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Asymmetric Reduction of Electron-Rich Ketones with Tethered Ru(II)/TsDPEN Catalysts Using Formic Acid/Triethylamine or Aqueous Sodium Formate

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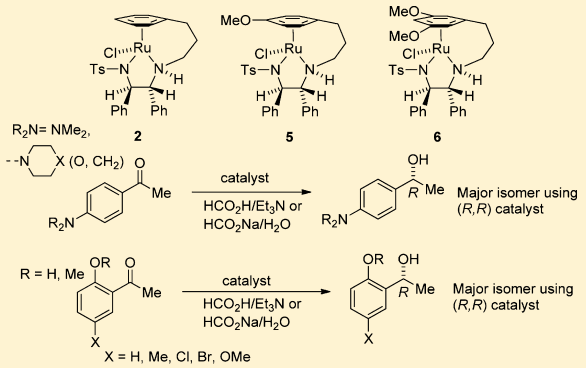
Supporting Information

ABSTRACT: The asymmetric transfer hydrogenation (ATH) of ketones under aqueous conditions using tethered Ru(II)/η^6-arene/diamine catalysts is described, as is the ATH of electron-rich substrates containing amine and methoxy groups on the aromatic rings. Although such substrates are traditionally challenging ones for ATH, the tethered catalysts work very efficiently. In the case of amino-substituted ketones, aqueous conditions give excellent results; however, for methoxy-substituted substrates, the more established formic acid/triethylamine system gives superior results.



INTRODUCTION

The use of Ru(II) catalysts containing a combination of an η^6-arene ring and a monosulfonated 1,2-diamine ligand, i.e., **1** (Figure 1), for the asymmetric reduction of ketones to alcohols has become widely adopted in recent years.[1−3] This class of catalyst is active in both asymmetric hydrogenation (AH),[2] where hydrogen gas is used as the reducing agent, and asymmetric transfer hydrogenation (ATH),[3−12] where isopropanol,[3] formic acid,[3] or sodium formate[4−12] is typically used as the reducing agent. In our own studies, we recently introduced a series of "tethered" Ru(II) complexes (Figure 1), typified by complex **2**, which additionally contain a covalent linkage between the diamine component and the arene ring.[13] This increases the stability of the complexes and their activity in reduction reactions, and in some cases, their use may be advantageous. Since our initial reports on tethered complexes, related complexes, including **3** and **4**, have been reported by other researchers.[14] Most recently, we have described the synthesis of methoxy-substituted complexes **5** and **6** (Figure 1) through an arene-displacement strategy.[13a]

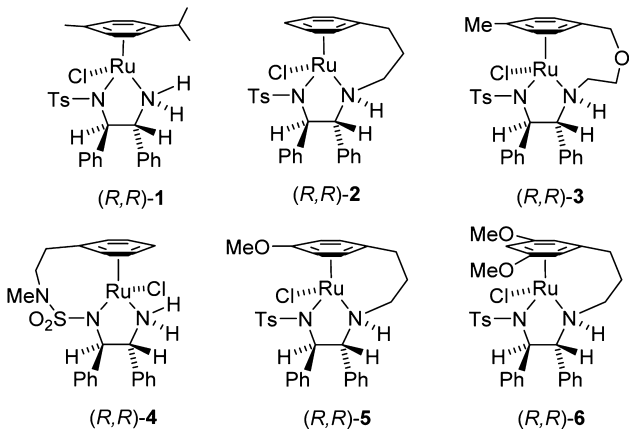


Figure 1. Arene/Ru(II)/TsDPEN catalysts used in asymmetric transfer hydrogenation (ATH). The stereochemical description refers to the configurations of the carbon atoms of the ligands. Although one enantiomer of catalyst is illustrated, both enantiomers of each have been prepared and tested.

Alongside the development of catalysts such as **1** for reductions in the formic acid/triethylamine system, several researchers have reported their use under aqueous conditions, using sodium formate or a similar salt as the reducing agent, and for the reduction of C═N as well as C═O bonds.[4−12] This modification affords a number of potential advantages, most notably the opportunity to use a more environmentally compatible solvent, as well as the potential to extract the product using an organic solvent and thus reuse the catalyst. In many cases, a neutral Ru(II) catalyst, e.g., **1**, or the Rh(III) or Ir(III) equivalent can be successfully employed,[4] although it is likely that a cationic intermediate species may be formed in situ due to replacement of Cl with a molecule of water; the use of the cationic aqua derivatives of **1**[4d,g] has been demonstrated. The control of the pH of the reaction has been found to be important for optimal results,[4] and the pivotal role of hydrogen bonding by the solvent during the reduction has been studied by molecular modeling.[4k] In some cases the sulphonamide

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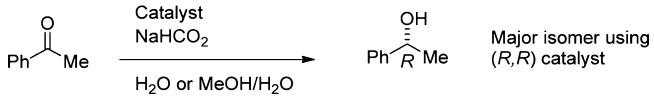
Table 1. ATH of Acetophenone Using 2, 5, and 6 in H_2O and H_2O/MeOH[a]



entry	catalyst	S/C	solvent	T/°C	t/h	conv/%	ee/%
1	(*S*,*S*)-**2**	100	H_2O	40	24	>99	97 (*S*)
2	(*R*,*R*)-**5**	100	H_2O	40	5	97	98 (*R*)
3	(*S*,*S*)-**2**	100	H_2O	60	1	99	88 (*R*)
4	(*R*,*R*)-**5**	100	H_2O	60	2	>99	97 (*R*)
5	(*R*,*R*)-**6**	100	H_2O	60	2	>99	77 (*R*)
6	(*R*,*R*)-**6**	500	H_2O	60	5	99	81 (*R*)
7	(*S*,*S*)-**2**	100	H_2O/MeOH[b]	60	1	>99	96 (*S*)
8	(*R*,*R*)-**5**	100	H_2O/MeOH[b]	60	0.5	96	98 (*R*)
9	(*R*,*R*)-**5**	500	H_2O/MeOH[b]	60	6	99	97 (*R*)
10	(*R*,*R*)-**6**	500	H_2O/MeOH[b]	60	3	99	85 (*R*)
11	(*R*,*R*)-**6**	500	H_2O/MeOH[c]	60	2	99	86 (*R*)
12	(*R*,*R*)-**5**	100	HCO_2NH_4/H_2O	60	22.5	56	98 (*R*)
13	(*R*,*R*)-**5**	100	SDS/H_2O	60	22.5	57	97 (*R*)
14 (run 1)	(*R*,*R*)-**5**[d]	100	H_2O	60	1	99	97 (*R*)
15 (run 2)	(*R*,*R*)-**5**[d]	100	H_2O	60	1	99	97 (*R*)
16 (run 3)	(*R*,*R*)-**5**[d]	100	H_2O	60	1.5	99	97 (*R*)
17 (run 4)	(*R*,*R*)-**5**[d]	100	H_2O	60	6.5	97	96 (*R*)

[a]H_2O/MeOH or H_2O refers to reduction using HCO_2Na (5 equiv), [b]1:1 water/MeOH. [c]1:0.5 water/MeOH. [d]*n*-Pentane (3 × 2 mL) was used to extract product after each cycle from the reaction mixture. One mole of HCO_2H was added to regenerate HCO_2Na.

diamine component may be modified, for example, by introduction of hydrophobic groups or fluorine-containing groups.[4f,t] Analogous reduction of aldehydes may be catalyzed by racemic versions of the catalysts.[4w,x] In several examples, the catalyst has been modified by the introduction of cationic[5] or anionic[6] groups, which improves their solubility in water and hence facilitates isolation of the reduction product through extraction with a nonpolar solvent such as hexane, while the catalyst remains in the aqueous phase and can be reused. Another strategy used to improve water solubility (and hence facilitate recyclability) of the catalysts involves their conversion to a derivative containing a poly(ethylene glycol) (PEG) chain, which can be attached to a number of positions on the catalyst structure.[7] Using this method, even substrates that are normally susceptible to side reactions (e.g., α-bromo ketones) can be reduced efficiently.[7b] Another widely studied strategy is to include either a surfactant (to form an emulsion) or a phase-transfer catalyst to facilitate the reaction,[8−10] which is otherwise biphasic. In several cases, addition of a surfactant is reported to give improved results, although this appears to be somewhat catalyst-dependent, since it is not always required. Reductions in water, of ketones and imines, has also been achieved using catalysts supported on polystyrene, silica, proteins, or other media.[11,12] The use of a support containing an iron salt permits separation of the catalyst from the bulk reaction using a magnet.[12]

