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[Ir(P—OP)]-Catalyzed Asymmetric Hydrogenation of Diversely Substituted C═N-Containing Heterocycles

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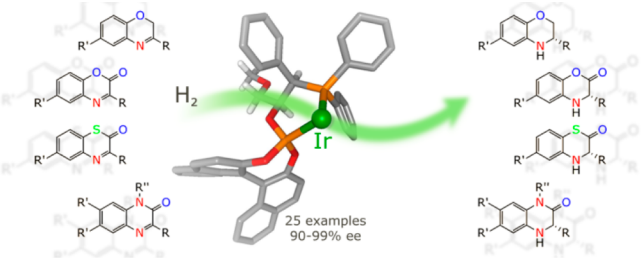
ABSTRACT



Iridium(I) complexes of enantiomerically pure phosphine-phosphite ligands ([Ir(Cl)(cod)(P—OP)]) efficiently catalyze the enantioselective hydrogenation of diverse C═N-containing heterocyclic compounds (benzoxazines, benzoxazinones, benzothiazinones, and quinoxalinones; 25 examples, up to 99% ee). A substrate-to-catalyst ratio as high as 2000:1 was reached.

Heterocyclic compounds are ubiquitous in biology and, therefore, are a mainstay in life, biotechnological, and materials science research.[1] Method development to access achiral heterocyclic compounds has been growing in scope and importance since the onset of organic synthesis. However, the development of general synthetic routes to enantiomerically pure (or highly enantioenriched) heterocyclic compounds remains challenging. Enantiomerically pure heterocyclic compounds are employed as important chiral building blocks in the synthesis of many pharmaceuticals.[2]

Enantioselective reduction of heteroaromatic compounds is one promising method: it benefits from a near infinite diversity of starting materials and minimizes the functional group manipulation inherent in many N-, O-, and S-heterocycle syntheses. Transition metal catalyzed asymmetric hydrogenation has been employed to reduce certain heteroaromatic derivatives (mainly quinolines and quinoxalines).[3] However, few reports of this chemistry deal

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(1) For example, see: (a) *Pharmaceutical Substances*; Kleemann, A., Engel, J., Kutscher, B., Reichert, D., Eds.; Thieme: Stuttgart, NY, 2001. (b) Roy, B.; De, N.; Majumdar, K. C. *Chem.—Eur. J* **2012**, *18*, 14560. (c) Yook, K. S.; Lee, J. Y. *Adv. Mater*. **2012**, *24*, 3169.

(2) For general texts on pharmaceutical applications of the types of chiral heterocycles described in this work, see ref 1, the following references and those cited therein: (a) Ilas, J.; Anderluh, P. S.; Dolenc, M. S.; Kikelj, D. *Tetrahedron* **2005**, *61*, 7325 (benzoxazinones). (b) Abraham, C. J.; Paull, D. H.; Scerba, M. T.; Grebinski, J. W.; Lectka, T. *J. Am. Chem. Soc*. **2006**, *128*, 13370 (quinoxalinones). (c) Smil, D. V.; Manku, S.; Chantigny, Y. A.; Leit, S.; Wahhab, A.; Yan, T. P.; Fournel, M.; Maroun, C.; Li, Z.; Lemieux, A.-M.; Nicolescu, A.; Rahil, J.; Lefebvre, S.; Panetta, A.; Besterman, J. M.; Deziel, R. *Bioorg. Med. Chem. Lett*. **2009**, *19*, 688 (quinoxalinones). (d) Rueping, M.; Stoeckel, M.; Sugiono, E.; Theissmann, T. *Tetrahedron* **2010**, *66*, 6565 (benzoxazines).

