A Convenient Asymmetric Synthesis of α-1-Arylalkylamines through the Enantioselective Hydrogenation of Enamides

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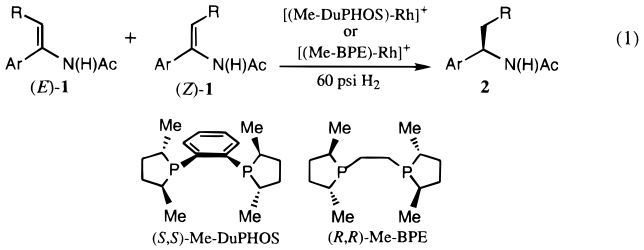
Optically active α-1-arylalkylamines constitute an important class of compounds that have been employed extensively as resolving agents,[1] chiral auxiliaries, and intermediates in the synthesis of a wide range of biologically active molecules.[2] The broad utility of α-1-arylalkylamine derivatives has stimulated relentless pursuit of practical asymmetric routes to these valuable compounds. In this regard, many reliable synthetic methods have been devised and generally involve optical resolution procedures, biocatalytic methods, or stoichiometric use of chiral precursors or chiral auxiliaries.[1−5] Asymmetric catalytic reduction of C═N or C═C double bonds potentially could provide a very efficient and convenient route to many chiral amine derivatives, yet only limited success has been achieved along these lines of research.[6,7] While very high enantioselectivities have been attained in the hydrogenation of α-enamide esters,[8] the development of similarly effective catalysts for asymmetric hydrogenation of α-arylenamides of type **1** has remained a challenging objective.[9] Toward this goal, we have found that cationic Rh catalysts based on our 1,2-bis(*trans*-2,5-dimethylphospholano)benzene (Me-DuPHOS) and 1,2-bis(*trans*-2,5-dimethylphospholano)ethane (Me-BPE) ligands effect the hydrogenation of N-acetyl α-arylenamides (**1**, R = H) to yield a wide variety of valuable α-1-arylethylamine derivatives with high enantioselectivities (≥90% ee). Moreover, an important and unique feature of our catalysts is the ability to tolerate β-substituents in both (*E*)- and (*Z*)-positions of enamides **1**, thus allowing the production of a diverse array of α-1-arylalkylamines **2** through hydrogenation of isomeric mixtures of enamide substrates.



We recently have shown that Rh and Ru catalysts bearing our DuPHOS or BPE ligands are extremely effective for enantioselective hydrogenation of a variety of prochiral unsaturated substrates.[10] These studies have highlighted an important advantage of our ligand design; the ability to readily vary the phospholane 2,5-substituents has allowed us to optimize enantioselectivities by matching the ligand sterics to the steric demands of substrates of interest. In an effort to develop a general asymmetric catalytic method for the preparation of α-1-arylalkylamines, we initially screened a series of Rh and Ru catalysts for efficacy in the hydrogenation of the model α-arylenamide **1a** (Ar = C_6H_5, R = H). We found that under a standard set of reaction conditions (MeOH, 22 °C, 60 psi H_2, S/C = 500, 12 h) cationic Rh complexes of the type $[(COD)Rh(DuPHOS)]^+OTf^-$ and $[(COD)Rh(BPE)]^+OTf^-$ behave as efficient catalyst precursors for the reduction of enamide **1a**. Moreover, we observed that enantioselectivities tended to increase with decreasing steric demand of the DuPHOS and BPE ligands (phospholane 2,5-susbtituents = Me, Et, Pr, *i*-Pr, Cy). This trend suggests that enamides **1** are rather sterically demanding substrates and in fact, more sterically demanding than standard α-enamide esters.[10c,f] Thus, hydrogenation of **1a** using the (*S*,*S*)-Me-DuPHOS-Rh catalyst afforded the product, N-acetyl-α-phenethylamine (**2a**), in 94.7% ee and (*S*) absolute configuration. Within the analogous series of BPE-Rh catalysts, (*R*,*R*)-Me-BPE-Rh provided (*R*)-**2a** with the highest enantioselectivity (95.2% ee). By comparision, directly analogous Rh catalysts bearing other well-known chiral diphosphines led to significantly lower enantioselectivities in the reduction of **1a** in MeOH under our prototypical conditions: (*R*)-BINAP (15.1% ee), (*S*,*S*)-CHIRAPHOS (40.7% ee), (*R*,*R*)-SKEWPHOS (7.1% ee), and (*R*,*R*)-DIOP (56.6% ee). Similarly, a Ru-BINAP catalyst derived from (*R*)-BINAP-$RuBr_2$ produced (*S*)-**2a** with low enantioselectivity (53.7% ee).

