Ligand Design

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P,S Ligands for the Asymmetric Construction of Quaternary Stereocenters in Palladium-Catalyzed Decarboxylative [4+2] Cycloadditions

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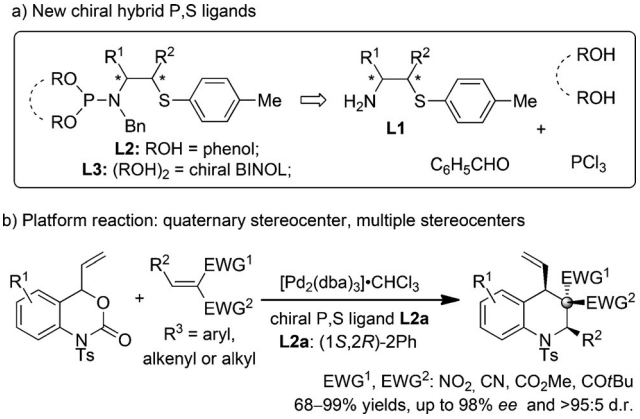
Abstract: *A new hybrid P,S ligand was exploited by combining a chiral β-amino sulfide and a simple diphenyl phosphite. The resultant ligand performs extremely well in a palladium-catalyzed asymmetric decarboxylative [4+2] cycloaddition reaction, thus generating multiple contiguous stereocenters and a chiral quaternary center. By doing so, a straightforward route to highly functionalized tetrahydroquinolines was developed with yields of up to 99%, as well as 98% ee and greater than 95:5 d.r. Moreover, mechanistic insights into this transformation and the possible stereocontrol are discussed.*

Asymmetric catalysis using organometallic complexes is an important and widely applied tool for the production of chiral fine chemicals.[1,2] The invention of robust chiral ligands, which assist in the stereocontrol and substrate activation for the central metal, has promoted the development of asymmetric metal catalysis.[3] There has been great success in recent decades regarding the use of ligands containing phosphorus,[4] nitrogen,[5] and oxygen[6] as donor atoms. Comparatively, only limited success was achieved in the development of chiral sulfide-containing ligands having good stereoinducing capacities.[7,8] In this study, we designed a new chiral hybrid P,S ligand by combining chiral sulfides and phosphoramidites. Introduction of additional trivalent P units to the chiral sulfide-containing ligands would favor the following: 1) the bidentate state could make up for the deficiency of donor and acceptor characteristics of the sulfur atom, and 2) it could also improve the chiral environment of sulfide–metal complexes.

The chiral hybrid P,S ligands **L2** and **L3** were prepared from easily available starting materials, the chiral β-amino sulfide **L1**,[9] benzaldehyde, phosphorus trichloride, and either phenol or chiral BINOL, respectively, by reductive amination and condensation (Scheme 1a).[10] The utility of these ligands was examined for the palladium-catalyzed asymmetric decarboxylative [4+2] cycloaddition (ADC) reaction[11,12] between vinyl benzoxazinanones and activated alkenes (Scheme 1b). This reaction is useful but challenging, and can, in one step, create three contiguous stereocenters and a chiral quaternary center.[13] In 2008, Tunge and co-workers[12a] developed a palladium-catalyzed ADC reaction of vinyl benzoxazinanones with benzylidene malononitriles, thus producing tetrahydroquinolines with two chiral centers in good yields and enantioselectivities. They failed, however, to expand the success of the Pd/Trost ligand catalyst system to other activated alkenes having two different electron-withdrawing groups.[14] Herein, we report that the chiral hybrid P,S ligand **L2a** is the best choice for this transformation because of its simple structure and excellent stereocontrol. Therefore, a straightforward route to highly functionalized tetrahydroquinolines[15,16] was developed, thus resulting in up to 99% yield, 98% *ee*, and greater than 95:5 d.r. under mild reaction conditions.