(3) For examples of the hydrogenation of quinolines and quinoxalines, see reviews a–c and the references cited therein: (a) Zhou, Y.-G. *Acc. Chem. Res*. **2007**, *40*, 1357. (b) Wang, D.-S.; Chen, Q.-A.; Lu, S.-M.; Zhou, Y.-G. *Chem. Rev*. **2012**, *112*, 2557. (c) Chen, Q.-A.; Ye, Z.-S.; Duan, Y.; Zhou, Y.-G. *Chem. Soc. Rev*. **2013**, *42*, 497. For examples of the asymmetric hydrogenation of other types of heterocycles, see: (d) Kuwano, R.; Kameyama, N.; Ikeda, R. *J. Am. Chem. Soc*. **2011**, *133*, 7312 (oxazoles). (e) Shi, L.; Ye, Z.-S.; Cao, L.-L.; Guo, R.-N.; Hu, Y.; Zhou, Y.-G. *Angew. Chem., Int. Ed*. **2012**, *51*, 8286 (isoquinolines). (f) Ye, Z.-S.; Chen, M.-W.; Chen, Q.-A.; Shi, L.; Duan, Y.; Zhou, Y.-G. *Angew. Chem., Int. Ed*. **2012**, *51*, 10181 (pyridines). (g) Ding, Z.-Y.; Chen, F.; Qin, J.; He, Y.-M.; Fan, Q.-H. *Angew. Chem., Int. Ed*. **2012**, *51*, 5706 (benzodiazepines). (h) Urban, S.; Beiring, B.; Ortega, N.; Paul, D.; Glorius, F. *J. Am. Chem. Soc*. **2012**, *134*, 15241 (thiophenes). (i) Ortega, N.; Urban, S.; Beiring, B.; Glorius, F. *Angew. Chem., Int. Ed*. **2012**, *51*, 1710 (benzofurans). (j) Iimuro, A.; Yamaji, K.; Kandula, S.; Nagano, T.; Kita, Y.; Mashima, K. *Angew. Chem., Int. Ed*. **2013**, *52*, 2046 (isoquinolines).

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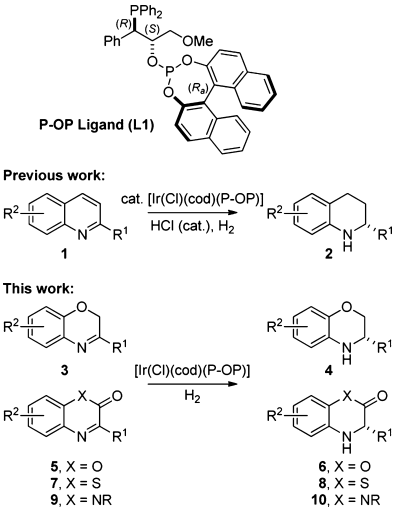
with the direct enantioselective hydrogenation of other C=N-containing heterocycles. Although the asymmetric reduction of other C=N-containing heterocycles has been efficiently achieved by chiral Brønsted acid catalyzed transfer hydrogenation (2*H*-benzo[*b*][1,4]oxazines **3**,[2d,4] 2*H*-benzo[*b*]-[1,4]oxazin-2-ones **5**,[4a] and quinoxalin-2(1*H*)-ones **9**;[5] Scheme 1) and by relay-catalyzed organocatalytic reduction[6] (**3** and **5**[7]), both with remarkably high enantioselectivities, only limited success has been reported in the standard asymmetric hydrogenation of the benzoxazines **3**.[8] Furthermore, to the best of the authors' knowledge, there are no reports of metal-mediated asymmetric hydrogenation of the other heterocyclic classes (**5**, 2*H*-benzo[*b*][1,4]thiazin-2-ones **7** and **9**).

We recently reported the hydrogenation of quinolines **1** mediated by iridium(I) complexes ([Ir(Cl)(cod)(P-OP)]) with high enantioselectivities (Scheme 1).[9] Herein we report the evaluation of these Ir−(P−OP) complexes as precatalysts for asymmetric hydrogenation of diversely substituted C=N-containing heterocyclic compounds **3**, **5**, **7**, and **9** (see Tables 1 and 2). Deuterium labeling experiments on the hydrogenation of 2-methylquinoline and **5a** have provided new insights into the involved tautomerization processes during hydrogenation and the stereoselectivity of H-delivery.

