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Highly Enantioselective Hydrogenation of Amides via Dynamic Kinetic Resolution Under Low Pressure and Room Temperature

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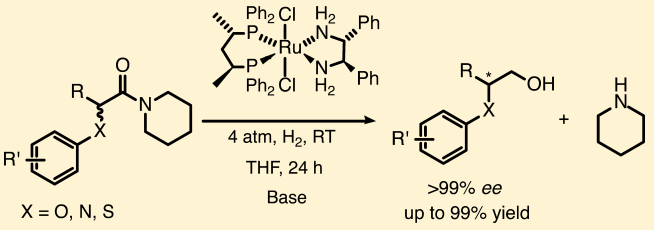
Supporting Information

ABSTRACT: High-throughput screening and lab-scale optimization were combined to develop the catalytic system *trans*-$RuCl_2$((*S*,*S*)-skewphos)((*R*,*R*)-dpen), 2-PrONa, and 2-PrOH. This system hydrogenates functionalized α-phenoxy and related amides at room temperature under 4 atm H_2 pressure to give chiral alcohols with up to 99% yield and in greater than 99% enantiomeric excess via dynamic kinetic resolution.



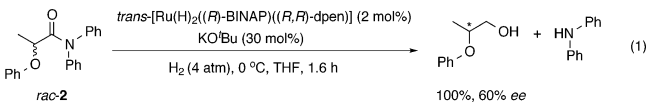
INTRODUCTION

Amides are the least reactive carboxylic acid derivatives. Their reduction often requires a stoichiometric amount of a reducing agent, and results in CO cleavage to generate amines.[1] Catalytic hydrogenations are an atom-economic and efficient alternative to stoichiometric reducing agents, but until recently, amide hydrogenations have required forcing conditions and high catalyst loadings.[2] Moderate to good activities were recently reported for amide hydrogenations with homogeneous catalysts under acidic conditions,[3] and with heterogeneous catalysts[4] under neutral conditions. These hydrogenations mostly proceed with net C−O cleavage. In contrast, homogeneous bifunctional[5a−e,6] and pincer[5f−n] catalysts typically hydrogenate amides with net C−N cleavage[5,6] to form the respective alcohol and amine under neutral or basic conditions. These catalysts offer moderate to high turnover numbers and a wide range of functional group tolerance.

In a recent mechanistic investigation,[6c] we found that one or both of the equatorial N−H groups in Noyori's hydrogenation catalyst, *trans*-RuH_2((*R*)-BINAP)((*R*,*R*)-dpen) (**1**, BINAP is 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl, dpen is 1,2-diphenyl-1,2-diaminoethane), are deprotonated by mixtures of *n*-BuLi and KO^{t}Bu in THF. The anion resulting from the monodeprotonation, *trans*-M^+[RuH_2((*R*,*R*)-H_2NCH(Ph)CH(Ph)$NH^{(-)}$)((*R*)-BINAP)] (M = Li or K) is extremely active toward the stoichiometric reduction of imides and amides, with reactions beginning as low as −80 °C.[6c] This result suggested that amides could be hydrogenated under low pressures and temperatures in the presence of high amounts of base. Further, under such conditions, the enantioselective hydrogenation of *alpha*-chiral racemic amides could occur with dynamic kinetic resolution (DKR). Highly enantioselective hydrogenations of racemic ketones (usually keto-esters) via DKR are well-known.[7] In contrast, there are only a handful of reports of enantioselective hydrogenations of aldehydes with DKR.[8a−c] To our knowledge, there are only two reports of the enantioselective hydrogenation of ester-type substrates with DKR.[5b,8d] Ikariya et al. reported the hydrogenation of *rac*-α-phenyl-γ-butyrolactone in 32% *ee* with a Cp*Ru-diamine catalyst at 80 °C under 50 atm H_2.[5b] A preliminary result describes the hydrogenation of alkyl 2-phenylpropanoate (alkyl: methyl, isobutyl, and isopropyl) by $RuCl_2$((*R*)-xylyl-BINAP)-((*S*,*S*)-dpen) at 40 °C in THF. The primary alcohol product, 2-phenyl-1-propanol, was obtained in near quantitative yield with *ee*'s ranging from 46 to 60% for methyl, isobutyl, and isopropyl groups, respectively.[8d] There are no reports of asymmetric amide hydrogenations. We now report the use of rapid screening to develop the highly enantioselective hydrogenation of racemic α-phenoxy-amides via DKR under mild conditions.

