2$)$_2$CHO	82	97

Table 3. Reactions of **16** with aldehydes using **14**-Zn(OTf)$_2$-Et$_3$N

Entry	Aldehyde	Yield (%)	ee (%)
1	^{i}C$_3$H$_7$CHO	95	96
2	^{c}C$_6$H$_{11}$CHO	88	97
3	Me$_3$CCH$_2$CHO	68	97
4	(*S*)-CH$_3$CH(OTBS)CHO	70	97:4(dr)
5	PhCHO (3.2 equiv. **14**)	57	97
6	TBSOCH$_2$CHO (2.2 equiv. **14**)	54	88



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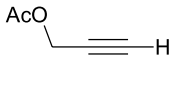
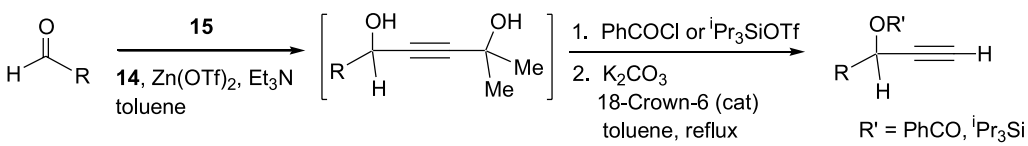


16

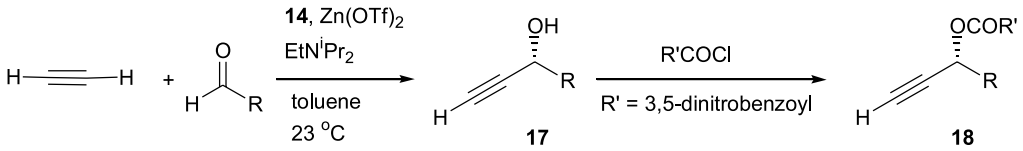
Acetylene itself was found to undergo enantioselective additions to aldehydes in the presence of **14** and Zn(OTf)$_2$.[17] As shown in Scheme 3, the products were isolated either as the propargylic alcohol **17** or the propargyl ester **18**. The reactions were carried out by first saturating a toluene solution of an aldehyde with acetylene in the presence of **14** (1.2 equiv.), Zn(OTf)$_2$ (1.1 equiv.) and EtN^{i}Pr$_2$ (1.2 equiv.) at −40°C. The reaction vessel was then sealed and allowed to stir at 23°C for 7–14 days. As the results in Table 4 show,

Table 4. Reactions of acetylene with aldehydes using **14**-Zn(OTf)$_2$-EtN^{i}Pr$_2$

Entry	Aldehyde	Yield (%)	ee (%)
1	^{n}C$_5$H$_{11}$CHO	30 (**17**)	97
2	^{i}C$_3$H$_7$CHO	76 (**18**)	98
3	^{c}C$_6$H$_{13}$CHO	70 (**17**)	98
4	Me$_3$CCHO	92 (**18**)	98
5	PhCHO	35 (**17**)	97
6	*trans*-PhCH=CHCHO	34 (**17**)	92
7	*trans*-PhCH=CHMeCHO	28 (**17**)	91



Scheme 2. Reaction of **15** with aldehydes to prepare propargylic compounds with a terminal alkyne function.

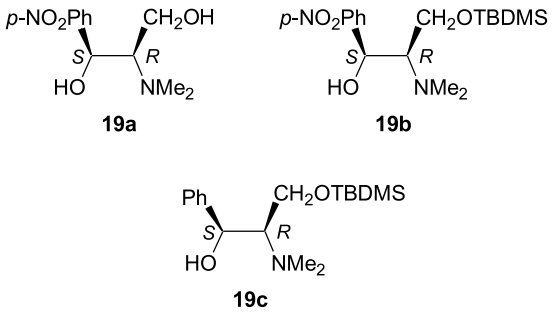


Scheme 3. Reaction of acetylene with aldehydes in the presence of **14** and $Zn(OTf)_2$.

although the yields of some of the reactions were low, the ee's were all very high.

Anand and Carreira further made the alkynylzinc addition catalytic in the presence of **14** by carrying out the reactions at 60°C rather than at room temperature.[18] This catalytic process generally used 20 mol% of $Zn(OTf)_2$, 20 mol% of **14**, 50 mol% of Et_3N, 1.2 equiv. of alkyne, and 1.0 equiv. of aldehyde, and was conducted in toluene at 60°C for 2–24 h. In this process, catalytic amounts of both the zinc reagent and the chiral ligand were used. High enantioselectivity and yield were achieved for the reaction of various alkynes with aliphatic aldehydes (Table 5). These reactions were also tolerant of air and moisture. They could even be conducted in the absence of solvent and still maintain high yield and high enantioselectivity. Because of the Cannizaro reaction of benzaldehyde under the reaction conditions, the alkyne addition to benzaldehyde proceeded in low yield.

Jiang et al. studied the use of the amino alcohols **19a–c** that are structurally similar to **14** for the reaction of alkynes with aldehydes in the presence of $Zn(OTf)_2$ and Et_3N.[19a] They found that ligand **19b** exhibited very high enantioselectivity comparable to **14**. Ligand **19a** also gave high ee's but very low yields. Table 6 summarizes the reactions utilized **19b**. Most of the reactions used 1.1 equiv. of **19b**, 1.05 equiv. of $Zn(OTf)_2$, 1.1 equiv. of Et_3N, 1.2 equiv. of alkyne and 1 equiv. of aldehyde. The reactions generally proceeded in toluene solution at room temperature for 2 h. Entry 4 lists the result for the reaction promoted by ligand **19c** which was similar to the use of **19b**. Entries 18–22 used catalytic amounts of **19b** (0.22 equiv.) and $Zn(OTf)_2$ (0.2 equiv.) and showed a small reduction in enantioselectivity. Jiang and co-workers also prepared a new zinc reagent, $Zn(OSO_2CF_2H)$.[19b] They found that $Zn(OSO_2CF_2H)$ behaved very similarly to $Zn(OTf)_2$ in the asymmetric alkynylzinc additions. It in combination with **19b** and Et_3N promoted the reaction of alkynes with various aldehydes with up to 99% ee.



