CHEMISTRY
A European Journal

A Journal of
ChemPubSoc Europe

Accepted Article

Title: Iridium-Catalyzed Asymmetric Hydrogenation of Unfunctionalized Exocyclic C=C Bonds

Authors: Jingzhao Xia, Guoqiang Yang, Ruijing Zhuge, Yangang Liu, and Wanbin Zhang

This manuscript has been accepted after peer review and appears as an Accepted Article online prior to editing, proofing, and formal publication of the final Version of Record (VoR). This work is currently citable by using the Digital Object Identifier (DOI) given below. The VoR will be published online in Early View as soon as possible and may be different to this Accepted Article as a result of editing. Readers should obtain the VoR from the journal website shown below when it is published to ensure accuracy of information. The authors are responsible for the content of this Accepted Article.

To be cited as: *Chem. Eur. J.* 10.1002/chem.201604298

Link to VoR: http://dx.doi.org/10.1002/chem.201604298

Supported by
ACES

WILEY-VCH

10.1002/chem.201604298

WILEY-VCH

COMMUNICATION

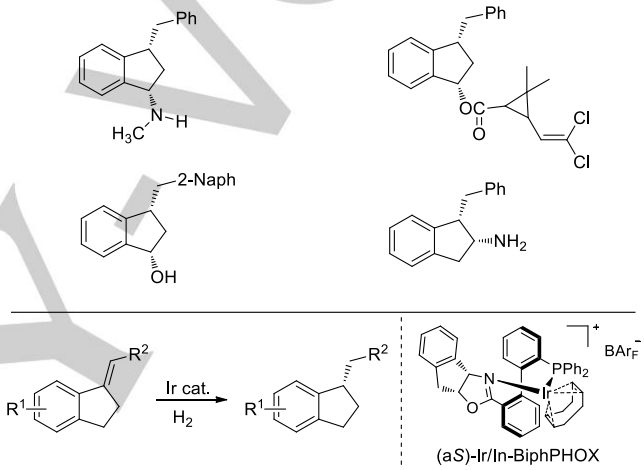
Iridium-Catalyzed Asymmetric Hydrogenation of Unfunctionalized Exocyclic C=C Bonds

Jingzhao Xia, Guoqiang Yang, Ruijing Zhuge, Yangang Liu, and Wanbin Zhang*

Abstract: An iridium-catalyzed asymmetric hydrogenation of unfunctionalized exocyclic C=C bonds was achieved using an axially flexible chiral phosphine-oxazoline ligand, providing the desired chiral 1-benzyl-2,3-dihydro-*1H*-indene products with up to 98% *ee*. This represents the first general hydrogenation of unfunctionalized exocyclic olefins with the highest selectivity reported thus far. The additive acetate ion plays an important role in the reaction's high enantioselectivity. The chiral product can be further transformed to key intermediates required for the synthesis of an important insecticide and a drug compound.

The enantioselective hydrogenation of unfunctionalized olefins has been established as a direct and efficient method for the preparation of optically active compounds.[1] Early successful examples were reported by Buchwald and co-workers using chiral metallocene complexes.[2] However, high catalyst loadings, long reaction times and high catalyst sensitivity have limited widespread application of this method. In 1997, Pfaltz discovered that using a phosphine-oxazoline ligand (PHOX)[3] as a chiral mimic of Crabtree's catalyst[4] could enantioselectively reduce unfunctionalized olefins, challenging substrates for ruthenium- and rhodium-catalytic systems because of the absence of a chelating group.[5,6] Iridium complexes bearing P,N-ligands,[7] have attracted much attention due to their high activity and good enantioselective control. Prompted by these groundbreaking discoveries, hundreds of chiral iridium-based catalysts have been developed and applied to the reduction of numerous unfunctionalized alkenes.[1,7] However, although a considerable number of reports have been published pertaining to the reduction of unfunctionalized acyclic di-, tri-, and tetrasubstituted olefins, as well as endocyclic olefins,[1,7,8] no general and efficient catalyst system has been developed for the asymmetric hydrogenation of unfunctionalized exocyclic olefins.[9]

Due to the large number of chiral benzofused five-membered rings encountered in pharmaceutical natural products and intermediates of key bioactive drugs (Scheme 1),[10] synthetic protocols for the straightforward and efficient construction of such skeletons are highly desired. Herein, we report a highly efficient iridium-catalyzed asymmetric hydrogenation of unfunctionalized exocyclic benzofused five-membered olefins. Additionally, the preparation of key intermediates required for the synthesis of an insecticide and a drug compound from our chiral product is also reported.



