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Synthetic Methods

Carbene-Catalyzed Enantioselective Hydrophosphination of α-Bromoenals to Prepare Phosphine-Containing Chiral Molecules

Rakesh Maiti[+], Jia-Lei Yan[+], Xing Yang, Bivas Mondal, Jun Xu, Huifang Chai, Zhichao Jin, and Yonggui Robin Chi**

Abstract: *Disclosed herein is the first carbene-organocatalyzed asymmetric addition of phosphine nucleophiles to the in situ generated α,β-unsaturated acyl azolium intermediates. Our reaction enantioselectively constructs carbon–phosphine bonds and prepares chiral phosphines with high optical purities. The phosphine products are suitable for transforming to chiral ligands or catalysts with applications in asymmetric catalysis. The diarylalkyl or trialkyl phosphine products from our catalytic reactions, air-sensitive and reactive in nature, can be trapped (and stored) in their sulfur-oxidized form for operational simplicities.*

Organophosphorus compounds with carbon-centered chiral tertiary phosphines are broadly used as ligands or organic catalysts for preparing bioactive compounds such as medicines (Figure 1a).[1,2] Asymmetric catalytic hydrophosphination (AHP) of electron-deficient olefins is an atom-economic approach for access to these chiral organophosphorus compounds (Figure 1b).[3] Most of such AHP reactions are mediated by transition metal catalysts.[4] The list of such successful metals includes Pd, Ni, Cu, Zn, Mg, etc. A drawback in many of these metal-catalyzed reactions is that the phosphine products can coordinate with the metals and thus cause catalyst poisoning.[2b] Metal-free organic catalytic approaches can avoid such catalyst poisoning problems. Unfortunately, such metal-free approach for this class of reactions is much less developed. To date, only two strategies appeared in the literature using organic catalysts (i.e., cinchona alkaloids[5] and pyrrolidines[6]) to achieve the AHP reaction as reported by Melchiorre[5,6a] and Cordova[6b,c] respectively (Figure 1b). These studies incorporate a cinchona alkaloid controlled enantioselective addition of $HPPh_2$ to nitroalkenes,[5] and chiral pyrrolidine-mediated addition of $HPPh_2$ to α,β-unsaturated aldehydes. Notably, moderate to high enantioselectivities with excellent yields were obtained in these reports. Despite of these two remarkable advancements to access carbon-centered chiral tertiary phosphines, a new organocatalytic system enabling a further improvement in substrate scope, especially the challenging β,β-disubstituted enals and various secondary phosphines, are still highly demanded.

We are interested in exploring *N*-heterocyclic carbene (NHC) organic catalysis[7] for new reactions and useful synthesis. The α,β-unsaturated azolium ester intermediates[8] generated via NHC catalysis can behave as effective Michael acceptors for asymmetric reactions. Research from our laboratories and others have recently demonstrated nitrogen and sulphur as heteroatom nucleophiles for asymmetric Michael-type reactions with α,β-unsaturated azolium ester

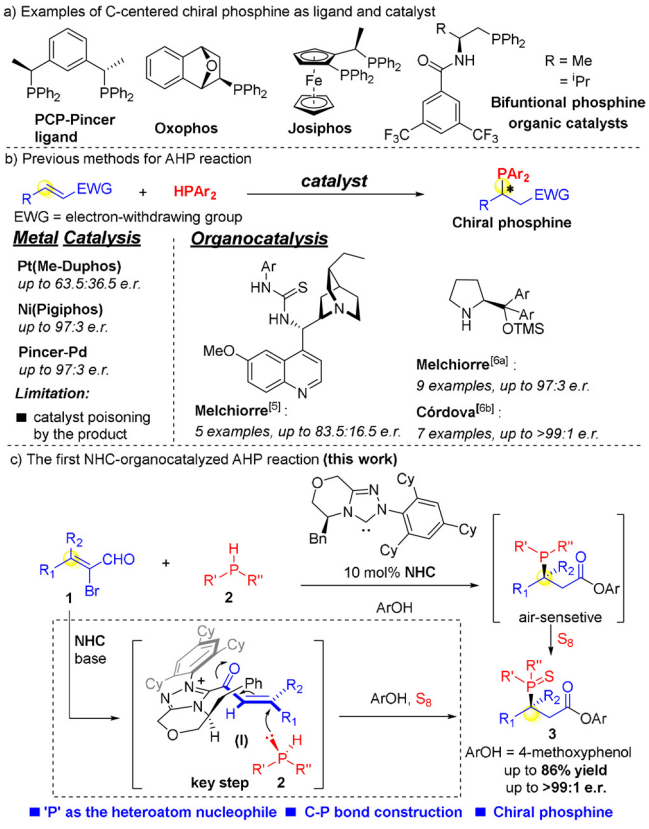

Figure 1. NHC-catalyzed nucleophilic addition of secondary hydrophosphine.

