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Bimetallic Catalysis: Asymmetric Transfer Hydrogenation of Sterically Hindered Ketones Catalyzed by Ruthenium and Potassium

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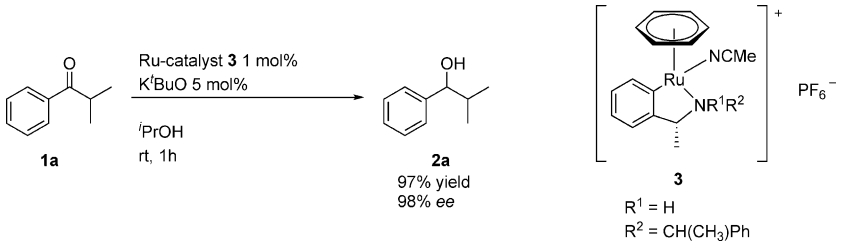
An efficient protocol for the asymmetric reduction of sterically hindered ketones under transfer-hydrogenation conditions was developed. The corresponding chiral alcohols were obtained in good to excellent yields with enantiomeric excess values up to 99%. The role of the cation associated with the base present in the reduction reaction was investigated. In contrast to previous studies on this catalyst system, potassium ions rather than lithium ions significantly enhanced the reaction outcome.

The chemical industry is steadily in need of efficient transformations for the formation of target substances in as few and atom-economical steps as possible. The search for greener protocols that both deliver the desired product and are environmentally benign is of high importance.[1] For the reduction of ketones into secondary alcohols, the use of sodium borohydride generates a stoichiometric amount of waste, and the use of molecular hydrogen is associated with certain risks owing to its high flammability.[2] An alternative method that is both mild and safe is the transfer-hydrogenation protocol initially developed by Meerwein, Verley, and Ponndorf.[3] This method builds on the use of isopropanol as the reductant together with a Lewis acid, and the only formed byproduct is acetone, which is easily removed. There are many protocols available for the transfer hydrogenation of ketones[4,5] and for the asymmetric transfer hydrogenation (ATH), for which prochiral ketones are converted into enantiomerically enriched alcohols.[2] A successful ATH protocol that demonstrated impressive enantiomeric excess (*ee*) was published by the group of Noyori in 1995.[6] Since then, a lot of effort has been put into the design of ligands and catalysts that would allow for increased catalytic efficiency and enantioselectivity, in combination with milder reaction conditions.[7] Furthermore, ATH can nowadays also be performed in water with excellent results.[8]

The reduction of sterically hindered substrates has been shown to be more difficult;[9] nevertheless, some successful protocols are available.[10] Feringa and co-workers showed in 2010 that the reduction of 2-methyl-1-phenylpropan-1-one (**1a**) into 2-methyl-1-phenylpropan-1-ol (**2a**) could be performed with a yield of 97% and an impressive *ee* of 98% with a short reaction time and a low catalyst loading (Scheme 1).[11] A drawback with these protocols is the need to synthesize and isolate the precatalyst prior to use.



Scheme 1. Recent ATH protocol for sterically hindered ketones that gives the desired enantiomerically enriched alcohol in excellent yield with excellent enantioselectivity.

We previously studied the use of ruthenium and rhodium catalysts containing amino acid derived ligands for the ATH of ketones.[12–14] The best performing catalyst for the asymmetric reduction of acetophenone (**4**) into (*S*)-1-phenylethanol (**5**) was found to be amino acid hydroxy amide **6** in combination with [Ru(*p*-cymene)Cl$_2$]$_2$. Upon performing the reduction in the presence of lithium chloride and sodium isopropoxide in a mixture of THF and isopropanol at 30 °C, the product was obtained in good yield with high selectivity (Scheme 2a). Unfortunately, this protocol proved less efficient for the reduction of more sterically demanding ketones (Scheme 2b).[15]