RESULTS AND DISCUSSION

Although the use of complex **1** in water has been extensively described,[4−12] the same use of the tethered derivatives has not been reported to date. In this article, we describe the results of our studies on the applications of tethered Ru(II) catalysts to the ATH of ketones under aqueous conditions, which can, in some cases, be advantageous for the reductions of certain classes of substrates. Initially, we investigated the reduction of acetophenone using tethered catalysts **2**, **5**, and **6** containing three-carbon linkers because these have proven to be highly versatile (Table 1).[13] Although almost complete reduction was achieved at 40 °C using **2** and **5**, the reaction was slow (entries 1 and 2); however, raising the temperature to 60 °C gave full reduction within 1 to 2 h. While there was only marginal loss of enantioselectivity using **5** (entries 2 and 4), complex **2** appeared to be more sensitive to the temperature change (entries 1 and 3). Complex **6** containing two methoxy groups was tested, and this also gave almost complete reduction even at S/C up to 500, although with a lower ee, as had been previously observed (entries 5 and 6).[13a]

Improved results were obtained using a 1:1 mixture of methanol and water,[11j,l] which improves catalyst solubility (entries 8−11). In this case, essentially complete reduction of acetophenone was achieved at 60 °C after 1 h or less at S/C 100 using each of the catalysts, with enantioselectivities matching those obtained at the lower temperatures in each case. The reaction using **5** at S/C 500 required 6 h for complete reduction and was followed over time (entry 9; see Supporting Information). Again, catalyst **6** exhibited high activity, possibly due to improved aqueous solubility (entries 10, 11), but moderate enantioselectivity. When using ammonium formate in place of sodium formate under purely aqueous conditions, the reaction was also incomplete, although a product of high ee was obtained (entry 12). The addition of sodium dodecyl sulfate (SDS) did not lead to an improved result, and incomplete conversion was observed after 22.5 h (entry 13). Following literature precedents on catalyst recycling in aqueous systems,[4−12] the formation of the product of the reduction in water was monitored, and this was then isolated after the completion of the reduction by extraction with a nonpolar organic solvent such as pentane or hexane. Addition of formic acid and fresh substrate to the remaining aqueous phase facilitated further reduction cycles (entries 14−17 for *n*-pentane; other examples are in the Supporting Information).

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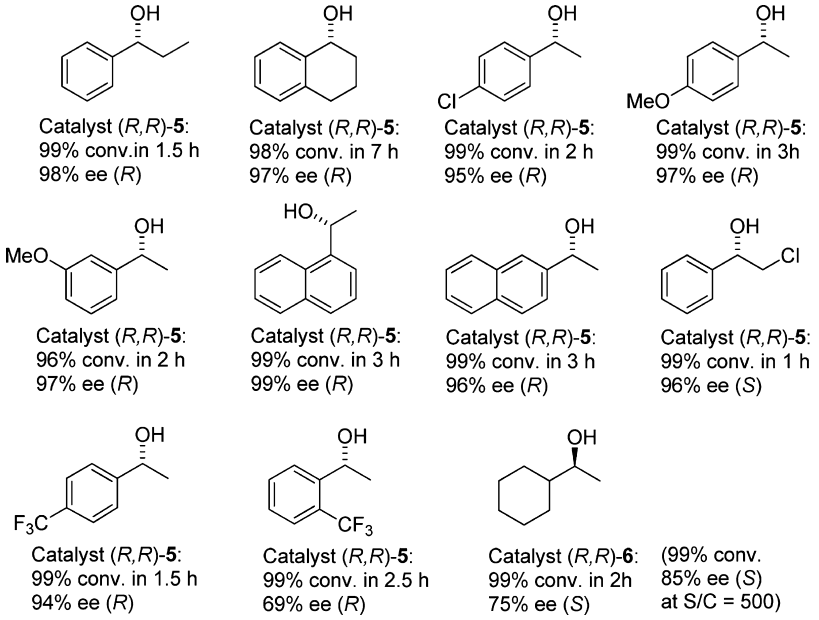
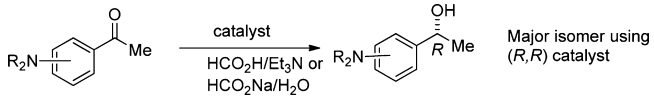


Figure 2. ATH of ketones using complexes (*R*,*R*)-**5** and (*R*,*R*)-**6** in water; S/C = 100, 60 °C, 5.0 equiv HCO_2Na.

Table 2. ATH of Amino Acetophenone Using 2 and 5[b]



entry	NR_2	catalyst	S/C	solvent[c]	*T*/rt or °C	*t*/h	conv (yield)/%[d]	ee/%
1	pNH_2	(*S*,*S*)-**2**	100	H_2O/MeOH	40	7.5	80 (72)	92 (*S*)
2	pNH_2	(*S*,*S*)-**2**	100	H_2O/MeOH	60	4.5	99 (79)	94 (*S*)
3	pNH_2	(*R*,*R*)-**5**	100	H_2O/MeOH	60	4.5	99 (75)	94 (*R*)
4	pNH_2	(*R*,*R*)-**1**	100	H_2O/MeOH	60	15.5	78 (ND[a])	91 (*R*)
5	pNH_2	(*R*,*R*)-**5**	100	FA/TEA	60	24	ND	[e]
6	pNH_2	(*S*,*S*)-**2**	100	*i*-PrOH	rt	144	50 (ND)	ND
7	$pNMe_2$	(*S*,*S*)-**2**	100	H_2O	28	3	76 (41)	88 (*S*)
8	$pNMe_2$	(*S*,*S*)-**2**	100	H_2O/MeOH	40	5	99 (76)	92 (*S*)
9	$pNMe_2$	(*R*,*R*)-**5**	100	H_2O/MeOH	60	4	97 (78)	91 (*R*)
10	$pNMe_2$	(*S*,*S*)-**2**	250	FA/TEA	45	6	93 (68)	91 (*S*)
11	$pNMe_2$	(*R*,*R*)-**2**	100	FA/TEA	40	45	95 (60)	93 (*R*)
12	$pNMe_2$	(*R*,*R*)-**2**	100	*i*-PrOH	28	26	35 (17)	ND
13	$N(CH_2)_4$	(*R*,*R*)-**2**	100	FA/TEA	40	72	100 (81)	87 (*R*)
14	$N(CH_2)_4$	(*R*,*R*)-**2**	100	H_2O/MeOH	40	69	98 (78)	89 (*R*)
15	$N(CH_2)_4$	(*S*,*S*)-**2**	100	H_2O/MeOH	40	70	98 (72)	89 (*S*)
16	$N(CH_2)_5$	(*R*,*R*)-**2**	100	FA/TEA	40	69	99 (68)	94 (*R*)
17	$N(CH_2)_5$	(*S*,*S*)-**2**	100	H_2O/MeOH	40	24	99 (84)	95 (*S*)
18	$N(CH_2)_2O(CH_2)_2$[f]	(*R*,*R*)-**2**	100	FA/TEA	40	23	99 (74)	94 (*R*)
19	$N(CH_2)_2O(CH_2)_2$[f]	(*S*,*S*)-**2**	100	H_2O/MeOH	40	45	100 (88)	91 (*S*)

[a]ND, not determined. [b]H_2O/MeOH or H_2O refers to reduction using HCO_2Na (5 equiv), FA/TEA refers to a 5:2 HCO_2H/Et_3N mixture. [c]1:1 H_2O/MeOH throughout. [d]Isolated yield given in parentheses. [e]Polymerization observed. [f]Morpholine.

In each case, however, the conversion took longer for each repeated run, reflecting the deactivation of the catalyst.