Scheme 1. Design and application of chiral hybrid P,S ligands based on β-amino sulfides. BINOL = 1,1′-bi-2-naphthol, dba = dibenzylideneacetone, EWG = electron-withdrawing group, Ts = 4-toluenesulfonyl.

In our preliminary work, the feasibility of known privileged chiral phosphoramidites[17] (**L3a–d**) together with a palladium(0) precursor were first tested for the palladium-catalyzed ADC reaction using the vinyl benzoxazinanone **1a** and nitroacrylate **2a** at room temperature in dichloromethane (DCM; Table 1). Satisfying results with both good reaction efficiency and selectivity were not achieved. For example, the reaction using Feringa's ligand **L3a**[18a] produced the desired chiral tetrahydroquinoline derivative **3aa** in high enantio- and diastereoselectivity. However, only a modest yield was obtained after 8 hours. You's ligand **L3b**[18b] also worked and resulted in 22% yield, −17% *ee*, and greater than 95:5 d.r. Furthermore, we found that no reaction occurred in the presence of chiral **L3c**[18c] and **L3d**.[18b] Then, our new chiral P,S ligands, **L3e** and **L3f**, were evaluated for the model reaction of **1a** and **2a** under the same reaction conditions.[19]

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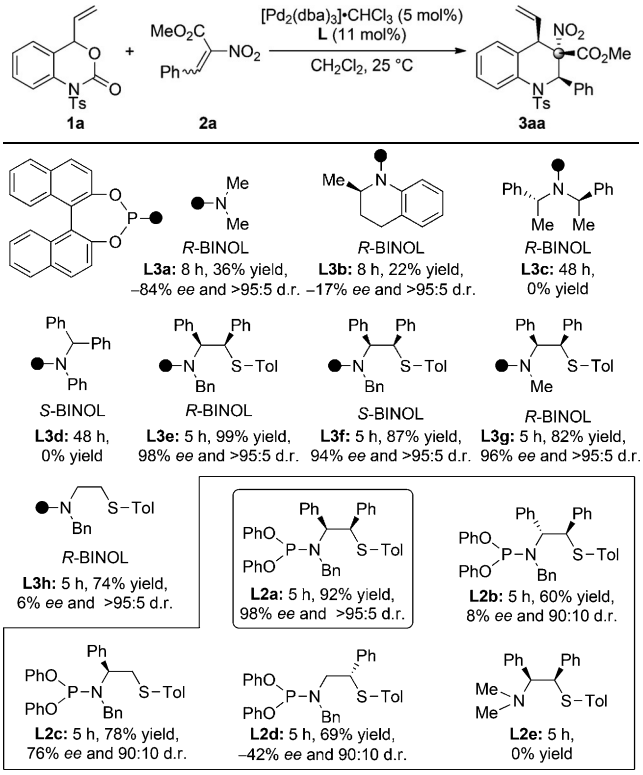
Table 1: Evaluation of chiral ligands.[a]

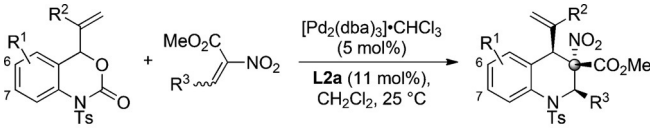


[a] Reaction conditions: 0.20 mmol of **1a** (1.0 equiv), 0.60 mmol of **2a** (3.0 equiv), $[Pd_2(dba)_3]\cdot CHCl_3$ (5 mol%), chiral ligand (11 mol%), 3.0 mL of CH_2Cl_2 and RT. Yield is that of the isolated product. The d.r. and *ee* values were determined by ^1H NMR analysis of the crude reaction mixture and by HPLC analysis, using a chiral stationary phase, of the purified **3aa**.