[*] Dr. Z. Jin, Prof. Dr. Y. R. Chi
Laboratory Breeding Base of Green Pesticide and Agricultural Bioengineering, Key Laboratory of Green Pesticide and Agricultural Bioengineering, Ministry of Education, Guizhou University
Huaxi District, Guiyang 550025 (China)
E-mail: robinchi@ntu.edu.sg
J. Xu, Prof. Dr. H. Chai
Guizhou University of Traditional Chinese Medicine
Guiyang 550025 (China)
E-mail: hfchai@126.com
R. Maiti,[+] J.-L. Yan,[+] X. Yang, B. Mondal, Prof. Dr. Y. R. Chi
Division of Chemistry & Mathematical Science, School of Physical & Mathematical Sciences, Nanyang Technological University
Singapore 637371 (Singapore)
[+] These authors contributed equally to this work.
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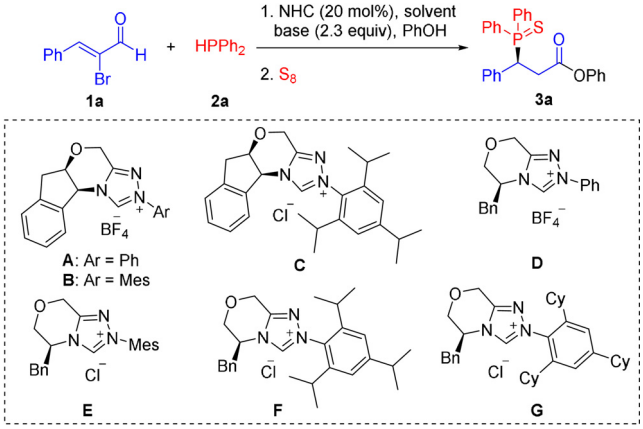
intermediates.[9] Here we disclose the first NHC-organocatalyzed asymmetric addition of phosphorus atom as a nucleophile to bromoenals (Figure 1c). Our reaction enantioselectively constructs a carbon–phosphine bond to prepare tertiary phosphines with high optical purities. Both diaryl- and dialkyl- secondary phosphines can be used as the nucleophiles; and enals bearing two substituents at the β-carbon are effective electrophiles. Since free phosphines are usually air-sensitive and can be oxidized by oxygen, our phosphine products are in situ trapped with sulphur for operational simplicities. Further transformation of our catalytic products can provide chiral bifunctional phosphines and bidentate bisphosphine ligands.

We chose α-bromocinnamaldehyde (**1a**) and diphenylphosphine (**2a**) as the model substrates to search for the suitable reaction conditions, with key results from the condition optimization summarized in Table 1 (see the ESI for details). The reaction was first conducted in PhCl as the solvent with DMAP as the base. Phenol was added as an external nucleophile to complete the catalytic cycle and regenerate the NHC catalyst. The addition of aminoindanol-derived triazolium salt (**A**) with an *N*-phenyl[10a] in the reaction as the NHC pre-catalyst led to the desired product (**3a**) in low yield with no enantioselectivity (Table 1, entry 1). Replacing the *N*-phenyl unit of **A** with an electron-donating and bulkier mesityl group (to get precatalyst **B**)[10b] provided the product **3a** in good yield, but without significantly improvement in enantioselectivity (Table 1, entry 2). To our delight, further increasement in the bulkiness of *N*-aryl substitutent by triisopropylphenyl motif (to get pre-catalyst **C**)[10c] resulted in an encouraging improvement in e.r. value (Table 1, entry 3, 90:10 e.r.). Further investigation of NHC precatalyst's effect on the reaction revealed that morpholine-based NHC catalysts (such as precatalyst **D**, **E** and **F**)[10d–f] showed better performance in both the enantioselectivity control and yield improvement compared with the corresponding aminoindanol-derived NHC precatalysts (Table 1, entries 4–6). Finally, we found that the bulkier cyclohexyl group substituted NHC precatalyst **G** was the optimal catalyst to promote the formation of **3a** with high yield and e.r. value (Table 1, entry 7). Further screening of solvents (Table 1, entries 8–10) eventually unveiled that toluene could behave as the most efficient one to mediate this asymmetric hydrophosphination reaction (Table 1, entry 10). Under these optimal conditions, **3a** could be afforded in 86% yield and 98:2 e.r. value (Table 1, entry 10). Other bases including organic and inorganic bases did not show any meaningful improvements in either product yields or enantioselectivies (Table 1, entries 11–12 and see Supporting Information).