A series of ketones was reduced using the methoxy-substituted tethered complexes **5** and **6** under aqueous conditions in order to demonstrate further applications of these catalysts (Figure 2). The conversions were almost complete in most cases, and the ee's reflected those obtained in ATH reactions in formic acid/triethylamine.[13,14] In the majority of cases, the ee's of the products exceeded 95% and in some cases were as high as 99%. Good results were observed for some substrates with functionality at the *ortho* position (tetralone, 1-acetylnaphthylene), which are also known to be reduced by **5** in high ee using the more established FA/TEA system.[13a] In contrast, the reduction of *ortho*-trifluoromethyl acetophenone gave a product in modest ee (69%), unlike that with the *para* equivalent, which was reduced in 94% ee. In most cases, the reactions were monitored over time, and this revealed little change to the ee as the reaction progressed (see

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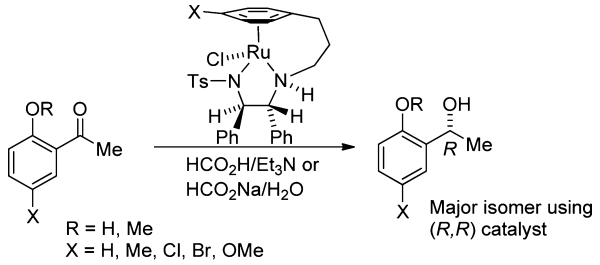
Table 3. Reductions of *ortho*-Hydroxy- and -Methoxy-Substituted Ketones Using Complexes 2 and 5[a]



entry	OR	X	catalyst	S/C	solvent	T/°C	t/h	conv (yield)/%[b]	ee/%
1	OH	Me	(*S*,*S*)-**2**	200	FA/TEA	40	5.5	99 (72)	94 (*S*)
2	OH	Me	(*R*,*R*)-**5**	200	FA/TEA	40	23	100 (100)	95 (*R*)
3	OH	Cl	(*S*,*S*)-**2**	200	FA/TEA	40	4.75	99 (72)	90 (*S*)
4	OH	Cl	(*R*,*R*)-**5**	200	FA/TEA	40	23	97 (94)	93 (*R*)
5	OH	Br	(*S*,*S*)-**2**	200	FA/TEA	40	4	>99 (65)	91 (*S*)
6	OH	Br	(*R*,*R*)-**5**	200	FA/TEA	40	5.5	98 (42)	94 (*R*)
7	OH	OMe	(*S*,*S*)-**2**	200	FA/TEA	40	5.5	92 (24)	93 (*S*)
8	OH	OMe	(*R*,*R*)-**5**	200	FA/TEA	40	6.5	91 (84)	93 (*R*)
9	OMe	H	(*S*,*S*)-**2**	200	FA/TEA	40	3.75	>95 (64)	68 (*S*)
10	OMe	H	(*S*,*S*)-**2**	200	H_2O	60	4	89	55 (*S*)
11	OMe	H	(*S*,*S*)-**2**	100	H_2O	60	5	98	58 (*S*)
12	OMe	H	(*R*,*R*)-**5**	200	FA/TEA	40	3.75	>98 (70)	96 (*R*)
13	OMe	H	(*R*,*R*)-**5**	100	H_2O	60	2	99	95 (*R*)
14	OMe	H	(*R*,*R*)-**5**	200	H_2O	60	3.5	92	96 (*R*)
15	OMe	OMe	(*S*,*S*)-**2**	200	FA/TEA	40	3.75	>99 (80)	69 (*S*)
16	OMe	OMe	(*R*,*R*)-**5**	200	FA/TEA	40	3.75	>99 (87)	90 (*R*)

[a]H_2O/MeOH or H_2O refers to reduction using HCO_2Na (5 equiv); FA/TEA refers to a 5:2 HCO_2H/Et_3N mixture, [b]Isolated yield, where determined, is given in parentheses.

Supporting Information). In the majority of cases, complex **5** was employed since this is known to give improved results over those obtained with the dimethoxy complex **6**. However, catalyst **6** was used for the reduction of acetyl cyclohexane since it is known to be more suited to alkyl/alkyl ketones for reasons that have been previously described.[13]

An advantage of the tethered catalysts relative to untethered ones is that a higher level of activity and stability is often observed.[13] Electron-rich substrates, for example, those containing amine-functionalized aromatic rings adjacent to the ketone, are regarded as challenging[15,16] and have proven to be difficult to reduce under formic acid/triethylamine conditions, primarily due to their low reactivity (see the Supporting Information for an experimental comparison of reduction rates) but also due to the possibility of a competing polymerization due to the reaction between the ketone and amine and subsequent reduction of an imine/iminium intermediate. Indeed, there is currently no report of the application of catalysts such as **1** to the asymmetric reduction of such substrates. Having demonstrated that the more reactive tethered catalyst was compatible with water as a solvent, we investigated the reductions of (aminoaryl)ketones under the same conditions. In this event, reduction under purely aqueous conditions proved to be difficult to reproduce reliably, possibly due to low substrate solubility. However, the use of a water/methanol combination (1:1) provided a means to achieve complete and asymmetric reduction of *para*-amino acetophenone, for the first time under ATH conditions, in essentially full conversion using 1 mol % of catalyst **2** or **5** (ca. 99% by GC) and a high ee of 94%, even at 60 °C, which was required for full conversion (Table 2, entries 1−3). In these tests, both **2** and **5** gave comparable results and were more active than the untethered complex (entry 4). As expected, attempted reduction in FA/TEA gave no significant reduction (entry 5), and the formation of a gum-like precipitate suggested some degree of polymerization. Attempted reduction in *i*-PrOH proved to be very sluggish (entry 6). In contrast, the tertiary amines, 4-dimethylaminoacetophenone, could be reduced efficiently under both aqueous and FA/TEA conditions, although *i*-PrOH was not effective (entries 7−12). A combination of water and methanol gave an improved result over that with pure water, however. Likewise, a series of *para*-substituted tertiary amine derivatives could be cleanly reduced in good conversion and ee (entries 13−19). Presumably, with these substrates, there is no possibility of a competing polymerization and hence side product formation is minimized. As far as we are aware, these are the first examples of asymmetric reduction by ATH of such highly electron-rich ketone substrates.

In addition, an extended investigation into asymmetric reductions of relatively unreactive electron-rich ketones containing *ortho*-hydroxy and -methoxy acetophenones under fully aqueous conditions was carried out (Table 3).[17] While we have reported that both **2** and **5** are excellent catalysts for the reduction of *ortho*-hydroxy acetophenone with FA/TEA (ee's commonly >99%),[13] *ortho*-methoxy ketones are reduced in higher ee using **5** than they are using **2**.[13a] In this event, all *ortho*-hydroxy acetophenones tested for reduction gave comparable and high ee's using both catalysts **2** and **5** in FA/TEA. 2′,5′-Dimethoxyacetophenone was reduced in higher ee using **5**, however. In the majority of cases, reduction of *ortho*-hydroxy or -methoxy acetophenones under aqueous conditions with either catalyst generally gave products in either lower conversions or ee compared to those with FA/TEA. For

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example, with 2-hydroxy-5-methylacetophenone, the best conversion under aqueous conditions was just 80% in 6 h at 60 °C, giving a product with an ee of 87% (*R*) using catalyst (*R*,*R*)-**5**. For 2-hydroxy-5-chloroacetophenone, the best ee was 63% (with (*R*,*R*)-**5**), and for 2-hydroxy-5-methoxyacetophenone, it was 61% (with (*R*,*R*)-**5**). For 2,5-dimethoxyacetophenone, the product ee's were essentially the same as those in FA/TEA, but the conversions were lower: 47−52% ee at ca. 9 h at 60 °C using either catalyst **2** or **5**. An exception was *ortho*-methoxy acetophenone itself (entries 10, 11, 13, and 14), which mirrored the FA/TEA results. Hence, this particular class of electron-rich substrate appears to be, in general, more compatible with reduction under FA/TEA conditions rather than aqueous. This may be due to solubility differences between the substrates.

In conclusion, Ru(II)/η^6-arene/diamine catalysts containing a tethering group have been demonstrated to be effective in the asymmetric reduction of ketones in water and water/methanol mixtures. Amino-substituted ketones, known for their low reactivity, have, for the first time, been reduced by ATH in high conversion and enantioselectivity under aqueous conditions and in the FA/TEA system. The reduction of hydroxyl- and methoxy-substituted ketones, in contrast, is less amenable to aqueous conditions and gives better results in FA/TEA. In certain situations, reductions in aqueous media may offer advantages over the more established FA/TEA conditions, and in these situations, the tethered catalysts are generally active and enantioselective.

EXPERIMENTAL SECTION

General Experimental. All reagents and solvents were used as purchased without further purification. All reactions were carried out under a nitrogen atmosphere, unless otherwise stated, and at the temperature specified in experimental procedures. Temperatures higher than room temperature (28 °C) were controlled using thermostatically controlled oil baths. NMR spectra were recorded on a 300 or 400 MHz instrument. Mass spectra were recorded on an ESI-quad instrument. High-resolution mass spectra were recorded on an ESI Q-TOF. IR spectra were recorded by FT-IR. Melting points were recorded using a melting point apparatus. Chiral HPLC measurements were made by HPLC linked to a PC with a chiral column (250 mm × 4.6 mm i.d.). Thin-layer chromatography was carried out on aluminum-backed silica gel 60 (F254) plates and visualized using 254 nm UV light or potassium permanganate solution.

