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Asymmetric Hydrophosphination of Heterobicyclic Alkenes: Facile Access to Phosphine Ligands for Asymmetric Catalysis

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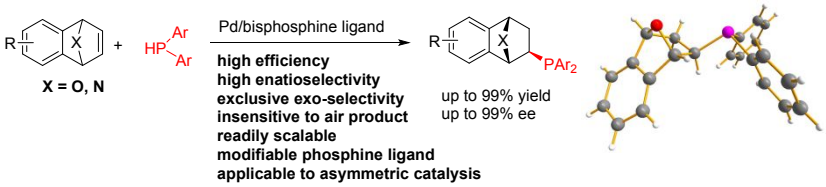
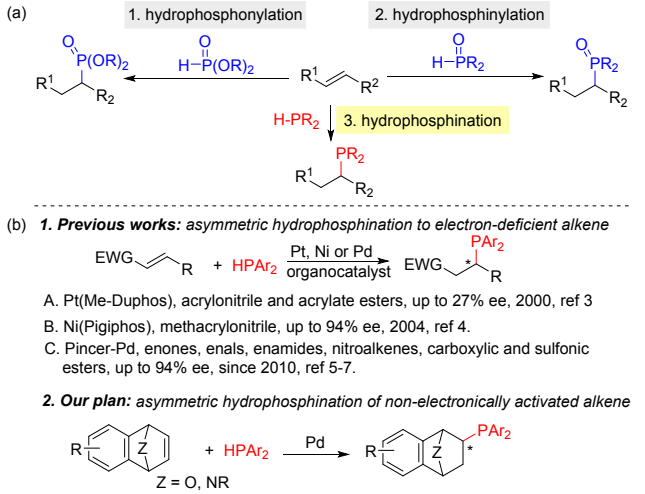
ABSTRACT: Asymmetric hydrophosphination is the most atomically economical and straightforward approach to the construction of chiral organophosphorus compounds. Good stereoselectivities have been achieved in asymmetric hydrophosphination of an electron-deficient C=C double bond, but substrates involving non-polar C=C bonds remain difficult and are rarely tackled. Herein, we report asymmetric hydrophosphination of a non-electronically activated double bond with a remarkably high degree of stereo control. This strategy offered an expedient and broadly applicable platform to prepare tertiary phosphines in high yields (up to 99% yield) and enantioselectivities (up to 99% ee). Particularly noteworthy is that these tertiary phosphine products were then successfully employed as phosphine ligands in enantioselective metal-catalyzed transformations with a high level of asymmetric induction.



KEYWORDS: Asymmetric Catalysis, Hydrophosphination, Chiral phosphine, Alkene, Ligand design.

Organophosphorus compounds are broadly utilized synthetic building blocks for accessing bioactive molecules and functional materials. Indeed, they also play significant roles in metal-catalyzed and organocatalytic transformations.[1] There are three major types of P−C bond construction from addition reactions to unsaturated compounds: 1) hydrophosphonylation or the addition of dialkyl phosphites; 2) hydrophosphinylation or the addition of secondary phosphine oxides; and 3) hydrophosphination or the addition of secondary phosphines to C=C double bonds (Scheme 1a). Of these three categories, asymmetric hydrophosphination is the most straightforward approach for generating optically active tertiary phosphines which are highly useful ligands in asymmetric catalysis.[2] Nevertheless, method of enantioselective addition of secondary phosphine to C=C double bond remains rudimentary as compared to the addition of dialkyl phosphates and secondary phosphine oxides. The main challenge arises from the former is that the new-born tertiary phosphine products would render the original complex coordinative saturated which negatively impacts catalyst efficiency and chiral induction ability. Thus, the development of a catalyst system allowing efficient asymmetric hydrophosphination of alkenes is highly desirable.



