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Aqueous asymmetric transfer hydrogenation using modular hydrophobic aminoalcohols

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Abstract—A series of new modular Ru/aminoalcohol systems were used as enantioselective catalysts in the asymmetric transfer hydrogenation reaction in both water and 2-propanol. The catalytic behavior exhibited in these two media follows different tendencies regarding the tunable ligand structure. While the bulkiness of the R^1 group has a positive effect on the activity for reactions in 2-propanol, ligands with bulky R^1 groups are generally less active in water. Additionally, cationic, anionic, and neutral surfactants do not improve the catalytic behavior in water.

1. Introduction

Sustainability concerns have led in recent times to increased research efforts aimed to decrease the environmental impact of chemical processes. For this reason, the atom economy[1] provided by catalytic reactions becomes crucial. To minimize the catalyst loading or to avoid treatments required for separation or removal from reaction products, different approaches to enantioselective catalysis have focused on the heterogenization of the catalytic system.[2]

On the other hand, the use of water as a solvent or even solvent-free methodologies is the strategy commonly used toward greener chemistry.[3] Water as a reaction medium is highly desirable since it is safe, non-toxic, environmentally friendly, and inexpensive. However, many transition metal catalysts are moisture sensitive, making aqueous catalysis only possible in extremely careful conditions. In addition, the insolubility of many organic compounds in water limits its application in various chemical transformations.

An interesting approach to aqueous catalysis is the use of water-soluble catalysts, which are assembled through the use of water-soluble ligands. Generally, water-soluble catalysts act in biphasic systems, the catalysts being in the aqueous phase and the substrate and product/s in the organic one. These systems present the possibility of catalyst recycling by simple phase separation. However, the application of most of these catalysts is limited by the rather long syntheses needed to introduce water-solubilizing groups in the catalyst structure. A way to overcome this difficulty is the use of stable hydrophobic catalysts directly on water,[4] an approach of interest for reactions taking place at the interphase between an organic substrate and water.

Enantioselective reduction of prochiral ketones to yield enantiopure secondary alcohols is of interest because of the importance of these alcohols as intermediates in the production of pharmaceuticals and advanced materials. Among the different catalytic methods reported to this end, the Asymmetric Transfer Hydrogenation (ATH) is of importance since it avoids the use of flammable hydrogen as a reducing agent.[5] The first successful examples were reported by Noyori et al., with ruthenium-based catalysts bearing monotosylated diamines or 1,2-aminoalcohols as chiral ligands. The most popular solvents for this catalytic reaction are either 2-propanol or the formic acid/triethylamine mixture, which act at the same time as hydrogen donors for the reduction process. Nevertheless, aqueous formate, which is used in nature by enzymes for reduction reactions, has been rarely used until quite recent reports by Xiao and co-workers[6a,b] and by Wills,[6c] who have shown the possibility of performing ATH in water using sodium formate as a hydrogenation agent. Most of the catalytic

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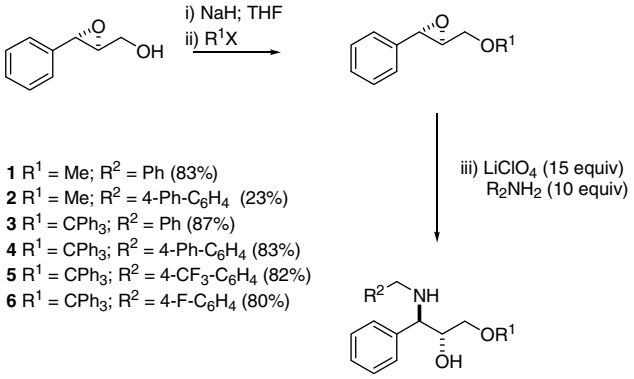
systems reported for the aqueous ATH bear *N*,*N* type ligands (amino-amide,[7] monotosylated[8] or sulfonated[9] diamine ligands, and imino-pyridines[10]). The use of aminoalcohols, which are also important ligands in this reaction, has been only quite recently reported.[11]

Given the interest in conducting this reaction in water, the search for new catalysts, which are active and stable in an aqueous medium, is a significant challenge. We report here on the use of a family of readily accessible chiral 1,2-aminoalcohols (**1**–**6**) as enantioselective ligands for the catalytic aqueous ATH reaction. Their tunable backbone allows for a programmed variation of their hydrophobic nature, and results on their catalytic activity show that reaction occurring at the surface of the organic substrate droplets dispersed in water is faster in some cases than homogeneous reactions in isopropanol mediated by the same catalytic systems (Fig. 1).