^{1}H NMR chemical shifts are reported in ppm downfield from TMS at 0 ppm. ^{13}C chemical shifts are reported relative to $CDCl_3$ at 77 ppm. Coupling constants (*J*) are recorded in Hz. Multiplicity in ^{1}H NMR are reported as singlet (s), broad singlet (br s), doublet (d), triplet (t), quartet (q), and multiplet (m). Infrared peaks are reported in cm^{-1}. Specific rotations are reported in deg dm^{-1} cm^3 g^{-1}. In order to provide a racemic sample to be used as a standard in HPLC, each ketone was reduced racemically using sodium borohydride. Catalyst **2** is commercially available in either enantiomeric form. Catalysts **5** and **6** were prepared as previously reported.[13a]

Protocol A: Asymmetric Transfer Hydrogenation (ATH) in Water or Water/Methanol. Catalyst (0.01 mmol) was placed in a Schlenk tube under an inert atmosphere followed by HCO_2Na (0.340 g, 5.0 mmol) and H_2O (1 mL). The mixture was degassed three times, and to this was added solution ketone (1.0 mmol) followed by degassing two times. The mixture was stirred at 60 °C. For chiral GC analysis during the course of a reaction, a small sample from the reaction mixture was diluted with Et_2O and H_2O. The organic layer was separated and filtered through a short column of silica using hexane/EtOAc (1:1). The filtrate was analyzed by chiral GC. After completion of the reaction, the reaction mixture was diluted with H_2O and extracted with Et_2O (2 × 5 mL). The organic layers were combined, dried over anhyd. Na_2SO_4, filtered, and concentrated to give crude product, which was purified by flash column chromatography. For reactions in H_2O/MeOH, the same procedure was followed using the solvent ratio (usually 1:1) given in the table.

Protocol B: Recycling of Catalyst Using *n*-Hexane/Pet.Ether/*n*-Pentane. Catalyst (0.01 mmol) was placed in a Schlenk tube under an inert atmosphere followed by HCO_2Na (0.340 g, 5.0 mmol) and H_2O (1 mL). The mixture was degassed three times, and to this was added ketone (1.0 mmol) followed by degassing two times. The mixture was stirred at 60 °C. The reaction was monitored by chiral GC following the procedure described for the aqueous reaction. After completion of the reaction, the reaction mixture was cooled to room temperature and diluted with *n*-hexane, pet. ether, or *n*-pentane (2 mL). The organic layers were separated, and this process was repeated again two times with the same solvent (2 mL). During this process, the catalyst separated out as a brown solid. The mixture was degassed two times followed by addition of HCO_2H (1 mmol). To this mixture was added ketone (1 mmol), and the mixture was stirred at 60 °C. The second and later cycles of the reaction were followed by chiral GC analysis.

Protocol C: Asymmetric Transfer Hydrogenation in FA/TEA. To a mixture of catalyst (0.002 mmol) in FA/TEA (5:2) (1.0 mL) was added ketone (2.0 mmol), and the mixture was stirred at the stated temperature under an inert atmosphere. The reaction was monitored by TLC following the same procedure as that for the aqueous reaction and worked up when complete or at the stated time. The reaction mixture was diluted with EtOAc (10 mL) and sat. $NaHCO_3$ soln (10 mL). The organic layer was separated, washed with H_2O (2 × 10 mL), dried over anhyd. Na_2SO_4, filtered, and concentrated to give a brown residue. The crude compound was analyzed by ^{1}H NMR to give the conversion and purified by flash chromatography on silica gel, if required.

Protocol D: Synthesis of Amino Ketones.[15,18] Fluoroacetophenone (1.00 equiv) was combined with aqueous amine (3.68 equiv) in a sealed pressure tube and heated at 100 °C for 24 h. The resulting oil solidified upon cooling on ice and was filtered in vacuo while washing with water to give the ketone. The solid was recrystallized in hot heptane and allowed to crystallize on ice. The pure ketone was collected by vacuum filtration and dried under high vacuum.

Protocol E: Racemic Reduction of Ketone Using Sodium Borohydride. To a solution of ketone (1.00 equiv) in methanol (0.9 mL per mmol ketone) and water (0.1 mL per mmol ketone) was added sodium borohydride (2.00 equiv). The reaction mixture was stirred at rt for 3.5 h. After monitoring by thin-layer chromatography (1:1 petroleum ether/ethyl acetate), the solvent was evaporated in vacuo and water (5 mL) was added. The compound was extracted using ethyl acetate (3 × 5 mL), and the combined organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo to give the racemic alcohol.

Protocol F: Reduction of Ketone with Isopropanol. Ketone (1.00 equiv), KOH in isopropanol (0.002 mol dm^{-3} 0.02 equiv KOH, 10 mL/mol ketone), and (*R*,*R*)-Ru/TsDPEN **2** (0.01 equiv) and were combined in a Schlenk tube, degassed, and stirred under nitrogen at room temperature. The reaction was monitored by thin-layer chromatography (1:1 petroleum ether/ethyl acetate) and visualized under UV light. After completion, the isopropanol was removed in vacuo and the reaction mixture was dissolved in dichloromethane (1 mL), washed with water (5 mL), and concentrated in vacuo to give the crude product, which was purified by flash chromatography on silica gel.

(*R*)-1-Phenylethanol.

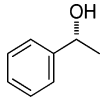

Table 1, entry 4. Preparation using ketone (120 mg, 1.0 mmol) and catalyst (*R*,*R*)-**5** (6.5 mg, 0.01 mmol) following protocol A (to the silica filtration step followed by removal of solvent) gave the crude alcohol product as a clear oil (99% conversion by GC analysis). $[\alpha]_D^{28}$ +58.1 (*c* 0.730 in $CHCl_3$) for 97% ee (*R*) (lit. value $[\alpha]_D^{27}$ +54.9 (*c* 1.0

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in $CHCl_3$) 96% ee (*R*));[13c] δ_H (300 MHz, $CDCl_3$) 7.38−7.24 (5H, m, Ph), 4.87 (1H, q, *J* 6.5 Hz), 2.07 (1H, br s), 1.48 (3H, d, *J* 6.5 Hz); δ_C (75 MHz, $CDCl_3$) 145.2, 127.9, 126.8, 124.8, 69.8, 24.5. Chiral GC analysis (CP-Chirasil -Dex-Cβ 25 m × 0.25 mm × 0.25 μm, *T* = 110 °C, *P* = 18 psi, He gas) 6.56 min (ketone), 14.61 min (*R* isomer), 16.50 min (*S* isomer).

(*R*)-1-(4-Aminophenyl)ethanol.

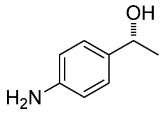
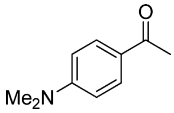


Table 2, entry 3. Preparation using ketone (134 mg, 1.0 mmol) and catalyst (*R*,*R*)-**5** (6.5 mg, 0.01 mmol) following protocol A gave the alcohol product (102 mg, 0.75 mmol, 75%) as an oil. $[\alpha]_D^{24}$ +43.1 (*c* 0.570 in MeOH) for 94% ee (*R*) (lit. value $[\alpha]_D^{27}$ +52.0 (*c* 0.54 in MeOH) 99% ee (*R*));[16b] δ_H (300 MHz, $CDCl_3$) 7.16 (2H, d, *J* 8.6 Hz), 6.66 (2H, d, *J* 8.6 Hz), 4.78 (1H, q, *J* 6.4 Hz), 3.61 (2H, br s), 1.80 (1H, br s), 1.45 (3H, d, *J* 6.4 Hz); δ_C (75 MHz, $CDCl_3$) 145.7, 135.9, 126.6, 115.0, 70.1, 24.7. Chiral HPLC analysis (OD-H Column: 0.46 cm × 25 cm, hexane/*i*-PrOH 80:20, 1.0 mL/min, 239 nM, 30 °C) t_R (min) = 18.61 min (*R* isomer), 28.76 min (*S* isomer).

1-[4-(Dimethylamino)phenyl]ethanone.



Preparation following protocol D using 4-fluoroacetophenone (0.50 g, 0.44 mL, 3.61 mmol) and 40% aqueous dimethylamine (1.5 mL, 13.3 mmol) for 22 h gave the ketone[19] (393.7 mg, 2.41 mmol, 66.9%) as a light yellow solid. mp 105 °C; ν_{max} 2904, 2811, 2651, 1649, 1585, 1357, 1229, 1068, 832, 593, 560, and 499 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.87 (2H, d, *J* 9.0 Hz), 6.66 (2H, d, *J* 9.0 Hz), 3.06 (6H, s), 2.51 (3H, s); δ_C (125 MHz, $CDCl_3$) 196.4, 153.4, 130.5, 125.4, 110.6, 40.0, 26.0; *m*/*z* (ESI) 186.1 ($[M + Na]^+$), 164.1 ($[M + H]^+$).

(*R*)-1-[(4′-Dimethylamino)phenyl]ethanol.

