

Letter

Highly Enantioselective Direct Asymmetric Reductive Amination of 2-Acetyl-6-Substituted Pyridines

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n 2019, a review of reductive amination in the synthesis of pharmaceuticals by Chusov et al. reported that reductive amination plays a paramount role in pharmaceutical and medicinal chemistry, owing to its synthetic merits and the ubiquitous presence of amines among biologically active compounds.¹ From their investigation on 343 medicinal substances, 21% of compounds were found to be produced by employing reductive amination at one or multiple synthetic steps. Among all of the amines, chiral primary amines are very important motifs or building blocks in numerous bioactive molecules and their widespread pharmaceutical applications.² Transition metal-catalyzed direct asymmetric reductive amination (DARA) of carbonyl compounds with transition metal hydrides represents the most straightforward route to enantiomerically enriched primary amines, in comparison with the conventional multistep procedure consisting of formation of a protected imine, followed by asymmetric hydrogenation and deprotection of the obtained chiral secondary amine.³ The DARA approach for obtaining chiral primary amines has been limited in comparison to well-known methodologies toward chiral secondary amines.⁴ The first instance of DARA for primary amines was demonstrated by Kadyrov and Riermeier in 2003, when they utilized a Ru catalyst on simple aryl ketones under asymmetric transfer hydrogenation conditions.⁵ Merck in conjunction with Takasago has invested heavily in this field, culminating in a landmark application in the synthesis of Sitagliptin.⁶ Takasago has also been involved in using DARA as an extension of their asymmetric hydrogenation methodologies,⁷ allowing them to develop their own applications as well as to collaborate with another industrial partner, DSM.8 In 2018, Schaub et al.9 and Zhang et al.¹⁰ reported Ru-catalyzed DARA of simple aryl ketones, employing ammonia or an ammonium salt as a nitrogen source, using hydrogen gas. Recently, there are some

advanced reports using DARA technology, such as a cascade reaction for lactams,¹¹ flow chemistry,¹² and application to an aliphatic ketone (a highly difficult substrate).¹³ Despite these promising results, there are no reports on the synthesis of chiral primary 1-(pyridin-2-yl)ethan-1-amines, useful chiral building blocks¹⁴ and/or ligands,¹⁵ prepared by transition metal-catalyzed DARA of 2-acetylpyridines with an ammonium salt and molecular hydrogen (Scheme 1). To the best of our knowledge, the only methodologies for using asymmetric synthesis to obtain chiral corresponding amines from 2-

Ru(OAc)₂{(S)-binap}

Scheme 1. Selected Biologically Active Compounds Containing a Chiral 1-(Pyridin-2-yl)ethan-1-amine Moiety



Received: March 11, 2021 Published: April 23, 2021





acetylpyridines have been a biocatalyst (transaminase) approach,¹⁶ reduction of an oxime and then diastereomeric salt resolution,¹⁷ and reduction of a chiral sulfonamide.¹⁸ Herein, we report a highly efficient asymmetric synthesis of corresponding chiral amines via DARA of 2-acetyl-6-substituted pyridines with >99% conversion and >99% ee.

We started our research with 2-acetyl-6-methoxypyridine (1a) as a model substrate in the presence of a commercially available BINAP-based ruthenium catalyst, $Ru(OAc)_2\{(S)-binap\}$, and various ammonium salts as the nitrogen source in THF under 0.8 MPa of hydrogen gas pressure (Table 1). This

Table 1. Effect of Ammonium Salt on DARA of 1a^a

N OMe	H ₂ (0.8 MPa), I	* N OMe		
1а		THF 90 °C, 17 h	№Н ₂ 2а	
entry	NH_4X	conversion (%) ^{b,c}	% ee of $2a^d$	
1 1	NH ₄ OAc	47.6 ^f	no data	
2 1	NH ₄ CO ₂ CF ₃	98.8	97.9	
3 N	NH ₄ SA ^e	90.5	77.6	