The dimeric amino alcohol derivatives **20a**,**b** were used by Braga et al. for alkynylzinc additions.[20] In these reactions, an alkyne was first treated with Et_2Zn and 5–10 mol% of the chiral ligand in THF at −20 to −30°C and then with an aldehyde. This procedure gave a propargylic alcohol with up to 82% yield and 60% ee. Ligand **20b** was better than **20a**

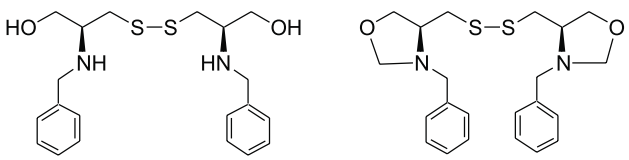
Table 5. Alkynylzinc additions to aldehydes catalyzed by **14**-$Zn(OTf)_2$-Et_3N

Entry	Alkyne	Aldehyde	*t* (h)	Yield (%)	ee (%)
1	$Bn_2NCH_2C{\equiv}CH$	$^cC_6H_{11}CHO$	2	91	97
2	$Ph(CH_2)_2C{\equiv}CH$	$^cC_6H_{11}CHO$	4	89	94
3	$PhC{\equiv}CH$	$^cC_6H_{11}CHO$	5	94	86
4	$TMSOCMe_2C{\equiv}CH$	Me_2CHCHO	5	77	98
5	$Ph(CH_2)_2C{\equiv}CH$	$^nC_7H_{15}CHO$	20	45	92
6	$Ph(CH_2)_2C{\equiv}CH$	Me_3CCHO	24	77	93
7	$TBSOCH_2C{\equiv}CH$	Me_3CCHO	5	81	93
8	$(EtO)_2CHC{\equiv}CH$	$^cC_6H_{11}CHO$	9	88	94
9	n-$C_4H_9C{\equiv}CH$	$^cC_6H_{11}CHO$	6	81	93
10	$TMSOCMe_2C{\equiv}CH$	$^cC_6H_{11}CHO$	4	80	99
11	$Et_3SiCH_2C{\equiv}CH$	$^cC_6H_{11}CHO$	7	85	96
12	$Bn_2NCH_2C{\equiv}CH$	$TIPSOCH_2CMe_2CHO$	5	80	95
13	$TBSOCH_2C{\equiv}CH$	$^cC_6H_{11}CHO$	5	88	90
14	$Bn_2NCH_2C{\equiv}CH$	$BnN(CH_2CH_2)_2CHCHO$	5	81	94
15	$Ph(CH_2)_2C{\equiv}CH$	$(CH_2{=}CHCH_2)_2CHCHO$	6	80	93
16	$Bn_2NCH_2C{\equiv}CH$	$^nC_7H_{15}CHO$	24	55	91

Table 6. Alkynylzinc additions to aldehydes using **19b**-$Zn(OTf)_2$-Et_3N

Entry	Alkyne	Aldehyde	Yield (%)	ee (%)
1	$PhC{\equiv}CH$	Me_2CHCHO	99	98
2	$Ph(CH_2)_2C{\equiv}CH$	Me_2CHCHO	99	>99
3	$PhC{\equiv}CH$	$^nC_6H_{13}CHO$	94	97
4	$PhC{\equiv}CH$	$^nC_6H_{13}CHO$	92	96
5	$Ph(CH_2)_2C{\equiv}CH$	$^nC_6H_{13}CHO$	94	99
6	$PhC{\equiv}CH$	$^cC_6H_{11}CHO$	99	97
7	$Ph(CH_2)_2C{\equiv}CH$	$^cC_6H_{11}CHO$	97	99
8	$PhC{\equiv}CH$	Et_2CHCHO	99	97
9	$Ph(CH_2)_2C{\equiv}CH$	Et_2CHCHO	99	98
10	$PhC{\equiv}CH$	$^cC_3H_5CHO$	93	94
11	$PhC{\equiv}CH$	PhCHO	85	97
12	$Ph(CH_2)_2C{\equiv}CH$	PhCHO	73	94
13	$^nC_4H_9C{\equiv}CH$	$^cC_6H_{11}CHO$	82	95
14	$TMSC{\equiv}CH$	$^cC_6H_{11}CHO$	83	96
15	$Me_3CC{\equiv}CH$	$^cC_6H_{11}CHO$	93	96
16	$^cC_3H_5C{\equiv}CH$	$^cC_6H_{11}CHO$	98	97
17	$TBDMSOCH_2C{\equiv}CH$	$^cC_6H_{11}CHO$	94	99
18	$PhC{\equiv}CH$	Me_2CHCHO	98	92
19	$PhC{\equiv}CH$	$^nC_6H_{13}CHO$	91	93
20	$PhC{\equiv}CH$	$^cC_6H_{11}CHO$	85	93
21	$PhC{\equiv}CH$	$^cC_6H_{11}CHO$	89	85
22	$PhC{\equiv}CH$	Et_2CHCHO	95	93

in the catalysis. The monomeric ligand **21** gave only racemic product for the alkynylzinc addition.



20a **20b**

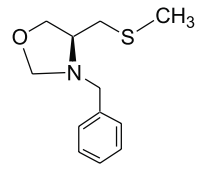


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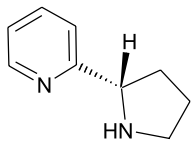
Table 7. Alkynylzinc additions to aldehydes catalyzed by **23a–c**

Entry	Alkyne	Aldehyde	Catalyst	T (°C)	t (h)	Yield[a] (%)	ee (%)
1	PhC≡CH	PhCHO	**23a**	rt	7	82	66
2	PhC≡CH	PhCHO	**23b**	rt	7	88	63
3	PhC≡CH	PhCHO	**23b**	rt	7	93	81
4	PhC≡CH	PhCHO	**23b**	0	15	64	90
5	PhC≡CH	PhCHO	**23c**	rt	7	87	81
6	PhC≡CH	$^{n}C_8H_{17}CHO$	**23b**	0	4	65	83
7	PhC≡CH	$^{c}C_6H_{11}CHO$	**23b**	0	10	88	91
8	PhC≡CH	^{t}BuCHO	**23b**	0	10	61	95
9	$^{n}C_6H_{13}C$≡CH	PhCHO	**23b**	rt	18	90	38
10	$^{n}C_6H_{13}C$≡CH	PhCHO	**23b**	rt	2	41(52)	78
11	$^{n}C_6H_{13}C$≡CH	PhCHO	**23b**	0	24	33(23)	71
12	$^{n}C_6H_{13}C$≡CH	$^{n}C_8H_{17}CHO$	**23b**	rt	1	62(22)	73
13	$^{n}C_6H_{13}C$≡CH	$^{n}C_8H_{17}CHO$	**23b**	0	17	31(23)	62
14	$^{n}C_6H_{13}C$≡CH	$^{c}C_6H_{11}CHO$	**23b**	rt	3	79(18)	82
15	$^{n}C_6H_{13}C$≡CH	^{t}BuCHO	**23b**	rt	3	67	87
16	Ph_3SiC≡CH	$^{c}C_6H_{11}CHO$	**23b**	rt	5	55	91

[a] The yields of the ethyl addition side products are given in the parenthesis.

2.2. Pyridyl ligands

The pyridyl amine ligand **22** was used by Falorni and co-workers to catalyze the addition of $(^{n}BuCC)_2Zn$ to benzaldehyde.[21] In ether at 20°C over 15 h, the propargylic alcohol product was obtained with 16% ee and 87% yield.