Scheme 1. Important drugs possessing chiral 2,3-dihydro-1*H*-indene skeleton and our method to prepare it.

Hydrogenation reaction conditions were conducted as listed in Table 1. We commenced our investigations using **1a** as the model substrate and with 1.0 mol% of the (a*S*)-Ir/*i*Pr-BiphPHOX ([Ir(**L1**)cod]BAr_F)[11] in different solvents under 40 bar of hydrogen. The reactions were carried out at room temperature for 24 hours (entries 1-6). Some common solvents often used in iridium-catalyzed asymmetric hydrogenations gave the desired product with full conversions and 37%-70% *ee*s (entries 1-3). Conversions decreased dramatically when the solvent was changed to 1,4-dioxane or THF. We assumed that coordinating effects of the solvents with the iridium deactivated the catalyst (entries 4-5). Gratifyingly, 80% *ee* was achieved with toluene as a solvent, but only 40% conversion was observed (entry 6). To drive the reaction to completion, the hydrogen pressure was increased from 40 to 60 bar and full conversion was observed within 24 hours. Further screening of solvents showed that *o*-xylene was the best solvent, giving the desired product with 81% *ee* (entries 7-9). Under 60 bar of H_2, and using *o*-xylene as the solvent of choice, we explored the effects of the ligands on the reaction. Firstly, the substitute on the oxazoline ring was changed to a bulky *tert*-Bu group, giving rise to a sharp decrease in both catalytic activity and enantioselectivity (entry 10). A Bn substituent improved the enantioselectivity slightly, but conversion decreased (entry 11). The novel ligand **L4** bearing a chiral indane-fused oxazoline gave

[*] J. Xia, Prof. Dr. Y. Liu, Prof. Dr. W. Zhang
School of Pharmacy
Dr. G. Yang, R. Zhuge, Prof. Dr. W. Zhang
School of Chemistry and Chemical Engineering
Shanghai Jiao Tong University
800 Dongchuan Road, Shanghai 200240 (China)
E-mail: wanbin@sjtu.edu.cn
Homepage: http://wanbin.sjtu.edu.cn

Supporting information for this article is given via a link at the end of the document.

Accepted Manuscript

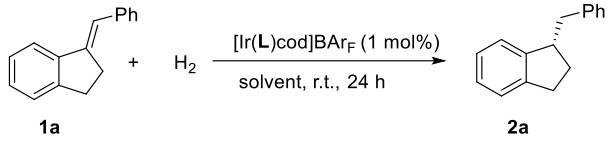
This article is protected by copyright. All rights reserved.

10.1002/chem.201604298

COMMUNICATION

the best result (entry 12). Other types of phosphine-oxazoline ligands, such as *t*Bu-PHOX (**L5**), planar-chiral mono-*t*Bu-Ru-PHOX (**L6**) and (a*S*)-*t*Bu-BinaphPHOX (**L7**), were also screened. Unfortunately, they also gave trace amounts of product (entries 13-15). To our delight, when 1 μL of AcOH was used as an additive in the reaction, the hydrogenation also proceeded smoothly and provided the best overall performance with full conversion and 93% *ee* (entry 16). Previous studies by the Pfaltz group have shown that the coordinating ion usually deactivates the Ir-catalyst towards hydrogenation of unfunctionalized olefins.[3d,3e] To detect results from the acetate ion or the proton of AcOH, AcONa was also used as an additive (entry 17). The results showed that the acetate ion plays a crucial role in improving the *ee* with AcOH.

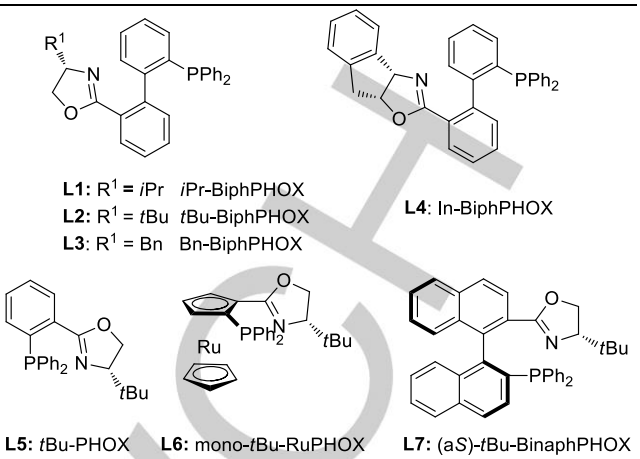
Table 1. Reaction optimization.[a]



