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Bicyclic Bridgehead Phosphoramidite-Based Hybrid Diphosphorus Ligands: Design, Synthesis, and Application in Catalytic Asymmetric Hydrogenation

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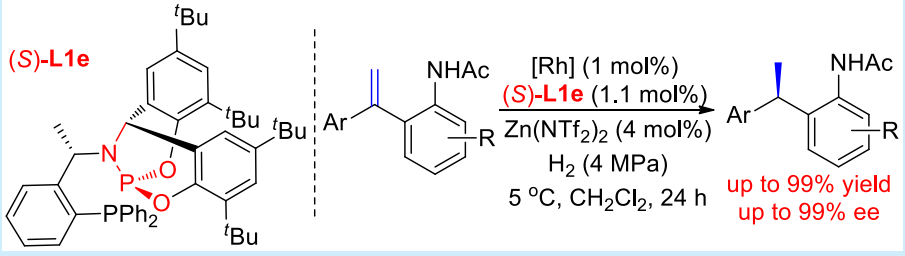
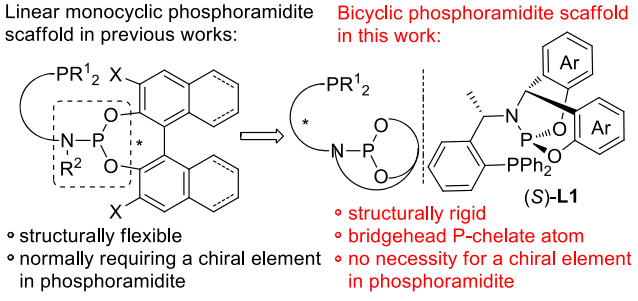


ABSTRACT: A strategy for chiral ligand design has been developed that allows for incorporation of an achiral bicyclic bridgehead phosphoramidite to generate a class of hybrid diphosphorus ligands for high activity and asymmetric control. Using this concept, a series of chiral phosphine–phosphoramidite ligands bearing the sole chirality at the ligand backbone have been prepared and successfully employed in the Rh-catalyzed asymmetric hydrogenation of 2-vinylanilides for the synthesis of optically active anilines bearing an *ortho*-tertiary benzylic stereocenter.

Metal-based asymmetric catalysis has been widely exploited for the synthesis of biologically and economically important chiral compounds.[1] This process typically requires a chiral ligand to achieve the goal of high reactivity and enantioselectivity. As the synthesis of the desired products in a satisfactory enantiopurity cannot always be reached using the existing catalysts, the disclosure of more powerful ligands has continued to be a central and long-standing task for asymmetric catalysis.[2] As an important component found in a diverse array of catalysts, a π-acceptor phosphoramidite structural motif has been recently used to construct chiral hybrid diphosphorus ligands, which displayed high potential in asymmetric catalysis, in particular hydrogenation and hydroformylation.[3−5] In all of these ligands, the phosphoramidite motif has a linear monocyclic structure (Scheme 1). One potential problem of this flexible arrangement is that the P-chelate atom is not held as closely in space to the chiral center at the ligand backbone, which may lead to a detrimental effect in the asymmetric inducement of a chiral catalyst. As a result, the enantioselectivity of existing ligands largely depends on the chiral element installed in the phosphoramidite framework by incorporation of structurally rigid axial–chiral biaryls or sterically hindered central–chiral TADDOL motifs (Scheme 1).

An alternative strategy for resolving this problem is increasing the rigidity of phosphoramidite skeleton, thus efficiently transferring the chiral information at the ligand backbone to the central metal. While this may potentially be overcome by incorportation of increasingly large *ortho* substitutents in biaryl motifs, we hypothesized that a fundamental approach to achieving such a goal could be realized through the construction of an achiral bicyclic bridgehead phosphoramidite scaffold by inclusion of the N–P bond as part of the bicyclic bridge (Scheme 1).[6] Furthermore, the bicyclic bridgehead structure could sub-

Scheme 1. Bicyclic Bridgehead Phosphoramidite Strategy for the Design of a Hybrid Diphosphorus Ligand



