CHEMISTRY
A European Journal

A Journal of
ChemPubSoc Europe

Accepted Article

Title: Asymmetric Synthesis of Optically Active Spirocyclic Indoline Scaffolds Applying an Enantioselective Reduction of 3H-Indoles

Authors: Magnus Rueping

To be cited as: *Chem. Eur. J.* 10.1002/chem.201605450

Link to VoR: http://dx.doi.org/10.1002/chem.201605450

Supported by
ACES

WILEY-VCH

10.1002/chem.201605450

WILEY-VCH

Asymmetric Synthesis of Optically Active Spirocyclic Indoline Scaffolds Applying an Enantioselective Reduction of Indoles

Ruediger Borrmann, Nils Knop, and Magnus Rueping*

Abstract: An enantioselective synthesis of spirocyclic indoline scaffolds was achieved by applying an asymmetric iridium catalyzed hydrogenation of 3H-indoles. Low catalyst loadings and mild reaction conditions provide a broad range of differently substituted products with excellent yields and enantioselectivities. The developed methodology allows an efficient synthesis of this important spirocyclic structural motif, which is present in numerous biologically active molecules and privileged structures in medicinal chemistry.

Indoles and indolines are among the most widespread motives in naturally occurring bioactive compounds, insecticides, herbicides and drugs.[1,2] In particular, the 2-aryl-indoline structural element represents an important and prevalent motive in biologically and pharmaceutically active molecules with antitumor, anti-infective and anti-proliferative activity.[3] Additionally, chiral 2-aryl-indolines are privileged structures in medicinal chemistry as they possess cardiovascular[4] and nervous system[5] activity (Figure 1).

Asymmetric hydrogenation reactions employing molecular hydrogen and transition metal catalysts are among the most efficient and economic methods to generate chiral molecules.[6] The enantioselective hydrogenation of imines, enamines and *N*-heteroarenes in particular represents the most important access towards chiral amines,[7,8] not only in academia, but importantly in industry[9] and drug discovery.[10] Thus, the most direct approach to synthesize chiral 2-aryl-indolines would be the application of an asymmetric hydrogenation of the corresponding indoles. However, indoles are challenging substrates and their enantioselective hydrogenation remained unsuccessful for a long time. Furthermore, the few existing reports are limited to either *N*-protected indoles[11] or to alkyl and benzyl substituents in 2-position of unprotected indoles.[12] Except for an example of a cyclization strategy[13] and kinetic resolution approaches,[14] the only direct access to unprotected chiral 2-aryl-indolines to date is an organocatalytic procedure.[15] Unfortunately, the latter procedures are as yet not efficient enough to compete with the metal catalyzed hydrogenations, in particular when larger amounts of product need to be prepared. Therefore, we decided to develop a metal catalyzed hydrogenation of indoles for the enantioselective synthesis of spirocyclic indoline scaffolds in which no protecting groups are needed (Scheme 1).

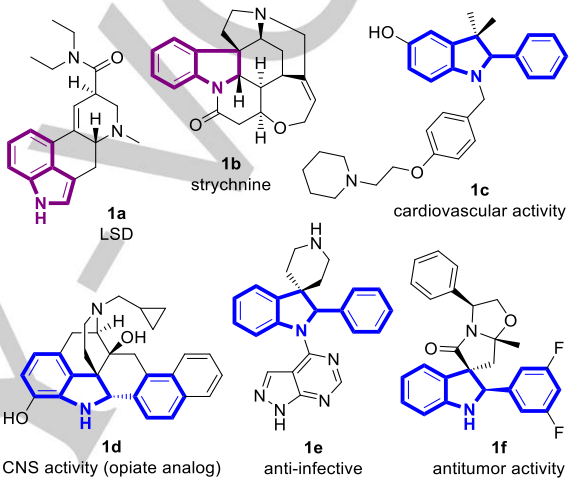
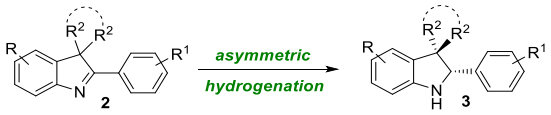


Figure 1. Bioactive and pharmacologically relevant indole and indoline scaffolds.

