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Highly Diastereoselective Hydrogenation of Imines by a Bimetallic Pd−Cu Heterogeneous Catalyst

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Abstract:

An efficient and practical heterogeneous bimetallic Pd−Cu/C catalyst was identified as an alternative to Raney nickel for the highly diastereoselective hydrogenation of imines prepared from prochiral ketones and α-phenylethylamines. Chiral amines were obtained with diastereomeric excess (de) up to 94% using Pd−Cu/C, while conventional Pd−C catalysts afforded only 72% de. Optimization showed that a robust process required a palladium/copper ratio of 4:1. Evidence for the influence of catalyst pretreatment which may change the structure of the catalyst and/or metal oxidation states on the selectivity of the reaction is discussed. The bimetallic catalyst system provided consistent results on scale and performed reliably on a variety of substrates.

Introduction

Chiral α-phenylalkylamines are key building blocks for the synthesis of many pharmaceuticals.[1] Among different asymmetric approaches[1,2] to this class of chiral amines, auxiliary-directed diastereoselective hydrogenation of imines using heterogeneous metal catalysts has been a subject of strong interest.[3] Bringmann et al. reported an approach which involved Raney nickel-catalyzed, highly diastereoselective reduction of acetophenone imines bearing an inexpensive α-phenylethylamine chiral auxiliary.[3a,b] The chiral primary amines were subsequently obtained by a highly regioselective hydrogenolysis of the bis-benzylic amines (Scheme 1).[3b−f,h,i,4] Nugent et al. have expanded the methodology to a wide array of substrates.[3g,h,j]

During the process development of peliglitazar (**4**),[5] a potent dual peroxisome proliferator-activated receptors (PPARs) α/γ agonist for the treatment of type 2 diabetes, Raney nickel was initially used in the hydrogenation of **1** to provide **2** with high selectivity (94% de) (Scheme 2). However, drawbacks to this process included the requirement for a high catalyst loading (∼ 60% wt/wt) resulting in poor suspension as well as special handling to remove water from the pyrophoric catalyst prior to the hydrogenation in order to minimize hydrolysis of the imine substrate. This prompted us to investigate safer and more process-friendly catalysts that would also deliver high facial selectivity during the hydrogenation. Herein, we report a highly diastereoselective hydrogenation of imines prepared from a variety of acetophenones and α-phenylethylamine chiral auxiliaries using a heterogeneous Pd−Cu/C bimetallic catalyst (A701023-4 from Johnson Matthey) as a safe and economical alternative to Raney nickel.

Results and Discussion

Various catalysts and methods were screened for the reduction of **1**. Hydrogenations performed with palladium on

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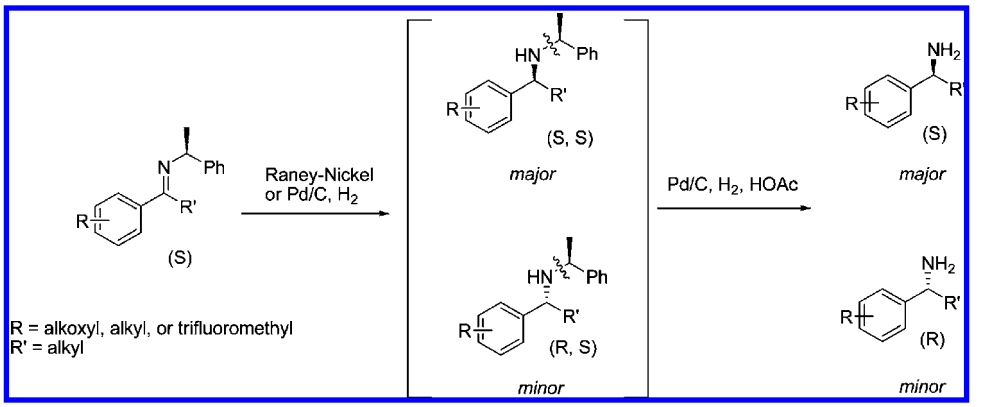
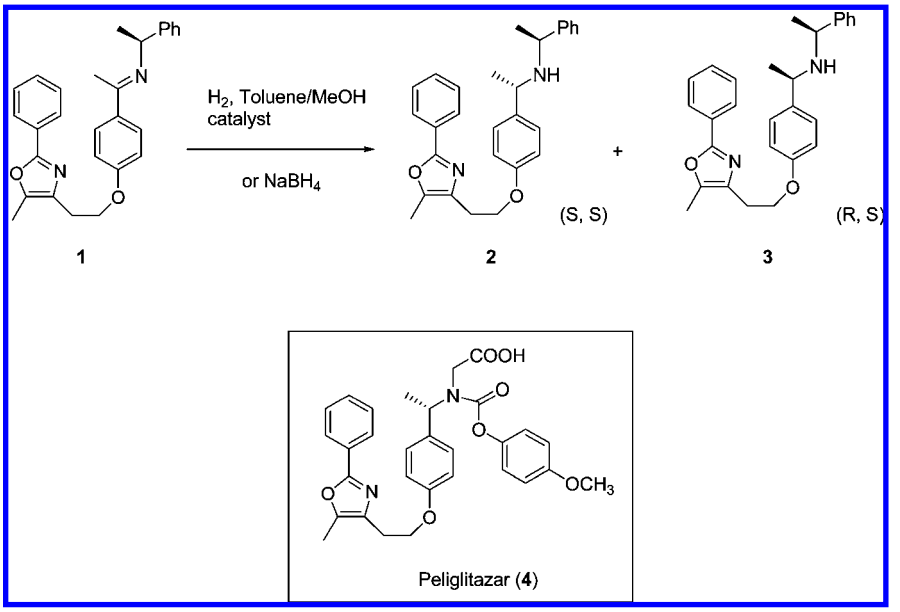
Scheme 1. **Catalytic reduction of α-phenylethylamine-substituted imines to chiral amines**