RESULTS AND DISCUSSION

The amide used for the rapid screening was racemic *N*,*N*-diphenyl-2-phenoxypropanamide (**2**). The hydrogenation of **2** by *trans*-RuH_2((*R*)-BINAP)((*R*,*R*)-dpen) (**1**) in THF[9] occurred under only 4 atm at 0 °C, in the presence of high amounts of base, to give diphenylamine and 2-phenoxy-1-propanol in 60% *ee* (eq 1). Based upon our earlier studies,[6c] we



predict that the catalyst is the active reducing agent *trans*-K^+[RuH_2((*R*,*R*)-H_2NCH(Ph)CH(Ph)$NH^{(-)}$)((*R*)-BINAP)].-This is the first example of an amide hydrogenation with DKR. High-throughput screening was used to develop a catalyst with high yield and enantioselectivity. Monophosphine (P), diphosphine (P−P), dpen, and multivalent ligands (P−N, P−N−P, and P−N−N−P) were screened for the hydrogenation

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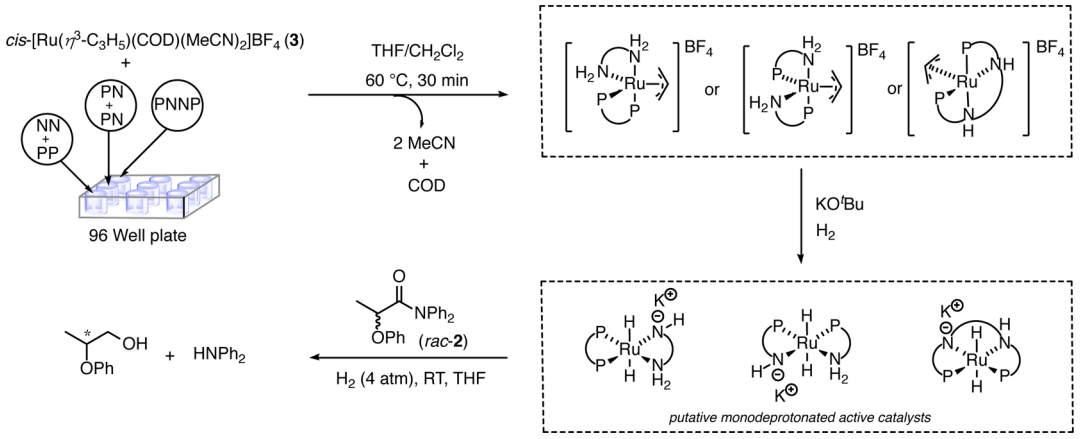
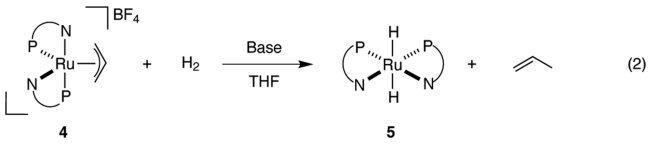


Figure 1. Strategy for the high-throughput screening process; in situ catalyst preparation (structures shown inside the square-bracket are proposed), and hydrogenation of **2**.

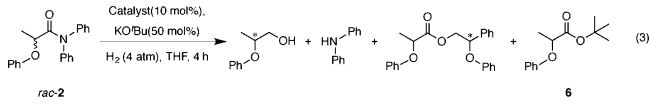
(See the complete list in the Supporting Information, pages S3, S15−S19). The catalysts were prepared with our standard catalytic precursor, *cis*-[Ru(η^3-C_3H_5)(MeCN)$_2$(COD)]BF_4 (**3**, COD is 1,5-cyclooctadiene) in a THF/CH_2Cl_2 solution (Figure 1).

