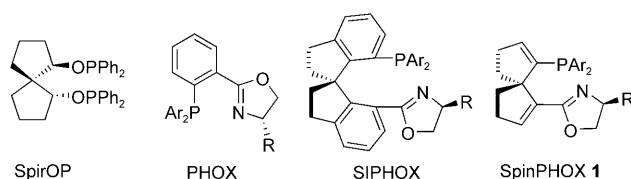


Spiro[4,4]-1,6-nonadiene-Based Phosphine–Oxazoline Ligands for Iridium-Catalyzed Enantioselective Hydrogenation of Ketimines**

Zhaobin Han, Zheng Wang, Xumu Zhang, and Kuiling Ding*

In chiral-ligand design, the right choice of skeleton and a suitable combination of the scaffold motif with the chelating coordination moiety can result in excellent enantioselective control of the catalysis.^[1] In this context, the spiro backbone has been recognized as one of the superior structures for the construction of chiral ligands^[2,3] since the pioneering work of Chan et al.^[4] with SpirOP (Scheme 1), derived from the



Scheme 1. The structures of chiral ligands SpirOP, PHOX, SIPHOX, and SpinPHOX (**1**). Ar: aryl.

enantiopure spiro[4,4]-nonane-1,6-diol,^[5] as the chiral ligand for rhodium-catalyzed asymmetric hydrogenation of α -dehydroamino acid derivatives. In terms of chelating moieties, phosphine–oxazoline (P,N) hybrid ligands (for example, PHOX; Scheme 1) represent one of the most versatile types of chiral inducers in various transition-metal-catalyzed reactions.^[6] By taking advantage of the spiro backbone and the chelating units of PHOX, Zhou and co-workers have recently developed a type of P,N ligand containing the spirobiindane skeleton (SIPHOX; Scheme 1); this ligand demonstrated excellent asymmetric induction in Ir^I-catalyzed asymmetric hydrogenation reactions.^[7]

Catalytic asymmetric hydrogenation of prochiral imines represents one of the most direct and efficient approaches for attaining optically active amines, one type of important building block for the synthesis of many biologically interesting substances.^[8] Although great efforts have been made in the last few decades, this area remains a major challenge, in contrast to the relative maturity of asymmetric hydrogenation of olefins or ketones, probably due to the *E/Z* isomeric mixture of imine substrates and the poisoning effect of the resultant amines on the catalysis.^[8a] Among the various catalytic systems developed so far,^[9–12] iridium complexes have proven to be highly efficient for this type of transformation.^[13] The use of P,N ligands in Ir^I-catalyzed asymmetric hydrogenation of imines was pioneered by Pfaltz and co-workers^[14] who used the PHOX ligand to mimic the coordination sphere of the Crabtree catalyst.^[15] Following this leading report, a variety of P,N-ligand-modified Ir^I complexes have been prepared and employed in the hydrogenation of ketimines, and some of them have proven to be very efficient.^[16] However, most of those catalysts are usually effective for *N*-aryl ketimine substrates. So far, *N*-alkyl ketimines remain very challenging substrates in terms of reactivity and enantioselectivity, as evidenced by the fact that these substrates can only be hydrogenated with moderate enantioselectivities in most cases.^[13,14,16]

As a continuation of our ongoing endeavor to seek chiral ligands with novel backbones, we became interested in developing the spiro[4,4]-1,6-nonadiene system with its readily accessible spiro backbone. The spiro[4,4]-1,6-nonadiene motif in SpinPHOX (an abbreviation for the spiro[4,4]-1,6-nonadiene-based phosphine–oxazoline ligands; **1** in Scheme 1) has only one chiral center and can be easily derived from spiro[4,4]-1,6-nonadiene by enolization under basic conditions,^[17] which avoids the complex stereochemistry and difficulties associated with diastereomer separation in spiro[4,4]nonane-based ligands. An obvious advantage of spiro[4,4]-1,6-nonadiene over spiro[4,4]nonane is the more convenient functionalization at the 1- and 6-positions of the backbone of the former, because these sp² carbon atoms are well suited for further anchoring of the chelating ligation moieties during chiral-ligand construction. Herein, we communicate the preliminary results on the development of one type of chiral phosphine–oxazoline ligands with the spiro[4,4]-1,6-nonadiene backbone (SpinPHOX, **1**) and their application in Ir^I-catalyzed enantioselective hydrogenation of ketimines. The reactions proceed smoothly under mild conditions, with particular asymmetric-induction efficiency for the more challenging *N*-alkyl ketimine substrates (up to 98% *ee*).