Next, we evaluated the effect of phenols on the reaction outcomes. The results are illustrated in Table 2. It was found

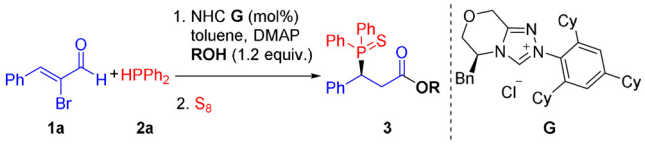
Table 1: Condition optimization.[a]



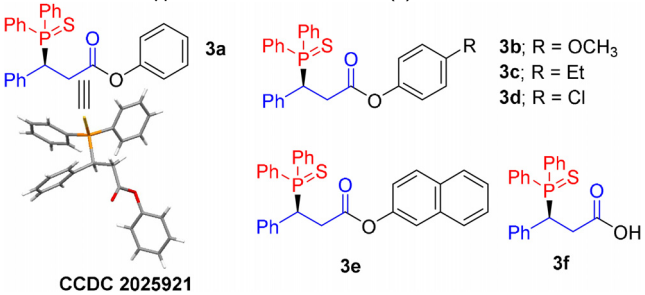
entry	conditions	yield [%][b]	er[c]
1	NHC **A**, DMAP, PhCl	29	50:50
2	NHC **B**, DMAP, PhCl	78	56:44
3	NHC **C**, DMAP, PhCl	50	90:10
4	NHC **D**, DMAP, PhCl	46	66:34
5	NHC **E**, DMAP, PhCl	97	63:37
6	NHC **F**, DMAP, PhCl	95	90:10
7	NHC **G**, DMAP, PhCl	95	96:4
8	NHC **G**, DMAP, THF	53	94:6
9	NHC **G**, DMAP, CH_2Cl_2	20	78:22
10	**NHC G, DMAP, toluene**	**86**	**98:2**
11	NHC **G**, DABCO, toluene	62	98:2
12	NHC **G**, CS_2CO_3, toluene	39	87:13

[a] Reaction conditions: **1a** (0.09 mmol.), **2a** (0.05 mmol), NHC pre-cat. (20 mol%), base (2.3 equiv), PhOH (1.2 equiv), solvent (1 mL) at RT for 12–24 hrs. [b] Yields were determined by ^{1}H NMR analysis with 1,3,5-trimethoxybenzene as the internal standard. [c] The e.r. values were determined via chiral-phase HPLC analysis. DMAP = 4-Dimethylaminopyridine. DABCO = 1,4-diazabicyclo[2.2.2]octane. See ESI for other screening of conditions.

Table 2: Screening of phenol.[a]



entry	ROH	product	NHC (mol%)	yield [%][b]	e.r[c]
1	Phenol	**3a**	**G** (20)	82	98:2
2	4-methoxyphenol	**3b**	**G** (20)	83	97:3
3	4-ethylphenol	**3c**	**G** (20)	65	93:7
4	4-chlorophenol	**3d**	**G** (20)	35	90:10
5	2-naphthol	**3e**	**G** (20)	80	96:4
6	H_2O	**3f**	**G** (20)	87	89:11
7	phenol	**3a**	**G** (10)	40	93:7
8	**4-methoxyphenol**	**3b**	**G (10)**	**81**	**98:2**
9	4-methoxyphenol	**3b**	**G** (5)[d]	73	96:4



[a] Reaction conditions: **1a** (0.18 mmol.), **2a** (0.1 mmol), NHC **G** pre-cat., DMAP (2.3 equiv), ArOH (1.2 equiv), solvent (2 mL), at RT for 24 hrs. [b] Isolated yield. [c] The e.r. values were determined via chiral-phase HPLC analysis. [d] The reaction was heated to 50°C, DMAP = 4-Dimethylaminopyridine.

