Organic LETTERS

Letter

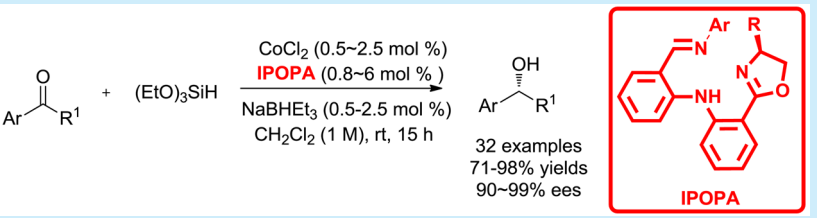
pubs.acs.org/OrgLett

Iminophenyl Oxazolinylphenylamine for Enantioselective Cobalt-Catalyzed Hydrosilylation of Aryl Ketones

Xu Chen and Zhan Lu*

Department of Chemistry, Zhejiang University, Hangzhou 310058, China

Supporting Information



ABSTRACT: A new family of chiral iminophenyl oxazolinylphenylamines (IPOPA) was designed and synthesized through three steps from commercially available starting materials. An efficient cobalt-catalyzed asymmetric hydrosilylation of simple ketones with a low catalyst loading of $CoCl_2$ and IPOPA was developed to afford chiral alcohols in good yields with high enantioselectivities.

The design of chiral privileged ligands is one of the most challenging, interesting, and efficient strategies for asymmetric catalysis.[1] Recently, tridentate ligands, such as pincer ligands,[2] showed unique properties for transitional metals in catalytic transformations. However, successful highly enantioselective transformations using earth-abundant transition metal catalysts, such as cobalt, are still limited.[3]

The imine group is regarded as a good redox ligand for first-row transition metals. However, only a few chiral imine ligands, such as salen ligands, have been generally established for highly enantioselective transformations.[4] Among them, *P*-salen type[4b,5] and *N*-salen type ligands[4c] are mainly limited to the asymmetric hydrogenation and transfer hydrogenation of ketones (Figure 1). Gao et al.[6] reported ruthenium- or rhodium-catalyzed asymmetric transfer hydrogenation of acetophenone using the *P*-salen type ligand to afford 1-phenylethanol in 5−40% ee. Morris and co-workers[5] demonstrated iron-catalyzed asymmetric hydrogenation of acetophenone with 27% ee and asymmetric transfer hydrogenation of ketones with 18−76% ee using the *P*-salen type ligand. The Beller group[7] reported iron-catalyzed asymmetric transfer hydrogenation of imines affording the corresponding amines in 29−97% ee. A *N*-salen type ligand was used in the ruthenium-catalyzed asymmetric transfer hydrogenation of acetophenone affording 1-phenylethanol in 7−76% ee.[4c]

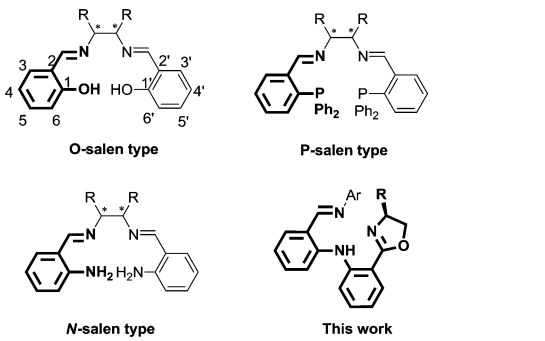


Figure 1. Chiral salen type ligands bearing imine group.

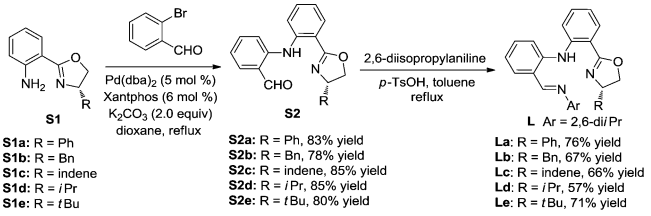
Most of the chiral salen type or semisalen type ligands have the chiral groups on the imine moiety. Chiral modifications at the 6-positions and planar chiral ferrocenyl moieties on the phenyl ring are rare.[8] Furthermore, to the best of our knowledge, chiral salen type ligands and their analogues bearing a chiral moiety at the 1-position have not been well explored in the asymmetric transformations so far. Inspired by salen type ligands and our previous works on ligand design,[9] we proposed to introduce an oxazoline as a chiral moiety onto the phenyl side in the aldehyde part. Here we reported a new type of chiral iminophenyl oxazolinylphenylamine (IPOPA) and its applications in cobalt-catalyzed highly enantioselective hydrosilylation of ketones.

