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Enantioselective hydrogenation of diaryl-substituted α,β-unsaturated nitriles

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Abstract—α,β-Unsaturated nitriles can be hydrogenated with enantioselectivities up to 88% ee using chiral ruthenium-diphenylphosphino bisaryl and bisheteroaryl complexes such as ruthenium(II)-BINAP and ruthenium(II)-BINP. Mechanistic investigations indicate that conversion is accelerated by electron-rich ligands and that an additional coordinative group needs be present in order to promote conversion. The chiral products are useful building blocks for the synthesis of histamine H_2 agonists of the arpromidine type.

Enantioselective hydrogenation has evolved into a powerful tool in synthetic chemistry and a diverse array of chiral compounds can now be accessed in enantiopure form through hydrogenation of carbon–carbon or carbon–heteroatom double bonds.[1] Although a wide range of prochiral substrates can be used as substrates, in the majority of the cases, enantioselectivity is greatly increased when a suitable coordination site is present, normally containing heteroatom functionalities as, for example, seen with acrylic acid derivatives, aminoalkenes, enol esters and other compound classes. The enantiodifferentiating hydrogenation of compounds lacking such moieties is substantially more difficult.[2]

α,β-Unsaturated nitriles are valuable and easily accessible building blocks in organic synthesis. However, a general methodology for the asymmetric hydrogenation of α,β-unsaturated nitriles has not yet been developed. Due to their electronic structure, nitriles prefer end-on coordination of metal ions, which is not suitable for hydrogenation of a conjugated double bond. Furthermore, chemoselection between the olefinic double bond and the nitrile group in hydrogenation poses an additional challenge.[3] Only recently, a chemoselective catalytic conjugate reduction of α,β-unsaturated nitriles, that is, not employing stoichiometric metal hydride reductants, was reported as a non asymmetric variant by Yun et al.[4] Apart from isolated cases such as the rhodium diphospine-mediated hydrogenation of α,β-unsaturated nitriles bearing additional carboxylate or phthalimido substituents,[5] there are no reports on the asymmetric hydrogenation of acrylonitrile derivatives.

In our studies towards developing a general enantioselective methodology for the preparation of optically active nitriles, we initially focused on β,β-diaryl acrylonitriles as the hydrogenation products can serve as building blocks for the synthesis of chiral arpromidines, a class of highly active histamine H_2 receptor agonists. These compounds are currently investigated for their use as positive inotropic and vasodilatory drugs.[6] The results of the catalyst screening for the asymmetric hydrogenation of *E*-3-(3,4-difluorophenyl)-3-(2-pyridyl)propenenitrile (*E*-**1**), which can be converted to **3** being one of the most potent H_2-agonists known to date (Scheme 1), are summarized in Table 1.

Due to the polarized nature of the olefinic double bond, we initially studied chiral hydride reagents such as BINAL-H for this conjugate reduction process.[7]

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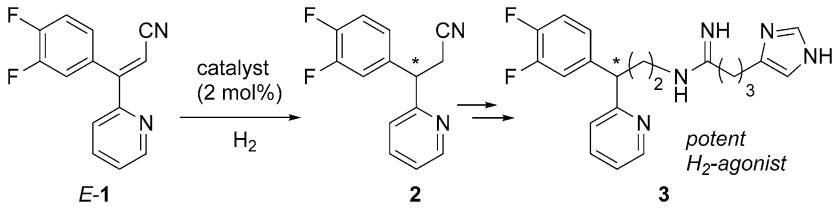


Scheme 1. Hydrogenation of acrylonitrile *E*-**1** as a key step for the synthesis of arpromidine analog **3**.