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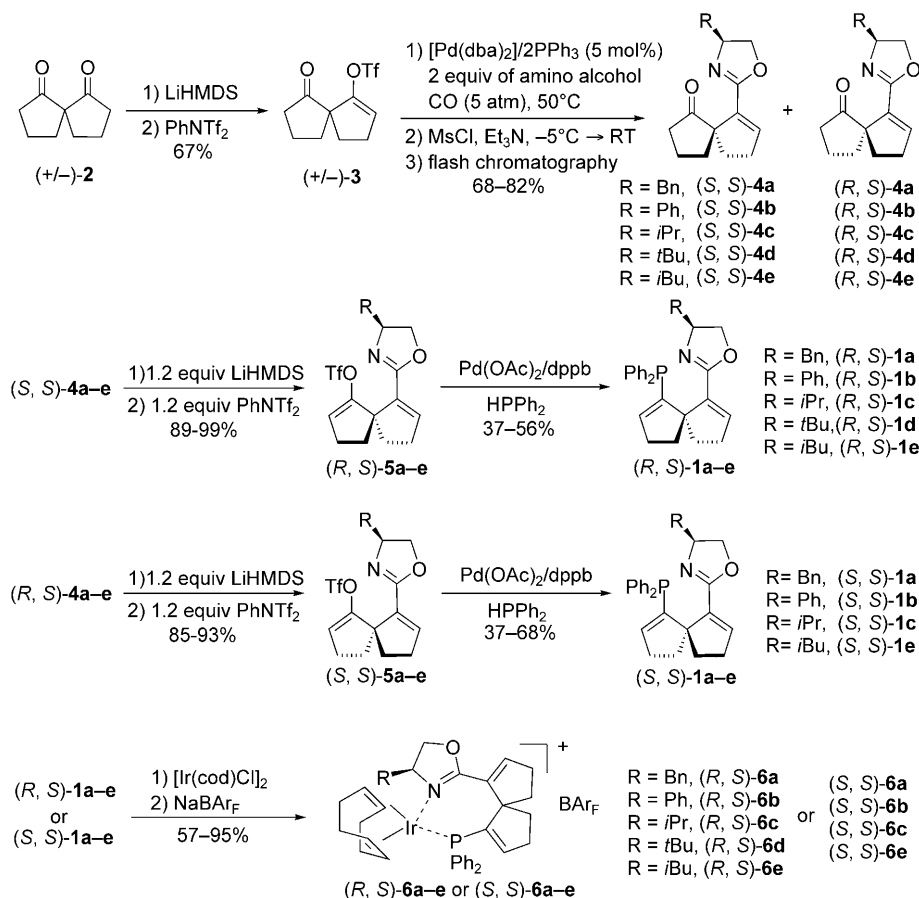
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As illustrated in Scheme 2, the synthesis of enantiopure SpinPHOX (**1**) ligands is quite simple and straightforward from readily available racemic spiro[4,4]nonane-1,6-dione

plished by Pd-catalyzed cross-coupling of enol triflates **5** with diphenylphosphane,^[21] to afford the target SpinPHOX (**1a–e**) ligands in 37–68 % yields. Cationic iridium(I) complexes of the SpinPHOX (**1**) ligands were readily prepared with a standard procedure^[22] by the reaction of [Ir(cod)Cl]₂ with the corresponding (*R,S*)-**1** or (*S,S*)-**1** in CH₂Cl₂ under reflux conditions, followed by counteranion exchange with NaBAR_F. The resultant complexes, (*R,S*)-**6a–e** and (*S,S*)-**6a–e**, are stable enough to allow purification by column chromatography on silica gel, with moderate to excellent yields (57–95 %) being attained.



Scheme 2. Synthesis of SpinPHOX ligands (*R,S*)-**1** and (*S,S*)-**1** and of their Ir^I complexes (*R,S*)-**6** and (*S,S*)-**6**. LiHMDS: lithium hexamethyldisilazane; Tf: trifluoromethanesulfonyl; dba: dibenzylideneacetone; Ms: methanesulfonyl; Bn: benzyl; dppb: 1,1'-bis(diphenylphosphanyl)butane; cod: cycloocta-1,5-diene; NaBAR_F: sodium tetrakis(3,5-bis(trifluoromethyl)phenyl)borate.