2. Results and discussion

It has been recently reported that the asymmetric transfer hydrogenation of aromatic ketones using Noyori's catalyst (Ru-(*R*,*R*)-TsDPEN) can be performed in an open atmosphere using water as a solvent with very good results.[3] Chiral aminoalcohols can in general be readily prepared, while some of them are even commercially available. However, to the best of our knowledge, there are only two reports using commercially available aminoalcohols as ligands for the ATH in water. Among them, (−)-ephedrine[11] gave the best activities, with enantioselectivities up to 78% for the reduction of acetophenone.

We reported some time ago the preparation of a family of modular aminoalcohols from enantiopure Sharpless epoxyalcohols. The steric and electronic properties of these ligands were conveniently tuned for the application in several catalytic processes[12] including ATH in 2-propanol.[12b] For the asymmetric transfer hydrogenation in an aqueous medium, we decided to test related ligands, bearing some structural changes. The general route followed for the synthesis of aminoalcohols **1**–**6** is based on the lithium perchlorate catalyzed,[13a] regioselective and stereospecific ring opening of a protected Sharpless enantiopure epoxide with a primary amine (Scheme 1).[13b] All new ligands are air stable, orange-yellowish oils, which have been characterized by ^{1}H and ^{13}C NMR spectroscopy, high resolution mass spectrometry, and specific rotation.



Scheme 1. Synthesis of ligands **1**–**6**.

A preliminary screening of the transfer hydrogenation of acetophenone in 2-propanol was conducted with aminoalcohols **1**–**4** (Scheme 2 and Table 1). These ligands showed that the bulkiness of the primary alcohol protecting group R^1 increases dramatically the activity of the catalyst (entries 1 and 2 vs 3 and 4 in Table 1), while enantioselectivity is mainly influenced by the R^2 substituent on the amino group (entries 1 and 3 vs 2 and 4). It is important to note the use of a 4-phenylbenzyl group as an amine substituent (R^2) that improved the selectivity of the process up to 90%. This ee is substantially higher than the previously reported with similar ligands bearing alkyl R^2 substituents as Me or Bu (ee: 76%; 0 °C; R^2: Bu).[12b]

The ATH in aqueous medium was conducted similarly, albeit under air. Formate was chosen as a hydrogen source

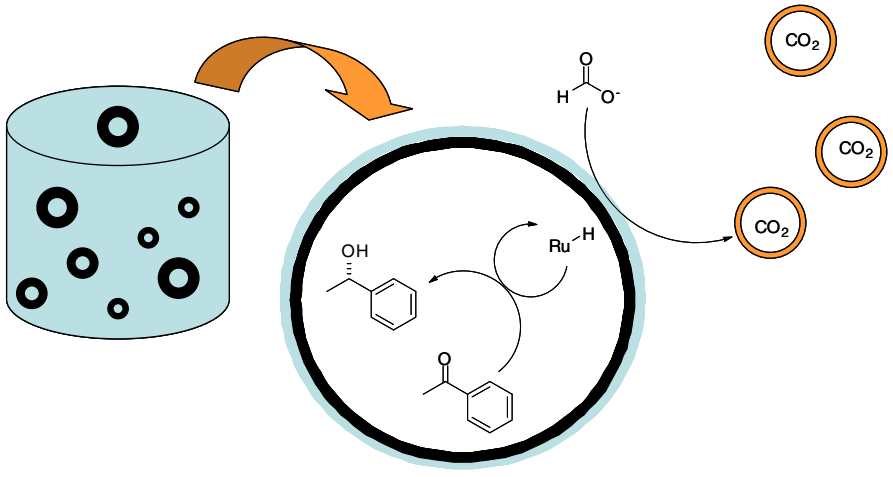
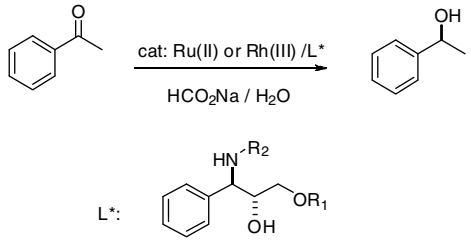


Figure 1. Cartoon representation of the use of hydrophobic catalysts in aqueous medium.