We recently developed a protocol for the tandem isomerization/asymmetric transfer hydrogenation of allylic alcohols in which ethanol was found to be the superior hydride source/solvent.[16] Using this protocol for the reduction of 2-methyl-1-phenylpropan-1-one (**1a**) resulted in the desired asymmetric alcohol in 90% conversion with 89% *ee* (Scheme 2c). The use of ethanol as the hydride donor can lead to side reactions owing to the formation of reactive acetaldehyde; however, in the reduction of **1a**, no trace amounts of possible condensation products were observed.[17]

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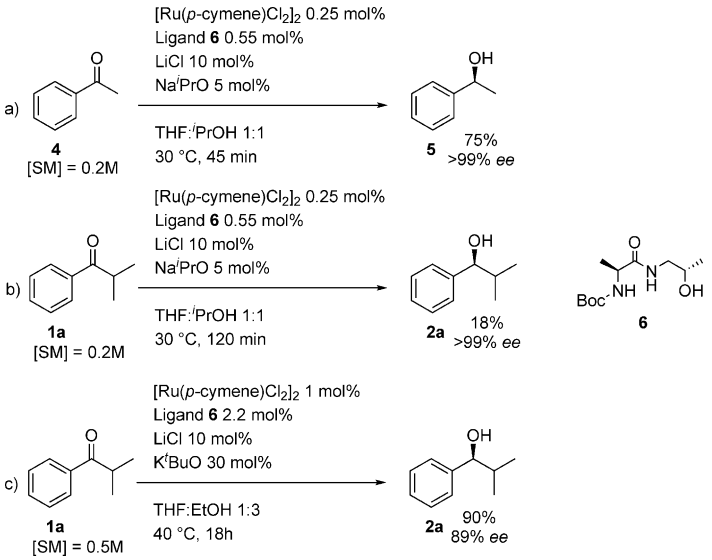


Scheme 2. a) Previous protocol developed for the reduction of acetophenones. b) Reduction of **1a** with the most efficient previous protocol. c) Reduction of **1a** by using conditions developed for the tandem isomerization/asymmetric transfer hydrogenation of allylic alcohols.

A thorough optimization showed that ethanol and isopropanol performed equally well as hydride sources (see the Supporting Information for additional data). Owing to the elongated reaction times required for the reduction of **1a**, we decided to use ethanol to avoid product racemization. The irreversible formation of ethyl acetate from in situ formed acetaldehyde trapped by ethanol would circumvent racemization and would be the driving force for the reduction of the more sterically demanding substrates.[14] Furthermore, the use of THF as the co-solvent was shown to improve the conversion, and the best mixture was dry ethanol/THF (3:2).[18] The use of nondried solvents resulted in slightly lower conversions into the desired alcohol. Furthermore, upon exchanging THF for the greener alternative 2-methyltetrahydrofuran, full conversion was observed, and the desired alcohol was obtained with 95% *ee*. The concentration of the reaction mixture was also evaluated, and the optimal conditions were found to include a ketone concentration of 0.25 M. Moreover, a screening of different bases showed that organic bases, such as triethylamine and proton sponge (Table 1, entries 1 and 2), were insufficient. Sodium carbonate could also not be used, which indicates that this base is too weak for ligand deprotonation or activation of the ruthenium dimer (Table 1, entry 3). With the use of the stronger bases potassium and sodium *tert*-butoxide, full conversion was obtained (Table 1, entries 4 and 5). Given that both evaluated butoxide bases showed the same excellent result, we decided to move on with the slightly less expensive potassium analogue, and we were able to decrease the base loading from 30 to 20 mol% without dramatic effects on conversion and enantiomeric excess (Table 1, entry 6). Furthermore, the use of lithium chloride was shown not to affect the reaction outcome, which is in contrast to previous studies performed with the use of this catalyst mixture (Table 1, entry 7).[15] Exchanging the base to sodium *tert*-butoxide at this loading resulted in a decreased conversion (Table 1, entry 8), which further supports the use of the potassium analogue.

Higher reaction temperatures showed, as expected, an increase in reaction rate and a slight decrease in the *ee* value. At lower temperature, the reaction was not complete after 48 h and the *ee* was not improved.