The present work began with enantioselective hydrogenation of the benzoxazines **3** (Table 1). Catalytic studies on the asymmetric hydrogenation of the diversely substituted benzoxazines **3a**−**h** were done using well-established iridium(I) complexes.[9] Optimal hydrogenation reaction conditions (catalyst loading, solvent, pressure, and temperature) were studied on model compound **3a**, which was efficiently hydrogenated with full conversion and 95% ee in THF at rt under 40 bar of H_2 using 0.5 mol % of [Ir(Cl)(cod)(**L1**)] as a precatalyst,[10] (see entry 1 in Table 1, and the Supporting Information (SI)). The enantioselectivity of the hydrogenation of **3a** was strongly solvent dependent: THF was among the solvents that provided the highest enantioselectivity.[11]

Scheme 1. Enantioselective Partial Hydrogenation of Heterocyclic Compounds



Additives are commonly used to improve catalytic activity in this chemistry.[3b,12] Unfortunately, addition of an array of achiral and chiral Brønsted acids did not lead to increased enantioselectivities in the hydrogenation of **3a**.[11] Once the optimal hydrogenation conditions for **3a** had been established, the hydrogenation of the remaining benzoxazines (**3b**−**h**) was studied. These results are summarized in Table 1. The catalyst efficiently mediated the asymmetric hydrogenation of **3b**−**h**, with high conversions and enantioselectivities (91 to 95% ee). Regardless of the position and the electronic nature of the substituents at the phenyl R^1 substituent, or replacing the R^2 group with chlorine, the enantioselectivities were high (91−93% ee; entries 2−8 in Table 1).

With respect to the benzoxazines **3**, complete hydrogenation of their carbonyl-containing analogs **5** required higher pressure (80 instead of 40 bar H_2) and catalyst loadings (2 mol % instead of 0.5 mol %). Under these conditions and with THF as solvent, compound **5a** was hydrogenated with excellent enantioselectivity (95% ee; entry 9 in Table 1). Addition of catalytic amounts of anhydrous HCl to the hydrogenation of **5a** enabled a reduction in the amount of catalyst used (down to 1 mol %), although at the expense of a slight decrease in ee.[11] To obtain the highest possible enantioselectivity, the asymmetric hydrogenation of the benzoxazinones **5b**−**e** (3-[*p*-X-phenyl]-, 6-chloro-, and 6-^{t}Bu-substituted derivatives), using [Ir(Cl)(cod)(**L1**)] as precatalysts and in the absence of HCl, was then studied. Although the hydrogenation of **5a** and of its methyl substituted analog **5b** proceeded with full conversion under the optimized reaction conditions, only partial hydrogenation of the remaining benzoxazinones (**5c**−**e**) was observed. Nevertheless, the enantioselectivities obtained with all the studied compounds were

(4) (a) Rueping, M.; Antonchik, A. P.; Theissmann, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 6751. (b) Rueping, M.; Sugiono, E.; Steck, A.; Theissmann, T. *Adv. Synth. Catal.* **2010**, *352*, 281. (c) Rueping, M.; Theissmann, T. *Chem. Sci.* **2010**, *1*, 473. (d) Bleschke, C.; Schmidt, J.; Kundu, D. S.; Blechert, S.; Thomas, A. *Adv. Synth. Catal.* **2011**, *353*, 3101. (e) Kundu, D. S.; Schmidt, J.; Bleschke, C.; Thomas, A.; Blechert, S. *Angew. Chem., Int. Ed.* **2012**, *51*, 5456.

(5) Rueping, M.; Tato, F.; Schoepke, F. R. *Chem.—Eur. J.* **2010**, *16*, 2688.

(6) Shi, F.; Gong, L.-Z. *Angew. Chem., Int. Ed.* **2012**, *51*, 11423.

(7) Chen, Q.-A.; Gao, K.; Duan, Y.; Ye, Z.-S.; Shi, L.; Yang, Y.; Zhou, Y.-G. *J. Am. Chem. Soc.* **2012**, *134*, 2442.