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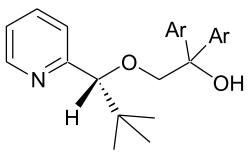
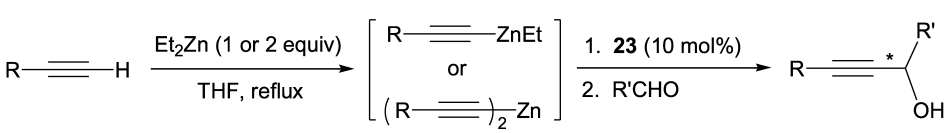
Ishizaki and Hoshino reported the use of the pyridyl alcohol ligands **23a–c** to catalyze the asymmetric alkynylzinc addition to aldehydes.[22] They first treated a terminal alkyne with $ZnEt_2$ in refluxing THF. This was expected to generate a dialkynylzinc or an alkynylethylzinc reagent depending upon the use of 0.5 or 1 equiv. of Et_2Zn versus the alkyne (Scheme 4). The in situ generated alkynylzinc was then added to an aldehyde in the presence of 10 mol% of **23a–c** at room temperature or 0°C. The results of these reactions are summarized in Table 7. Ligand **23b** containing the bulky α-naphthyl group at the tertiary alcohol carbon showed the highest enantioselectivity among the three ligands. It catalyzed the reaction of phenylacetylene with benzaldehyde, cyclohexanecarboxaldehyde and pivalic aldehyde with 90, 91 and 95% ee, respectively (entries 4,7,8). The reactions of phenylacetylene and aliphatic alkynes with unbranched aliphatic aldehydes gave much lower ee's. Entries 2 and 9 used the dialkynylzinc reagents which showed lower ee's than entries 3 and 10 that used the alkynylethylzincs. All the other entries also used the alkynylethylzincs. The reactions of the aliphatic alkyne in entries 10–14 with aldehydes showed significant ethyl additions.



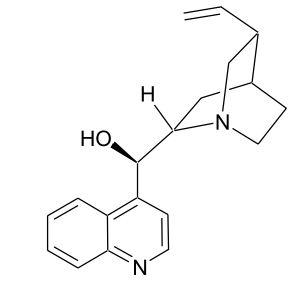
23a: Ar = Ph
23b: Ar = α-naphthyl
23c: Ar = β-naphthyl

2.3. Alkaloid Ligands

Alkaloids cinchonidine (**24**) and quinidine (**25**) were examined for the alkynylzinc additions to aldehydes by Kamble and Singh.[23] It was found that **24** (40 mol%) catalyzed the reaction of phenylacetylene (3 equiv.) with aryl and alkyl aldehydes with 62–85% ee at −20°C in methylene chloride in the presence of $Ti(O^{i}Pr)_4$ (3 equiv.) and Et_2Zn (3 equiv.). Without $Ti(O^{i}Pr)_4$, the ee was very low. Ligand **25** as well as other ligands **26–28** gave 4–60% ee for the reaction of phenylacetylene with benzaldehyde in the presence of Et_2Zn with or without $Ti(O^{i}Pr)_4$.



Scheme 4. The alkynylzinc additions to aldehydes catalyzed by **23a–c**.



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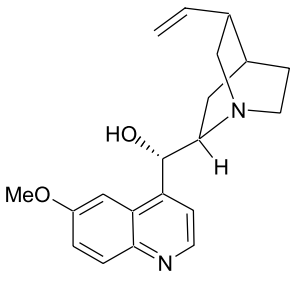

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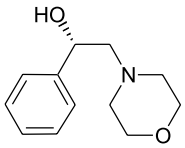

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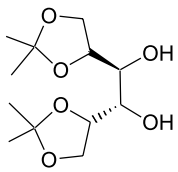

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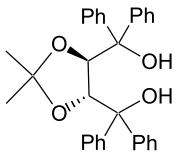

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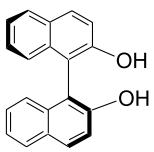
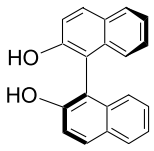
3. Asymmetric alkynylzinc additions to aldehydes using 1,1′-binaphthyl ligands

Axially chiral 1,1′-binaphthyl compounds have found extensive applications in many asymmetric processes, especially in the field of asymmetric catalysis.[24–26] Among the numerous optically active 1,1′-binaphthyls, 1,1′-bi-2-naphthol [(*S*)- or (*R*)-BINOL] is the most readily available and inexpensive compound. Combinations of the enantiomerically pure BINOL with various Lewis acid metal complexes have exhibited remarkably diverse catalytic properties in many asymmetric organic reactions. High enantioselectivity has also been discovered for BINOL and its derivatives in the alkynylzinc additions to aldehydes. These results are discussed below.



(*S*)-BINOL



(*R*)-BINOL

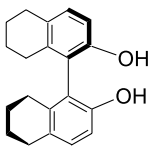
3.1. BINOL- and H_8BINOL-Ti(O^iPr)$_4$ as catalysts

At about the same time, the research groups of Pu and Chan were independently working on the use of BINOL for the asymmetric alkynylzinc additions. They found that BINOL in combination with Ti(O^iPr)$_4$ could effect the highly enantioselective alkynylzinc additions to aldehydes.[27–31] They each used a different alkylzinc precursor and developed a quite different experimental procedure for the catalysis.

Chan and co-workers studied both BINOL and its partially hydrogenated derivative H_8BINOL for the reaction of phenylacetylene with aldehydes.[27] In their experiments, phenylacetylene (1.3 equiv.) was first mixed with Me_2Zn (1.2 equiv.) in toluene at 0°C. To this solution, a mixture of the ligand (20 mol%) with Ti(O^iPr)$_4$ (1.5 equiv.) in THF was added followed by the aldehyde. The reaction mixture was maintained at 0°C for overnight before aqueous work up. As the results summarized in Table 8 show, (*R*)-H_8BINOL in general had somewhat higher enantioselectivity than (*R*)-BINOL under the reaction conditions. It showed high enantioselectivity for the addition to *para* and *meta*-substituted benzaldehydes, but not very high for an *ortho*-substituted benzaldehyde and aliphatic aldehydes.

Table 8. Phenylacetylene additions to aldehydes catalyzed by (*R*)-BINOL- or (*R*)-H_8BINOL-Ti(O^iPr)$_4$-Me_2Zn

Entry	Ligand	Aldehyde	Yield (%)	ee (%)
1	(*R*)-BINOL	PhCHO	84	90
2		*o*-ClPhCHO	88	64
3		*m*-ClPhCHO	88	92
4		*p*-ClPhCHO	87	92
5		*p*-MePhCHO	83	86
6	(*R*)-H_8BINOL	PhCHO	85	92
7		*o*-ClPhCHO	90	76
8		*m*-ClPhCHO	87	95
9		*p*-ClPhCHO	84	86
10		*p*-FPhCHO	82	87
11		*p*-BrPhCHO	89	94
12		*p*-NO_2PhCHO	89	95
13		*m*-NO_2PhCHO	88	96
14		2-Naphthylaldehyde	75	80
15		*p*-CF_3PhCHO	89	93
16		*p*-MePhCHO	84	96
17		Me_2CHCHO	84	82
18		$^cC_6H_{11}$CHO	86	74
19		$CH_3CH_2CH_2CHO$	87	77



(*R*)-H_8BINOL

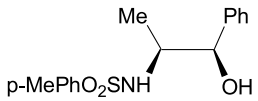
Using *N*-tolylsulfonyl ephedrine **29** as the co-catalyst improved the enantioselectivity of the BINOL-Ti(O^iPr)$_4$ catalyst.[28] The results in Table 9 show that in the presence of 10 mol% (*S*)-BINOL, 10 mol% **29**, 15 mol% Ti(O^iPr)$_4$ and 2 equiv. Me_2Zn, the reactions of phenylacetylene (1 equiv.) and aryl aldehydes (1 equiv.) in THF at 0°C gave high enantioselectivity. They found that using phenol as additive also improved the catalytic properties of the BINOL-Ti(O^iPr)$_4$ especially for the phenylacetylene addition to *ortho*-substituted benzaldehyde and aliphatic aldehydes (Table 10).[29] The phenylacetylene additions were conducted at 0°C in THF using aldehyde, (*R*)-BINOL, phenol, Ti(O^iPr)$_4$ and Me_2Zn with a molar ratio of 1:0.1:0.1:0.3:1.2.