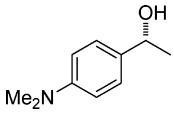
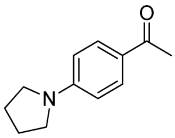


Table 2, entry 9. Preparation using ketone (81.5 g, 0.50 mmol) and catalyst (*R*,*R*)-**5** (3.3 mg, 0.005 mmol) following protocol A gave the alcohol product (65 mg, 0.39 mmol, 78%) as a clear oil. $[\alpha]_D^{27}$ +54.2 (*c* 0.710 in $CHCl_3$) for 91% ee (*R*) (lit. value $[\alpha]_D^{25}$ +51.8 (*c* 21.0 in $CHCl_3$) 86% ee (*R*));[20] δ_H (400 MHz, $CDCl_3$) 7.25 (2H, d, *J* 8.7 Hz), 6.72 (2H, d, *J* 8.7 Hz), 4.81 (1H, q, *J* 6.4 Hz), 2.93 (6H, s), 1.62 (1H, br s), 1.47 (3H, d, *J* 6.4 Hz); δ_C (100 MHz, $CDCl_3$) 150.3, 133.7, 126.5, 112.6, 70.1, 40.7, 24.7. Chiral HPLC analysis (OD-H Column: 0.46 cm × 25 cm, hexane/*i*-PrOH 95:5, 1.0 mL/min, 256 nM, 30 °C) t_R (min) = 15.21 min (*R* isomer), 17.15 min (*S* isomer).

1-[4-(Pyrrolidin-1-yl)phenyl]ethanone.



Preparation following protocol D using 4-fluoroacetophenone (1.0 g, 0.88 mL, 7.22 mmol), pyrrolidine (2.22 mL, 26.6 mmol), and deionized water (3.34 mL) for 23 h gave the ketone[21] (1061 mg, 3.90 mmol, 72.3%) as a dark yellow solid; mp 129 °C; ν_{max} 2962, 2849, 1650, 1588, 1351, 1181, 1157, and 820 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.87 (2H, d, *J* 9.0 Hz), 6.53 (2H, d, *J* 9.0 Hz), 3.40−3.35 (4H, m), 2.50 (3H, s), 2.07−2.02 (4H, m, CH_2CH_2); δ_C (125 MHz, $CDCl_3$) 196.3, 151.0, 130.7, 124.9, 110.6, 47.6, 26.0, 25.5; *m*/*z* (ESI) 212.0 ($[M + Na]^+$), 190.1 ($[M + H]^+$).

(*S*)-1-[4-(Pyrrolidin-1-yl)phenyl]ethanol.

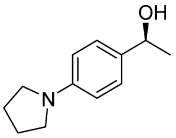
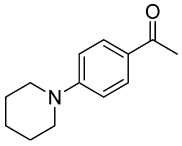


Table 2, entry 15. Preparation using ketone (76 g, 0.40 mmol) and catalyst (*S*,*S*)-**2** (2.5 mg, 0.004 mmol) following protocol A gave the alcohol product (54.6 mg, 0.286 mmol, 72%) as a white solid. mp 67 °C; $[\alpha]_D^{22}$ −17.9 (*c* 0.07 in CH_3OH) 89% ee (*S*); (found (ESI) $[M + H]^+$ 192.1398, $C_{12}H_{18}NO$ requires $[M + H]^+$ 192.1383); ν_{max} 3400, 2950, 2850, 1650, 1510, 1400, 1300, 1200, 1050, 850, 750, 550 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.25 (2H, d, *J* 8.4 Hz), 6.56 (2H, d, *J* 8.4 Hz), 4.82 (1H, q, *J* 6.5 Hz), 3.32−3.26 (4H, m), 2.03−1.98 (4H, m), 1.49 (3H, d, *J* 6.5 Hz); δ_C (100 MHz, $CDCl_3$) 147.6, 132.5 126.6, 111.5, 70.3, 47.7, 25.5, 24.7; *m*/*z* (ESI) 192.1 ($[M + H]^+$). Chiral HPLC analysis (IC, 25 cm × 4.6 mm column, *i*-PrOH/hexane 1:9, 1.0 mL/min, *T* = 25 °C, λ = 256 nm) t_R = 23.4 min (*S* isomer), 28.2 min (*R* isomer).

1-[4-(Piperidin-1-yl)phenyl]ethanone.



Preparation following protocol D from 4-fluoroacetophenone (1.0 g, 0.88 mL, 7.22 mmol), piperidine (2.64 mL, 26.6 mmol), and deionized water (3.96 mL) for 26 h gave the ketone[22] (0.792 g, 3.90 mmol, 53.9%) as a dark yellow solid; mp 86 °C; ν_{max} 2941, 2924, 2845, 1653, 1589, 1510, 1423, 1354, 1223, 1124, 915, 818 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.86 (2H, d, *J* 9.1 Hz), 6.86 (2H, d, *J* 9.1 Hz), 3.38−3.34 (4H, m), 2.51 (3H, s), 1.70−1.67 (6H, m); δ_C (125 MHz, $CDCl_3$) 196.4, 154.4, 130.5, 126.7, 113.2, 48.6, 26.0, 25.4, 24.4; *m*/*z* (ESI) 226.1 ($[M + Na]^+$), 204.1 ($[M + H]^+$).

(*S*)-1-[4-(Piperidin-1-yl)phenyl]ethanol.

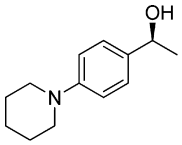
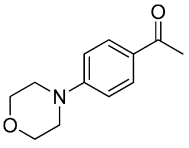


Table 2, entry 17. Preparation using ketone (50 mg, 0.25 mmol) and catalyst (*S*,*S*)-**2** (1.5 mg, 0.0025 mmol) following protocol A gave the alcohol product (42.7 mg, 0.21 mmol, 84%) as a white solid. mp 82.4 °C; $[\alpha]_D^{22}$ −10.5 (*c* 0.1 in CH_3OH) 95% ee (*S*) (lit.[23] $[\alpha]_D^{21}$ +37.6 (*c* 1.434 in CH_3OH) 97.6% ee (*R*)); ν_{max} 3300, 2950, 2800, 1650, 1510, 1400, 1250, 1200, 1150, 1100, 1075, 1050, 1000, 850, 750, 700 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.25 (2H, d, *J* 8.7 Hz), 6.92 (2H, d, *J* 8.7 Hz), 4.83 (1H, q, *J* 6.5 Hz), 3.18−3.14 (4H, m), 1.76−1.70 (4H, m), 1.60−1.52 (2H, m), 1.48 (3H, d, *J* 6.5 Hz); δ_C (100 MHz, $CDCl_3$) 151.8, 136.3, 126.3, 116.4, 70.1, 50.7, 25.8, 24.7, 24.3; *m*/*z* (ESI) 206.1 ($[M + H]^+$). Chiral HPLC analysis (IC, 25 cm × 4.6 mm column, *i*-PrOH/hexane 1:9, 1.0 mL/min, *T* = 25 °C, λ = 256 nm) t_R = 14.04 min (*S* isomer), 15.38 min (*R* isomer).

1-[4-(Morpholin-4-yl)phenyl]ethanone.



Preparation following protocol D from 4-fluoroacetophenone (0.50 g, 0.44 mL, 3.61 mmol), morpholine (2.64 mL, 13.3 mmol) and deionized water (1.72 mL) for 22 h gave the ketone[23] (396 mg, 1.93 mmol, 53.5%) as a light yellow solid; mp 97 °C; ν_{max} 2841, 1657, 1592, 1513, 1425, 1360, 1240, 1170, 927, 817 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.90 (2H, d, *J* 9.1 Hz), 6.87 (2H, d, *J* 9.1 Hz), 3.86 (4H, t, *J* 5.0 Hz), 3.31 (4H, t, *J* 5.0 Hz), 2.53 (3H, s); δ_C (125 MHz, $CDCl_3$) 196.5,

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154.2, 130.4, 128.1, 113.3, 66.6, 47.5, 26.2; *m*/*z* (ESI) 228.0 ([M + Na]$^+$), 206.1 ([M + H]$^+$).

(*S*)-1-[4-(Morpholin-4-yl)phenyl]ethanol.