(8) (a) Gao, K.; Yu, C.-B.; Wang, D.-S.; Zhou, Y.-G. *Adv. Synth. Catal.* **2012**, *354*, 483. (b) Hu, J.; Wang, D.; Zheng, Z.; Hu, X. *Chin. J. Chem.* **2012**, *30*, 2664. (c) Fleischer, S.; Zhou, S.; Werkmeister, S.; Junge, K.; Beller, M. *Chem.—Eur. J.* **2013**, *19*, 4997.

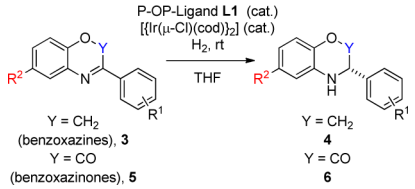
(9) (a) Núñez-Rico, J. L.; Fernández-Pérez, H.; Benet-Buchholz, J.; Vidal-Ferran, A. *Organometallics* **2010**, *29*, 6627. (b) Fernández-Pérez, H.; Etayo, P.; Panossian, A.; Vidal-Ferran, A. *Chem. Rev.* **2011**, *111*, 2119.

(10) The catalytic performance of a set of neutral and cationic iridium complexes derived from the P−OP ligands developed by the authors has been assessed in the asymmetric hydrogenation of these types of substrates. For the complete set of results, see the SI.

(11) For a complete summary of the hydrogenation results of these types of substrates, see section G of the SI.

(12) For example, see: Nagano, T.; Iimuro, A.; Schwenk, R.; Ohshima, T.; Kita, Y.; Togni, A.; Mashima, K. *Chem.—Eur. J.* **2012**, *18*, 11578 and the references cited therein.

Table 1. Asymmetric Hydrogenation of Compounds **3a**–**h** and **5a**–**e** Mediated by Complex [Ir(Cl)(cod)(**L1**)]



entry	Y, R^1, R^2, (substrate)	cat. (mol %), pH_2 (bar)[a]	conv (%)[b], ee (%)[c] (config)[d]
1	CH_2, H, H, (**3a**)	0.5, 40	99, 95 (*S*)
2	CH_2, *p*-Br, H, (**3b**)	0.5, 40	99, 92 (*S*)
3	CH_2, *p*-Cl, H, (**3c**)	0.5, 40	99, 91 (*S*)
4	CH_2, *p*-Me, H, (**3d**)	0.5, 40	99, 91 (*S*)
5	CH_2, *p*-MeO, H, (**3e**)	0.5, 40	99,[e] 91 (*S*)
6	CH_2, *p*-Ph, H, (**3f**)	0.5, 80	99, 93 (*S*)
7	CH_2, *m*-Br, H, (**3g**)	0.5, 40	99, 91 (*S*)
8	CH_2, H, Cl, (**3h**)	0.5, 40	96, 91 (*S*)[f]
9	CO, H, H, (**5a**)	2, 80	99, 95 (*S*)
10	CO, *p*-Me, H, (**5b**)	2, 80	99, 97 (S)
11	CO, *p*-MeO, H, (**5c**)	2, 80	51,[e] 99 (S)
12	CO, H, Cl, (**5d**)	2, 80	62,[e] 89 (S)
13	CO, H, ^{t}Bu, (**5e**)	2, 80	49,[e] 94 (S)

[a] Reaction conditions: [{Ir(μ-Cl)(cod)}$_2$]/P–OP ligand/substrate = 1:2.2:100, 0.5:1.1:100, or 0.25:0.55:100 for precatalyst levels of 2, 1, or 0.5 mol %, respectively, at rt, 20 h and 0.20 M in THF. The values shown are the average of at least two runs. [b] Conversions were determined by ^{1}H NMR. Typical isolated yields after column chromatography were >95%. [c] Determined by HPLC analysis using chiral stationary phases. [d] Absolute configuration was assigned by comparison with literature data. [e] Isolated yields: **4e**, 93%; **6c**, 45%; **6d**, 54%; and **6e**, 42%. [f] Absolute configuration was tentatively assigned by analogy based on the stereochemical outcome for analogous substrates.

