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Enantioselective synthesis of *P*-chiral tertiary phosphine oxides with an ethynyl group *via* Cu(I)-catalyzed azide–alkyne cycloaddition†

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We report the highly enantioselective synthesis of *P*-chiral tertiary phosphine oxides featuring an ethynyl group *via* Cu(I)-catalyzed azide–alkyne cycloaddition. Newly developed chiral pyridinebisoxazolines (PYBOX) bearing a bulky C4 shielding group play an important role in achieving excellent enantioselectivity while suppressing side bis-triazoles formation in desymmetrizing prochiral diethynylphosphine oxides. Notably, by tuning the size of the C4 shielding group, it is possible to achieve excellent remote enantiofacial control in desymmetrizing phosphole oxide-diynes with the prochiral *P*-center farther from the ethynyl group *by four covalent bonds*. Time-dependent enantioselectivity is observed for these desymmetric CuAAC reactions, suggesting a synergic combination of a desymmetrization and a kinetic resolution, and our ligands prove to be better than unmodified PYBOX in both steps. This finding contributes to a highly enantioselective kinetic resolution of racemic ethynylphosphine oxides. The resulting chiral ethynylphosphine oxides are versatile *P*-chiral synthons, which can undergo a number of diversifying reactions to enrich structural diversity.

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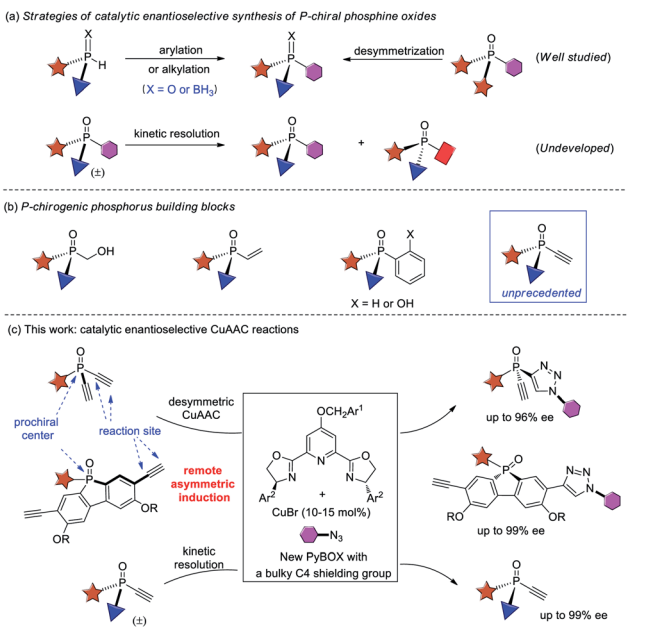
Introduction

P-chiral phosphorus compounds have widespread applications in many areas such as agrochemistry, biology and pharmacy.[1] In particular, they are regarded as a class of promising ligands or organocatalysts, because they can organize the chirality proximate to the catalytic center.[2,3] However, their application is rather limited, as compared with the more readily available phosphines with axial, spiro, planar, or carbon-centered chirality. In view of the crucial role of phosphorus ligands[4] and organocatalysts[5] in asymmetric catalysis, it is important to develop efficient protocols for the facile access of *P*-stereogenic phosphorus molecules.

Conventional syntheses of *P*-chiral phosphines require using a stoichiometric amount of chiral starting materials or chiral reagents.[6] However, recent progress in the field of asymmetric catalysis has provided some elegant protocols[1a,7] that are mainly based on two synthetic strategies, the arylation or alkylation of secondary phosphine oxides[8] or secondary phosphines[9] and the desymmetrization of prochiral phosphorus compounds[10] (Scheme 1a). Despite much progress, catalytic enantioselective synthesis of versatile *P*-chiral phosphorus building blocks is still very limited.

Because the electronic and steric properties of tertiary phosphines can be readily tuned over a very wide range by



Scheme 1 Access to *P*-stereogenic compounds.

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varying their substituents,[4,5,11] a library of *P*-chiral phosphines with high structural diversity is very helpful for reaction development. Therefore, *P*-chiral building blocks featuring a versatile synthetic handle, capable of undergoing various diversifying reactions to enrich structure diversity, are much sought after. They also offer the promise of developing new chiral ligands or organocatalysts *via* modular combination with other functionalities. Although *P*-chiral synthons with a hydroxymethyl or vinyl group are known,[1a] those with an ethynyl group are unprecedented.[12] As an acetylene group has many possibilities for elaboration,[13] the resulting optically active *P*-chiral synthons are very useful, but their enantioselective catalytic synthesis is very difficult, due to the shortage of efficient methods to form stereocenters bearing an acetylene group.[14]

On the other hand, while kinetic resolution is a fundamental strategy to access chiral materials,[15] catalytic kinetic resolution of racemic *P*-chiral molecules is undeveloped. In principle, it is a promising strategy to access two distinct *P*-chiral phosphine derivatives (Scheme 1a). To our knowledge, only two elegant protocols have been disclosed, the dynamic kinetic resolution of phospholene oxides by Hayashi *et al.*,[16] and the kinetic resolution of phosphinic amides by Cramer *et al.*[17] Herein, we report a highly enantioselective synthesis of diverse *P*-chiral tertiary phosphine oxides with an acetylene group *via* Cu(I)-catalyzed azide–alkyne cycloaddition (CuAAC) by desymmetrization and kinetic resolution (Scheme 1c).