The 2-aryl-indolenine substrates can be readily prepared via a hindered Fischer-indole-synthesis from commercially available hydrazines and alkyl-aryl-ketones in a one-pot procedure[16] which provides a straightforward way to prepare a variety of 2-aryl 3,3-disubstituted spirocyclic indoline substrates. Here, we report a first successful asymmetric hydrogenation protocol for the synthesis of 2-aryl 3,3-spirocyclic indolines.[17,18]



Scheme 1. Asymmetric hydrogenation of 3*H*-indoles.

We commenced our studies with the asymmetric hydrogenation of model substrate **2a** applying different metal catalysts (Table 1). While palladium, platinum and rhodium BINAP complexes showed very low activity, ruthenium failed to give satisfying enantioselectivity. Iridium complexes, however, showed good reactivity and provided a promising selectivity of 56%*ee* (entry 7). Further reaction optimization involved the use of different counterions which typically do have a great impact on the reactivity or selectivity of the reaction. We screened several counterions by addition of their corresponding sodium or

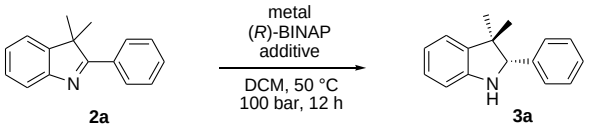
[a] Dr. Rüdiger Borrmann, M.Sc. Nils Knop, Prof. Dr. Magnus Rueping
Institute of Organic Chemistry, RWTH Aachen
Landoltweg 1, 52074 Aachen (Germany)
Fax: (+49) 241-809-2665
E-mail: magnus.rueping@rwth-aachen.de
Prof. Dr. M. Rueping
King Abdullah University of Science and Technology (KAUST)
KAUST Catalysis Center (KCC)
Thuwal, 23955-6900 (Saudi Arabia)
E-mail: magnus.rueping@Kaust.edu.sa

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

10.1002/chem.201605450

silver salts and *in situ* formation of the active catalysts. To our surprise, none of the tested additives improved the enantioselectivity, neither halide sources for catalyst activation nor acid additives for substrate activation were beneficial for the reaction outcome.

Table 1. Survey of metal precursors and additives.



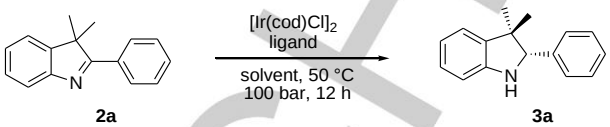
2a **3a**

Entry[a]	Catalyst precursor	Additive (6 mol%)	Conv. [%]	*ee*[b] [%]	abs. config.
1	$Rh(cod)_2BF_4$	--	5	12	(*R*)
2	Rh(cod)acac	--	10	14	(*S*)
3	$[Rh(cod)Cl]_2$	--	<5	n.d.[c]	n.d.[c]
4	$Ir(cod)_2BF_4$	--	44	24	(*S*)
5	Ir(cod)acac	--	<5	n.d.[c]	n.d.[c]
6	$[Ir(cod)OMe]_2$	--	>95	1	(*R*)
7	**$[Ir(cod)Cl]_2$**	**--**	**>95**	**56**	**(*R*)**
8	$[Ir(cod)Cl]_2$	$AgBF_4$	89	33	(*R*)
9	$[Ir(cod)Cl]_2$	$AgPF_6$	>95	33	(*R*)
10	$[Ir(cod)Cl]_2$	$AgAsF_6$	90	28	(*R*)
11	$[Ir(cod)Cl]_2$	$AgSbF_6$	88	22	(*R*)
12	$[Ir(cod)Cl]_2$	NaBArF[d]	92	3	(*S*)
13	$[Ir(cod)Cl]_2$	AgTFA[e]	>95	19	(*R*)
14	$[Ir(cod)Cl]_2$	$AgNTf_2$[f]	>95	48	(*R*)