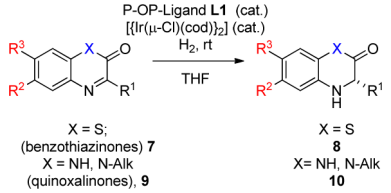
very high (89 to 99% ee for **5a**–**e**; see entries 9–13, in Table 1).

Hydrogenation of the thio- and aza-analogs of benzoxazinones **5** (compounds **7** and **9**, respectively) was subsequently explored. The benzothiazinones **7a**–**c** were efficiently hydrogenated under 80 bar of H_2 using 2 mol % of the standard catalyst (full conversion, up to 96% ee; entries 1–3, Table 2), regardless of the electronic nature of the substituents at R^1.

To the best of the authors' knowledge, this is the first-ever reported asymmetric hydrogenation of these sulfur-containing heterocycles. The quinoxalinones **9a**–**9i** also were hydrogenated very efficiently (conversions from 89 to 99%, and ee from 90 to 99%; entries 4–12 in Table 2) using the [Ir(Cl)(cod)(**L1**)] complex as precatalysts at lower pressure and lower catalyst loading than their sulfur analogs (see Table 2). Interestingly, the catalytic systems tolerate diverse substitution at the N1 position of the quinoxalinones: either no protecting group (**9a**) or a wide variety of protecting groups, including Me (**9d**), MOM (**9h**), and Bn (**9i**), with excellent enantioselectivity (99% ee; entries 4, 7, 11 and 12, respectively, in Table 2). For the *N*-methyl substituted derivative, a catalyst loading as low as 0.05 mol % resulted in almost full conversion (96%) and perfect enantioselectivity (99%, entry 7 in Table 2). Higher enantioselectivities were consistently observed for the quinoxalinones with an aryl substituent at R^1 (**9a**–**b**, **9d**–**e**, and **9g**–**i**) than for the alkyl-substituted compounds **9c** and **9f** (ee *ca.* 90%; entries 6 and 9 in Table 2). To the best of the authors' knowledge, these are the first-ever reported examples of asymmetric hydrogenation of the quinoxalinones **9**.

In summary, Ir(I) complexes of the enantiomerically pure phosphine-phosphite ligand **L1** efficiently catalyze the enantioselective hydrogenation of a wide array of heterocyclic C=N-containing derivatives (benzoxazines, benzoxazinones, benzothiazinones, and quinoxalinones; 25 examples, up to 99% ee). In the best case, a substrate-to-catalyst ratio of up to 2000 was used. To the best of the authors' knowledge, the work described here includes the first-ever reported examples of transition metal catalyzed asymmetric hydrogenation of the benzoxazinones **5**, the benzothiazinones **7**, and the quinoxalinones **9**.

Table 2. Asymmetric Hydrogenation of Compounds **7a**–**c** and **9a**–**i** Mediated by Complex [Ir(Cl)(cod)(**L1**)]



entry	X, R^1, R^2, R^3, (substrate)	cat. (mol %), pH_2 (bar)[a]	conv (%)[b], ee (%)[c] (config)[d]
1	S, Ph, H, H (**7a**)	2, 80	99, 94 (*S*)[f]
2	S, *p*-Me-C_6H_4, H, H (**7b**)	2, 80	99, 95 (*S*)[f]
3	S, *p*-MeO-C_6H_4, H, H (**7c**)	2, 80	99, 96 (*S*)[f]
4	NH, Ph, H, H (**9a**)	0.1, 40	98, 99 (*S*)
5	NH, *p*-Me-C_6H_4, H, H (**9b**)	0.5, 40	96,[e] 99 (*S*)[f]
6	NH, Me, Me, Me (**9c**)	2, 80	99, 90 (*S*)[f]
7	NMe, Ph, H, H (**9d**)	0.05, 40	96,[e] 99 (*S*)[f]
8	NMe, *p*-Me-C_6H_4, H, H (**9e**)	0.5, 40	89,[e] 99 (*S*)[f]
9	NMe, Me, Me, Me (**9f**)	0.5, 80	99, 90 (*S*)[f]
10	NMe, Ph, Cl, Cl (**9g**)	0.5, 40	96, 99 (*S*)[f]
11	NMOM, Ph, H, H (**9h**)	0.5, 40	96, 99 (*S*)[f]
12	NBn, Ph, H, H (**9i**)	0.5, 40	94, 99 (*S*)[f]