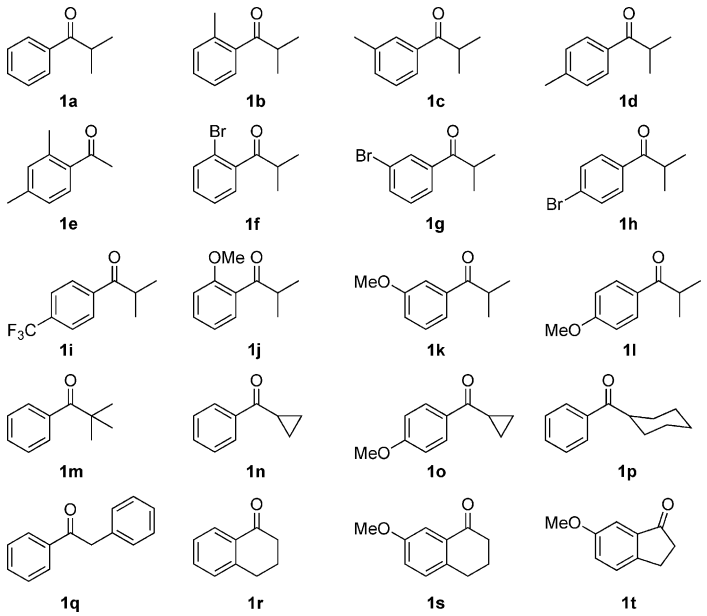
The scope was thereafter investigated on a series of sterically demanding substrates with different electronic properties (Scheme 3 and Table 2). Benchmark ketone **1a** was readily reduced, and alcohol **2a** was isolated in high yield with a high *ee* value (Table 2, entry 1). The reduction of more sterically hindered ketone **1b** resulted in poor conversion (Table 2, entry 2). Less hindered analogues **1c** and **1d** were reduced in higher conversions, and the alcohols were obtained with good *ee* values (Table 2, entries 3 and 4). 2,4-Dimethylacetophenone (**1e**), which has steric hindrance on the aromatic ring similar to that of **1b** and **1d**, was reduced in high conversion and enantioselectivity (Table 2, entry 5). Comparing the reactivity of ketone **1b** with that of ketone **1e**, one can see that **1e** only has steric hindrance on one side of the carbonyl group; this is in contrast to **1b**, which is blocked on both sides. This feature may be the main explanation for the reduced reactivity of ketone **1b**. There is a clear trend in the outcome of the reduction of the bromo-substituted ketones (Table 2, entries 6–8), for which the most hindered 2-substituted analogue showed significantly lower reactivity. The substrate containing the electron-withdrawing trifluoromethyl group (i.e., compound **1i**) was reduced in high conversion; however, a lower *ee* value was observed for this compound (Table 2, entry 9).

In general, 3- and 4-substituted substrates demonstrated similar reactivities and selectivities, whereas the 2-substituted

Table 1. Screening of bases.[a]

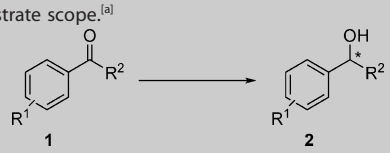
Entry	Base	Conversion [%][b]	*ee* [%][c]
1	triethylamine	0	–
2	proton sponge[d]	0	–
3	Na_2CO_3	0	–
4	NaO*t*Bu	99	95
5	KO*t*Bu	99	95
6[e]	KO*t*Bu	93	95
7[e,f]	KO*t*Bu	99	95
8[e,f]	NaO*t*Bu	72	94

[a] Reaction conditions: $[Ru(p\text{-cymene})Cl_2]_2$ (1 mol%), ligand **6** (2.2 mol%), ketone **1a** (1 mmol, 0.25 M reaction solution), dry ethanol and dry THF (3:2) as solvent, base (30 mol%), and LiCl (10 mol%). All reactions were performed at 40 °C for 24 h. [b] Conversion was determined by ^{1}H NMR spectroscopy. [c] The *ee* was measured by GLC on a chiral stationary phase (CP Chirasil DEX CB). [d] 1,8-Dimethylaminonaphthalene. [e] Base (20 mol%). [f] Without LiCl.