Solutions of **3**, 1 equiv of a P−P ligand, and (*R*,*R*)-dpen were allowed to react for 30 min at 60 °C to displace the MeCN and COD ligands.[6a,10] Solutions of **3**, P−N (2 equiv) or P−N−P (1 equiv), or P−N−N−P (1 equiv) ligands were used without (*R*,*R*)-dpen. The resulting allylic-Ru precursors were then mixed at room temperature with KO^{t}Bu (5 equiv) and the racemic amide **2** (10 equiv) and allowed to react under 4 atm H_2 for 4 h. We previously reported that allylic Ru precursors such as [Ru(η^3-C_3H_5)(P−N)$_2$]BF_4 (**4**) react with H_2 and base in THF to form the dihydride catalysts *trans*-RuH_2(P−N)$_2$ (**5**) and propylene (eq 2).[6a] The large excess of KO^{t}Bu ensured that **2** underwent rapid tautomerization and that the putative catalysts, such as **5**, were activated by deprotonation of the N−H groups.

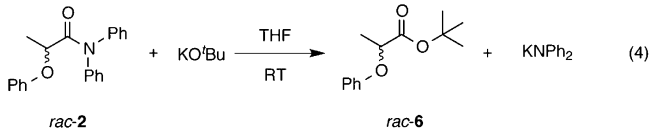


(2)

The results from the rapid screening are arranged into four categories. Category I, with little to no hydrogenation product (38 wells); category II, with moderate to low amounts of **2** remaining (12 wells); category III, with no **2** remaining, but with varying amounts of products (7 wells); and category IV, with complete conversion to diphenylamine and 2-phenoxy-1-propanol (17 wells). The Supporting Information (pages S15−S19) shows the ligands in each category. The amide **2** was present as a racemic mixture in the wells with starting material remaining, showing that the hydrogenations proceeded via dynamic kinetic resolution.[11]



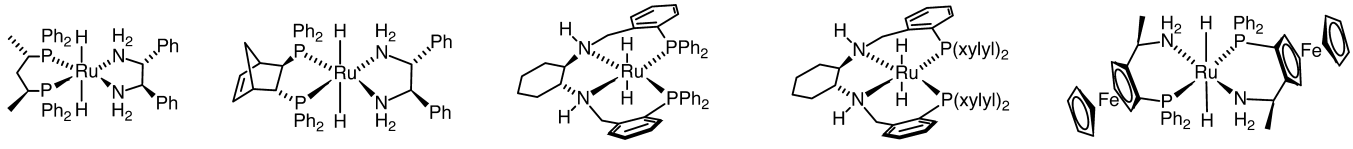
(3)



(4)

The products in categories II and III were mixtures of the expected diphenylamine and 2-phenoxy-1-propanol, but to our surprise, the ^{t}Bu- and 2-phenoxy-1-propyl esters (4 diastereomers) of the parent amide **2** also formed (eq 3). A control reaction between **2** and KO^{t}Bu in THF resulted in exchange of diphenylamine to form the ^{t}Bu ester *rac*-CH_3(PhO)$CHCO_2{}^t$Bu (**6**) on the time scale of the hydrogenation (eq 4). Thus, the rapid screening occurred to some extent via hydrogenation of the esters formed by the reaction between **2** and KO^{t}Bu or the alkoxide of the product alcohol $KOCH_2CH(OPh)CH_3$. Indeed, the ^{t}Bu ester **6** and diphenylamine were present in the reactions that did not go to completion. The results from the screening are therefore indicative and not definitive.

The catalysts in category IV produced only 2-phenoxy-1-propanol and diphenylamine. Figure 2 shows the catalysts (**7**−**11**) from category IV that were the most enantioselective. They consisted of (P−P)(N−N), (P−N)$_2$, and (P−N−N−P) catalyst systems, and formed the product with *ee*'s ranging from 17 to ∼60%. The hydrogenation was then optimized with



7	8	9	10	11
2: 4 h,100%, 29% *ee*	**2**: 4 h,100%, 17% *ee*	**2**: 4 h,100%, 41% *ee*	**2**: 4 h,100%, 60% *ee*	**2**: 4 h,100%, 44% *ee*
12: 3 h,100%, 25% *ee*	**12**: 16 h, 100%, 16% *ee*	**12**: 17 h, 100%, 44% *ee*	**12**: 23 h, 100%, 35% *ee*	**12**: 18 h, 0%, --- % *ee*

Figure 2. Putative dihydride catalysts of active category IV, their yield (%), and *ee* (%) for the hydrogenation of *rac*-**2** and *rac*-**12**.