Enantioselectivities attained in the present hydrogenations were found to be relatively insensitive to solvent. For example, similar ee's were achieved in the Me-DuPHOS-Rh-catalyzed reduction of **1a**: MeOH (94.7% ee), C_6H_6 (94.3% ee), EtOAc (95.7% ee), *i*-PrOH (95.8% ee), THF (91.4% ee), and CF_3CH_2-OH (91.8% ee). In general, high ee's were achieved consistently in either the protic solvent MeOH or the aprotic EtOAc, thus allowing the reaction to be conducted in two solvents with rather different properties. Likewise, minor pressure variations had little effect on selectivities in the hydrogenation of **1a** using the Me-DuPHOS-Rh catalyst in MeOH; ee's varied by ≤1.5% ee over the pressure range 10−90 psi.

The general utility of the Me-DuPHOS-Rh and Me-BPE-Rh catalysts was revealed through production of a panoply of α-1-

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Table 1. Rh-Catalyzed Asymmetric Hydrogenation of α-Arylenamides **1** (R = H)[a]

entry	AR in **1** (R = H)	optimum ligand	% ee[b] (confign)[c]
1	C_6H_5[d]	(*R*,*R*)-Me-BPE	95.2 (*R*)
2	*p*-CH_3-C_6H_4	(*R*,*R*)-Me-BPE	96.5 (*R*)
3	*p*-CF_3-C_6H_4	(*S*,*S*)-Me-DuPHOS	95.6 (*S*)[e]
4	*p*-CH_3O-C_6H_4	(*R*,*R*)-Me-BPE	95.3 (*R*)[e]
5	*p*-CF_3O-C_6H_4	(*S*,*S*)-Me-DuPHOS	96.2 (*S*)[e]
6	*p*-Br-C_6H_4	(*R*,*R*)-Me-BPE	95.8 (*R*)
7	*p*-F-C_6H_4	(*R*,*R*)-Me-BPE	95.0 (*R*)[e]
8	*p*-MeS-C_6H_4	(*R*,*R*)-Me-BPE	96.3 (*R*)[e]
9	*m*-Br-C_6H_4	(*S*,*S*)-Me-DuPHOS	96.8 (*S*)[e]
10	*m*-CH_3-C_6H_4	(*S*,*S*)-Me-DuPHOS	94.9 (*S*)[e]
11	*o*-Br-C_6H_4	(*R*,*R*)-Me-BPE[f]	89.0 (*R*)[e,g]
12	*o*-F-C_6H_4	(*R*,*R*)-Me-BPE	95.7 (*R*)[e]
13	*o*-CH_3-C_6H_4	(*R*,*R*)-Me-BPE	74.8 (*R*)[e]
14	2,6-$F_2C_6H_3$	(*R*,*R*)-Me-BPE	97.8 (*R*)[e]
15	3,4,5-$(MeO)_3C_6H_2$	(*S*,*S*)-Me-DuPHOS	95.6 (*S*)
16	2-naphthyl	(*S*,*S*)-Me-DuPHOS	95.6 (*S*)
17	2-furanyl	(*S*,*S*)-Me-DuPHOS	96.1 (*S*)[e]
18	2-thienyl	(*S*,*S*)-Me-DuPHOS	97.5 (*S*)

[a] Reactions were conducted at 22 °C and an initial H_2 pressure of 60 psi using 0.10−0.25 M methanol solutions of substrate and the catalyst precursors [(*S*,*S*)-Me-DuPHOS-Rh(COD)]$^+$OTf$^-$ or [(*R*,*R*)-Me-BPE-Rh(COD)]$^+$OTf$^-$ (0.2 mol %), unless otherwise noted. Reaction time was 15 h, and complete (100%) conversion was observed in all cases. [b] Enantiomeric excesses were determined by chiral capillary GC using Chrompack's Chirasil-L-Val column (25 m). [c] Absolute configurations were confirmed by comparing the sign of optical rotation of **2**, or hydrolyzed product, with that of known N-acetylamines or free amines, respectively (see supporting information). [d] Enamide **1a** (entry 1) was prepared following the procedure outlined by Kagan and coworkers in ref 9a,b. To our knowledge, all other enamides in Table 1 are new and were prepared via the same method as that employed for **1a**. The procedure used and characterization data for all new enamides are provided as supporting information. [e] Absolute configurations for these products were assigned by analogy, through comparison of sign of optical rotation and chiral GC elution order with configurationally defined products (see supporting information). [f] Reaction performed in ethyl acetate. [g] Enantiomeric excess determined by HPLC (CHIRALCEL OJ; 15:85 2-propanol/hexane).