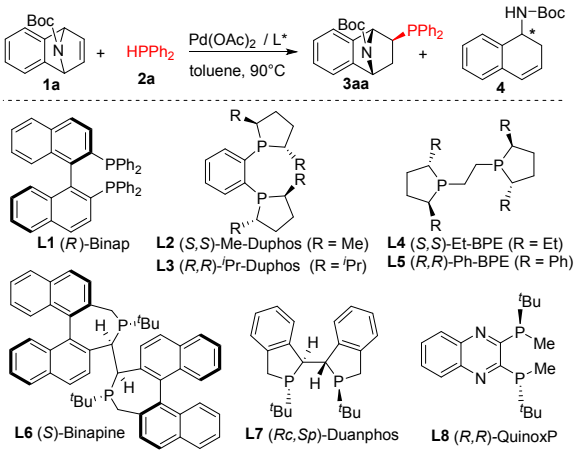
Scheme 1. (a) Classification of P−H bond addition reactions; (b) Transition metal-catalyzed asymmetric hydrophosphination of alkenes

In 2000, Glueck pioneering reported the Pt(Me-Duphos)-catalyzed asymmetric addition of secondary phosphines to acrylonitrile and acrylate esters, though with low enantioselectivities (Scheme 1b).[3] Successful metal-catalyzed asymmetric hydrophosphination of methacrylonitrile was later shown by Togni.[4] In 2010, Duan[5] and Leung[6] reported the hydrophosphination reaction of electron-deficient enones

catalyzed by chiral PCP-pincer palladium complex and phosphapalladacycle catalyst, respectively. Since then, examples of the palladium-catalyzed conjugate addition of diarylphosphines to α,β-unsaturated carbonyl compounds have emerged.[7] Notable complementary examples of asymmetric organocatalytic hydrophosphination of α,β-unsaturated carbonyl compounds were presented by Córdova[8] and Melchiorre.[9] While good stereoselectivities have been achieved in metal-catalyzed and organocatalytic asymmetric hydrophosphination of electron-deficient double bonds, substrates such as those involving non-polar C=C bonds remain challenging and are rarely tackled. The inherent difficulty of this addition reaction is attributed to the lower reactivity of simple/non-polar alkenes susceptible to nucleophilic attack versus electronically activated alkenes. Han reported Pd-catalyzed hydrophosphorylation of norbornenes with more reactive five-membered cyclic (pinacolato)P(O)−H, suggesting that bicyclic alkenes were good substrates in C-P bond formation.[10] In fact, the hydrophosphination of non-polar alkenes is still challenging, and it would be highly desirable to develop a catalyst system that facilitates this transformation, especially with high enantioselectivity. Such a scheme would directly afford a new series of chiral phosphine ligands.

Heterobicyclic alkenes are ideal substrates to be activated by transition metal complexes due to the angle strain and the proximal heteroatom coordination.[11] Indeed, upon using the proposed modular reaction between commercially available alkene and HPR_2, a new family of chiral phosphine ligands would be made easily and effectively. Furthermore, N or O atoms on the bridge of the heterobicyclic alkene might provide an additional coordinating site to transition metal; this would form a chiral bidentate complex for obtaining high level chiral induction.[12] Thus, we started to embark this investigation using azabenzonorbornadiene and diphenylphosphine as model substrates (Table 1). Initial screening of Pd precursors revealed that $Pd(OAc)_2$ was superior. Strongly chelating ligands result in good enantioselective control. High ee values were observed with bulkier ligands, i.e., **L3**, **L5,** and **L6** (Table 1, entries 3, 7, 8). Some other bisphosphine ligands led to a fair amount of reductive ring-opening product **4** where $HPPh_2$ was the H donor.[13] (*R,R*)-Ph-BPE **L5** gave an 82% yield of **3aa** with the best ee (98%), yet with 11% yield of byproduct **4** with 89% ee, in toluene at 90°C for 6 h. To our delight, the byproduct could be suppressed by adding 10 mol % $Fe(OAc)_2$ (the screening of additive, see Table S1). With the optimized catalyst system, the desired chiral phosphine product **3aa** was obtained exclusively in 95% yield with 97% ee (Table 1, entry 6). The yield and ee were further improved to 97% and 99%, respectively, by lowering the reaction temperature from 90°C to 70°C (Table 1, entry 10). Other solvents such as DME, dioxane, and THF also gave good yields and high ees (see the Supporting Information). The resulting phosphine product **3aa** was found highly air stable which is in contrast to other reported phosphines generated via 1,4-addition, where those products were required to oxidize to stable phosphine oxides *in situ* by H_2O_2 or to be reduced to phosphine-borane by *in situ* reaction with $NaBH_4$.[5-9]