1a **2a**

Entry	Solvent	Ligand[b]	H_2 (bar)	Conv.[%][c]	*ee* [%][d]
1	CH_2Cl_2	**L1**	40	>99	37
2	$ClCH_2CH_2Cl$	**L1**	40	>99	55
3	benzene	**L1**	40	>99	70
4	1,4-dioxane	**L1**	40	28	73
5	THF	**L1**	40	N.R.	--
6	toluene	**L1**	40	40	80
7	toluene	**L1**	60	>99	76
8	*m*-xylene	**L1**	60	>99	79
9	*o*-xylene	**L1**	60	>99	81
10	*o*-xylene	**L2**	60	39	45
11	*o*-xylene	**L3**	60	87	83
12	*o*-xylene	**L4**	60	>99	84
13	*o*-xylene	**L5**	60	<5	--
14	*o*-xylene	**L6**	60	<5	--
15	*o*-xylene	**L7**	60	<5	--
16[e]	*o*-xylene	**L4**	60	>99	93
17[f]	*o*-xylene	**L4**	60	>99	91

[a] Reaction conditions: ratio of substrate/catalyst (S/C) = 100, 2 mL solvent. [b] When **L1**~**L4** are used, the axial chirality of catalysts is a*S*. [c] Determined by ^{1}H NMR spectroscopy. [d] Enantioselectivity was determined by HPLC using a chiral Daicel column. [e] AcOH (1 μL, 0.34 equiv.) as an additive. [f] AcONa (0.3 equiv.) as an additive.



With the optimized reaction conditions in hand, the asymmetric hydrogenation of substituted (*E*)-1-benzylidene-2,3-dihydro-*1H*-indene was conducted at room temperature using the complex iridium-**L4** ((a*S*)-Ir/In-BiphPHOX,1 mol%) in *o*-xylene (2 mL), under 60 bar of hydrogen for 24 hours (Table 2). Various substrates **1** bearing unfunctionalized exocyclic double bonds could be easily converted into chiral substituted 1-benzyl-2,3-dihydro-1*H*-indenes **2**. The R^1 electron-withdrawing and electron-donating groups had no effect on the conversion (entries 1-12). Reduction of substrates bearing 4-Cl or 6-CH_3 groups provided a slightly lower enantioselectivity with 91% *ee* and 90% *ee*, respectively (entries 2 and 9), whereas substrates bearing aryl groups with 5-substituted electron-withdrawing F, Cl, Br substituents, were all reduced with higher *ees* (entries 4-7). It is worth noting that when the ratio of substrate/catalyst was 1000, the reaction also proceeded smoothly within 48 hours with no loss of enantioselectivity (entry 6). Di-substituted 5,6-$(OMe)_2$ and 5,6-Cl_2 substrates[12] were also tested with our optimized conditions affording their corresponding products with 93% *ee* and 98% *ee*, respectively (entries 11 and 12). Substrates with substituents on the R^2 phenyl ring were also evaluated. With 2-Br as a substituent, the enantiomeric ratio dramatically decreased with the desired product being obtained with only 78% *ee* (entry 13). The hydrogenation of other substrates in which substituents were present on the R^2 aryl ring also gave their corresponding products with full conversion and 89%-92% *ee* (entries 14-19). The more bulky substrate with a 2-naphthyl substituent was reduced with 97% *ee* (entry 20). Since substrates with unfunctionalized alkyl R^2 groups cannot be prepared with the *E*-configuration in pure form, substrates bearing hydroxymethyl or methoxymethyl R^2 groups were tested with our catalytic system. It was found that all of these substrates could be hydrogenated with full conversions and poor or moderate *ee* (entry 21 and 22). (*Z*)-3-Benzylidene-2,3-dihydrobenzofuran could also be reduced with 93% *ee* (entry 23). The reduction of a benzo-six membered substrate only gave its corresponding product with 75% *ee* (entry 24). These results represent the first highly asymmetric hydrogenation of cyclic systems bearing unfunctionalized exocyclic C=C bonds to afford benzo-five membered chiral compounds.

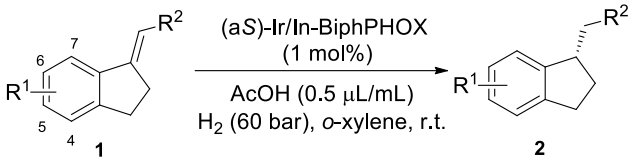
Accepted Manuscript

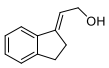
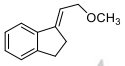
This article is protected by copyright. All rights reserved.