Scheme 2. ATH reaction in water using ligands **1**–**6**.

Table 1. Transfer hydrogenation in 2-propanol using aminoalcohols **1**–**4**

Entry	Ligand	Time (h)	Conversion[a] (%)	ee[a] (%)
1	**1**	6	22	80 (*S*)
2	**2**	24	13	86 (*S*)
3	**3**	4	>99	82 (*S*)
4	**4**	6	51	90 (*S*)

Reaction conditions: $[RuCl(p\text{-cymene})]_2$ (0.004 mmol); ligand (0.016 mmol); 2-propanol (6.8 mL); KOH (0.029 mmol; 0.08 M in 2-propanol); acetophenone (0.4 mmol; 0.5 M in 2-propanol); temperature: 25 °C (see Section 4).

[a] Determined by GC, with a β-DEX 120 column.

because for Ru/aminoalcohol systems reaction rates are faster in basic media (HCOONa, initial pH 7.3; HCOOH–NEt_3–H_2O with $HCOOH/NEt_3 = 1/1.7$, initial pH 5.7).[11b] As a representative procedure, a suspension of the ruthenium precursor and the ligand was stirred in water for 2 h at room temperature. The solution became yellow in color although part of the precursor remained as a solid. Then, formate and acetophenone were directly added and the solution was vigorously stirred or shaken, ensuring a homogeneous emulsion with no phase separation during the whole process. The solution was stirred for 12 or 24 h at room temperature, while the progress of the reaction was followed by GC.

To find the best conditions for the aqueous ATH, we initially studied the reaction performed with the catalytic system containing ligand **1** (Table 2). At 25 °C, conversions of 35% and 60% after 12 h and 24 h, respectively, were recorded. This shows that although less active in water, the catalyst Ru/**1** is stable for hours in this medium. Interestingly, the enantioselectivity was maintained as high as in the reaction performed in 2-propanol (82% ee versus 80% ee). 1-Phenylethanol with the same absolute configuration (*S*) was obtained in water and in isopropanol.

When the temperature was increased to 40 °C, which is the temperature at which other reported systems have been tested,[11b] a decrease in conversion was observed, albeit the ee kept constant, probably indicating a decomposition of the catalyst. The use of $[RhClCp^*]_2$[14] as the catalyst precursor led to a more active catalyst, as reported for diamine-containing systems,[6a] but the enantioselectivity was only moderate (entry 4, 53% ee). An increase in temperature up to 40 °C with the Rh/**1** system led to an important increase in reaction rate but enantioselectivity deteriorated slightly.

Table 2. Aqueous asymmetric transfer hydrogenation using chiral aminoalcohols **1**–**6**

Entry	Ligand	Temp (°C)	Time (h)	Conv.[a] (%)	ee[a] (%)
1	**1**	25	12	35	81 (*S*)
2[b]	**1**	25	12	41	79 (*S*)
3	**1**	25	24	60	82 (*S*)
4	**1**	40	24	47	81 (*S*)
5[c]	**1**	25	12	58	53 (*S*)
6[c]	**1**	40	12	94	48 (*S*)
7[d]	**1**	25	24	14	67 (*S*)
8[e]	**1**	25	24	13	84 (*S*)
9	**2**	25	24	25	83 (*S*)
10	**3**	25	24	52	70 (*S*)
11[b,f]	**3**	25	24	60	60 (*S*)
12[b]	**3**	25	24	72	60 (*S*)
13	**4**	25	24	60	68 (*S*)
14[g]	**4**	25	24	33	61 (*S*)
15	**5**	25	24	49	67 (*S*)
16	**6**	25	24	52	68 (*S*)

Reaction conditions: $[RuCl_2(p\text{-cymene})_2]_2$ (0.0125 mmol); ligand (0.05 mmol); water (2 mL); NaHCOO (6.25 mmol); acetophenone (1.25 mmol); acetophenone/Ru: 50.

[a] Determined by GC with a β-DEX 120 column at 120 °C isotherm.

