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PII: S0040-4039(16)31602-1
DOI: http://dx.doi.org/10.1016/j.tetlet.2016.11.111
Reference: TETL 48397

To appear in: *Tetrahedron Letters*

Received Date: 10 October 2016
Revised Date: 24 November 2016
Accepted Date: 28 November 2016

Please cite this article as: Ge, C., Liang, R-X., Liu, R-R., Xiang, B., Jia, Y-X., Ir(I)-Catalyzed Enantioselective Hydrogenolysis of 3-Aryl-3-hydroxyisoindolin-1-ones, *Tetrahedron Letters* (2016), doi: http://dx.doi.org/10.1016/j.tetlet.2016.11.111

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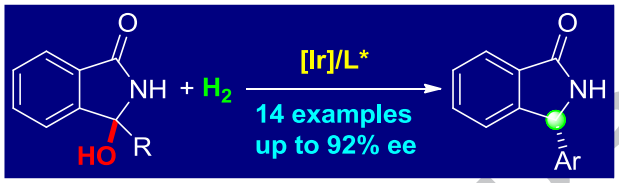

Tetrahedron Letters
journal homepage: www.elsevier.com/locate/tetlet

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College of Chemical Engineering, Zhejiang University of Technology, Hangzhou 310014, China

ARTICLE INFO

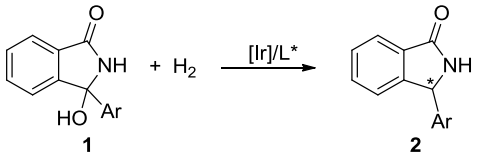
Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Hemiaminal
Iridium
Asymmetric hydrogenolysis

ABSTRACT

An enantioselective hydrogenolysis of 3-aryl-3-hydroxyisoindolin-1-ones under H_2 has been developed by using Ir(I)/(*R*)-MeO-Biphep complex as a catalyst. Cyclic diaryl methylamides were obtained in moderate to excellent yields and up to 92% ee.

As important class of organic compounds, chiral amines are unique subunits occurring in natural and unnatural bioactive molecules and widely used as chiral catalysts, chiral reagents, and resolving reagents in organic synthesis.[1] As a result, considerable attention has been paid to the synthesis of chiral amines and numerous reliable approaches have therefore been developed. Amongst, the transition-metal-catalyzed asymmetric hydrogenation of prochiral imines and enamines represents one of the most efficient and convenient approaches toward chiral amines and their derivatives.[2] On the other hand, enantioselective hydrogenolysis of hemiaminals, stable precursors of imines,[3] enabled an alternative access to chiral amines. Zhou and co-workers developed an attractive enantioselective hydrogenolysis of 3-alkyl-3-hydroxyisoindolin-1-ones by employing chiral phosphoric acid as catalyst and Hantzsch ester as hydride source, efficiently achieving cyclic *N*-carbonyl chiral amides in modest to excellent enantioselectivitis.[4] Our group realized the asymmetric hydrogenolysis of 3-aryl-3-hydroxyisoindolin-1-ones based on the same type of chiral catalyst and with benzothiazolines as hydride donors, which led to chiral 3-arylisoindolinones, cyclic diaryl methylamides, in good to excellent yields and modest to excellent enantioselectivities.[5] You and co-workers disclosed an enantioselective hydrogenolysis of cyclic indolyl-substituted 3-hydroxyisoindolin-1-ones to achieve chiral tetrahedron-β-carbolines in excellent yields and enantioselectivities.[6] Despite of these progress, the aforementioned reports exclusively relied on the use of chiral phosphoric acids as catalyst and organic molecules as hydride donors. We noted that Pd-catalyzed asymmetric hydrogenolysis reactions have been well developed through enantioselective C-O or C-X bonds cleavage processes,[7] while utilization of other transition metals in homogenous enantioselective hydrogenolysis, in particular for the synthesis of chiral amines, are still very rare. So far, there has no example reported for the asymmetric hydrogenolysis of hemiaminals employing chiral metal catalyst. Herein, we communicated a Ir(I)-catalyzed enantioselective hydrogenolysis of 3-aryl-3-hydroxyisoindolin-1-ones, which resulted in 3-arylisoindolinones, important building blocks in biologically active molecules, in moderate to excellent yields and moderate to good enantioselectivities (Scheme 1).