10.1002/chem.201604298

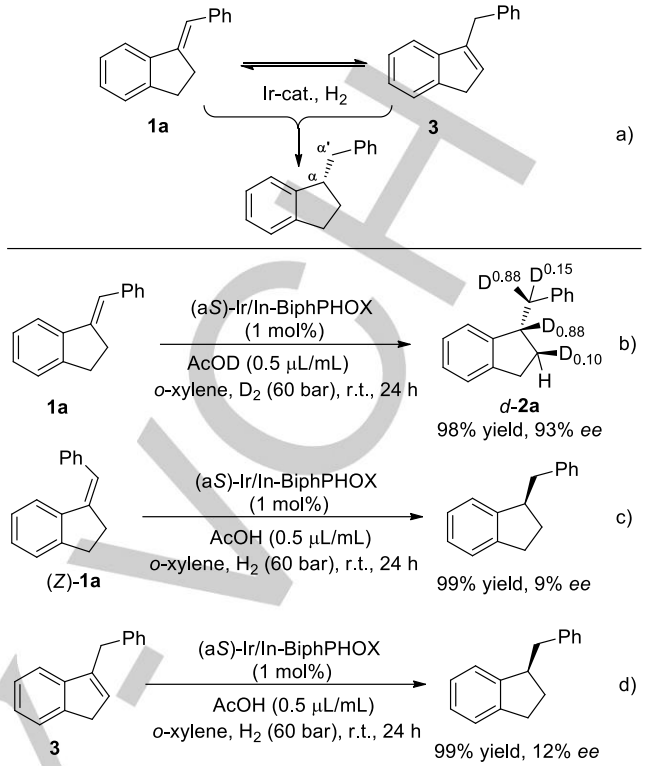
COMMUNICATION

Table 2. Substrate scope.[a]



Entry	R^1; R^2	Product [**2**]	Yield [%][b]	*ee* [%][c]
1	H; Ph	**2a**	99	93
2	4-Cl; Ph	**2b**	98	91
3	4-Br; Ph	**2c**	98	95
4	5-F; Ph	**2d**	99	96
5	5-Cl; Ph	**2e**	98	96
6[d]	5-Cl; Ph	**2e**	98	96
7	5-Br; Ph	**2f**	97	98
8	6-Br; Ph	**2g**	96	92
9	6-CH_3; Ph	**2h**	97	90
10	6-OCH_3; Ph	**2i**	98	92
11	5,6-$(OCH_3)_2$; Ph	**2j**	96	93
12[e]	5,6-Cl_2; Ph	**2k**	97	98
13	H; 2-BrC_6H_4	**2l**	96	78
14	H; 3-FC_6H_4	**2m**	96	94
15	H; 3-ClC_6H_4	**2n**	97	89
16	H; 3-$CH_3C_6H_4$	**2o**	97	91
17	H; 4-FC_6H_4	**2p**	98	90
18	H; 4-ClC_6H_4	**2q**	99	92
19	H; 4-$CH_3C_6H_4$	**2r**	97	90
20	H; 2-naphthyl	**2s**	96	97
21		**2t**	98	22
22		**2u**	96	78
23		**2v**	96	93
24		**2w**	99	75

[a] Reaction conditions: (a*S*)-Ir/In-BiphPHOX (1 mol%), 2 mL *o*-xylene, AcOH (1 μL), 60 bar H_2, r.t., 24 hours. [b] Isolated yields obtained by column chromatography. [c] Enantioselectivity was determined by HPLC using a chiral Daicel column. [d] The ratio of substrate/catalyst was 1000, 48 hours, AcOH (10 μL, 5 μL/mL). [e] The absolute configuration of **2k** was determined by X-ray crystallographic analysis.[12]



Scheme 2. Deuterium labelling study and asymmetric hydrogenation of unfunctionalized (*Z*)-**1a** and endocyclic olefin.

It has been reported that the double bond of cyclic systems with exocyclic-olefins can isomerize to the more stable internal double bond in iridium-catalyzed hydrogenation reactions.[9a,13] To determine if this occurred in our catalytic system (Scheme 2, a), we conducted three experiments. The deuterium labelling study showed that isomerization of the olefin did occur under our hydrogenation conditions (Scheme 2, b), but that the α and α' positions were the main deuterated sites. A control experiment showed that hydrogenation of (*Z*)-**1a** gave **2a** with very low ee and with the opposite optical selectivity (Scheme 2, c). Deuterium labelling $D^{0.15}$ at the α' position suggests that *E*-*Z* isomerization may occur but that the high *ee* is not the result of hydrogenation of the (*Z*)-isomer generated from (*E*)-**1a**. When endocyclic olefin substrate **3** was hydrogenated under the standard asymmetric catalytic conditions (Scheme 2, d), product **2a** was also obtained with very low *ee* and with the opposite optical selectivity. All of these experiments suggest that the high enantioselectivities observed in these reactions are a result of the hydrogenation of the (*E*)-exocyclic olefin (For more mechanistic study, see SI file).

