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Nickel-Catalyzed Asymmetric Hydrogenation of Hydrazones

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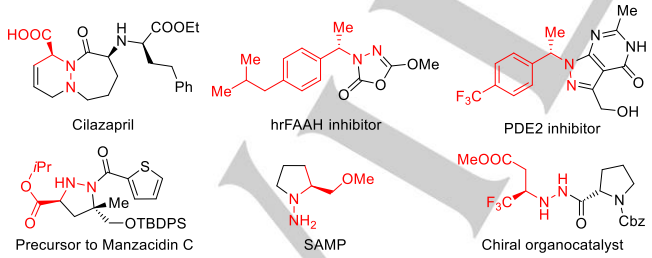
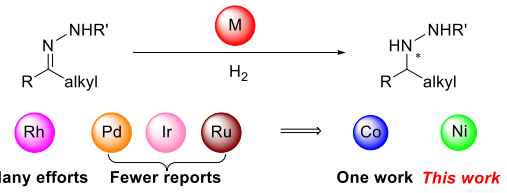
Abstract: An efficient nickel–catalyzed asymmetric hydrogenation of hydrazones to chiral hydrazines has been realized with up to 99% yield and 99.4:0.6 er. Deuterium labelling experiments indicated that the hydrazone substrates undergo imine-enamine tautomerization in the mixed solvents. Studies on the effects of acids revealed that the required acid assistance promoted the dissociation of the active nickel catalyst in the catalytic cycle.

Optically active hydrazines and their derivatives are privileged structural motifs for the construction of various functional compounds in pharmaceutical, agrochemical and organic reagents (Scheme 1).[1] Such N−N bond containing compounds can be synthesized by several methods, such as N−N bond formation from chiral amines, rearrangement from chiral halide ureas, and the alkylation of hydrazines with chiral haloalkanes, etc.[2] As an asymmetric approach, the transition metal-catalyzed asymmetric hydrogenation of hydrazones has emerged to be the most direct method for the synthesis of chiral hydrazines.[3-8]



Scheme 1. Representative chiral hydrazine-based compounds.

In 1992, Burk and co-workers reported the first enantioselective reduction of hydrazones via a Rh/DuPhos catalyst.[4] Since then, many noble transition metal catalysts have been developed for the asymmetric hydrogenation of hydrazones, with the majority being Rh catalysts[5] and fewer examples of Pd,[6] Ir[7] and Ru[8] catalysts (Scheme 2). However, these metal catalysts are very expensive and environmentally harmful so their broader applications are hindered. Therefore, the development of earth-abundant transition metal catalysts for use in asymmetric hydrogenation has great potential due to their low cost and environmental friendliness. Recently, catalytic asymmetric hydrogenation using earth-abundant transition metals,[9] such as Mn,[10] Fe,[11] Co,[12] Ni[13] and Cu,[14] has been developed rapidly for the synthesis of various chiral compounds. However, only a few of these metal catalysts have been applied to the asymmetric hydrogenation of hydrazones.[12h,15] In 2015, Zhou and co-workers reported a Ni-catalyzed asymmetric transfer hydrogenation of hydrazones using a HCOOH/Et_3N hydrogen source, affording chiral hydrazines with excellent results.[15] In 2019, we also disclosed a highly efficient Co-catalyzed asymmetric hydrogenation of hydrazones based on H_2 gas (Scheme 2).[12h] Inspired by our recent works in transition metal-catalyzed asymmetric hydrogenations[16] and nickel-catalyzed asymmetric reactions,[13f-h,17] herein we report the first nickel-catalyzed asymmetric hydrogenation of hydrazones using H_2 gas as the hydrogen source for the efficient synthesis of chiral hydrazines (Scheme 2).



Scheme 2. Synthesis of chiral hydrazines via transition metal-catalyzed asymmetric hydrogenation of hydrazones.

Initially, *N'*-(1-phenylethylidene)benzohydrazide (**1a**) was selected as the model substrate to explore the feasibility of this nickel-catalyzed asymmetric hydrogenation of hydrazones. Preliminary solvent screening showed that the hydrogenation failed to proceed in commonly used solvents but worked smoothly in a mixed solvent system consisting of 2,2,2-trifluoroethanol (TFE) and acetic acid (see SI for details). Next, several commercially available chiral bisphosphine ligands were screened (Table 1). When electron-rich chiral dialkyl phosphine