Scheme 3. Hindered ketones that were evaluated with this protocol.

Table 2. Substrate scope.[a]



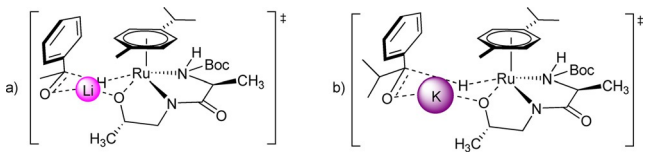
Entry	Ketone	Alcohol	Conv. [%]	Yield [%]	*ee* [b] [%]	Absolute configuration[c]
1	**1a**	**2a**	99	85	94	*S*
2	**1b**	**2b**	6	–	–	–
3	**1c**	**2c**	75	71	>99	–
4[d]	**1d**	**2d**	99	98	92	*S*
5	**1e**	**2e**	99	73	91	–
6	**1f**	**2f**	14	–	–	–
7[d]	**1g**	**2g**	99	98	93	–
8	**1h**	**2h**	nd	84	92	–
9[e]	**1i**	**2i**	99	98	81	–
10	**1j**	**2j**	10	–	–	–
11	**1k**	**2k**	90	86	94	–
12[f,g]	**1l**	**2l**	63	–	92	–
13	**1m**	**2m**	9	–	–	–
14	**1n**	**2n**	92	89	92	*S*
15[d]	**1o**	**2o**	nd	45	89	–
16[g]	**1p**	**2p**	99	97	>99	*S*
17[e]	**1q**	**2q**	99	97	92	*S*
18[g]	**1r**	**2r**	nd	88	88	*S*
19[g]	**1s**	**2s**	nd	87	88	*S*
20	**1t**	**2t**	51	–	33	–

[a] Reaction conditions: $[Ru(p\text{-cymene})Cl_2]_2$ (1 mol%), ligand **6** (2.2 mol%), ketone (1 mmol, 0.25 M reaction solution), dry ethanol and dry THF (3:2) as solvent, KO*t*Bu (20 mol%). All reactions were performed at 40 °C for 24 h. Conversion was determined by ^{1}H NMR spectroscopy. nd = not determined. [b] The *ee* was measured by GLC analysis on a chiral stationary phase (CP Chirasil DEX CB) and by HPLC analysis on a chiral stationary phase (AD, AS, OB, and ODH columns). [c] Value for the optical rotation was compared with a suitable reference to determine the absolute configuration. [d] $[Ru(p\text{-cymene})Cl_2]_2$ (2 mol%), ligand **6** (4.4 mol%), KO*t*Bu (40 mol%). [e] $[Ru(p\text{-cymene})Cl_2]_2$ (0.5 mol%), ligand **6** (1.1 mol%), KO*t*Bu (10 mol%). [f] Determined by ^{1}H NMR spectroscopy by using 1,3,5-trimethoxybenzene as an internal standard. [g] 0.5 M reaction solution.

analogues displayed poor reactivities. This trend was also valid for the methoxy-substituted substrates, for which poor conversion was observed for ketone **1j** (Table 2, entry 10). Ketones **1k** and **1l** were more reactive, and alcohol **2k** was isolated in good yield and enantioselectivity (Table 2, entry 11), whereas alcohol **2l** was formed in high enantioselectivity, but the product proved difficult to isolate (Table 2, entry 12). Sterically demanding *tert*-butyl ketone (**1m**) was not efficiently reduced under these conditions (Table 2, entry 13), whereas the cyclopropyl-substituted ketones were reduced in moderate to good conversions with moderate to good *ee* values (Table 2, entries 14 and 15). Cyclohexyl phenyl ketone (**1p**) was reduced in excellent yield with excellent enantioselectivity (Table 2, entry 16), and 2-phenylacetophenone (**1q**) was smoothly converted into its corresponding alcohol (Table 2, entry 17). Moreover, some less hindered ketones were evaluated by using this protocol. Cyclic alcohols **2r** and **2s** were obtained in good yields with good *ee* values, albeit with slightly lower selectivities than those previously observed by using protocols developed in our laboratories. The asymmetric reduction of compound **1t** resulted in moderate conversion with low enantiomeric excess. Furthermore, acetophenone was reduced to 1-phenylethanol (**5**) in good conversion; however, the enantiomeric excess was lower than that previously observed by using other protocols based on amino acid ligands (in this case 82% *ee*).[16] Propiophenone was successfully reduced into the corresponding alcohol with 99% conversion and 94% *ee*.