[a] Reaction conditions: **2a** (0.1 mmol), metal precursor (5 mol%; 2.5 mol% for the dimeric species $[Rh(cod)Cl]_2$ and $[Ir(cod)Cl]_2$), (*R*)-BINAP (6 mol%), DCM (2 mL, 0.05 M), 50 °C, 100 bar H_2, 12 h, additive (none or 6 mol%); [b] Determined by SFC using Chiralcel OD-H column; [c] Not determined; [d] Sodium *tetrakis*-[3,5-bis(trifluoromethyl)-phenyl]borate;[19] [e] Silver trifluoroacetate; [f] Silver bis(trifluoromethylsulfonyl)-imide.

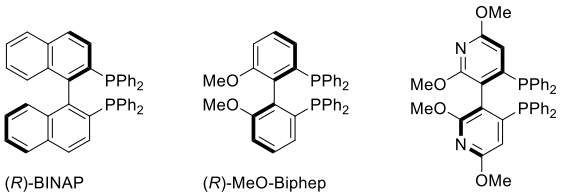
Subsequently, we evaluated various solvents (Table 2) and the use of chlorinated solvents including chloroform and 1,2-dichloroethane improved the enantioselectivity to 71% *ee* (entry 3). Polar solvents such as alcohols, acetonitrile, and dioxane gave inferior results. However, toluene, etheric solvents, and THF turned out to be efficient, with the latter one providing the best result (79% *ee*, entry 10). Typically, the chiral ligand has a tremendous impact on the enantioinduction, especially in asymmetric hydrogenations. Among various tested ligands, axially chiral diphosphines derived from the BINAP framework proved to be efficient. SYNPHOS (83% *ee*, entry 13), DIFLUORPHOS (82% *ee*, entry 15) and SEGPHOS based structures with substituents on the phosphorous aryl rings (91% ee, 96% ee, entries 16 and 17) were superior. Overall, the *m*-xylyl substituted DM-SEGPHOS was found to be the best ligand showing high reactivity and excellent enantioselectivity (96% *ee*, entry 17). Having a promising catalytic system in hands, we evaluated additional parameters including temperature, hydrogen pressure, and concentration (Table 2, entries 18-21). Temperature is an important parameter with noticeable impact on the enantioselectivity. On one hand, high reactivity is observed at elevated temperatures, which is desirable in order to minimize catalyst loading and reaction time.

Table 2. Survey of solvents and ligands.



2a **3a**

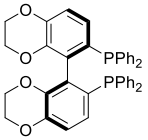
Entry[a]	Solvent	Ligand[b]	Conv. [%]	*ee*[c] [%]	abs. config.
1	DCM	BINAP	>95	56	(*R*)
2	$CHCl_3$	BINAP	>95	66	(*R*)
3	DCE	BINAP	76	71	(*R*)
4	toluene	BINAP	>95	62	(*S*)
5	acetone	BINAP	5	34	(*S*)
6	MeCN	BINAP	75	12	(*R*)
7	MeOH	BINAP	18	16	(*R*)
8	dioxane	BINAP	>95	12	(*S*)
9	Et_2O	BINAP	>95	69	(*S*)
10	**THF**	**BINAP**	**35**	**79**	**(*S*)**
11	THF	MeO-BIPHEB	73	79	(*S*)
12	THF	P-Phos	>95	79	(*S*)
13	THF	SYNPHOS	86	83	(*S*)
14	THF	SEGPHOS	88	69	(*S*)
15	THF	DIFLUORPHOS	>95	82	(*S*)
16	THF	DTBM-SEGPHOS	94	91	(*S*)
17	THF	DM-SEGPHOS	>95	96	(*S*)
18[d]	THF	DM-SEGPHOS	>95	97	(*S*)
19[d,e]	THF	DM-SEGPHOS	>95	98	(*S*)
20[d,e,f]	**THF**	**DM-SEGPHOS**	**>95**	**98**	**(*S*)**
21[d,e,f,g]	THF	DM-SEGPHOS	>95	97	(*S*)