[a] Reaction conditions: [{Ir(μ-Cl)(cod)}$_2$]/P–OP ligand/substrate = 1:2.2:100, 0.5:1.1:100, or 0.25:0.55:100 for precatalyst levels of 2, 1, or 0.5 mol %, respectively, at rt, 20 h and 0.20 M in THF. The values shown are the average of at least two runs. [b] Conversions were determined by ^{1}H NMR. Typical isolated yields after column chromatography were >95%. [c] Determined by HPLC analysis using chiral stationary phases. [d] Absolute configuration was assigned by comparison with literature data. [e] Isolated yield: for **10b**, 92%; for **10d**, 92%; for **10e**, 85%. [f] Absolute configuration was tentatively assigned by analogy based on the stereochemical outcome for analogous substrates.

The literature includes only a few experimental or theoretical mechanistic studies on the hydrogenation of heteroaromatic compounds (mainly, of quinolines).[13]

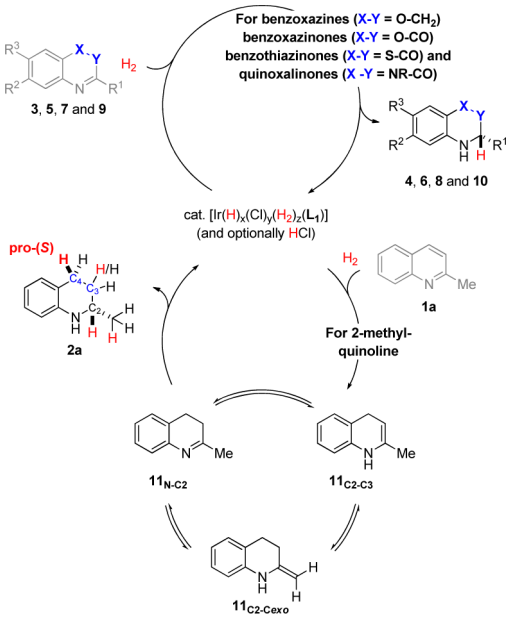
(13) For example, see: (a) Baralt, E.; Smith, S. J.; Hurwitz, J.; Horváth, I. T.; Fish, R. H. *J. Am. Chem. Soc.* **1992**, *114*, 5187. (b) Sanchez-Delgado, R. A.; Rondon, D.; Andriollo, A.; Herrera, V.; Martin, G.; Chaudret, B. *Organometallics* **1993**, *12*, 4291. (c) Bianchini, C.; Meli, A.; Vizza, F. *Eur. J. Inorg. Chem.* **2001**, 43. (d) Wang, D.-W.; Wang, X.-B.; Wang, D.-S.; Lu, S.-M.; Zhou, Y.-G.; Li, Y.-X. *J. Org. Chem.* **2009**, *74*, 2780. (e) Dobereiner, G. E.; Nova, A.; Schley, N. D.; Hazari, N.; Miller, S. J.; Eisenstein, O.; Crabtree, R. H. *J. Am. Chem. Soc.* **2011**, *133*, 7547.