We were gratified that, this reaction achieved full conversion within 5 hours at room temperature and produced **3aa** in high yield and stereocontrol. Surprisingly, the chirality of the BINOL backbone (**L3e** versus **L3f**) and the benzyl or methyl substituents (**L3e** and **L3g**) on the nitrogen atom had no effect on the enantioselectivity. These results indicate that the structure of the hybrid P,S ligands can be further simplified. Therefore, the chiral ligand **L3h**, which lacks diphenyl groups, was tested for the model reaction. However, it gave **3aa** in good yield and high diastereoselectivity, but essentially in racemic form. The hybrid P,S ligands wherein the chiral BINOL is replaced by two phenoxy groups still maintained the reaction efficiency and selectivity at the same level (**L2a**: 92% yield, 98% *ee*, and > 95:5 d.r.). Thus, the β-amino sulfide backbone may play a vital role in the stereoinduction process. To verify this idea, ligands wherein one of the phenyl groups was removed from the backbone were synthesized and tested for the reaction. Indeed, moderate enantioselectivity (**L2c**: 78% yield, 76% *ee* and 90:10 d.r.; **L2d**: 69% yield, −42% *ee* and 90:10 d.r.) was observed for the model reaction. In addition, the relative conformation of the phenyl groups also affected the stereocontrol of this palladium-catalyzed ADC reaction. The model reaction using the *anti*-configured ligand **L2b** produced the desired product in very low enantioselectivity (60% yield, 8% *ee*, and 90:10 d.r.). In addition, the phosphoramidite unit was shown to be essential for the catalytic activity, as no reaction occurred when the chiral β-dimethylamino sulfide ligand **L2e** was used for this transformation. Therefore, **L2a**, which combines nonchiral diphenyl phosphite components and chiral β-amino sulfide components, was identified as an appropriate choice for this palladium-catalyzed DCA reaction.[10]

After establishing the optimal reaction conditions, we sought to evaluate the scope of the vinyl benzoxazinanone component in this palladium-catalyzed ADC reaction. As shown in Table 2, a wide range of vinyl benzoxazinanones

Table 2: Substrate scope.[a]



Entry[a]	**1**: R^1, R^2; **2**: R^3	**3**	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	**1a:** H, H; **2a:** Ph	**3aa**	92	> 95:5	98
2	**1b:** 6-Me, H; **2a:** Ph	**3ba**	70	> 95:5	98
3	**1c:** 6-MeO, H; **2a:** Ph	**3ca**	96	> 95:5	98
4	**1d:** 7-Cl, H; **2a:** Ph	**3da**	79	> 95:5	98
5	**1e:** 7-CF_3, H; **2a:** Ph	**3ea**	89	> 95:5	98
6	**1f:** 8-F, H; **2e:** 3-$MeOC_6H_4$	**3fe**	97	> 95:5	98
7	**1g:** H, Me; **2a:** Ph	**3ga**	68	> 95:5	81
8	**1a:** H, H; **2b:** 4-MeC_6H_4	**3ab**	90	> 95:5	97
9	**1a:** H, H; **2c:** 2-MeC_6H_4	**3ac**	72	> 95:5	96
10	**1a:** H, H; **2d:** 3,4-$OCH_2OC_6H_4$	**3ad**	99	> 95:5	98
11	**1a:** H, H; **2e:** 3-$MeOC_6H_4$	**3ae**	99	> 95:5	98
12	**1a:** H, H; **2f:** 2-naphthyl	**3af**	99	> 95:5	98
13	**1a:** H, H; **2g:** 4-FC_6H_4	**3ag**	92	> 95:5	97
14	**1a:** H, H; **2h:** 3-ClC_6H_4	**3ah**	99	> 95:5	98
15	**1a:** H, H; **2i:** 4-BrC_6H_4	**3ai**	72	> 95:5	96
16	**1a:** H, H; **2j:** 3-thienyl	**3aj**	97	> 95:5	98
17	**1a:** H, H; **2k:** cinnamenyl	**3ak**	99	62:38	92/96
18	**1a:** H, H; **2l:** cyclohexyl	**3al**	77	75:25	96/81