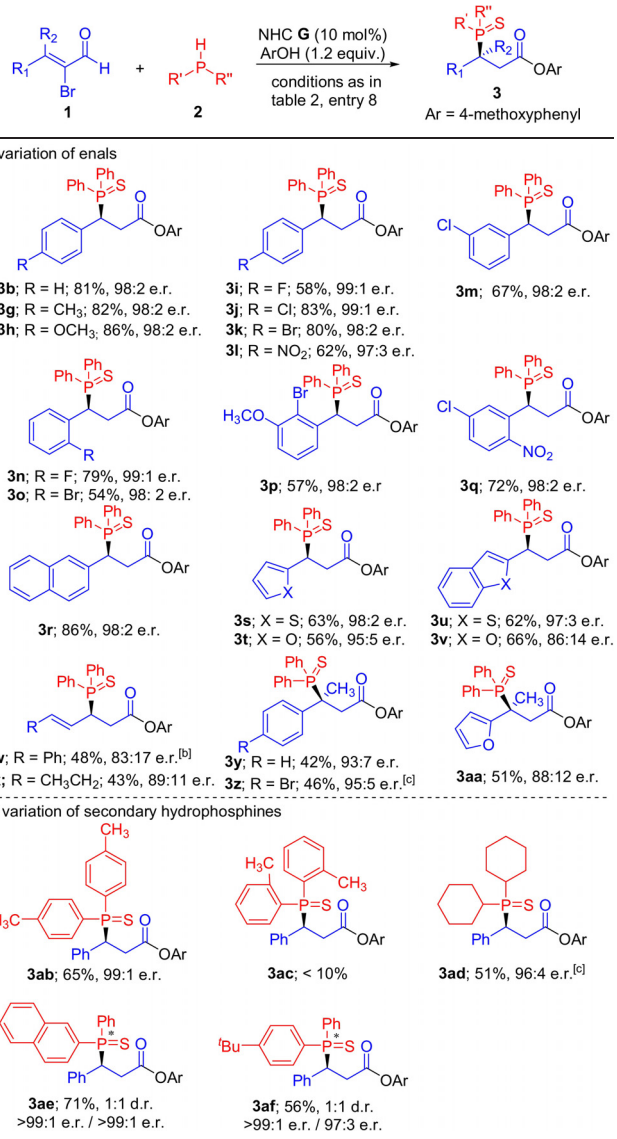
that phenol and phenols containing electron-donating group (such as 4-methoxy and 4-ethyl phenol) stimulated the reaction more efficiently than phenol containing electron-withdrawing group (4-chlorophenol) in terms of both yield and e.r. value (Table 2, entries 1–4). More bulkier 2-naphthol was also effective to furnish the desired product in good results (Table 2, entry 5). Interestingly, H_2O was potent to promote this catalytic reaction, providing the hydrophosphination product in high yield with satisfactory enantioselectivity (Table 2, entry 6). When the catalyst loading was reduced to 10 mol%, 4-methoxyphenol gave better results than phenol (Table 2, entries 7–8), with the desired product **3b** obtained in 81% yield and 98:2 e.r. value. The catalyst loading could be further reduced to 5 mol% without affecting the outcomes significantly with 4-methoxyphenol as nucleophile (Table 2, entry 9), although in this case reaction was required to be performed at 50 °C. The absolute configuration of **3a** was confirmed by X-ray analysis.[11]