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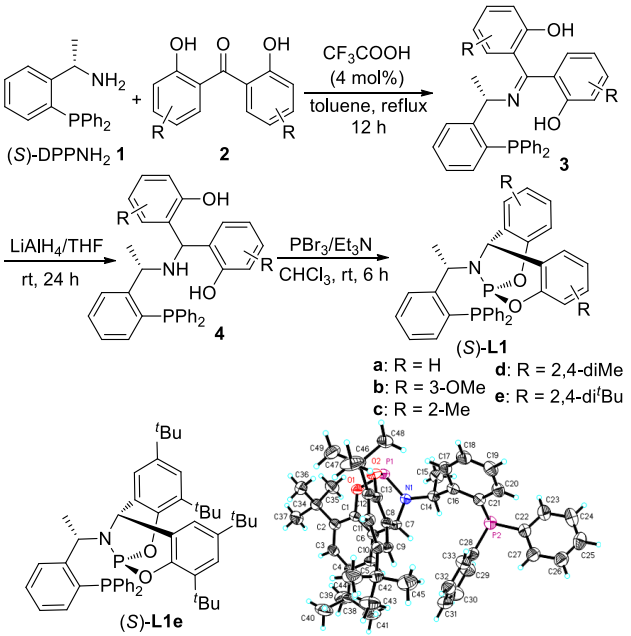
stantially enhance the π-acceptor ability of phosphoramidite due to its inherent geometrical constraint, and the steric environment around the bridgehead P atom can be finely tuned by simply changing the substituents on the bicyclic backbone. We believed that this strategy would provide an opportunity to generate new chiral ligand classes for unique activity and asymmetric control. Surprisingly, to the best of our knowledge, this bicyclic bridgehead phosphoramidite strategy has never been explored for chiral hybrid ligand design. Herein, we report our findings in the design, synthesis, and successful implementation of new chiral hybrid phosphine−phosphoramidite ligands featuring a unique bicyclic bridgehead P-chelate atom for the first Rh-catalyzed enantioselective hydrogenation of 2-vinylanilides, demonstrating the potential of this strategy in hybrid ligand design.

The synthesis of chiral phosphine−phosphoramidite ligand **L1** was achieved in several straightforward steps starting with (*S*)-1-[2-(diphenylphosphino)phenyl]ethylamine [(*S*)-DPPNH$_2$ **1**][5] and bis(2-hydroxyphenyl)methanones **2**, whereby the requisite bicyclic bridgehead phosphoramidite skeleton can be readily constructed as outlined in Scheme 2. Initially,

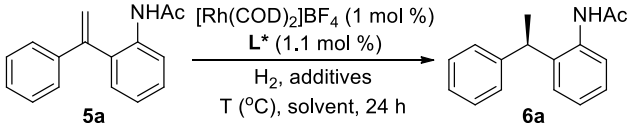
Scheme 2. Modular Synthesis of Chiral Phosphine−Bicyclic Bridgehead Phosphoramidite Ligands (*S*)-L1 and Crystal Structure of (*S*)-L1e



the condensation of (*S*)-DPPNH$_2$ **1** with ketones **2** was performed in refluxing toluene under the catalysis of CF_3COOH, which led to the formation of imines **3**. Imines **3** were then reduced by $LiAlH_4$ to produce secondary amines **4**. The key step for the formation of structurally rigid bicyclic bridgehead phosphoramidite could be smoothly performed by the reaction of **4** with PBr_3 in $CHCl_3$ with Et_3N as the acid scavenger, thus leading to the target phosphine−phosphoramidite ligands **L1**. It is important to note that these ligands are structurally stable, and samples of the ligand have been stored for several months without any changes as determined by NMR detection. The structure of these ligands was confirmed after obtaining an X-ray crystal structure of (*S*)-**L1e**.[7]

