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P-Stereogenic Phosphines Directed Copper(I)-Catalyzed Enantioselective 1,3-Dipolar Cycloadditions

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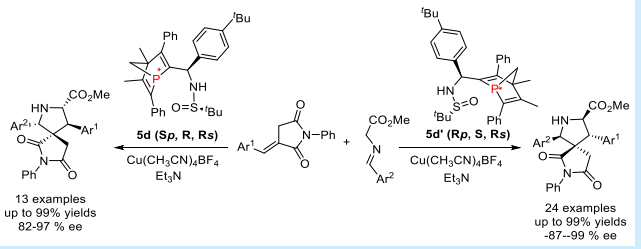
Supporting Information

ABSTRACT: A new pair of *P*-stereogenic ligands with multiple chiral centers were synthesized and used in the copper(I)-catalyzed enatioselective [3 + 2] cycloaddition of iminoesters with alkenes. A variety of highly functionalized pyrrolidines were obtained in excellent yield and enatioselectivity. This is the first example of a pair of *P*-stereogenic ligands working as pseudoenantiomers to tune the enantio- and diastereoselective 1,3-dipolar cycloaddition, and providing a pair of enantiomerically pure pyrrolidines, respectively.



Optically active compounds are of great importance with applications in the synthesis of natural products, pharmaceuticals, agrochemicals, and functional materials.[1] The stereochemical configurations of organic compounds usually have tremendous effects on their biological and pharmacological activities,[2] but the development of the efficient method for the stereoselective construction of optically active compounds remains as an unmet synthetic challenge. Transition-metal catalyzed reaction is a powerful tool.[3] The steric and electronic properties of metal catalysis can be dramatically tuned by the ligands.[4] Consequently, a large number of chiral ligands with diverse structures have been developed over the past decades.[5] However, selecting the correct pair of enantiomeric catalysts for the enantioselective synthesis of chiral molecules with multiple stereogenic centers in one step is more challenging.[6] Since, in most case, only one of the stereoisomers can provide high stereoselectivity.[7] Thus, selective construction of chiral molecules bearing multiple stereocenters with full control of the absolute and relative configuration is still an elusive goal.

P-Stereogenic ligands play a very important role in early studies of homogeneous asymmetric catalysis.[8] For example, Knowles reported an unbound *P*-stereogenic ligand and successfully applied their catalytic system (DIPAMP-Rh(I) complex) to the industrial synthesis of L-DOPA (Figure 1 (1)).[9] In 2002, Zhang's group reported a partial-bounded *P*-stereogenic ligand, which showed high enantioselectivity and activity in the Rh-catalyzed asymmetric hydrogenation of various dehydroamino acids (Figure 1 (2)).[10] These early syntheses and catalytic explorations of *P*-stereogenic ligands have paved the way for the application of *P*-stereogenic phosphines as chiral ligands in asymmetric synthesis.[11]

Unfortunately, the previous results of *P*-stereogenic phosphine-promoted metal-catalyzed asymmetric reactions only focused on asymmetric hydrogenation and other reactions were not explored so far. However, the instability of the *P*(III)-

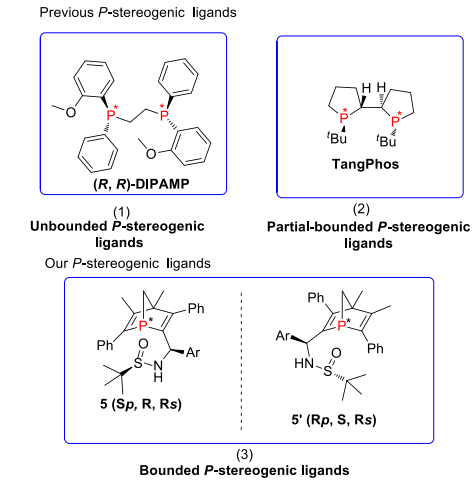


Figure 1. Different *P*-stereogenic ligands.

stereogenic center, the complicated synthesis process and the expansive purification procedure may hinder their practical applications. The development of a simple procedure for preparations of novel *P*-stereogenic ligands is highly demanded.

