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RESEARCH ARTICLE

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Diastereoselective Synthesis of P-Chirogenic and Atropoisomeric 2,2'-bis(phosphino)-1,1'-binaphthyls Enabled by Internal Phosphine Oxide Directing Groups

Qingquan Xue,[a] Shangfei Huo,[a] Tingyi Wang,[a] Zeming Wang,[a] Jianli Li,[b] Meifang Zhu*,[a] and Weiwei Zuo*,[a]

Abstract: The diphosphine ligand family that merges both axial and P-centered chirality may exhibit superior or unique properties. Here, we report a phosphine oxide (chiral or achiral) group-directed reaction for diastereoselectively introducing P-centered chirality into the 2-position of the axially chiral 2'-phosphine-oxide-1,1'-binaphthyl scaffold. This process proceeds through a lithium-bromide exchange reaction of 2-bromo-2'-phosphine-oxide-1,1'-binaphthyl and electrophilic reaction with dichlorophosphines followed by treatment with a nucleophilic organometallic reagent, to afford unsymmetrical 2-phosphino-2'-phosphine-oxide-1,1'-binaphthyls with the combination of one binaphthyl axial chirality and one or two tunable P-chirogenic phosphorus center(s) having a variety of P-substituents. The final diastereomerically pure 2,2'-bis(phosphino)-1,1'-binaphthyls were obtained by quantitative and regiospecific reduction of the phosphine oxide directing groups. The preliminary catalytic results using the hybrid-chirality ligand demonstrated its capability to induce higher stereoselectivity in the metal complex-catalyzed asymmetric hydrogenation of alkyl-alkyl ketone.

Introduction

Transition metal complexes of axially chiral 2,2'-substituted-1,1'-binaphthyl-based diphosphine ligands, represented by the iconic 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP), have been shown to display excellent stereoselectivity in a variety of catalytic reactions.[1] Additionally, since the pioneering work of Knowles,[2] P-chirogenic phosphines have constituted an important category of chiral ligands for a wide range of catalytic applications.[3] We envisaged that merging the structural characteristics of both atropisomerism and chirality at the P-center would create a new family of chiral phosphine ligands that would allow further fine-tuning of the enantioinduction of the resulting chiral ligands, by a chiral cooperativity between these two types of asymmetric elements.[4]

However, due to some challenges there are currently no synthetic methods available for the reliable access to diastereomerically pure 2,2'-substituted-1,1'-binaphthyl-based diphosphine ligands that are also chirogenic at one or both phosphorus centers. First, there has been no efficient method that can produce a 1,1'-binaphthyl-based C-P bond in a highly diastereoselective manner. The biaryl-lithium intermediate generated by a lithium-halide exchange reaction and the subsequent electrophilic quenching with chlorophosphine derivatives utilized by Cereghetti[5] and Buchwald[6] in the production of corresponding P-chirogenic atroposiomeric mono or diphosphines ligands resulted in moderated diastereoisomeric purities. This approach required further purification such as recrystallization, which usually led to low yields of the diastereomerically pure products. Transition metal complex-catalyzed coupling of a secondary phosphine oxide with binaphthyl electrophiles and related C-P cross-coupling reactions were also attempted to synthesize P-chirogenic binaphthyl monophosphines.[7] This method is limited not only by the low efficiency of C-P bond formation but also by the availability of the chiral secondary phosphine oxide starting precursors. In addition, the products are prone to racemization at the phosphorus center due to the high temperatures required to achieve high conversion and therefore generally result in diastereomeric mixtures.[7a,c,e] Also the racemisation of the P-chirogenic phosphine-oxide moieties in all subsequent reduction attempts was another problem that hampered the high diastereoselectivity. Second, the introduction of P-chirality with a predictable and variable P-configuration has never been reported, largely due to the abovementioned racemization process and the limited availability of the starting precursors. Our initial results indicated that the ephedrine method,[8] which is usually very efficient in constructing P-centered chirality, also proved to be ineffective and led to the formation of a diastereomeric mixture.

Inspired by Chen's work[9] on the highly stereoselective synthesis of ferrocene-based P-chirogenic phosphine ligands, we developed a new method to diastereoselectively introduce stereogenic phosphorus moieties into the axially chiral 1,1'-binaphthyl backbone with controllable P-configuration and excellent stereoselectivity, thus allowing the synthesis of unsymmetrical 2,2'-bis(phosphino)-1,1'-binaphthyl ligands that incorporate both axial and P-centered chiralities.

