J|A|C|S COMMUNICATIONS

Published on Web 07/01/2009

Enantioselective Hydrogenation of N−H Imines

Guohua Hou,[†] Francis Gosselin,*[,‡,§] Wei Li,[†] J. Christopher McWilliams,[‡] Yongkui Sun,[‡] Mark Weisel,[‡] Paul D. O'Shea,[§] Cheng-yi Chen,[‡] Ian W. Davies,[‡] and Xumu Zhang*[,†]

Department of Process Research, Merck Research Laboratories, P.O. Box 2000, Rahway, New Jersey 07065, Department of Process Research, Merck Frosst Centre for Therapeutic Research, 16711 Route Trans-Canadienne, Kirkland, Québec, Canada H9H 3L1, and Department of Chemistry, Rutgers, The State University of New Jersey, 610 Taylor Road, Piscataway, New Jersey 08854-8066

Received May 1, 2009; E-mail: francis_gosselin@merck.com; xumu@rutgers.edu

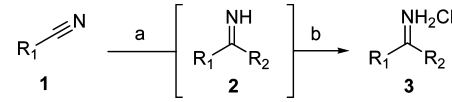
Chiral amines are ubiquitous structural elements of small-molecule pharmaceuticals and agrochemicals that improve human life. While several approaches have been developed to prepare chiral amines, decades of research have evolved catalytic hydrogenation into a technology ideally suited for their stereoselective synthesis.[1] Although success has been achieved with enantioselective hydrogenation of protected enamides, enamines, and imines, many catalysts fail to deliver the same levels of control and efficiency demonstrated with ketones and olefins.[1−3] Diminished enantioselectivities may be observed because of ambiguous catalyst−substrate interactions complicated by imine−enamine tautomerization and interconversion of imine *E*/*Z* stereoisomers.[1] Furthermore, available methods often require cumbersome protecting group manipulations to provide a substrate suited for hydrogenation and subsequent release of the desired amine products.

We report herein the first examples of efficient, atom-economical, enantioselective hydrogenations of *unprotected* N−H imines,[4] a fundamental step in the development of an ideal direct asymmetric reductive amination of ketones. To the best of our knowledge, N−H ketoimines have been completely overlooked as substrates for enantioselective hydrogenation. This is possibly because they have been considered difficult to synthesize and isolate and often exist as complex mixtures of *E*/*Z* isomers and imine−enamine tautomers. Multigram amounts of N−H ketoimines **3a**−**3v** were readily prepared via organometallic addition to nitriles **1** followed by quenching with anhydrous MeOH and isolation of the corresponding hydrochloride salts as single isomers, free-flowing, bench-stable solids (Scheme 1).

Inspired by a number of imine hydrogenation studies,[5,6] we anticipated that rigid electron-rich ligands could lead to high enantioselectivities with N−H ketoimines (Scheme 2). Our initial evaluation began with hydrogenation of N−H imine **3a** as the model substrate with a series of catalysts. Few promising results were obtained using Rh-phosphine catalysts. A number of electron-rich chiral Ir-phosphine complexes were also evaluated (Table 1, entries 1−4). While poor results were obtained using TangPhos,[7a] DuanPhos,[7b] BINAP,[7c] and Me-DuPhos,[7d] we were gratified to find that axially chiral Ir-(*S*,*S*)-f-binaphane[7e] (Figure 1) was a promising candidate for further optimization. Only moderate conversion was observed in most solvents (Table 1, entries 5−8). Use of MeOH as solvent gave complete conversion albeit with poor enantioselectivity (Table 1, entry 11). We found that the best enantioselectivity was obtained using CH_2Cl_2 as solvent (80% ee, Table 1, entry 6). We optimized the solvent combination and ratio with MeOH to achieve complete conversion and high enantioselectivity (Table 1, entries 12−18). Interestingly, under these optimized conditions we observed a negative impact on enantioselectivities when the chloride counterion in **3a** was replaced with noncoordinating counterions: methanesulfonate (75% conversion, 51% ee), PF_6^- (90% conversion, 91% ee), BF_4^- (99% conversion, 88% ee).

A variety of N−H imine substrates **3a**−**3v** were then examined using the Ir-f-binaphane catalyst system (Table 2). The bulkiness of the R_2 group in substrates had an influence on the enantioselectivities. As the R_2 group changed from Me to *tert*-Bu, the enantioselectivity of the product gradually decreased from 93% to 80% ee (entries 2−5). Substrates bearing both electron-donating

Scheme 1. Synthesis of N−H Imines[a]



[a] Conditions: (a) R_2MgX or R_2Li, in MTBE or THF; MeOH quench. (b) HCl in Et_2O.