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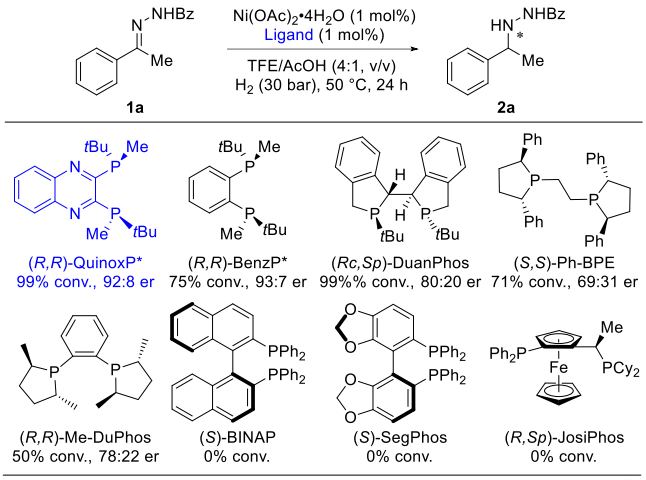
ligand (*R,R*)-QuinoxP* was used, full conversion with 92:8 er was achieved. Other chiral dialkyl phosphine ligands, such as (*R,R*)-BenzP*, (*Rc, Sp*)-DuanPhos, (*S,S*)-Ph-BPE and (*R,R*)-DuPhos, also worked well for this reaction (50-99% conv., 69:31-93:7 er), albeit not performing as well as (*R,R*)-QuinoxP*. In contrast, no reaction occurred when using chiral diaryl phosphine ligands, such as (*S*)-BINAP, (*S*)-SegPhos and (*R,Sp*)-JosiPhos. These results indicate that the electron-rich ligands could enhance the activities of the nickel catalysts in accordance with literature reports and our previous research.[13]

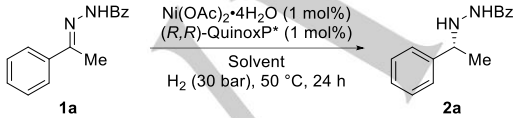
Table 1. Ligands screening.[a]



[a] Conditions: **1a** (0.2 mmol), solvent (1 mL). The conversions were calculated from ^{1}H NMR spectra. The er values were determined by HPLC using chiral stationary phases.

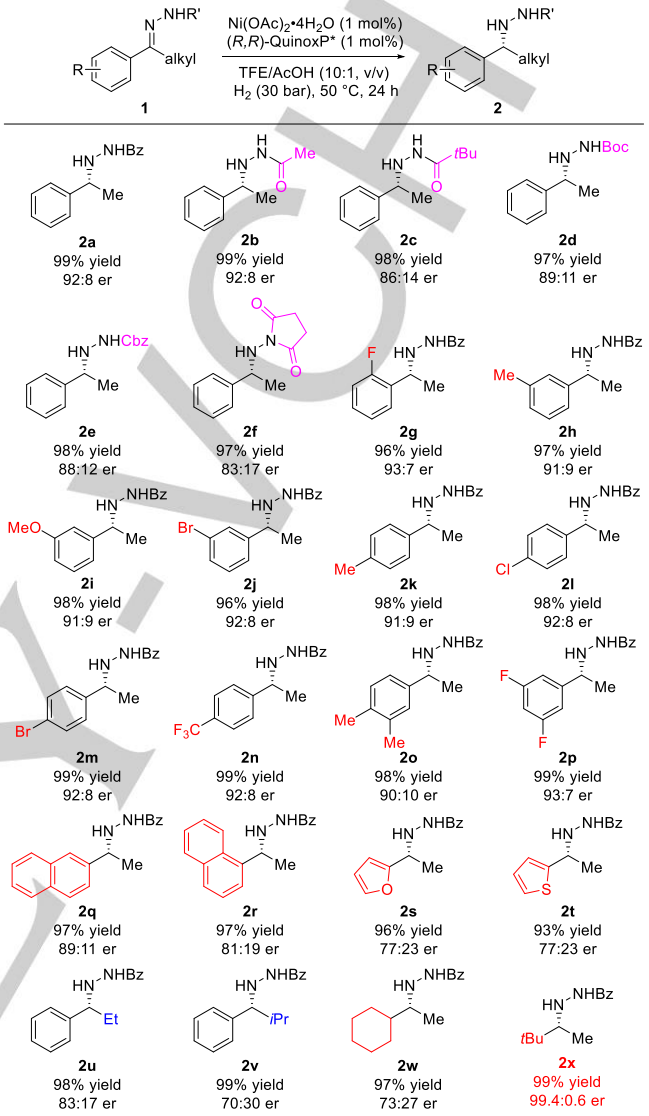
Further investigations focused on the solvent effect in the presence of acetic acid (Table 2). Replacing TFE with other protic solvents, such as MeOH, EtOH and *i*PrOH, resulted in a significant decrease in the reactivity, albeit with a slight increase in the enantioselectivity (entries 1-4). The special role of TFE in this reaction is similar to that in some metal-catalyzed reactions; the TFE is suspected of acting as a stabilizer of the active catalyst, or hydrogen bond donor of the substrate.[18] Similar to previous studies,[13f-h] the hydrogenation did not proceed in aprotic solvents, such as THF, PhMe and CH_2Cl_2 (entries 5-7). Different ratios of AcOH were also tested (entries 8-12), with the comparatively best results (92:8 er) being obtained when the reaction was carried out in a solution of TFE/AcOH (v/v =10:1, entry 9).