Table 1. Ligand screening for Pd-catalyzed asymmetric hydrophosphination of azabenzonorbornadienes with diphenylphosphines[a]

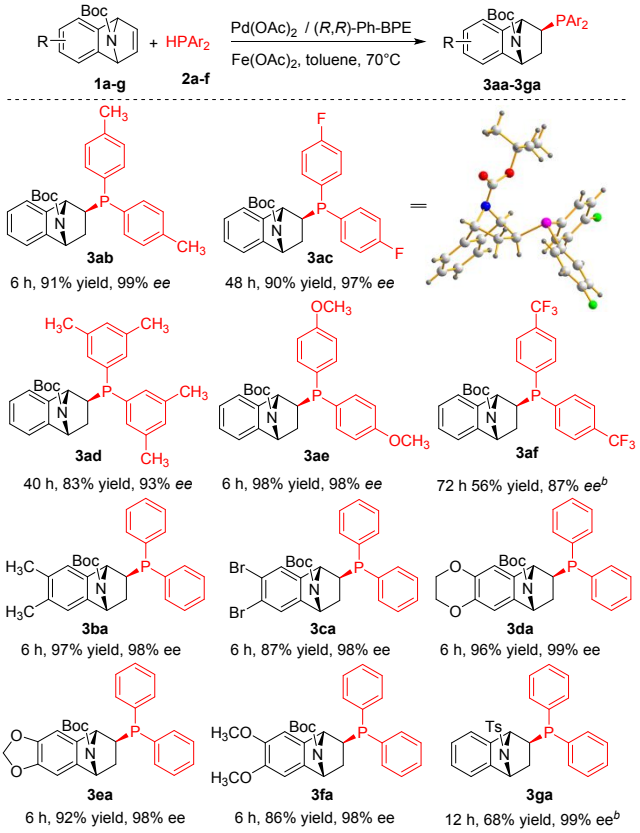


			3aa		4	
entry	ligand	time (h)	yield (%)[b]	ee (%)[c]	yield (%)[b]	ee (%)[c]
1	**L1**	72	45	17	-	-
2	**L2**	12	71	82	16	39
3	**L3**	12	70	93	16	88
4	**L4**	6	70	79	16	51
5	**L5**	6	82	98	11	89
6[d]	**L5**	6	95	97	trace	-
7	**L6**	6	53	96	45	>99
8	**L7**	12	81	86	8	-
9	**L8**	12	92	81	trace	-
10[d, e]	**L5**	6	97	99	trace	-

[a]Reaction conditions: $Pd(OAc)_2$ (5 mol %) and Ligand (6 mol %) in toluene (2 mL) were stirred at r.t. for 30 min under argon. **1a** (0.1 mmol) and **2a** (0.2 mmol) were added, and the reaction mixtures were stirred at 90°C for time indicated. [b]Isolated yields. [c]Determined by HPLC analysis. [d]10 mol % $Fe(OAc)_2$ was added as additive. [e]The reaction was performed at 70 °C.