Table 9. Phenylacetylene additions to aldehydes catalyzed by (*S*)-BINOL-Ti(O^iPr)$_4$-Me_2Zn and the Sulfonamide **29**

Entry	Aldehyde	Yield (%)	ee (%)
1	PhCHO	83	96
2	*o*-NO_2PhCHO	83	88
3	*m*-NO_2PhCHO	82	>99
4	*p*-NO_2PhCHO	82	99
5	*p*-BrPhCHO	85	99
6	*m*-ClPhCHO	84	97
7	*p*-ClPhCHO	86	95
8	2-Naphthylaldehyde	81	95
9	*p*-MeOPhCHO	78	95
10	*p*-MePhCHO	79	92

Table 10. Phenylacetylene additions to aldehydes catalyzed by (*R*)-BINOL-Ti(O^iPr)$_4$-Me_2Zn and phenol

Entry	Aldehyde	Yield (%)	ee (%)
1	PhCHO	85	96
2	*o*-ClPhCHO	82	88
3	*m*-ClPhCHO	84	95
4	*p*-ClPhCHO	83	95
5	*p*-BrPhCHO	81	94
6	2-Naphthylaldehyde	63	94
7	$^cC_6H_{11}CHO$	82	86
8	$CH_3CH_2CH_2CHO$	91	88
9	Me_2CHCHO	92	90



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In the procedure developed by Pu and co-workers for the use of BINOL-Ti(O^iPr)$_4$ to catalyze the alkynylzinc additions to aromatic aldehydes, Et_2Zn instead of Me_2Zn was used to prepare the alkynylzinc reagent.[30] A less than stoichiometric amount of Ti(O^iPr)$_4$ was also used. Following is a typical procedure for this catalysis. The first step involved the heating of a toluene solution of phenylacetylene (2.2 equiv.) and Et_2Zn (2 equiv.) at reflux under nitrogen for 5 h. It was then cooled to room temperature and combined with (*S*)-BINOL (20 mol%), methylene chloride, Ti(O^iPr)$_4$ (50 mol%), and benzaldehyde (1 equiv.). After 4 h reaction and aqueous work up, the propargylic alcohol product was isolated in 77% yield and 96% ee. Table 11 summarizes the results for the addition of alkynes to various aromatic aldehydes using this procedure. It shows that phenylacetylene reacts with *o*-, *m*-, or *p*-substituted benzaldehydes containing either electron-donating or electron-withdrawing substituents with excellent enantioselectivity (entries 1–12). The additions to other aromatic aldehydes such as 2-furaldehyde, 1-napthaldehyde and 2-naphthaldehyde proceeded with high enantioselectivity as well (entries 13–15). Triisopropylsilylacetylene was also used for the addition to benzaldehyde and showed high ee (entry 16). The triisopropylsilyl group of the propargyl alcohol product from this reaction can be easily removed for further reaction or functionalization.

Table 11. Alkynylzinc additions to aromatic aldehydes catalyzed by (*S*)-BINOL-Ti(O^iPr)$_4$-Et_2Zn

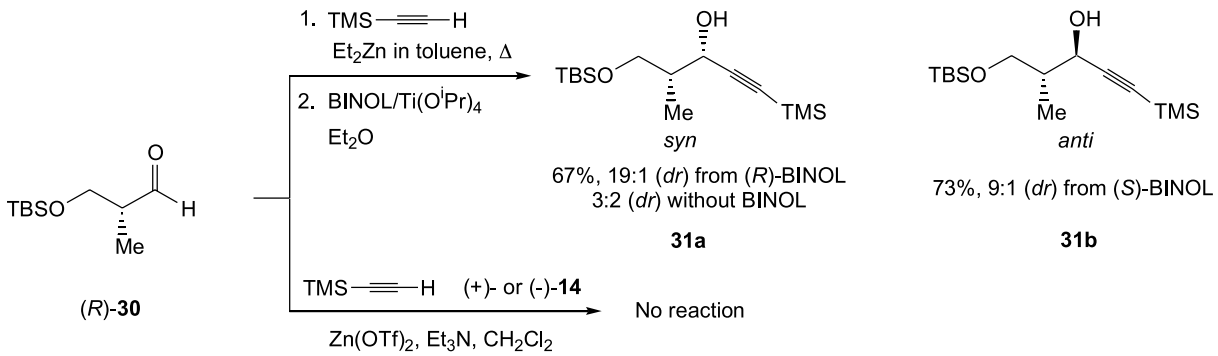
Entry	Alkyne	Aldehyde	Yield (%)	ee (%)
1	PhC≡CH	PhCHO	77	96
2	PhC≡CH	*p*-FPhCHO	74	96
3	PhC≡CH	*p*-NO_2PhCHO	79	97
4	PhC≡CH	*p*-ClPhCHO	81	92
5	PhC≡CH	*m*-ClPhCHO	79	92
6	PhC≡CH	*o*-ClPhCHO	95	92
7	PhC≡CH	*p*-MePhCHO	93	97
8	PhC≡CH	*m*-MePhCHO	77	94
9	PhC≡CH	*o*-MePhCHO	81	96
10	PhC≡CH	*o*-MeOPhCHO	73	93
11	PhC≡CH	*m*-MeOPhCHO	78	93
12	PhC≡CH	*p*-MeOPhCHO	97	94
13	PhC≡CH	2-Furaldehyde	72	92
14	PhC≡CH	1-Naphthylaldehyde	71	92
15	PhC≡CH	2-Naphthylaldehyde	77	98
16	$^iPr_3SiC$≡CH	PhCHO	75	92

Table 12. Phenylacetylene additions to aliphatic aldehydes and α,β-unsaturated aldehydes catalyzed by (*S*)-BINOL-Ti(O^iPr)$_4$-Et_2Zn

Entry	Aldehyde	Yield (%)	ee (%)
1	$^nC_8H_{17}CHO$ (distilled)	96	91
2	$^nC_8H_{17}CHO$	66	91
3	$^nC_7H_{15}CHO$	70	93
4	$^nC_4H_9CHO$	91	93
5	Me_2CHCHO	84	97
6	CH_3CH_2CHO	60	94
7	$^cC_6H_{11}CHO$	58	95
8	$PhCH_2CH_2CHO$	99	93
9	$PhCH_2CHO$	93	91
10	*trans*-MeCH=CHCHO	92	96
11	*trans*-MeCH=CMeCHO	93	96
12	*trans*-PhCH=CHCHO	89	97
13	*trans*-PhCH=CMeCHO	96	99
14	$^nC_8H_{17}CHO$	94	94
15	$^nC_8H_{17}CHO$	92	96
16	$^nC_8H_{17}CHO$	92	95
17	$^nC_8H_{17}CHO$	77	96
18	$^nC_8H_{17}CHO$	96	96