Table 2. Reaction Optimization.[a]



Entry	Solvent (v/v)	Conv. (%)[b]	er (%)[b]
1	TFE/AcOH = 4:1	99	92:8
2	MeOH/AcOH = 4:1	23	93:7
3	EtOH/AcOH = 4:1	13	93:7
4	*i*PrOH/AcOH = 4:1	5	-
5	THF/AcOH = 4:1	0	-
6	Tolene/AcOH = 4:1	Trace	-
7	CH_2Cl_2/AcOH = 4:1	Trace	-
8	TFE/AcOH = 2:1	99	92:8
9	TFE/AcOH = 10:1	99	92:8
10	TFE/AcOH = 20:1	99	91:9
11	TFE/AcOH = 40:1	99	91:9
12	TFE/AcOH = 100:1	93	91:9

[a] Reaction conditions otherwise noted: **1a** (0.2 mmol), solvent (1 mL), the absolute configuration of product was determined as *R* by comparison of the specific rotations with the literature data[12h]. [b] The conversions were detected by ^{1}H NMR spectra and the er values were determined by HPLC using a chiral stationary phase.



Scheme 3. Substrate scope. Reaction conditions: **1** (0.2 mmol), $Ni(OAc)_2 \cdot 4H_2O$ (0.002 mol), (*R,R*)-QuinoxP* (0.002 mmol), TFE/AcOH (10:1, v/v, 1 mL), H_2 (30 bar), 50 °C, 24 h; Isolated yields; The er values were determined by chiral HPLC.

With the optimized conditions in hand (Table 2, entry 9), the scope of the nickel-catalyzed asymmetric hydrogenation of hydrazones was studied (Scheme 3). At first, a number of acetophenone-derived hydrazones with different protecting groups were synthesized and tested. Acetyl protected hydrazone **1b** gave the same results as **1a** (99% yield and 92:8 er). Other protecting groups from CO*t*Bu to diacyl were also investigated, but the corresponding products were obtained with the enantioselectivities not as good as the model substrate (**2c-f**). Thus, the substrates bearing Bz group were mainly studied. As shown in Scheme 3, both electron-rich and electron-poor substituents on the aryl rings were well tolerated regardless of their position, giving the desire products in high yields and good enantioselectivities (**2g-n**, 96-99% yields, 91:9-93:7 er). Disubstituted substrates were also successfully reacted to provide good enantioselectivities (**2o**, **p**). Replacing the phenyl

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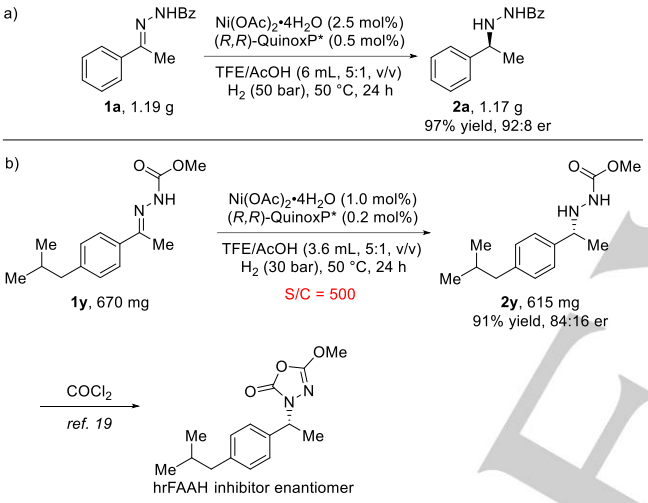
group with a 1- or 2-naphthyl substituent provided moderate enantioselectivities (**2q**, **r**). The reaction was also applicable to heteroaryl substrates (**1s**, **t**) affording the corresponding products with the same 77:23 er. Changing the methyl group to other alkyl groups did not affect the reaction activity, but the enantioselectivity decreased significantly (**2u, v**). It should be noted that dialkyl substrates were also explored and the *tert*-butyl-substituted product was obtained with an excellent 99.4: 0.6 er (**2w**, **x**).

To demonstrate the synthetic utility of this method, an asymmetric hydrogenation of **1a** was conducted on a gram scale (Scheme 4a). The reaction was carried out with the catalytic system of a higher ratio of nickel salts according to our previous studies,[13f,h] affording the desired product **2a** in 97% yield and 92:8 er. Additionally, the synthetic application of this protocol was also demonstrated in the asymmetric synthesis of hydrazine **2y**, a key intermediate for the preparation of a hrFAAH inhibitor enantiomer, in which hydrazone **1y** was hydrogenated to chiral hydrazine **2y** at a lower catalyst loading (S/C = 500), with 91% yield and 84:16 er (Scheme 4b).[19]



Scheme 4. Gram scale reaction.