Scheme 2. Asymmetric Hydrogenation of N−H Imines

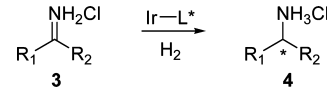


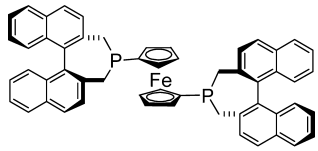
Table 1. Asymmetric Hydrogenation of **3a** (R_1 = 4-Tolyl, R_2 = Methyl)[a]

entry	ligand	solvent	% conv[b]	% ee[c]
1	TangPhos	TFE[d]	99	0
2	DuanPhos	TFE	41	8
3	BINAP	TFE	40	14
4	Me-DuPhos	TFE	20	20
5	(*S*,*S*)-**5**	TFE	31	52
6	(*S*,*S*)-**5**	CH_2Cl_2	60	80
7	(*S*,*S*)-**5**	Toluene	15	70
8	(*S*,*S*)-**5**	DCE[e]	60	32
9	(*S*,*S*)-**5**	EtOAc	37	38
10	(*S*,*S*)-**5**	THF	30	20
11	(*S*,*S*)-**5**	MeOH	99	9
12	(*S*,*S*)-**5**	MeOH/TFE (2:1)	99	10
13	(*S*,*S*)-**5**	MeOH/DCE (2:1)	99	20
14	(*S*,*S*)-**5**	MeOH/CH_2Cl_2 (1:2)	99	89
15	(*S*,*S*)-**5**	MeOH/CH_2Cl_2 (2:1)	99	95[f]
16	(*S*,*S*)-**5**	MeOH/CH_2Cl_2 (2:1)	99	95[g]
17	(*S*,*S*)-**5**	MeOH/CH_2Cl_2 (2:1)	98	95[h]
18	(*S*,*S*)-**5**	MeOH/CH_2Cl_2 (2:1)	99	73[i]

[a] Reaction conditions: [Ir(COD)Cl]$_2$/phosphine/substrate = 2.5:5:100, 1:1 ligand/metal, rt, 100 atm of H_2, 18 h. [b] Determined by GC analysis. [c] Determined by chiral GC analysis of the corresponding acetamides (see Supporting Information). [d] 2,2,2-Trifluoroethanol. [e] 1,2-Dichloroethane. [f] 30 atm of H_2. [g] 10 atm of H_2. [h] 5 atm of H_2. [i] 10 atm of H_2, S/C = 100, 48 h.

[†] Rutgers, The State University of New Jersey.
[‡] Merck Research Laboratories.
[§] Merck Frosst Centre for Therapeutic Research.

10.1021/ja903319r CCC: $40.75



(*S*,*S*)-f-Binaphane, (*S*,*S*)-**5**

Figure 1

Table 2. Enantioselective Hydrogenation of N−H Imines[a]

entry	R_1	R_2	product	yield (%)[b]	ee (%)[c]
1	4-MeC_6H_4 (**3a**)	Me	**4a**	95	95 (*R*)[d]
2	C_6H_5 (**3b**)	Me	**4b**	93	93 (*R*)
3	C_6H_5 (**3c**)	Et	**4c**	92	86 (*R*)
4	C_6H_5 (**3d**)	*n*-Bu	**4d**	92	88 (*R*)
5	C_6H_5 (**3e**)	*t*-Bu	**4e**	90	80 (*R*)
6	4-MeOC_6H_4 (**3f**)	Me	**4f**	95	93 (*R*)
7	4-FC_6H_4 (**3g**)	Me	**4g**	95	92 (*R*)
8	4-ClC_6H_4 (**3h**)	Me	**4h**	95	94
9	4-BrC_6H_4 (**3i**)	Me	**4i**	94	93 (*R*)
10	4-$CF_3C_6H_4$ (**3j**)	Me	**4j**	93	93 (*R*)
11	3-MeC_6H_4 (**3k**)	Me	**4k**	95	92
12	3-MeOC_6H_4 (**3 L**)	Me	**4 L**	94	94
13	3-ClC_6H_4 (**3m**)	Me	**4m**	92	92
14	3-BrC_6H_4 (**3n**)	Me	**4n**	93	91
15	2-MeC_6H_4 (**3o**)	Me	**4o**	92	81
16	2-MeOC_6H_4 (**3p**)	Me	**4p**	93	92 (*R*)
17	2-ClC_6H_4 (**3q**)	Me	**4q**	92	81
18	1-naphthyl (**3r**)	Me	**4r**	95	93
19	2-naphthyl (**3s**)	Me	**4s**	94	92 (*R*)
20	*t*-Bu (**3t**)	Me	**4t**	90	17 (*R*)
21	cyclohexyl (**3u**)	Me	**4u**	91	73 (*R*)
22	4-MeC_6H_4 (**3v**)	Ph	**4v**	95	23 (*R*)