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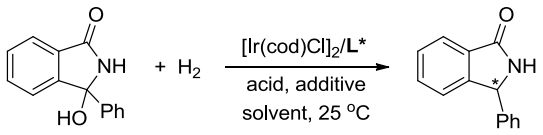
Scheme 1. Ir-catalyzed asymmetric hydrogenolysis of 3-aryl-3-hydroxyisoindolin-1-ons.

Initially, 3-hydroxy-3-phenyl-isoindolin-1-one **1a** was used as model substrate to optimize reaction condition. Upon exposure to 30 atm H_2 under the catalysis of $[Ir(cod)Cl]_2$ with (*S*)-BINAP as a ligand, the reaction underwent smoothly in the presence of 1.0 equiv CF_3CO_2H at 25 °C to afford the desired product **2a** in 89% isolated yield and 63% ee (Table 1, entry 1). Encouraged by this primary result, solvent effect was then investigated. The reaction in toluene led to product **2a** in a slightly higher enantioselectivity while the yield was decreased to 76% (entry 2). The yield and ee were both increased in DCE solvent (entry 4), while no reaction occurred in THF (entry 3). $CHCl_3$ was finally determined to be the best choice in terms of the obtained enantioselectivity (78% ee, entry 5). Additives, such as 4Å molecular sieves, Na_2SO_4, and $MgSO_4$, were then introduced to remove the formed H_2O during the reaction (entries 6-8). To our delight, the product was obtained in 91% yield and 80% ee when $MgSO_4$ was added to the reaction (entry 7). Other organic acids tested, such as $TsOH•H_2O$ and CF_3SO_3H, resulted in inferior results (entries 9-10). To further improve the enantioselectivity, other commercially available chiral diphosphine ligands, such as (*R*)-Synphos, (*R*)-Segphos, and (*R*)-MeO-Biphep, were examined in the reaction

(entries 11-15). Comparable results were obtained for (*R*)-Synphos and (*R*)-Segphos; however, with respect to the yield (97%) and enantioselectivity (86%) (*R*)-MeO-Biphep was determined to be the best choice of ligand (entry 14). Furthermore, higher enantioselectvities could be achieved by lowering H_2 pressure and the reaction temperature albeit decreased product yields were obtained (entries 16-18).

Table 1 Reaction condition optimization[a]



1a 2a

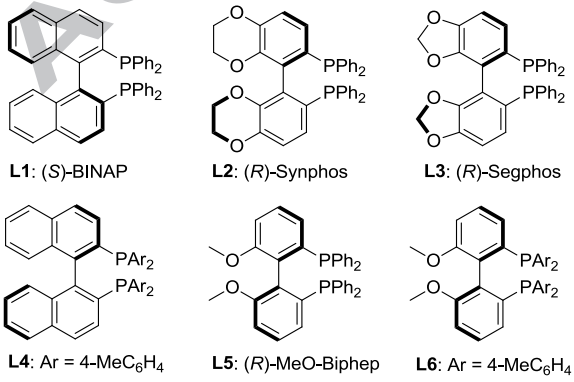
Entry	L*	H_2 (atm)	Acid	Additive	Solvent	Yield (%)[b]	Ee (%)[c]
1	**L1**	30	CF_3CO_2H	/	DCM	89	63
2	**L1**	30	CF_3CO_2H	/	toluene	76	65
3	**L1**	30	CF_3CO_2H	/	THF	NR	/
4	**L1**	30	CF_3CO_2H	/	DCE	91	68
5	**L1**	30	CF_3CO_2H	/	$CHCl_3$	83	78
6	**L1**	30	CF_3CO_2H	4Å MS	$CHCl_3$	97	57
7	**L1**	30	CF_3CO_2H	$MgSO_4$	$CHCl_3$	91	80
8	**L1**	30	CF_3CO_2H	Na_2SO_4	$CHCl_3$	89	80
9	**L1**	30	$TsOH•H_2O$	$MgSO_4$	$CHCl_3$	33	62
10	**L1**	30	CF_3SO_3H	$MgSO_4$	$CHCl_3$	54	32
11	**L2**	30	CF_3CO_2H	$MgSO_4$	$CHCl_3$	86	68
12	**L3**	30	CF_3CO_2H	$MgSO_4$	$CHCl_3$	86	63
13	**L4**	30	CF_3CO_2H	$MgSO_4$	$CHCl_3$	80	86
14	**L5**	30	CF_3CO_2H	$MgSO_4$	$CHCl_3$	97	86
15	**L6**	30	CF_3CO_2H	$MgSO_4$	$CHCl_3$	96	72
16	**L5**	10	CF_3CO_2H	$MgSO_4$	$CHCl_3$	92	86
17	**L5**	1	CF_3CO_2H	$MgSO_4$	$CHCl_3$	75	89
18[d]	**L5**	1	CF_3CO_2H	$MgSO_4$	$CHCl_3$	36	92

[a] Raction conditions: **1a** (0.2 mmol), 1.5 mol% $[Ir(cod)Cl]_2$, **L*** (3.3 mol%), acid (1 equiv), additive (100 mg), and solvent (2.0 mL) at 25 °C for 48 h.