With the optimized reaction conditions in hand (Table 2, entry 8), we next moved to assess the generality of the reaction (Table 3). At first, we examined the substrates scope of various α-bromoenal derivatives (**1**) with respect to **2a** as the model secondary phosphine substrate. α-bromocinnamaldehydes with both electron-donating groups (such as methyl and methoxyl) and electron-withdrawing groups (such as halogens and NO_2) were all tolerated at the 4-position of the phenyl ring, giving the corresponding products in good to high yields and excellent enantioselectivities (**3g-3l**). Introducing halogen atoms at the 3-position or 2-position of the phenyl ring led to the products in satisfactory results (**3m-3o**). α-bromocinnamaldehydes containing disubstituted benzene ring were also proved to be suitable substrates in our reaction (**3p** and **3q**). The replacement of the β-phenyl group of α-bromocinnamaldehyde by naphthyl moiety has a very little effect on the outcomes (**3r**). The phenyl ring in cinnamaldehyde could also be switched to heteroaryl units, affording the corresponding products in moderate yields without affecting the enantioselectivities significantly (**3s-3v**). Besides, α-bromocinnamaldehyde with a further transferable alkenyl group could undergo hydrophosphination reaction under the optimized conditions at 0 °C, affording the product **3w** in 48% yield and 83:17 e.r. Alkyl substituted α-bromodienal was also compatible in our strategy, providing **3x** in acceptable yield with 89:11 e.r. value. Notably, the challenging β,β-disubstituted enals could be used in our catalytic system, with the desired products isolated in moderate yields and high enantiopurities (**3y** and **3z**). Replacing the phenyl ring of β,β-disubstituted α-bromoenal by furan unit could lead product **3aa** in 51% yield and 88:12 e.r.

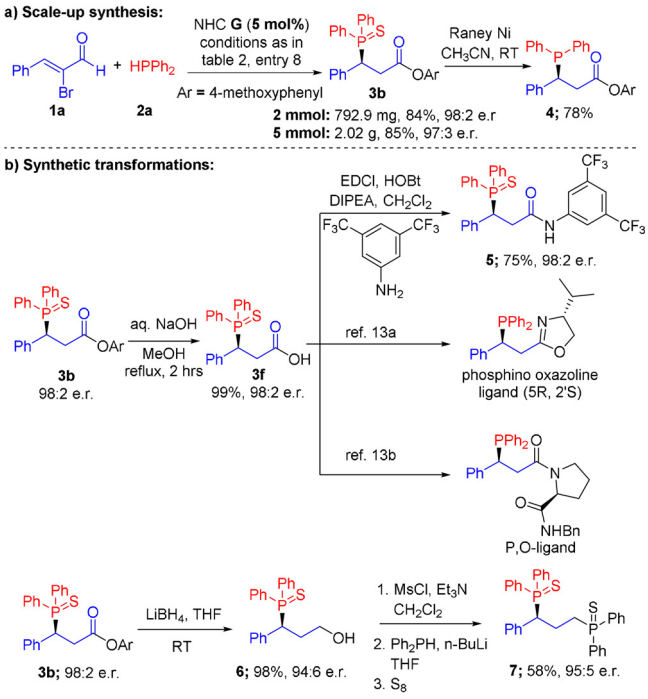
Different secondary phosphines were also tested under the standard reaction conditions with α-bromocinnamaldehydes **1a** as the model substrate. The reaction with di-*p*-tolylphosphine as the nucleophile proceeded smoothly and delivered **3ab** in good results (65% yield, 99:1 e.r.). When di-*o*-tolylphosphine was used, only trace amount of product (**3ac**) was detected. This is probably due to the higher steric hindrance around the P-center. Interestingly, bulky di-cyclohexyl-phosphine was also amenable under our catalytic reaction conditions, furnishing the product **3ad** in 51% yield and 96:4 e.r. value. Although P-stereogenic organophosphorus molecules often show enhanced efficacy in asymmetric catalysis because of its proximity to the activated center, a few catalytic approaches have been developed to obtain these compounds.[12] Here our protocol was proved to be efficient to access these compounds, as employment of unsymmetric secondary hydrophosphines in our catalytic system gave the desired product **3ae** and **3af** bearing a P-stereogenic center in moderate yields and excellent optical purities.