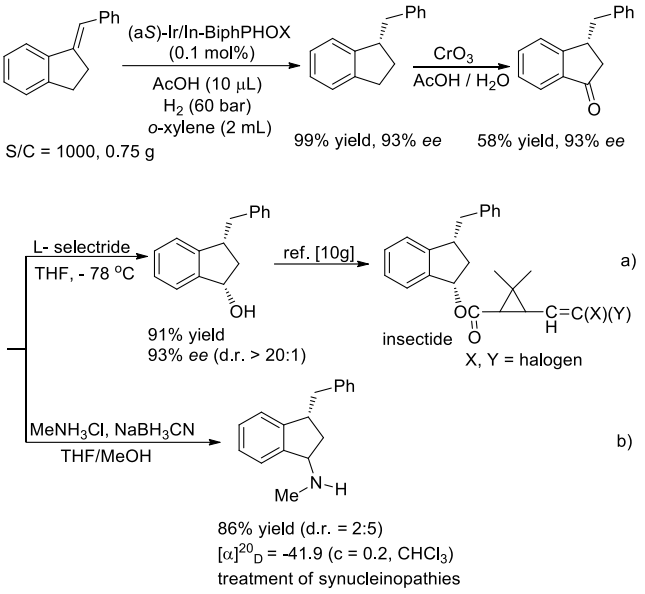
To demonstrate the potential application of this simple and highly efficient catalytic asymmetric hydrogenation, we prepared a key intermediate required for the the synthesis of an insectide.[10g] Our hydrogenated product was oxidatied with CrO_3 under AcOH/H_2O[14] with 58% yield and 93% *ee*, then reduced to (1*S*,3*R*)-3-benzyl-2,3-dihydro-*1H*-inden-1-ol. Enantioselectivity was retained with >20:1 d.r.. According to a patent,[10g] this intermediate can be further transformed into a series of insecticides (Scheme 3, a). An additional transformation was

Accepted Manuscript

This article is protected by copyright. All rights reserved.

10.1002/chem.201604298

possible in the presence of $MeNH_3Cl$ and $NaBH_3CN$, of which the product (obtained in 86% yield) can be used for treatment of synucleinopathies (Scheme 3, b).[15]



Scheme 3. Further transformations.

In conclusion, we have developed an efficient asymmetric hydrogenation of unfunctionalized exocyclic olefins using an Ir catalyst with an axially flexible chiral phosphine-oxazoline ligand, enantiomerically enriched benzofused five-membered ring substrates could be prepared. Furthermore, an acetate ion was found to be an effective additive to give the desired products with high enantioselectivities.

Acknowledgements

This work was partly supported by the National Nature Science Foundation of China (Nos. 21302124 and 21232004), Science and Technology Commission of Shanghai Municipality (Nos. 14XD1402300 and 15Z111220016). Our thanks also go to the Instrumental Analysis Center of SJTU.

Keywords: asymmetric hydrogenation • iridium • unfunctionalized • exocyclic olefin • synthetic methods

[1] For reviews, see: a) M. P. Carroll, P. J. Guiry, *Chem. Soc. Rev*. **2014**, *43*, 819; b) J. J. Verendel, O. Pàmies, M. Diéguez, P. G. Andersson, *Chem. Rev.* **2014**, *114*, 2130; c) T. Imamoto in Hydrogenation (Ed.: I. Karamé), Intech, Rijeka, **2012**, Chap. 1, pp. 3–30; d) Y. Zhu, K. Burgess, *Acc. Chem. Res.* **2012**, *45*, 1623; e) D. H. Woodmansee, A. Pfaltz, *Chem. Commun*. **2011**, *47*, 7912; f) O. Pàmies, P. G. Andersson, M. Diéguez, *Chem. Eur. J.* **2010**, *16*, 14232; g) T. L. Church, P. G. Andersson, *Coord. Chem. Rev.* **2008**, *252*, 513; h) S. J. Roseblade, A. Pfaltz, *Acc. Chem. Res.* **2007**, *40*, 1402; i) X. Cui, K. Burgess, *Chem. Rev.* **2005**, *105*, 3272; j) A. Pfaltz, J. Blankenstein, R. Hilgraf, E. Hörmann, S. McIntyre, F. Menges, M. Schönleber, S. P. Smidt, B. Wüstenberg, N. Zimmermann, *Adv. Synth. Catal.* **2003**, *345*, 33; k) W. Tang, X. Zhang, *Chem. Rev*. **2003**, *103*, 3029.