[b] Shaker.

[c] $[RhCl_2Cp^*]_2$ used as the catalyst precursor.

[d] CTAB added as cationic surfactant (1.25 mmol, 100%).

[e] SDS added as anionic surfactant (1.25 mmol, 100%).

[f] DiMePEG added as neutral surfactant (0.125 mmol, 10%).

[g] SDS added as anionic surfactant (0.025 mmol, 2%).

According to this result, the rest of the experiments in this study were performed using as optimized conditions: 25 °C, $[RuCl_2(p\text{-cymene})]_2$ as the ruthenium source and sodium formate as hydrogen donor in neat water as the only solvent.

Amino alcohols **2**–**6** showed moderate activities (up to 60% of conversion) after 24 h (entries 9–13 in Table 2) working at a 1/50 Ru/substrate ratio, thus suggesting possible mass transfer limitations at the organic-aqueous interphase. Anionic, cationic, and neutral surfactants as SDS, CTAB, and DiMePEG, respectively, were added to increase the miscibility of reactants in the water phase and/or interphase (entries 7 and 8) and, hence, to improve the catalytic behavior of the system.[15] Surprisingly, a negative effect in conversion was observed with both the ionic surfactants. This could be due to the existence of interactions between the surfactant molecules and the ruthenium species at the droplet surface, with the consequence of the catalytic sites being partially blocked. The enantioselectivity did not change when using SDS, indicating that the catalytically active species is the same. With CTAB, in turn, a slight decrease in enantioselectivity is observed. Effect of the neutral agent DiMePEG was limited to a small decrease of catalytic activity.

Additionally, electronic effects on the ligand backbone were analyzed by placing electron-withdrawing groups (fluoride and trifluoromethyl) in the *para*-position of the aromatic ring in the R^2 substituent in the structure of ligand **3** (ligands **5** and **6**). This had no effect on the catalytic activity or the enantioselectivity (entries 10 vs 15 and 16 in Table 2).

3. Conclusion

In summary, a series of new modular aminoalcohols **1**–**6** have been prepared in good yields from enantiopure phenylglycidol and used as ligands in the ruthenium-catalyzed ATH both in water and in 2-propanol as reacting media. The tunable structure of **1**–**6** allows for a programmed variation of their hydrophobic nature. Results on ATH show that, for some of the ligands studied, reaction in aqueous media is faster than in isopropanol. In isopropanol, acetophenone is reduced with enantioselectivities up to 90%. Quite significantly, the catalytic behaviors of these systems in water and in isopropanol follow different trends regarding the structure of the chiral ligand (bulkiness of the R^1 substituent) which has different effects in isopropanol versus water: while bulky R^1 substituents dramatically accelerate reductions in isopropyl alcohol, an opposite effect is observed in water. This fact suggests that bulky groups prevent proper access of the substrate to the metallic specie at the substrate/water interphase. The enantioselectivity recorded under aqueous conditions in the ATH of acetophenone reaches 83%, only slightly below than in isopropanol. This result opens the possibility of using hydrophobic systems in catalytic reactions performed in water as the only solvent.

4. Experimental

4.1. Ligand 1: (1*R*,2*R*)-1-(Benzylamino)-3-methoxy-1-phenylpropan-2-ol

A mixture of (2*S*,3*S*)-2-(methoxymethyl)-3-phenyloxiran (250 mg, 1.52 mmol), lithium perchlorate (2.4 g, 22.8 mmol) and benzylamine (1.6 mL, 15.2 mmol) in 4 mL of acetonitrile was reacted under nitrogen at 80 °C overnight. After that time, reaction was analyzed by TLC and determined to be complete. Work-up included the addition of water (10 mL) and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were dried and concentrated under reduced pressure. The residual oil was purified by flash chromatography on deactivated silica (2.5% Et_3N v/v) eluting with hexane-ethyl acetate 80:20 to afford the desired aminoalcohol (340.6 mg, 83%), $[\alpha]_D^{24} = -466.3$ (*c* 1.03, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.40–7.28 (m, 10H, CH_{arom}), 3.98–3.94 (m, 1H, C*H*–NH), 3.91 (d, $J = 4.9$ Hz, 1H, C*H*–OH), 3.87 (br, 2H, CH_2–NH), 3.76 (d, $J = 13.2$ Hz, 1H, CH_2–OMe), 3.57 (d, $J = 13.2$ Hz, 1H, CH_2–OMe), 3.29 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 128.8–127.2 (CH_{arom}), 73.9 (CH_2–OMe), 72.6 (CH–OH), 64.6 (CH–NH), 59.2 (CH_3), 51.5 (CH_2–NH). ESI +ve for $C_{17}H_{22}NO_2$ [M+H] 272.1651; found 272.1656.

