Advanced Synthesis & Catalysis

DOI: 10.1002/adsc.201301128

Modular Synthesis of Ar-BINMOL-Phos for Catalytic Asymmetric Alkynylation of Aromatic Aldehydes with Unexpected Reversal of Enantioselectivity

Tao Song,[a] Long-Sheng Zheng,[a] Fei Ye,[a] Wen-Hui Deng,[a] Yun-Long Wei,[a] Ke-Zhi Jiang,[a] and Li-Wen Xu[a,b,*]

[a] Key Laboratory of Organosilicon Chemistry and Material Technology of Ministry of Education, Hangzhou Normal University, Hangzhou, Zhejiang 310003, People's Republic of China
Fax: (+86)-571-2886-5135; e-mail: liwenxu@hznu.edu.cn

[b] Key Laboratory of Applied Surface and Colloid Chemistry, Ministry of Education (MOE) and School of Chemistry and Chemical Engineering, Shaanxi Normal University, Xi'an 710062, People's Republic of China
E-mail: licpxulw@yahoo.com

Received: December 13, 2013; Revised: February 2, 2014; Published online: ■■ ■■, 0000

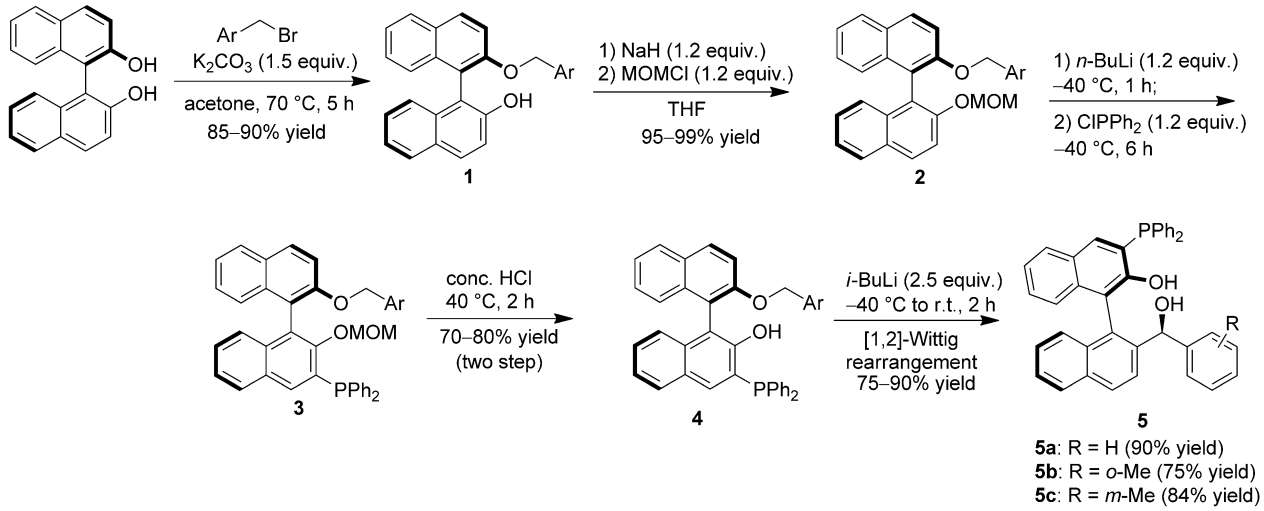
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201301128.

Abstract: An interesting group of multifunctional phosphines (Ar-BINMOL-Phos; Ar-BINMOL = 1,1′-binaphthalene-2-α-arylmethanol-2′-ol) with multi-stereogenic centers of axial and sp^3-central chirality has been prepared successfully from a single chiral source through a concise synthetic route, in which the neighbouring lithium-promoted [1,2]-Wittig rearrangement proceeding with excellent diastereoselectivity and enantioselectivity is the key process in this approach. Also, in the catalytic alkynylation of aromatic aldehydes with terminal alkynes, the combination of these Ar-BINMOL-Phos ligands with dimethylzinc was found to be an effective catalyst system to afford predominantly the *S*-configured propargylic alcohols, whereas the additional use of calcium hydride and *n*-butyllithium along with the same Ar-BINMOL-Phos ligands gave the *R*-configured products in high yields and excellent enantioselectivities (up to >99% *ee*).

Keywords: alkynylation; asymmetric catalysis; chiral ligands; chirality inversion; phosphines

In asymmetric organometallic catalysis, chiral ligands generally play a critical role in numerous stereoselective transformations. Thus the design and synthesis of efficient chiral ligands is an area of permanent interest for developing efficient enantioselective metal-catalyzed reactions that provide facile access to optically pure compounds.[1] Besides, for a chiral ligand with a single absolute configuration, the phenomenon of chirality inversion in ligand-directed asymmetric reactions is also a very interesting topic in asymmetric catalysis and organic synthesis.[2] However, it is not an easy task to obtain two enantiomers, either in (*S*)- or (*R*)-form, to be produced using the same chiral ligand. In this regard, where possible, it would be highly important in asymmetric catalysis for both enantiomers of a product to be produced using chiral ligands with switchable stereoselectivity. As a distinctive and switchable stereoselectivity in chirality transfer of chiral ligands or catalysts, the phenomena of enantioselectivity inversion have been realized widely in many catalytic asymmetric reactions in the past decades.[2]

Despite the successful application of asymmetric catalysis to the preparation of a single enantiomer with a certain chiral catalyst, the strategies involving enantiodivergent catalysis that enable dual or reversible enantiocontrol still remain an unexpected and significant challenge. Recently, on the basis of the same chiral ligands or catalysts, great progress has been made by several groups in this context,[3–10] for example, reversal of enantioselectivity has been realized by tuning the conformational flexibility of chiral catalysts in asymmetric Michael reaction,[3] the addition of zinc metal to an iron complex in the asymmetric hydrosilylation of ketones,[4] the use of different metal salt catalysts,[5] achiral counteranion-induced reversal of enantioselectivity in ruthenium-catalyzed hydrogenation,[6] achiral acid- or base-induced switch in the organocatalytic aldol and Mannich reactions,[7] chiral anion-dependent inversion in ruthenium-catalyzed hydrohydroxyalkylation,[8] temperature-dependent reversal of enantioselectivity in the hydroformylation of styrene,[9] and others.[10]



Scheme 1. Synthesis of chiral Ar-BINMOL-Phos (**5**).