Scheme 2. **Setting the chiral benzylic center of peliglitazar**



charcoal (Pd−C) provided **2** in only modest diastereomeric excess (72% de). To improve diastereoselectivity, two approaches were pursued. First, chiral additives were screened to investigate the possibility of exerting double stereodifferentiation. Chiral additives are known to induce enantioselectivity during *achiral* imine hydrogenations over Pd−C.[6] However, to our knowledge, there are no analogous examples reported in the literature on the improvement of diastereoselectivity of *chiral* imine hydrogenations over heterogeneous catalysts modified with chiral additives.[7] Application of this approach to **2** led to the finding that Pd−C catalyst modified with (−)-cinchonidine improved selectivity to 90% de (Table 1). No improvements in de were observed when D-alanine or L-tartaric acid were used as chiral additives. We next examined the impact of using Pd catalysts modified by nonchiral additives or other metals.[3j,o] While marginal improvements in diastereoselectivity were observed using DABCO, interestingly, two heterogeneous bimetallic catalysts, Pd−Cu and Pd−Na (both on activated carbon), demonstrated excellent diastereoselectivity (94% de). The influence of the cometal on the catalyst performance in bimetallic palladium catalysts are known.[8a] To our knowledge, enhancements to the *diastereo*selectivity of imine reductions using bimetallic palladium catalysts have not been reported. The closest example in the literature is a report by Klabunovskii et al.[8b] on the use of Pd−Cu in the asymmetric hydrogenation of ethyl acetoacetate in the presence of L-tartaric acid to introduce

Table 1. **Diastereomeric excess (de) in the hydrogenation of chiral imines**[a]

entry	catalyst (additive)	de (%)
1	Raney-nickel	94
2	Pd−C	72
3	Pd−C (L-tartatic acid)	70
4	Pd−C (D-alanine)	72
5	Pd−C ((−)-cinchonidine)	88
6	Pd−C ((−)-cinchonidine) premixed	90
7	Pd−C DABCO	82
8	Pd−Cu/C	94
9	Pd−Na/C	92

[a] $NaBH_4$ afforded 78% de. Conversions for all entries are between 90−100%.

(6) Gobolos, S.; Tfirst, E.; Margitfalvi, J. L.; Hayes, K. S. *J. Mol. Catal. A: Chem* **1999**, *146*, 129.

(7) A noteworthy example is that good diastereomeric excess was achieved in the hydrogenation of an imine bearing an α-phenylethylamine chiral auxiliary with a rhodium−chiral phosphine ligand, albeit a homogeneous catalysis system, see: Lensink, C.; de Vries, J. G. *Tetrahedron: Asymmetry* **1993**, *4*, 215.

(8) (a) Coq, B.; Figueras, F. *J. Mol. Catal. A: Chem* **2001**, *173*, 117. (b) Kuznetsova, T. I.; Murina, I. P.; Vedenyapin, A. A.; Akimov, V. M.; Klabunovskii, E. I. *React. Kinet. Catal. Lett.* **1988**, *37*, 363.