[2] a) M. V. Troutman, D. H. Appella, S. L. Buchwald, *J. Am. Chem. Soc.* **1999**, *121*, 4916; b) R. D. Broene, S. L. Buchwald, *J. Am. Chem. Soc.* **1993**, *115*, 12569; c) V. P. Conticello, L. Brard, M. A. Giardello, Y. Tsuji, M. Sabat, C. L. Stern, T. J. Marks, *J. Am. Chem. Soc.* **1992**, *114,* 2761.

[3] a) S. Bell, B. Wüstenberg, S. Kaiser, F. Menges, T. Netscher, A. Pfaltz, *Science* **2006**, *311*, 642; b) G. Helmchen, A. Pfaltz, *Acc. Chem. Res.* **2000**, *33*, 336; c) D. G. Blackmond, A. Lightfoot, A. Pfaltz, T. Rosner, P. Schnider, N. Zimmermann, *Chirality* **2000**, *12*, 442; d) A. Lightfoot, P. Schnider, A. Pfaltz, *Angew. Chem.* **1998**, *110*, 3047; *Angew. Chem. Int. Ed.* **1998**, *37*, 2897; e) P. Schnider, G. Koch, R. Prétôt, G. Wang, F. M. Bohnen, C. Krüger, A. Pfaltz, *Chem. Eur. J.* **1997**, *3*, 887.

[4] R. Crabtree, *Acc. Chem. Res.* **1979**, *12*, 331.

[5] a) Y. Kita, S. Hida, K. Higashihara, H. S. Jena, K. Higashida, K. Mashima, *Angew. Chem.* **2016**, *128*, 8439; *Angew. Chem. In. Ed.* **2016**, *55*, 8299*;* b) G. S. Forman, T. Ohkuma, W. P. Hems, R. Noyori, *Tetrahedron Lett.* **2000**, *41*, 9471; c) K. Inagaki, T. Ohta, K. Nozaki, H. Takaya, *J. Organomet. Chem.* **1997**, *531*, 159; d) T. Ohta, H. Ikegami, T. Miyake, H. Takaya, *J. Organomet. Chem.* **1995**, *502*, 169; e) R. Noyori, *Science* **1990**, *248*, 1194.

[6] For selected recent examples of Co or Fe-catalyzed hydrogenation of unfunctionalized olefins, see: a) J. Chen, C. Chen, C. Ji, Z. Lu, *Org. Lett.* **2016**, *18*, 1594; b) N. Guo, M.-Y. Hu, Y. Feng, S.-F. Zhu, *Org. Chem. Front*. **2015**, *2*, 692; c) P. J. Chirik, *Acc. Chem. Res.* **2015**, *48*, 1687; d) M. R. Friedfeld, M. Shevlin, J. M. Hoyt, S. W. Krska, M. T. Tudge, P. J. Chirik, *Science* **2013**, *342*, 1076; e) S. Monfette, Z. R. Turner, S. P. Semproni, P. J. Chirik, *J. Am. Chem. Soc.* **2012**, *134*, 4561; f) R. P. Yu, J. M. Darmon, J. M. Hoyt, G. W. Margulieux, Z. R. Turner, P. J. Chirik, *ACS Catal*. **2012**, *2*, 1760.

[7] For selected papers on the development of P,N-ligands, see: a) B. Qu, L. P. Samankumara, S. Ma, K. R. Fandrick, J.-N. Desrosiers, S. Rodriguez, Z. Li, N. Haddad, Z. S. Han, K. McKellop, S. Pennino, N. Grinberg, N. C. Gonnella, J. J. Song, C. H. Senanayake, *Angew. Chem.* **2014**, *126*, 14656; *Angew. Chem. Int. Ed.* **2014**, *53*, 14428; b) X. Wang, Z. Han, Z. Wang, K. Ding, *Angew. Chem*. **2012**, *124*, 960; *Angew. Chem. Int. Ed.* **2012**, *51*, 936; c) S.-F. Zhu, Y.-B. Yu, S. Li, L.-X. Wang, Q.-L. Zhou, *Angew. Chem.* **2012**, *124*, 9002; *Angew. Chem. Int. Ed.* **2012**, *51*, 8872; d) M. G. Schrems, E. Neumann, A. Pfaltz, *Angew. Chem.* **2007**, *119,* 8422; *Angew. Chem. Int. Ed.* **2007**, *46*, 8274; e) S.-F. Zhu, J.-B. Xie, Y.-Z. Zhang, S. Li, Q.-L. Zhou, *J. Am. Chem. Soc.* **2006**, *128*, 12886; f) D. Liu, W. Tang, X. Zhang, *Org. Lett.* **2004**, *6*, 513; g) W. Tang, W. Wang, X. Zhang, *Angew. Chem.* **2003**, *115*, 973; *Angew. Chem. Int. Ed.* **2003**, *42*, 943.