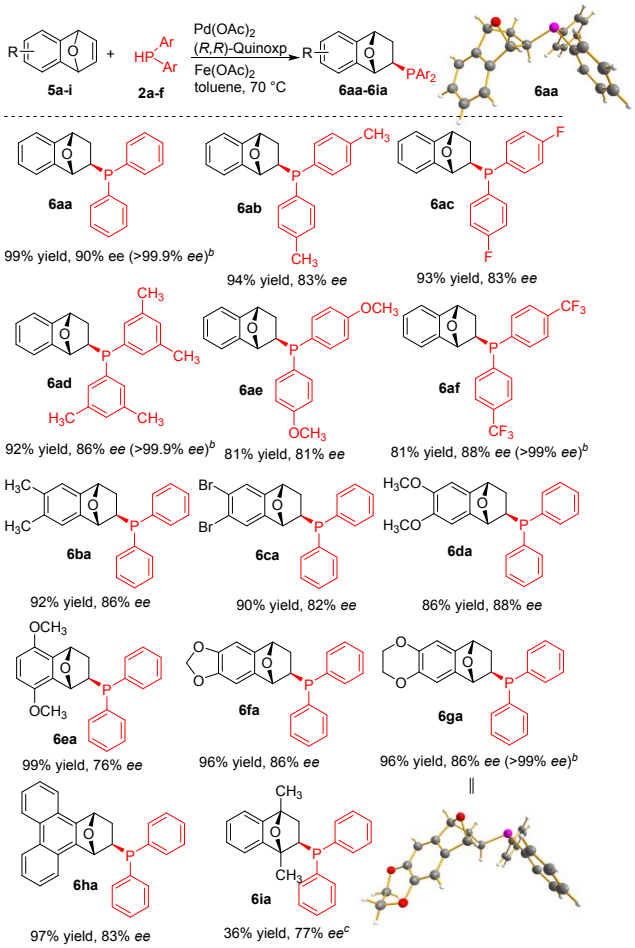
With optimized conditions in hand, we next investigated the substrate scope of both azabenzonorbornadienes and diarylphosphines (Scheme 2). Aryl moieties (**2b-2f**) with a variety of substituents were successfully applied to the reaction with **1a**, and gave the corresponding addition products **3ab-3af** in 56-98% yields with the enantioselectivities ranging from 87% to 99% ees. Diarylphosphine with an electron-withdrawing CF_3 group was found to be slightly sluggish under these reaction conditions, and gave **3af** in 56% yield with 87% ee after prolonged reaction time. The reaction partner of azabenzonorbornadienes **1b-f** with various substituents at the aromatic moiety proceeded well, and provided the products **3ba-3fa** in 86-97% yield and 98-99% ee. The bromo group in **3ca** remained intact under these conditions and allowed further potential functionalization. The nature of the substituted group on the nitrogen atom in azabenzonorbornadienes played a critical role to the product yield. When the Ts group was used instead of the Boc group, the product yield of **3ga** decreased to 68% although the ee value remained excellent. To demonstrate the practicability, we also performed a scale-up experiment using 6.80 g (28 mmol) of azabenzonorbornadienes **1a** as the substrate. This protocol offered excellent product yield of **3aa** (10.94 g, 91%) without compromising the enantioselectivity (99% ee). The absolute configuration of **3ac** was determined by

X-ray diffraction analysis, and other products **3** were assigned by analogy.[14]



[a]Reaction conditions: $Pd(OAc)_2$ (5 mol %), $Fe(OAc)_2$ (10 mol %), and (*R,R*)-Ph-BPE (6 mol %) in toluene (2 mL) were stirred at r.t. for 30 min under argon. **1a-j** (0.1 mmol) and **2a-f** (0.2 mmol) were added, and the reaction mixtures were stirred at the 70°C for indicated period of time. Isolated yields were shown; ees were determined by HPLC analysis. [b]The reaction was not completed.