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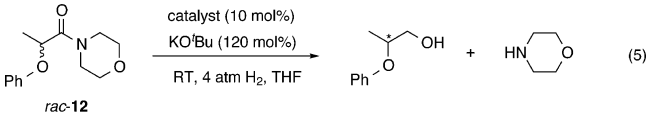
these category IV catalysts with larger scale individual reactions. We employed *rac*-2-phenoxy-1-(morpholine)-1-propanone (**12**) to minimize displacement of the amine group by alkoxides. In control NMR experiments, *rac*-**12** did not undergo displacement of the morpholine by either KO^{t}Bu or *rac*-$KOCH_2CH(OPh)CH_3$ under the hydrogenation conditions. This *N*,*N*-dialkyl amide was less reactive than the *N*,*N*-diphenyl amide **2**, and 12 equiv of KO^{t}Bu (per Ru) was required to hydrogenate *rac*-**12** at room temperature under 4 atm H_2 (eq 5). Figure 2 also shows the activity and selectivity of **7**−**11** toward the hydrogenation of *rac*-**12**.



Catalyst **11** was inactive under these conditions. The dixylyl- (**10**) and diphenylphosphino- (**9**) (*R*,*R*)-P−N−N−P catalysts required 23 and 17 h, respectively, to form 2-phenoxy-1-propanol in 35 and 44% *ee*. The (*R*,*R*)-norphos/(*R*,*R*)-dpen catalyst **8** required a similar amount of time (16 h), but was less enantioselective (16%). The (*S*,*S*)-skewphos/(*R*,*R*)-dpen catalyst **7** was significantly more active, and the reaction went to completion after 3 h with 25% *ee*. In all cases, esters and aldehydes could not be detected by NMR. The most active phosphine, (*S*,*S*)-skewphos in catalyst **7**, was used for subsequent optimizations with the diamines shown in Figure 3.

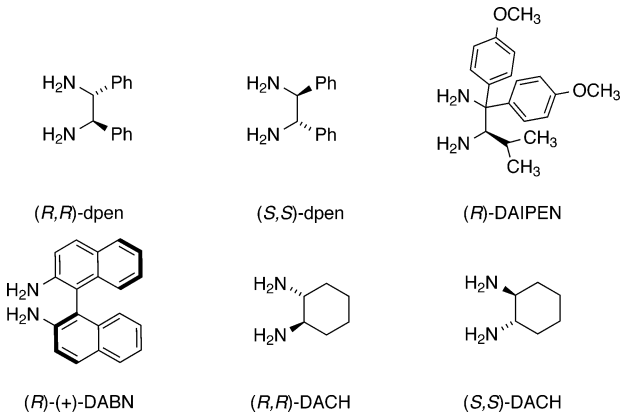
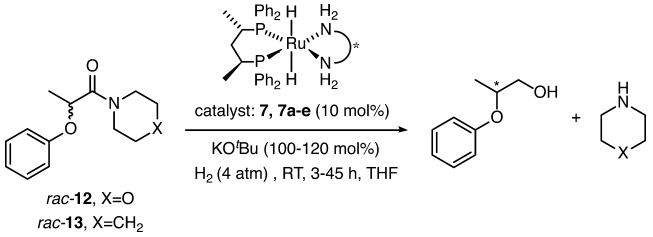


Figure 3. Structures of diamine ligands used for catalyst optimization.

During these optimization studies, we found that the piperidine amide, *rac*-2-phenoxy-1-(piperidine)-1-propanone (**13**), gave higher *ee* than *rac*-**12**. Table 1 summarizes the results.