[8] For selected recent examples, see: a) B. K. Peters, J. Liu, C. Margarita, W. Rabten, S. Kerdphon, A. Orebom, T. Morsch, P. G. Andersson, *J. Am. Chem. Soc.* **2016**, *138*, 11930; b) B. Qu, L. P. Samankumara, J. Savoie, D. R. Fandrick, N. Haddad, X. Wei, S. Ma, H. Lee, S. Rodriguez, C. A. Busacca, N. K. Yee, J. J. Song, C. H. Senanayake, *J. Org. Chem.* **2014**, *79*, 993; c) T. L. Church, T. Rasmussen, P. G. Andersson, *Organometallics* **2010**, *29*, 6769; d) P. Tolstoy, M. Engman, A. Paptchikhine, J. Bergquist, T. L. Church, A. W.-M. Leung, P. G. Andersson, *J. Am. Chem. Soc.* **2009**, *131*, 8855; e) M. Diéguez, J. Mazuela, O. Pàmies, J. J. Verendel, P.G. Andersson, *J. Am. Chem. Soc.* **2008**, *130*, 7208; f) S. Kaiser, S. P. Smidt, A. Pfaltz, *Angew. Chem.* **2006**, *118*, 5318; *Angew. Chem. Int. Ed.* **2006**, *45*, 5194; g) C. Hedberg, K. Källström, P. Brandt, L. K. Hansen, P. G. Andersson, *J. Am. Chem. Soc.* **2006**, *128*, 2995; h) S. McIntyre, E. Hörmann, F. Menges, S. P. Smidt, A. Pfaltz, *Adv. Synth. Catal*. **2005**, *347*, 282. For examples of mechanistic studies, see: i) S. Gruber, A. Pfaltz, *Angew. Chem.* **2014**, *126*, 1927; *Angew. Chem. Int. Ed.* **2014**, *53*, 1896; j) S. Gruber, M. Neuburger, A. Pfaltz, *Organometallics* **2013**, *32*, 4702; k) C. Mazet, S. P. Smidt, M. Meuwly, A. Pfaltz, *J. Am. Chem. Soc.* **2004**, *126*, 14176; l) Y. Fan, X. Cui, K. Burgess, M. B. Hall, *J. Am. Chem. Soc.* **2004**, *126*, 16688; m) P. Brandt, C. Hedberg, P. G. Andersson, *Chem. Eur. J.* **2003**, *9*, 339; n) R.

Accepted Manuscript

This article is protected by copyright. All rights reserved.

H. Crabtree, P. C. Demou, D. Eden, J. M. Mihelic, C. A. Parnell, J. M. Quirk, G. E. Morris, *J. Am. Chem. Soc.* **1982**, *104*, 6994.

[9] a) M. R. Friedfeld, M. Shevlin, G. W. Margulieux, L.-C. Campeau, P. J. Chirik, *J. Am. Chem. Soc.* **2016**, *138*, 3314; b) R. P. Yu, J. M. Darmon, C. Milsmann, G. W. Margulieux, S. C. E. Stieber, S. DeBeer, P. J. Chirik, *J. Am. Chem. Soc*. **2013**, *135*, 13168; c) C.-B. Yu, Y.-G. Zhou, *Angew. Chem.* **2013**, *125,* 13607; *Angew. Chem. Int. Ed.* **2013**, *52*, 13365; d) K. H. Hopmann, *Organometallics* **2013**, *32*, 6388; e) K. H. Hopmann, A. Bayer, *Organometallics* **2011**, *30*, 2483; f) S. K. Chakka, B. K. Peters, P. G. Andersson, G. E. M. Maguire, H. G. Kruger, T. Govender, *Tetrahedron: Asymmetry* **2010**, *21*, 2295; g) J. Bayardon, J. Holz, B. Schäffner, V. Andrushko, S. Verevkin, A. Preetz, A. Börner, *Angew. Chem.* **2007**, *119*, 6075; *Angew. Chem. Int. Ed.* **2007**, *46*, 5971; h) T. Ohta, H. Ikegami, T. Miyake, H. Takaya, *J. Organomet. Chem.* **1995**, *502*, 169.