Scheme 2. Substrate scope of azabenzonorbornadiene and diarylphosphines[a]



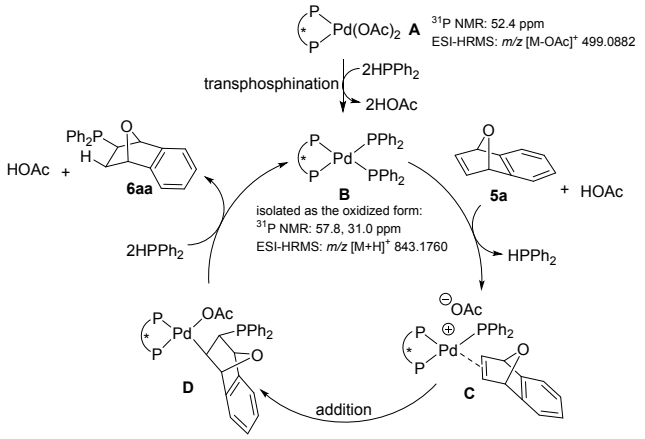
[a]Reaction conditions: $Pd(OAc)_2$ (5 mol %), $Fe(OAc)_2$ (10 mol %), and (*R,R*)-QuinoxP (6 mol %) in toluene (2 mL) was stirred at r.t. for 30 min under argon. **5a-j** (0.15 mmol) and **2a-f** (0.3 mmol) were added, and the reaction mixtures were stirred at the 70°C for 12 h. Isolated yields were shown; ees were determined by HPLC analysis. [b]ees after recrystallization are parentheses. [c]The reaction was not completed.

Scheme 3. Substrate scope of oxabenzonorbornadiene and diarylphosphines[a]

Encouraged by the capacity for asymmetric hydrophosphination of azabenzonorbornadienes, we next focused on oxabenzonorbornadienes (Scheme 3).[15] The optimal reaction conditions for asymmetric hydrophosphination of oxabenzonorbornadienes was in toluene at 70°C with 5 mol % $Pd(OAc)_2$, 6 mol % (*R,R*)-QuinoxP, and 10 mol % $Fe(OAc)_2$ (see Supporting Information for screening details). In addition to diphenylphosphine, both electron-rich and -poor diarylphosphines **2b-2f** were found applicable nucleophiles in reacting with oxabenzonorbornadiene **(5a)**. This reaction afforded the corresponding chiral phosphines **6aa-6af** in excellent yields and high enantioselectivities (81-99% yield, 81-90% ee) (Scheme 3). Essentially no significant electronic effect was observed on the substituted oxabenzonorbornadiene substrates, and the desired adducts **6ba-6ha** were given in high yields (86-99%) with consistently good enantioselectivities (76-88% ee). Substrate **5h** has an extended aromatic structure also

gave a high yield and good ee. Steric hindered oxabenzonorbornadienes **5i** reacted smoothly with diphenylphosphine to give the desired product with 77% ee, yet in low conversion. To show the synthetic utility of this method, we performed a gram-scale experiment with 3 mol % of Pd catalyst. Product **6aa** was afforded in excellent yield (1.704 g, 86%) and ee (90%) from substrate **1a** (6 mmol, 0.864 g). Although the product enantioslectivities were slightly lower when compared with the products from azabenzonorbornadienes, the final adducts can be easily recrystallized to give the enantiopure form, and the ee levels of **6aa**, **6ad**, **6af**, **6ga** were all improved to >99%, in which they are ready to serve as chiral ligands for further applications in asymmetric catalysis.