Results and discussion

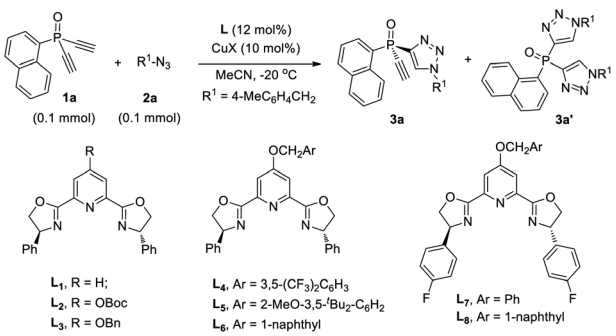
Desymmetric CuAAC of prochiral diethynyl-phosphine oxides

The CuAAC reaction, concurrently discovered by the groups of Meldal[18] and Sharpless,[19] has found application in many areas.[20] However, its application to enantioselective catalysis has met with limited success.[21] In 2005, Fokin and Finn pioneered this study, and demonstrated that it was possible to develop enantioselective CuAAC *via* desymmetrization or kinetic resolution.[22] Eight years later, we developed the first highly enantioselective CuAAC, by desymmetrizing oxindole-diynes.[23a] Uozumi and Xu also disclosed nice desymmetric CuAAC reactions of prochiral dialkynes.[23c–f] In general, a challenge in developing desymmetric CuAAC is how to suppress side bis-triazoles formation while achieving excellent enantiocontrol, because most known protocols afford substantial amounts of achiral bis-triazoles, with few substrates able to achieve excellent ee values.[22–24] On the other hand, the application of CuAAC for the kinetic resolution of racemic alkynes or azides is in its infancy,[22,25] although Topczewski most recently made a notable advance with an elegant dynamic kinetic resolution of allylic azides.[26] We speculate that asymmetric CuAAC is a promising approach to access *P*-chiral synthons featuring an acetylene group, by desymmetrization or kinetic resolution (Scheme 1c). The advantages of this method include: (1) easy access to di- and monoethynyl-phosphine oxides **1** and **4** (one-pot, 2–3 steps, see ESI†); and (2) the usefulness of the *P*-chiral phosphine oxides **3** and **4**. They may act as organocatalysts[5b,d] as well as precursors to various *P*-chiral phosphine derivatives. Notably, *P*-chiral phosphines bearing a triazole moiety are unknown, the properties of which are interesting to explore.

We began by attempting the desymmetrizing CuAAC of diyne **1a** and azide **2a** (Table 1). It is worth mentioning that the desymmetrization of diethynylphosphine oxides is unprecedented, although several desymmetrizing reactions of dialkynylphosphine oxides have been reported since the seminar work of Tanaka *et al.*[27] Prochiral diynes bearing terminal alkynes are very difficult substrates for the intermolecular desymmetric reactions, because their linear shape makes it difficult to achieve good enantioselectivity and to suppress side difunctionalization.[28] As expected, it was hard to achieve high enantioselectivity and **3a**/**3a′** ratio in this research. The reaction was first conducted in the condition we optimized for the desymmetric CuAAC of oxindole-diynes, by using catalyst PYBOX $\mathbf{L_1}$/CuCl and 2,5-hexanedione as the solvent.[23a] Unfortunately, product **3a** was obtained in only 8% ee, with a poor 2.0 : 1 ratio of **3a**/**3a′** (entry 1). Further screenings revealed that if running in MeCN, the reaction could give **3a** in 63% yield and 83% ee, with **3a**/**3a′** ratio up to 6.8 : 1 (entry 2).

To suppress the formation of the side bis-triazoles **3a′** while improving the enantioselectivity, we tried modifying $\mathbf{L_1}$ by a C4 shielding group to improve its chiral pocket, to prevent the interaction of the alkynyl group of monotriazole **3a** with the copper center. It was postulated that a C4 group may cooperate with the substituent at the chiral centers of the ligand, to enhance the enantiotopic group discrimination, and to prevent the ethynyl group of chiral monotriazoles **3** from interacting with the copper for a further CuAAC, leading to better mono-

Table 1 Condition optimization



Entry	L	Solvent	CuX	**3a**/**3a′**[a]	Yield of **3a**[b] (%)	ee of **3a**[c] (%)
1[d]	$\mathbf{L_1}$	Dione[e]	CuCl	2.0 : 1	33	8
2	$\mathbf{L_1}$	MeCN	CuCl	6.8 : 1	63	83
3	$\mathbf{L_2}$	MeCN	CuCl	5.1 : 1	51	84
4	$\mathbf{L_3}$	MeCN	CuCl	10.4 : 1	71	90
5	$\mathbf{L_4}$	MeCN	CuCl	6.4 : 1	60	84
6	$\mathbf{L_5}$	MeCN	CuCl	12.0 : 1	79	91
7	$\mathbf{L_6}$	MeCN	CuCl	13.9 : 1	80[f]	93
8	$\mathbf{L_7}$	MeCN	CuCl	11.4 : 1	77	91
9	$\mathbf{L_8}$	MeCN	CuCl	9.3 : 1	74	89
10	$\mathbf{L_6}$	MeCN	CuBr	13.9 : 1	80[f]	95