Table 1. Catalytic enantioselective hydrogenation of the α,β-unsaturated nitrile *E*-**1**[a]

Entry	Catalyst[b]	E^0_{ligand} [V]	Solvent	T [°C]	$p(H_2)$ [bar]	t [h]	Conversion (%)[c]	ee (%)
1	Li[Al(H)((+)-(*R*)-BINOLate)(OEt)][d]	n.d.	THF	−78 to 0	—	12	Decomp.[e]	*rac*
2[f]	[Rh((+)-(*R*)-BINAP)(COD)]ClO_4	+0.63	CH_2Cl_2	50	50	144	0	—
3	[Ru((+)-(*R*)-BINAP)Cl_2·dmf$_n$]	+0.63	CH_2Cl_2	50	100	48	100	51 (*S*)[g]
4	[Ru((+)-(*R*)-TolBINAP)Cl_2·dmf$_n$]	+0.65	CH_2Cl_2	50	100	48	100	52 (*S*)
5	[Ru((+)-(*S*)-tetraMe-BITIANP)Cl_2·dmf$_n$]	+0.83	CH_2Cl_2	50	100	48	60	52 (*S*)
6	[Ru((±)-BIMIP)Cl_2·dmf$_n$]	+1.15	CH_2Cl_2	50	100	60	27	–[h]
7	[Ru((+)-(*S*)-tetraMe-BITIOP)Cl_2·dmf$_n$]	+0.57	CH_2Cl_2	50	100	48	100	53 (*R*)
8	[Ru((−)-(*S*)-N-Me-2-BINP)Cl_2·dmf$_n$]	+0.52	CH_2Cl_2	50	100	24	100	80 (*R*)
9	[Ru((−)-(*S*)-N-Me-2-BINP)Cl_2·dmf$_n$]	+0.52	CH_2Cl_2	50	25	72	55	81 (*R*)
10	[Ru((−)-(*S*)-N-Me-2-BINP)Cl_2·dmf$_n$]	+0.52	CH_2Cl_2	37	100	48	70	88 (*R*)

[a] For a general procedure, see Ref. 16. Unless otherwise noted, there were no side reactions, and products could be isolated quantitatively according to conversion.
[b] 2 mol % catalyst was used (except in entry 1).
[c] Conversion was determined by ^{1}H NMR of the crude mixture.
[d] Used as a reagent (3 equiv).
[e] Decomposition of the starting material, 9% isolated yield of **2**.
[f] Both in the presence and absence of Et_3N (2 mol %); COD = 1,5-cyclooctadiene.
[g] Configuration of the major enantiomer being indicated, see Ref. 17.
[h] Racemic ligand.

Unfortunately, this approach furnished only racemic products and suffered from side reactions even at low temperatures (entry 1). Similarly, chiral rhodium diphosphine complexes such as [Rh((+)-(*R*)-BINAP)(COD)]-ClO_4, which are extremely effective catalysts for the enantioselective hydrogenation of acetamidoacrylates and related compounds,[1,8] turned out to be unsuitable catalysts for this transformation. Even after prolonged periods, no conversion was observed (entry 2). In contrast, ruthenium-based catalysts exhibited high activities in this reaction. The ruthenium-BINAP system [Ru((+)-(*R*)-BINAP)Cl_2·dmf$_n$] developed by Noyori[9,10] led to complete conversion of the acrylonitrile **1** and furnished the chiral product in 51% ee (entry 3). BINAP and Tol-BINAP performed very similarly in this process (entries 3,4). In order to improve the enantioselection, a series of other chiral diphosphine ligands were investigated.

Diphenylphosphino biheteroaryls (Fig. 1), which are synthetically more easily accessible than the carbocyclic bisaryl systems,[11] were also tested as ligands for this transformation. These ligands offer the possibility of fine-tuning the electron-donor properties at the phosphorous atoms. Normally, electronic-rich diphosphines are superior ligands in terms of both conversion and enantioselectivity in ruthenium and rhodium-catalyzed hydrogenations of olefins and carbonyl compounds.[12] Variation of the electron density of the biheteroaryl diphosphines revealed a similar correlation in case of the hydrogenation of α,β-unsaturated nitriles. The electron-poor ligands (as determined by their electrochemical oxidation peak potential E^0)(+)-(*S*)-tetraMe-BITIANP and (±)-BIMIP led to poor conversions and no improvement of enantioselectivity was observed (entries 5 and 6 in Table 1). In contrast, smooth conversion was observed with electron-rich ligands such as (+)-(*S*)-tetraMe-BITIOP and (−)-(*S*)-N-Me-2-BINP (entries 7,8). In the latter case, the enantiomeric excess could be raised to 81%. Reducing the hydrogenation pressure led to a decreased reaction rate, but left the enantioselec-