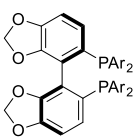
(*R*)-BINAP

(*R*)-MeO-Biphep

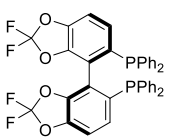
(*R*)-P-Phos



(*R*)-Syn-Phos



(*R*)-Seg-Phos: Ar = Ph
(*R*)-DM-Seg-Phos: Ar = m-xylyl
(*R*)-DTBM-Seg-Phos: Ar = 3,5-di-^{t}Bu-4-OMe-Ph



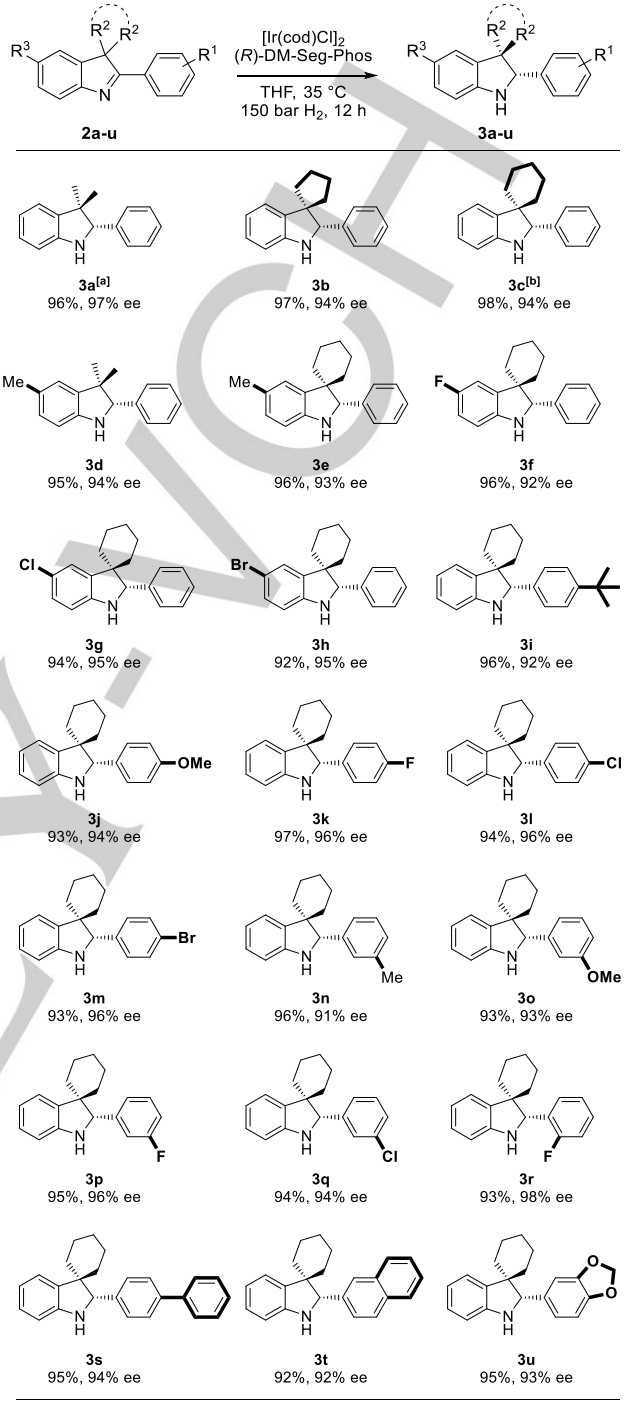
(*R*)-DIFLUORPHOS

[a] Reaction conditions: **2a** (0.1 mmol), $[Ir(cod)Cl]_2$ (2.5 mol%), ligand (6 mol%), solvent (2 mL, 0.05 M), 50 °C, 100 bar H_2, 12 h; [b] All ligands in (*R*)-configuration; [c] Determined by SFC using Chiralcel OD-H column; [d] 30 °C; [e] 150 bar H_2; [f] solvent (1 mL, 0.1 M); [g] $[Ir(cod)Cl]_2$ (0.5 mol%), ligand (1.2 mol%).