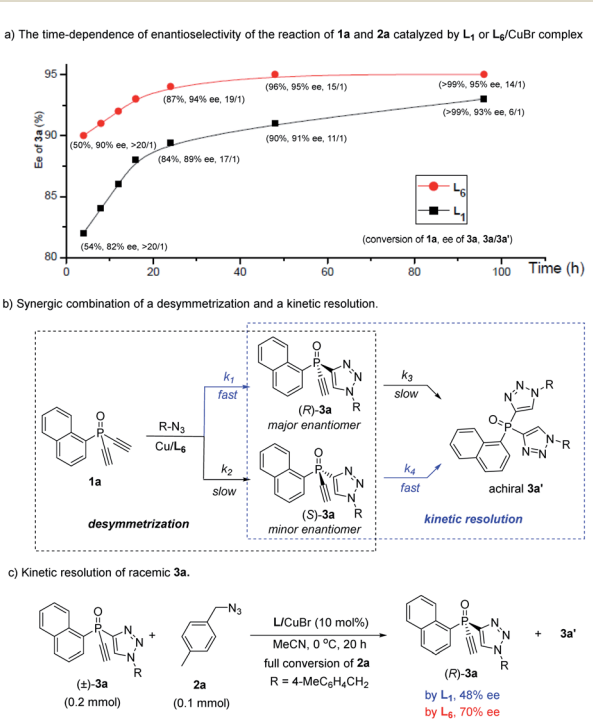
[a] Determined by ^{1}H NMR. [b] NMR yield by using 1,3,5-trimethoxybenzene as the internal standard. [c] Determined by chiral HPLC analysis. [d] Reaction at 0 °C, 36 h. [e] Dione = 2,5-hexanedione. [f] Yield of the isolated product **3a**.

and bis-triazoles (M/D) ratio. Several modified PYBOX $\mathbf{L_{2-8}}$ were accessed in three or four steps (see ESI†) and subjected to the model reaction. Gratifyingly, the presence of a suitable C4 shielding group could indeed bring about beneficial effects. While ligand $\mathbf{L_2}$ with a *tert*-butoxycarbonyl group failed to improve the **3a**/**3a**′ ratio (entry 3), ligand $\mathbf{L_3}$ (ref. 29) with a flexible OBn group raised the **3a**/**3a**′ ratio to over 10 : 1, giving **3a** in 90% ee (entry 4). This encouraged us to vary the benzyl group to other bulkier substituents. Ligand $\mathbf{L_4}$ with an electron-deficient phenyl group led to a poor result (entry 6), but $\mathbf{L_5}$ with an electron-rich substituent increased both the enantioselectivity and the **3a**/**3a**′ ratio (entry 6). Ligand $\mathbf{L_6}$ with a 1-naphthylmethoxy group further enhanced the **3a**/**3a**′ ratio to 13.9/1, giving **3a** in 80% yield and 93% ee (entry 7). The variation of the substituent at the chiral center of the ligand affected the result as well, as shown by the performance of ligands $\mathbf{L_{7,8}}$ (entry 8 *vs.* 4, 9 *vs.* 7). Further varying CuCl to CuBr increased the ee to 95%, with the **3a**/**3a**′ ratio unchanged (entry 10).

The high **3a**/**3a**′ ratio and ee value achieved by ligand $\mathbf{L_6}$ were very impressive. For a better understanding of the role of $\mathbf{L_6}$, we evaluated the time-dependent enantioselectivity of the reaction of **1a** and **2a**, because Uozumi *et al.* previously showed that the desymmetric CuAAC of diynes bearing prochiral biaryls was a synergic combination of a desymmetrization and a kinetic resolution.[30a] As shown in Scheme 2a, whether using $\mathbf{L_1}$ or $\mathbf{L_6}$ as the ligand, the enantioselectivity of **3a** gradually improved with increasing levels of conversion of the reaction, while the **3a**/**3a**′ ratio decreased. This suggests that the formation of the undesired achiral **3a**′ was beneficial for the ee value of **3a**. In the presence of the chiral catalyst, the consumption of the minor enantiomer (*S*)-**3a**, generated in the initial desymmetric CuAAC, was faster than that of the major enantiomer (*R*)-**3a** (Scheme 2b). Therefore, the reaction of **1a** and **2a** was also a synergic merger of a desymmetrization and a kinetic resolution,[30] where $k_1 > k_2$ and $k_4 > k_3$, representing a favorable scenario to obtain (*R*)-**3a** with high ee value.

Notably, our ligand $\mathbf{L_6}$ was superior to $\mathbf{L_1}$ in both the desymmetrization and the kinetic steps. Whereas similar conversion of **1a** was found with a time of 4 h, with **3a**/**3a**′ ratio over 20 : 1 in both cases, the use of $\mathbf{L_6}$ gave **3a** with a clearly higher ee than by using $\mathbf{L_1}$ (90 *vs.* 82%), suggesting that $\mathbf{L_6}$ could achieve better enantiotopic group discrimination. On the other hand, when $\mathbf{L_1}$ was used, the **3a**/**3a**′ ratio decreased to a greater extent as the reaction proceeded. This implied that the minor enantiomer of **3a** was consumed more in the kinetic resolution, and that the high ee value obtained using $\mathbf{L_1}$ was at the expense of the chemical yield of product **3a**. Furthermore, ligand $\mathbf{L_6}$ was also better than $\mathbf{L_1}$ in the kinetic resolution of racemic monotriazole **3a** (Scheme 2c), in terms of the ee of recovered (*R*)-**3a** (70% *vs.* 48%). This result also implied that our new PYBOX ligands might be promising to develop kinetic resolution shown in Scheme 1.