The chiral IPOPA could be synthesized from 2-aminophenyl-2-oxazolines **S1** which could be easily obtained from two different strategies: one is the condensation reaction of commercially available 2-cynoaniline with chiral amino alcohols;[10] another protocol developed by our group is the cross-coupling reaction of commercially available2-iodoaniline with oxazoline.[11]Palladium-catalyzed cross-coupling reactions of **S1** with 2-bromobenzaldehyde gave the C−N bond formation products **S2** in 78−85% yields. Condensation reactions with substituted anilines produced the desired IPOPA (**L**) in 57−76% yields (Scheme 1).

Received: August 2, 2016

DOI: 10.1021/acs.orglett.6b02260
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 1. Synthesis of Iminophenyl Oxazolinylphenylamines Ligands

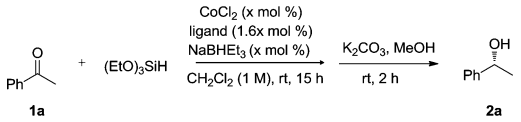


With the new ligand in hand, we tried to explore its catalytic applications. Chiral secondary alcohols are important building blocks for preparing bioactive molecules.[12] Enantioselective reduction of prochiral ketones, such as asymmetric hydrogenation,[12,13] hydroboration,[9b,13g,14] and hydrosilylation,[13c,g,15] is one of the most fundamental protocols to afford these compounds. Asymmetric hydrosilylation of ketones has emerged as an attractive method to afford the secondary alcohols due to its mild conditions and manipulative simplicity. Owing to economical and environmentally benign advantages, cobalt as a earth-abundant transition metal has been used as a central metal of precatalysts.[3] The first cobalt-catalyzed asymmetric hydrosilylations has been reported in 1991 by Brunner and Amberger in which 0.5 mol % of cobalt complexes with a chiral monooxazolinylpyridine ligand and $PhSiH_3$ as a reducing reagent were used to give chiral 1-phenylethanol with a moderate enantioselectivity (56% *ee*).[16] Asymmetric hydrosilylations of ketones have also been realized with cobalt and *N,N,N*-bis(oxazolinylphenyl)amine (Bopa)[17] by Nishiyama et al. in 2010.[18] Although high reactivities and enantioselectivities were observed in some cases, a 5 mol % of catalyst loading was used and the reaction performed at 65 °C. In 2011, Chan et al. reported cobalt-catalyzed asymmetric hydrosilylation of electron-deficient aryl ketones with $PhSiH_3$ in the presence of 10 mol % of catalyst and dipyridylphosphine ligand to afford the corresponding alcohols in 5−99% yields and with up to 96% ee.[19] In 2012, Gade et al. found 2.5 mol % of cobalt complexes could catalyze asymmetric hydrosilylation reaction of aryl ketones using the 1,3-bis(2-pyridylimino)isoindoline (BPI) as a ligand to afford chiral alcohols in 0−100% yield with up to 91% ee.[20] Although a few cobalt-catalyzed hydrosilylation systems with high enantioselectivities have been developed, there still exist some drawbacks, such as the high catalyst loading and reaction temperature, as well as reaction activities sensitive to the electronic nature of substrates. So, it is necessary to develop a new catalytic system that performs this reaction using a lower catalyst loading under mild conditions.

Cobalt-catalyzed asymmetric hydrosilylation of simple acetophenone **1a** was chosen as a model reaction. Brief optimization studies with different silanes, reductants, and solvents (see in Supporting Information, Table S1) at room temperature under nitrogen were conducted, and the reaction was quenched with K_2CO_3/MeOH (saturated). $(EtO)_3SiH$ was chosen as a reductant, $NaBHEt_3$ as an activating agent of the precatalyst, and DCM as a solvent.