The opposite hand of dpen, (*S*,*S*)-, decreased both the activity and *ee* of the catalyst (Table 1, entry 2). The highest *ee* with **12** (58% *ee*, 45 h, entry 5,) was obtained with (*R*,*R*)-*trans*-1,2-diaminocyclohexane ((*R*,*R*)-DACH). The (*S*,*S*)-DACH was less enantioselective (entry 6). The piperidine amide, *rac*-2-phenoxy-1-(pipyridine)-1-propanone (**13**), was hydrogenated in 56% *ee* with the (*R*,*R*)-DACH catalyst, but with only 8.3% yield (21 h, entry 7). The (*R*,*R*)-dpen catalyst **7** was more active toward **13**, giving 96% yield after 3.5 h in comparable *ee* (44% *ee*, entry 8). With **7** as the catalyst, reducing the amount of KO^{t}Bu from 10 to 1.1 equiv reduced the yield (14%, 20 h) but increased the *ee* to 88% (entry 9). This *ee* indicates that the kinetic selectivity of **7** between the enantiomers of **13** is high.

Table 1. Optimization Studies for the Enantioselective Hydrogenation of 12 and 13[a]

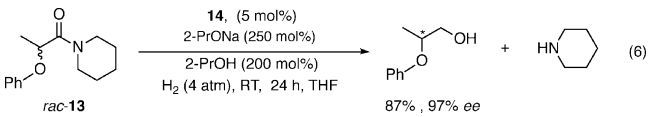


entry	sub	cat	diamine ligand	time (h)	yield (%)[b]	*ee* (%)[c]
1	**12**	7	(*R*,*R*)-dpen	3	100	25
2	**12**	7a	(*S*,*S*)-dpen	16.5	100	12
3	**12**	7b	(*R*)-DAIPEN	42	100	18
4	**12**	7c	(*R*)-(+)-DABN	16	0	-
5	**12**	7d	(*R*,*R*)-DACH	45	96	58
6	**12**	7e	(*S*,*S*)-DACH	41	98	29
7[d,e]	**13**	7d	(*R*,*R*)-DACH	21	8.3	56
8[d,e]	**13**	7	(*R*,*R*)-dpen	3.5	96	44
9[d,f]	**13**	7	(*R*,*R*)-dpen	20	14	88
10[d,g]	**13**	7	(*R*,*R*)-dpen	24	89	93

[a]Cat:KO^{t}Bu:**12** or **13** = 1:12:10, [**12** or **13**] = 0.06 M in THF. [KO^{t}Bu] = 0.072 M in THF. [b]Determined using ^{1}H NMR spectroscopy. [c]Determined using HPLC with a Daicel CHIRALPAK IB (4.6 mm i.d. × 250 mm) chiral column. [d]For entries 7−10, **13** is used as a substrate. [e]Cat:KO^{t}Bu:**13** = 1:10:10, [KO^{t}Bu] = 0.06 M in THF. [f]Cat:KO^{t}Bu:**13** = 1:1.1:10, [KO^{t}Bu] = 0.0065 M in THF. [g]Cat:KO^{t}Bu:**13**:isopropanol = 1:30:20:100.

The theoretical *ee* of the remaining **13** would be 6.6% in the opposite direction if racemization did not occur during this hydrogenation. The measured *ee* of isolated **13** was 5% in the opposite direction, confirming that racemization was relatively slow in the absence of excess KO^{t}Bu. Satisfyingly, addition of 2-PrOH (100 equiv) and KO^{t}Bu (30 equiv) enabled the dynamic kinetic resolution to occur with 20 equiv of substrate in 93% *ee* and 89% yield (entry 10).