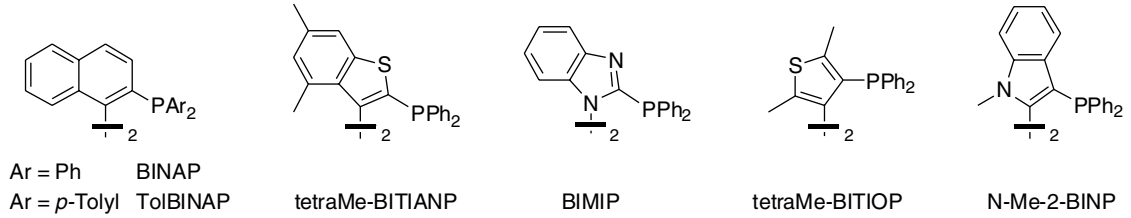
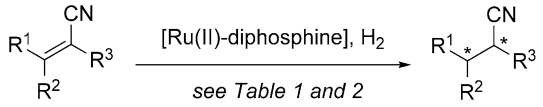


Figure 1. Bisaryl- and bisheteroaryl diphosphine ligands for asymmetric hydrogenations.

tivity unaffected. In contrast, through lowering the reaction temperature, the level of enantioselectivity was further increased to 88% ee (entries 9 and 10).

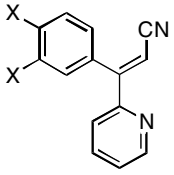
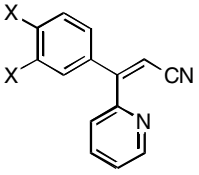
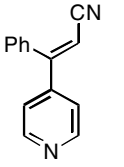
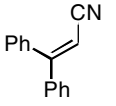
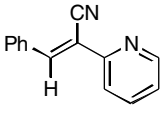
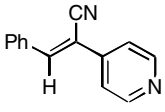
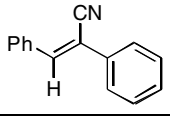
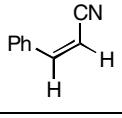
In order to gain insights into the reaction mechanism, the *Z*-isomer of **1** and compounds **4**–**10** were synthesized and subjected to hydrogenation using the established [Ru((*R*)-BINAP)Cl_2·dmf_n] catalyst (Scheme 2). The results are summarized in Table 2. The hydrogenation of *Z*-**1** proceeded much slower than with the *E*-isomer,[13] furnishing the product in low ee and opposite configuration (entries 1 and 2). In addition, traces of *E*-**1** were detected in the reaction mixture after hydrogenation. As the reaction products are stable under hydrogenation conditions, this implies that ruthenium catalysts are able to isomerize the *E*/*Z*-isomers of α,β-unsaturated nitriles, similarly to the Ru-catalyzed isomerization of α,β-unsaturated carbonyl compounds investigated by Takaya et al.[14] Furthermore, this result also indicates that the configuration at the nitrile-bearing α-carbon atom plays a crucial role in the selection of the enantiofaces. Nevertheless, the influence of the pyridyl substituent as a possible coordinative site for the ruthenium catalysts was investigated through hydrogenation of **5** and **6**. In these constitutional isomers with very similar electronic properties, only **5** contains the nitrogen in the *ortho*-position of the pyridyl substituent. Whilst the expected result (100% conversion and +39% ee with (+)-(*R*)-BINAP as a ligand, −81% ee with (−)-(*S*)-N-Me-2-BINP) was obtained when *E*-**5** was subjected to hydrogenation, the isomer *E*-**6** could not be converted at all (entries 5–7). Similarly, the β,β-diphenyl acrylonitrile **7** did not undergo any conversion (entry 6). An analogous observation was made when α-substituents were present as in the nitriles **8**–**10**. In these cases, the *ortho*-nitrogen of **8** was a requirement for conversion (entries 9–11). In contrast, *Z*-cinnamonitrile (**11**) was readily converted into the saturated achiral product (entry 12). These results demonstrate the difficulties inherent to the hydrogenation of α,β-unsaturated nitriles and the need for additional coordinative sites when acrylonitriles bearing more than one substituent are used.[15]