Highly enantioselective alkynylzinc additions to aliphatic aldehydes and α,β-unsaturated aldehydes were also achieved by using the BINOL-Ti(O^iPr)$_4$-Et_2Zn method.[31] The results summarized in Table 12 used a procedure different from the addition to aromatic aldehydes. In a typical experiment, a toluene solution of phenylacetylene (4 equiv.) and Et_2Zn (4 equiv.) was heated under nitrogen at reflux for 1 h. It was then combined with (*S*)-BINOL (40 mol%), diethyl ether and Ti(O^iPr)$_4$ (1 equiv.) sequentially at room temperature. Nonyl aldehyde (1 equiv., distilled) was added and stirring was continued for an additional 4 h. After work up, the product 1-phenyl-1-undecyn-3-ol of 91% ee was obtained in 96% yield. As the results in Table 12 show, the BINOL-Ti(O^iPr)$_4$ catalyzed phenylacetylene addition to unbranched as well as branched aliphatic aldehydes proceeds with high enantioselectivity (entries 1–9). In entry 2, the undistilled nonyl aldehyde was used and gave product of high ee but lower yield. The reactions of phenylacetylene with α,β-unsaturated aldehydes showed high ee's (entries 10–13). The results of entries 14–18 were obtained by increasing the amount of BINOL to up to 1 equiv.

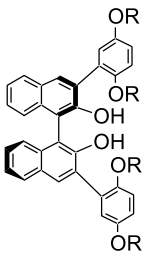
Marshall and Bourbeau examined additions of trimethylsilylacetylene to various α-chiral aldehydes.[32,33] Under Pu's conditions using the BINOL-Ti(O^iPr)$_4$-Et_2Zn method, high diastereoselectivity was observed for the reaction of (*R*)-**30** (Scheme 5). The *syn* diastereomer **31a** was obtained in 19:1 diastereomeric ratio (*dr*) from (*R*)-BINOL, and the *anti* diastereomer **31b** was obtained in 9:1 *dr* from (*S*)-BINOL. In these reactions, catalyst-control dominated the stereoselectivity although (*R*)-BINOL matched the chirality of (*R*)-**30** better than (*S*)-BINOL did. Without BINOL, the *syn:anti* ratio was 3:2. No product was obtained by using the (+)- or (−)-**14**+$Zn(OTf)_2$+Et_3N method. For the reactions of compounds **32**–**34** with trimethylsilylacetylene, the chirality-matched (*R*)-BINOL led to good diastereoselectivity and the unmatched (*S*)-BINOL gave low diastereoselectivity (Scheme 6). The aliphatic aldehyde **35**



Scheme 5. Trimethylsilylacetylene addition to the enantiomerically pure aldehyde (*R*)-**30**.

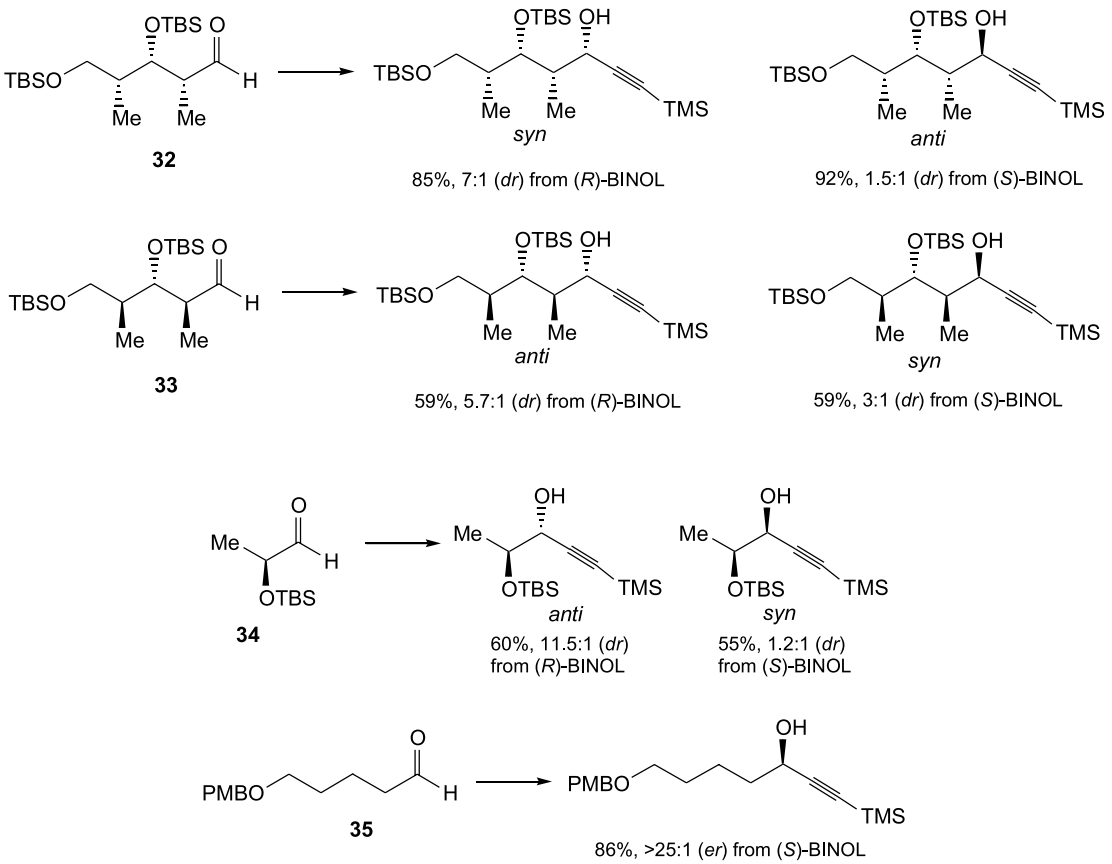
reacted with trimethylsilylacetylene with excellent enantioselectivity.