Here we report the enantioselective alkynylation of aldehydes by the featured Ar-BINMOL-based phosphine, in which we describe the unique effect of lithium and calcium upon the absolute configuration of the products because of switchable stereoselectivity in this catalytic alkynylation reaction.

Recently, we have developed a practical methodology for the preparation of an interesting type of chiral diols with multi-stereogenic centers, Ar-BINMOLs, in which the simple axial chiral monoalkylated BINOLs could be converted into optically pure 1,1′-binaphthalene-2-α-arylmethanol-2′-ols (Ar-BINMOLs) with axial and sp^3-central chirality through an asymmetric [1,2]-Wittig rearrangement.[11] In this approach, the process of axial-to-central chirality transfer led to the synthesis of a broad of range of chiral 1,1′-binaphthalene-2-α-arylmethanol-2′-ols with various substituted groups. Over the past years, they have proved to be attractive chiral ligands in several enantioselective transformations.[12] On the basis of previous findings,[11,12] we have continued to design and synthesize Ar-BINMOL-based P-ligands endowed with axial and sp^3-central chirality. We believe that the 3-position of the substituent on the Ar-BINMOLs may also be very important for asymmetric induction, particularly for the introduction of an additional heteroatom-based binding center on this type of multi-stereogenic ligand.

Initially, we developed an efficient approach to prepare Ar-BINMOL-based phosphine ligands through an asymmetric [1,2]-Wittig rearrangement, which provided versatile and optically pure P-ligands for the asymmetric alkynylation of aromatic aldehydes. The synthesis of the Ar-BINMOL-based phosphine ligands is outlined in Scheme 1. The benzyl ether of 1,1′-binaphthol (BINOL) **1** could be obtained easily from benzyl bromide and BINOL. And after protection of the naphthol group with chloromethylmethyl ether (MOMCl), we then achieved the introduction of diphenylphosphine to the molecule **2** that led to the formation of protected phosphine **3**. Because of the low reactivity of compound **3** in the [1,2]-Wittig rearrangement,[11] it was then converted to into **4**. Notably, the intermediate was difficult to be purified by flash column chromatography because it contained traces of by-product **1a** ($<5\%$) with similar polarity (detected by TLC and GC-MS). Since the trace by-product did not affect the next [1,2]-Wittig rearrangement, the product **4** was used directly for the next step. Subsequently, the syntheses of synthetically useful Ar-BINMOL-based phosphine ligands **5a–c** with axial and sp^3 central chirality were performed smoothly through neighbouring lithium-promoted [1,2]-Wittig rearrangements.[11] The total yields of the desired products were quite high (Scheme 1), and the enantiomeric excesses of the desired chiral Ar-BINMOL-Phos (**5**) were $>99\%$ *ee*. It is noteworthy that the easy modulation of the R group would be useful for the modification of such phosphine ligands for asymmetric catalysis.

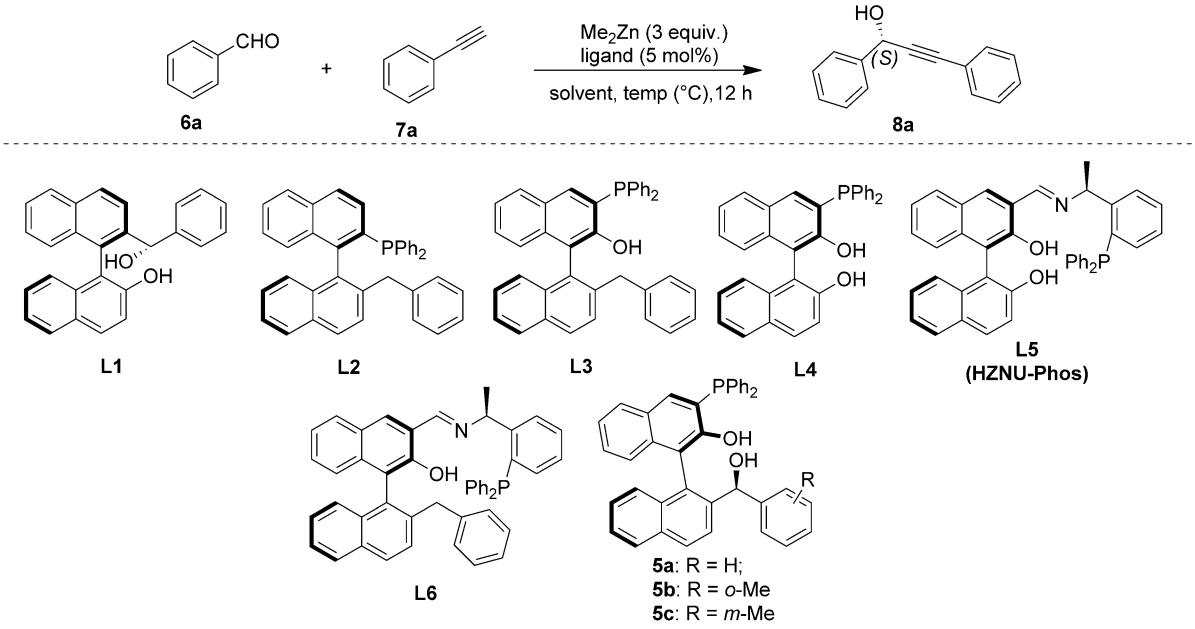
To demonstrate the value of chiral Ar-BINMOL-Phos (**5**) in promoting asymmetric transformations, we chose the alkynylation of aromatic aldehydes as a model reaction because the alkynylation products of such reactions, chiral propargylic alcohols, are important intermediates in the synthesis of fine chemicals, natural products, and therapeutic agents.[13] In the past decades, much interest has been focused on the catalytic synthesis of chiral propargylic alcohols though the organozinc reagents-promoted addition of a terminal acetylene to an aldehyde.[14] After the pioneering work by Carreira et al. on the alkynylation of aldehydes with stoichiometric (+)-*N*-methylephedrine, $Zn(OTf)_2$, and triethylamine,[15] a number of