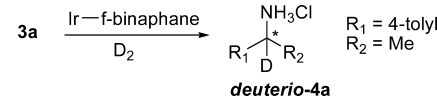
[a] Conditions: $[Ir(COD)Cl]_2$/(*S*,*S*)-f-binaphane/substrate = 2.5:5:100, 10 atm of H_2, rt, 20 h, >99% conversion. [b] Isolated yields of hydrochloride salts. [c] Determined by chiral GC analysis of the corresponding acetamides (see Supporting Information). [d] Absolute configuration determined by comparison with literature (see Supporting Information for other entries).[8]

and -withdrawing substituents on the aromatic ring in R_1 were hydrogenated with uniformly high enantioselectivities (entries 6−14). Both the 1- and 2-naphthyl N−H imines afforded product amines in 92 and 93% ee, respectively (entries 18 and 19). We found that the presence of either a methyl or chloro substituent at the *ortho*-position resulted in a slightly reduced ee (entry 15 and 17). The reduction of enantioselectivity may be attributed to the steric hindrance of the *ortho*-substituents in the substrates. However, an *ortho*-methoxy group did not exhibit a similar effect (entry 16). Significant erosion in enantioselectivity was observed when the aryl substituent was replaced with a sterically hindered *tert*-butyl group (entry 20). Finally, the Ir catalyst showed promising enantioselectivities on dialkyl imine **3u** and diaryl imine **3v**, substrates with a more limited steric and electronic bias (entries 21−22).

Preliminary mechanistic information was garnered through isotopic labeling of imine **3a** with D_2 in MeOH/CH_2Cl_2 (Scheme 3). ^1H NMR analysis of the crude product showed exclusive formation of α-*deuterio*-amine hydrochloride **4a**, suggesting a pathway consistent with reduction of the imine tautomer.[3] In addition, enantioface selection of imine **3a** by the Ir-f-binaphane catalyst was found to be identical to that of 4′-methylacetophenone.[9]

In conclusion, we have developed an unprecedented, operationally simple, and mild asymmetric hydrogenation of N−H ketoimines. This method allows the enantioselective synthesis of chiral amines without use of protecting groups. Further studies are underway and will be reported in due course.

Scheme 3. Isotopic Labeling of **3a**



***deuterio*-4a**

Acknowledgment. X.Z. and G.H. thank the National Institutes of Health (GM58832) for financial support.

Supporting Information Available: Experimental procedures, characterization, analysis of enantioselectivities of hydrogenation products (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) For reviews, see: (a) Tang, W.; Zhang, X. *Chem. Rev.* **2003**, *103*, 3029. (b) Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069. (c) Shultz, C. S.; Krska, S. W. *Acc. Chem. Res.* **2007**, *40*, 1320. (d) de Vries, J. G., Elsevier, C. J., Eds. *Handbook of Homogeneous Hydrogenation*; Wiley-VCH: Weinheim, 2007.

(2) (a) Oppolzer, W.; Wills, M.; Starkemann, C.; Bernardinelli, G. *Tetrahedron Lett.* **1990**, *31*, 4117. (b) Willoughby, C. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1992**, *114*, 7562. (c) Willoughby, C. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 8952. (d) Lee, N. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 5985. (e) Charette, A. B.; Giroux, A. *Tetrahedron Lett.* **1996**, *37*, 6669. (f) Tararov, V. I.; Kadyrov, R.; Riermeier, T. H.; Holz, J.; Börner, A. *Tetrahedron Lett.* **2000**, *41*, 2351. (g) Blaser, H.-U.; Malan, C.; Pugin, B.; Spindler, F.; Steiner, H.; Studer, M. *Adv. Synth. Catal.* **2003**, *345*, 103. (h) Cobley, C. J.; Henschke, J. P. *Adv. Synth. Catal.* **2003**, *345*, 195. (i) Hou, G.-H.; Xie, J.-H.; Wang, L.-X.; Zhou, Q.-L. *J. Am. Chem. Soc.* **2006**, *128*, 11774. (j) Imamoto, T.; Iwadate, N.; Yoshida, K. *Org. Lett.* **2006**, *8*, 2289. (k) Wang, Y.-Q.; Lu, S.-M.; Zhou, Y.-G. *J. Org. Chem.* **2007**, *72*, 3729. (l) Li, C.; Xiao, J. *J. Am. Chem. Soc.* **2008**, *130*, 13208. (m) Li, C.; Wang, C.; Villa-Marcos, B.; Xiao, J. *J. Am. Chem. Soc.* **2008**, *130*, 14450. (n) Hou, G.-H.; Xie, J.-H.; Yan, P.-C.; Zhou, Q.-L. *J. Am. Chem. Soc.* **2009**, *131*, 1366. (o) Shirai, S.-y.; Nara, H.; Kayaki, Y.; Ikariya, T. *Organometallics* **2009**, *28*, 802.