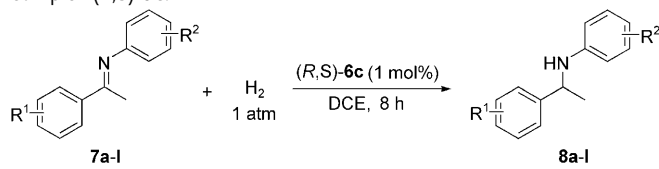
(**2**).^[18] The spiro diketone **2** was first converted into the mono-enol triflate ester **3** under basic conditions.^[17] The Pd-catalyzed carbonylation of **3** in the presence of a variety of enantiopure *S*-amino alcohols directly afforded the corresponding hydroxy amides in nearly quantitative yields.^[19] The resulting hydroxy amides were readily converted into the corresponding oxazolines, **4**, by treatment with MsCl in the presence of triethylamine.^[20] To our delight, the two diastereomers, (*S,S*)-**4a–e** and (*R,S*)-**4a–e**, respectively, could all be readily separated by flash chromatography on the gram scale with high yields (66–86 % for the two steps from racemic **3**). It is obvious that the present protocol can significantly simplify the synthetic route because it avoids the use of enantiopure spiro diketone **2** as the starting material. The isolated enantiomers of (*S,S*)-**4a–e** and (*R,S*)-**4a–e** were allowed to react with PhNTf₂ in the presence of LiHMDS to give the triflate derivatives (*R,S*)-**5a–e** and (*S,S*)-**5a–e**, respectively, in excellent yields (85–99 %). The introduction of the diphenylphosphine group to the spiro backbone was then accom-

plished by Pd-catalyzed cross-coupling of enol triflates **5** with diphenylphosphane,^[21] to afford the target SpinPHOX (**1a–e**) ligands in 37–68 % yields. Cationic iridium(I) complexes of the SpinPHOX (**1**) ligands were readily prepared with a standard procedure^[22] by the reaction of [Ir(cod)Cl]₂ with the corresponding (*R,S*)-**1** or (*S,S*)-**1** in CH₂Cl₂ under reflux conditions, followed by counteranion exchange with NaBAR_F. The resultant complexes, (*R,S*)-**6a–e** and (*S,S*)-**6a–e**, are stable enough to allow purification by column chromatography on silica gel, with moderate to excellent yields (57–95 %) being attained.

With iridium complexes (*R,S*)-**6** and (*S,S*)-**6** in hand, we then investigated their asymmetric induction in the catalytic hydrogenation of imines by using *N*-(1-phenylethylidene)aniline (**7a**) as a model substrate with a catalyst loading of 1 mol %. After screening of a variety of reaction conditions (see the Supporting Information, Table S1) including the solvent, temperature, and hydrogen pressure, the reaction performed in 1,2-dichloroethane (DCE) at 10 °C and 1 atm of H₂ turned out to be optimal. Such an ambient pressure of hydrogen is particularly favorable for practical manipulation of the hydrogenation process. The chirality at the spiro backbone of **6** was found to have a significant impact on the asymmetric induction of the catalysis. The combination of an *R* configuration of the spiro backbone and an *S* configuration of the oxazoline moiety was disclosed as a matched case (as in (*R,S*)-**6a–e**). Further examination of the substituent effect of the oxazoline moiety of complexes (*R,S*)-**6a–e** on the catalysis (see the Supporting Information, Table S1) revealed that catalyst (*R,S*)-**6c** (bearing an *i*Pr group in the ligand) was the best in terms of both reactivity and enantioselectivity; it afforded the corresponding hydrogenation product (*R*)-**8a** in quantitative yield with up to 91 % *ee* (Table 1, entry 1).

Accordingly, a variety of *N*-aryl ketimines with various substituents were hydrogenated under 1 atm of H₂ in the presence of (*R,S*)-**6c** (1 mol %) at 10 °C to afford the corresponding chiral amines with good to excellent enantioselectivities (88–95 % *ee*; Table 1, entries 1–12). It should be noted that when the catalyst loading of (*R,S*)-**6c** was reduced to 0.5 mol %, the hydrogenation of **7a** still proceeded smoothly under ambient pressure of H₂ at 10 °C and afforded (*R*)-**8a** in >99 % yield and with 92 % *ee* (Table 1, entry 13).