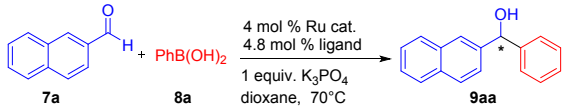
On the basis of a preliminary NMR study (see the Supporting Information), we proposed a mechanistic pathway for this catalysis (Scheme 4). Chiral palladium complex **A** is formed by the $Pd(OAc)_2$ and (*R,R*)-QuinoxP. The formation of intermediate **A** was observed and confirmed by ^{31}P NMR experiments. Transphosphination between the diarylphosphine and the chiral palladium **A** probably affords the palladium phosphido complex **B**. Then, oxabenzonorbornadiene **5a** coordinates to complex **B** and produces the Pd-phosphido-alkene complex **C**. Subsequent nucleophilic attack of the diarylphosphido group on palladium to the C=C double bond of oxabenzonorbornadiene provides intermediate **D**. Protonlysis with diarylphosphine affords the phosphine product **6aa** and regenerates the active palladium complex **B**. The catalytic cycle consists of transphosphination, coordination, phosphine addition, and protonolysis.



Scheme 4. Proposed mechanism.

The investigation of efficient chiral ligands remains the center of research in asymmetric catalysis. The most developed and explored chiral monophosphine ligands are often focused on biaryl, spiro, ferrocenyl, TADDOLs, and other frameworks.[16] Enjoying the effective asymmetric hydrophosphination of aza- and oxabenzonorbornadienes, many aza-monophosphine ligands **3aa-3ga** and oxa-monophosphine ligands **6aa-6ia** were obtained in high yields with excellent enantioselectivities in one step. We thus attempted to apply these oxa- and aza-benzonorbornadiene-backbone chiral ligands in Ru-catalyzed arylation of aldehydes. In fact, there are limited examples of the asymmetric addition of arylboronic acids to aryl aldehydes, unlike the extensive studies of the asymmetric arylation of α,β-unsaturated carbonyl compounds and imines. Only chiral rhodium[17] and two ruthenium catalysts[18] have been described. Certainly, aldehydes are more difficult substrates than imines or activated ketones for achieving high enantioselectivities. To our delight, initial test in Table 2 showed monophosphine ligand **6aa** with an oxabenzonorbornadiene backbone provided the arylation product **9aa** in 99% yield with 85% ee (Table 2, entry 4). The more sterically hindered Oxaphos **6ad** with a xylyl group in the phosphino moiety gave comparable yield and ee (Table 2, entry 5). The reaction rate decreased when the ratio of Ru and ligand was 1:2, only 72% yield and 82% ee were obtained even in 90 h (Table 2, entry 7 *vs* 4). To better understand the structure of the active Ru catalyst for this transformation, a Ru-Oxaphos complex was prepared at a 1:1 ratio (see the Supporting Information). Similar yield and ee value were obtained when the complex was used as a catalyst, suggesting that Oxaphos **6aa** acted as a mixed bidentate ligand (Table 2, entry 8).

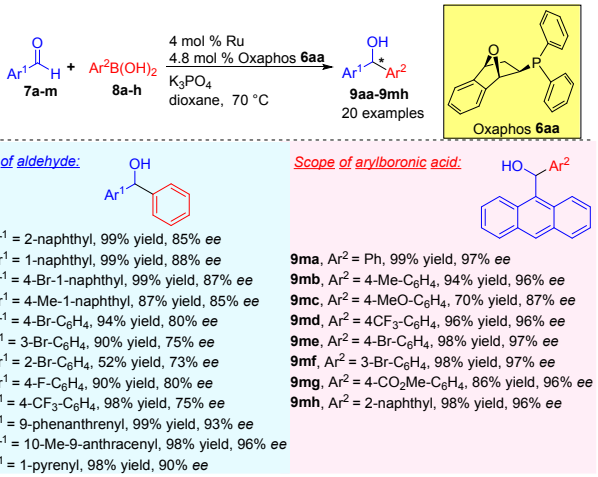
Table 2. Ligand screening for Ru-catalyzed asymmetric addition of phenylboronic acid to 2-naphthaldehyde[a]



entry	ligand	time (h)	yield (%)[b]	ee (%)[c]
1	(*R*)-Azaphos **3aa**	24	98	67
2	(*R*)-4-F-Azaphos **3ac**	24	94	60
3	(*R*)-4-MeO-Azaphos **3ae**	24	92	61
4	(*R*)-Oxaphos **6aa**	12	99	85
5	(*R*)-3,5-Me_2-Oxaphos **6ad**	24	99	84
6	(*R*)-CF_3-Oxaphos **6af**	48	80	80
7[d]	(*R*)-Oxaphos **6aa**	90	72	82
8[e]	(*R*)-Oxaphos **6aa** complex	12	92	84