10.1002/chem.201605450

On the other hand, lower temperatures ensure a better enantiofacial discrimination resulting in higher *ee* values, but often at the expense of moderate reactivity. By screening several temperatures, we found an optimum between reactivity and enantioselectivity at 30 °C (97% *ee*, entry 18). Higher temperatures of up to 70 °C resulted in a slight decrease in enantioselectivity (95% *ee*), while lower temperatures of 25 °C and 20 °C resulted in a dramatic loss of reactivity (20% and <5% conversion, respectively). Subsequently, we investigated the influence of hydrogen pressure. Interestingly, low pressure of 20 bar still gave full conversion and 95% *ee*, which represents remarkably mild conditions for such a hydrogenation. However, high pressures had a positive effect on the enantioselectivity (98% *ee*, entry 19). Additionally, concentration effects were studied. Diluted solutions resulted in lower reactivity and enantioselectivity, while higher concentrations provided better results (98% *ee*, entry 20). Finally, we lowered the catalyst loading to 0.5 mol% $[Ir(cod)Cl]_2$ still achieving full conversion and satisfying 97% *ee* (entry 21).

With the best conditions in hand, we applied this newly developed asymmetric hydrogenation to differently substituted 2-aryl 3,3-disubstituted indolenines (Scheme 2). In general, the hydrogenation protocol can be applied to various substituted indolenines and the products are obtained in good yields and with acceptable enantioselectivities. Substituents in 3-position (**3a-c**, 96-98%, 94-97% *ee*) are not limited to methyl groups but also tolerate cyclic alkyl residues giving rise to highly valuable spirocyclic indolines in excellent yields. Notably, indoline **3c** was synthesized on a 2 mmol scale (>500 mg), demonstrating the potential of upscaling our protocol. We retained the spiro-cyclohexyl motif and investigated substitutions in 5-position (**3d-h**, 92-96%, 92-95% *ee*). To our delight, halides including fluorine, chlorine and bromine were tolerated without showing dehalogenated side products. This fact is most likely caused by the selective catalyst and the comparatively mild reaction conditions. Further variations of the substrate scope were achieved by modification of the substituents in 2-position of the indolenine framework. *Para*-substituted phenyl rings (**3i-m**, 93-97%, 92-96% *ee*) with electron donating and electron withdrawing groups provided excellent yields and enantioselectivities as well as halides, again showing no dehalogenation. We were also interested in different substitution patterns and found equally good results for *meta*-substituted phenyl rings (**3n-q**, 93-96%, 91-96% *ee*) and more complex substituents (**3s-u**, 92-95%, 92-94% *ee*) including biphenyl or annulated bicycles. Substrates with *ortho*-substituted phenyl rings in 2-position however are sterically hindered. However, their hydrogenated products are still obtained with a high level of enantiomeric excess (**3r**, 93%, 98% *ee*).



Scheme 2. Substrate scope of the iridium catalyzed enantioselective hydrogenation of 2-aryl-3*H*-indoles. Reaction conditions: **2** (0.1 mmol), $[Ir(cod)Cl]_2$ (1 mol%), (*R*)-DM-Seg-Phos (2.4 mol%), THF (1 mL, 0.1 M), 35 °C, 150 bar, 12 h; enantiomeric ratios determined by SFC using Chiralcel OD-H column; [a] 30 °C; [b] 2 mmol scale (>500 mg substrate).

In summary, we have developed a highly enantioselective synthesis of valuable disubstituted and spirocyclic 2-aryl-indoline scaffolds which represent an important class of biologically active molecules and privileged structures in medicinal chemistry. The hydrogenation protocol shows good functional

group compatibility and a variety of functional groups are tolerated. Noteworthy, also halides including fluorine, chlorine, and bromine can be applied and no dehalogenation has been observed due to the mild reaction conditions and low catalyst loading (1 mol%) applied. In addition the protocol is amenable to upscaling and the products are obtained in good yields and acceptable enantioselectivities (21 examples, 92-98%, 91-98% *ee*). Given that no protecting groups are needed and low catalyst loadings together with molecular hydrogen can be applied under mild and operationally convenient reaction conditions, this protocol should be of practical value.