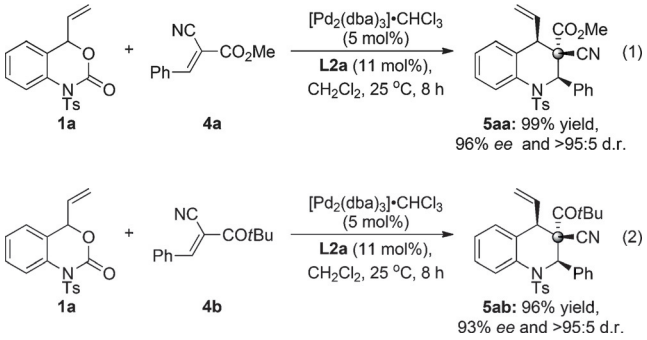
[a] Reaction conditions: 0.20 mmol of **1** (1.0 equiv), 0.60 mmol of **2** (3.0 equiv), $[Pd_2(dba)_3]\cdot CHCl_3$ (5 mol%), chiral ligand **L2a** (11 mol%), 3.0 mL of CH_2Cl_2 and RT. [b] Yield of isolated product. [c] Determined by ^1H NMR analysis of the crude reaction mixture. [d] Determined by HPLC analysis of the purified product using a chiral stationary phase.

with a variety of substituents on the benzene ring reacted well using **L2a**. The position (*para*, *meta*, *ortho*) and the electronic nature (electron-rich groups: MeO, Me; electron-deficient groups: CF_3, F, Cl) of the substituents did not affect either the enantio- and diastereoselectivity of the products (entries 1–6), albeit with yields ranging from 70 to 97%. The methallyl benzoxazinanone **1g** was compatible with this reaction, and the corresponding tetrahydroquinoline **3ga** was produced in satisfactory yield and stereoselectivity (entry 7). The ADC reactions of this type of substrate remain a challenge, because the *anti* conformation of the π–Pd–allyl complexe is favored over the *syn* conformation and homocyclization products are always formed.[14] A single crystal of **3ba** was obtained, and thus, the absolute configuration of these products was clearly

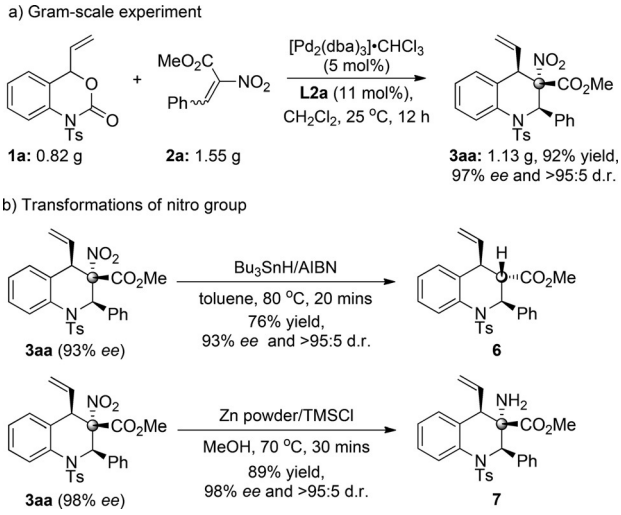
established to be such that the nitro group is in an *anti* conformation relative to the vinyl group.[20]

Next, we examined the versatility of the nitroacrylate substrates. A diverse array of aryl-substituted methyl 2-nitroacrylates were effective reaction components. Variations in steric and electronic effects on the aryl groups were compatible with this catalyst system, thus achieving a high level of stereocontrol (Table 2, entries 8–15). Nitroacrylates containing halogens (e.g., F, Cl and Br) were also applicable to the present transformation, thus providing good results for the halogen-substituted tetrahydroquinoline derivatives (entries 13–15). We also found that the heteroaryl-substituted methyl 2-nitroacrylates performed well in this reaction. For example, the thiophenyl-substituted product **3aj** was obtained in 97% yield, 98% *ee*, and greater than 95:5 d.r. under standard reaction conditions (entry 16). Methyl 2-nitroacrylates containing alkenyl and alkyl groups were examined for this transformation. For example, when nitroacrylate substrates with cinnamenyl (**2k**) and cyclohexyl (**2l**) substituents were subjected to the catalyst system, the corresponding products **3ak** and **3al** were obtained in good enantioselectivities, albeit with modest diastereoselectivities (entries 17 and 18).