^aReactions were conducted for 17 h at 90 °C in THF using Ru(OAc)₂{(S)-binap}under 0.8 MPa of hydrogen pressure. ^bDetermined by HPLC analysis. Conditions: L-column-2 ODS (5 µm, 150 mm \times 4.6 mm), mobile phase A consisting of a 190/5/5 phosphate buffer/MeCN/MeOH mixture, mobile phase B consisting of a 50/ 140/10 phosphate buffer/MeCN/MeOH mixture, phosphate buffer preparation, 1.3 g of H₃PO₄ and 9 mL of 1 mol/L aqueous KOH/ 1000 mL of water, gradient of 0% to 100% B from 0 to 32.5 min and 100% B from 32.5 to 40 min, flow rate of 1.0 mL/min, oven temperature of 25 °C, UV detection at 254 nm, $t_{\rm R}$ = 9.1 and 9.5 min (2a), $t_{\rm R}$ = 24.8 min (1a). ^cCalculation method: 100-HPLC area % of 1a. ^dDetermined by chiral HPLC analysis. Conditions: CHIRALPAK AY-RH column (5 μ m, 150 mm × 4.6 mm), 65/35 0.1% AcOH aqueous solution/MeCN mixture, 1.0 mL/min, UV 254 nm. The sample was derivatized to the N-benzoylated form with BzCl and Et₃N. $t_{\rm R}$ = 16.2 min (major N-benzoylated enantiomer), $t_{\rm R}$ = 17.7 min (minor N-benzoylated enantiomer). ^eAmmonium salicylate. ^fComplex mixture.

nitrogen source screen found that ammonium trifluoroacetate was superior to ammonium acetate or salicylate, providing (S)-1-(6-methoxypyridin-2-yl)ethan-1-amine (**2a**) with the highest level of enantioselectivity (entries 1–3). We chose to perform the study under low-hydrogen pressure (0.8 MPa) conditions that are operationally friendly from an industrial viewpoint.

To identify the effect of the ruthenium catalyst, some commercially available RuX{(S)-binap} catalysts were investigated using ammonium trifluoroacetate as the ammonium source (Table 2). All catalysts gave the same results in terms of conversion and enantioselectivity. These results unambiguously showed that trifluoroacetate anion from ammonium trifluoroacetate would readily interconvert with acetate or chloride anions on the ruthenium center. Moreover, Noyori and co-workers have prepared Ru(OCOCF₃)₂{(*R*)-binap} by treating Ru(OAc)₂{(*R*)-binap} with 2 equiv of trifluoroacetic acid in CH₂Cl₂¹⁹

A variety of solvents were examined, and THF was identified as optimal, furnishing good conversion and amine selectivity (Table 3, entry 4). Alcohols such as methanol, ethanol, and 2propanol gave some lipophilic substances on HPLC analysis (entries 1–3 and 7). Hydrophobic solvents such as toluene, EtOAc, and CH_2Cl_2 gave relatively more alcohol formation

Table 2. Effect of $RuX\{(S)$ -binap $\}$ on DARA of $1a^{a}$



^{*a*}Reactions were conducted for 17 h at 90 $^{\circ}$ C in THF using a RuX{(S)-binap} under 0.8 MPa of hydrogen pressure.

Tuble 3. Encet of Reaction Solvent on Dination of the	Table	3.	Effect	of	Reaction	Solvent	on	DARA	of	1a	۹
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N OMe	H ₂ (0.8 MPa) Ru(OAc) ₂ {(S)-binap} (s/c 1 NH ₄ CO ₂ CF ₃ (2.0 equiv) solvent 90 °C, 17 h	50)	OMe + 2a	N OMe OH 2a'
			HPLC area	%
entry	solvent	1a	2a	2a'
1	methanol	38.7	1.7	2.3
2	ethanol	41.6	4.5	2.4
3	2-propanol	52.8	6.0	1.3
4	THF	3.6	72.2	1.6
5	toluene	33.7	44.0	10.4
6	EtOAc	13.9	60.9	5.0
7	trifluoroethanol	46.5	4.5	7.3
8	CH_2Cl_2	0.3	48.3	32.4

"Reactions were conducted for 17 h at 90 °C in the indicated solvent using $Ru(OAc)_2\{(S)$ -binap} under 0.8 MPa of hydrogen pressure.

(2a') as an undesired product (entries 5, 6, and 8). The enantiomeric excess of 2a was not measured when checking the conversion.