Table 2. **Elemental analysis[a] of hydrogenation catalysts**

sample	Cu	Pd	C	O	Al	Pd−Cu	Cu/(Pd + Cu) (%)
Pd−Cu−Al_2O_3	0.6	2.9	3.1	56.5	36.9	4.8/1	17
Pd−Cu−C	0.7	2.7	94.7	1.2	0	3.9/1	20

[a] Elemental analysis of Pd−Cu on alumina and Pd−Cu on carbon catalysts.

modest *enantio*selectivity. Due to the superior diastereoselectivity observed with the Pd−Cu and Pd−Na, we studied the chiral imine hydrogenation using these catalysts.

During process optimization using Pd−Na/C and Pd−Cu/C catalysts, it was observed that diastereoselectivity was not reproducible from batch to batch. While increasing the levels of sodium did not yield consistent de, increasing the amount of copper on the solid support from 0.03 wt % to 1.0 wt % led to consistently high de, although a decrease in catalytic activity of the Pd−Cu/C catalyst was noted at higher copper loading. The total time to achieve 99.5% conversion increased from 3 h at 0.03 wt % Cu to 11 h at 1.0 wt % Cu. These observations led us to focus on further optimization of the Pd−Cu bimetallic catalyst system.

Carbon-supported Pd−Cu bimetallic catalysts typically contain 50−60 wt % water. To prevent the hydrolysis of imine substrates to the corresponding ketones, it was necessary to use the dry catalysts, which can be obtained from Johnson Matthey. For improved safety, substitution of the carbon support for noncombustible alumina was explored. However, dry Pd−Cu/alumina catalysts consistently resulted in slightly lower de (86%). To improve the selectivity of these catalysts, additional factors were explored. Elemental analysis (Table 2) showed that the Pd−Cu ratio is slightly higher for the Pd−Cu/alumina catalyst. The marginal difference of copper (∼ 3%) suggested surface composition should not be the primary factor for low de. This prompted us to consider the various oxidation states present in our bimetallic catalyst. To do this we examined the surface oxidation states using X-ray photoelectron spectroscopy (XPS) (also called electron spectroscopy for chemical analysis (ESCA))[10] (Figure 1). In comparison to the ESCA spectra of Pd−Cu/C catalyst (red line), Pd−Cu/alumina spectra (black line) showed lower levels of copper and palladium oxides based on the representative binding energies for Pd, PdO, Cu, Cu_2O, and CuO (335, 336.3, 932.4, 932.5, and 933.7 eV, respectively). To test the hypothesis that higher levels of metal oxides might be a factor, Pd−Cu/alumina catalyst was pretreated with pure oxygen at 170 °C for 14 h prior to the hydrogenation. However, it should be noted that this treatment may affect both the oxidation state and the surface structure. Under hydrogenation conditions, the palladium oxide is readily reduced,[11] but copper stays in the oxide form.[12] When this catalyst was used for the hydrogenation of **1**, the de improved to 92%, while untreated catalyst gave 86% de. This experiment suggested that the pretreatment of the catalyst resulted in changing the surface in terms of structure and/or chemical state of the copper and had an effect on the selectivity by possibly changing adsorption properties of the substrate on the catalyst. It is known from the literature that surface structure and oxidation state of the metal may play a role in selectivity.[13]

From the above findings, the most attractive options available to support plant scale-up for the hydrogenation of **1** with high facial selectivity were as follows: (a) Employment of alumina supported bimetallic catalyst following oxygen pretreatment or (b) a dry carbon-supported 5% Pd−Cu (palladium/copper weight ratio ∼4:1) catalyst. On the basis of the higher de obtained with the latter, Pd−Cu/C was selected to demonstrate the efficiency of the process on a 400-g scale.

The imine was prepared by azeotropic distillation in the presence of $Ti(OiPr)_4$. It should be noted that imine formation was required versus using one-pot reductive amination due to the low conversion observed in the reductive amination. The hydrogenation of imine was carried out in a toluene/methanol (50:50) solution to afford **2** with 94% de. No debenzylation was observed in the Pd−Cu/C catalyzed hydrogenation. The reaction mixture was debenzylated through regioselective hydrogenolysis with 10% Pd−C,[3a] affording **6** in 73% isolated yield (Scheme 3). The manifestation of this result is that the Pd−Cu bimetallic system is scalable to provide an efficient and practical approach to prepare chiral amines with high diastereoselectivity.