To probe the reaction pathway of this asymmetric hydrogenation, a series of deuterium labeling experiments were conducted (Figure 1). Firstly, the reaction was carried out in TFE/AcOH solution under 20 bar of D_2. Deuterium (77%) was incorporated on the prochiral carbon atom and trace deuterium incorporation was observed at the α-methyl group (Figure 1a). When the above experiment was repeated with TFE-*d*1/AcOD and H_2, the deuterium positions were reversed, in which deuterium incorporation on the prochiral carbon atom was 7% and 81% at the α-methyl group (Figure 1b). Performing the hydrogenation reaction in TFE-*d*1/AcOD under 20 bar of D_2 resulted in the corresponding product with the deuterium being incorporated at both the prochiral carbon atom and α-methyl group (95% and 77% respectively, Figure 1c). Finally, the hydrogenation reaction was conducted without the nickel catalyst, and the substrate **1a** was obtained with 93% deuterium incorporation at the α-methyl group (Figure 1d). These results indicate that the hydrogen on the prochiral carbon mainly originates from H_2(D_2) gas and the hydrazone substrates undergo imine-enamine tautomerization in the mixed solvent system.

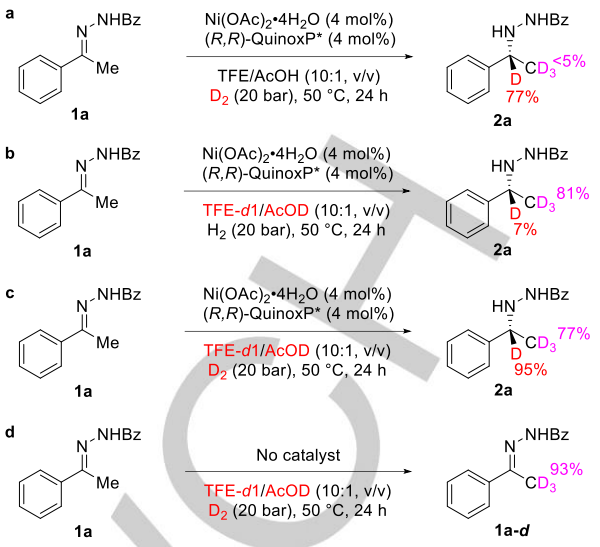
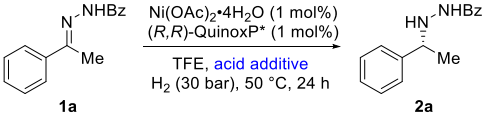


Figure 1. Deuterium labeling experiments.

In order to explore the role of the acid, other different organic acids, taking into consideration their solubility in TFE, were investigated on a 2 eq. scale (Table 3). No reaction occurred in the absence of acid (entry 1). The tested weak acids all worked well to give comparable results to that obtained with AcOH, regardless of their steric hindrance and chirality (entries 2-7). When strong acids were added to the reaction, such as TsOH and TFA, only decomposed complex was discovered, even when the amount of TsOH was reduced to 0.2 equiv. (entries 8-10). The control experiments suggest that the reaction can be slightly poisoned by the addition of product (entries 11-12). Considering the hydrazine products possess the basic N-N bonds that deactivate the catalyst, we hypothesize that the addition of weak acid could promote the dissociation of the active nickel catalyst.

Table 3. Influence of acid.[a]



entry	acid additive (2 equiv.)	pKa (H_2O)	conv. (%)[b]	er (%)[c]
1	-	-	Trace	-
2	AcOH	4.76	99	91:9
3	EtCOOH	4.88	99	91:9
4	*t*BuCOOH	5.03	95	89.5:10.5
5	PhCOOH	4.20	99	91:9
6	(*S*)-2-Phenylpropanoic acid	4.34	99	91:9
7	(*R*)-2-Phenylpropanoic acid	4.34	99	91:9
8	TsOH·H_2O	-2.80	-[d]	-
9	TFA	-0.25	-[d]	-
10	TsOH·H_2O (0.2 equiv)	-2.80	-[e]	-
11[f]	-	-	94	83:17
12[g]	-	-	74	86:14

[a] Reaction conditions otherwise noted: **1a** (0.2 mmol), solvent (1 mL); [b] The conversions were detected by ^{1}H NMR spectra. [c] The er values were determined by HPLC using a chiral stationary phase. [d] The substrate was decomposed. [e] No product was detected and 5% of substrate was decomposed. [f] 30 mol% catalyst was used. [g] 30 mol% catalyst was used in the presence of 30 mol% product **2a** (92:8 er). TsOH: *p*-toluenesulfonic acid, TFA: CF_3COOH.

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According to the above research results and previous studies in the Ni(II)-catalyzed asymmetric hydrogenations,[13] we envisage that the active catalyst is chiral nickel hydride complex **3**, which is generated from the heterolysis of H_2 by the nickel catalyst, and a plausible reaction pathway is proposed as follows (Figure 2). Complex **3** coordinates with substrate **1a** to form complex **4**, albeit with the rapid transformation between **1a** and its enamine **5** under the presence of AcOH. Intramolecular hydride transfer of complex **4** to form complex **6**, followed by the coordination of H_2 produces complex **7**, which undergoes subsequent sigma-bond metathesis to form complex **8**.[13f,h] Complex **8** releases the hydrogenation product **2a** and the nickel hydride complex **3** is regenerated with the help of AcOH.