Table 1: Asymmetric hydrogenation of *N*-aryl ketimines **7a–l** catalyzed by complex **(R,S)-6c**.^[a]



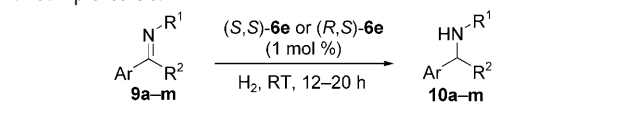
Entry	Imine	R ¹	R ²	Conv. [%] ^[b]	ee [%] ^[c]
1	7a	H	H	> 99	91 (R)
2	7b	4-Me	H	> 99	88 (–)
3	7c	4-Cl	H	> 99	92 (+)
4	7d	4-Br	H	99	91 (R)
5	7e	3-Cl	H	> 99	93 (–)
6	7f	3-Br	H	> 99	93 (–)
7	7g	4-CF ₃	H	> 99	92 (–)
8	7h	3,4-(CH ₃) ₄	H	> 99	95 (+)
9	7i	H	4-MeO	> 99	90 (+)
10	7j	H	4-Me	97	92 (+)
11	7k	H	4-Br	> 99	89 (+)
12	7l	4-Cl	4-MeO	> 99	91 (+)
13 ^[d]	7a	H	H	> 99	92 (R)
14 ^[e]	7a	H	H	> 99	92 (R)

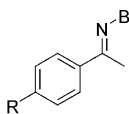
[a] Unless otherwise noted, the reactions were performed with 0.15 mmol of **7a–l** in DCE (1.5 mL) under 1 atm of hydrogen atmosphere in the presence of 1 mol % of **(R,S)-6c** at 10 °C. [b] Determined by ¹H NMR spectroscopy. [c] The ee values were determined by chiral HPLC with a Chiracel OD column, and the absolute configurations were determined by comparison of the optical rotation with that in the literature.^[7b] [d] 0.5 mol % of **(R,S)-6c** was used. [e] 0.1 mol % of **(R,S)-6c** was used under 20 atm of H₂ with a reaction time of 20 h.

When the catalyst loading was further reduced to 0.1 mol %, complete conversion of **7a** was achieved within 20 h under 20 atm of H₂ to provide the corresponding amine with the same enantiomeric excess (Table 1, entry 14).

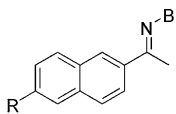
Catalysts **6** were not only efficient for the hydrogenation of *N*-aryl ketimines but also showed remarkable reactivity and enantioselectivity in the hydrogenation of more-challenging *N*-alkyl ketimines to provide *N*-alkyl amine derivatives in a convenient process. After a survey of iridium catalysts **6a–e** in the hydrogenation of *N*-(1-phenylethylidene)benzylamine (**9a**; see the Supporting Information, Table S2), catalysts **(S,S)-6e** or **(R,S)-6e** turned out to be optimal in terms of both reactivity and enantioselectivity of the catalysis. *N*-(1-Phenylethylidene)benzylamine (**9a**), prepared in a 13:1 ratio of *E/Z* isomers, was hydrogenated with complete conversion in the presence of **(S,S)-6e** (1 mol %) under 1 atm of H₂ in dichloroethane, to afford *(S)*-*N*-benzyl-*N*-(1-phenylethyl)amine (**10a**) with 91 % ee (Table 2, entry 1). To our knowledge, this value represents the highest enantioselectivity attained so far in the catalytic asymmetric hydrogenation of an *N*-benzylphenylketimine with iridium catalysts.^[13,14,16] The advantage of the use of *N*-benzylketimines over their *N*-aryl analogues is that the *N*-benzylamine product allows the facile selective removal of the *N*-benzyl group by simple hydrogenation with Pd/C catalysis to give the free primary amine.^[23] Other related *N*-(1-arylethylidene)-benzylamine derivatives, **9b–f**, were also hydrogenated by using the same catalyst under 5 atm of H₂ with 87–99 % of