Results and Discussion

The key to the success of this strategy was the utilization of a 2'-position phosphine oxide group, in either stereogenic or achiral form, as the directing group for the subsequent introduction of the second chiral phosphine group and its regio- and stereospecific deoxygenation (Scheme 1).[10]

Specifically, (R_A)-2-bromo-2'-phosphine-oxide-1,1'-binaphthyl (**1**) undergoes a lithium-bromide exchange and further reacts with dichlorophosphine (R^3PCl_2) to afford

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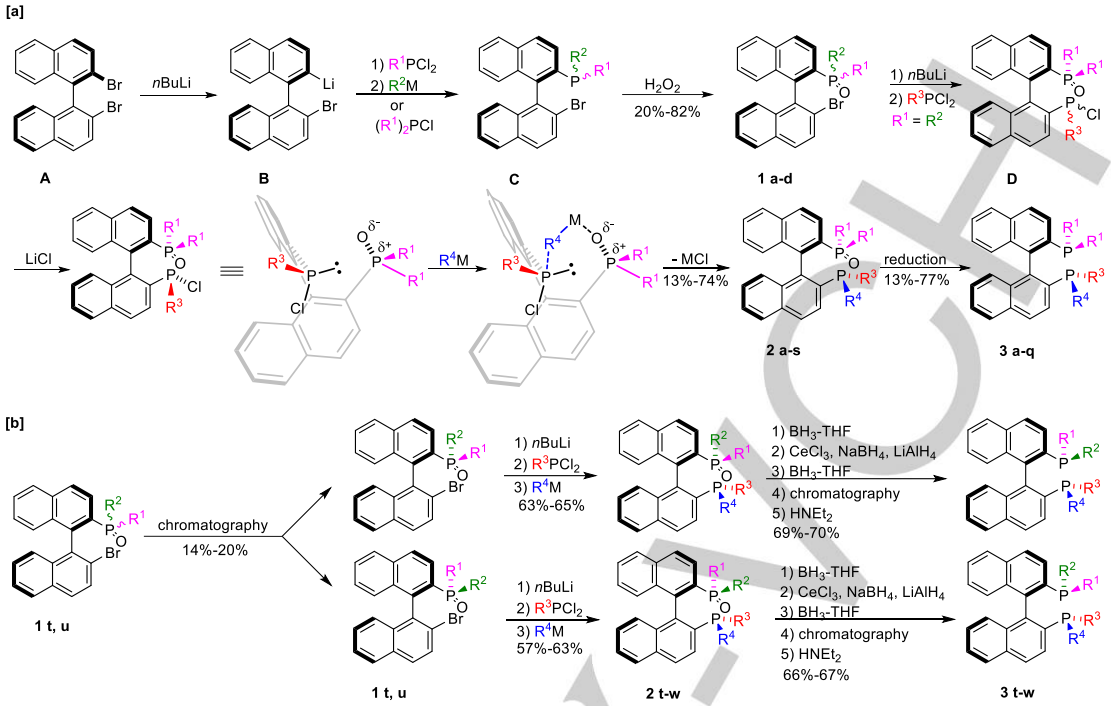

Scheme 1. Strategies for the synthesis of unsymmetrical (R_A)-2,2'-diphosphino-1,1'-binaphthyls that comprise both axial and P-centered chiralities. **a)** The synthesis of unsymmetrical (R_A)-2,2'-diphosphino-1,1'-binaphthyls (**3 a-q**) that possess one stereogenic phosphorus center by employing phosphine oxide induced P-chirality-recognition protocol and the regioselective deoxygenation of the phosphine oxide directing groups. **b)** The synthesis of unsymmetrical (R_A)-2,2'-bis(phosphino)-1,1'-binaphthyls that bear two P-chirogenic centers by similar strategies.

a P-chiral monochlorophosphine intermediate (D). Treatment of such a monochloro-substituted intermediate with another organometallic reagent (R^4M, M= Li, MgBr) results in a highly diastereoselective nucleophilic substitution process that favors formation of (R_A)-2-phosphino-2'-phosphine-oxide-1,1'-binaphthyls (**2**) possessing one axial binaphthyl chirality and a P-stereogenic center, with only one single diastereomer being formed for all P-substituents except 1'-bromo-ferrocen-1-yl (Scheme 1a). The high diastereoselectivity in this nucleophilic substitution step is rationalized by an internal assistance of the phosphine oxide in the organometallic attack, particularly Grignard, in the anti-position of the P-Cl bond. It is possible that one chlorophosphine epimer reacts, when the second quickly epimerizes in the presence of lithium halide salt.[11]