Now that we have a better understanding of the superiority of our newly developed PYBOX ligand $\mathbf{L_6}$ over the parental $\mathbf{L_1}$ in the desymmetric CuAAC reaction of **1a** and **2a**, we next evaluated the scope of this desymmetric CuAAC with respect to differently substituted dialkynylphosphine oxides **1** and azides **2** under the optimized condition (Table 2). All reactions were run in MeCN at −20 °C, using 10 mol% of the chiral catalyst and a **1**/**2** ratio of 1.0/1.0. The substituent of dialkynylphosphine oxides obviously influenced the reaction. Dialkynylphosphine oxides **1a–d** with 1-naphthyl or 2-substituted phenyl group worked well to afford the monotriazoles **3a–d** in good yield and excellent ee (entries 1–4). However, dialkynylphosphine oxides **1e–f**, with a 3-MeO or 3-bromophenyl group gave the corresponding products **3e–f** in lower M/D ratios (entries 5, 6). Oxide **1g** bearing a 4-*tert*-butylphenyl group afforded product **3g** in 90% ee and an M/D ratio of 10 : 1 (entry 7). Unfortunately, *tert*-butyl substituted oxide **1h** gave adduct **3h** in diminished 75% ee and an M/D ratio of 3 : 1 (entry 8). A variety of aliphatic azides **2b–h** all worked well to give adducts **3i–o** in good yield, excellent ee and a high M/D ratio (entries 9–15). The absolute configuration of product **3b** is assigned by X-ray analysis.



Scheme 2 Reaction profiles.

Kinetic resolution of monoethynylphosphine oxide

Since ligand $\mathbf{L_6}$ could achieve better result in the kinetic resolution of racemic monotriazole **3a** (Scheme 2c), we next tried the kinetic resolution of alkynylphosphine oxide **4a** using azide **2a** under the same condition. To our delight, the use of 0.5 equiv. of azide **2a** relative to **4a** allowed the reaction to work well, affording monotriazole **5a** in 44% yield and 85% ee, with (*S*)-**4a** recovered with 80% ee and 44% yield.

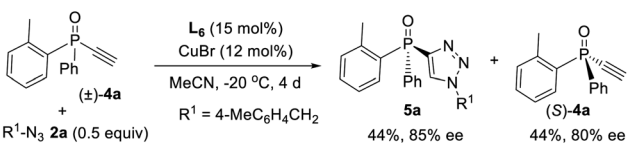
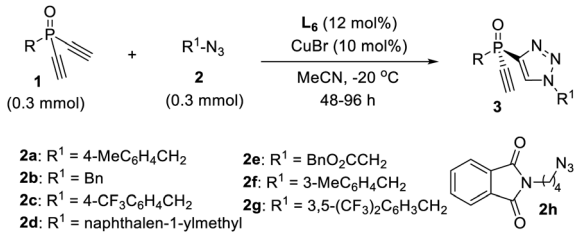


Table 2 Scope of asymmetric CuAAC of **1** and **2**



Entry	1	2	3	3/3′[a]	Yield of 3[b] (%)	ee of 3[c] (%)
1	**1a:** R = 1-naphthyl	**2a**	**3a**	14 : 1	80	95
2	**1b:** R = 2-MeC_6H_4	**2a**	**3b**	18 : 1	81	94
3	**1c:** R = 2-BrC_6H_4	**2a**	**3c**	11 : 1	77	95
4[d]	**1d:** R = 2-EtC_6H_4	**2a**	**3d**	12 : 1	72	92
5[e]	**1e:** R = 3-$MeOC_6H_4$	**2a**	**3e**	7 : 1	65	92
6[e]	**1f:** R = 3-BrC_6H_4	**2a**	**3f**	4 : 1	60	83
7[e]	**1g:** R = 4-*t*-BuC_6H_4	**2a**	**3g**	10 : 1	80	90
8	**1h:** R = *t*-Bu	**2a**	**3h**	3 : 1	51	75
9	**1b**	**2b**	**3i**	20 : 1	85	96
10	**1b**	**2c**	**3j**	20 : 1	83	95
11	**1b**	**2d**	**3k**	16 : 1	84	91
12	**1b**	**2e**	**3l**	14 : 1	77	90
13	**1b**	**2f**	**3m**	23 : 1	80	93
14	**1b**	**2g**	**3n**	13 : 1	72	91
15	**1b**	**2h**	**3o**	16 : 1	73	90

[a] Determined by ^{1}H NMR analysis. [b] Yield of the isolated products **3**. [c] Determined by chiral HPLC analysis. [d] **1** : **2** = 1.05 : 1. [e] **1** : **2** = 1 : 1.05.

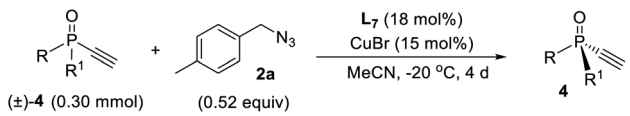
Further optimization provided a condition for the kinetic resolution of alkynylphosphine oxide **4**, by using $\mathbf{L_7}$ as the ligand and 0.52 equiv. of azide **2a** (Table 3). Accordingly, chiral *o*-methylphenyl-substituted phosphine oxides **4a–g** featuring an acetylene group were accessed in 85–99% ee values, regardless of whether the R^1 group was a substituted phenyl, 2-thienyl, cyclohexyl, or isopropyl (entries 1–7). On varying the 2-methylphenyl group to an 2-bromophenyl or a 1-naphthyl group, the corresponding alkynylphosphine oxides **4h** and **4i** were also resolved in 44–45% yields and 95–97% ee (entries 8, 9). The racemic ethynylphosphine oxides **3a**, **3b**, with a triazole group, could also be readily resolved to afford chiral **3a** and **3b** in good recovery and ee values (entries 10 and 11). With the acetylene group, these *P*-chiral phosphine oxides could undergo different diversifying reactions to enhance structural diversity. The bromophenyl group in adducts **4b**, **4d**, and **4h** also offered the promise for further modification. The absolute configuration of product **4a** was assigned by X-ray analysis.