In addition to nitroacrylate substrates, this palladium catalyst system can be successfully applied to the ADC reaction of other activated alkenes containing two different electron-withdrawing groups. For example, when the cyano-containing activated alkenes with either an ester group (**4a**) or a keto group (**4b**) were used as reactants, the corresponding tetrahydroquinolines with cyano and ester or keto functional groups were produced in high yields with high *ee* and d.r. values [Eqs. (1) and (2)]. The absolute configuration of **5aa** was confirmed by single-crystal X-ray diffraction, and the cyano group was found to have a *syn* conformation relative to the vinyl group.[20]



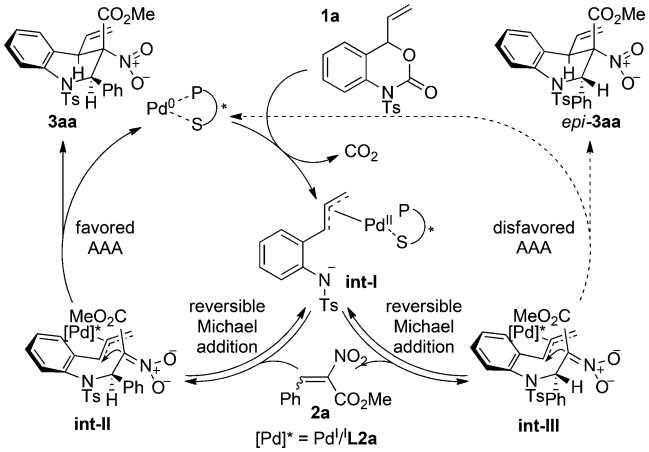
To demonstrate the utility of this reaction methodology, a gram-scale reaction of **1a** and **2a** was conducted using the our catalyst system. The chiral product **3aa** was obtained with good reaction efficiency and selectivity (Scheme 2a). In addition, the nitro group is a versatile functional group in organic synthesis, not only for its use as an activating group but also for its potential convertion into many other functional groups.[21] For example, the nitro group on **3aa** can be easily removed using tributyltin hydride.[21] This operation



Scheme 2. Demonstration of synthetic utility.

provided an alternative route to the 3-ester-incorporated tetrahydroquinoline **6** (Scheme 2b), which is difficult to access directly through a palladium-catalyzed ADC reaction of **1a** and methyl cinnamate. Moreover, the nitro group can be selectively converted into an amino group in good yield, in the presence of a vinyl group, thus leaving the stereochemical properties unaffected (Scheme 2b).[22]

A possible mechanistic pathway for this palladium-catalyzed ADC reaction is outlined in Scheme 3. Initially, the decarboxylation reaction of **1a** may be promoted by the