Table 2: Asymmetric hydrogenation of *N*-alkyl ketimines in the presence of complexes **6e**.^[a]

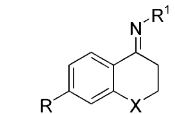




9a–f
a: R = H
b: R = OMe
c: R = Me
d: R = F
e: R = Cl
f: R = Br



9g,h
g: R = H
h: R = OMe



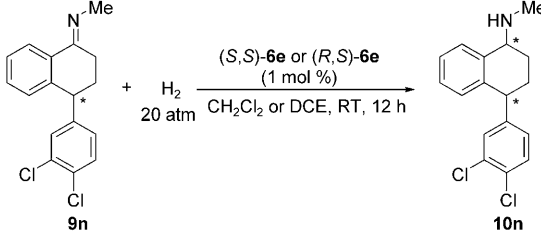
9i–m
i: R = H, X = CH₂, R¹ = Bn
j: R = OMe, X = CH₂, R¹ = Bn
k: R = H, X = CH₂, R¹ = Me
l: R = H, X = CH₂, R¹ = *i*Bu
m: R = H, X = O, R¹ = Bn

Entry	Imine (<i>E/Z</i> ratio)	Catalyst	Solvent	P _{H₂} [atm]	t [h]	Conv. [%] ^[b]	ee [%] ^[c]
1	9a (13:1)	(S,S)-6e	DCE	1	12	> 99	91 (S)
2	9b (17:1)	(S,S)-6e	DCE	5	20	> 99	90 (–)
3	9c (13:1)	(S,S)-6e	DCE	5	20	> 99	89 (–)
4	9d (22:1)	(S,S)-6e	DCE	5	20	> 99	88 (–)
5	9e (20:1)	(S,S)-6e	DCE	5	20	87	91 (–)
6	9f (17:1)	(S,S)-6e	DCE	5	20	90	89 (–)
7	9g (15:1)	(R,S)-6e	CH ₂ Cl ₂	20	12	> 99	92 (+)
8	9h (18:1)	(R,S)-6e	CH ₂ Cl ₂	20	12	> 99	93 (+)
9	9i (> 100:1)	(R,S)-6e	CH ₂ Cl ₂	20	12	99	96 (R)
10	9j (> 100:1)	(R,S)-6e	CH ₂ Cl ₂	20	12	> 99	95 (+)
11	9k (> 100:1)	(R,S)-6e	CH ₂ Cl ₂	20	12	> 99	98 (–)
12	9l (> 100:1)	(R,S)-6e	CH ₂ Cl ₂	20	12	> 99	96 (–)
13	9m (> 100:1)	(R,S)-6e	CH ₂ Cl ₂	20	12	> 99	98 (+)

[a] For the reaction conditions, see footnote [a] in Table 1. [b] Determined by ¹H NMR spectroscopy. [c] Determined by HPLC on a Chiracel AD-H column using the *N*-acetyl derivatives of **10a–m**.

conversion to provide the corresponding optically active *N*-benzylamines with ee values of 88–91 % (Table 2, entries 2–6). For the hydrogenation of *N*-(1-(naphth-2-yl)ethylidene)benzylamine derivatives **9g** and **9h** with *E/Z* ratios of 15:1 and 18:1, respectively, **(R,S)-6e** was found to be more enantioselective than **(S,S)-6e** and to afford the corresponding benzylamines with 92–93 % ee at 20 atm of H₂ in dichloromethane (Table 2, entries 7 and 8). It should be noted that this type of catalyst is particularly effective for the hydrogenation of *N*-alkyl ketimines derived from tetralone analogues to give the corresponding *N*-benzyl-, *N*-methyl-, or *N*-isobutyl-1,2,3,4-tetrahydronaphthalen-1-amine derivatives, a type of key intermediate for the synthesis of biologically important molecules, with 95–98 % ee (Table 2, entries 9–13). These results are unprecedented in the transition-metal-catalyzed asymmetric hydrogenation of *N*-alkyl ketimines derived from tetralone analogues.