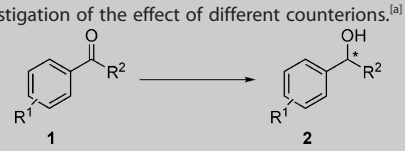
In earlier studies, with the use of this class of catalysts, the addition of lithium chloride was demonstrated to play a key role in the asymmetric reduction.[13,15] The proposed explanation is the formation of a tight bimetallic transition state in which the lithium ion and the hydride is delivered to the substrate according to Scheme 4a. In the current protocol, the use of lithium chloride as the additive showed no enhancements (Table 1, compare entries 6 and 7). Nevertheless, high enantiomeric excess values were still obtained in the ketone reductions, and we, therefore, postulate that potassium plays a similar bridging role in the transition state. The larger ionic radius of potassium would open a less rigid transition state and, therefore, would allow increased space for sterically demanding substrates (Scheme 4b).

To further investigate the influence of the cation on the reaction outcome, a series of experiments performed by using



Scheme 4. a) Previously reported plausible transition state for ATH in the presence of a lithium ion. b) Proposed transition state involving a potassium ion.

Table 3. Investigation of the effect of different counterions.[a]



1 2

Entry	Base	Additive	Conv.[b] [%]	*ee*[c] [%]
1	LiO*t*Bu	–	72	93
2	LiO*t*Bu	[12-crown-4][d]	70	91
3	NaO*t*Bu	–	72	94
4	NaO*t*Bu	[15-crown-5][d]	20	78
5	KO*t*Bu	–	99	95
6	KO*t*Bu	[18-crown-6][d]	19	45
7	KO*t*Bu	[18-crown-6][e]	90	92
8	KO*t*Bu[f]	–	60	90
9	KO*t*Bu[f]	LiCl[g]	56	90
10	KO*t*Bu[f]	KCl[g]	70	95

[a] Reaction conditions: $[Ru(p\text{-cymene})Cl_2]_2$ (1 mol%), ligand **6** (2.2 mol%), ketone **1a** (1 mmol, 0.25 M reaction solution), dry ethanol and dry THF (3:2) as solvent, base (20 mol%). All reactions were performed at 40 °C for 24 h. [b] Conversion was determined by ^{1}H NMR spectroscopy. [c] The *ee* was measured by GLC analysis on a chiral stationary phase (CP Chirasil DEX CB). [d] 40 mol%. [e] 2 mol%. [f] 7 mol%. [g] 10 mol%.

different complexation agents were undertaken (Table 3). The bases used were *tert*-butoxide salts containing cations of different sizes, LiO*t*Bu, NaO*t*Bu, and KO*t*Bu, in combination with the crown ethers [12-crown-4], [15-crown-5], and [18-crown-6] (Table 3, entries 1–6). In general, the addition of crown ethers to the reaction mixture decreased both the conversion and the enantioselectivity, which strongly indicates that the cation plays a crucial role in the reaction. No inhibition of the catalyst was observed if small amounts (2 mol%) of the crown ether were added, which shows that the trends observed are not a result of catalyst inhibition by the additive (Table 3, entry 7). There was only a small difference in conversion and enantioselectivity for the reactions performed with the use of the lithium base (Table 3, entries 1 and 2), which is in line with previous results with the use of [12-crown-4] to trap lithium ions.[13] In reactions containing sodium or potassium *tert*-butoxide, significant decreases in both the conversion and enantioselectivity were observed if the crown ethers were present in the reaction mixture (Table 3, entries 3–6). The largest difference was seen by using KO*t*Bu, for which the addition of [18-crown-6] reduced the *ee* from 95 to 45%.