With these new chiral hybrid ligands in hand, we turned our attention to test their performance in an enantioselective transformation. Anilines are previleged building blocks for medicinal chemistry and materials science;[8] however, one deficiency for their synthesis resided in the lack of efficient procedures for the construction of *ortho* chirality of branched alkyl substituents, mostly depending on the asymmetric alkylation of arenes.[9] We envisioned that the catalytic asymmetric hydrogenation of readily available 2-vinylanilides may provide a concise and powerful approach to constructing *ortho*-tertiary benzylic stereocenters of anilines for its inherent efficiency and atom economy. However, few successful examples suggest the challenging nature of this task.[10] To this end, we undertook a screen of chiral ligands for Rh-catalyzed hydrogenation of 2-(1-phenylvinyl)anilide **5a**. However, no ligand displayed a somewhat satisfactory enantioselectivity, although high reactivity was observed in some cases, except the linear monocyclic phosphine−phosphoramidite ligand resulting in a promising ee of 37% (for details, see the Supporting Information). This result suggested that a hybrid phosphine−phosphoramidite ligand may be a suitable ligand class, thus encouraging us to evaluate the efficiency of our newly developed bicyclic bridgehead phosphoramidite-based ligands **L1** in this challenging hydrogenation. Gratifyingly, initial screening revealed that most of these new ligands were effective for the hydrogenation (Table 1, entries 1−5), albeit with not so satisfactory enantioselectivity, with 2,4-di^{t}Bu-substituted variant **L1e** generating **6a** in 99% yield with a promising enantioselectivity of 70% ee, superior to all of the tested ligands (entry 5). This result demonstrated the potential of this new bicyclic design strategy. The presence of *tert*-butyl groups at the *ortho* and *para* positions of the phenol rings improves the π-accepting properties of phosphoramidite

Table 1. Optimization of Conditions for Rh-Catalyzed Hydrogenation of 2-(1-Phenylvinyl)anilide 5a[a]



entry	L*	T (°C)	solvent	H_2 (MPa)	yield (%)[b]	ee (%)[c]
1	**L1a**	40	CH_2Cl_2	6	99	6
2	**L1b**	40	CH_2Cl_2	6	99	10
3	**L1c**	40	CH_2Cl_2	6	60	26
4	**L1d**	40	CH_2Cl_2	6	99	30
5	**L1e**	40	CH_2Cl_2	6	99	70
6	**L1e**	25	CH_2Cl_2	6	98	91
7	**L1e**	25	MeOH	6	99	15
8	**L1e**	25	toluene	6	99	31
9	**L1e**	25	dioxane	6	99	86
10	**L1e**	25	CH_2Cl_2	4	98	91
11	**L1e**	5	CH_2Cl_2	4	45	90
12[d]	**L1e**	5	CH_2Cl_2	4	95	95
13[e]	**L1e**	5	CH_2Cl_2	4	99	95
14[e,f]	**L1e**	5	CH_2Cl_2	4	98	94

[a]Reaction conditions: **5a** (0.125 mmol, 1.0 equiv), $[Rh(COD)_2]BF_4$ (1 mol %), **L*** (1.1 mol %), and additives (4 mol %) in 2 mL of solvent under a H_2 atmosphere at the indicated temperature for 24 h. [b]Isolated yield. [c]Enantiomeric excess value determined by chiral HPLC. [d]$Zn(OTf)_2$ as the additive. [e]$Zn(NTf_2)_2$ as the additive. [f]S/C = 1000.