[10] a) Y. Donde, J. H. Nguyen, WO2015048553A1, **2015**; b) F. Pohlki, U. Lange, M. Ochse, B. Behi, C. W. Hutchins, US2012040948A1, **2012**; c) P. T. Lansbury, C. J. Justman, WO2009036275A1, **2009**; d) J. Pontillo, Y. Gao, W. S. Wade, D. Wu, W. K. Eccles, US2006276454A1, **2006**; e) R. Kolanos, U. Siripurapu, M. Pullagurla, M. Riaz, V. Setola, B. L. Roth, M. Dukata, R. A. Glennona, *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1987; f) D. C. Horwell, W. Howson, W. P. Nolan, G. S. Ratcliffe, D. C. Rees, H. M. G. Willems, *Tetrahedron* **1995**, *51*, 203; g) E. L. Plummer, N. Tonawanda, US4362744A, **1982**.

[11] a) Y. Liu, I. D. Gridnev, W. Zhang, *Angew. Chem.* **2014**, *126*, 1932; *Angew. Chem. Int. Ed.* **2014**, *53*, 1901; b) Y. Liu, W. Zhang, *Angew. Chem.* **2013**, *125*, 2259; *Angew. Chem. Int. Ed.* **2013**, *52*, 2203; c) Y. Liu, D. Yao, K. Li, F. Tian, F. Xie, W. Zhang, *Tetrahedron* **2011**, *67*, 8445; d) Y. Liu, G. Yang, D. Yao, F. Tian, W. Zhang, *Sci. China Ser. B* **2011**, *54*, 87; e) F. Tian, D. Yao, Y. Liu, W. Zhang, *Adv. Synth. Catal.* **2010**, *352*, 1841; f) F. Tian, D. Yao, Y. J. Zhang, W. Zhang, *Tetrahedron* **2009**, *65*, 9609.

[12] CCDC 1481434 [(*R*)-1-benzyl-5,6-dichloro-2,3-dihydro-*1H*-indene] contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[13] a) J. Mazuela, P.-O. Norrby, P. G. Andersson, O. Pàmies, M. Diéguez, *J. Am. Chem. Soc.* **2011**, *133*, 13634; b) Y. Zhu, Y. Fan, K. Burgess, *J. Am. Chem. Soc.* **2010**, *132*, 6249; c) M. C. Perry, X. Cui, M. T. Powell, D.-R. Hou, J. H. Reibenspies, K. Burgess, *J. Am. Chem. Soc.* **2003**, *125*, 113.

[14] E. J. Eisenbraun, W. M. Harms, V. A. Palaniswamy, H. H. Chen, P. J. Porcaro, T. F. Wood, M. Chien, *J. Org. Chem.* **1982**, *47*, 342.

[15] Y. Herzig, L. Lerman, W. Goldenberg, D. Lerner, H. E. Gottlieb, A. Nudelman, *J. Org. Chem.* **2006**, *71*, 4130.

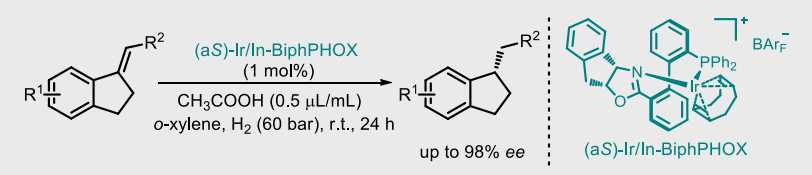
WILEY-VCH Accepted Manuscript

This article is protected by copyright. All rights reserved.

10.1002/chem.201604298

WILEY-VCH

COMMUNICATION



*Jingzhao Xia, Guoqiang Yang, Ruijing Zhuge, Yangang Liu, and Wanbin Zhang**

Page No. – Page No.

Iridium-Catalyzed Asymmetric Hydrogenation of Unfunctionalized Exocyclic C=C Bonds

Enjoy (E)XO: A general asymmetric hydrogenation of unfunctionalized exocyclic C=C bonds was developed using an Ir/biphenyl-phosphine-oxazoline ligand complex. An acetate ion additive plays an important role in giving products with high enantioselectivities. The chiral product can be further transformed to key intermediates required for the synthesis of an insecticide and a drug compound.

WILEY-VCH Accepted Manuscript

This article is protected by copyright. All rights reserved.