[a]Reaction conditions: $[RuCl_2(cymene)]_2$ (2 mol %), ligand (4.8 mol %) in the dioxane (2 mL) was stirred at r.t. for 30 min under argon. **7a** (0.15 mmol), K_3PO_4 (0.15 mmol) and **8a** (0.3 mmol) were added. The reaction mixture was stirred at 70 °C for the time indicated. [b]Isolated yields. [c]Determined by HPLC analysis. [d]Ligand (*R*)-Oxaphos **6aa** (9.6 mol %, Ru:ligand = 1:2) was used. [e]Formerly prepared Ru-Oxaphos complex (Ru:ligand = 1:1) was used.

The scope of the Ru-catalyzed addition of arylboronic acids to aldehydes was presented in Scheme 5. Naphthaldehydes provided good yields and selectivities (**9aa**, **9ba, 9ca,** and **9da**). The enantioselectivities of the phenylation of aldehydes having ortho-substituents on the arene ring were lower than those obtained with meta or para-substituted aromatic aldehydes (**9ga** *vs* **9ea, 9fa**). Higher yields and ee values were observed when pi-extended aromatic aldehydes were employed (**9ja**, **9ka, 9la,** and **9ma**). In the Ru-catalyzed asymmetric addition of arylboronic acids to anthracene-9-carbaldehyde, excellent yields and ees were achieved regardless of the electronic properties and substitution pattern of arylboronic acids (**9ma-9mh**). Thus, the present catalytic system is highly effective in the asymmetric synthesis of diarylmethanols having polynuclear aromatic rings (>96% ee for most polynuclear aromatic aldehydes).



[a]Reaction conditions: $[RuCl_2(cymene)]_2$ (2 mol %) and (*R*)-Oxaphos **6aa** (4.8 mol %) in the dioxane (2 mL) were stirred at r.t. for 30 min under argon. **7a-m** (0.15 mmol), K_3PO_4 (0.15 mmol), and **8a-h** (0.3 mmol) were added, and the reaction mixtures were stirred at 70°C for the indicated period of time. Isolated yields; ee values were determined by HPLC.

Scheme 5. Ru-catalyzed asymmetric addition of phenylboronic acid to aryl aldehydes[a]

In conclusion, unlike hydrophosphinylation and hydrophosphonylation in generating phosphine oxides and phosphites, respectively, the hydrophosphination is still less developed. Here, we report a general asymmetric hydrophosphination of heterobicyclic benzonorbornadienes with diarylphosphines.[19] This method offered a direct and atom efficient access to chiral tertiary phosphines in high yields (up to 99% yield) with excellent enantioselectivities (up to 99% ee). Particularly noteworthy is that the resulting new family of chiral phosphine products have been successfully applied to the Ru-catalyzed asymmetric arylation of aldehydes with arylboronic acids, which highlighted their considerable potential for asymmetric catalysis. The modular structure and easy accessibility of monophosphines bearing aza- or oxa-benzonorbornadiene backbones makes it possible to optimize the ligand structure for a wide range of reactions catalyzed by a variety of transition metals. We anticipate that these unique monophosphines will open up a new platform in developing new chiral phosphine ligands.

ASSOCIATED CONTENT

Supporting Information. This material is available free of charge via the Internet at http://pubs.acs.org. Experimental procedures, screening of reaction conditions, mechanistic study and characterization data for all new compounds (PDF).

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Author Contributions

All authors have given approval to the final version of the manuscript.

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