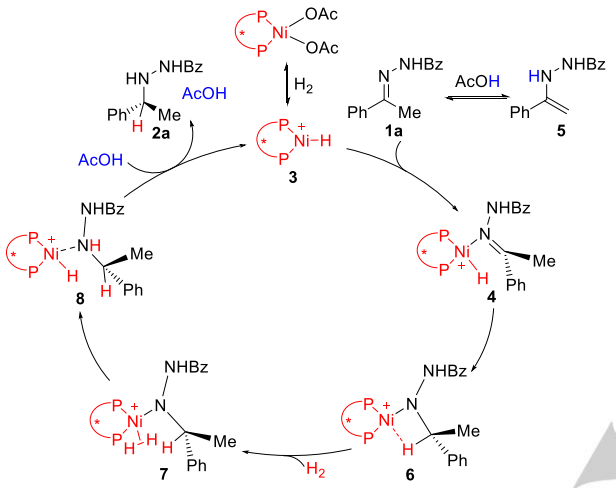

Figure 2. Proposed mechanism.

In summary, an efficient asymmetric hydrogenation of hydrazones was developed using an earth-abundant metal nickel catalyst. A series of chiral hydrazines were synthesized with up to 99% yield and 99.4:0.6 er. An imine-enamine tautomerization of the hydrazone substrates was observed as evidenced by the deuterium labelling experiments. Mechanistic studies indicated that the addition of acid promoted the dissociation of the active nickel catalyst in the catalytic cycle.

Acknowledgments

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Conflict of interest

The authors declare no conflict of interest.

Keywords: asymmetric hydrogenation • nickel • hydrazones • chiral hydrazines • imine-enamine tautomerization

[1] a) T. Szucs, *Drugs* **1991**, *41*, 18; b) D. Enders, H. Eichenauer, *Angew. Chem. Int. Ed. Engl.* **1976**, *15*, 549; c) Y. Yamashita, S. Kobayashi, *J. Am. Chem. Soc.* **2004**, *126*, 11279; d) S. Shirakawa, P. J. Lombardi, J. L. Leighton, *J. Am. Chem. Soc.* **2005**, *127*, 9974; e) N. C. Giampietro, J. P. Wolfe, *J. Am. Chem. Soc.* **2008**, *130*, 12907; f) K. Tran, P. J. Lombardi, J. L. Leighton, *Org. Lett.* **2008**, *10*, 3165; g) J. M. Coteron, D. Catterick, J. Castro, M. J. Chaparro, B. Díaz, E. Fernández, S. Ferrer, F. J. Gamo, M. Gordo, J. Gut, L. de las Heras, J. Legac, M. Marco, J. Miguel, V. Muñoz, E. Porras, J. C. de la Rosa, J. R. Ruiz, E. Sandoval, P. Ventosa, P. J. Rosenthal, J. M. Fiandor, *J. Med. Chem.* **2010**, *53*, 6129; h) L. O. Davis, *Org. Prep. Proced. Int.* **2013**, *45*, 437; i) E. Gould, T. Lebl, A. M. Z Slawin, M. Reid, T. Davies, A. D. Smith, *Org. Biomol. Chem.* **2013**, *11*, 7877.

[2] For reviews, see: a) U. Ragnarsson, *Chem. Soc. Rev.* **2001**, *30*, 205; b) S. Tšupova, U. Mäeorg, *Heterocycles* **2014**, *88*, 129; c) G. LeGoff, J. Ouazzani, *Bioorg. Med. Chem.* **2014**, *22*, 6529; d) Q. Guo, Z. Lu, *Synthesis* **2017**, *49*, 3835. For recent examples, see: e) P. Yang, C. Zhang, Y. Ma, C. Zhang, A. Li, B. Tang, J. Zhou, *Angew. Chem. Int. Ed.* **2017**, *56*, 14702; *Angew. Chem.* **2017**, *129*, 14894; f) D. E. Polat, D. D. Brzezinski, A. M. Beauchemin, *Org. Lett.* **2019**, *21*, 4849.

[3] For reviews, see: a) W. Tang, X. Zhang, *Chem. Rev.* **2003**, *103*, 3029; b) J.-H. Xie, S.-F. Zhu, Q.-L. Zhou, *Chem. Rev.* **2011**, *111*, 1713; c) D.-S. Wang, Q.-A. Chen, S.-M. Lu, Y.-G. Zhou, *Chem. Rev.* **2012**, *112*, 2557; d) Z. Zhang, N. A. Butt, W. Zhang, *Chem. Rev.* **2016**, *116*, 14769; e) C. S. G. Seo, R. H. Morris, *Organometallics* **2019**, *38*, 47.