The diastereomerically pure epimer having an opposite configuration at the phosphorus center can be easily made simply by reversing the introduction order of the P-substituents (R^3 and R^4), e.g., by first engaging R^4PCl_2 and then treating with R^3M. More importantly, when combined with the borane protection strategy, the $CeCl_3/NaBH_4/LiAlH_4$ mixture was found to be an efficient reducing system to deoxygenate the directing phosphine oxide group cleanly, while leaving the chiral phosphino group intact, to allow the stereoselective synthesis of the target P-chirogenic BINAP derivatives (**3 a-q**).

The effectiveness of this methodology was further illustrated in the efficient synthesis of unsymmetrical (R_A)-2,2'-bis(phosphino)-1,1'-binaphthyls with two P-chirogenic phosphorus atoms, through the first installation of a P-chirogenic phosphine oxide group on the 2'-position of the binaphthyl backbone in an epimeric mixture (Scheme 1b). The individual diastereomerically pure isomers of (R_A)-2-bromo-2'-phosphine-oxide-1,1'-binaphthyls were isolated and then subjected to the above phosphine oxide-directed P-chirality recognition processes to independently afford the phosphine oxide-phosphine ligands that incorporate three adjacent stereocenters. Same reduction of the phosphine oxide directing groups afford all four possible stereoisomers, which are inaccessible *via* alternative methods.

The stereoselective synthesis starts with the preparation of (R_A)-2-bromo-2'-phosphine-oxide-1,1'-binaphthyls (**1**) (Table 1). (R_A)-2,2'-Dibromo-1,1'-binaphthyl was first lithiated at -90 °C in a glovebox for 5 min and then successfully quenched with chlorophosphine to give (R_A)-2-bromo-2'-phosphine-oxide-1,1'-binaphthyl (**1**) in moderate to good yields after oxidation with H_2O_2. No binaphthyl axial chirality racemization under such low reaction temperature and short reaction period was observed, as revealed by chiral high-performance liquid chromatography (HPLC) analysis (see Supporting Information, Figure S2).[12]

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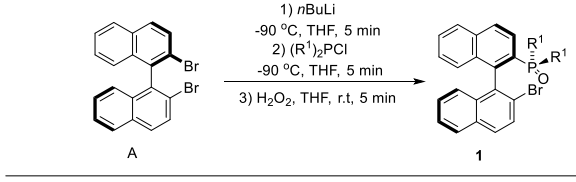
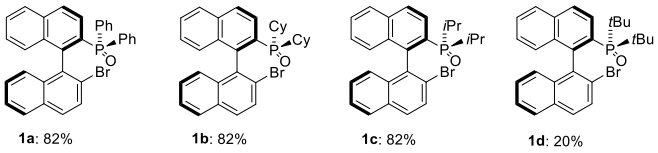
Table 1: The synthesis of (R_A)-2-bromo-2'-phosphine-oxide-1,1'-binaphthyls.[a]





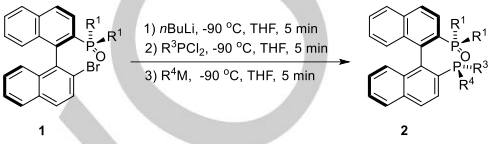
[a] Isolated yields.