N,O-based and diol ligands have been employed as chiral catalysts or ligands in these reactions. For example, the use of 1,1′-bi-2-naphthol (BINOL) and its derivatives in conjunction with Ti(O-*i*-Pr)$_4$ and organozinc reagents to facilitate alkynylation of aldehydes has been reported by the groups of Pu and Chan independently.[16,17] These conditions provided good yield and enantioselectivity with a range of substrates. Other examples include amino alcohols, imino alcohols, hydroxyl sulfamides, hydroxy carboxamides, oxazolidines, and miscellaneous catalysts.[18] Despite the big number of chiral ligands described so far for this reaction, as yet, a phosphine catalyst or ligand has not been successfully developed for the catalytic asymmetric alkynylation of aldehydes with high enantioselectivity.[19a] Only Sawamura and co-workers have ever reported that a Cu(I)-phosphine complex could be used as an efficient catalyst in this reaction.[19b] In addition, the strong demand for perfect chirality-transfer of a catalyst with perfect enantioselectivity still motivates chemists to develop good strategies or catalysts in this reaction with truly perfect enantioselectivity for at least one substrate (>99% *ee*). And our aim was also to develop an efficient Ar-BINMOL-derived phosphine catalyst system with multi-stereogenic centers enabling both enantiomers of a product to be produced with a single chiral ligand. This would ultimately provide a facile approach to the development of controllable chirality in the synthesis of optically pure propargylic alcohols.

Thus, we began our investigation by examining the catalytic activity of various Ar-BINMOL-derived phosphine ligands (Ar-BINMOL-Phos) in the alkynylation of benzaldehyde **6a** with terminal alkyne **7a**. Simultaneously, we also investigated the catalytic activity of phosphine-free Ar-BINMOL **L1** and other phosphine ligands (**L2–L4**). As shown in Table 1, different Ar-BINMOL-Phos ligands were effective in this reaction, and the alkynylation of benzaldehyde **6a** with terminal alkyne **7a** proceeded smoothly in good yields and promising enantioselectivities (entries 1–3, 68–85% isolated yields and 63–70% *ee*). Interestingly, the influence of the phosphine moiety on Ar-BINMOL-Phos (**5**) was found to be significant, because employment of the simple Ar-BINMOL (**L1**) led to almost no reaction under similar reaction conditions (entry 4). The C_2-axially chiral monophosphine (Ph-NNP, **L2**)[20] prepared from Ar-BINMOL was also not effective in this reaction (entry 5). It was found that the sp^3-central chirality of the secondary alcohol on Ar-BINMOL-Phos was also one of the most important groups due to low activity of phosphine ligand **L3** (entry 6, <10% yield with this ligand).[21] Surprisingly, the Endo-Shibata's BINOL-derived phosphine **L4**[22] with only C_2-axial chirality exhibited poor catalytic activity and enantioselective induction in this reaction (entry 7), which supported indirectly the importance of the hydroxy group at the benzylic position on Ar-BINMOL-Phos ligands in this reaction. It also should be noted that the combinational use of triphenylphosphine and Ar-BINMOL (**L1**) could not promote the occurrence of alkynylation (entry 10). Also surprisingly, the ligands **L5** and **L6** with multi-binding centers of phosphine and Schiff base[23] resulted in excellent yields but with almost no enantioselectivity (entries 8 and 9). Thus in this alkynylation reaction, the Ar-BINMOL-Phos (**5a**) was one of the most promising phosphine ligands, whereas all the other phosphine ligands tested herein resulted in poor yields or low enantioselectivities. In additional investigations, **5a** was utilized to screen the reaction conditions, such as solvents and temperature. These studies demonstrated that the nature of the solvent dramatically impacted on the selectivity and activity of chiral ligand **5a** (entries 11–15 and Supporting Information, Table S2). The effect of temperature and commercially available Me_2Zn in different solvents on the zinc/**5a**-mediated alkynylation of benzaldehyde was also investigated (entries 16–18). In summary, as shown in Table 1 and Table S1 in the Supporting Information, the best result in terms of enantioselectivity was obtained at −10 °C in Et_2O (marked as Method A, 85% yield and 70% *ee*) while the yield was decreased slightly in comparison to that at higher temperature.