On the other hand, a highly enantioselective CuAAC of ethynylphosphine oxide **4** to *P*-chiral phosphine oxides **5** featuring a 1,2,3-triazole moiety is also developed by slightly optimizing the condition (Table 4). By using ligand $\mathbf{L_8}$ and adjusting the ratio of azides **2** to alkynylphosphine oxide **4**, a range of different *P*-chiral *P*-substituents could be tolerated, including substituted phenyl, 2-thienyl, 1-napththyl, and aliphatic groups, to afford interesting *P*-chiral phosphine oxides bearing a 1,2,3-triazole moiety.

Remote desymmetrization

Achieving remote enantiofacial control is still challenging in asymmetric catalysis. If prostereogenic centers are located farther from the reaction sites, it is very difficult to develop a highly enantioselective remote desymmetrization reaction because of diminished chiral bias.[28,31] Most protocols are based

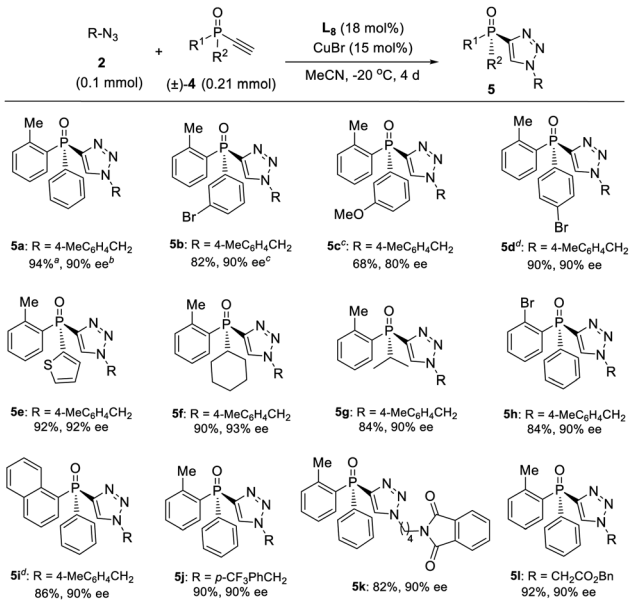
Table 3 Kinetic resolution of **4**



Entry	4 (R, R^1)	Recovery[a] (%)	ee[b] (%)	*s*[c] factor
1	**4a:** (2-MeC_6H_4, Ph)	42	96	21
2	**4b:** (2-MeC_6H_4, 3-BrC_6H_4)	47	91	29
3	**4c:** (2-MeC_6H_4, 3-$MeOC_6H_4$)	43	85	12
4	**4d:** (2-MeC_6H_4, 4-BrC_6H_4)	42	94	18
5	**4e:** (2-MeC_6H_4, 2-thienyl)	48	99	116
6	**4f:** (2-MeC_6H_4, cyclohexyl)	44	94	23
7	**4g:** (2-MeC_6H_4, isopropyl)	43	90	16
8	**4h:** (2-BrC_6H_4, Ph)	44	95	25
9	**4i:** (1-Naphthyl, Ph)	45	97	36
10[d]	**3a**	42	93	17
11[d]	**3b**	44	92	20

[a] The recovery of **4**. [b] Determined by chiral HPLC analysis. [c] $s = \ln[(1 - C)(1 - ee)]/\ln[(1 - C)(1 + ee)]$; C refers to the conversion of (±)-**4**, [1-(recovery of **4**)]. [d] 0.55 equiv. of **2a** was used at −10 °C for 4 d.

Table 4 Enantioselective CuAAC of **4** and **2**

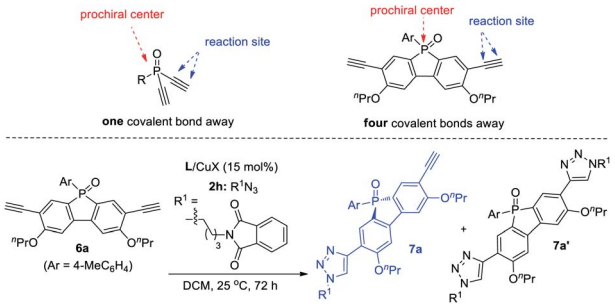


[a] Yield of the isolated products **5** based on the azide **2**. [b] Determined by chiral HPLC analysis. [c] 0.25 mmol (±)-**4**. [d] 0.23 mmol (±)-**4**.

on substrates with the prostereogenic center being separated from the functionality by up to three covalent bonds.[32] Remote intermolecular desymmetrization at a distance of four or more covalent bonds separation is rare.[33] Now that our PYBOX ligands $\mathbf{L_6}$ showed superiority over parental $\mathbf{L_1}$ in suppressing side reactions and improving enantioselectivity, we tried varying the size of the C4 shielding groups of these ligands to develop desymmetric CuAAC of phosphole oxide-diynes **6**, whose ethynyl group is four covalent bonds from phosphine.