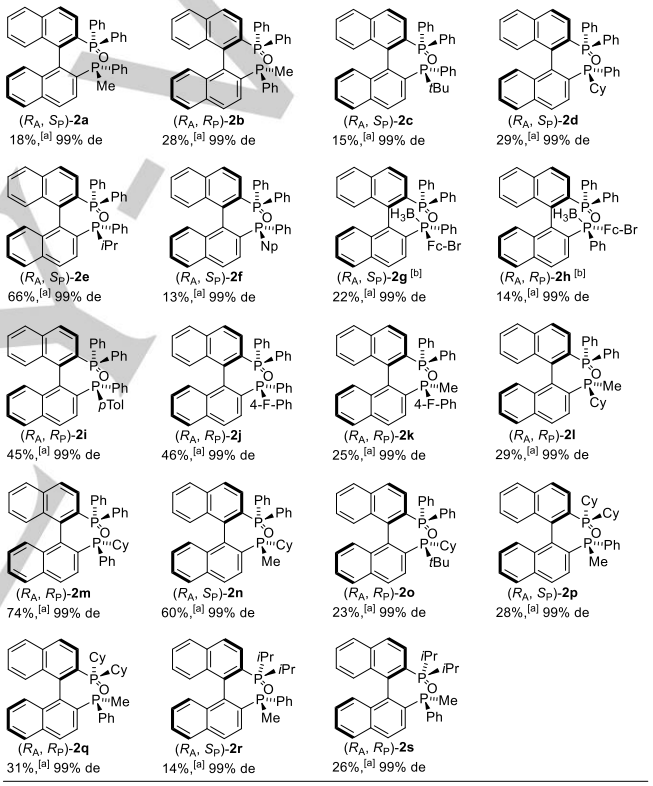
Similar to the ferrocenyl analogous procedure,[9] the diastereoselective installation of a second P-chiral phosphino group involves the following: first, a lithium-bromide exchange process at the (R_A)-2-bromo-2'-phosphine-oxide-1,1'-binaphthyl, second, a reaction with alkyl- or arylchlorophosphines (R^3PCl_2) to yield a monochloro-phosphine intermediate, and third, a nucleophilic substitution reaction by an organometallic reagent R^4M (Table 2). For example, the binaphthyl monoanion generated from (R_A)-**1a** and *n*-butyl lithium sequentially reacts with dichlorophenylphosphine and methyl magnesium bromide to afford (R_A, S_P)-**2a** in a 63% NMR yield, with only one diastereomer being observed. Similar to the installation step of the first phosphine oxide group, the reactions proceed without epimerization of the binaphtyl moiety (checked by chiral HPLC, see Supporting Information section for details).

Interestingly, the epimer (R_A, R_P)-**2b** with an opposite configuration at the chiral P center was readily accessible simply by reversing the introduction sequence of the phenyl and methyl groups. More importantly, this epimer was also formed as a single diastereomer in high yield based on the ^{31}P NMR analysis. The absolute configurations of the chiral phosphorus center of (R_A, S_P)-**2a** and (R_A, R_P)-**2b** were determined by single-crystal X-ray diffraction analysis of the *bis*(phosphine oxide) analog (R_A, S_P)-**4b**,obtained by H_2O_2 oxidation of **2b** (see Supporting Information, Figure S168), and further confirmed by the stereochemistry of the deoxygenated products (R_A, S_P)-**3a** and (R_A, R_P)-**3b** (*vide infra*). The $^{31}P\{^1H\}$ NMR analysis of these two epimers shows a distinct difference between the chemical shifts of the centrally chiral phosphorus nucleus. The (R_A, S_P) isomer **2a** presents resonances at -37.81 and 27.47 ppm, while the opposite epimer (R_A, R_P)-**2b** shows signals at -35.45 and 27.98 ppm, respectively (see Supporting Information, Figure S33 and Figure S36).

The high diastereoselectivity in the synthesis of (R_A)-**2a-2o** from (R_A)-**1a** was found to be general for most substituents except 1'-bromo-ferrocen-1-yl (Table 2). A series of (R_A)-2-phosphino-2'-phosphine-oxide-1,1'-binaphthyls having a P-centered chirality on the 2-position phosphorus atom with various substituents, including alkyl, cyclic alkyls, aryls and naphthyl, were stereoselectively prepared by employing different dichlorophosphines and using the appropriate organometallic reagents for the nucleophilic substitution step. Replacement of **1a** with **1b** and **1c** results in a similar reaction pattern to afford the corresponding products (R_A)-**2p-2s** possessing methyl and phenyl P-substituents and predictable configurations, also in acceptable yields and high diastereomeric purities (de> 99%).

Table 2: The synthesis of (R_A)-2-phosphino-2'-phosphine-oxide-1,1'-binaphthyls that bear one P-stereogenic center.