In previous studies on this particular catalyst system we demonstrated that a minimum of 3 equivalents of base in relation to the amount of ligand was necessary for a successful reaction outcome.[12a] Hence, approximately 7 mol% base would be sufficient in the current setup, but this was not the case (Table 3, entry 8). The addition of lithium chloride to the reaction mixture did not increase the conversion or enantioselectivity (Table 3, entry 9). On the contrary, the addition of potassium chloride resulted in a significant improvement in the enantioselectivity (Table 3, entry 10), which indicates that potassium plays an essential role in the reaction, in line with the proposal in Scheme 4b.

The results presented herein are complementary to those obtained with earlier protocols based on $[Ru(p\text{-cymene})Cl_2]_2$ and amino acid hydroxyamide ligands, which demonstrated high efficiency, low catalyst loading, and short reaction times for the reduction of aryl alkyl ketones. Nevertheless, these protocols showed limitations for sterically hindered ketones, which were reduced with high enantioselectivity, albeit in low yields. The current protocol circumvents this problem and delivers sterically demanding secondary alcohols in moderate to high yields with good to excellent *ee* values. The major differences between the current and previous catalytic systems are changes to the solvent system and the amount of added base. These two factors appear to have a most positive influence on the lifetime of the catalyst, which in contrast to earlier studies show catalytic activity even after a reaction time of 24 h. The extended catalyst lifetime is likely the reason for the high yields, also for sterically demanding substrates. We previously successfully used LiCl as an additive in the ATH of prochiral ketones, for which lithium ions play an important role in generating a tight transition state for hydride transfer. However, in contrast to these observations, the current protocol shows enhanced activity and selectivity if potassium ions are used as either the counterion of the base or as an additive to the reaction mixture. The larger potassium ion would allow for a more flexible transition state, which would better fit the increased size of hindered ketones. As a consequence, sterically demanding substrates are reduced in higher yields and with higher enantioselectivity. This mechanistic insight could open up further applications and modifications of the current catalytic system.

Experimental Section

General

All reactions were performed under a nitrogen atmosphere with oven-dried glassware.

General procedure for the asymmetric transfer hydrogenation of sterically hindered ketones

The catalyst precursor $[Ru(p\text{-cymene})Cl_2]_2$ (6.2 mg, 0.01 mmol) was treated under vacuum in a capped vial for 10 min. Dry THF (1.60 mL) and dry ethanol (1.80 mL) were added, followed by a 0.11 M stock solution of ligand **6** in dry ethanol (0.20 mL, 0.022 mmol, 2.2 mol%)[18] and the ketone (1.0 mmol). The resulting mixture was stirred for 15 min at 40 °C. The reaction was initiated by the addition of a 0.5 M stock solution of KO*t*Bu in dry ethanol (0.40 mL, 0.20 mmol, 20 mol%). Aliquots were withdrawn at suitable intervals (see details in the tables) and were then pressed though a pad of silica with ethyl acetate as the eluent. The resulting solutions were analyzed by ^{1}H NMR spectroscopy, GLC on a chiral stationary phase (CP Chirasil DEX CB), or HPLC on a chiral stationary phase (AD, AS, OB, and ODH columns).

To isolate the product, the crude material was filtered through a pad of silica with ethyl acetate as the eluent to remove metal residues and the ligand, and this was followed by concentration and purification by column chromatography.

Acknowledgements

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Keywords: asymmetric catalysis · hindered ketones · reduction · ruthenium · transfer hydrogenation

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[18] The ethanol used was purchased as 99% pure and stored over flame-dried 4 Å molecular sieves.

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