Acknowledgements

The authors thank Solvias AG and Evonik Industries AG for donation of chiral ligands and metal salts.

Keywords: indole · asymmetric reduction · iridium catalyzed · spirocycle · pharmacophore

[1] a) A. J. Kochanowska-Karamyan, M. T. Hamann, *Chem. Rev.* **2010**, *110*, 4489–4497; b) M. Ishikura, K. Yamada, *Nat. Prod. Rep.* **2009**, *26*, 803–852.

[2] Z. Jin, *Nat. Prod. Rep.* **2011**, *28*, 1126–1142.

[3] a) G. S. Kauffman, C. Li, B. S. Lippa, J. Morris, G. Pan, WO2006090261A1, **2006**; b) R. Surakanti, S. Sanivarapu, C. Thulluri, P. S. Iyer, R. S. Tangirala, R. Gundla, U. Addepally, Y. L. Murthy, L. Velide, S. Sen, *Chem. Asian J.* **2013**, *8*, 1168–1176.

[4] a) J. W. Ullrich, *Patent*WO0051982A1, **2000**; b) J. W. Ullrich, *Patent*US6358943, **2002**.

[5] W. J. Welsh, S. J. Yu, A. Nair, *Patent* WO2004026819A2, **2004**.

[6] *The Handbook of Homogeneous Hydrogenation* (Eds.: J. G. de Vries, C. J. Elsevier), Vol. 1, Wiley-VCH, Weinheim, **2007**.

[7] For selected books and book chapters, see: a) *Stereoselective formation of amines* (Eds.: W. Li, X. Zhang), Springer, Heidelberg, **2014**; b) H.-U. Blaser, F. Spindler,*Catalytic Asymmetric Hydrogenation of C=N Functions*, in *Organic Reactions* (Eds.: S. E. Denmark *et al.*), John Wiley & Sons, **2009**; c) F. Spindler, H.-U. Blaser, *Enantioselective Hydrogenation of C=N Functions and Enamines*, in *The Handbook of Homogeneous Hydrogenation* (Eds. J. G. de Vries, C. J. Elsevier), Vol. 1, Wiley-VCH, Weinheim, **2007**; d) H.-U. Blaser, F. Spindler, *Hydrogenation of Imino Groups*, in *Comprehensive Catalysis* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer-Verlag, Berlin, Heidelberg, **2000**.

[8] For selected reviews, see: a) J.-H. Xie, S.-F. Zhu, Q.-L. Zhou, *Chem. Rev.* **2011**, *111*, 1713–1760; b) D.-S. Wang, Q.-A. Chen, S.-M. Lu, Y.-G. Zhou, *Chem. Rev.* **2012**, *112*, 2557–2590; c) Y.-G. Zhou, *Acc. Chem. Res.* **2007**, *40*, 1357–1366; d) Q.-A. Chen, Z.-S. Ye, Y. Duan, Y.-G. Zhou, *Chem. Soc. Rev.* **2013**, *42*, 497–511; e) N. Fleury-Brégeot, V. de la Fuente, S. Castillón, C. Claver, *ChemCatChem* **2010**, *2*, 1346–1371; f) K. H. Hopmann, A. Bayer,*Coord. Chem. Rev.* **2014**, *268*, 59–82; g) Z. Yu, W. Jin, Q. Jiang, *Angew. Chem. Int. Ed.* **2012**, *51*, 6060–6072; h) B.Balakrishna, J. L. Nunez-Rico, A. Vidal-Ferran, *Eur. J. Org. Chem.* **2015**, 5293–5303.

[9] H.-U. Blaser, B. Pugin, F. Spindler, *Asymmetric Hydrogenation*, in *Organometallics as Catalysts in the Fine Chemical Industry* (Eds. M. Beller, H.-U. Blaser), Springer-Verlag, Berlin, Heidelberg, **2012**.