In the final improvement, the convenient, moderately air stable, pure dichloride precursor *trans*-$RuCl_2$((*S*,*S*)-skewphos)-((*R*,*R*)-dpen) (**14**) was utilized with 2-PrONa as base[12] (50 equiv) in the presence of 2-PrOH (40 equiv), to hydrogenate 20 equiv of **13** under 4 atm H_2 to form 2-phenoxy-1-propanol in 87% yield and 97% *ee* (eq 6). Table 2 shows the amides



hydrogenated under our optimized conditions. Most of the phenoxy amides were hydrogenated in yields that ranged from 87 to 99%. The *ee*'s of the product 2-aryloxy-1-propanols ranged from 95 to >99%. The reaction proceeded in high yield and *ee* with aromatic fluorides (entry 2), chlorides (entry 3), and even bromides (entry 4). There was little effect of steric crowding at the *para*-phenyl position on the reaction, as substitution of hydrogen (entry 1) by a *tert*-butyl group (entry 6) decreased the yield by only 3%, while the *ee* remained relatively unchanged. The methoxy amide (entry 5) was hydrogenated in moderate yield (78.1%) and in 97% *ee*, suggesting that electron-donating groups at the *para*-position partially hinder the reaction. Moving the fluoride from the *para*- (entry 2) to the *meta*-position (entry 7) increased the yield

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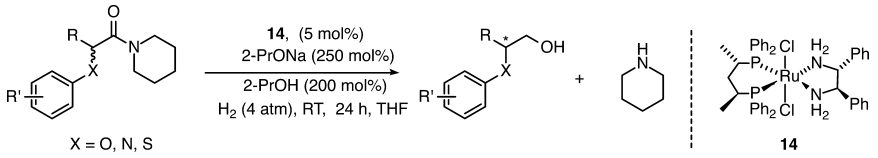
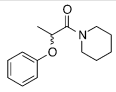
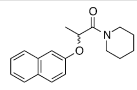
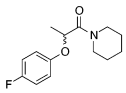
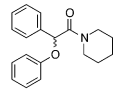
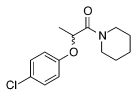
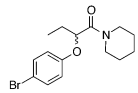
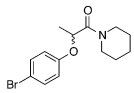
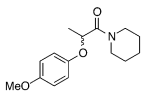
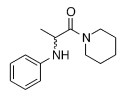
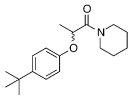
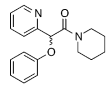
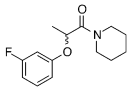
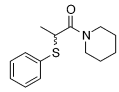
Table 2. Enantioselective Hydrogenation of Functionalized Racemic Amides[a]

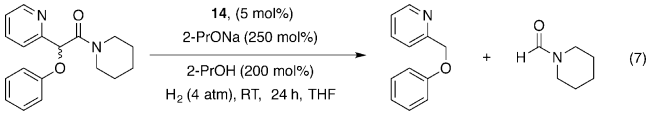


entry	substrate	yield (%)[b]	*ee* (%)[c]	entry	substrate	yield (%)[b]	*ee* (%)[c]
1		87	97 (*R*)[i]	8		93.5	96
2		87 (92.6)[d]	96 (95)[d]	9		91.7	84
3		91.7	>99 (*R*)[j]	10		60	95
4		94	>99	11		66	46
5		78.1	97	12[e]		47.5 (71, (69))[f]	74 (72)[f]
6		84	97	13		100	---
7		99 (95)[h]	96	14[g]		16	74

[a]Reaction conditions (unless otherwise noted) **14**:2-PrONa:amide:2-PrOH = 1:50:20:40, [amide] = 0.6 M in THF. [b]Determined using ^{1}H NMR spectroscopy. [c]Determined using chiral GC-MS or HPLC. [d]**14**:2-PrONa:amide:2-PrOH = 1:250:100:100, [amide] = 0.6 M in THF, reaction carried at 50 atm H_2 pressure. [e]KO^{t}Bu used as the base. [f]Reaction performed at 50 atm H_2 pressure at 0 °C, 69% yield with respect to internal standard. [g]**14**:KO^{t}Bu:amide = 1:5:20, reaction performed at 30 atm H_2 pressure. [h]Isolated yield by flash chromatography on silica silica gel. [i]$[\alpha]_D^{22} = -29.3$ @ 97% *ee* (c = 1.87, $CHCl_3$); lit. $[\alpha]_D^{20} = -12.1$ @ 40% *ee* (c = 1.0, $CHCl_3$).[8a] [j]$[\alpha]_D^{22} = -33.1$ @ > 99% *ee* (c = 1.11, $CHCl_3$); lit. $[\alpha]_D^{25} = -35.1$ @ > 99% *ee* (c = 1.0, $CHCl_3$).[19]

from 87 to 99% with no change in *ee*. The (2-napthoxy) amide (entry 8) reacted in comparable yield (93.5%) and *ee* (96%). The exchange of a methyl for a phenyl group alpha to the carbonyl (entry 9) did not significantly affect the yield (91.7%) but reduced the *ee* to 84%.