In view of our preliminary results on the Ar-BINMOL-Phos (**5a**)-promoted nucleophilic addition of terminal alkyne **7a** to benzaldehyde **6a**, the next logical step was to investigate the effect of various additives for enhancement of the enantioselective induction of **5a** in this reaction. Screening of numerous additives, for example, chiral amino acids, Lewis acids, Lewis base, and organometallic reagents (Table 2 and Supporting Information, Table S3), revealed that improvement of the enantioselectivity in this catalytic asymmetric alkynylation of aldehydes was not an easy task. Fortunately, we found that the use of 10 mol% *n*-BuLi with the above reaction conditions led to higher enantioselectivity (74% *ee*) with the opposite absolute configuration of **8a** (entry 2). However, the yield of **8a** was sacrificed with only 30% in the presence of 10 mol% *n*-BuLi. More interestingly, the combinational use of *n*-BuLi and CaH_2 led to a superior level of reaction efficiency. To test the synergistic effect of *n*-BuLi and CaH_2 in this reaction, we investigated the effect of temperature and the catalytic amounts of *n*-BuLi and CaH_2 on the enantioselectivity (entries 4–7, see also Supporting Information, Table S4 and Table S5). It should be noted that the mixture of ligand **5a** and CaH_2 was not completely soluble in the solvent, and the addition of *n*-BuLi led to the formation of a clear solution, in which a possible bimetallic complex probably arises from the introduction of lithium to a calcium alkoxide or aryloxide of Ar-BINMOL-Phos (**5a**). Although the exact struc-

Table 1. Zinc/ligand-promoted alkynylation of benzaldehyde: Effect of ligands, temperature, and solvents on yields and enantioselectivity (Method A).[a]

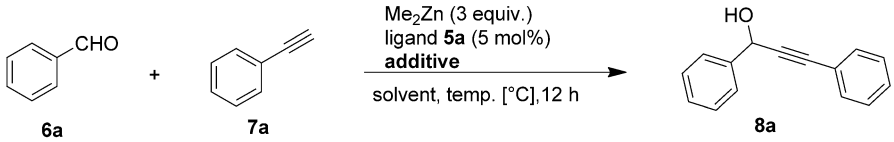


Entry	Ligand	Solvent	Temperature [°C]	Yield [%][b]	*ee* [%][c]
1	**5a**	Et_2O	−10	85	70
2	**5b**	Et_2O	−10	75	68
3	**5c**	Et_2O	−10	68	63
4	**L1**	Et_2O	−10	trace	–
5	**L2**	Et_2O	−10	trace	–
6	**L3**	Et_2O	−10	trace	–
7	**L4**	Et_2O	−10	10	3
8	**L5**	Et_2O	−10	95	1
9	**L6**	Et_2O	−10	94	0
10	**L1** + PPh_3[d]	Et_2O	−10	trace	–
11	**5a**	THF	−10	trace	–
12	**5a**	MeO-*t*-Bu	−10	50	68
13	**5a**	toluene	−10	61	58
14	**5a**	DME	−10	trace	–
15	**5a**	DCM	−10	10	21
16	**5a**	Et_2O	0	89	63
17	**5a**	Et_2O	−20	40	70
18	**5a**	Et_2O	−15	65	68[e]

[a] Reaction conditions: 0.5 mmol of aldehyde, 1.5 mmol of alkyne, 0.025 mmol of ligand, 1.5 mmol of Et_2Zn (1.0 mol/L, in toluene), 1.0 mL of solvent. DME = 1,2-dimethoxyethane, DCM = dichloromethane.
[b] Isolated yields.
[c] The *ee* value was determined by HPLC with a chiral column (see Supporting Information).
[d] The combinational use of 5 mol% of ligand **L1** and 5 mol% of PPh_3.
[e] Et_2Zn in hexane solution was used in this reaction.

ture of lithium-calcium complex with Ar-BINMOL-Phos **5a** is not clear at present, the striking feature of this study was the confirmation that 20 mol% of both *n*-BuLi and CaH_2 led to good enantioselectivity and isolated yield at 0 °C (entry 6, 85% yield and 87% *ee*, denoted as Method B). These promising results promoted us to examine the effect of solvents. To our delight, when dimethylzinc in toluene solution (1.0 mol/L) was used, we found that Et_2O was still the optimal solvent for the reactions evaluated in this work (entries 8–14). Unexpectedly, when dimethylzinc in hexane solution (1.0 mol/L) was used in this alkynylation reaction, DCM was also a suitable solvent in term of isolated yield or enantioselectivity (entry 15, 81% yield and 90% *ee*, denoted as Method C). It is suggested that the bimetallic Ca/Li-based catalyst

Table 2. Effect of additives and solvents on yields and enantioselectivity in the zinc/**5a**-mediated alkynylation of benzaldehyde.[a]



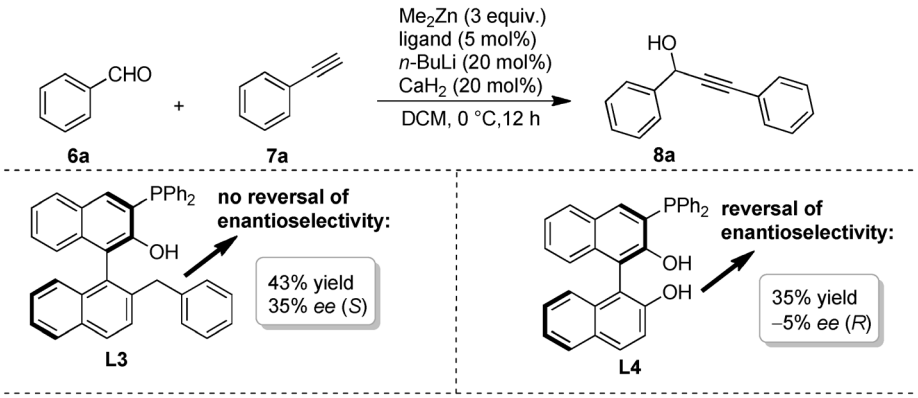
Entry	Additive	Solvent	Temperature [°C]	Yield [%][b]	*ee* [%][c]
1	LiCl	Et_2O	−10	48	30 (*S*)
2	*n*-BuLi	Et_2O	−10	30	74 (*R*)
3	CaH_2	Et_2O	−10	40	63 (*S*)
4	*n*-BuLi/CaH_2	Et_2O	−10	68	62 (*R*)
5	*n*-BuLi/CaH_2	Et_2O	0	79	82 (*R*)
6[d]	*n*-BuLi/CaH_2	Et_2O	0	85	87 (*R*)
7[e]	*n*-BuLi/CaH_2	Et_2O	0	70	32 (*R*)
8[d]	*n*-BuLi/CaH_2	CH_3CN	0	43	5 (*R*)
9[d]	*n*-BuLi/CaH_2	MeOH	0	trace	–
10[d]	*n*-BuLi/CaH_2	DCM	0	30	41 (*R*)
11[d]	*n*-BuLi/CaH_2	toluene	0	56	50 (*R*)
12[d]	*n*-BuLi/CaH_2	1,4-dioxane	0	46	74 (*R*)
13[d]	*n*-BuLi/CaH_2	DCM	0	68	82 (*R*)
14[d]	*n*-BuLi/CaH_2	THF	0	10	49 (*R*)
15[d,f]	*n*-BuLi/CaH_2	DCM	0	81	90 (*R*)