The substrate scope was then evaluated with the optimized DARA conditions in hand (Scheme 2). A series of 2-acetyl-6substituted pyridines were successfully converted to the chiral corresponding amines with good to excellent enantioselectivity (>94% ee) regardless of the type of substituent group, such as aryl, alkyl, and halogen (entries 2a-2f). When 2-acetyl-6-arylsubstituted pyridines were used, the enantioselectivity tended to be decreased by an increased level of electron withdrawal (entries 2f and 2g). Although 2-acetylisoquinoline was converted to the corresponding amine, the enantioselectivity was not good (entry 2h). However, DARA of 2-acetylpyridine, 2-acetyl-4-methoxypyridine, and 2-acetyl-5-methoxypyridine did not proceed (entries 2s, 2v, and 2w) and 2-acetyl-3bromopyridine gave poor conversion (2n). These results revealed that the substituent at position 6 on the pyridine ring was extremely important for excellent enantioselectivity and conversion. Among the 2-acetyl-6-substituted pyridines, the conversion of 2-acetyl-6-methylesterpyridine (20) was poor and 2-acetyl-6-pyridone (2x) showed no reaction. Diaryl ketone (2t) and fused ring ketone (2u) also showed no reaction. With replacement of the pyridyl group to phenyl or naphthyl groups, most of the substrate was recovered (2p-2r). However, when a β -keto ester or β -keto amide was used instead of the 2-acetylpyridines, high conversion and enantioselectivity were achieved similar to 2-acetyl-6-substituted pyridine (2i-2l). Interestingly, 1-(pyridin-2-yl)propan-2one, which is extended by one carbon between the carbonyl





^aReaction conditions: ketone 1 (6.6 mmol), NH₄(OCOCF₃) (13.2 mmol), Ru(OAc)₂{(S)-binap} (s/c 150), THF (50 mL), H₂ (0.8 MPa), 90 °C, 17 h. The free amines (2a, 2d, 2e, 2g, and 2j) were obtained as HCl salts after acid–base extraction. The conversion was directly determined by HPLC.

and pyridyl groups compared to **2b**, also gave an excellent result (**2m**). The target reaction proceeded cleanly, in an almost peak to peak fashion on HPLC analysis, for the good substrates (**2a**-**2m**). The substrates that did not have a 6-substituted group on the pyridine ring or 2-pyridone showed no reaction (**2s**-**2x**). Transition metal-aided asymmetric hydrogenation of functionalized imines is generally considered to proceed by way of a metal chelate complex in which the N=C bond and a functional group heteroatom are simultaneously coordinated to the metal center.^{19,20} In our cases, 6-substituted functional groups, regardless of type, might aid the Ru to promote the asymmetric reaction as the triggering atom.

In summary, we have demonstrated the highly direct asymmetric reductive amination of 2-acetyl-6-substituted pyridines using a simple ruthenium chiral catalyst, Ru- $(OAc)_2\{(S)$ -binap}. With ammonium trifluoroacetate as the nitrogen source, various chiral corresponding amines were synthesized in excellent enantioselectivities and yields. The admirable performance of the methodology proposes an attractive direct route for synthesis of chiral amines from ketones.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00848.

Experimental procedures, NMR spectra, and HPLC traces of products (PDF)

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

The authors thank SPERA colleagues Hideya Mizufune, Toshihiko Fujitani, and David Cork for their helpful discussion during this study.

REFERENCES

(1) Afanasyev, O. I.; Kuchuk, E.; Usanov, D. L.; Chusov, D. Reductive Amination in the Synthesis of Pharmaceuticals. *Chem. Rev.* **2019**, *119*, 11857–11911.

(2) Yin, Q.; Shi, Y.; Wang, J.; Zhang, X. Direct catalytic asymmetric synthesis of α -chiral primary amines. *Chem. Soc. Rev.* **2020**, *49*, 6141–6153.

(3) (a) Ohkuma, T.; Arai, N. Advancement in Catalytic Asymmetric Hydrogenation of Ketones and Imines, and Development of Asymmetric Isomerization of Allylic Alcohols. *Chem. Rec.* 2016, 16, 2801–2819. (b) Nugent, T. C.; Negru, D. E.; El-Shazly, M.; Hu, D.; Sadiq, A.; Bibi, A.; Umar, M. N. Sequential Reductive Amination-Hydrogenolysis: A One-Pot Synthesis of Challenging Chiral Primary Amines. *Adv. Synth. Catal.* 2011, 353, 2085–2092. (c) Bellizzi, M. E.; Bhatia, A. V.; Cullen, S. C.; Gandarilla, J.; Kruger, A. W.; Welch, D. S. Asymmetric Synthesis of a TRPV1 Antagonist via tert-Butanesulfina-mide-Directed Reductive Amination with a Chromanone. *Org. Process Res. Dev.* 2014, 18, 303–309.