[b] Isolated yield.

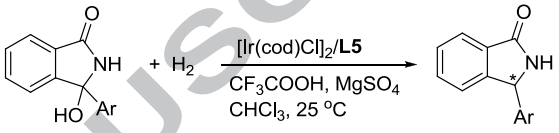
[c] Determined by chiral HPLC analysis.

[d] At 0 °C.



To demonstrate the substrate scope of this reaction, various 3-aryl-3-hydroxyisoindolin-1-ones (**1a-1o**) were tested under the optimized reaction conditions (Table 1, entry 14). As shown in Table 2, most of the reactions proceeded smoothly to furnish the desired products in moderate to excellent yields, whereas the enantioselectivities were influenced by the electronic property of the aryl group. Electron-donating substituents facilitated the reaction to result in excellent yields and good enantioselectivities with an exception of 3-MeO-substrate **1i** (entry 9); however, lower yields and ees were obtained for substrates **1j** and **1k** bearing fluorine and trifluoromethyl substituents at the *meta*-position (entries 10 and 11), and even no reaction occurred for the substrate **1n** containing two trifluoromethyl groups at C3 and C5 position of benzene. Lower enantioselectivity was also observed for the substrate bearing two *tert*-butyl substituents owing to the steric hindrance (entry 13). It's noted that the absolute configuration of the product **2a** was determined to be *R* by the comparison of its optical rotation with our previous report.[5]

Table 2 Substrate scope for the asymmetric hydrogenolysis[a]



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Entry	Ar	Yield[b] (%)	Ee[c] (%)
1	Ph (**1a**)	97	86 (*R*)
2	4-Et-C_6H_4 (**1b**)	99	81
3	3-Me-C_6H_4 (**1c**)	92	86
4	2-Me-C_6H_4 (**1d**)	72	76
5	4-MeO-C_6H_4 (**1e**)	98	85
6	4-Cl-C_6H_4 (**1f**)	93	74
7	4-^{t}Bu-C_6H_4 (**1g**)	93	75
8	4-Ph-C_6H_4 (**1h**)	89	75
9	3-MeO-C_6H_4 (**1i**)	89	56
10	3-F-C_6H_4 (**1j**)	65	53
11	4-CF_3-C_6H_4 (**1k**)	50	69
12	2-Naphth (**1l**)	78	71
13	3,5-di^{t}Bu-C_6H_3(**1m**)	84	56
14	3,5-diCF_3-C_6H_3 (**1n**)	NR	/

[a] Reaction conditions: **1** (0.2 mmol), 1.5 mol% $[Ir(cod)Cl]_2$, **L5** (3.3 mol%), CF_3COOH (1 equiv), and $MgSO_4$ (100 mg) in $CHCl_3$ (2.0 mL) at 25 °C for 48 h.

[b] Isolated yield.

[c] Determined by chiral HPLC analysis.

In summary, we have developed an efficient asymmetric hydrogenolysis of racemic 3-aryl-3-hydroxyisoindolin-1-ones by employing $[Ir(cod)Cl]_2$/(*R*)-MeO-Biphep as a catalyst under H_2 pressure. A range of cyclic diaryl methylamines were afforded in moderate to excellent yields and up to 92% ee in the presence of CF_3CO_2H and $MgSO_4$ additives. It represents the first example of enantioselective hydrogenolysis of hemiaminals using transition-metal catalyst.

Acknowledgments

We are grateful for the financial support from the National Natural Science Foundation of China (21372202 and 21502169) and the Natural Science Foundation of Zhejiang Province (LR14B020001 and LQ15B020003).

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.03.138.

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Highlights

► Transition-metal-catalyzed asymmetric hydrogenolysis of hemiaminal is developed
► Molecular hydrogen is used as hydride source
► Chiral iridium complex is used for the first time in asymmetric hydrogenolysis