Based on our recent work with 1-phosphanorbornadienes,[12] novel bounded *P*-stereogenic ligands (**S***p*, **R**, **R***s* and **R***p*, **S**, **R***s*) were developed from 1-phosphanorbornadiene derivatives (Figure 1 (3)).[13] The synthesis of optically pure *P*-stereogenic ligands started with the phosphole (**1**) as shown in Scheme 1. First, 1-phosphanorbornadiene (**2**) was obtained easily through the [1, 5] shifts and Diels−Alder reaction of 2H-phosphole with an alkyne. Then the cheap (*R*)-2-methyl-

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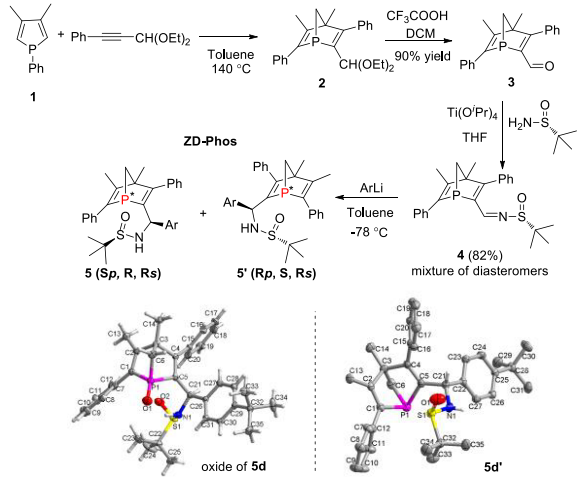
Scheme 1. Stereoselective Preparation of a Novel Class of *P*-Stereogenic Ligands with Multiple Stereogenic Centers

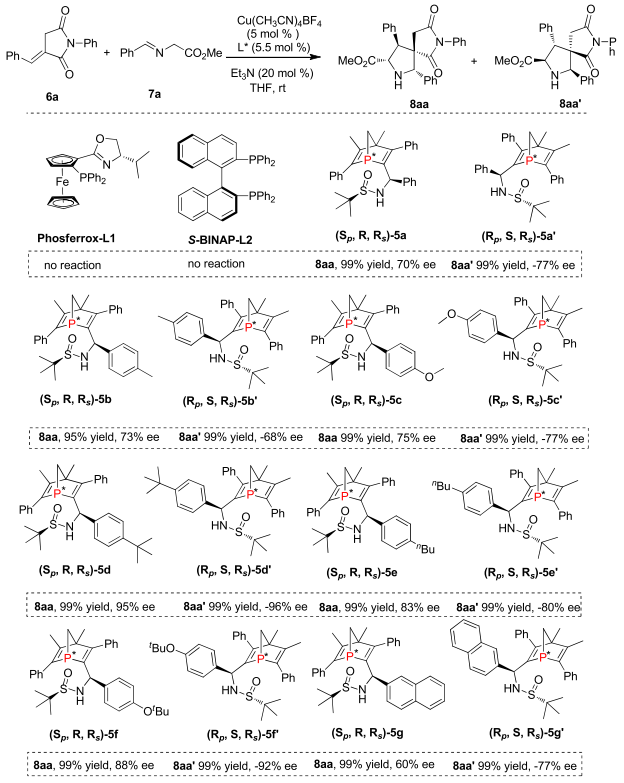


propane-2-sulfinamide motif ($ 0.68/g, J&K Scientific) was introduced to give imine (**4**). Next, the addition of lithium reagent[14,15] to N-*tert*-butanesulfinyl imine **4** resulted in the formation of a new carbon stereogenic center adjacent to the 1-phosphanorbornadiene skeleton. A pair of air-stable diastereomers (**5**, **5′**) could be obtained easily by flash column chromatography with good yield, which were called as ZD-Phos. The absolute configurations of ZD-Phos ligands were established by single crystal X-ray diffraction analysis of **5d′** and the oxide of **5d**.

In 2015, Deng and co-workers reported the copper-catalyzed asymmetric 1,3-dipolar cycloaddition of azomethine ylides with the CO_2Me-appended α-alkylidene succinimide by N, O ligands.[16] The synthetic importance of enantioselective and diastereoselective 1,3-dipolar cycloaddition with the assembly of diverse pyrrolidines[17] from relatively cheap and easily accessible phenyl-appended α-alkylidene succinimides[18] and azomethine ylides was considered. The screening was initiated by the examination of a series of commercially available **Phosferrox-L1** and *S*-**BINAP-L2**. Unfortunately, no desired adduct was obtained. To our delight, when the Cu-$(CH_3CN)_4BF_4$/(**S***p*, **R**, **R***s*)-**5a** complex was used as the catalyst, and NEt_3 as the base, at −50 °C, the desired product was obtained in 99% yield and −65% ee (SI, Table S1, entry 1). After screening catalysts, bases, solvents, and temperature, we found that the use of the Cu$(CH_3CN)_4BF_4$/(**S***p*, **R**, **R***s*)-**5a** complex as the catalyst, NEt_3 as the base, in THF, at room temperature (SI, Table S1) was optimal to generate the desired product (Table S1, entry 17). Next, we investigated the catalytic performance of these two sets of diastereoisomeric *P*-stereogenic ligands (**5**, **5′**) in this reaction. It was found that these diastereomeric ligands showed high catalytic activity (95−99% yields) and diastereoselectivity (>20:1 dr), but with reverse stereoselectivity (Scheme 2). The optimized conditions for further research were Cu$(CH_3CN)_4BF_4$ (5 mol %) and **5d** or **5d′** (5.5 mol %) in THF at room temperature (**5d**, 95% ee; **5d′**, −96% ee). The structure and stereochemistry of **8** were characterized by a combination of NMR, HPLC, HRMS spectra, and single crystal X-ray analysis (**8aa**, **8aa′**) (see Supporting Information).