[10] H.-U. Blaser, *Industrial Asymmetric Hydrogenation,* in *Applications of Transition Metal Catalysis in Drug Discovery and Development: An Industrial Perspective* (Eds.: M. L. Crawley, B. M. Trost), John Wiley & Sons, Inc., Hoboken, NJ, USA, **2012**.

[11] a) R. Kuwano, K. Sato, T. Kurokawa, D. Karube, Y. Ito, *J. Am. Chem. Soc.* **2000**, *122*, 7614–7615; b) R. Kuwano, K. Kaneda, T. Ito, K. Sato, T. Kurokawa, Y. Ito, *Org. Lett.* **2004**, *6*, 2213–2215; c) R. Kuwano, M. Kashiwabara, K. Sato, T. Ito, K. Kaneda, Y. Ito, *Tetrahedron: Asymmetry* **2006**, *17*, 521–535; d) R. Kuwano, M. Kashiwabara, *Org. Lett.* **2006**, *8*, 2653–2655; e) A. Baeza, A. Pfaltz, *Chem. Eur. J.* **2010**, *16*, 2036–2039.

[12] a) D.-S. Wang, Q.-A. Chen, W. Li, C.-B. Yu, Y.-G. Zhou, X. Zhang, *J. Am. Chem. Soc.* **2010**, *132*, 8909–8911; b) D.-S. Wang, J. Tang, Y.-G. Zhou, M.-W. Chen, C.-B. Yu, Y. Duan, G.-F. Jiang, *Chem. Sci.* **2011**, *2*, 803–806; c) Y. C. Xiao, C. Wang, Y. Yao, J. Sun, Y. C. Chen, *Angew. Chem. Int. Ed.* **2011**, *50*, 10661–10664; d) Y. Duan, L. Li, M. W. Chen, C. B. Yu, H. J. Fan, Y. G. Zhou, *J. Am. Chem. Soc.* **2014**, *136*, 7688–7700; e) J. L. Núñez-Rico, H. Fernández-Pérez, A. Vidal-Ferran, *Green Chem.* **2014**, *16*, 1153–1157; f) T. Touge, T. Arai, *J. Am. Chem. Soc.* **2016**, *138*, 11299–11305.

[13] K. Sharma, J. R. Wolstenhulme, P. P. Painter, D. Yeo, F. Grande-Carmona, C. P. Johnson, D. J. Tantillo, M. D. Smith, *J. Am. Chem. Soc.* **2015**, *137*, 13414–13424.

[14] a) V. Gotor-Fernández, P. Fernández-Torres, V. Gotor, *Tetrahedron: Asymmetry* **2006**, *17*, 2558–2564; b) M. Lopez-Iglesias, E. Busto, V. Gotor, V. Gotor-Fernandez, *J. Org. Chem.* **2012**, *77*, 8049–8055; c) X. L. Hou, B. H. Zheng, *Org. Lett.* **2009**, *11*, 1789–1791; c) K. Saito, Y. Shibata, M. Yamanaka, T. Akiyama, *J. Am. Chem. Soc.* **2013**, *135*, 11740–11743.