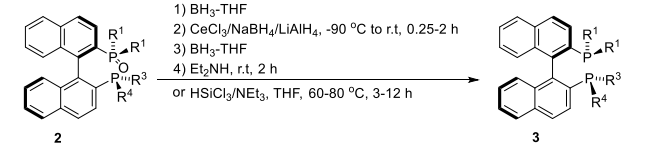


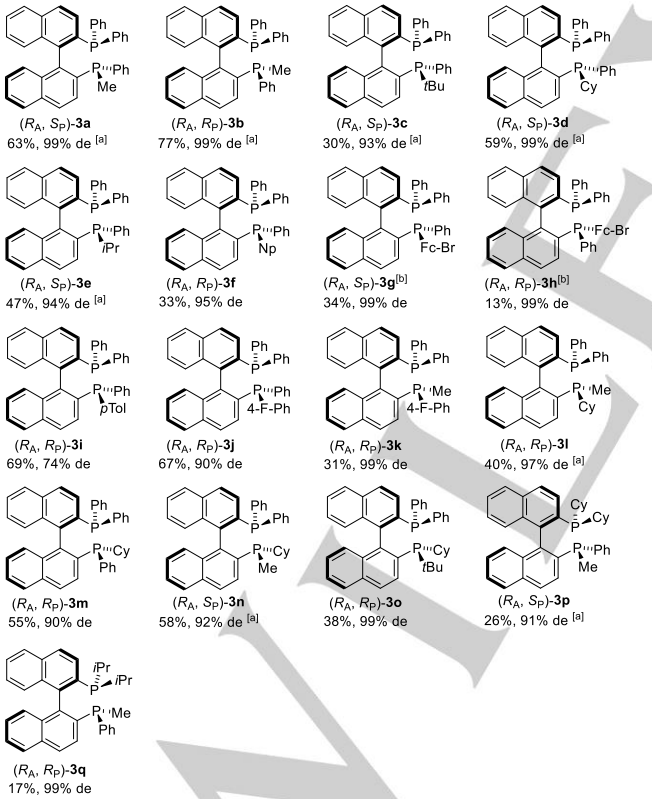
[a] Isolated yield. [b] Two epimers separated by column chromatography. Br-Fc = 1'-bromo-ferrocen-1-yl.

The (R_A)-2-phosphino-2'-phosphine-oxide-1,1'-binaphthyls were subjected to deoxygenation by various reducing agents to synthesize free P-chirogenic diphosphine BINAP derivatives. The combination of trichlorosilane/triethylamine at 60-80 °C can reduce all of the tested substrates from (R_A)-**2a** to (R_A)-**2s**, but for many substrates, obvious P-chirality epimerization was observed (Table 3). A further search for efficient reducing agents that regioselectively deoxygenate the phosphine oxide group while leaving the P-chiral center intact led to the finding of a combination of $CeCl_3/NaBH_4/LiAlH_4$ in a ratio of 5:5:3, which was first reported by Imamoto.[13] With a slight modification of Imamoto's procedure, the chiral phosphorus center was first

protected by a borane group prior to the deoxygenation process by reacting the (R_A)-2-phosphino-2'-phosphine-oxide-1,1'-binaphthyls with one equivalent of BH_3-THF, and the deoxygenation then proceeded regioselectively on the phosphine oxide group with negligible racemization at the protected P-chirogenic phosphine moiety, affording only one major diastereomer in >90% NMR analysis yield. The borane group could be easily removed by reacting with diethylamine at room temperature. The $^{31}P\{^1H\}$ NMR spectra of diastereomerically pure (R_A, S_P)-**3a** and (R_A, R_P)-**3b** prepared by this reduction process are shown in Figure 1, which indicates no epimerization of the P-chirogenic center for both substrates. Single crystals suitable for X-ray diffraction of the epimers (R_A, S_P)-**3a** and (R_A, R_P)-**3b** were both obtained, and the molecular structures are shown in Figure 2. Overall, for other substrates of (R_A)-**2c**-**2s**, the reductions using this mixture offered straightforward transformations within 2 h.

Table 3: The synthesis of unsymmetrical (R_A)-2,2'-bis(phosphino)-1,1'-binaphthyls that bear one P-stereogenic center.





[a] Comparable diastereoselectivities can be obtained with trichlorosilane/triethylamine. For all substrates, the NMR yields are higher than 90%. [b] Br-Fc = 1'-bromo-ferrocen-1-yl. The crude and isolated products have same de %.