Various chiral ligands were investigated (Table 1, entries 1−5) under the conditions of 2.0 equiv of triethoxysilane in the presence of 2.5 mol % of $CoCl_2$, 4 mol % of ligand, and 2.5 mol % of $NaHBEt_3$ in a solution of DCM, and **La** was found to be the best ligand for hydrosilylation to afford the chiral alcohol in a quantitive yield with 97% ee (entry 1). The control experiments without $CoCl_2$ or ligands also produce the racemic

Table 1. Optimization with Different Ligands and Amounts of Catalysts[a]



entry	ligand	*x*	yield (%)[b]	ee (%)[c]
1	**La**	2.5	99	97
2	**Lb**	2.5	82	89
3	**Lc**	2.5	67	82
4	**Ld**	2.5	48	94
5	**Le**	2.5	89	92
6[d]	**La**	2.5	68	0
7[e]	**La**	2.5	70	0
8	**La**	0.5	96	97

[a]The reactions were conducted using **1a** (1.0 mmol), $(EtO)_3SiH$ (2.0 mmol) in a solution of DCM (1 mL) at room temperature under an atmosphere of N_2 for 15 h. [b]Yields were determined using TMSPh as an internal standard. [c]*Ee* values were determined by chiral HPLC analysis. [d]Without $CoCl_2$. [e]Without ligand.

alcohols efficiently in good yields (entries 6 and 7) which suggested a combination of $CoCl_2$ and ligand could readily inhibit the background reaction.[21] Even with 0.5 mol % of catalyst, the reaction could also afford the desired product in 96% yield and 97% ee (entry 8).

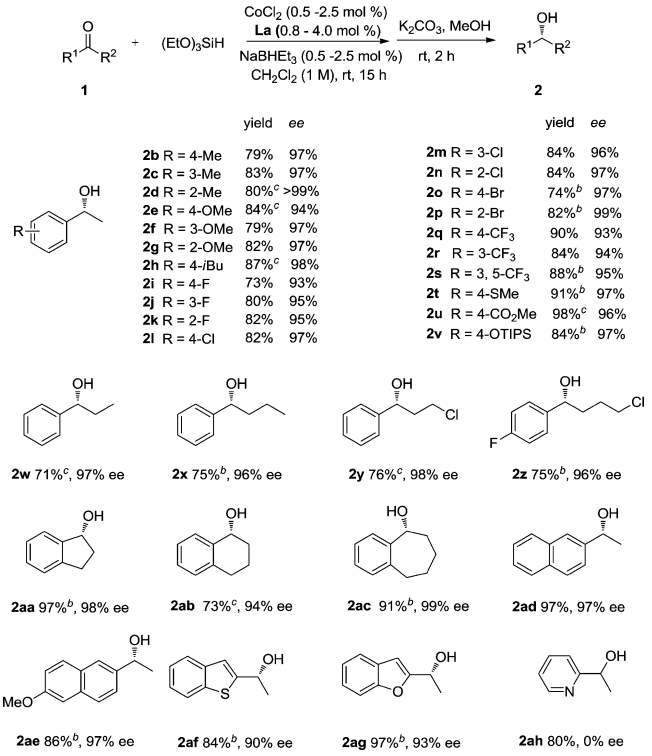
With standard conditions in hand, the scope of substrate shown in Scheme 2 was studied. Acetylbenzenes with electron-rich and -poor substituents on *ortho*-, *meta*-, and *para*-positions, such as halides, ether, ester, thioether, silyl ether, and trifluoromethyl, could undergo asymmetric hydrosilylation reactions to deliver the corresponding chiral alcohols in 65−98% yields with 93−99% ee. Using long alkyl groups instead of a methyl group, hydrosilylation reactions could be carried out to afford **2w−2z** with 96−98% ee, even in the presence of chloroalkanes. The more sterically hindered ketones, such as isobutyrophenone and *tert*-butyl phenyl ketone, were not suitable for these catalytic conditions. The cyclic alcohols (**2aa−2ac**) could be also obtained smoothly with 94−99% ee. Heterocycles, such as 2-naphthyl, benzothienyl, and benzofuranyl, were suitable for this transformation. The reaction of 2-acetylpyridine afforded the **2ah** in 80% yield, however, without any enantioselectivity.