In addition to demonstrating the scalability of the Pd−Cu/C bimetallic catalyst system, we were interested in expanding the

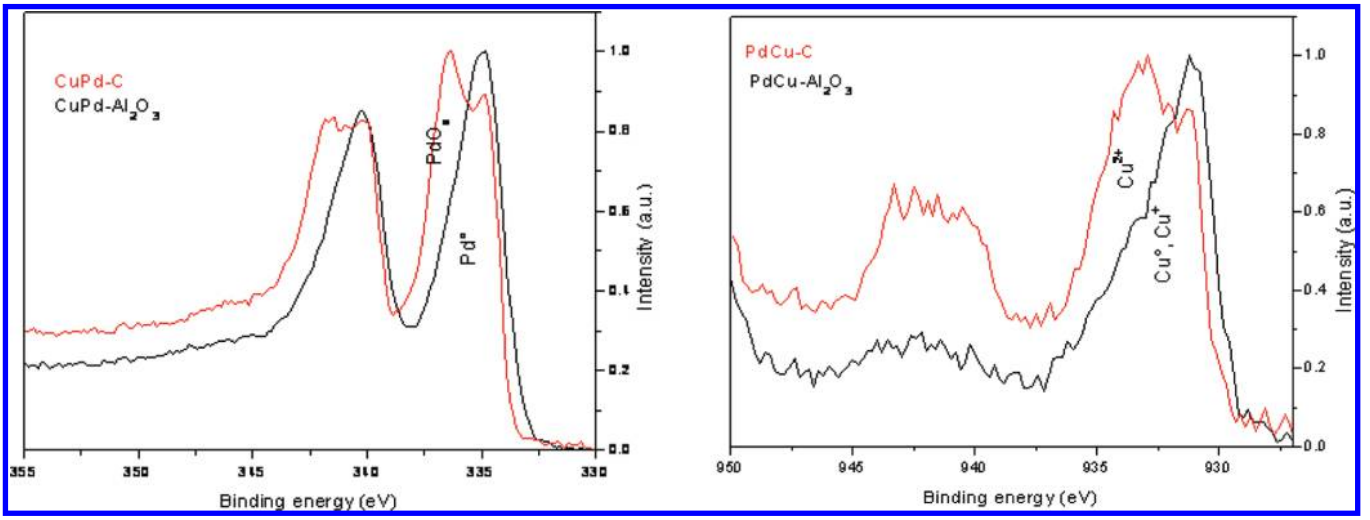


Figure 1. **X-ray photoelectron spectra of Pd−Cu/C and Pd−Cu/alumina (untreated with O_2).**

Scheme 3. **Conversion of the ketone precursor to the chiral benzylic primary amine 6**

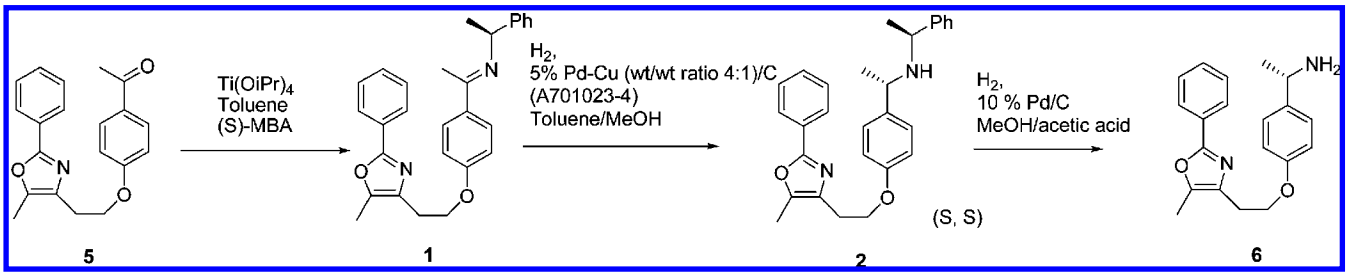
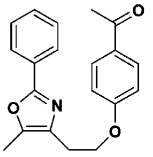
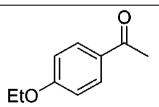
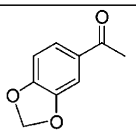
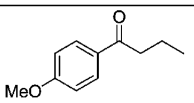
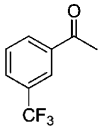
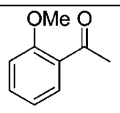