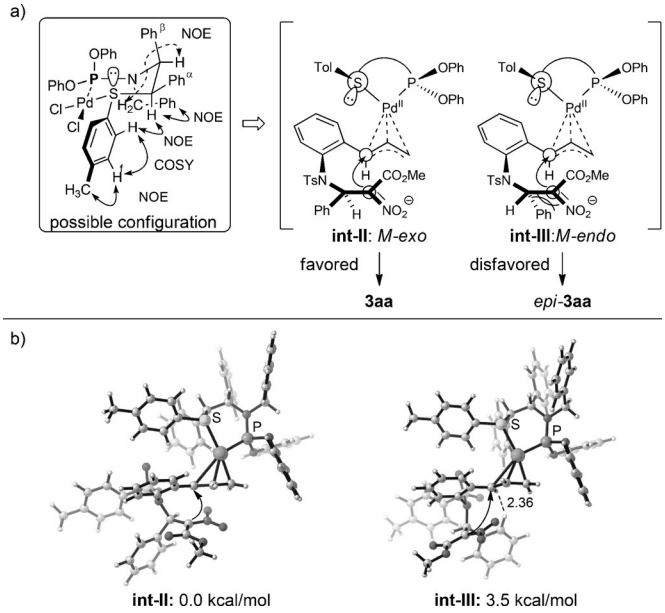


Scheme 3. Proposed reaction mechanism. AAA = asymmetric allylic alkylation.

chiral palladium(0) catalyst, which is generated in situ from $[Pd_2(dba)_3]\cdot CHCl_3$ and **L2a**. At this stage, the palladium-stabilized zwitterionic intermediate **int-I** is produced, that is, an organometallic species containing an electrophilic π-allyl palladium component and a nucleophilic amide anion component. The Michael addition of this transient species to **2a** may produce a new zwitterionic intermediate (**int-II**) and its stereoisomer **int-III**. Finally, the intramolecular allylation reaction of the π-allyl palladium portion and the nitro anion

portion selectively provides the desired product **3aa** and its stereoisomer *epi*-**3aa**. Meanwhile, the active chiral palladium catalyst regenerates to complete the catalytic cycle. As highlighted in previous work, the Michael addition reaction may be a reversible process.[23] If it is faster than the subsequent asymmetric allylation process, the distribution of **int-II** and **int-III** and the parent alkene geometry of **2a** would not affect the absolute stereocontrol (enantioselectivity and diastereoselectivity).[12a] The results in Table 2 are in accordance with this mechanistic explanation.

To elucidate the stereocontrol of the reaction, a possible rigid configuration of a six-membered palladium–ligand chelate in solution is likely, as demonstrated using two-dimensional NMR spectroscopy (NOE: nuclear Overhauser effect; COSY: correlated spectroscopy). As shown in Scheme 4a (left), the large *para*-tolyl substituent adjacent to the sulfur donor is in an *anti* orientation with α-Ph to avoid an unfavorable steric interaction. Thus, *M-exo* and *M-endo* conformations of **int-II** and **int-III** (Scheme 4a, right) were proposed accordingly. The carbon-carbon formation process occurring at the opposite position of the phosphorus donor is likely the result of the well-known *trans* effect.[8a,b] To shed light on the stereoselectivity, density functional theory (DFT) calculations using the method of B3-LYP1 and the standard 6–31G(d) basis set (SDD basis set for Pd) were performed to optimize the geometries of **int-II** and **int-III** (see the Supporting Information for details). As depicted in Scheme 4b, the intermediate **int-II**, having an *exo* type phenyl group, exhibited much lower energies than **int-III**, having an *endo* type phenyl group. The former intermediate is favored because of the reduced steric repulsion between the phenyl ring and the allylic group. As a result, the observed **3aa** would be generated by an external attack of the nitro anion in **int-II** to the π-allyl palladium complex from the back side.



Scheme 4. Stereochemical analysis: a) Proposed stereoinducing modes. b) Calculated structures of possible π-allylic palladium intermediates and their relative energies.

In conclusion, we have developed a new hybrid P,S ligand by assembling nonchiral diphenyl phosphite components and chiral β-amino sulfide components. Its remarkable ability to control the absolute stereochemistry of multiple contiguous stereocenters, including a chiral quaternary center, was successfully demonstrated for the palladium-catalyzed ADC reaction. A wide range of highly functionalized tetrahydroquinolines were thus readily produced at room temperature. We believe that this type of hybrid P,S ligand will have significant potential for the development of additional transition-metal-catalyzed asymmetric transformations, and further research on this subject is underway in our laboratory.

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