3.2. 3,3′-Substituted BINOL-Ti(O^{i}Pr)$_4$ catalysts

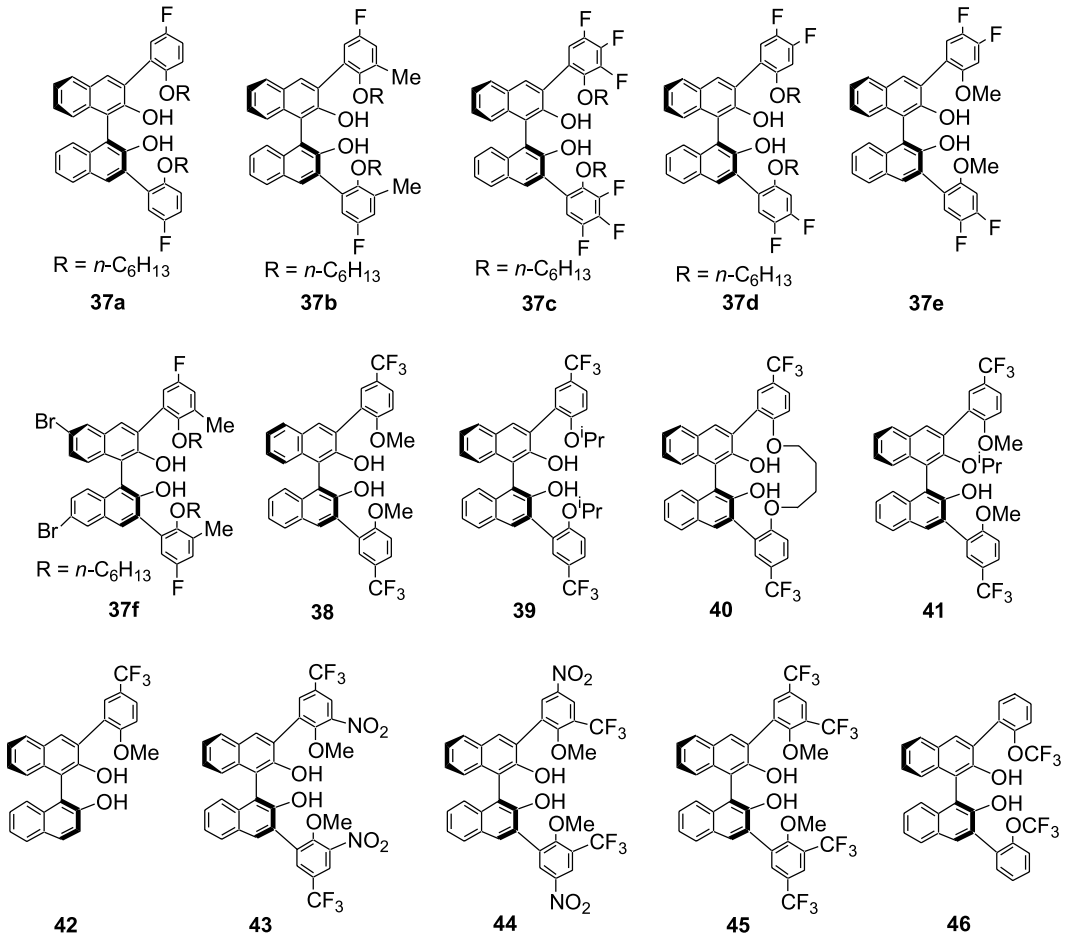


36

Pu and co-workers studied the use of 3,3′-substituted BINOLs in the asymmetric organozinc additions. They found that compound **36** catalyzed the highly enantioselective reaction of dialkylzincs with a broad range of aldehydes including *o*-, *m*- or *p*-substituted benzaldehydes, unbranched or branched aliphatic aldehydes, and vinyl or alkynyl aldehydes (90–>99% ee).[34,35] This ligand was also highly enantioselective for the asymmetric diphenylzinc addition to aldehydes (83–94% *ee*).[36] The electronic properties of ligand **36** were tuned by introducing electron-withdrawing groups to prepare ligands **37a–f**.[37] Ligand **37d** with four fluorine substituents on the 3,3′-anisyl groups showed significantly improved catalytic properties over **36** in the diphenylzinc addition to aldehydes. These compounds together with other further modified ligands **38–46** were used to catalyze the reaction of terminal alkynes with aldehydes. However, all of



Scheme 6. Reactions of various functional aldehydes with trimethylsilylacetylene catalyzed by BINOL-Ti(O^{i}Pr)$_4$-Et$_2$Zn.



these compounds were found not good for the reaction of phenylacetylene with benzaldehyde in the presence of Et_2Zn with or without $Ti(O^iPr)_4$. Enantioselectivities in the range of 0–67% were observed.

The binaphthyl compound **47** that contains *para*-phenyl-substituted 3,3′-anisyl groups was found to be superior to the ligands **36**–**46** for the alkynylzinc addition.[38] This compound (20 mol%) catalyzed the reaction of phenylacetylene with benzaldehyde in the presence of Et_2Zn (2.0 equiv.) and $Ti(O^iPr)_4$ (1.0 equiv.) in THF at room temperature to give the propargylic alcohol product with 80% ee The steric effect of the substituent at the para position of the 3,3′-anisyl groups of **47** was investigated. Ligand **48** with the bulky tertiary butyl groups was prepared. It further improved the enantioselectivity of **47**. Using **48** avoided the reflux step in the preparation of an alkynylzinc reagent. The reagent was prepared by stirring a THF solution of the ligand (10 mol%), phenylacetylene (2.2 equiv.) and Et_2Zn (2 equiv.) at room temperature for 12 h. The zinc complex generated from the reaction of **48** with Et_2Zn catalyzed the formation of an alkynylzinc reagent from phenylacetylene and Et_2Zn. The alkynylzinc was then combined with $Ti(O^iPr)_4$ (50 mol%) and benzaldehyde (1 equiv.) to give the propargylic alcohol in 80% yield and 89% ee. The use of **48** to catalyze the reaction of phenylacetylene with other aromatic aldehydes is summarized in entries 1–5 of Table 13. These results are compared

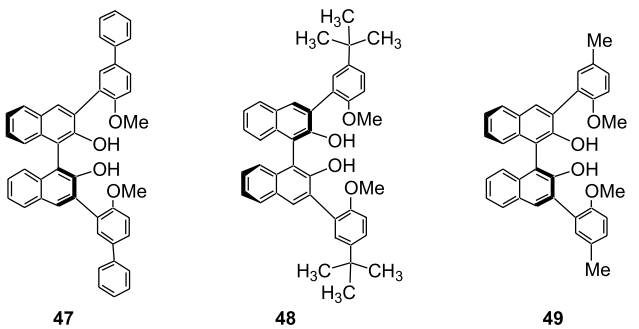


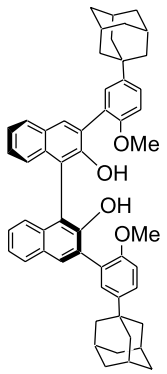
Table 13. Asymmetric additions of phenylacetylene to aromatic aldehydes catalyzed by **48** and **49** in the presence of Et_2Zn and $Ti(O^iPr)_4$

Entry	Aldehyde	Catalyst	ee (%)	Config.
1	PhCHO	**48**	89	*R*
2	*m*-ClPhCHO	**48**	84	*R*
3	*p*-FPhCHO	**48**	84	*R*
4	*p*-MePhCHO	**48**	85	*R*
5	*m*-MePhCHO	**48**	89	*R*
6	*m*-ClPhCHO	**49**	56	*S*
7	*p*-FPhCHO	**49**	73	*S*
8	*p*-MePhCHO	**49**	81	*S*
9	*m*-MePhCHO	**49**	83	*S*

with the use of ligand **49** that contains *p*-methyl group on the 3,3′-anisyls (entries 6–9). In general, ligand **48** showed higher enantioselectivity than **49**. The catalytic activity of **48** was also significantly higher than **49**. As expected, **48** and **49** gave rise to enantiomeric products.