Table 3. **Exploration of different acetophenone substrates scope using Pd−Cu/C catalyst**[a]

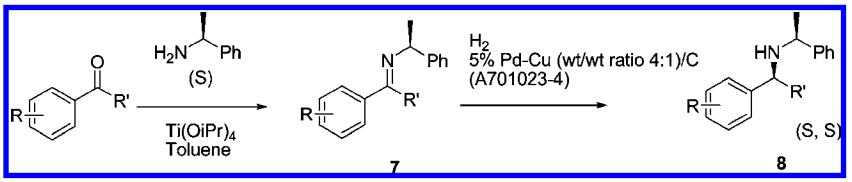
Entry	Ketone	Ketimine **7**	Secondary Amine **8**	
		E / Z	d.e. (%)	Conversion
1		92 / 8	94	95 %
2		94.3 / 5.7	88	92 %
3		93.7 / 6.3	92	89 %
4		76.7 / 23.3	92	95 %
5		95.8 / 4.2	86	Quantitative
6		33.3 / 66.6	78	90 %

[a] (*R*)-α-phenylethylamine was used. Note: all the *E*/*Z* configurations were determined by proton NMR and diastereomeric excess by GC as well as proton NMR.

substrate scope (Table 3). A variety of aryl ketimines **7** were synthesized from the corresponding aryl ketones in the presence of $Ti(OiPr)_4$. The hydrogenation reactions were carried out at 25 psig and ambient temperature in the presence of 5% palladium−copper (palladium/copper weight ratio ~4:1) on activated carbon. The hydrogenated products were obtained in de ranging between 86 to 94% with the exception of entry 6. Notably, both electron-rich and -deficient aryl ketones were successfully hydrogenated. The *E*/*Z* ratio of the ketimines **7** and diastereoisomeric excess of secondary amines **8** were determined by proton NMR on the basis of chemical shift correlations.[3k] It is plausible that (*S*,*S*) resulted from hydrogenation at the less hindered side of *E* configuration of the ketimine and (*R*,*S*) resulted from *Z* configuration of the ketimine (Scheme 4). In the case of entry 4 (Table 3), a high de (92%) was

(9) Boyd, D. R.; Jennings, W. B.; Waring, L. C. *J. Org. Chem.* **1986**, *51*, 992.
(10) Satterfield, C. *Heterogeneous Catalysis in Industrial Practice*, 2nd ed.; McGraw-Hill: New York, 1991; p 165.
(11) McKinney, P. V. *J. Am. Chem. Soc.* **1933**, *55*, 3626.
(12) Kim, M. H.; Ebner, J. R.; Friedman, R. M.; Vannice, M. A. *J. Cat.* **2002**, *208*, 381.
(13) Somorjai, G. A.; Park, J. Y. *Angew. Chem. Int. Ed* **2008**, *47*, 9212.

Scheme 4



observed despite the low *E*/*Z* ratio (77/23) of the starting ketimine. This effect is possibly attributed to rapid *E*/*Z* isomerization[9] coupled with slow kinetically controlled hydrogenation (Curtin−Hammett principle).

Experimental Section

Screening Conditions (Table 1). All the reactions (entries 1−9) were carried out in a 5-mL solution of toluene/methanol (1:1 (v/v)) with an Endeavor Catalyst Screening System (Biotage) on a 500 mg scale at 25 psig and 25 °C for 16 h. Raney nickel (60 wt %) (Grace Davidson 2800) was used for entry 1. Entries 2−7 used 10 wt % of 5% Pd−C from Johnson Matthey. Entries 3−6 used 0.3 equiv of chiral additives. Entry 6 used a Pd−C and (−)-cinchonidine premix prepared by stirring 0.3 equiv of (−)-cinchonidine with 10 wt % 5% Pd−C in methanol for 30 min and leaving overnight, followed by filtration through a Whatman filtering paper. The wet catalyst was used as is. Entry 7 used 0.15 equiv of DABCO. Entry 8 used 10 wt % of 5% Pd/0.03 wt % Cu/C from Johnson Matthey. Entry 9 used 5 wt % of 3% Pd/0.01 wt % Na/C from Engelhard. Diastereomeric excess was determined by GC on a DB-1 HT column (15 m × 0.32 mm) and proton NMR. GC program for diastereoisomers **2** and **3**: T_{inj} = 250 °C and T_{det} = 300 °C, carrier gas He flow 1.6 mL/min, 150 °C, then 10 °C/min to 280 °C, then 20 °C/min to 350 °C (hold 5 min), retention time for **2** (13 min), and **3** (13.1 min). For product primary amine **6**, the enantiomeric excess was determined by Chiral HPLC using a Chiralcel OD-H 5 μm 4.6 mm × 150 mm column. LOD (loss on drying) was determined by Mettler Toledo moisture analyzer.