Encouraged by the remarkable enantioselectivity in the hydrogenation of the *N*-methylimine of tetralone (**9k**) with catalyst **(R,S)-6e** (Table 2, entry 11), we subsequently employed our methodology to the asymmetric synthesis of sertraline ((+)-*cis*-(1*S*,4*S*)-1-methylamino-4-(3,4-dichlorophenyl)tetralin, **(S,S)-10n**), an antidepressant chiral drug.^[24] As shown in Table 3, asymmetric hydrogenation of racemic imine precursor **9n** in the presence of catalyst **(R,S)-6e**

Table 3: Synthesis of sertraline by asymmetric hydrogenation of *N*-methylimine **9n** in the presence of catalysts **6e**.^[a]


Entry	Imine	Catalyst	<i>ee</i> value of 10n [%] ^[b]		<i>cis/trans</i> ^[c] ratio of 10n
			<i>cis</i>	<i>trans</i>	
1	(±)- 9n	(<i>R,S</i>)- 6e	89 (1 <i>R</i> ,4 <i>R</i>)	98 (1 <i>R</i> ,4 <i>S</i>)	53:47
2	(±)- 9n	(<i>S,S</i>)- 6e	3 (1 <i>S</i> ,4 <i>S</i>)	68 (1 <i>S</i> ,4 <i>R</i>)	95:5
3	(<i>R</i>)- 9n	(<i>R,S</i>)- 6e	> 99 (1 <i>R</i> ,4 <i>R</i>)	> 99 (1 <i>S</i> ,4 <i>R</i>)	97:3
4	(<i>S</i>)- 9n	(<i>R,S</i>)- 6e	> 99 (1 <i>S</i> ,4 <i>S</i>)	> 99 (1 <i>R</i> ,4 <i>S</i>)	5:95
5 ^[d]	(<i>R</i>)- 9n	(<i>S,S</i>)- 6e	> 99 (1 <i>R</i> ,4 <i>R</i>)	> 99 (1 <i>S</i> ,4 <i>R</i>)	91:9
6	(<i>S</i>)- 9n	(<i>S,S</i>)- 6e	> 99 (1 <i>S</i> ,4 <i>S</i>)	> 99 (1 <i>R</i> ,4 <i>S</i>)	> 99:1

[a] For the reaction conditions, see footnote [a] in Table 1. [b] Determined by HPLC on a Chiralcel AD-H column by using the *N*-acetyl derivatives of **10n**. [c] Determined by ¹H NMR spectroscopy. [d] The conversion was 91 %.

afforded the chiral amine isomers *cis*-**10n** and *trans*-**10n** with excellent enantioselectivities (89 and 98 % *ee*, respectively) in a ratio of approximately 1:1 (Table 3, entry 1). On the other hand, catalyst (*S,S*)-**6e** showed excellent diastereoselectivity with the *cis* isomer as the major product (95:5), albeit with unsatisfactory *ee* values (Table 3, entry 2). These results prompted us to employ enantiopure imine (*R*)-**9n** or (*S*)-**9n** as the substrate for the hydrogenation with (*R,S*)-**6e** or (*S,S*)-**6e** as the catalyst (Table 3, entries 3–6). We were pleased to find that catalyst (*R,S*)-**6e** is highly *cis* diastereoselective (97:3 d.r.) for the hydrogenation of (*R*)-**9n** and afforded the major *R,R* isomer of **10n** with > 99% *ee* (Table 3, entry 3). Furthermore, catalyst (*S,S*)-**6e** showed extremely high *cis* selectivity (> 99:1 d.r.) in the hydrogenation of (*S*)-**9n** and afforded sertraline ((1*S*,4*S*)-**10n**) in the enantiopure form in quantitative yield (Table 3, entry 6).

In summary, a new class of chiral phosphine–oxazoline ligands (SpinPHOX, **1**) based on the spiro[4.4]-1,6-nonadiene backbone has been developed by simple transformations from readily available racemic spiro[4.4]nonane-1,6-dione. The cationic iridium complexes **6** were found to be highly efficient in the hydrogenation of a broad range of ketimines, particularly in the reaction with challenging *N*-alkyl imines of ketones, and the corresponding optically active amines were obtained with *ee* values of up to 98 %. Complex (*S,S*)-**6e** was successfully employed in the catalytic asymmetric synthesis of the antidepressant chiral drug sertraline. The excellent performance of this type of ligand in the iridium-catalyzed asymmetric hydrogenation of imines will stimulate future efforts to explore new applications of these ligands in other transition-metal-catalyzed asymmetric reactions and to further understand the underlying mechanistic aspects that account for the high enantioselective control.

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