[a] *Reaction conditions:* 0.5 mmol of aldehyde, 1.5 mmol of alkyne, 0.025 mmol of ligand, 1.5 mmol of Et_2Zn (1.0 mol/L, in toluene), and additive (10 mol%), 1.0 mL of solvent; DMC is dimethyl carbonate.
[b] Isolated yields.
[c] The *ee* value was determined by HPLC with a chiral column.
[d] 20 mol% of *n*-BuLi and CaH_2.
[e] 30 mol% of *n*-BuLi and CaH_2.
[f] Method C: dimethylzinc in *n*-hexane solution was used (1 mol/L) in this procedure, and other conditions were similarly to those of Method B (entry 6).

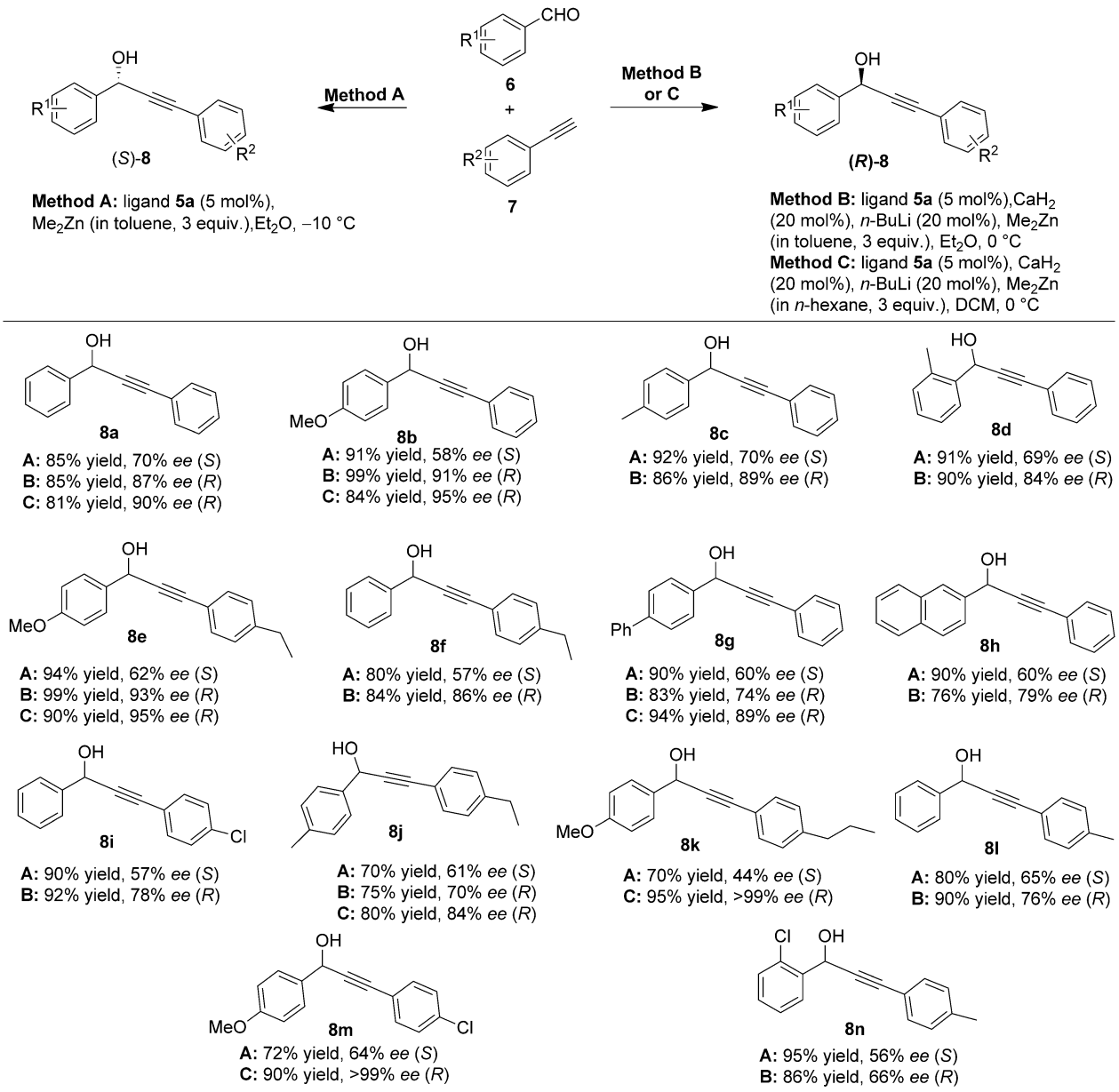
system was sensitive to solvents because of the relatively unstable conformation of a possible supermolecular complex.