A gram-scale reaction of **1ad** was carried out to afford the **2ad** in 92% yield with 99% ee (Scheme 3).

A plausible mechanism[22] of cobalt-catalyzed hydrosilylation of ketones was proposed in Figure 2. For the initial step, we proposed that 1 equiv of $NaBHEt_3$ played the role of base to accelerate the deprotonation of IPOPA−cobalt dichloride complexes to form IPOPA−cobalt chloride intermediates which could undergo a hydride−chloride exchange process with $(EtO)_3SiH$ to generate the proposed cobalt hydride species **A**. The cobalt hydride species **A** could undergo coordination with ketone to form intermediate **B** followed by the migration insertion of ketone into the Co−H bond to give complex **C**. The transmetalation of complex **C** with $(EtO)_3SiH$ regenerated the active cobalt species and simultaneously provided the hydrosilylation product **D** which underwent a desilylation reaction under basic conditions to afford the corresponding alcohol. A primary model for predicting the stereochemical outcome of the migration insertion step was proposed (Model I in Figure 2). During the migration insertion

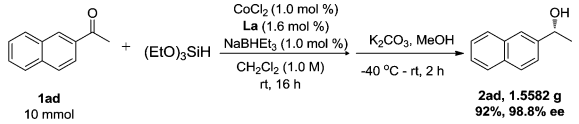
DOI: 10.1021/acs.orglett.6b02260
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 2. Scope for Asymmetric Hydrosilylation of Ketones[a]



[a]Standard conditions: unless otherwise noted, $CoCl_2$ (0.5 mol %), **La** (0.8 mol %), $NaBHEt_3$ (0.5 mol %), ketone (1 mmol), $(EtO)_3SiH$ (2.0 equiv), DCM (1 mL), rt, 15 h. [b]$CoCl_2$ (1.0 mol %), **La** (1.6 mol %), $NaBHEt_3$ (1.0 mol %). [c]$CoCl_2$ (2.5 mol %), **La** (4.0 mol %), $NaBHEt_3$ (2.5 mol %).

Scheme 3. Gram-Scale Reaction



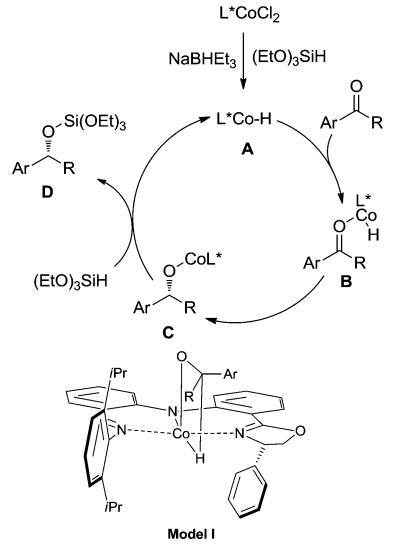


Figure 2. A plausible mechanism for the cobalt-catalyzed ketone hydrosilylation.

of ketone into the Co−H bond, it was disfavored that the complex **A** approached from the *Re*-face of aryl ketone due to the steric hindrance effect between the aryl group on ketone and the isopropyl group on imine. Due to the steric hindrance effect between the sterically bulky isopropyl or *tert*-butyl group and the isopropyl group on imine, the reactions of more sterically hindered isobutyrophenone and *tert*-butyl phenyl ketone did not occur. A lower steric effect was exhibited when complex **A** approached from the *Si*-face of aryl ketone which was consistent with the absolute configuration of the product.

In summary, a new family of chiral iminophenyl oxazolinylphenylamines (IPOPA) was designed and synthesized over three steps from commercially available starting materials. An efficient cobalt-catalyzed highly enantioselective hydrosilylation of simple ketones with a low catalyst loading of $CoCl_2$ and IPOPA ligand was developed to afford the chiral alcohols in good yields with high enantioselectivities. Various asymmetric transformations based on the IPOPA ligand will be explored in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02260.