(4) (a) Yuan, S.; Gao, G.; Wang, L.; Liu, C.; Wan, L.; Huang, H.; Geng, H.; Chang, M. The combination of asymmetric hydrogenation of olefins and direct reductive amination. *Nat. Commun.* **2020**, *11*, 621. (b) Wu, Z.; Du, S.; Gao, G.; Yang, W.; Yang, X.; Huang, H.; Chang, M. Secondary amines as coupling partners in direct catalytic asymmetric reductive amination. *Chem. Sci.* **2019**, *10*, 4509–4514. (c) Huang, H.; Liu, X.; Zhou, L.; Chang, M.; Zhang, X. Direct Asymmetric Reductive Amination for the Synthesis of Chiral β -Arylamines. *Angew. Chem., Int. Ed.* **2016**, *55*, 5309–5312. (d) Wakchaure, V. N.; Zhou, J.; Hoffmann, S.; List, B. Catalytic Asymmetric Reductive Amination of a-Branched Ketones. *Angew. Chem., Int. Ed.* **2010**, *49*, 4612–4614. (e) Gao, G.; Du, S.; Yang, Y.; Lei, X.; Huang, H.; Chang, M. Direct Asymmetric Reductive

Amination for the Synthesis of (S)-Rivastigmine. Molecules 2018, 23, 2207-2215. (f) Huang, H.; Wu, Z.; Gao, G.; Zhou, L.; Chang, M. Iridium-catalyzed direct asymmetric reductive amination of aromatic ketones. Org. Chem. Front. 2017, 4, 1976-1980. (g) Bondarev, O.; Bruneau, C. Indirect and direct catalytic asymmetric reductive amination of 2-tetralone. Tetrahedron: Asymmetry 2010, 21, 1350-1354. (h) Li, C.; Villa-Marcos, B.; Xiao, J. Metal-Brønsted Acid Cooperative Catalysis for Asymmetric Reductive Amination. J. Am. Chem. Soc. 2009, 131, 6967-6969. (i) Zhou, S.; Fleischer, S.; Jiao, H.; Junge, K.; Beller, M. Cooperative Catalysis with Iron and a Chiral Bronsted Acid for Asymmetric Reductive Amination of Ketones. Adv. Synth. Catal. 2014, 356, 3451-3455. (j) Kim, K.; Lee, C. Y.; Cheon, C. H. Enantioselective Synthesis of β -Arylamines via Chiral Phosphoric Acid-Catalyzed Asymmetric Reductive Amination. J. Org. Chem. 2015, 80, 6367-6374. (k) Chang, M.; Liu, S.; Huang, K.; Zhang, X. Direct Catalytic Asymmetric Reductive Amination of Simple Aromatic Ketones. Org. Lett. 2013, 15, 4354-4357. (1) Gautier, F. M.; Jones, S.; Li, X.; Martin, S. J. Org. Biomol. Chem. 2011, 9, 7860-7868. (m) Wakchaure, V. N.; Nicoletti, M.; Ratjen, L.; List, B. Towards a Practical Brønsted Acid Catalyzed and Hantzsch Ester Mediated Asymmetric Reductive Amination of Ketones with Benzylamine. Synlett 2010, 18, 2708-2710.

(5) Kadyrov, R.; Riermeier, T. H. Highly Enantioselective Hydrogen-Transfer Reductive Amination: Catalytic Asymmetric Synthesis of Primary Amines. *Angew. Chem., Int. Ed.* **2003**, *42*, 5472–5474.

(6) Matsumura, K.; Zhang, X.; Hori, K.; Murayama, T.; Ohmiya, T.; Shimizu, H.; Saito, T.; Sayo, N. Practical, Catalytic Enantioselective Hydrogenation to Synthesize N-Unprotected β -Amino Esters. Org. Process Res. Dev. **2011**, 15, 1130–1137.

(7) Steinhuebel, D.; Sun, Y.; Matsumura, K.; Sayo, N.; Saito, T. Direct Asymmetric Reductive Amination. *J. Am. Chem. Soc.* **2009**, *131*, 11316–11317.

(8) Busscher, G. F.; Lefort, L.; Cremers, J. G. O.; Mottinelli, M.; Wiertz, R. W.; Lange, B.; Okamura, Y.; Yusa, Y.; Matsumura, K.; Shimizu, H.; de Vries, J. G.; de Vries, A. H. M. Efficient preparation of an N-aryl β -amino acid via asymmetric hydrogenation and direct asymmetric reductive amination en route to Ezetimibe. *Tetrahedron: Asymmetry* **2010**, *21*, 1709–1714.