To further demonstrate the utility of our method, large scale AHP (2 mmol and 5 mmol scale) have been carried out (Scheme 1a). After reducing the catalytic loading to only 5 mol%, the optically enriched C-centered tertiary phosphine sulfide **3b** can be afforded in 84% yield (792.9 mg) with 98:2 e.r. value at 2 mmol scale. To our delight, the target product of

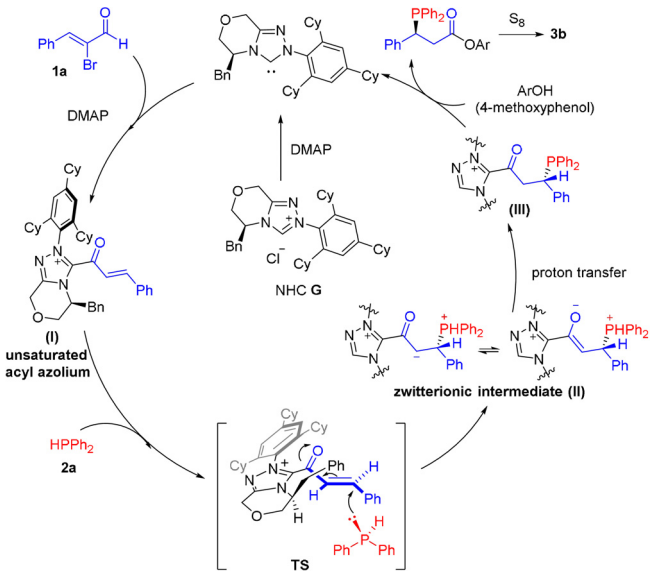
Table 3: Substrates Scope.[a]



[a] Isolated yields of the products and the e.r. values were determined via chiral-phase HPLC analysis. [b] The reaction was carried out at 0 °C for 48 h. [c] 20 mol% NHC was used.



Scheme 1. Scale-up synthesis and synthetic transformations.



Scheme 2. Postulated reaction mechanism.

3b can be afforded in an even higher yield (85 %, 2.02 g) with an excellent 97:3 er value when the reaction was performed at 5 mmol scale. Under Raney Ni reductive conditions, free chiral tertiary phosphine **4** was successfully obtained in 78 % yield. Notably, this free phosphine product is quite stable when stored under nitrogen atmosphere (over six months). We next showed effective conversion of our chiral product into interesting bifunctional phosphine (**5**) and bidentate phosphine ligands (**6** and **7**). Hydrolysis of compound **3b** under basic condition gave the acid product **3 f** in excellent yield. Further amidation could lead to the optical pure H-bond donor bifunctional phosphine (**5**) in 75 % yield without any erosion in the enantioselectivity. The product **3 f** could also be transformed to the bidentate phosphino oxazoline ligand[13a] and P,O-ligand[13b] (used in Pd-catalyzed asymmetric allylic alkylation[13b,c]) in an efficient manner.[13] Additionally, direct reduction of **3b** with $LiBH_4$ furnished the alcohol product **6** in 98 % yield with slight decline in enantiopurity. Thereafter, important chiral bidentate bis-phosphine (**7**) ligand could be accessed by protecting the -OH group of compound **6** with MsCl, followed by nucleophilic substitution reaction with $HPPh_2$ under the basic conditions.

The postulated reaction pathway is illustrated in Scheme 2. Briefly, addition of the NHC catalyst to α-bromoenal under basic conditions leads to the well-established unsaturated acyl azolium intermediate **I**. The key step here is the nucleophilic addition of secondary hydrophosphine to intermediate **I**. Highly nucleophilic $HPPh_2$ adds to the intermediate **I** and forms the zwitterionic intermediate **II**. Then, intermediate **II** converts to the intermediate **III** immediately through a proton transfer process (See ESI for detailed mechanism). During the AHP, the morpholine moiety controls the approach of the secondary hydrophosphine to **I**, resulting in the nucleophilic addition of $HPPh_2$ from *Si* face of the unsaturated acyl azolium (**I**) preferentially (Scheme 2, **TS**). Finally, the NHC is released from **III** by 4-methoxyphenol, followed by the oxidation of chiral phosphine with S_8 to afford the terminal product (**3b**) in high enantiopurity.

In summary, we have developed a carbene-catalyzed asymmetric hydrophosphination of enals. Key step in our approach involves a highly selective addition of 'P' atom of secondary phosphine to NHC-bonded α,β-unsaturated acyl azolium intermediate. The reaction affords chiral phosphines with highly optical purities. Further transformations of our products lead to bifunctional molecules with applications as ligands for asymmetric catalysis. Further studies in employing phosphine atom in catalysis or bioactivity studies, including constructing molecules with phosphine-centered chiralities, are in progress in our laboratories.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: asymmetric hydrophosphination · chiral phosphine · C–P bond construction · N-heterocyclic carbene

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