Experimental details, characterization data of all compounds, and copies of ^1H and ^{13}C NMR spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: luzhan@zju.edu.cn.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the NSFC (21472162) and the National 973 Program (2015CB856600) for financial support.

■ REFERENCES

(1) (a) Yoon, T. P.; Jacobsen, E. N. *Science* **2003**, *299*, 1691−1693. (b) *Privileged Chiral Ligands and Catalysts*; Zhou, Q.-L., Ed.; Wiley-VCH: Weinheim, 2011.

(2) (a) Deng, Q.-H.; Melen, R. L.; Gade, L. H. *Acc. Chem. Res.* **2014**, *47*, 3162−3173. (b) Selander, N.; Szabó, K. J. *Chem. Rev.* **2011**, *111*, 2048−2076. (c) O'Reilly, M. E.; Veige, A. S. *Chem. Soc. Rev.* **2014**, *43*, 6325−6369. (d) Gunanathan, C.; Milstein, D. *Chem. Rev.* **2014**, *114*, 12024−12087.

(3) Pellissier, H.; Clavier, H. *Chem. Rev.* **2014**, *114*, 2775−2823.

(4) (a) Baleizão, C.; Garcia, H. *Chem. Rev.* **2006**, *106*, 3987−4043. (b) Li, Y.-Y.; Yu, S.-L.; Shen, W.-Y.; Gao, J.-X. *Acc. Chem. Res.* **2015**, *48*, 2587−2598. (c) Karamé, I.; Jahjah, M.; Messaoudi, A.; Tommasino, M. L.; Lemaire, M. *Tetrahedron: Asymmetry* **2004**, *15*, 1569−1581.

(5) Sui-Seng, C.; Freutel, F.; Lough, A. J.; Morris, R. H. *Angew. Chem., Int. Ed.* **2008**, *47*, 940−943.

(6) Gao, J.-X.; Zhang, H.; Yi, X.-D.; Xu, P.-P.; Tang, C.-L.; Wan, H.-L.; Tsai, K. R.; Ikariya, T. *Chirality* **2000**, *12*, 383−388.

(7) Zhou, S.-L.; Fleischer, S.; Junge, K.; Das, S.; Addis, D.; Beller, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 8121−8125.

(8) (a) Hosoya, N.; Hatayama, A.; Irie, R.; Sasaki, H.; Katsuki, T. *Tetrahedron* **1994**, *50*, 4311−4322. (b) Sasaki, H.; Irie, R.; Hamada, T.; Suzuki, K.; Katsuki, T. *Tetrahedron* **1994**, *50*, 11827−11838. (c) Zhang, X.; Luck, R. L.; Fang, S.-Y. *J. Organomet. Chem.* **2011**,