It is worth mentioning that phosphole oxide-based π-conjugated systems[34] have drawn great attention because of their unique electronic properties, such as low-lying LUMO resulting from effective σ*–π* orbital interaction.[35] While the diverse synthesis of new phosphole oxide derivatives is of current interest, chiral analogues of this π-system are unknown. In light of this, the study of asymmetric CuAAC of phosphole oxide-diyne **6** not only acts as a testing ground to evaluate the performance of our ligands $\mathbf{L_5}$–$\mathbf{L_8}$ in remote enantiofacial control, but also affords chiral phosphole oxide derivatives of potential use. The desymmetrization of diyne **6a** indeed proved to be difficult. The best result obtained using ligand $\mathbf{L_1}$ is to use CH_2Cl_2 as the solvent, providing **7a** in 88% ee, albeit in 45% yield due to the poor ratio of **7a**/**7a**′ (entry 1, Table 5). Gratifyingly, our ligands $\mathbf{L_{5,6}}$ with a bulky shielding group afforded improved results. Ligand $\mathbf{L_5}$, with the bulkiest group, gave **7a** in 62% yield, 96% ee, and 4.6 : 1 ratio of **7a**/**7a**′ (entry 2), but ligand $\mathbf{L_6}$ gave **7a** in lower 93% ee and 3.5 : 1 of **7a**/**7a**′ (entry 3). This further suggested that by tuning the size of the C4 shielding group of PYBOX ligands, it is possible to develop highly enantioselective desymmetric CuAAC reactions of different prochiral systems. The subsequent optimization showed that $\mathbf{L_5}$/CuBr

Table 5 Enantioselective CuAAC of **6a**



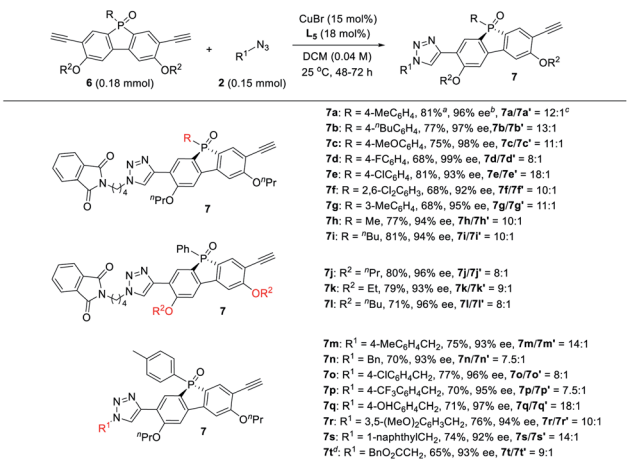
Entry	L	CuX	**6a**/**2h**	**7a**/**7a**′[a]	Yield of **7a**[b] (%)	ee of **7a**[c] (%)
1	$\mathbf{L_1}$	CuCl	1.0 : 1	1.9 : 1	45	88
2	$\mathbf{L_5}$	CuCl	1.0 : 1	4.6 : 1	62	96
3	$\mathbf{L_6}$	CuCl	1.0 : 1	3.5 : 1	57	93
4	$\mathbf{L_5}$	CuBr	1.0 : 1	6.6/1	66	98
5	$\mathbf{L_5}$	CuBr	1.2 : 1	12.0/1	81	98

[a] Determined by ^{1}H NMR analysis. [b] NMR yield using anisole as the internal standard. [c] Determined by chiral HPLC analysis.

could afford **7a** in 98% ee, with a **7a**/**7a**′ ratio up to 6.6 : 1 (entry 4). By further changing the ratio of **6a** and **2h** from 1.0 : 1 to 1.2 : 1, the **7a**/**7a**′ ratio jumped to 12 : 1 without the erosion of ee value (entry 5).

Next, the generality of the desymmetric CuAAC reaction of phosphole-diynes **6** was tested by performing the reaction in CH_2Cl_2 at 25 °C, using 18 mol% $\mathbf{L_5}$ and 15 mol% CuBr, as shown in Table 6. Both aryl and alkyl *P*-substituents could be tolerated, giving the desired products **7a–i** in good yield, with high 7/7′ ratio. Diynes with different ether groups all gave adducts **7j–l** with good results. Various azides also worked well to furnish monotriazoles **7m–t** in good yield and high 7/7′ ratio. Notably,

Table 6 CuAAC of phosphole oxide-diynes



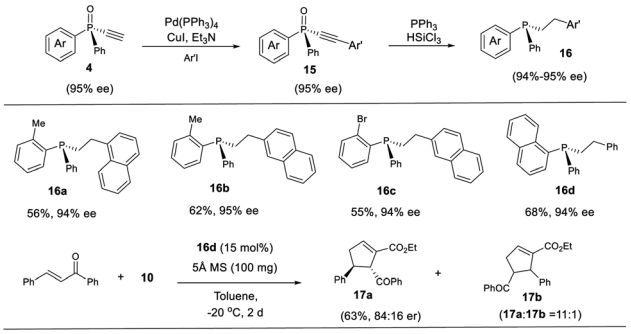
[a] Yield of the isolated products **7**. [b] Determined by chiral HPLC analysis. [c] Determined by the yield of the isolated products of 7/7′. [d] 20 mol% of CuBr and 24 mol% of $\mathbf{L_5}$.

chiral phospholes **7** were all obtained in >90% ee. The absolute configuration of product 7° was assigned by X-ray analysis. The remote desymmetrization of diynes with ethynyl group five covalent bonds away from *P*-prochiral central was also attempted, but the enantioselectivity was unsatisfactory.[36]

Product elaboration

The thus obtained *P*-chiral tertiary phosphine oxides featuring an ethynyl group are useful for the diverse synthesis of *P*-chiral phosphine derivatives. For example, a Gram-scale synthesis gave product **3a** in 95% ee with **3a**/**3a′** ratio of 11/1. A Sonogashira reaction followed by a reduction readily converted **3a** to tertiary phosphine **9** without erosion of ee value. Interestingly, phosphine **9** can react with alkenyl ester to give phosphine oxide **11** in 95% ee, with the triazole moiety being replaced. Similarly, tertiary phosphine **12** obtained from **5a** also underwent such a replacement reaction to furnish product **13** in 89% ee.[37] The structure of the major diastereomer of **14**, accessed from the reduction of **13**, was confirmed by X-ray analysis. Based on the absolute configuration of the phosphine of **14**, it turned out that in the replacement reaction, the configuration of tertiary phosphine **9** or **12** was reversed (Scheme 3).