In an effort to promote the privileged inversion of enantioselectivity in this reaction, we also compared the catalytic activity of **L3** and **L4** in the presence of *n*-BuLi and CaH_2 (Scheme 2). Unfortunately, both P-ligands without additional sp^3-central chirality resulted in poor yields and low enantioselectivities.

After chiral Ar-BINMOL-Phos **5a** was identified as a reactive and enantioselective ligand for the alkynylation of benzaldehyde, the scope of this reaction was further examined under the optimized conditions with a series of other alkynes and aromatic aldehydes. Notably, to clarify the interesting and unexpected rever-



Scheme 2. Phosphine **L3** or **L4**-mediated alkynylation of benzaldehyde: The role of sp^3-central chirality of Ar-BINMOL-Phos **5a**.



Scheme 3. Synthesis of both enantiomers of propargylic alcohols *via* enantioselective Ar-BINMOL-Phos **5a** promoted alkynylation of aldehydes under different conditions (Methods A, B, and C, respectively).

sal of the enantioselectivity, the alkynylation reaction was carried out using different methods (methods A, B, and C) related to the experimental results of Table 1 and Table 2 (Scheme 3). With the method A, the desired (*S*)-alkynylation products **8a–m** were obtained in good to excellent yields (68–94%) and moderate to good enantioselectivities (44-70% *ee*). As anticipated, all reactions proceeded smoothly under the reaction conditions of method B or C to give the alkynylation products with good to excellent enantioselectivities (up to >99% *ee*) and yields, and the observed enantioselectivity is the opposite to that of the lithium-free alkynylation even in the presence of the same chiral ligand **5a**. For the results of method B, some representative data are provided in Scheme 3. Alkynes and aromatic aldehydes evaluated in this work resulted in the formation of the corresponding *R*-configured propargylic alcohols at high levels of yields and enantioselectivities (up to 93% *ee*). For example, 1-(4-methoxyphenyl)-3-phenylprop-2-yn-1-ol (**8b**) and 3-(4-ethylphenyl)-1-(4-methoxyphenyl)prop-2-yn-1-ol (**8e**) were obtained with 91% *ee* and 93% *ee*, respectively, under the reaction conditions of method B. Interestingly, the method C gave the desired products in better enantioselectivities in some cases than did method A or method C. Especially for

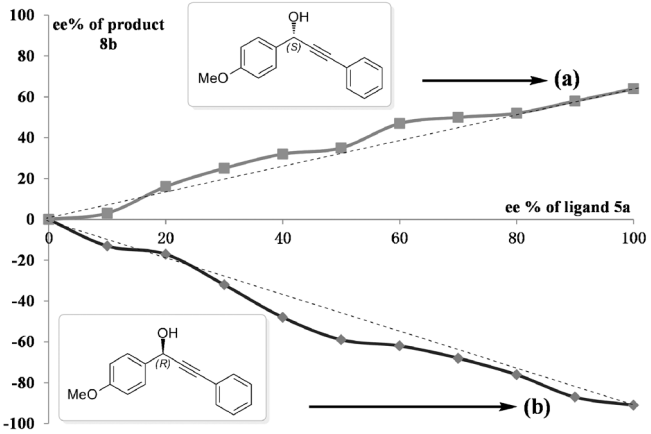


Figure 1. Non-linear effects in Ar-BINMOL-Phos **5a** mediated nucleophilic addition of terminal alkyne **7a** to 4-methoxybenzaldehyde **6b** under different conditions (**A** or **B**). Experimental ee_{prod} *vs.* ee_{cat} with different catalytic systems based on Ar-BINMOL-Phos **5a**. Method A: no addition of any additive in Et_2O (■, line **a**). Method B: standard conditions with CaH_2/*n*-BuLi (20 mol%/20 mol%) as additive in Et_2O (◆, line **b**).

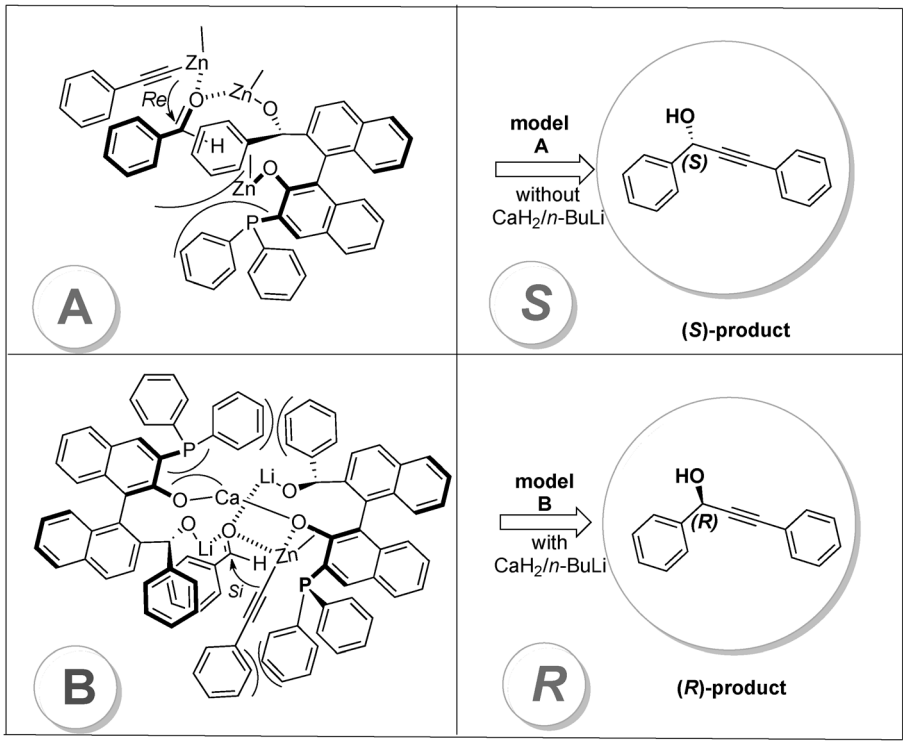
the case of 1-(4-methoxyphenyl)-3-(4-propylphenyl)-prop-2-yn-1-ol (**8k**) or 3-(4-chlorophenyl)-1-(4-methoxyphenyl)prop-2-yn-1-ol (**8m**), excellent enantioselectivity as well as yield was achieved (>99% *ee*). Notably, the aromatic aldehydes bearing electron-withdrawing groups led to poor enantioselectivity in this reaction. For example, **8n** was only obtained in 56% *ee* or 66% *ee* under method A or method B, respectively. Although the alkynylation of aromatic aldehydes is not perfect for all the substrates, this outcome represents a rare example of accessing both enantiomers of an asymmetric transformation by using a chiral ligand possessing a common chiral source.