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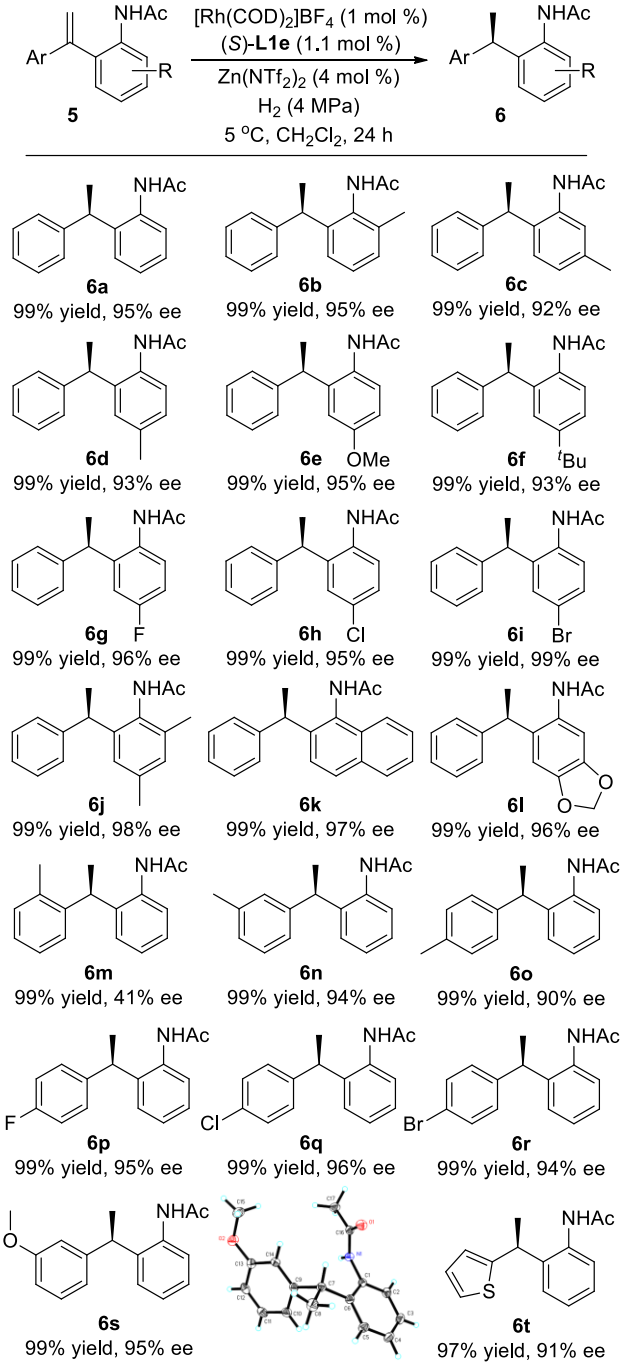
by enhancing geometrical constraints through steric repulsion, thus favoring the increase in reactivity.[6] The result also indicated that the chirality at the ligand backbone is enough for asymmetric control, and an additional chiral element in the bicyclic phosphoramidite framework is not necessary. To further improve the performance, we next optimized the hydrogenation conditions. Decreasing the temperature to 25 °C resulted in a significant increase in the enantioselectivity to 91% ee without a compromise in reactivity (entry 6). The following screening of the solvents such as MeOH, toluene, and 1,4-dioxane revealed that all of these reaction media gave inferior outcomes with respect to the ee value as compared with CH_2Cl_2 (entries 6−9). Decreasing the H_2 pressure to 4 MPa had no influence on the reactivity or enantioselectivity (entry 10). However, an attempt to further improve the performance by decreasing the reaction temperature to 5 °C proved unsuccessful, leading to a decreased yield of only 45% (entry 11). Recently, May et al. have reported that the addition of several Lewis acids could dramatically improve the rate of the Rh-catalyzed asymmetric hydrogenation.[11] For this purpose, we examined a series of Lewis acid additives, with which $Zn(OTf)_2$ and $Zn(NTf_2)_2$ were found to significantly promote the hydrogenation as anticipated (entries 12 and 13, respectively). With the addition of 4 mol % $Zn(NTf_2)_2$, an excellent performance was achieved even when the hydrogenation was performed at a catalyst loading of 0.1 mol %, demonstrating the efficiency of this catalytic system (entry 14).