[15] a) M. Rueping, C. Brinkmann, A. P. Antonchick, I. Atodiresei, *Org. Lett.* **2010**, *12*, 4604-4607; b) A. D. Lackner, A. V. Samant, F. D. Toste, *J. Am. Chem. Soc.* **2013**, *135*, 14090–14093; c) Reviews on organocatalytic hydrogenations and examples: M. Rueping, E. Sugiono, F. R. Schoepke *Synlett,* **2010**, 852-865; d) M. Rueping, J. Dufour, F. R. Schoepke, *Green Chemistry*, **2011**, *13,* 1084-1105; e) M. Rueping, B. J. Nachtsheim, R. M. Koenigs, W. Ieawsuwan, *Chem. Eur. J.* **2010**, *16*, 13116-13126; f) M. Rueping, E. Sugiono, A. Steck, T. Theissmann *Adv. Synth. Catal.* **2010**, 352, 281-287, g) M. Rueping, B. N. Nachtsheim *Synlett* **2010**, 119-12; h) M. Fleischmann, D. Drettwan, E. Sugiono, M. Rueping, R. M. Gschwind, *Angew. Chem. Int. Ed.* **2011**, *50*, 6364–6369; i) M. Rueping, R. M. Koenigs, *Chem.Commun.* **2011**, 47, 304-306; k) H. Kim, E. Sugiono, Y. Nagata, M. Wagner, M. Bonn, M. Rueping, J. Hunger *ACS Catal.* **2015***, 5,* 6630-6633; l) C.-C. Hsiao, H.-H. Liao, E. Sugiono, I. Atodiresei, M. Rueping, *Chem. Eur. J*. **2013**, *19*, 9775-9779.

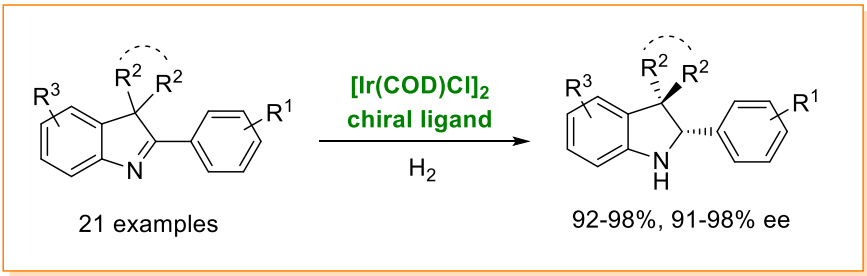
[16] M. Tomasulo, S. Sortino, A. J. P. White, F. M. Raymo, *J. Org. Chem.* **2005**, *70*, 8180–8189.

[17] During the submission of this manuscript, a related protocol appeared: Z. Yang, F. Chen, Y. He, N. Yang, Q.-H. Fan, *Angew. Chem. Int. Ed.* **2016**, *55*, 13863–13866.

[18] For selected examples for the reduction of related 2,3,3,-trimethylindolenine, see: a) G. Zhu, X, Zhang, *Tetrahedron: Asymmetry* **1998**, *9*, 2415–2418; b) H.-U. Blaser, H.-P. Buser, R. Häusel, H.-P. Jalett, F. Spindler, *J Organomet Chem.* **2001**, *621*, 34–38; c) D. Liu, W. Li, X. Zhang, *Tetrahedron: Asymmetry* **2004**, *15*, 2181–2184; d) C. J. Cobley, J. P. Henschke, *Adv. Synth. Catal.* **2003**, *345*, 195–201; e) R. Giernoth, M. S. Krumm, *Adv. Synth. Catal.* **2004**, *346*, 989–992; f) L. Qiu, F. Y. Kwong, J. Wu, W. H. Lam, S. Chan, W.-Y. Yu, Y.-M. Li, R. Guo, Z. Zhou, A. S. C. Chan, *J. Am. Chem. Soc.* **2006**, *128*, 5955–5965; g) V. Sumerin, K. Chernichenko, M. Nieger, M. Leskelä, B. Rieger, T. Repo, *Adv. Synth. Catal.* **2011**, *353*, 2093–2110; h) A. M. Kluwer, R. J. Detz, Z. Abiri, A. M. van der Burg, J. N. H. Reek, *Adv. Synth. Catal.* **2012**, *354*, 89–95.

[19] a) S. P. Smidt, N. Zimmermann, M. Studer, A. Pfaltz, *Chem. Eur. J.* **2004**, *10*, 4685–4693; b) W. Li, G. Hou, M. Chang, X. Zhang, *Adv. Synth. Catal.* **2009**, *351*, 3123–3127; c) 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*, 33–43; d) B. Wüstenberg, A. Pfaltz, *Adv. Synth. Catal.* **2008**, *350*, 174–178.

10.1002/chem.201605450



Entry for the Table of Contents (Please choose one layout)