Although most of the early studies on iridium-mediated hydrogenations suggested mechanistic pathways involving inner-sphere coordination of the substrate to the metal center,[13a–d] recent computational studies[14] have revealed that outer-coordination mechanistic pathways involving stepwise proton and hydride transfers[15] are more favored.[13e] Crabtree, Eisenstein et al. have shown that the catalytic cycle for iridium-mediated hydrogenation of 2-methylquinoline[13e] starts with its protonation followed by delivery of hydride to C4. Tautomerization of the resulting dihydroquinoline $\mathbf{11_{C2-C3}}$ to the C=N containing tautomer $\mathbf{11_{N-C2}}$, followed by a second protonation and hydride transfer to this tautomer,[13e] leads to the final tetrahydroquinoline **2**.

To gain deeper insight into the hydrogenation process, a series of labeling experiments were performed in which 2-methylquinoline **1a** and the benzoxazinone **5a** were hydrogenated using H_2/10 mol % of DCl, D_2/10 mol % of HCl, and D_2/10 mol % of DCl. Benzoxazinone **5a** reacted as expected with the labeled reagents. When D_2 was used, full incorporation of deuterium at C2 was observed (see Scheme 2; the H-atoms marked in red indicate the deuterium-labeled positions).[16] Conversely, no observable incorporation of deuterium was observed when H_2/10 mol % of DCl was used.[17]

Hydrogenation of 2-methylquinoline (**1a**) with the labeled reagents afforded a mixture of isotopic isomers incorporating deuterium atoms at C2, C3, and C4, as well at the methyl carbon of the quinoline (see structure **2a** in Scheme 2; the H-atoms marked in red indicate the deuterium-labeled positions).[16] When D_2 was used, full incorporation of deuterium at C2 was observed in the reduced product in all cases. Variable degrees of deuterium incorporation at C3, C4 and at the methyl group were obtained, depending on the labeling conditions. Surprisingly, when 10 mol % of DCl was used, a *ca.* 8% degree of deuterium incorporation at the methyl group was observed in the absence of D_2.[17] Deuteriation at the methyl group clearly indicates that dihydroquinoline $\mathbf{11_{C2-Cexo}}$ is formed and that it participates in the tautomeric equilibrium after the addition of the first H_2 molecule. A detailed analysis of the structure of deuteriated derivatives of **2a** revealed that, while deuterium is incorporated at C3 with no facial preference, deuteride is delivered with moderate stereoselectivity to C4

Scheme 2. Possible Pathways for the Hydrogenation of C=N-Containing Heterocycles



(*ca.* 2:1 incorporation ratio in favor of the pro-(*S*) position in C4 in the deuteriated derivatives of **2a**).[17] Overall, several labeling studies on the asymmetric reduction of analogous heterocycles have been published to date,[18] but the findings reported here demonstrate several important unreported issues in this chemistry. First, they elucidate the nature of the tautomerization processes after the first addition of H_2 and reveal a complex scenario, in which the $\mathbf{11_{C2-Cexo}}$ isomer also participates in the equilibria previous to the addition of the second H_2 molecule. Second, they suggest that the stereoselectivity of hydrogen incorporation at C4 would be compatible with asymmetric induction at this carbon during hydrogenation, in the event of being substituted.

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Supporting Information Available. Text and figures covering experimental procedures, analytical and spectral characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

(14) DFT calculations on iridium-mediated hydrogenations involving C=N bonds (imines: Hopmann, K. H.; Bayer, A. *Organometallics* **2011**, *30*, 2483; quinoline: see ref 13e) suggest that inner-sphere mechanisms are less favored.

(15) See the seminal work of Oro and co-workers (Martin, M.; Sola, E.; Tejero, S.; Andres, J. L.; Oro, L. A. *Chem.—Eur. J.* **2006**, *12*, 4043), who proposed and applied this stepwise concept.

(16) Deuterium–hydrogen exchange took place at nitrogen either during the chromatographic purification or during spectroscopic analysis, and N-deuterated compounds were not observed.

(17) For a summary of the labeling studies, see section K of the SI.

(18) See refs 3j , 4c, and: Yan, P.-C.; Xie, J.-H.; Hou, G.-H.; Wang, L.-X.; Zhou, Q.-L. *Adv. Synth. Catal.* **2009**, *351*, 3243.

The authors declare no competing financial interest.