arylethylamine derivatives with high enantioselectivities. Table 1 lists selectivities achieved using the optimum catalyst identified for each individual enamide substrate **1**.[11] Overall, Me-DuPHOS-Rh and Me-BPE-Rh catalysts performed comparably with the substrates listed in Table 1 and generally furnished products with enantioselectivities differing by ≤2% ee. Moreover, the Et-DuPHOS-Rh catalyst afforded similarly high enantioselectivities in certain cases but did not display the substrate generality enjoyed by the Me-DuPHOS-Rh and Me-BPE-Rh catalysts. Thus, our asymmetric hydrogenation process provides a convenient route to a variety of highly enantiomerically-enriched ring-substituted α-phenethylamine derivatives. Substitution at the meta or para positions of the parent enamide **1a** did not greatly influence the enantioselectivites. No significant substituent electronic effects on the ee's were observed. Hydrogenation of enamide **1** possessing a *p*-thiomethyl substituent (entry 8) demonstrated tolerance to potentially detrimental sulfur-bearing groups. Substitution at the ortho position of **1a** did affect selectivities. Hydrogenation with (*R*,*R*)-Me-BPE-Rh under our standard conditions yielded 2-fluoro- and 2,6-difluoro-α-phenethylamine derivatives with high enantioselectivities (95.7% and 97.8% ee, respectively). A minimal increase in the steric nature of the ortho substituent to 2-methyl or 2-bromo, however, led to a significant decrease in selectivity, wherein the products were obtained in 74.8% and 81.3% ee, respectively. The more rigid Me-DuPHOS-Rh catalyst provided these products in only 58.0% and 62.1% ee, respectively. Varying the solvent to EtOAc allowed the 2-bromophenethylamine derivative to be obtained in 89.0% ee

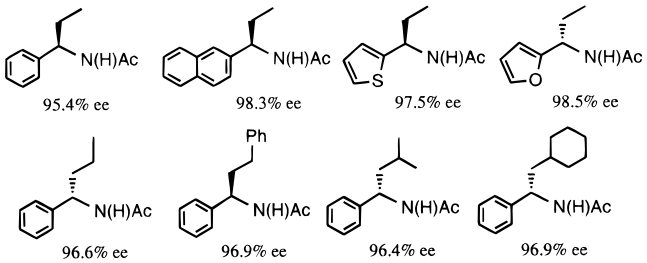

Figure 1. Asymmetric catalytic synthesis of α-arylalkylamine derivatives. (*R*)- (*S*)-amines derived from (*R*,*R*)-Me-BPE-Rh and (*S*,*S*)-Me-DuPHOS-Rh catalysts, respectively.

(entry 11). These results further indicate the sterically demanding nature of enamide substrates **1**.

We next examined whether our catalysts could effectively hydrogenate α-arylenamides possessing β-substituents (i.e., **1**; R ≠ H). The ability to hydrogenate such substrates would vastly expand the types of chiral amine derivatives available through this methodology. We were pleased to find that a variety of β-substituted enamides could be reduced to the corresponding α-1-arylalkylamine derivatives **2** with high enantioselectivities (Figure 1). Importantly, we have found that isomeric mixtures of (*E*)- and (*Z*)-enamides **1** (*E*/*Z* isomer ratios varied from ca. 1:1 to 4:1) may be employed in these hydrogenation reactions, with no apparent detrimental effect on the selectivity. This finding was critical for development of a useful route to α-1-arylalkylamines, as we have been unable to prepare or purify the separate (*E*)- and (*Z*)-enamide isomers. Thus, an array of isomeric enamides **1** possessing both linear and branched β-alkyl substituents and an assortment of different α-aryl groups were hydrogenated with enantioselectivities ≥95% ee using either the Me-DuPHOS-Rh or the Me-BPE-Rh catalysts. A rational for why the Me-BPE-Rh and Me-DuPHOS-Rh catalysts are capable of tolerating β-substituents in both (*E*)- and (*Z*)-positions of enamides **1** awaits further mechanistic study. Preliminary deuteration studies suggest that neither isomerization to N-acylimines nor interconversion of geometric enamides is involved in enamide hydrogenation reactions.[10c,f,12]

In conclusion, our Me-DuPHOS-Rh and Me-BPE-Rh catalysts have been found to allow efficient hydrogenation of α-arylenamides **1**, thus providing practical access to a broad range of valuable α-1-arylalkylamine derivatives in highly enantiomerically-enriched form. A unique feature of this system is the ability of our catalysts to hydrogenate mixtures of (*E*)- and (*Z*)-enamides with high enantioselectivities, hence obviating the need to prepare isomerically pure substrates. The present study further demonstrates the versatility and utility of our DuPHOS-Rh and BPE-Rh hydrogenation catalysts for the production of chiral building blocks of medicinal and biological interest. Future studies will attempt to decipher the effects (steric and/or electronic)[13] responsible for the high enantioselectivities we observe in these hydrogenation reactions.

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Supporting Information Available: Experimental details, including preparation of α-arylenamides (**1**), hydrogenation procedure, spectral and analytical data, and ee determinations for amine derivatives **2** (25 pages). Ordering information is given on any current masthead page.

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