4.2. Ligand 2: (1*R*,2*R*)-1-(Biphenyl-4-ylmethylamino)-3-methoxy-1-phenylpropan-2-ol

See ligand **1** for synthesis. Yield: 23%, $[\alpha]_D^{24} = -4.1$ (*c* 0.96, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 7.92–7.42 (m, 14H, CH_{arom}), 4.22 (d, $J = 13$ Hz, 1H, CH_2–NH), 4.06 (d, $J = 13$ Hz, 1H, CH_2–NH), 4.04 (d, $J = 5.0$ Hz, 1H, C*H*–NH), 4.01–3.98 (m, 1H, C*H*–OH), 3.32 (br dd, 1H, CH_2–OMe), 3.29 (br dd, 1H, CH_2–OMe), 3.29 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.8 (C), 135.9 (C), 134.0 (C), 132.1 (C), 128.8–124.0 (CH_{arom}), 73.8 (CH_2–OMe), 72.7 (CH–OH), 65.2 (CH–NH), 59.1 (CH_3), 49.5 (CH_2–NH). ESI +ve for $C_{23}H_{26}NO_2$ [M+H] 348.1964; found 348.1978.

4.3. Ligand 3: (1*R*,2*R*)-1-(Benzylamino)-1-phenyl-3-(trityloxy)propan-2-ol

See ligand **1** for synthesis. Yield: 87%, $[\alpha]_D^{23} = -193.7$ (*c* 0.99, $CHCl_3$); ^1H NMR; (400 MHz, $CDCl_3$) 7.45–7.15 (m, 25H, CH_{arom}), 4.03 (d, $J = 5.3$ Hz, 1H, C*H*–NH), 3.95-3.89 (m, 1H, C*H*–OH), 3.76 (d, $J = 12.9$ Hz, 1H, CH_2–NH), 3.58 (d, $J = 12.9$ Hz, 1H, CH_2–NH), 3.19 (dd, $J = 9.7$ Hz, $J = 4.4$ Hz, 1H, CH_2–OCPh$_3$), 2.96 (dd, $J = 9.7$ Hz, $J = 4.4$ Hz, 1H, CH_2–OCPh$_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.9 (C), 139.9 (C), 139.1 (C), 128.7–127.1 (CH_{arom}), 87.1 (C), 72.7 (CH–OH), 65.2 (CH–NH), 64.6 (CH_2–OCPh$_3$), 51.6 (CH_2–NH). ESI +ve for $C_{35}H_{34}NO_2$ [M+H] 500.2590; found 500.2576.

4.4. Ligand 4: (1*R*,2*R*)-1-(Biphenyl-4-ylmethylamino)-1-phenyl-3-(trityloxy)propan-2-ol

See ligand **1** for synthesis. Yield: 83%, $[\alpha]_D^{22} = +34.9$ (*c* 1.09, $CHCl_3$); ^1H NMR; (400 MHz, $CDCl_3$) δ 7.96–7.14 (m, 29H, CH_{arom}), 4.01 (d, $J = 5.3$ Hz, 1H, C*H*–NH), 3.91–3.87 (m, 1H, C*H*–OH), 3.75 (d, $J = 12.9$ Hz, 1H, CH_2–NH), 3.58 (d, $J = 12.9$ Hz, 1H, CH_2–NH), 3.19 (dd, $J = 9.9$ Hz, $J = 4.1$ Hz, 1H, CH_2–OCPh$_3$), 2.95 (dd, $J = 9.9$ Hz, $J = 4.1$ Hz, 1H, CH_2–OCPh$_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.9 (C), 141.2 (C), 140.1 (C), 139.4 (C), 128.9–127.1 (CH_{arom}), 87.1 (C), 73.0 (CH–OH), 65.5 (CH–NH), 64.8 (CH_2–OCPh$_3$), 51.3 (CH_2–NH). ESI +ve for $C_{41}H_{38}NO_2$ [M+H] 576.2903; found 576.2910.