[4] a) M. J. Burk, J. E. Feaster, *J. Am. Chem. Soc.* **1992**, *114*, 6266; b) M. J. Burk, J. P. Martinez, J. E. Feaster, N. Cosford, *Tetrahedron* **1994**, *50*, 4399; c) M. J. Burk, M. F. Gross, *Tetrahedron Lett.* **1994**, *35*, 9363.

[5] a) A. Yamazaki, I. Achiwa, K. Horikawa, M. Tsurubo, K. Achiwa, *Synlett* **1997**, *1997*, 455; b) T. Ireland, K. Tappe, G. Grossheimann, P. Knochel, *Chem. - Eur. J.* **2002**, *8*, 843; c) K. Tappe, P. Knochel, *Tetrahedron: Asymmetry* **2004**, *15*, 91; d) A. Gavryushin, K. Polborn, P. Knochel, *Tetrahedron: Asymmetry* **2004**, *15*, 2279; e) N. Yoshikawa, L. Tan, J. C. McWilliams, D. Ramasamy, R. Sheppard, *Org. Lett.* **2010**, *12*, 276; f) N. Haddad, B. Qu, S. Rodriguez, L. van der Veen, D. C. Reeves, N. C. Gonnella, H. Lee, N. Grinberg, S. Ma, D. Krishnamurthy, T. Wunberg, C. H. Senanayake, *Tetrahedron Lett.* **2011**, *52*, 3718; g) Q. Hu, Y. Hu, Y. Liu, Z. Zhang, Y. Liu, W. Zhang, *Chem. - Eur. J.* **2017**, *23*, 1040; h) D. Fan, Y. Hu, F. Jiang, Z. Zhang, W. Zhang, *Adv. Synth. Catal.* **2018**, *360*, 2228.

[6] a) Y.-Q. Wang, S.-M. Lu, Y.-G. Zhou, *J. Org. Chem.* **2007**, *72*, 3729; b) Z.-P. Chen, S.-B. Hu, J. Zhou, Y.-G. Zhou, *ACS Catal.* **2015**, *5*, 6086; c) Z.-P. Chen, M.-W. Chen, L. Shi, C.-B. Yu, Y.-G. Zhou, *Chem. Sci.* **2015**, *6*, 3415; d) Z.-P. Chen, S.-B. Hu, M.-W. Chen, Y.-G. Zhou, *Org. Lett.* **2016**, *18*, 2676.

[7] M. Chang, S. Liu, K. Huang, X. Zhang, *Org. Lett.* **2013**, *15*, 4354.

[8] C. H. Schuster, J. F. Dropinski, M. Shevlin, H. Li, S. Chen, *Org. Lett.* **2020**, *22*, 7562.

[9] For reviews, see: a) K. Gopalaiah, *Chem. Rev.* **2013**, *113*, 3248; b) H. Pellissier, H. Clavier, *Chem. Rev.* **2014**, *114*, 2775; c) Y.-Y. Li, S.-L. Yu, W.-Y. Shen, J.-X. Gao, *Acc. Chem. Res.* **2015**, *48*, 2587; d) Z. Zhang, N. A. Butt, M. Zhou, D. Liu, W. Zhang, *Chin. J. Chem.* **2018**, *36*, 443; e) L. Alig, M. Fritz, S. Schneider, *Chem. Rev.* **2019**, *119*, 2681; f) Y. Liu, X.-Q. Dong, X. Zhang, *Chin. J. Org. Chem.* **2020**, *40*, 1096; g) F. Agbossou-Niedercorn, C. Michon, *Coordin. Chem. Rev.* **2020**, *425*, 213523; h) J. Wen, F. Wang, X. Zhang, *Chem. Soc. Rev.* **2021**, *50*, 3211; i) J. Chen, W. Zhang, *Chin. J. Org. Chem.* **2020**, *40*, 4372; j) Y. Tian, L. Hu, Y.-Z. Wang, X. Zhang, Q. Yin, *Org. Chem. Front.* **2021**, *8*, 2328.

[10] For recent examples, see: a) M. B. Widegren, G. J. Harkness, A. M. Z. Slawin, D. B. Cordes, M. L. Clarke, *Angew. Chem. Int. Ed.* **2017**, *56*, 5825; *Angew. Chem.* **2017**, *129*, 5919; b) M. Garbe, K. Junge, S. Walker, Z. Wei, H. Jiao, A. Spannenberg, S. Bachmann, M. Scalone, M. Beller, *Angew. Chem. Int. Ed.* **2017**, *56*, 11237; *Angew. Chem.* **2017**, *129*, 11389; c) L. Zhang, Y. Tang, Z. Han, K. Ding, *Angew. Chem. Int. Ed.* **2019**, *58*, 4973; *Angew. Chem.* **2019**, *131*, 5027; d) F. Ling, H. Hou, J. Chen, S. Nian, X. Yi, Z. Wang, D. Song, W. Zhong, *Org. Lett.* **2019**, *21*, 3937; e) L. Zhang, Z. Wang, Z. Han, K. Ding, *Angew. Chem. Int. Ed.* **2020**, *59*, 15565; *Angew. Chem.* **2020**, *132*, 15695; f) L. Zeng, H. Yang, M. Zhao, J. Wen, J. H. R. Tucker, X. Zhang, *ACS Catal.* **2020**, *10*, 13794.