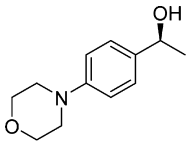


Table 2, entry 19. Preparation using ketone (50 mg, 0.24 mmol) and catalyst (*S*,*S*)-**2** (1.5 mg, 0.0024 mmol) following protocol A gave the alcohol product (37.3 mg, 0.18 mmol, 88%) as a brown solid. mp 90 °C; $[\alpha]_D^{24}$ −25.3 (*c* 0.075 in $CHCl_3$) 91% ee (*S*) (lit.[20] $[\alpha]_D^{25}$ 45.9 (*c* 1.0 in $CHCl_3$) 93% ee (*R*)); ν_{max} 3343, 2832, 1609, 1514, 1449, 1262, 1208, 1118, 1090, 1062, 920, 818, 624, 560, 446 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.30 (2H, d, *J* 8.7 Hz), 6.88 (2H, d, *J* 8.7 Hz), 4.82 (1H, q, *J* 6.5 Hz), 3.82 (4H, t, *J* 5.0 Hz), 3.12 (4H, m), 1.80 (1H, br s), 1.45 (3H, t, *J* 6.5 Hz); δ_C (100 MHz, $CDCl_3$) 150.8, 137.3, 126.4, 115.7, 70.0, 66.9, 49.4, 24.9; *m*/*z* (ESI) 230.0 ([M + Na]$^+$), 208.1 ([M + H]$^+$). Chiral HPLC analysis (IC, 25 cm × 4.6 mm column, *i*-PrOH/hexane 1:9, 1.0 mL/min, *T* = 25 °C, λ = 256 nm) t_R = 29.2 min (*S* isomer), 35.2 min (*R* isomer).

(*R*)-2-(1-Hydroxyethyl)-4-methylphenol..[17,24a]

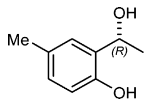


Table 3, entry 2. Preparation using ketone (150 mg, 1.0 mmol) and catalyst (*R*,*R*)-**5** (3.3 mg, 0.005 mmol) following protocol C gave the alcohol product (152 mg, 1.0 mmol, 100%) as a clear oil. $[\alpha]_D^{32}$ +24.1 (*c* 0.36 in $CHCl_3$) 95% ee (*R*); δ_H (300 MHz, $CDCl_3$) 7.69 (1H, br s), 6.97 (1H, dd, *J* 1.8, 8.2 Hz), 6.80−6.73 (2H, m), 5.01 (1H, q, *J* 6.6 Hz), 2.65 (1H, br s, CHO*H*), 2.25 (3H, s), 1.57 (3H, d, *J* 6.6 Hz); δ_C (75 MHz, $CDCl_3$) 152.5, 128.7, 128.4, 127.5, 126.4, 116.3, 71.1, 22.9, 19.9; Chiral HPLC (IA Column: (0.46 × 25 cm), 1 mL/min, 10% *i*-PrOH/90% Hexane; 256 nm UV, 30 °C) t_R = 7.83 min (*S* isomer), 8.53 min (*R* isomer).

(*R*)-4-Chloro-2-(1-hydroxyethyl)phenol.[24b]

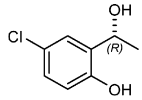


Table 3, entry 4. Preparation using ketone (170 g, 1.0 mmol) and catalyst (*R*,*R*)-**5** (3.3 mg, 0.005 mmol) following protocol C gave the alcohol product (162 mg, 0.94 mmol, 94%) as a clear oil. $[\alpha]_D^{30}$ +18.5 (*c* 0.46 in $CHCl_3$) 93% ee (*R*); δ_H (300 MHz, $CDCl_3$) 8.01 (1H, br s), 7.11 (1H, dd, *J* 2.4, 8.7 Hz), 6.95 (1H, d, *J* 2.4 Hz), 6.78 (1H, d, *J* 8.7 Hz), 5.01 (1H, q, *J* 6.6 Hz), 2.80 (1H, br s), 1.56 (3H, d, *J* 6.6 Hz); δ_C (75 MHz, $CDCl_3$) 153.9, 129.8, 128.7, 126.3, 124.6, 118.4, 71.1, 23.4; Chiral HPLC (IA Column: (0.46 × 25 cm), 1 mL/min, 10% *i*-PrOH/90% Hexane; 256 nm UV, 30 °C) t_R = 7.52 min (*S* isomer), 8.10 min (*R* isomer).

(*S*)-4-Bromo-2-(1-hydroxyethyl)phenol.[25]

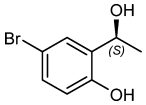


Table 3, entry 5. Preparation using ketone (215 g, 1.0 mmol) and catalyst (*S*,*S*)-**2** (3.3 mg, 0.005 mmol) following protocol C gave the alcohol product (141 mg, 0.65 mmol, 65%) as a clear oil. $[\alpha]_D^{30}$ −23.6 (*c* 0.68 in $CHCl_3$) 91% ee (*S*); δ_H (300 MHz, $CDCl_3$) 7.97 (1H, br s), 7.26 (1H, dd, *J* 2.4, 8.6 Hz), 7.10 (1H, d, *J* 2.4 Hz), 6.76 (1H, d, *J* 8.6 Hz), 5.04 (1H, q, *J* 6.6 Hz), 2.45 (1H, br s), 1.59 (3H, d, *J* 6.6 Hz); δ_C (100 MHz, $CDCl_3$) 154.6, 131.6, 130.4, 129.2, 119.0, 111.8, 71.1, 23.4; Chiral HPLC (IA Column: (0.46 × 25 cm), 1 mL/min, 10% *i*-PrOH/90% Hexane; 256 nm UV, 30 °C) t_R = 7.95 min (*S* isomer), 8.75 min (*R* isomer).

(*R*)-2-(1-Hydroxyethyl)-4-methoxyphenol..[17,25]

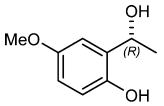


Table 3, entry 8. Preparation using ketone (166 g, 1.0 mmol) and catalyst (*R*,*R*)-**5** (3.2 mg, 0.005 mmol) following protocol C gave the alcohol product (142 mg, 0.84 mmol, 84%) as a clear oil. $[\alpha]_D^{30}$ +9.3 (*c* 0.55 in $CHCl_3$) 92% ee; (*R*); δ_H (250 MHz, $CDCl_3$) 7.42 (1H, br s), 6.79 (1H, d, *J* 8.8 Hz), 6.71 (1H, dd, *J* 2.8, 8.8 Hz), 6.54 (1H, d, *J* 2.8 Hz), 5.01 (1H, q, *J* 6.7 Hz), 3.73 (3H, s), 2.39 (1H, br s), 1.57 (3H, d, *J* 6.7 Hz); δ_C (100 MHz, $CDCl_3$) 153.0, 149.2, 129.2, 117.6, 113.7, 112.3, 71.6, 55.8, 23.3; Chiral HPLC (IA Column: (0.46 × 25 cm), 1 mL/min, 10% *i*-PrOH/90% Hexane; 256 nm UV, 30 °C) t_R = 11.57 min (*S* isomer), 12.74 min (*R* isomer).

(*S*)-1-(2-Methoxyphenyl)ethanol.

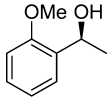


Table 3, entry 9. Preparation using ketone (150 mg, 1.0 mmol) and catalyst (*S*,*S*)-**5** (3.2 mg, 0.005 mmol) following protocol C gave the alcohol product (98 mg, 0.64 mmol, 64%) as a clear oil. $[\alpha]_D^{32}$ −13.9 (*c* 0.39 in $CHCl_3$) 68% ee (*S*) (lit[26] $[\alpha]_D^{20}$ +32.3 (*c* 2.0 in $CHCl_3$) 94% ee (*R*)); δ_H (250 MHz, $CDCl_3$) 7.35 (1H, dd, *J* 1.8, 7.5 Hz), 7.25 (1H, ddd, *J* 1.8, 8.1, 8.1 Hz), 6.97 (1H, ddd, *J* 1.0, 7.5, 7.5 Hz), 6.89 (1H, dd, *J* 1.0, 8.1 Hz), 5.11 (1H, q, *J* 6.6 Hz), 3.87 (3H, s), 1.52 (3H, d, *J* 6.6 Hz); δ_C (100 MHz, $CDCl_3$) 156.5, 133.5, 128.3, 126.1, 120.8, 110.4, 66.5, 55.3, 22.9; Chiral GC; (CP-Chirasil-Dex-Cβ, 25 m × 0.25 mm × 0.25 μm column, oven temperature 150 °C, inj.: split 220 °C, det.: FID 250 °C, 18 psi He) t_R = 5.84 min (*S* isomer), 6.30 min (*R* isomer).

(*S*)-1-(2,5-Dimethoxyphenyl)ethan-1-ol.