4.5. Ligand 5: (1*R*,2*R*)-1-(4-Fluorobenzylamino)-1-phenyl-3-(trityloxy)propan-2-ol

See ligand **1** for synthesis. Yield: 82%. $[\alpha]_D^{23} = -221.7$ (*c* 0.99, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.39–6.97 (m, 24 H, CH_{arom}), 3.95 (d, $J = 5.3$ Hz, 1H, C*H*–NH), 3.88–3.84 (m, 1H, C*H*–OH), 3.68 (d, $J = 13.2$ Hz, 1H, CH_2–NH), 3.50 (d, $J = 13.2$ Hz, 1H, CH_2–NH), 3.18 (dd, $J = 9.7$ Hz, $J = 4.4$ Hz, 1H, CH_2–OCPh$_3$), 2.94 (dd, $J = 9.8$ Hz, $J = 4.2$ Hz, 1H, CH_2–OCPh$_3$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.8 (C), 139.2 (C), 136.0 (C), 129.9–115.2 (CH_{arom}), 72.8 (CH–OH), 65.2 (CH–NH), 64.4 (CH_2–OCPh$_3$), 50.9 (CH_2–NH). ESI +ve for $C_{35}H_{33}NO_2F$ [M+H] 518.2495; found 518.2484.

4.6. Ligand 6: (1*R*,2*R*)-1-Phenyl-1-(4-(trifluoromethyl)-benzylamino)-3-(trityloxy)propan-2-ol

See ligand **1** for synthesis. Yield: 80%, $[\alpha]_D^{23} = -193.7$ (*c* 0.99, $CHCl_3$); ^1H NMR; (400 MHz, $CDCl_3$): δ 7.62–7.10 (m, 24H, CH_{arom}), 3.94 (d, $J = 5.0$ Hz, 1H, C*H*–NH), 3.88–3.84 (m, 1H, C*H*–OH), 3.75 (d, $J = 13.5$ Hz, 1H, CH_2–NH), 3.56 (d, $J = 13.5$ Hz, 1H, CH_2–NH), 3.20 (dd, $J = 9.8$ Hz, $J = 4.5$ Hz, 1H, CH_2–OCPh$_3$), 2.96 (dd,

$J = 9.9$ Hz, $J = 4.4$ Hz, 1H, CH_2–$OCPh_3$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.9 (C), 128.7–125.5 (CH_{arom}), 73.1 (CH–OH), 65.6 (CH–NH), 64.8 (CH_2–$OCPh_3$), 51.4 (CH_2–NH). ESI +ve for $C_{36}H_{33}NO_2F_3$ [M+H] 568.2463; found 568.2455.

4.7. Asymmetric transfer hydrogenation in 2-propanol

The reactions in Table 1 were performed under argon. $[RuCl_2(p\text{-cymene})]_2$ (0.004 mmol) and the aminoalcohol (0.016 mmol) were placed in 2-propanol (6.84 mL) at 80 °C and reacted for 30 min giving a yellow solution. Then the mixture is allowed to reach 25 °C and a solution of KOH (0.029 mmol; 0.08 M in 2-propanol) and of acetophenone (0.4 mmol; 0.5 M in 2-propanol) were added. The reaction proceeded for the reported times at room temperature. After reaction time, the reaction mixture was passed through a silica plug to eliminate metal traces and analyzed by GC with a β-DEX 120 column.

4.8. Aqueous asymmetric transfer hydrogenation

The metal precursor (0.0125 mmol) and the aminoalcohol (0.05 mmol) were placed in 2 mL of distilled water and stirred for 2 h at the corresponding temperature. Then sodium formate (6.25 mmol) and acetophenone (1.25 mmol) were added and the reaction was vigorously stirred (see Table 2 for times and type of agitation). After a suitable reaction time, diethyl ether was added and the organic phase was extracted (3 × 5 mL). The combined organic phases were dried with $MgSO_4$ and passed through a short silica plug to eliminate metal traces. The sample was analyzed by GC with a β-DEX 120 column.

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