[11] For recent examples, see: a) J. F. Sonnenberg, K. Y. Wan, P. E. Sues, R. H. Morris, *ACS Catal.* **2017**, *7*, 316; b) C. S. G. Seo, T. Tannoux, S. A. M. Smith, A. J. Lough, R. H. Morris, *J. Org. Chem.* **2019**, *84*, 12040; c) C. K.

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Blasius, N. F. Heinrich, V. Vasilenko, L. H. Gade, *Angew. Chem. Int. Ed.* **2020**, *59*, 15974; *Angew. Chem.* **2020**, *132*, 16108.

[12] For recent examples, see: a) D. Zhang, E.-Z. Zhu, Z.-W. Lin, Z.-B. Wei, Y.-Y. Li, J.-X. Gao, *Asian J. Org. Chem.* **2016**, *5*, 1323; b) M. R. Friedfeld, M. Shevlin, G. W. Margulieux, L.-C. Campeau, P. J. Chirik, *J. Am. Chem. Soc.* **2016**, *138*, 3314; c) J. Chen, C. Chen, C. Ji, Z. Lu, *Org. Lett.* **2016**, *18*, 1594; d) J. Guo, X. Shen, Z. Lu, *Angew. Chem. Int. Ed.* **2017**, *56*, 615; *Angew. Chem.* **2017**, *129*, 630; e) J. Guo, B. Cheng, X. Shen, Z. Lu, *J. Am. Chem. Soc.* **2017**, *139*, 15316; f) M. R. Friedfeld, H. Zhong, R. T. Ruck, M. Shevlin, P. J. Chirik, *Science* **2018**, *360*, 888; g) H. Zhong, M. R. Friedfeld, P. J. Chirik, *Angew. Chem. Int. Ed.* **2019**, *58*, 9194; *Angew. Chem.* **2019**, *131*, 9292; h) Y. Hu, Z. Zhang, J. Zhang, Y. Liu, I. D. Gridnev, W. Zhang, *Angew. Chem. Int. Ed.* **2019**, *58*, 15767; *Angew. Chem.* **2019**, *131*, 15914; i) P. Viereck, S. Krautwald, T. P. Pabst, P. J. Chirik, *J. Am. Chem. Soc.* **2020**, *142*, 3923; j) H. Zhong, M. Shevlin, P. J. Chirik, *J. Am. Chem. Soc.* **2020**, *142*, 5272; k) X. Du, Y. Xiao, J.-M. Huang, Y. Zhang, Y.-N. Duan, H. Wang, C. Shi, G.-Q. Chen, X. Zhang, *Nat. Commun.* **2020**, *11*, 3239.

[13] For recent examples, see: a) M. Shevlin, M. R. Friedfeld, H. Sheng, N. A. Pierson, J. M. Hoyt, L.-C. Campeau, P. J. Chirik, *J. Am. Chem. Soc.* **2016**, *138*, 3562; b) W. Gao, H. Lv, T. Zhang, Y. Yang, L. W. Chung, Y.-D. Wu, X. Zhang, *Chem. Sci.* **2017**, *8*, 6419; c) X. Li, C. You, S. Li, H. Lv, X. Zhang, *Org. Lett.* **2017**, *19*, 5130; d) J. Long, W. Gao, Y. Guan, H. Lv, X. Zhang, *Org. Lett.* **2018**, *20*, 5914; e) Y.-Q. Guan, Z. Han, X. Li, C. You, X. Tan, H. Lv, X. Zhang, *Chem. Sci.* **2019**, *10*, 252; f) B. Li, J. Chen, Z. Zhang, I. D. Gridnev, W. Zhang, *Angew. Chem. Int. Ed.* **2019**, *58*, 7329; *Angew. Chem.* **2019**, *131*, 7407; g) Y. Hu, J. Chen, B. Li, Z. Zhang, I. D. Gridnev, W. Zhang, *Angew. Chem. Int. Ed.* **2020**, *59*, 5371; *Angew. Chem.* **2020**, *132*, 5409; h) D. Liu, B. Li, J. Chen, I. D. Gridnev, W. Zhang, *Nat. Commun.* **2020**, *11*, 5935; i) Y. Liu, Z. Yi, X. Yang, H. Wang, C. Yin, M. Wang, X.-Q. Dong, X. Zhang, *ACS Catal.* **2020**, *10*, 11153; j) F. Wang, X. Tan, T. Wu, L.-S. Zheng, G.-Q. Chen, X. Zhang, *Chem. Commun.* **2020**, *56*, 15557; k) G. Liu, K. Tian, C. Li, C. You, X. Tan, H. Zhang, X. Zhang, X.-Q. Dong, *Org. Lett.* **2021**, *23*, 668.