With this established reaction system in hand, we examined the substrate scope with respect to azomethine ylides and α-alkylidene succinimides. As shown in Table 1, with ligand **5d′**,

Scheme 2. Optimization of Various Chiral *P*-Ligands for the Copper-Catalyzed Cycloaddition[a]



[a]Reactions were performed with **6a** (0.1 mmol), **7a** (0.2 mmol) in THF (2.0 mL). Reaction time: 20 h. [b]Isolated yield. [c]Ee was determined by HPLC analysis.

excellent yields and ee values were obtained in most cases. α-Alkylidene succinimides bearing either electron-donating or electron-withdrawing groups such as MeO (entry 5), F (entries 7−9), Cl (entries 10, 11), Br (entries 12, 13), NO_2 (entry 16), and CN (entry 17) reacted smoothly with **7** to furnish the corresponding products **8′** with up to >20:1 diastereoselectivity in 94%−99% yields and excellent enantioselectivity (−87 to −99% ee). α-Alkylidene succinimides with 2-naphthyl, 3-thienyl, and 2-furyl substituents also worked well with this reaction (Table 1, entries 18−20). Various azomethine ylides were used, and good results were obtained (93−99% yield, −95 to −99% ee, Table 1, entries 21−24).

Next, we tested the catalytic property of the combination of copper(I) and **5d**. The results are summarized in Table 2. The reactions were applicable to a wide range of α-alkylidene succinimides bearing different aromatic groups, regardless of the steric and electronic properties (Table 2, entries 1−9). Various arene pyrrolidines were obtained in 99% yield and 93−97% ee (Table 2, entries 10−11). Finally, the scope of azomethine ylides was also examined. The reaction proceeded smoothly, and excellent yields with high ee (91−93% ee) were obtained (Table 2, entries 12−13). It should be noted that only one isomer was obtained in all reactions.

It is noteworthy that the reaction could be performed on gram scale, and **8aa′** was obtained in 94% yield (1.65 g) with excellent diastereo- and enantioselectivity (>20:1 d.r., 94% ee). Gratifyingly, the enantiopure **8aa′** (>98% ee) could be easily obtained by simple recrystallization from isopropyl alcohol. To demonstrate the synthetic utility, further methylation, reduc-

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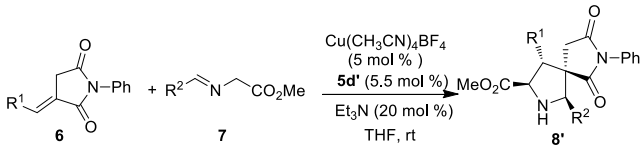
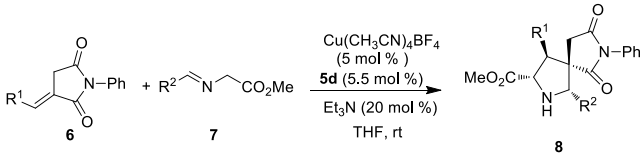
Table 1. [3 + 2] Annulations Catalyzed by Copper/5d′[a]



entry	R^1	R^2	yield (%)[b]	ee (%)[c]
1	Ph	Ph	(**8aa′**) 99	−96
2	2-MeC_6H_4	Ph	(**8ba′**) 95	−99
3	3-MeC_6H_4	Ph	(**8ca′**) 99	−91
4	4-MeC_6H_4	Ph	(**8da′**) 95	−91
5	4-MeO-C_6H_4	Ph	(**8ea′**) 99	−93
6	4-^{t}BuC_6H_4	Ph	(**8fa′**) 99	−94
7	2-FC_6H_4	Ph	(**8ga′**) 99	−88
8	3-FC_6H_4	Ph	(**8ha′**) 99	−97
9	4-FC_6H_4	Ph	(**8ia′**) 99	−88
10	2-ClC_6H_4	Ph	(**8ja′**) 99	−90
11	3-ClC_6H_4	Ph	(**8ka′**) 99	−91
12	2-BrC_6H_4	Ph	(**8la′**) 94	−97
13	3-Br-C_6H_4	Ph	(**8ma′**) 99	−99
14	2-Cl-6-FC_6H_3	Ph	(**8na′**) 99	−90
15	2-Br-4-FC_6H_3	Ph	(**8oa′**) 99	−97
16	2-$NO_2C_6H_4$	Ph	(**8pa′**) 97	−92
17	4-NCC_6H_4	Ph	(**8qa′**) 99	−87
18	2-naphthyl	Ph	(**8sa′**) 99	−90
19	3-thienyl	Ph	(**8ta′**) 99	−94
20	2-furyl	Ph	(**8ua′**) 96	−87
21	Ph	3,4-$(OMe)_2C_6H_3$	(**8ab′**) 93	−95
22	Ph	3-FC_6H_4	(**8ac′**) 95	−97
23	Ph	2-Br-5-FC_6H_3	(**8ad′**) 99	−99
24	Ph	4-$CF_3C_6H_4$	(**8ae′**) 99	−95