Scale-Up. *(S)-1-(4-(2-(5-methyl-2-phenyloxazol-4-yl)ethoxy)phenyl)ethanamine (6).* To a 4-L toluene solution was added ketone **5** (400 g, 1.24 mol, 1.0 equiv), (*S*)-α-phenylethylamine (181 g, 1.49 mol, 1.2 equiv), and $Ti(OiPr)_4$ (91.6 g, 0.322 mol, 0.26 equiv). The reaction mixture was refluxed under azeotropic distillation to achieve 99.1% conversion after 23 h. The reaction mixture was cooled and inverse quenched to a 2 N NaOH solution. After filtration and phase split, the toluene solution was concentrated to 2 L. To the above toluene concentrate was added 2 L of methanol and 5% Pd−Cu/C dry catalyst with Pd−Cu (w/w) ratio of 4:1 from Johnson Matthey (A701023-4) (25 g, 6.25 wt/wt% based on ketone **5**) in a 5-L Buchi reactor. The reaction was carried out at 25 °C under 25 psig of hydrogen. Reaction was complete after 10.5 h to afford diastereomeric excess of 94%. The reaction mixture was filtered through a 0.5 μm polypropylene Cuno filter to remove the catalyst. To the filtrate was added 30 wt % of 10% Pd−C (Degussa NE/W E101), followed by the addition of acetic acid (149 g, 2.48 mol, 2.0 equiv). The debenzylation reaction was carried out at 50 °C and 40 psig. Isolation was carried out in a 10-L Chemglass reactor. Methanol was distilled off, followed by the addition of 400 mL of isopropanol and 150 mL of acetic acid. The mixture was stirred for 15 min, followed by addition of 3 L of water. After phase split, the product-rich aqueous solution was added into 2.6 L of 2 N NaOH to afford a slurry. The slurry was then filtered and dried to 0.64% LOD to obtain **6** (293 g, 73% isolated yield) as a white solid with HPLC area purity of 96% and enantiomeric purity of 94% ee. $[\alpha]_D^{25}$ −13.99° (*c* 10, DCM); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97 (dd, J = 2.0, 8.3 Hz, 2H), 7.38−7.44 (m, 3H), 7.24 (d, J = 8.8 Hz, 2H), 6.86 (d, J = 8.8 Hz, 2H), 4.23 (t, J = 6.8 Hz, 2H), 4.05 (q, J = 6.3 Hz, 1H), 2.97 (t, J = 6.8 Hz, 2H), 2.37 (s, 3H), 1.56 (s, N−H, 2H), 1.34 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.7, 156.9, 144.4, 139.5, 132.3, 129.3, 128.2, 127.3, 126.2, 125.5, 114.1, 66.8, 50.8, 26.8, 26.1, 10.8; HRMS ESI Calcd for $C_{20}H_{22}N_2O_2$: $(M + H)^+$ 323.1760; found 323.1758.

Conclusions

In summary, high diastereoselectivities were observed in the hydrogenation of imines with a bimetallic Pd−Cu/C catalyst. Key advantages of this new method are improved safety compared with those of Raney nickel, no issues with catalyst suspension, and enhanced operational scalability. It was demonstrated that a reliable process resulted from using a bimetallic 5% Pd−Cu/C catalyst with Pd−Cu (w/w) ratio of 4:1. Preliminary data from X-ray photoelectron spectroscopy suggest that diastereoselectivity could be influenced by the oxidation states at both palladium and copper. Effectiveness of the bimetallic Pd−Cu system was demonstrated on a plant scale for our key peliglitazar intermediate, offering a practical approach to prepare chiral amines with high diastereoselectivity.

Note Added after Print Publication: In the version published June 10, 2010, Jale Müslehiddinoğlu should have been designated a corresponding author. This has been corrected in this version posted August 24, 2010.

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