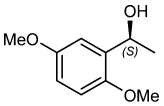
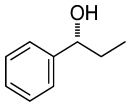


Table 3, entry 15. Preparation using ketone (147 g, 1.0 mmol) and catalyst (*S*,*S*)-**2** (3.2 mg, 0.005 mmol) following protocol C gave the alcohol product (147 mg, 0.80 mmol, 80%) as a clear oil. $[\alpha]_D^{32}$ −15.8 (*c* 0.60 in $CHCl_3$) 69% ee (*S*) (lit[27] $[\alpha]_D^{27}$ −23.6 (c 1.4 in $CHCl_3$) 76% ee (*S*)); δ_H (300 MHz, $CDCl_3$) 6.92 (1H, d, *J* 2.8 Hz), 6.79 (1H, d, *J* 8.9 Hz), 6.73 (1H, dd, *J* 2.8, 8.9 Hz), 5.04 (1H, dq, J 5.5, 6.4 Hz), 3.81 (3H, s), 3.76 (3H, s), 2.60 (1H, d, *J* 5.5 Hz), 1.47 (3H, d, *J* 6.4 Hz); δ_C (100 MHz, $CDCl_3$) 153.8, 150.6, 134.8, 112.4, 112.3, 111.4, 66.4, 55.8, 55.7, 23.0; Chiral GC; (CP-Chirasil-Dex-Cβ, 25 m × 0.25 mm × 0.25 μm column, oven temperature 150 °C, inj.: split 220 °C, det.: FID 250 °C, 18 psi He) t_R = 15.72 min (*R* isomer), 16.93 min (*S* isomer).

(*R*)-1-Phenyl-1-propanol.



Preparation using ketone (134 mg, 0.133 mL, 1.0 mmol) and catalyst (*R*,*R*)-**5** (6.5 mg, 0.01 mmol) following protocol A (to silica filtration step followed by removal of solvent) gave the crude alcohol product as a clear oil (99% conversion by GC analysis). $[\alpha]_D^{29}$ = +53.6 (*c* 0.75 in $CHCl_3$) 98% ee (*R*) (lit.[28] $[\alpha]_D^{25}$ = −47.2 (*c* 0.65 in $CHCl_3$) 99% ee (*S*)); δ_H (400 MHz, $CDCl_3$) 7.36−7.25 (5H, m), 4.58 (1H, t, *J* 6.4 Hz), 2.03 (1H, br s), 1.87−1.68 (2H, m), 1.48 (3H, t, *J* 7.0 Hz); δ_C (125 MHz, $CDCl_3$) 144.6, 128.4, 127.5, 126.0, 76.0, 31.9, 10.1. Chiral GC analysis (CP-Chirasil-Dex-Cβ 25 m × 0.25 mm × 0.25 μm, *T* = 115 °C, *P* = 18 psi, He gas) t_R = 8.48 min (ketone), 19.39 min (*R* isomer), 21.00 min (*R* isomer).

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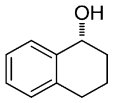
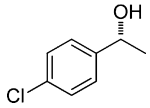
(*R*)-1-Tetralol.



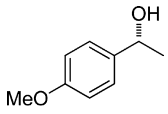
Preparation using ketone (146 mg, 0.0133 mL, 1.0 mmol) and catalyst (*R*,*R*)-**5** (6.5 mg, 0.01 mmol) following protocol A (to silica filtration step followed by removal of solvent) gave the crude alcohol product as a clear oil (98% conversion by GC analysis). $[\alpha]_D^{28}$ −30.5 (*c* 1.000 in $CHCl_3$) 97% ee (*R*) (lit.[29] $[\alpha]_D$ +34.4 (*c* 1.01 in $CHCl_3$) 98% ee (*S*)); δ_H (400 MHz, $CDCl_3$) 7.47−7.37 (1H, m), 7.22−7.05 (3H, m), 4.78 (1H, br s), 2.89−2.65 (2H, m), 2.03−1.74 (5H, m); δ_C (125 MHz, $CDCl_3$) 138.8, 137.1, 129.0, 128.6, 127.6, 126.2, 68.2, 32.2, 29.2, 18.8. Chiral GC analysis (CP-Chirasil-Dex-C*β* 25 m × 0.25 mm × 0.25 *μ*m, *T* = 120 °C, *P* = 18 psi, He gas) t_R = 24.70 min (ketone), 44.00 min (*S* isomer), 45.12 min (*R* isomer).

(*R*)-1-(4-Chlorophenyl)ethanol.



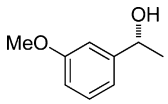
Preparation using ketone (153.5 mg, 0.130 mL, 1.0 mmol) and (*R*,*R*)-**5** (6.5 mg, 0.01 mmol) following protocol A (to silica filtration step followed by removal of solvent) gave the crude alcohol product as a clear oil (99% conversion by GC analysis). $[\alpha]_D^{26}$ +45.0 (*c* 0.840 in $CHCl_3$) 95% ee (*R*) (lit[30] $[\alpha]_D$ +38.6 (*c* 1.01 in $CHCl_3$) 88% ee (*R*)); δ_H (400 MHz, $CDCl_3$) 7.30 (4H, br s), 4.86 (1H, q, *J* 6.4 Hz), 2.00 (1H, br s), 1.48 (3H, d, *J* 6.4 Hz); δ_C (100 MHz, $CDCl_3$) 143.6, 132.4, 128.3, 126.2, 69.1, 24.7. Chiral GC analysis (CP-Chirasil-Dex-C*β* 25 m × 0.25 mm × 0.25 *μ*m, *T* = 150 °C, *P* = 18 psi, He gas) t_R = 4.48 min (ketone), 7.75 min (*R* isomer), 8.56 min (*S* isomer).

(*R*)-1-(4-Methoxyphenyl)ethanol.



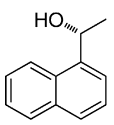
Preparation using ketone (150 mg, 1.0 mmol) and catalyst (*R*,*R*)-**5** (6.5 mg, 0.01 mmol) following protocol following protocol A (to silica filtration step followed by removal of solvent) gave the crude alcohol product as a clear oil (99% conversion by GC analysis). $[\alpha]_D^{26}$ +47.4 (*c* 0.610 in $CHCl_3$) 97% ee (*R*) (lit.[13c] $[\alpha]_D^{27}$ +32.3 (*c* 1.0 in $CHCl_3$) 90% ee (*R*)); δ_H (300 MHz, $CDCl_3$) 7.30 (2H, d, *J* 8.7 Hz), 6.88 (2H, d, *J* 8.7 Hz), 4.85 (1H, q, *J* 6.4 Hz), 3.80 (3H, s), 1.88 (1H, br s), 1.48 (3H, d, *J* 6.4 Hz); δ_C (75 MHz, $CDCl_3$) 158.4, 137.4, 126.0, 113.2, 69.4, 54.7, 24.4. Chiral GC analysis (CP-Chirasil-Dex-C*β* 25 m × 0.25 mm × 0.25 *μ*m, *T* = 130 °C, *P* = 18 psi, He gas) t_R = 13.20 min (ketone), 18.04 min (*R* isomer), 19.81 min (*S* isomer).

(*R*)-1-(3-Methoxyphenyl)ethanol.



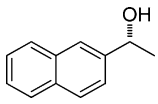
Preparation using ketone (150 mg, 0.137 mL, 1.0 mmol) and catalyst (*R*,*R*)-**5** (6.5 mg, 0.01 mmol) following protocol A (to silica filtration step followed by removal of solvent) gave the crude alcohol product as a clear oil (96% conversion by GC analysis). $[\alpha]_D^{28}$ +38.1 (*c* 0.670 in $CHCl_3$) 97% ee (*R*) (lit.[8b] $[\alpha]_D^{23}$ +31.8 (*c* 2.0 in $CHCl_3$) 94% ee (*R*)); δ_H (300 MHz, $CDCl_3$) 7.26 (1H, dd, *J* 8.1, 8.1 Hz), 6.95−6.93 (2H, m), 6.82−6.78 (1H, m), 4.86 (1H, q, *J* 6.3 Hz), 3.81 (3H, s), 1.94 (1H, br s), 1.48 (3H, d, *J* 6.3 Hz); δ_C (75 MHz, $CDCl_3$) 159.2, 147.0, 128.5, 117.0, 112.3, 110.3, 69.7, 54.6, 24.5. Chiral GC analysis (CP-Chirasil-Dex-C*β* 25 m × 0.25 mm × 0.25 *μ*m, *T* = 140 °C, *P* = 18 psi, He gas) t_R = 6.45 min (ketone), 11.75 min (*R* isomer), 12.69 min (*S* isomer).

(*R*)-1-(1-Naphthyl)ethanol.



