CHEMISTRY
A EUROPEAN JOURNAL

DOI: 10.1002/chem.200501384

The Importance of Alkali Cations in the [{$RuCl_2$(*p*-cymene)}$_2$]–Pseudo-dipeptide-Catalyzed Enantioselective Transfer Hydrogenation of Ketones

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Abstract: We studied the role of alkali cations in the [{$RuCl_2$(*p*-cymene)}$_2$]–pseudo-dipeptide-catalyzed enantioselective transfer hydrogenation of ketones with isopropanol. Lithium salts were shown to increase the enantioselectivity of the reaction when *i*PrONa or *i*PrOK was used as the base. Similar transfer-hydrogenation systems that employ chiral amino alcohol or monotosylated diamine ligands are not affected by the addition of lithium salts. These observations have led us to propose that an alternative reaction mechanism operates in pseudo-dipeptide-based systems, in which the alkali cation is an important player in the ligand-assisted hydrogen-transfer step. DFT calculations of the proposed transition-state (TS) models involving different cations (Li^+, Na^+, and K^+) confirm a considerable loosening of the TS with larger cations. This loosening may be responsible for the fewer interactions between the substrate and the catalytic complex, leading to lower enantiodifferentiation. This mechanistic hypothesis has found additional experimental support; the low *ee* obtained with [$BnNMe_3$]OH (a large cation) as base can be dramatically improved by introducing lithium cations into the system. Also, the complexation of Na^+, K^+, and Li^+ cations by the addition of [15]crown-5 and [18]crown-6 ethers and cryptand 2.1.1 (which selectively bind to these cations and, thus, increase their bulkiness), respectively, to the reaction mixture led to a significant drop in the enantioselectivity of the reaction. The lithium effect has proved useful for enhancing the reduction of different aromatic and heteroaromatic ketones.

Keywords: amino acids · amino alcohols · asymmetric catalysis · hydrogen transfer · ruthenium

Introduction

During the last decade, asymmetric transfer hydrogenation has enjoyed tremendous popularity among chemists working in the field of catalysis. This process allows for easy preparation of enantiomerically enriched alcohols[1–8] and amines[2–4,8] from prochiral ketones and imines in the presence of asymmetric catalysts and avoids the hazardous use of molecular hydrogen. Despite the number of efficient catalysts introduced in recent years for these particular transformations, further improvement of catalyst performance, especially concerning enantioselectivity, is a continuing challenge. Thus, the design of new ligands as well as new metal complexes possessing desirable catalytic properties is of high importance. Better catalysts can be obtained by the introduction of appropriate achiral promoters, which can improve dramatically the characteristics of existing catalytic systems, virtually making it possible in some cases "to make good asymmetric catalysis perfect".[9] Such additives often act to deoligomerize structures to form the desired catalyst species. The use of bases as additives can enable a more rapid dissociation of the catalyst–product complex through ligand-exchange reactions. Additives like molecular sieves can, for example, remove water produced in the reaction that might be detrimental to the catalyst. Furthermore, certain additives can be used to poison undesirable catalyst species, thereby enhancing the performance of the desired catalyst. Another important result of modifying a catalytic system by the addition of achiral promoters could be a better mechanistic understanding of the catalytic process, with far-reaching consequences.

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Previously, we reported on the [{$RuCl_2$(*p*-cymene)}$_2$]–pseudo-dipeptide catalytic system which, in the presence of base, allowed for asymmetric transfer hydrogenation of ketones in isopropanol, yielding the corresponding alcohols with high enantioselectivity.[10–13] The pseudo-dipeptides were prepared in a straightforward fashion from vicinal amino alcohols and *N*-protected amino acids.[14] Upon re-examination of this catalytic system, we found that the introduction of an alkali cation along with the base had a direct influence on the outcome of the reduction reaction. Here, we present unprecedented results showing a highly synergetic effect between the ruthenium catalyst and alkali cations. In addition, we report on how the enantioselectivity of the alcohols formed can be improved by careful tuning of the system by using appropriate alkali cations.