Scheme 2. Asymmetric hydrogenation of various α,β-unsaturated nitriles.

In conclusion, the ruthenium diphosphine-mediated enantioselective hydrogenation of α,β-unsaturated nitriles has been achieved with up to 88% ee,[16,17] offering a new access to chiral arpromidine precursors. Mechanistic investigations revealed that electron-rich diphosphine ligands accelerate conversion of these transformations. Furthermore, the stereoselection observed with

Table 2. Catalytic hydrogenation of di- and monoaryl-substituted α,β-unsaturated nitriles with [Ru((+)-(*R*)-BINAP)Cl_2·dmf_n] according to Scheme 2[a]

Entry	Substrate		Conversion (%)[b]	ee (%)	Entry	Substrate		Conversion (%)[b]	ee (%)
1		*E*-**1**: X = F	100	51 (*S*)[c]	2		*Z*-**1**	70	8[d] (*R*)
3		*E*-**4**: X = Cl	90	53 (*R*)[e]	4		*Z*-**4**	26	*rac*[e]
5		*E*-**5**: X = H	100	39 (*S*)					
6		*E*-**5**: X = H	100	81 (*R*)[f]					
7		*E*-**6**	0	—	8		**7**	0	—
9		**8**	100	—[g]	10		**9**	0	—
11		**10**	0	—	12		**11**	100	N/A

[a] For a general procedure, see Ref. 16. Unless otherwise noted, there were no side reactions, and products could be isolated quantitatively according to conversion.
[b] Conversion was determined by ^{1}H NMR of the crude mixture.
[c] Configuration of the major enantiomer being indicated, see Ref. 17.
[d] Traces of *E*-**1** were formed during the reaction.
[e] (−)-(*S*)-BINAP was used as the ligand.
[f] (−)-N-(*S*)-Me-2-BINP was used as a ligand.
[g] HPLC-measurements not reproducible (stereocenter not stable).

E/*Z*-isomers outlined the importance of the configuration at the α-carbon. A strong dependence on the presence and position of further heteroatoms, probably serving as coordination sites, emphasizes the intrinsic difficulties of these conversions. A comprehensive study along these lines is now in progress in our laboratories.