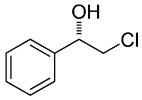
Preparation using ketone (170 mg, 0.152 mL, 1.0 mmol) and catalyst (*R*,*R*)-**5** (6.5 mg, 0.01 mmol) following protocol A (to silica filtration step followed by removal of solvent) gave the crude alcohol product as a clear oil (99% conversion by GC analysis). $[\alpha]_D^{32}$ +60.3 (*c* 0.910 in $CHCl_3$) 99% ee (*R*) (lit.[31] $[\alpha]_D$ +67.3 (*c* 0.4 in $CHCl_3$) 100% ee (*R*)); δ_H (400 MHz, $CDCl_3$) 8.10 (1H, d, *J* 8.4 Hz), 7.86 (1H, dd, *J* 7.2, 2.0 Hz)7.76 (1H, d, *J* 8.4 Hz), 7.76 (1H, d, *J* 7.2 Hz), 7.53−7.44 (3H, m), 5.65 (1H, q, *J* 6.4 Hz), 2.08 (1H, br s), 1.65 (3H, d, *J* 6.4 Hz); δ_C (125 MHz, $CDCl_3$) 141.4, 133.7, 130.3, 128.8, 127.9, 126.0, 125.6, 125.4, 123.1, 122.0, 67.1, 24.3. Chiral GC analysis (CP-Chirasil-Dex-C*β* 25 m × 0.25 mm × 0.25 *μ*m, *T* = 160 °C, *P* = 18 psi, He gas) t_R = 10.37 min (ketone), 21.01 min (*S* isomer), 22.40 min (*R* isomer).

(*R*)-1-(2-Naphthyl)ethanol.



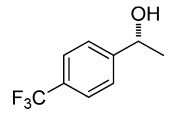
Preparation using ketone (170 g, 1.0 mmol) and catalyst (*R*,*R*)-**5** (6.5 mg, 0.01 mmol) following protocol A (to silica filtration step followed by removal of solvent) gave the crude alcohol product as a clear oil (99% conversion by GC analysis). $[\alpha]_D^{28}$ +46.4 (*c* 0.850 in $CHCl_3$) 96% ee (*R*) (lit.[9a] $[\alpha]_D^{23}$ +46.7 (*c* 1.02 in $CHCl_3$) 92% ee (*R*)); δ_H (400 MHz, $CDCl_3$) 7.87−7.73 (4H, m), 7.54−7.40 (3H, m), 5.04 (1H, q, *J* 6.4 Hz), 1.98 (1H, br s), 1.48 (3H, d, *J* 6.4 Hz); δ_C (125 MHz, $CDCl_3$) 143.1, 133.3, 132.9, 128.3, 127.9, 127.7, 126.2, 125.8, 123.8, 70.6, 25.2. Chiral GC analysis (CP-Chirasil-Dex-C*β* 25 m × 0.25 mm × 0.25 *μ*m, *T* = 150 °C, *P* = 18 psi, He gas) t_R = 18.92 min (ketone), 30.87 min (*R* isomer), 33.38 min (*S* isomer).

(*S*)-1-Phenyl-2-chloroethanol.



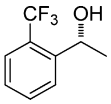
Preparation using ketone (155 g, 1.0 mmol) and catalyst (*R*,*R*)-**5** (6.5 mg, 0.01 mmol) following protocol A (to silica filtration step followed by removal of solvent) gave the crude alcohol product as a clear oil (99% conversion by GC analysis). $[\alpha]_D^{32}$ +61.8 (*c* 0.810 in $CHCl_3$) 96% ee (*S*) (lit.[32] $[\alpha]_D^{22}$ +53.8 (*c* 1.0 in $CHCl_3$) >99% ee (*S*)); δ_H (400 MHz, $CDCl_3$) 7.39−7.31 (5H, m), 4.75 (1H, m), 3.60 (1H, dd, *J* 11.4, 3.6 Hz), 3.48 (1H, dd, *J* 11.4, 8.6 Hz), 2.55 (1H, d, *J* 3.2 Hz); δ_C (100 MHz, $CDCl_3$) 138.3, 128.1, 127.9, 125.5, 73.5, 50.3. Chiral GC analysis (CP-Chirasil-Dex-C*β* 25 m × 0.25 mm × 0.25 *μ*m, *T* = 150 °C, *P* = 18 psi, He gas) t_R = 6.96 min (ketone), 9.00 min (*S* isomer), 9.60 min (*R* isomer).

(*R*)-1-(4-Trifluoromethylphenyl)ethanol.



Preparation using ketone (188 g, 1.0 mmol) and catalyst (*R*,*R*)-**5** (6.5 mg, 0.01 mmol) following protocol A (to silica filtration step followed by removal of solvent) gave the crude alcohol product as a clear oil (99% conversion by GC analysis). $[\alpha]_D^{29}$ +32.5 (*c* 0.690 in $CHCl_3$) 94% ee (*R*) (lit.[33] $[\alpha]_D^{22}$ +29.3 (*c* 1.0 in $CHCl_3$) >99% ee (*R*)); δ_H (300 MHz, $CDCl_3$) 7.62−7.60 (2H, m), 7.48−7.46 (2H, m), 4.95 (1H, q, *J* 6.4 Hz), 2.11 (1H, br s), 1.49 (3H, d, *J* 6.4 Hz); δ_C (75 MHz, $CDCl_3$) 149.1, 128.2 (q *J* 30 Hz, $ArCCF_3$), 125.3, 124.8, 123.3 (q *J* 270 Hz, CF_3), 69.3, 24.8. Chiral GC analysis (CP-Chirasil-Dex-C*β* 25 m × 0.25 mm × 0.25 *μ*m, *T* = 120 °C, *P* = 18 psi, He gas) t_R = 5.02 min (ketone), 13.92 min (*R* isomer), 17.19 min (*S* isomer).

(*R*)-1-(2-Trifluoromethylphenyl)ethanol.



Preparation using ketone (188 g, 0.149 mL, 1.0 mmol) and catalyst (*R*,*R*)-**5** (6.5 mg, 0.01 mmol) following protocol A (to silica filtration step followed by removal of solvent) gave the crude alcohol product as a clear oil (99% conversion by GC analysis). $[\alpha]_D^{25}$ +34.8 (*c* 1.11 in

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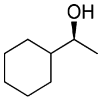
$CHCl_3$) 69% ee (*R*) (lit.[28] $[\alpha]_D^{22}$ −45.4 (*c* 0.661 in MeOH) 97% ee (*S*)); δ_H (300 MHz, $CDCl_3$) 7.82 (1H, br d, *J* 7.8 Hz), 7.61−7.56 (2H, m), 7.36 (1H, d, *J* 7.5 Hz), 5.37−5.29 (1H, m), 2.03 (1H, br s), 1.48 (3H, d, *J* 6.6 Hz); δ_C (75 MHz, $CDCl_3$) 144.4, 131.8, 126.7, 126.5, 124.6, 123.1 (q, $^3J_{C-F}$ 280 Hz, CF_3; note outer peaks of q weak), 65.1, 25.8 ($ArCCF_3$ not identified). Chiral GC analysis (CP-Chirasil-Dex-Cβ 25 m × 0.25 mm × 0.25 μm, *T* = 110 °C, *P* = 18 psi, He gas) t_R = 5.30 min (ketone), 16.74 min (*R* isomer), 19.44 min (*S* isomer).

(*S*)-1-Cyclohexylethanol.



Preparation using ketone (126 g, 0.138 mL, 1.0 mmol) and catalyst (*R*,*R*)-**6** (1.4 mg, 0.002 mmol) following protocol A (to silica filtration step followed by removal of solvent) gave the crude alcohol product as a clear oil (99% conversion by GC analysis). $[\alpha]_D^{26}$ −3.0 (*c* 0.560 in $CHCl_3$) 85% ee (lit.[34] $[\alpha]_D^{22}$ +2.7 (*c* 0.5 in $CHCl_3$) 75% ee (*R*)); δ_H (500 MHz, $CDCl_3$) 3.58−3.50 (1H, m), 1.87−1.65 (5H, m), 1.50 (1H, br s), 1.33−1.18 (4H, m), 1.15 (3H, d, *J* 6.3 Hz), 1.10−0.89 (2H, m); δ_C (125 MHz, $CDCl_3$) 72.2, 45.1, 28.7, 28.4, 26.5, 26.2, 26.1, 20.4. Chiral GC analysis of acetate derivative (CP-Chirasil-Dex-Cβ 25 m × 0.25 mm × 0.25 μm, *T* = 100 °C, *P* = 18 psi, He gas) t_R = 13.80 min (*S* isomer), 18.64 min (*R* isomer).

■ ASSOCIATED CONTENT

Supporting Information

Extended tables of results, including time-course studies, comparison of rates of electron-rich and electron-poor substrates, ^{1}H NMR spectra, and chiral GC/HPLC spectra. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b00990.

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Notes

The authors declare no competing financial interest.

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