On the basis of the previous excellent works on zinc-mediated alkynylation,[13–15] as well as Kagan's non-linear stereochemical effect[24] and the electrospray ionization mass spectrometry (ESI-MS) analysis of the present catalyst system, we hypothesized that the different enantioselective inductions arise from the formation of a possible zinc-containing complex with one or two ligands, respectively. In the previous report,[24] the non-linear stereochemical effect of catalyst enantiopurity on product enantiomeric excess has been an important diagnostic tool in mechanistic studies of asymmetric reactions. Our results of this non-linear study, graphically depicted in Figure 1, demonstrated that the non-linear curve with a slightly positive non-linear effect might be attributed to the multi-metal centers-involved aggregation of the Me_2Zn and Ar-BINMOL-Phos. Unfortunately, it is difficult to distinguish the difference between the two catalytic systems, namely that with or that without lithium/calcium.

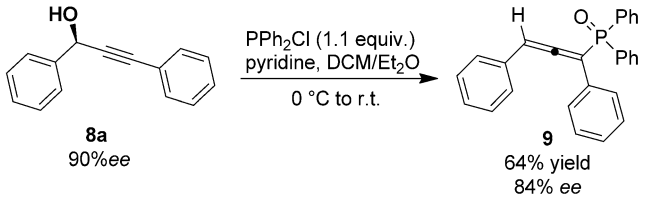
Although a detailed mechanistic discussion is also difficult for the additive-free Ar-BINMOL-Phos-mediated alkynylation of aldehydes at present, we proposed the model **A** shown in Scheme 4 (method A, without CaH_2/*n*-BuLi), similarly to a previous working model of 1,2-addition of organozinc reagents to aldehydes.[25] However, the proof of the coordination based on ^{31}P NMR spectroscopy was not successful because the phosphine is very unstable under the reaction conditions. Thus, according to the reaction results and the ESI-MS analysis (see the Supporting Information), a catalytic model or transition state was proposed as model B in Scheme 4. Especially from the ESI(+)-MS analysis (see Supporting Information, Figure S5), it is suggested that the use of *n*-BuLi and CaH_2 in the alkynylation of aldehydes is likely to generate a complicated dimer or oligomer of Ar-BINMOL-Phos-based complex with multi-metal centers derived from calcium aryloxide of two Ar-BINMOL **5a** in the presence of strong base (*n*-butyllithium)[26] (model B, Scheme 4), in which the oxygen of the aldehyde was binding with the zinc center of the alkynylzinc molecule and lithium alkoxide of Ar-BINMOL-Phos. Also, the possible aromatic interaction (π–π stacking of Ar-BINMOL-Phos-based complex with substrate)[27] and steric effects of the Ph_2P group could stabilize this transition state. Thus this arrangement resulted in the *Si* face-attack of a zinc acetylide species to aldehyde acceptor, which provides the enantioselective access to *R*-configured propargylic alcohol (up to >99% *ee*). Although a detailed mechanistic investigation involving CaH_2 will form part of future studies, the participation of CaH_2 in the formation of the bimetallic lithium/calcium-based complex could be responsible for the improvement of conversion.

At last, considering the broad applications of propargylic alcohols and allenes in organic synthesis,[13,28] we sought to demonstrate the utility of the chiral propargylic alcohol for the synthesis of allenylic diphenylphosphine oxides that could be easily prepared from the reaction of propargylic alcohols with diphenylchlorophosphine (Ph_2PCl).[29] Interestingly, there is no report on the synthesis of the corresponding chiral allenylic diphenylphosphine oxides. As shown in Scheme 5, the 3-phenyl-1,2-allenylic diphenylphosphine oxide could be prepared in good enantioselectivity (84% *ee*) from the starting material with 90% *ee*.

In summary, we have successfully developed an interesting family of multifunctional chiral phosphines (Ar-BINMOL-Phos, also named as HZNU-ABP) with multi-stereogenic centers of axial and sp^3-central chirality from a single chiral source (BINOL) through a concise synthetic route, in which the enantioselective [1,2]-Wittig rearrangement mediated by neighbouring lithium is the key process in this diastereose-



Scheme 4. Proposed transition states for the Ar-BINMOL-Phos (**5a**) mediated alkynylation of aromatic aldehyde with terminal alkyne with or without CaH_2/*n*-BuLi.