Replacing the methyl for an ethyl group (entry 10) reduced the yield (60%) but did not significantly affect the *ee* (95%), while replacing the phenoxy group for a methoxy group (entry 11) reduced both yield (66%) and *ee* (46%). 1-(*N*-Phenylalanyl)piperidine (entry 12) was hydrogenated to 2-anilino-1-propanol with 47.5% yield and 74% *ee*. This result demonstrates that the catalyst system can be used to prepare chiral *β*-amino alcohols. Chiral *β*-amino alcohols are important building blocks in the synthesis of chiral auxiliaries[13] and unnatural amino acids.[14] To our surprise, exchanging the methyl with a 2-pyridyl group alpha to the carbonyl (entry 13) gave 1-formylpiperidine and 2-(phenoxymethyl) pyridine (eq 7). We recently reported a similar catalytic C−C cleavage reaction under these mild conditions.[15] Further research is required to investigate this phenomena.



(7)

2-Phenylthio-1-(1-piperidinyl)-1-propanone (entry 14) was hydrogenated using 25 mol % of KO^{t}Bu at room temperature under 30 atm to give the chiral *β*-thio alcohol in 16% yield and 74% *ee*.

The turnover number of these reactions may be limited by the buildup of secondary amine product under these mild conditions. As well, the 2-PrOH and the buildup of primary alcohol product will also inhibit the catalyst. These alcohols will form secondary and primary Ru alkoxides by reaction with Ru amides such as **15**.[16b] This process is reversible in the presence

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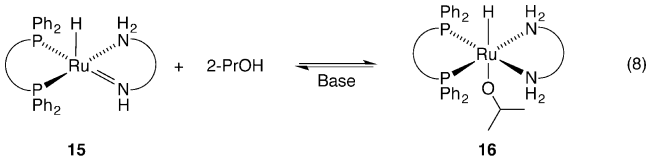
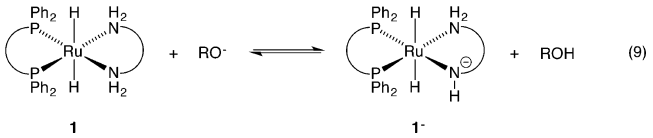
of base (eq 8).[16b] We propose that 2-PrOH and product alcohols slow the hydrogenations by reducing the steady-state



concentration of Ru-amides such as **15** during catalysis.[16b] We note that alkoxides such as **16** do not undergo net reactions with H_2 and ketones, nor do they hydrogenate ketones under mild conditions.[16a] A second potential mechanism by which 2-PrOH and the product alcohol may hinder the hydrogenation is by shifting the deprotonation equilibrium of **1** toward the dihydride (eq 9). Although the basicity of both the RO^- and $\mathbf{1}^-$



would be affected by the presence of alcohol, eq 9 would still shift to the left with the increase in alcohol concentration that occurs as the hydrogenation proceeds. Both of these mechanisms predict that higher turnover numbers will be achieved if the pressure of H_2 is increased, which would increase the steady-state concentration of $\mathbf{1}^-$, but not significantly affect the *ee*.[17] Therefore, we carried out the hydrogenation 100 equiv of **17** (2-(4-fluorophenoxy)-1-(1-piperidinyl)-1-propanone) at 50 atm H_2, and as predicted, the reaction proceeded in 92.6% yield in 95% *ee* (Table 2, entry 2, parentheses). The product of this hydrogenation is an intermediate for a treatment of glaucoma in canines.[18] The hydrogenation of 1-(*N*-phenylalanyl)piperidine at 50 atm H_2 pressure also increased the yield from 47.5 to 71% without affecting the *ee* significantly (Table 2, entry 12, parentheses).