DOI: 10.1021/acs.orglett.6b02260
Org. Lett. XXXX, XXX, XXX−XXX

696, 2047−2052. (d) Zhang, X.; Luck, R. L.; Fang, S.-Y. *Organometallics* **2011**, *30*, 2609−2616.
(9) (a) Chen, J.; Xi, T.; Ren, X.; Cheng, B.; Guo, J.; Lu, Z. *Org. Chem. Front.* **2014**, *1*, 1306−1309. (b) Chen, J.; Cheng, B.; Cao, M.; Lu, Z. *Angew. Chem., Int. Ed.* **2015**, *54*, 4661−4664. (c) Guo, J.; Chen, J.; Lu, Z. *Chem. Commun.* **2015**, *51*, 5725−5727. (d) Chen, J.; Chen, C.; Ji, C.; Lu, Z. *Org. Lett.* **2016**, *18*, 1594−1597.
(10) Wolińska, E. *Tetrahedron* **2013**, *69*, 7269−7278.
(11) (a) Chen, J.; Xi, T.; Lu, Z. *Org. Lett.* **2014**, *16*, 6452−6455. (b) Xi, T.; Mei, Y.; Lu, Z. *Org. Lett.* **2015**, *17*, 5939−5941.
(12) Noyori, R.; Ohkuma, T. *Angew. Chem., Int. Ed.* **2001**, *40*, 40−73.
(13) (a) Ikariya, T.; Murata, K.; Noyori, R. *Org. Biomol. Chem.* **2006**, *4*, 393−406. (b) Zhang, W.-C.; Chi, Y.-X.; Zhang, X.-M. *Acc. Chem. Res.* **2007**, *40*, 1278−1290. (c) Malacea, R.; Poli, R.; Manoury, E. *Coord. Chem. Rev.* **2010**, *254*, 729−752. (d) Klingler, F. D. *Acc. Chem. Res.* **2007**, *40*, 1367−1376. (e) *New Frontiers in Asymmetric Catalysis*; Mikami, K., Lautens, M., Eds.; Wiley: Hoboken, NJ, 2007; pp 12−22. (f) Shang, G.; Li, W.; Zhang, X.-M. Transition-metal-catalyzed homogeneous asymmetric hydrogenation, 7. In *Catalytic Asymmetric Synthesis*, 3rd ed.; Ojima, I., Ed.; Wiley: Hoboken, NJ, 2010; pp 384−413. (g) Komiya, S.; Shimizu, H.; Nagasaki, I. Industrial Application of the Asymmetric Reduction of C═O and C═N Bonds, including Enamides and Enamines, 9.5. In *Comprehensive Chirality*; Yamamoto, H., Carreira, E., Eds.; Elsevier: Amsterdam, 2012; pp 83−103.
(14) (a) Deloux, L.; Srebnik, M. *Chem. Rev.* **1993**, *93*, 763−784. (b) Midland, M. M. *Chem. Rev.* **1989**, *89*, 1553−1561. (c) Cho, B. T. *Chem. Soc. Rev.* **2009**, *38*, 443−452. (d) Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1986−2012. (e) *New Frontiers in Asymmetric Catalysis*; Mikami, K., Lautens, M., Eds.; Wiley: Hoboken, NJ, 2007; pp 22−25.
(15) (a) Riant, O.; Mostefaï, N.; Courmarcel, J. *Synthesis* **2004**, *18*, 2943−2958. (b) Diez-Gonzalez, S.; Nolan, S. P. *Acc. Chem. Res.* **2008**, *41*, 349−358.
(16) Brunner, H.; Amberger, K. *J. Organomet. Chem.* **1991**, *417*, C63−C65.
(17) McManus, H. A.; Guiry, P. J. *J. Org. Chem.* **2002**, *67*, 8566−8573.
(18) Inagaki, T.; Phong, L. T.; Furuta, A.; Ito, J.; Nishiyama, H. *Chem. - Eur. J.* **2010**, *16*, 3090−3096.
(19) Yu, F.; Zhang, X.-C.; Wu, F.-F.; Zhou, J.-N.; Fang, W.-J.; Wu, J.; Chan, A. S. C. *Org. Biomol. Chem.* **2011**, *9*, 5652−5654.
(20) Sauer, D. C.; Wadepohl, H.; Gade, L. H. *Inorg. Chem.* **2012**, *51*, 12948−12958.
(21) (a) Addis, D.; Zhou, S. L.; Das, S.; Junge, K.; Kosslick, H.; Harloff, J.; Lund, H.; Schulz, A.; Beller, M. *Chem. - Asian J.* **2010**, *5*, 2341−2345. (b) Manas, M. G.; Sharninghausen, L. S.; Balcells, D.; Crabtree, R. H. *New J. Chem.* **2014**, *38*, 1694−1700. (c) Revunova, K.; Nikonov, G. I. *Chem. - Eur. J.* **2014**, *20*, 839−845.
(22) (a) Ojima, I.; Nihonyanagi, M.; Nagai, Y. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 3722−3722. (b) Ojima, I.; Kogure, T.; Kumagai, M.; Horiuchi, S.; Sato, T. *J. Organomet. Chem.* **1976**, *122*, 83−97. (c) Bleith, T.; Wadepohl, H.; Gade, L. H. *J. Am. Chem. Soc.* **2015**, *137*, 2456−2459.

DOI: 10.1021/acs.orglett.6b02260
Org. Lett. XXXX, XXX, XXX−XXX