Scheme 5. Synthesis of chiral allenylic diphenylphosphine oxide **9** from chiral propargylic alcohol **8a**.

lective synthesis of Ar-BINMOL-Phos ligands. In the subsequent study, we evaluated these ligands in the catalytic alkynylation of aromatic aldehydes with terminal alkynes. The combination of these Ar-BINMOL-Phos ligands with $ZnMe_2$ afforded predominantly the *S*-configured propargylic alcohols, whereas the additional use of CaH_2 and *n*-BuLi along with the same Ar-BINMOL-Phos ligands gave the *R*-configured products in high yields and excellent enantioselectivities (up to >99% *ee*). Thus it was demonstrated that the lithium-induced unexpected reversal of enantioselectivity takes place in this catalytic alkynylation. Notably, the Ar-BINMOL-Phos with privileged multichirality presented herein can access both enantiomers from a single chiral source by the addition of a catalytic amount of an organolithium reagent. Further investigation involving the application and elucidation of Ar-BINMOL-Phos ligand, and the detailed mechanism of corresponding reactions will be carried out and reported in the near future.

Experimental Section

The compounds of **1a–c** and **2a–c** have already been reported in our previous work.[11,13f]

General Procedure for the Synthesis of Ligands 5a–c

4.8 mL (12 mmol) of a 2.5 M *n*-BuLi solution in hexanes were dropwise added to a solution of compound **2a** (4.202 g, 10 mmol) in 50 mL of THF at −40 °C. Then the resulting solution was stirred at −40 °C for 1 h, and subsequently, 10 mL a solution of PPh_2Cl (2.15 mL, 12 mmol, 1.2 equiv.) in THF were added slowly at the same temperature. The reaction mixture was then stirred for 6 h until almost full conversion of **2a** by TLC analysis. The reaction was quenched with saturated aqueous NH_4Cl (5 mL) and stirred vigorously for 5 min. The aqueous phase was extracted with ethyl acetate (3×40 mL). The combined organic layers were dried over Na_2SO_4, and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel [petroleum ether/EtOAc, 10/1 (v/v)] to give of the compound **3a** as a yellow oil; yield: 4.77 g (79%). The product **3a** was used directly for the next step.

5 mL of 12 M aqueous HCl were added to a solution of compound **3a** (4.77 g, 7.9 mmol) in 30 mL of THF at room temperature. The reaction mixture was warmed to 40 °C and stirred for another 2 h, before being diluted with water (3×

30 mL) and extracted with ethyl acetate (3×30 mL). The combined organic layers were dried over Na_2SO_4, and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel [petroleum ether/EtOAc, 10/1 to 5/1 (v/v)] to give compound **4a** as a yellow solid; yield: 3.98 g (90% total yield for two steps from **2a**). The product **4a** was difficult to purify by flash column chromatography because it contained traces of by-product **1a** (< 5%) with similar polarity. Since the trace by-product did not affect the next [1,2]-Wittig rearrangement, the product **4a** was used directly for the next step.

To a solution of compound **4a** (3.98 g, 0.71 mmol) in 30 mL of THF, 14.5 mL (17.78 mmol) of 1.23 M *i*-BuLi solution in hexanes were added at −40 °C for 5 min, and the colour of the mixture turn to that of jasper, and then the reaction was carried out at room temperature for another 2 h. Then the reaction was quenched with saturated aqueous NH_4Cl (10 mL) and stirred for 5 min. The aqueous phase was extracted with ethyl acetate (3×30 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel [petroleum ether/EtOAc, 10/1 to 5/1 (v/v)] to give Ar-BINMOL-Phos ligand **5a**; yield: 3.58 g (90% yield)

General Procedure for the Zinc-Mediated Asymmetric Addition of Aromatic Alkynes to Aldehydes

A solution of Me_2Zn (1.5 mL, 1.0 M in toluene, 1.5 mmol, 3 equiv.) and phenylacetylene were added to the solution of ligand **5a** (14 mg, 0.025 mmol) in dry diethyl ether (1 mL) at room temperature. The resulting mixture was stirred for 1 h and cooled to −10 °C. And then the benzaldehyde was added (0.5 mmol, 50.4 μL) to the solution. The reaction mixture was stirred for another 24 h at −10 °C, before being quenched with saturated aqueous NH_4Cl (3 mL) and extracted with Et_2O (3×10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel.

General Procedure for the Lithium/Calcium-Promoted Zinc-Mediated Asymmetric Addition of Aromatic Alkynes to Aldehydes

A solution of *n*-BuLi (40 μL, 0.1 mmol) was added to the mixture of ligand **5a** (14 mg, 0.025 mmol) and CaH_2 (4.2 mg, 0.1 mmol) in dry DCM (1 mL) at 0 °C. It should be noted that the mixture of ligand **5a** and CaH_2 was not completely soluble in the solvent, and the addition of *n*-BuLi led to the formation of a clear solution. Then the resulting mixture was stirred for 0.5 h at 0 °C. Subsequently, Me_2Zn (1.5 mL, 1.0 M in hexane, 1.5 mmol) and phenylacetylene were added to the reaction mixture at this temperature and stirring was continued for another 0.5 h. After the benzaldehyde was added (0.5 mmol, 50.4 μL) in one portion, the reaction was stirred at this temperature for 72 h until almost full conversion of the aldehyde by TLC analysis. Then the reaction was quenched with saturated aqueous NH_4Cl (3 mL) and stirred vigorously for 5 min. The aqueous phase was extracted with DCM (3×10 mL), and the combined organic layers were dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel.

Acknowledgements

This project was supported by the National Natural Science Founder of China (No. 21173064, 51203037, and 51303043), Zhejiang Provincial Natural Science Foundation of China (R14B030003), and the Program for Excellent Young Teachers in Hangzhou Normal University (HNUEYT, JTAS 2011-01-014) is appreciated. XLW thanks Prof. Y. Lu (National University of Singapore) for his help.

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