Figure 4 shows our proposed structure of the active catalyst **18** in the presence of 2-PrONa. This proposal is

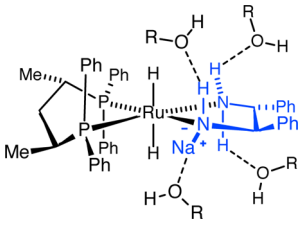


Figure 4. Proposed structure of the active catalyst **18** with possible interactions with 2-PrOH, primary alcohol products, etc. The skewphos is in the *δ*-skew configuration.

based upon our earlier observation that deprotonating one N–H group of the BINAP-dpen dihydride **1** substantially increased its activity toward amide reductions.[6c] The mechanism(s) by which 2-PrOH increases the *ee* of these hydrogenations is not obvious. We recently published the solid-state structure of the dichloride **14** that contains (*S*,*S*)-skewphos in a chair conformation with one methyl group equatorially disposed, the other methyl group axial, and with the phenyl rings in a pseudoachiral spatial disposition.[15,20] (*S*,*S*)-Skewphos also adopts a C_2-dissymmetric *δ*-skew conformation with both methyl groups in equatorial orientations and with the phenyl rings in a chiral spatial disposition.[20,21] It is believed that the asymmetric induction of the skew conformation is higher than the chair.[20,21] Skewphos adopts either the chair or skew conformation in Rh, Pd, and Pt compounds in the solid state,[21] and the conformations of skewphos-Rh complexes are fluxional in room temperature alcohol solutions.[21a] Thus, there is no obvious correlation between the conformation of (*S*,*S*)-skewphos in solid **14** and the active catalyst **18** in solution. One possible mechanism by which 2-PrOH increases the *ee* of the amide hydrogenations, therefore, is by favoring the *δ*-skew conformation in **18**, increasing the net asymmetric induction of the catalyst.

As discussed above, it is likely the active catalyst is the monodeprotonated species **18**. Similar monodeprotonated catalysts were first proposed by Chen based upon rate studies of ketone hydrogenations.[22] They were also investigated by computational studies on ketone hydrogenations.[23] As well, there are many studies on the role of alcohols on the rate and selectivity of ketone bifunctional hydrogenations.[24] Apart from our preliminary observations, we are aware of no detailed mechanistic studies on amide bifunctional hydrogenations. Figure 4 shows some of the hydrogen and ionic bonds that may form between 2-PrOH (R = 2-Pr) and the N–H or N^-–Na^+ groups in **18**. Any of these interactions could influence the enantioselectivity of the hydrogenation. In principle, THF, ^{t}BuOH, the product alcohol, the various alkoxides present over the course of the amide reduction, and piperidene can engage in similar bonding with **18**. The system is complex, and a detailed study of the structure and reactivity of the putative intermediates would be required to unravel the stereochemical forces that lead to the major enantiomer of the product.

We note that the catalytic hydrogenation of the racemic ester *rac*-2-propyl 2-phenoxy-1-propanoate **19** proceeded in 35% *ee*, confirming that the piperidine group in **13** does not undergo significant exchange with 2-propoxide during hydrogenation. Interestingly, the hydrogenation of the racemic aldehyde 2-phenoxypropanal **20** produced 2-phenoxy-1-propanol after only 30 min, but in 9% *ee*. This low *ee* indicates that the aldehyde is either not an intermediate in the hydrogenation of the parent amide **13** or that, if it forms, it does not epimerize before it is reduced to the alcohol product.

■ CONCLUSIONS

The combination of the mechanistic observation that deprotonation of the N–H bonds in these bifunctional catalysts increases their reducing power, along with rapid screening and optimization lead to remarkably high *ee*'s for hydrogenation of a variety of functionalized amides via DKR under mild conditions. High *ee*'s are obtained by the addition of 2-PrOH. It is probable that 2-PrOH bonds to the diastereomeric transition states of the enantioselective step, favoring one pathway over the other. Further studies are required to investigate these mechanistic inferences and the origins of enantioselection.

■ EXPERIMENTAL SECTION

For experimental details see Supporting Information.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b12254.

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Text, tables, and figures giving experimental procedures and characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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