(9) Gallardo-Donaire, J.; Hermsen, M.; Wysocki, J.; Ernst, M.; Rominger, F.; Trapp, O.; Hashmi, A. S. K.; Schäfer, A.; Comba, P.; Schaub, T. Direct Asymmetric Ruthenium-Catalyzed Reductive Amination of Alkyl–Aryl Ketones with Ammonia and Hydrogen. J. Am. Chem. Soc. 2018, 140, 355–361.

(10) (a) Tan, X.; Gao, S.; Zeng, W.; Xin, S.; Yin, Q.; Zhang, X. Asymmetric Synthesis of Chiral Primary Amines by Ruthenium-Catalyzed Direct Reductive Amination of Alkyl Aryl Ketones with Ammonium Salts and Molecular H₂. J. Am. Chem. Soc. **2018**, 140, 2024–2027. (b) Lou, Y.; Hu, Y.; Lu, J.; Guan, F.; Gong, G.; Yin, Q.; Zhang, X. Dynamic Kinetic Asymmetric Reductive Amination: Synthesis of Chiral Primary β -Amino Lactams. Angew. Chem., Int. Ed. **2018**, 57, 14193–14197. (c) Hu, L.; Zhang, Y.; Zhang, Q. W.; Yin, Q.; Zhang, X. Ruthenium-Catalyzed Direct Asymmetric Reductive Amination of Diaryl and Sterically Hindered Ketones with Ammonium Salts and H₂. Angew. Chem., Int. Ed. **2020**, 59, 5321–5325.

(11) Shi, Y.; Tan, X.; Gao, S.; Zhang, Y.; Wang, J.; Zhang, X.; Yin, Q. Direct Synthesis of Chiral NH Lactams via Ru-Catalyzed Asymmetric Reductive Amination/Cyclization Cascade of Keto Acids/Esters. *Org. Lett.* **2020**, *22*, 2707–2713.

(12) Johnson, M. D.; May, S. A.; Haeberle, B.; Lambertus, G. R.; Pulley, S. R.; Stout, J. R. Design and Comparison of Tubular and Pipes-in-Series Continuous Reactors for Direct Asymmetric Reductive Amination. *Org. Process Res. Dev.* **2016**, *20*, 1305–1320.

(13) (a) Ghosh, T.; Ernst, M.; Hashmi, A. S. K.; Schaub, T. Ruthenium Catalyzed Direct Asymmetric Reductive Amination of Simple Aliphatic Ketones Using Ammonium Iodide and Hydrogen. *Eur. J. Org. Chem.* **2020**, 2020, 4796–4800. (b) Villa-Marcos, B.; Li, C.; Mulholland, K. R.; Hogan, P. J.; Xiao, J. Bifunctional Catalysis:

Direct Reductive Amination of Aliphatic Ketones with an Iridium-Phosphate Catalyst. *Molecules* **2010**, *15*, 2453–2472.

(14) (a) Lee, W.; Crawford, J. J.; Aliagas, I.; Murray, L. J.; Tay, S.; Wang, W.; Heise, C. E.; Hoeflich, K. P.; La, H.; Mathieu, S.; Mintzer, R.; Ramaswamy, S.; Rouge, L.; Rudolph, J. Synthesis and evaluation of a series of 4-azaindole-containing p21-activated kinase-1 inhibitors. Bioorg. Med. Chem. Lett. 2016, 26, 3518-3524. (b) Hauss, D. J.; Fogal, S. E.; Ficorilli, J. V.; Price, C. A.; Roy, T.; Jayaraj, A. A.; Keirns, J. J. Lipid-Based Delivery Systems for Improving the Bioavailability and Lymphatic Transport of a Poorly Water-Soluble LTB₄ Inhibitor. J. Pharm. Sci. 1998, 87, 164-169. (c) Thress, K.; MacIntvre, T.; Wang, H.; Whitston, D.; Liu, Z.; Hoffmann, E.; Wang, T.; Brown, J. L.; Webster, K.; Omer, C.; Zage, P. E.; Zeng, L.; Zweidler-McKay, P. A. Identification and preclinical characterization of AZ-23, a novel, selective, and orally bioavailable inhibitor of the Trk kinase pathway. Mol. Cancer Ther. 2009, 8, 1818-1827. (d) Kraus, R. L.; Li, Y.; Gregan, Y.; Gotter, A. L.; Uebele, V. N.; Fox, S. V.; Doran, S. M.; Barrow, J. C.; Yang, Z.; Reger, T. S.; Koblan, K. S.; Renger, J. J. In Vitro Characterization of T-Type Calcium Channel Antagonist TTA-A2 and In Vivo Effects on Arousal in Mice. J. Pharmacol. Exp. Ther. 2010, 335, 409-417.