Acknowledgements

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References and notes

1. For excellent reviews, see: (a) Ohkuma, T.; Kitamura, M.; Noyori, R. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; Wiley-VCH: New York, 2000; pp 1–110; (b) Genet, J. P. *Acc. Chem. Res.* **2003**, *36*, 908; (c) Clapham, S. E.; Hadzovic, A.; Morris, R. H. *Coord. Chem. Rev.* **2005**, *248*, 2201; (d) Crepy, K. V. L.; Imamoto, T. *Adv. Synth. Catal.* **2003**, *345*, 79.
2. (a) Cui, X. H.; Burgess, K. *Chem. Rev.* **2005**, *105*, 3272; (b) Ohta, T.; Ikegami, H.; Miyake, T.; Takaya, H. *J. Organomet. Chem.* **1995**, *502*, 169; (c) Reiser, O. *Nachr. Chem. Tech. Lab.* **1996**, *44*, 380.
3. (a) De Bellefon, C.; Fouilloux, P. *Catal. Rev.* **1994**, *36*, 459; (b) Gomez, S.; Peters, J. A.; Maschmeyer, T. *Adv. Synth. Catal.* **2002**, *344*, 1037; (c) Kukula, P.; Studer, M.; Blaser, H.-U. *Adv. Synth. Catal.* **2004**, *346*, 1487.
4. Kim, D.; Park, B.-M.; Yun, J. *Chem. Commun.* **2005**, 1755.
5. (a) Burk, M. J.; de Koning, P. D.; Grote, T. M.; Hoekstra, M. S.; Hoge, G.; Jennings, R. A.; Kissel, W. S.; Le, T. V.; Lennon, I. C.; Mulhern, T. A.; Ramsden, J. A.; Wade, R. A. *J. Org. Chem.* **2003**, *68*, 5731; (b) Saylik, D.; Campi, E. M.; Donohue, A. C.; Jackson, W. R.; Robinson, A. J. *Tetrahedron: Asymmetry* **2001**, *12*, 657.
6. (a) Buschauer, A. *J. Med. Chem.* **1989**, *32*, 1963; (b) Buschauer, A.; Friese-Kimmel, A.; Baumann, G.; Schunack, W. *Eur. J. Med. Chem.* **1992**, *27*, 321; (c) Dove, S.; Elz, S.; Seifert, R.; Buschauer, A. *Mini-Rev. Med. Chem.* **2004**, *4*, 941.
7. Noyori, R.; Tomino, I.; Yamada, M.; Nishizawa, M. *J. Am. Chem. Soc.* **1984**, *106*, 6717.
8. For detailed mechanistic studies of this reaction, see: Landis, C. R.; Halpern, J. *J. Am. Chem. Soc.* **1987**, *109*, 1746.
9. Noyori, R.; Takaya, H. *Acc. Chem. Res.* **1990**, *23*, 345.
10. For efficient preparation of Ru-BINAP catalysts, see: (a) Kitamura, M.; Tokunaga, M.; Ohkuma, T.; Noyori, R. *Tetrahedron Lett.* **1991**, *32*, 4163; (b) Takaya, H.; Ohta, T.; Inoue, S.-i.; Tokunaga, M.; Kitamura, M.; Noyori, R. *Org. Synth.* **1994**, *72*, 74.
11. (a) Benincori, T.; Brenna, E.; Sannicolò, F.; Trimarco, L.; Antognazza, P.; Cesarotti, E.; Demartin, F.; Pilati, T. *J. Org. Chem.* **1996**, *61*, 6244; (b) Benincori, T.; Cesarotti, E.; Piccolo, O.; Sannicolò, F. *J. Org. Chem.* **2000**, *65*, 2043; (c) Benincori, T.; Rizzo, S.; Sannicolò, F. *J. Heterocycl. Chem.* **2002**, *39*, 471.
12. For recent discussions of electronic effects in asymmetric hydrogenations, see: (a) Dubrovina, N. V.; Tararov, V. I.; Monsees, A.; Spannenberg, A.; Kostas, I. D.; Börner, A. *Tetrahedron: Asymmetry* **2005**, *16*, 3640; (b) Jeulin, S.; de Paule, S. B.; Ratovelomanana-Vidal, V.; Genet, J. P.; Champion, N.; Dellis, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 320; (c) Jones, Z. A.; Ph.D. Dissertation, University of Cambridge, 2005.
13. The formation of stable seven-membered chelate rings of the ruthenium catalyst and the *Z*-isomer cannot be ruled out as it was observed that ruthenium(II) in these solutions was considerably less sensitive to oxygen than the corresponding systems containing the *E*-isomer.