With reaction conditions identified that lead to high yield and enantioselectivity in model hydrogenation, we next sought to establish the substrate scope for the hydrogenation with the Rh/(*S*)-**L1e** catalyst, and representative results are listed in Scheme 3. A range of 2-(1-arylvinyl)acetanilides **5a−t** were hydrogenated for the first time to give the corresponding chiral acetanilides **6a−t**, respectively, bearing an *ortho*-tertiary benzylic stereocenter in nearly quantitative yields. The catalytic system presented here showed a high tolerance to the substitution pattern and electronic properties of the substituent on the anilido moiety of substrates. A variety of *para*, *meta*, *ortho*, and disubstituted anilide substrates (**5a−l**) were quite hydrogenated in excellent enantioselectivities (92−99% ee). The hydrogenation was sensitive to the substitution pattern on the phenyl ring of the 1-arylvinyl moiety. Thus, *o*-methyl-substituted substrate **5m** led to enantioselectivity much lower than those of its *para* and *meta* analogues (**5n** and **5o**, respectively).

The electronic properties of the substituent on the 1-arylvinyl moiety had little effect on the enantioselectivity, and all substrates with a *para* substituent were hydrogenated in high to excellent enantioselectivities (90−96% ee). Heteroaromatic substrate **5t** also worked well, resulting in the corresponding hydrogenation product **6t** in 91% ee. The absolute configuration of 2-(1-arylethyl)acetanilides was unambiguously determined by X-ray structure analysis of **6s**, to which an *R* configuration was assigned.[7]

The conformational orientation of a chiral bicyclic bridgehead phosphoramidite-based hybrid diphosphorus ligand in its coordinated form was established after obtaining an X-ray crystal structure of the Rh(acac)[(*S*)-**L1c**] complex (Figure 1),[7] in which the bidentate coordination mode of (*S*)-**L1c** with Rh was unambiguously confirmed. On the basis of our experiments, and previous mechanistic studies of asymmetric hydrogenation with hybrid bidentate-P ligands,[5,12] a transition

Scheme 3. Substrate Scope[a]



[a]Reaction conditions: **5** (0.125 mmol, 1.0 equiv), $[Rh(COD)_2]BF_4$ (1.0 mol %), (*S*)-**L1e** (1.1 mol %), and $Zn(NTf_2)_2$ (4 mol %) in 2 mL of CH_2Cl_2 under a H_2 pressure of 4 MPa at 5 °C for 24 h. Yields of isolated products are given. The enantiomeric excess was determined by chiral HPLC.

state **S-I** is proposed to explain the observed stereochemistry as shown in Figure 1.

In summary, the structurally rigid achiral bicyclic bridgehead phosphoramidite as a superb component has been applied for the first time in the design of chiral hybrid diphosphorus ligands, with which a series of chiral hydrid phosphine−phosphoramidite ligands have been developed. Remarkably, in these ligands, the chiral element for asymmetric control is

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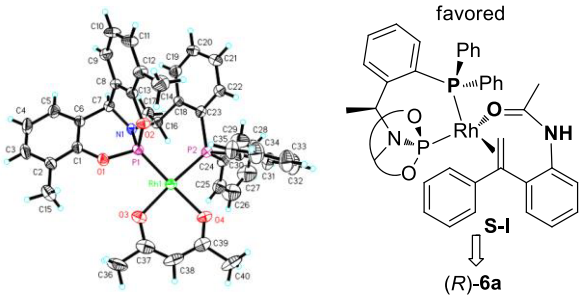

Figure 1. Crystal structure of the Rh(acac)[(*S*)-**L1c**] complex (left) and proposed model of stereochemistry (right).

installed in the ligand backbone, and the additional chirality in the phosphoramidite framework is not required. Using these new ligands, a highly enantioselective Rh-catalyzed hydrogenation of 2-vinylanilides was realized, in which a catalytic amount of $Zn(NTf_2)_2$ additives could dramatically improve the reactivity, thus providing concise access to a variety of optically active anilines bearing an *ortho*-tertiary benzylic stereocenter. We believed that this design strategy should offer new possibilities for the development and implementation of new ligand classes in a large variety of selective transformations. Further studies of this are underway in our laboratories and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c02978.

(PDF)

Accession Codes

CCDC 2090263, 2090819, and 2098769 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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