(15) (a) Canary, J. W.; Allen, C. S.; Castagnetto, J. M.; Wang, Y. Conformationally Driven, Propeller-like Chirality in Labile Coordination Complexes. J. Am. Chem. Soc. **1995**, 117, 8484–8485. (b) Chelucci, G.; Pinna, G. A.; Saba, A. Chiral 8-amino substituted 2-phenyl-5,6,7,8-tetrahydro-6,6-dimethylmethanoquinolines as chiral ligands for enantioselective catalysis: palladium catalysed allylic substitution and addition of diethylzinc to benzaldehyde. Tetrahedron: Asymmetry **1997**, 8, 2571–2578. (c) Haas, J.; Piguel, S.; Wirth, T. Reagent-Controlled Stereoselective Iodolactonizations. Org. Lett. **2002**, 4, 297–300.

(16) (a) Mangas-Sanchez, J.; Sharma, M.; Cosgrove, S. C.; Ramsden, J. I.; Marshall, J. R.; Thorpe, T. W.; Palmer, R. B.; Grogan, G.; Turner, N. J. Asymmetric synthesis of primary amines catalyzed by thermotolerant fungal reductive aminases. *Chem. Sci.* 2020, *11*, 5052–5057. (b) Martínez-Montero, L.; Gotor, V.; Gotor-Fernández, V.; Lavandera, I. Stereoselective amination of racemic sec-alcohols through sequential application of laccases and transaminases. *Green Chem.* 2017, *19*, 474–480. (c) Paul, C. E.; Rodríguez-Mata, M.; Busto, E.; Lavandera, I.; Gotor-Fernández, V.; Gotor, V.; Gotor, V.; García-Cerrada, S.; Mendíola, J.; de Frutos, Ó.; Collado, I. Transaminases Applied to the Synthesis of High Added-Value Enantiopure Amines. *Org. Process Res. Dev.* 2014, *18*, 788–792.

(17) Brunner, H.; Niemetz, M. Enantioselective Catalysis CXLI [1]. Tridentate Ligands with 1-(Pyridin-2-yl)ethylamine as Chiral Building Block in the Enantioselective Transfer Hydrogenation of Acetophenone. *Monatsh. Chem.* **2002**, *133*, 115–126.

(18) (a) Chelucci, G.; Baldino, S.; Solinas, R.; Baratta, W. Asymmetric synthesis of 1-substituted-1-(pyridin-2-yl)methylamines by diastereoselective reduction f enantiopure *N-p*-toluenesulfinyl ketimines. *Tetrahedron Lett.* **2005**, *46*, 5555–5558. (b) Chelucci, G.; Baldino, S.; Chessa, S.; Pinna, G. A.; Soccolini, F. An easy route to optically active 1-substituted-1-pyridyl-methylamines by diastereose-lective reduction of enantiopure *N-tert*-butanesulfinyl ketimines. *Tetrahedron: Asymmetry* **2006**, *17*, 3163–3169.

(19) Kobayashi, S.; İshitani, H. Catalytic Enantioselective Addition to Imines. *Chem. Rev.* **1999**, *99*, 1069–1094.

(20) (a) Ohta, T.; Takaya, H.; Noyori, R. Stereochemistry and Mechanism of the asymmetric hydrogenation of unsaturated carboxylic acids catalyzed by BINAP-Ruthenium (II) dicarboxylate complexes. *Tetrahedron Lett.* **1990**, *31*, 7189–7192. (b) Ashby, M. T.; Halpern, J. Kinetics and Mechanism of Catalysis of the Asymmetric Hydrogenation of α,β -Unsaturated Carboxylic Acids by Bis-(carboxylato){2,2'-bis(diphenylphosphino)-1,1'-binaphthyl} ruthenium(II), [Ru^{II}(BINAP)(O₂CR)₂]. *J. Am. Chem. Soc.* **1991**, *113*, 589–594.