14. Ohta, T.; Miyake, T.; Seido, N.; Kumobayashi, H.; Takaya, H. *J. Org. Chem.* **1995**, *60*, 357.
15. Using pyridine as a stoichiometric or catalytic additive did not increase conversion with unreactive substrates. Therefore, pyridine substituents most likely serve as coordination sites.
16. *Representative procedure*: All substrates were prepared according to the literature procedures and *E*/*Z*-isomers were separated by column chromatography. The ruthenium catalyst was prepared according to the general procedure by Noyori (Ref. 10). The catalyst (2 mol %) was added to a degassed solution of the substrate in dichloromethane (approx. 0.01 M) in a stainless steel autoclave. The autoclave was immediately sealed, flushed with hydrogen (3×) before setting pressure and temperature. After the reaction, the mixture was condensed in vacuo and conversion was determined by ^{1}H NMR. Unless otherwise indicated, no side reactions were observed and the products could be isolated quantitatively according to conversion. The enantiomeric excess was determined by chiral GC using a Restek Rt-βDEXcst colum (30 m). The product was analyzed after isolation by column chromatography. Analytical data for **2** (100% conversion, 95% isolated yield, 51% ee): IR (film): $\nu = 3059$, 2932, 2248 (C≡N), 1609, 1591, 1433, 1284, 1119, 751, 622 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$) $\delta = 3.09$ (dd, $J = 16.7$, 8.3 Hz, 1H, CH_2), 3.31 (dd, $J = 16.7$, 7.1 Hz, 1H, CH_2), 4.39 (br t, $J = 7.9$ Hz, 1H, CHCH$_2$), 7.03–7.24 (m, 5H, aryl-*H*), 7.63 (ddd, $J = 7.9$, 7.5, 1.6 Hz, 1H, pyridyl-*H*), 8.61 (ddd, $J = 4.8$, 1.6, 0.8 Hz, 1H, pyridyl-*H*). ^{13}C{^{1}H} NMR (62.9 MHz, $CDCl_3$) $\delta = 22.4$ (d, J(C,F) = 1.0 Hz, *C*H$_2$CN), 48.4 (d, J(C,F) = 1.6 Hz, Ar$_2$*C*HCH$_2$), 116.9 (dd, J(C,F) = 18.4, 0.8 Hz, aryl-*C*), 117.7 (dd, J(C,F) = 17.8, 1.1 Hz, aryl-*C*), 118.4 (CN), 122.6 (pyridyl-C), 123.3 (pyridyl-C), 124.0 (dd, J(C,F) = 6.4, 3.2 Hz, aryl-C), 137.0 (pyridyl-C), 137.7 (dd, J(C,F) = 5.1, 3.8 Hz, aryl-C), 149.5 (pyridyl-C), 149.9 (dd, J(C,F) = 248.0, 12.7 Hz, C-F), 150.5 (dd, J(C,F) = 248.6, 12.7 Hz, C-F), 158.7 (d, J(C,F) = 0.8 Hz, pyridyl-C). MS (EI(70 eV)): *m*/*z* (%) = 244 (100) [M$^+$], 243 (54) [M$^+$−H], 216 (12) [M$^+$−HCN−H], 204 (85) [M$^+$−CH$_2$CN]. GC (30 m Rt-βDEXcst, 0.7 bar H_2, 170 °C): tr((+)-**2**) = 33.7 min, tr((−)-**2**) = 34.6 min. Elemental analysis: $C_{14}H_{10}F_2N_2$ (244.3) calcd C 68.83%, H 4.13%, N 11.47%; found: C 68.66%, H 4.13%, N 11.31%. Optical rotation (51% ee) $[\alpha]_D^{24}$ +53.9 (*c* 1.02, $CHCl_3$).
17. *Determination of absolute configuration of the products*: The hydrogenation product of *E*-**4** (X = Cl) was reduced with $LiAlH_4$ to the corresponding amine (80%, no racemization observed), being previously described in enantiomerically pure form: (a) Zabel, M.; Breu, J.; Rau, F.; Range, K.-J.; Krey, A.; Uffrecht, A.; Buschauer, A. *Acta Cryst.* **2000**, *C56*, 250; (b) Schuster, A.; Götte, C.; Bernhardt, G.; Buschauer, A. *Chirality* **2001**, *13*, 285. The configuration of all other products was assigned in analogy to these results.