The *P*-chiral monoethynylphosphine oxides **4** can be used to develop a new *P*-chiral organocatalysts. For instance, *via* a two-step transformation, *P*-chiral monophosphine **16** can be readily accessed from **4** with undiminished ee value. Initially, the capacity of these phosphines was evaluated in the [3 + 2] cycloaddition of chalcone and **10** that Fu developed by using an axially chiral monophosphine catalyst,[38] with up to 84 : 16 er for product **17a** being obtained. This suggests the potential of *P*-chiral monoethynylphosphine oxides **4** for developing *P*-chiral ligand or organocatalysts. Notably, with an methyl or bromo group on the ortho position of phenyl ring, the resulting chiral monophosphines could be readily modified to increase the structural diversity (Scheme 4).[3d]

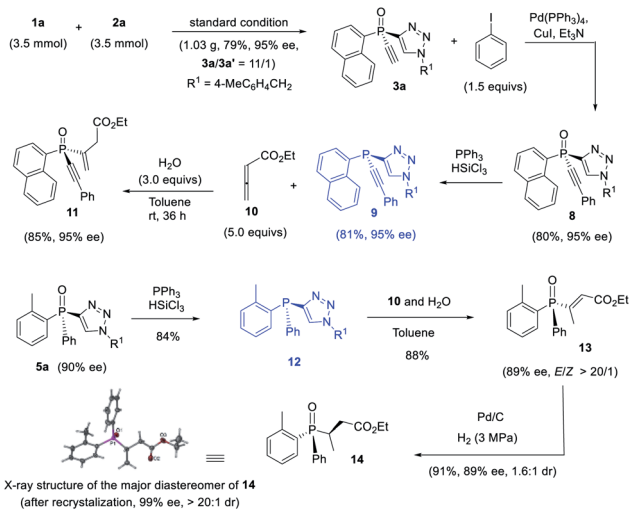


Scheme 4 The synthesis of *P*-chiral monophosphine **16** and their application.

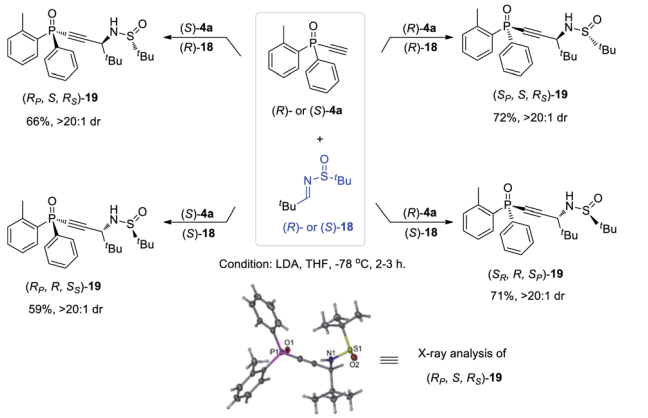
The versatility of monoethynylphosphine oxides **4** as a *P*-chiral phosphorus building block is further demonstrated by a diastereodivergent[39] Mannich reaction with chiral imines **18** derived from enantiopure *tert*-butylsulfinamide. Because both (*R*)- and (*S*)-**4a** can be readily obtained in excellent ee values *via* the above established kinetic resolution, it is convenient to take the alkyl–imine addition reaction[40] to modularly access four isomers of compounds **19** by using either (*R*)- or (*S*)-**18**. The resulting multifunctional *P*-chiral phosphine oxide **19** contains three different chiral centers, one carbon and two heteroatom chiralities, which is an attractive framework to develop new chiral ligands and organocatalysts (Scheme 5).[41]

Furthermore, *P*-chiral monoethynylphosphine oxides **4** can undergo sequential Glaser coupling and reduction to give 4-bis((*R*)-dialkynylphosphine)butane **20**, which could form a digold Au(I) complex, the structure of which was confirmed by X-ray analysis (Scheme 6).

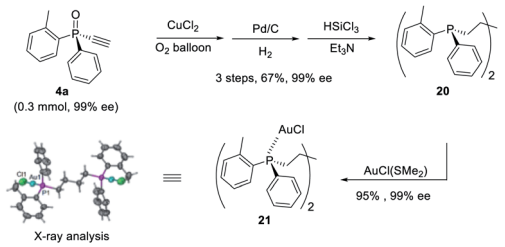
The optically active phosphole oxides **7** are also intriguing targets for optoelectronic studies. The extension of the π-plane of phosphole oxides is known to be beneficial for π–π stacking and electron-spin delocalization, and may tune the electron affinity of the π-systems. The presence of a triazole moiety should result in an extended π-plane to bring about some beneficial effects. In addition, compounds **7** may be further



Scheme 3 The elaboration of *P*-chiral phosphine oxides **3a** and **5a** with a triazole substituent.