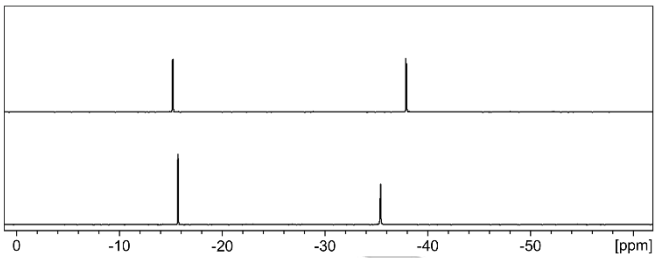


Figure 1. The $^{31}P\{^1H\}$ NMR spectrum (243 MHz, $CDCl_3$) of (R_A, S_P)-**3a** and (R_A, R_P)-**3b**. Top, (R_A, S_P)-**3a**, δ: -15.20, -37.93, d, J^{PP} = 14.6 Hz; bottom, (R_A, R_P)-**3b**, δ: -15.71, -35.42, d, J^{PP} = 11.7 Hz.

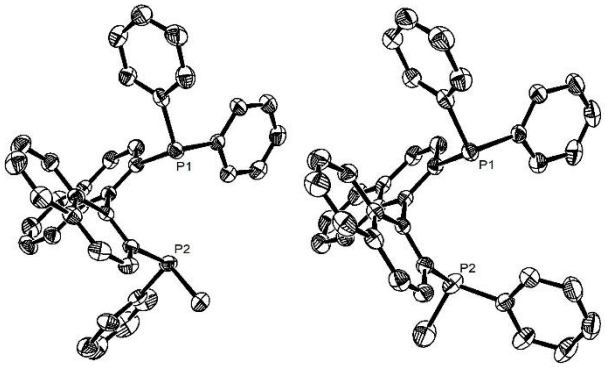
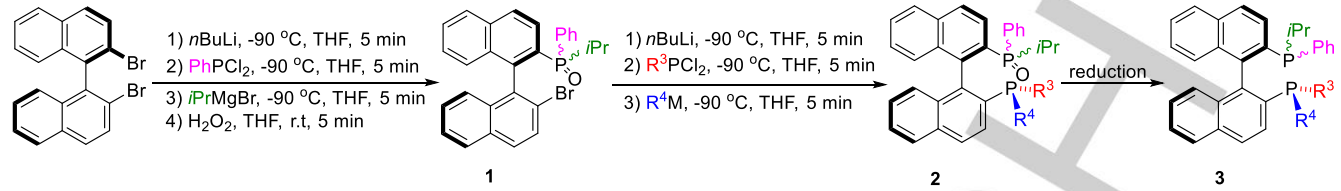


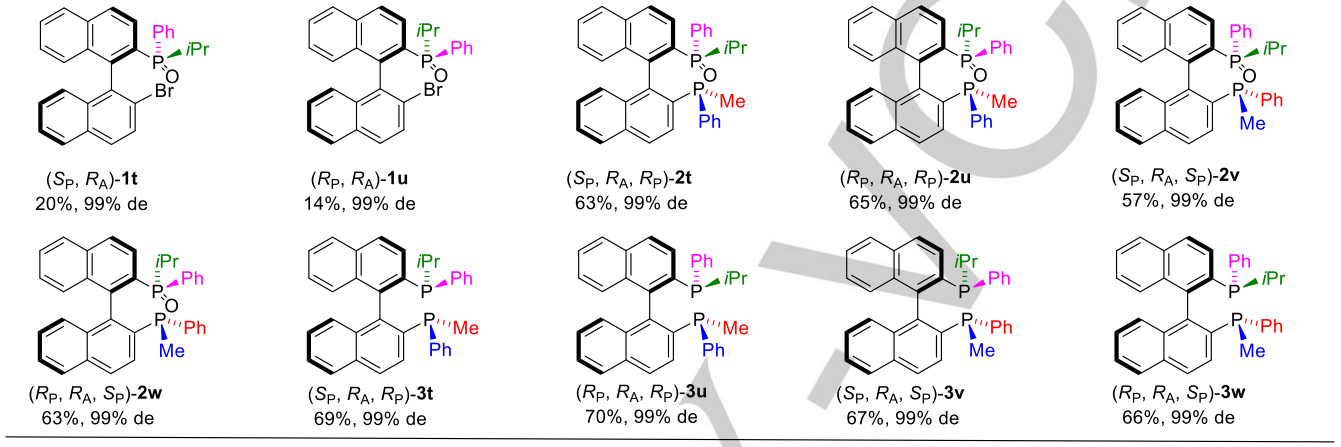
Figure 2. The molecular structures of (R_A, S_P)-**3a** and (R_A, R_P)-**3b**. The hydrogen atoms are omitted for clarity and the thermal ellipsoids are depicted at a 30% probability level.