(3) For enantioselective hydrogenation of unprotected enamines in the synthesis of β-amino acids, see: (a) Hsiao, Y.; Rivera, N. R.; Rosner, T.; Krska, S. W.; Njolito, E.; Wang, F.; Sun, Y.; Armstrong, J. D.; Grabowski, E. J. J.; Tillyer, R. D.; Spindler, F.; Malan, C. *J. Am. Chem. Soc.* **2004**, *126*, 9918. (b) Matsumura, K.; Zhang, X.; Saito, T. U.S. Patent 7,015,348 B2, 2004 (Takasago).

(4) (a) Gosselin, F.; O'Shea, P. D.; Roy, S.; Reamer, R. A.; Chen, C.-y.; Volante, R. P *Org. Lett.* **2005**, *7*, 355. (b) Chen, G.-M.; Brown, H. C. *J. Am. Chem. Soc.* **2000**, *122*, 4217, and references cited therein.

(5) (a) Zhang, W.; Chi, Y.; Zhang, X. *Acc. Chem. Res.* **2007**, *40*, 1278. (b) Yang, Q.; Shang, G.; Gao, W.; Deng, J.; Zhang, X. *Angew. Chem., Int. Ed.* **2006**, *45*, 3832. (c) Shang, G.; Yang, Q.; Zhang, X. *Angew. Chem, Int. Ed.* **2006**, *45*, 6360. (d) Xiao, D.; Zhang, X. *Angew. Chem., Int. Ed.* **2001**, *40*, 3425.

(6) (a) Sablong, R.; Osborn, J. A. *Tetrahedron Lett.* **1996**, *37*, 4937. (b) Kainz, S.; Brinkman, A.; Leither, W.; Pfaltz, A. *J. Am. Chem. Soc.* **1999**, *121*, 6421. (c) Jiang, X.-B.; Minnaard, A. J.; Hessen, B.; Feringa, B. L.; Duchateau, A. L. L.; Andrien, J. G. O.; Boogers, J. A. F.; de Vries, J. G. *Org. Lett.* **2003**, *5*, 1503. (d) Trifonova, A.; Diesen, J. S.; Chapman, C. J.; Andersson, P. G. *Org. Lett.* **2004**, *6*, 3825. (e) Moessner, C.; Bolm, C. *Angew. Chem., Int. Ed.* **2005**, *44*, 7564.

(7) (a) TangPhos: (*1S*,*1S*′,*2R*,*2R*′)-1,1′-di-*tert*-butyl-(2,2′)-diphospholane. (b) DuanPhos: (*1S*,*1*′*S*,*2R*,*2*′*R*)-2,2′-di-*tert*-butyl-2,3,2′,3′-tetrahydro-1*H*,1′*H*-(1,1′)-biisophosphindolyl. (c) BINAP: (*R*)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl. (d) MeDuPhos: 1,2-bis[(*2R*,*5R*)-2,5-dimethylphospholano]benzene. (e) (*S*,*S*)-f-binaphane: 1,1′-bis[(*S*)-4,5-dihydro-3*H*-binaphtho[2,1-*c*:1′,2′-*e*]phosphepino]ferrocene.

(8) Smith, H. E.; Neergard, J. R.; de Paulis, T.; Chen, F.-M. *J. Am. Chem. Soc.* **1983**, *105*, 1578.

(9) Hydrogenation of 4′-methylacetophenone with Ir-f-binaphane gave (*R*)-α-4-dimethylbenzenemethanol (30% conversion, 64% ee, $[\alpha]^{20}_{589}$ +27.4° (*c* = 0.2, MeOH); lit.: $[\alpha]^{20}_{589}$ +43.8° (*c* = 0.914, MeOH) for 99.8% ee: Mathre, D. J; Thompson, A. S; Douglas, A. W.; Hoogsteen, K.; Carroll, J. D.; Corley, E. G.; Grabowski, E. J. J. *J. Org. Chem.* **1993**, *58*, 2880.

JA903319R