3.3. 3,3′-Substituted BINOL catalyst without Ti(O^{i}Pr)$_4$

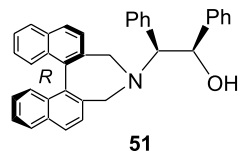
The 3,3′-anisyl substituted binaphthyl ligands were also used to catalyze the reaction of phenylacetylene with aldehydes in the absence of Ti(O^{i}Pr)$_4$. It was found that compound **50** with bulky *p*-adamantyl groups on its 3,3′-anisyls is a very good ligand.[39] The reactions were conducted by addition of Et_2Zn (2.0 equiv.) to a THF solution of **50** (10 mol%) at room temperature. The mixture was then combined with phenylacetylene (1.5 equiv.) and benzaldehyde (1 equiv.) to give the propargylic alcohol product with 75% yield and 84% ee. This procedure was applied to the reaction of phenylacetylene with other aldehydes and the results are summarized in Table 14. Enantioselectivities ranging from 80–94% *ee* were achieved for the reaction of phenylacetylene with aromatic aldehydes containing electron-donating or electron-withdrawing substituents at the *o*-, *m*-, or *p*-positions. In these reactions, the alkynylzinc was in competition with Et_2Zn. This led to lower yields of the alkynylzinc additions in some cases. The advantage of **50** is that unlike BINOL or **48**, Ti(O^{i}Pr)$_4$ is not required.



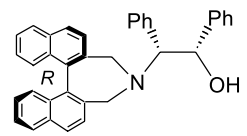
50

3.4. 1,1′-Binaphthyl-derived amino alcohol ligands

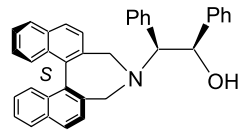
Chan and co-workers designed ligands **51**–**54** that combined the structures of both 1,1′-binaphthyls and amino alcohols.[40] These compounds were used to catalyze alkynylzinc additions to aldehydes. Among these ligands, compound **51** showed much higher enantioselectivity than compounds **52**–**54**. It (10 mol%) catalyzed the reaction of phenylacetylene (2.4 equiv.) with aromatic aldehydes in the presence of Me_2Zn (2.2 equiv.) in high conversions (>95%). The reactions were conducted in toluene solution over 6–24 h. At 0°C, the highest ee (90%) was observed for the reaction of *o*-bromobenzaldehyde. The reactions of other aromatic aldehydes with phenylacetylene gave 61–87% ee's. The reaction of *o*-nitrobenzaldehyde with 1-pentyne showed 85% ee. At −20°C, compound **51** (20 mol%) catalyzed the reaction of *o*-chlorobenzaldehyde with phenylacetylene with up to 93% ee. Very low enantioselectivity was observed for additions to aliphatic aldehydes.



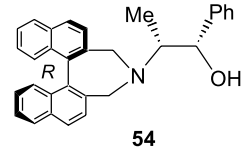
51



52



53



54

Table 14. Reactions of phenylacetylene with aromatic aldehydes catalyzed by **50**-Et_2Zn without Ti(O^{i}Pr)$_4$

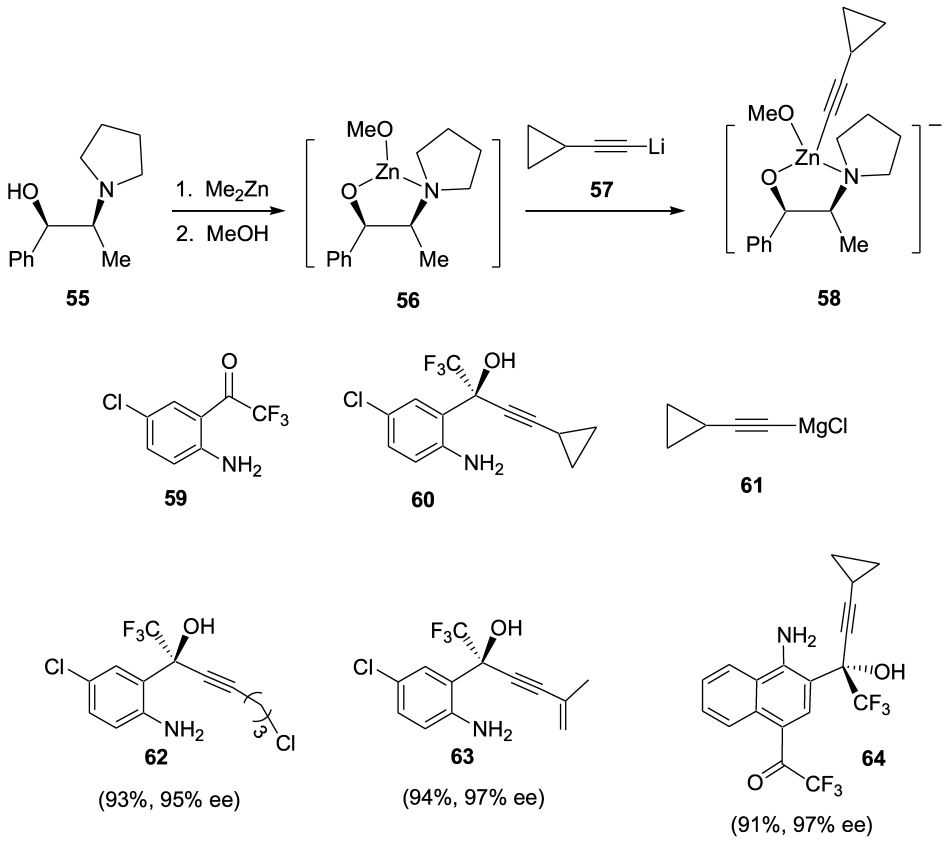
Entry	Aldehyde	Yield (%)	ee (%)
1	PhCHO	75	84
2	PhCHO (0°C)	42	88
3	PhCHO (4 equiv. Et_2Zn)	48	92
4	*o*-ClPhCHO	74	94
5	*p*-ClPhCHO	75	85
6	*o*-MePhCHO	72	84
7	*m*-MePhCHO	63	84
8	*o*-MeOPhCHO	64	91
9	*m*-MeOPhCHO	71	85
10	1-Naphthylaldehyde (0°C)	45	80

4. Asymmetric alkynylzinc additions to ketones

Unlike the alkynylzinc additions to aldehydes, much less work on the asymmetric alkynylzinc additions to ketones has been reported. This is mostly due to the much lower reactivity of ketones towards organozinc reagents.[8]

Tan and co-workers reported a stoichiometric asymmetric alkynylzinc addition to activated ketones for the synthesis of Efavirenz, a drug for AIDS treatment.[41] They first treated the amino alcohol **55** with 1 equiv. of Me_2Zn and then with 1 equiv. of methanol which presumably generated the zinc alkoxide **56** (Scheme 7). The alkynyllithium **57** was added to form an alkynylzinc reagent **58**. Complex **58** reacted with ketone **59** that was activated with the strongly electron withdrawing trifluoromethyl group. At room temperature, the tertiary-propargylic alcohol product **60** was obtained with 83% yield and 83% ee. When the alkynylithium reagent **57** was replaced with the Grignard reagent **61**, the ee was increased to 87%. When neopentyl alcohol was used as the additive instead of methanol, under the optimized conditions, the addition of the zinc reagent **58** (1.5 equiv.), derived from **61**, to **59** in THF/toluene gave up to 98% ee at room temperature. Other propargylic alcohols such as **62**–**64** were also obtained with high yields and high enantioselectivity. As shown in the synthesis of **64**, an ortho amino group activates the carbonyl group of the diketone substrate.