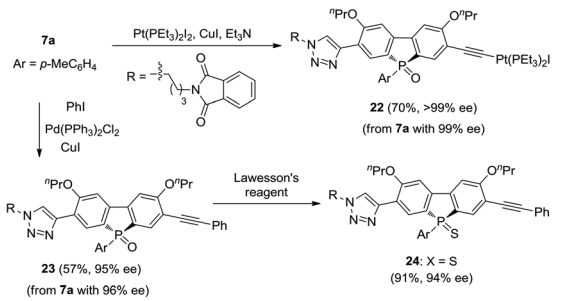
Scheme 5 Diastereodivergent synthesis of *P*-chiral tertiary phosphine oxides sulfinamide **19**.



Scheme 6 The synthesis of digold Au(I) complex **21**.

elaborated by manipulating the acetylene group. For example, an unprecedented phosphole oxide-based chiral platinum(II) acetylide **22** was readily accessed from enantiopure **7a**, which might be interesting for the studies in the areas of organometallic gels, solar cells and luminescent materials, in view of the importance of Pt–acetylide as functional units.[42] Starting from **7a**, a Sonogashira coupling gave an extended π-system **23** in 57% yield, without the erosion of ee value. Chiral *P*-sulfide **24** was obtained from **23** upon treating with Lawesson's reagent. We initially checked the optical properties of compounds **6a**, **7a**, **23** and **24**, with absorption and emission data shown below. As compared with **6a**, the UV/vis absorption and emission band maxima of compound **7a** are slightly red-shifted, but that of product **23** with extended π-system is obviously red-shifted. In addition, the quantum yield (QY) of **7a** was significantly higher than that of **6a** (0.40 *vs.* 0.14) and the chiral *P*-sulfide **24** showed lower QY than that of **23**. These results showed that the properties of chiral phosphole 7 could be readily tuned for optoelectronic applications (Scheme 7).

We also examined the CD spectra of **7a**, and found (*R*)-**7a** showed an obvious positive first (λ = 270 nm) and negative second (λ = 235 nm) Cotton effect peak (Fig. 1). (*S*)-**7a** showed mirror image with (*R*)-**3a** in the 230–300 nm region. In the region of 300–400 nm, (*R*)/(*S*)-**7a** also showed symmetry CD spectrum,



Compound	Absorption λ_{abs} [nm][a]	Fluorescence λ_{max} (nm)	Φ_F[b]
6a	267, 276, 350, 365	400	0.14
7a	270, 280, 352, 367	405	0.40
23	280, 290, 365, 382	421	0.33
24	282, 298, 367, 385	420	0.09

[a]At a concentration of 2.0 × 10^{-5} M in CH_2Cl_2. [b]Excited at λ = 350 nm, measured relative to quinine sulfate.

Scheme 7 The Synthesis of **22**–**24** and their photophysical properties.

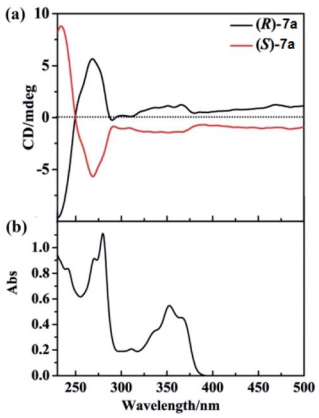


Fig. 1 (a) CD spectra of (*R*)-**7a** (black line) and (*S*)-**7a** (red line) at 2 × 10^{-5} M (10 mm path length) in CH_2Cl_2 at 25 °C. (b) UV-vis spectra of (*R*)-**7a** in CH_2Cl_2 at 25 °C.

however, no Cotton effect peak were observed. The highest optical anisotropy factor was observed at 235 nm (gabs = 3 × 10^{-4}) for both (*R*)-**7a** and (*S*)-**7a**, this value was in the region of most chiral organic molecule (from 10^{-5} to 10^{-2}). Based on these data, we tried to measure the circularly polarized luminescence (CPL) of (*R*)/(*S*)-**7a** with CPL-200. Unfortunately, due to the low chiral optical activity of these compound and measurement limit (glum ~ 10^{-4}), we failed to collect high quality CPL spectrum.

Conclusions

In conclusion, we have developed highly enantioselective CuAAC reactions for the synthesis of *P*-chiral phosphorus synthons featuring a versatile ethynyl group, which can undergo various diversifying reactions to access structurally diverse *P*-chiral phosphine derivatives. Importantly, newly developed PYBOX-type ligands featuring a C4 bulky shielding group offer a flexible solution for the development of enantioselective CuAAC: by varying the C4 shielding group,[43] the desymmetrization of diethynylphosphine oxides **1**, the kinetic resolution of monoethynylphosphine oxides **4**, and the remote desymmetrization of phosphole-diynes 7 is developed, affording the corresponding *P*-chiral phosphine derivatives in excellent enantioselectivity. The exploitation of new PYBOX ligands bearing various types of C4 shielding groups to develop asymmetric CuAAC reactions for the synthesis of optically active alkynes or azides, as well as the application of the resulting *P*-chiral synthons for the development of new ligands and catalysts is ongoing in our laboratory.

Conflicts of interest

There are no conflicts to declare.

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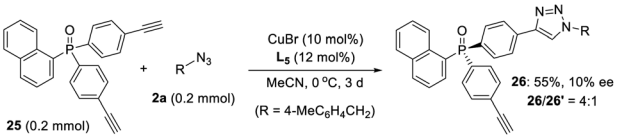

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43 We provided a tentative model to explain the role of the C4 shielding group of PYBOX ligands, as well as the observed enantiofacial control of the desymmetrization of diynes **1** based on the absolute configuration of products **3**. Please see page S75 and S76 of the ESI.†