[14] O. V. Zatolochnaya, S. Rodríguez, Y. Zhang, K. S. Lao, S. Tcyrulnikov, G. Li, X.-J. Wang, B. Qu, S. Biswas, H. P. R. Mangunuru, D. Rivalti, J. D. Sieber, J.-N. Desrosiers, J. C. Leung, N. Grinberg, H. Lee, N. Haddad, N. K. Yee, J. J. Song, M. C. Kozlowski, C. H. Senanayake, *Chem. Sci.* **2018**, *9*, 4505.

[15] H. Xu, P. Yang, P. Chuanprasit, H. Hirao, J. Zhou, *Angew. Chem. Int. Ed.* **2015**, *54*, 5112; *Angew. Chem.* **2015**, *127*, 5201.

[16] a) J. Chen, Z. Zhang, B. Li, F. Li, Y. Wang, M. Zhao, I. D. Gridnev, T. Imamoto, W. Zhang, *Nat. Commun.* **2018**, *9*, 5000; b) J. Li, Y. Ma, Y. Lu, Y. Liu, D. Liu, W. Zhang, *Adv. Synth. Catal.* **2019**, *361*, 1146; c) D. Fan, Y. Liu, J. Jia, Z. Zhang, Y. Liu, W. Zhang, *Org. Lett.* **2019**, *21*, 1042; d) J. Li, Y. Lu, Y. Zhu, Y. Nie, J. Shen, Y. Liu, D. Liu, W. Zhang, *Org. Lett.* **2019**, *21*, 4331; e) Y. Lu, J. Li, Y. Zhu, J. Shen, D. Liu, W. Zhang, *Tetrahedron* **2019**, *75*, 3643; f) J. Zhang, J. Jia, X. Zeng, Y. Wang, Z. Zhang, I. D. Gridnev, W. Zhang, *Angew. Chem. Int. Ed.* **2019**, *58*, 11505; *Angew. Chem.* **2019**, *131*, 11629; g) J. Chen, F. Li, F. Wang, Y. Hu, Z. Zhang, M. Zhao, W. Zhang, *Org. Lett.* **2019**, *21*, 9060; h) D. Fan, J. Zhang, Y. Hu, Z. Zhang, I. D. Gridnev, W. Zhang, *ACS Catal.* **2020**, *10*, 3232.

[17] a) M. Quan, X. Wang, L. Wu, I. D. Gridnev, G. Yang, W. Zhang, *Nat. Commun.* **2018**, *9*, 2258; b) X. Wang, M. Quan, F. Xie, G. Yang, W. Zhang, *Tetrahedron Lett.* **2018**, *59*, 1573; c) M. Quan, L. Wu, G. Yang, W. Zhang, *Chem. Commun.* **2018**, *54*, 10394; d) L. Wu, G. Yang, W. Zhang, *CCS Chem.* **2019**, *1*, 623; e) H. Nagae, J. Xia, E. Kirillov, K. Higashida, K. Shoji, V. Boiteau, W. Zhang, J.-F. Carpentier, K. Mashima, *ACS Catal.* **2020**, *10*, 5828.

[18] a) T. C. Forschner, A. R. Cutler, *Organometallics* **1985**, *4*, 1247; b) B. Milani, A. Anzilutti, L. Vicentini, A. S. Santi, E. Zangrando, S. Geremia, G. Mestroni, *Organometallics* **1997**, *16*, 5064; c) H. T. Teunissen, C. J. Elsevier, *Chem. Commun.* **1998**, 1367; d) H. Abe, H. Amii, K. Uneyama, *Org. Lett.* **2001**, *3*, 313; e) Y. Duan, L. Li, M.-W. Chen, C.-B. Yu, H.-J. Fan, Y.-G. Zhou, *J. Am. Chem. Soc.* **2014**, *136*, 7688.

[19] J. Z. Patel, T. Parkkari, T. Laitinen, A. A. Kaczor, S. M. Saario, J. R. Savinainen, D. Navia-Paldanius, M. Cipriano, J. Leppanen, I. O. Koshevoy, A.Poso, C. J. Fowler, J. T. Laitinen, T. Nevalainen, *J. Med. Chem.* **2013**, *56*, 8484.

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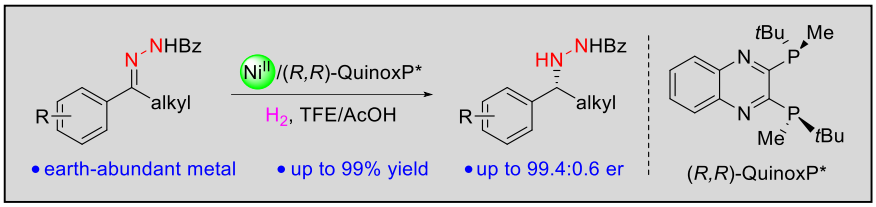

An asymmetric hydrogenation of hydrazones with a unique nickel catalyst has been developed for the synthesis of chiral hydrazines with up to 99% yield and 99.4:0.6 er and a broad substrate scope.

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