The above method was extended to the synthesis of a range of modified BINAP ligands possessing two P-chirogenic centers, a task that is very challenging if the other existing procedures are employed (Table 4). This process commences with the installation of a chiral isopropylphenylphosphine oxide directing group at the 2'-position of the 1,1'-binaphthyl backbone in a diastereomeric mixture in a 1.4:1 ratio (Scheme 1 and Table 4). The phosphine oxide diastereomeric mixtures were separated by column chromatography to independently afford the diastereomerically pure (R_A)-2-bromo-2'-isopropylphenylphosphine-oxide-1,1'-binaphthyls (S_P, R_A)-**1t** and (R_P, R_A)-**1u** in 20% and 14% yields, respectively. The stereochemistry of (R_P, R_A)-**1u** was also determined by single-crystal X-ray diffraction (see Supporting Information, Figure S172).

Further sequential treatment of the individual diastereomerically pure (R_A)-2-bromo-2'-isopropylphenylphosphine-oxide-1,1'-binaphthyl [(S_P, R_A)-**1t** or (R_P, R_A)-**1u**] with *n*-butyl lithium, methyl dichlorophosphine and phenylmagnesium bromide afforded new diastereomerically pure 2-methylphenylphosphino-2'-isopropylphenylphosphine-oxide-1,1'-binaphthyls [(S_P, R_A, R_P)-**2t** and (R_P, R_A, R_P)-**2u**], each of which bears two P-chirogenic centers and a binaphtyl axial chirality, in 63% and 65% yield, respectively. The molecular structure of (S_P, R_A, R_P)-**2t** is shown in the Supporting Information, Figure S173.

Table 4: The synthesis of (R_A)-2-bromo-2'-phosphine-oxide-1,1'-binaphthyls that bear a chirogenic phosphine oxide directing group and their syntheses of unsymmetrical (R_A)-2,2'-bis(phosphino)-1,1'-binaphthyls that are stereogenic at both phosphorus atoms. [a]





[a] All the yields are isolated yields.

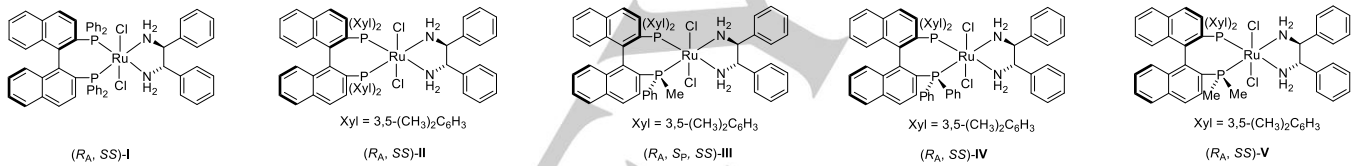
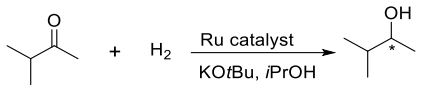


Figure 3. Ruthenium complexes for asymmetric hydrogenation of ketone (See Supporting Information for the detailed synthetic procedures).

Similar to the above cases, the initial borane protection of (S_P, R_A, R_P)-**2t** and the subsequent deoxygenation of the boronato adduct with $CeCl_3$/$NaBH_4$/$LiAlH_4$ at low temperature (-90 °C) proceeded regiospecifically and stereoselectively at the phosphine oxide group with inversion of configuration at the phosphorus center to afford new unsymmetrical (S_P, R_A, R_P)-2,2'-diphosphino-1,1'-binaphthyls (**3t**) that bear two P-chirogenic phosphine moieties on each side of the 1,1'-binaphthyl backbone, with only one diastereomer being formed (see Supporting Information section for inversion of the P-chirality). (R_P, R_A, R_P)-**2u**, which has (R_P)-configurations at the phosphine-oxide and phosphine moieties, gives rise to the corresponding diastereomerically pure diphosphine product (R_P, R_A, R_P)-**3u**. The other two diastereomers of (S_P, R_A, S_P)-**2v** and (R_P, R_A, S_P)-**2w** with opposite configurations to those of **2t** and **2u** at the second installed chiral phosphorus atoms are also easily accessible simply by reversing the introduction sequence of the methyl and phenyl groups, and the corresponding free diphosphines (S_P, R_A, S_P)-**3v** and (R_P, R_A, S_P)-**3w** were easily obtained by employing the same deoxygenation and purification procedures. Therefore, all four structurally possible diastereomers can be independently and stereoselectively prepared with good yields.