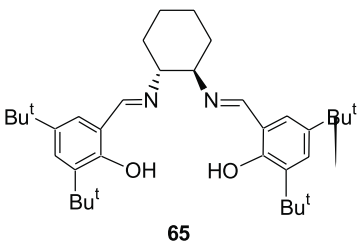
Jiang et al. reported that the amino alcohol **19b** catalyzed the addition of alkynes to α-keto esters with high enantioselectivity (Scheme 8).[42] The reactions were generally conducted in toluene solution at 70°C for 2 days using **19b** (0.22 equiv.), $Zn(OTf)_2$ (0.2 equiv.), Et_3N (0.3 equiv.), an alkyne (3 equiv.) and an α-keto ester. The results are summarized in Table 15. The reactions with aromatic keto



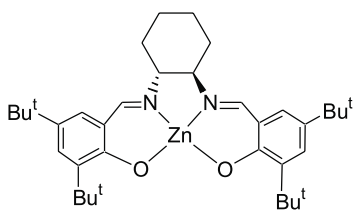
Scheme 7. Preparation of the chiral alkynylzinc reagent **58**.

esters proceeded better than that with the acyclic aliphatic substrate of entry 10. Formation of an enloate under the basic reaction condition might have contributed to the low yield for the addition to this keto ester (entry 10). The keto lactones in entries 11 and 12 could not form enolates and showed both high yield and high enantioselectivity.

A catalytic asymmetric alkynylzinc addition to unactivated ketones has been developed recently.[43] Cozzi found that the enantiomerically pure salen **65** (20 mol%) catalyzed the reaction of phenylacetylene (3 equiv.) with acetophenone in the presence of Me_2Zn (3 equiv.) in toluene to give the corresponding propargylic tertiary alcohol in 72% yield and 61% ee. When these conditions were applied to the additions of various alkynes to various methyl alkyl or aryl ketones, ee's up to 81% were achieved. In these reactions, the zinc salen complex **66** was believed to be the active catalyst.



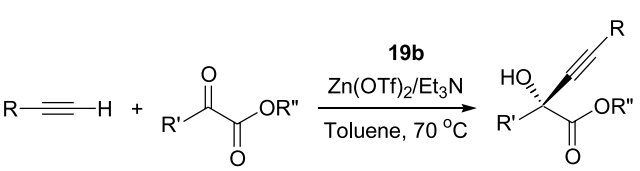
65



66

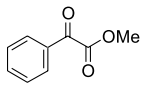
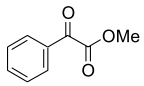
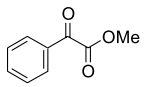
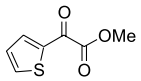
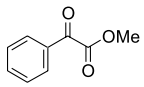
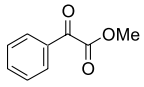
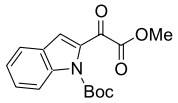
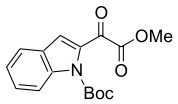
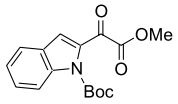
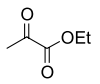
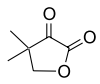
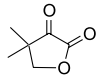
5. Summary[44]

In the past few years, great progresses have been made on asymmetric alknylzinc additions to aldehydes. Highly enantioselective and commercially available catalysts have been discovered. Among these catalysts, the N-methylephedrine (**14**)-based method of Carreira's shows high practical value in asymmetric alkynylzinc additions mostly to aliphatic aldehydes.[18] The BINOL-Ti(O^iPr)$_4$ catalyst systems developed by Pu[30,31] and Chan[27,28] are also practically very useful. Especially, the method using BINOL-Ti(O^iPr)$_4$-Et_2Zn has exhibited generally high enantioselectivity for alkynylzinc additions to aromatic, aliphatic and α,β-unsaturated aldehydes.[30,31] Limitations of these two methods in the additions to chiral aldehydes have also been observed in the work of Marshall and Bourbeau.[33] Further



Scheme 8. Reaction of alkynes with α-keto esters catalyzed by **19b** and $Zn(OTf)_2$.

Table 15. Alkynylzinc additions to α-keto esters using the amino alcohol **19b** and $Zn(OTf)_2$

Entry	Alkyne	Ketone	Yield (%)	ee (%)
1	PhC≡CH		91	89
2	PhC≡CH		87	88
3	PhC≡CH		83	92
4	PhC≡CH		93	73
5	$PhCH_2CH_2C{\equiv}CH$		88	94
6	$TBSOCH_2C{\equiv}CH$		83	91
7	PhC≡CH		81	83
8	$PhCH_2CH_2C{\equiv}CH$		76	86
9	$TBSOCH_2C{\equiv}CH$		67	81
10	PhC≡CH		11	92
11	PhC≡CH		95	94
12	$PhCH_2CH_2C{\equiv}CH$		93	94

improvements are needed for more functionalized substrates.

Another challenge in this field is the catalytic asymmetric alkynylzinc addition to ketones. Although high enantioselectivities have been achieved for the reaction of some highly activated ketones as demonstrated by Jiang using **19b**,[42] the reactions of unactivated simple ketones are still underdeveloped. The work of Cozzi using the salen zinc complex **66** is very promising, but the observed enantioselectivities are still less than satisfactory.[43] With the continuous efforts of the researchers in this area, there is no doubt that highly enantioselective catalysts for the alkynylzinc addition to various types of ketones will be obtained in the not too distant future. Alkynylzinc additions to both aldehydes and ketones for the asymmetric synthesis of propargylic alcohols should play increasingly important roles in general organic synthesis.

Acknowledgements

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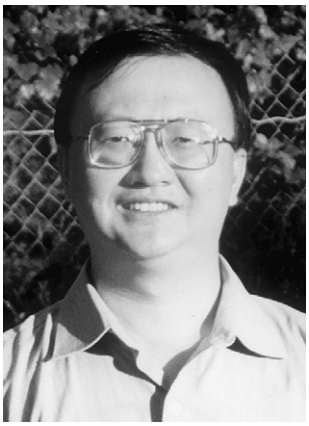
Biographical sketch



Lin Pu was born in 1965 in Xuyong, Sichuan Province, P. R. China. He received his B.S. degree in chemistry from Sichuan University in 1984. He then obtained the Doering Fellowship (the Chemistry Graduate Program of China) for graduate study in the US and enrolled in the Department of Chemistry at University of California San Diego in 1985. Under the supervision of Professor Joseph M. O'Connor, he obtained his Ph.D. degree in 1990. From January 1991 to November 1992, he studied in Professor Henry Taube's laboratory at Stanford University as a post-doctoral fellow. From November 1992 to August 1994, he joined Professor Robert H. Grubbs' research group at California Institute of Technology to continue his post-doctoral training. In the fall of 1994, he was appointed as an assistant professor in the Department of Chemistry at North Dakota State University. In 1997, he moved to University of Virginia as an associate professor in the Department of Chemistry. He became a professor of chemistry at University of Virginia in 2003. The research projects in his laboratory focus on the design and synthesis of novel chiral molecules and macromolecules for applications in areas such as asymmetric catalysis, enantioselective fluorescent sensors, and electrical and optical materials.