[a]Reactions were performed with **6** (0.1 mmol), **7** (0.2 mmol) in THF (2.0 mL), reaction time: 20h. [b]Isolated yield. [c]Determined by HPLC analysis.

Table 2. [3 + 2] Annulations Catalyzed by Copper/5d[a]

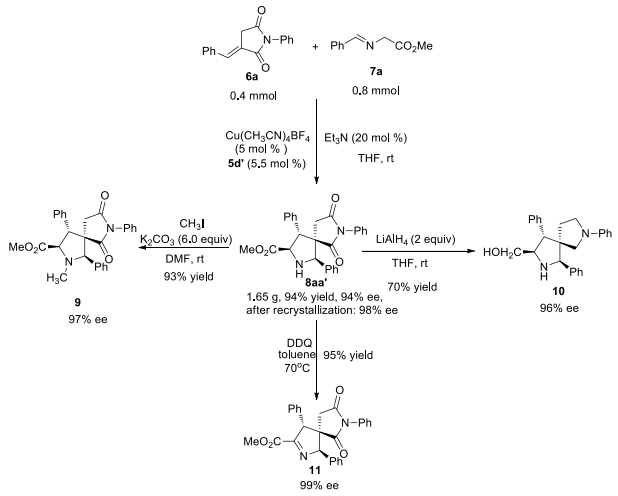


entry	R^1	R^2	yield (%)[b]	ee (%)[c]
1	Ph	Ph	(**8aa**) 99	95
2	2-MeC_6H_4	Ph	(**8ba**) 96	96
3	3-MeC_6H_4	Ph	(**8ca**) 94	95
4	2-FC_6H_4	Ph	(**8ga**) 99	82
5	4-FC_6H_4	Ph	(**8ia**) 99	96
6	2-ClC_6H_4	Ph	(**8ja**) 99	91
7	3-BrC_6H_4	Ph	(**8ma**) 90	93
8	2-Cl-6-FC_6H_3	Ph	(**8na**) 91	93
9	4-CNC_6H_4	Ph	(**8qa**) 99	97
10	styryl	Ph	(**8ra**) 99	97
11	2-naphthyl	Ph	(**8sa**) 99	93
12	Ph	3-FC_6H_4	(**8ac**) 99	93
13	Ph	2-Br-5-FC_6H_3	(**8ad**) 99	91

[a]Reactions were performed with **6** (0.1 mmol), **7** (0.2 mmol) in THF (2.0 mL). Reaction time: 20 h. [b]Isolated yield. [c]Determined by HPLC analysis.

tion, and oxidation of **8aa′** provided *N*-methyl extro-pyrrolidine **9**, diazaspiro[4.4]nonane **10**, and 2-pyrroline **11**, respectively (Scheme 3). The absolute configuration of **10** was established by single-crystal X-ray diffraction analysis.

Scheme 3. Gram Experiment and Application of 8aa′



In summary, we developed a novel and practical method for the synthesis of air-stable *P*-stereogenic ligands with three chiral centers. These pair of ligands can be synthesized and separated easily, even at gram scale. With these new chiral 1-phosphanorbornadienes, highly stereoselective construction of pyrrolidines with opposite stereoselectivities was developed by the copper(I)-catalyzed enantiodivergent and diastereoselective 1,3-dipolar cycloaddition. Extensions of these *P*-stereogenic ligands with other chiral compounds are in progress in our group.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00734.

Experimental procedures, X-ray diffraction data for **oxide of 5d** (CCDC 1834641), **5d′** (CCDC 1900533), **8aa** (1900534), **8aa′** (1872449), **10** (1872448) and spectroscopic data for all new compounds including ^{1}H, ^{31}P, and ^{13}C NMR spectra (PDF)

Accession Codes

CCDC 1834641, 1872448−1872449, and 1900533−1900534 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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