Preliminary catalytic results revealed the advantage of hybrid-chirality ligands in inducing higher stereoselectivities in its ruthenium complexes for the asymmetric hydrogenation of ketones. A challenging substrate, 3-methyl-2-butanone, was used because it was usually reduced with very low enantioselectivities.[14] The results are shown in Table 5. While the traditional Noyori catalysts (R_A, SS)-**I** and (R_A, SS)-**II** (Figure 3) containing only one axial chirality of the binaphthyl group show 32% and 50% enantiomeric excess, respectively, the hybrid-chlirality analogue (R_A, S_P, SS)-**III** (Figure 3) exhibited an obviously increased enantio-purity of 63% under otherwise the identical conditions. Interestingly, the unsymmetrical but not P-chirogenic analogues (R_A, SS)-**IV** and (R_A, SS)-**V** also show lower enantioselectivities than (R_A, S_P, SS)-**III**. This 63% enantio-purity, although slightly inferior to the highest value that was obtained in the Rh-PennPhos complex,[14a] clearly demonstrated the merit of using a hybrid-chirality diphosphine ligand to achieve higher enantioselectivity.

Table 5: Ruthenium complex-catalyzed asymmetric hydrogenation of 3-methyl-2-butanone. [a]



Precatalyst	Yield (%)[b]	ee (%)[b]	Config.[c]
(R_A, SS)-**I**	10	32	*S*
(R_A, SS)-**II**	100	50	*S*
(R_A, S_P, SS)-**III**	100	63	*S*
(R_A, SS)-**IV**	100	40	*S*
(R_A, SS)-**V**	100	55	*S*

[a] Reactions conditions: reaction temperature 25 °C, 10 atm of H_2, reaction time 3 h, [catalyst] = 1.2×10^{-2} M, [substrate] = 2.4 M, [KO*t*Bu] = 1.1×10^{-2} M, isopropanol as solvent. [b] Determined by gas chromatography (GC). [c] The absolute configurations were obtained by GC by comparison to known standards.

Conclusion

In summary, a series of unsymmetrical 2,2'-bis(phosphino)-1,1'-binaphthyls with one or two P-chirogenic centers were prepared for the first time by virtue of phosphine oxide directing groups and their regioselective and stereoselective reductions. The phosphine oxide directing group was advantageous in achieving high diastereoselectivity, while the reduction reaction that proceeded at low temperature by the combination of $CeCl_3$/$NaBH_4$/$LiAlH_4$, assisted by the borane protection strategy, allowed overcoming the frequently encountered but yet unsolved problem of P-chirality racemization. The hybrid-chirality ligand has demonstrated its unique property in inducing higher stereoselectivity of the corresponding ruthenium catalyst in the asymmetric hydrogenation of 3-methyl-2-butanone.

Acknowledgements

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Conflicts of interest

Donghua University has issued a patent titled "Diphosphine chiral compound having both phosphorus central chirality and dinaphthalene axial chirality and preparation method thereof" (CN108690074A).

Keywords: Asymmetric synthesis • Phosphane ligands • P-chirogenic • Atropisomeric • Axial to point chirality transfer

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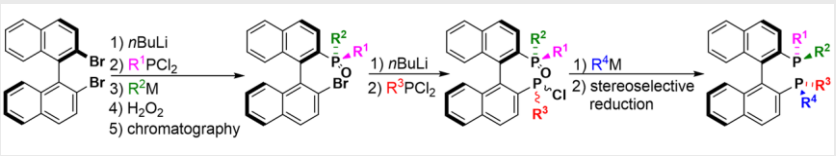

Atropisomeric and P-chirogenic 2,2'-bis(phosphino)-1,1'-binaphthyls with configurationally controllable chiral phosphorus center(s) were synthesized with excellent diastereoselectivity, enabled by 2'-phosphine oxide directing groups and their regio- and stereospecific reductions.

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Diastereoselective Synthesis of P-Chirogenic and Atropoisomeric 2,2'-bis(phosphino)-1,1'-binaphthyls Enabled by Internal Phosphine Oxide Directing Groups