Results and Discussion

A metal complex used in asymmetric catalysis normally acquires its specific catalytic properties from a combination of metal–ligand interactions and the chiral space that the ligands create around the actual center of reactivity. Other factors affecting the overall activity and selectivity of a catalytic system include solvent effects and the use of noncoordinated counterions. In nature, highly selective enzymes serve as good examples of how efficient catalysis can be performed based on these simple considerations. However, to function properly, numerous enzymes require additional co-catalysts that assist and participate in the overall catalytic process. This principle of adding co-catalysts or certain additives, chiral or achiral, can effectively change and improve an existing asymmetric catalytic reaction that involves transition-metal catalysts. With this in mind, we investigated the outcome of adding different additives to the [{$RuCl_2$(*p*-cymene)}$_2$]–pseudo-dipeptide catalytic system.

Effect of achiral additives: The [{$RuCl_2$(*p*-cymene)}$_2$]–pseudo-dipeptide-catalyzed enantioselective transfer hydrogenation of ketones is highly sensitive towards the amount of base that is added during the reduction reaction. We found that the addition of less than three equivalents, with respect to the catalyst (i.e., typically <3 mol%), of either sodium hydroxide or isopropoxide to the reaction mixture resulted in little or no conversion of the ketone to the secondary alcohol. By adding a base, we introduce an additional metal ion to the system, an alkali ion, which could potentially act as a Lewis acid to activate the substrate and thereby influence the overall reactivity of the system. We were intrigued to see whether the nature of this metal cation could have any influence on the catalytic reduction reaction and, therefore, we performed a number of transfer-hydrogenation reactions in which different metal salts were added to the reaction mixture (Table 1).

The addition of strong Lewis acids, such as scandium triflate or titanium isopropoxide, had a negative effect on the reactivity of the system (entries 2 and 3, Table 1) relative to our standard reaction setup (i.e., the reduction of acetophenone in 0.2 M 2-propanol with 0.5 mol% of [{$RuCl_2$(*p*-cymene)}$_2$], 1.1 mol% of the pseudo-dipeptide ligand, and 5 mol% of sodium isopropoxide). Copper salts were found to completely inhibit the reduction reaction, and the addition of silver triflate resulted in a somewhat lower conversion than that obtained under the standard conditions (entries 4–6, Table 1). The addition of alkali salts gave some interesting results; reactions with sodium or potassium chloride as additive gave similar results to the nonadditive reaction (entries 7 and 8, Table 1), whereas the addition of lithium chloride resulted in a higher enantioselectivity of the product 1-phenylethanol (entry 9, Table 1). Apparently, modification of the [{$RuCl_2$(*p*-cymene)}$_2$]–pseudo-dipeptide–*i*PrONa system by addition of lithium chloride (10 mol%) led to a slight increase in the selectivity of the reduction reaction. Similar behavior was also observed when other lithium salts were used as additives (entries 10–13, Table 1). The enhanced enantioselectivity observed upon addition of lithium salts prompted us to investigate further the origin and nature of this effect. In the standard reaction setup, we used sodium isopropoxide as the base; we found that replacing the sodium base by its lithium congener resulted in the same *ee* enhancement (entries 3 and 8, Table 2) as that observed when LiCl was added. Thus, by employing the stereochemically matching ligands **1**, **3**, **5**, and **7** (Figure 1) in combination with a lithium salt or base in the reaction, we observed an average increase in enantioselectivity of 3%. In the most favorable case, involving ligand **3**, we obtained 1-phenylethanol in high yield and with excellent enantioselectivity (98% *ee*) after 30 min (entry 7, Table 2). The behavior of their mismatched congeners was more complex and depended on the nature of the substituents at the stereogenic centers. Surprisingly, in the case of the mismatched ligand **6**, the *ee* was increased by as much as 49% upon addition of LiCl (entry 14, Table 2).

Table 1. Effect of additives on the [{$RuCl_2$(*p*-cymene)}$_2$]–pseudo-dipeptide-catalyzed transfer hydrogenation of acetophenone.[a,b]

Entry	Additive	Conversion [%][c]	*ee* [%][c]
1	–	83	92 (*S*)
2	$Sc(OTf)_3$ (1 mol%)	3	>99 (*S*)
3	$Ti(OiPr)_4$ (5 mol%)	30	94 (*S*)
4	$CuCl_2$ (10 mol%)	–	n.d.
5	CuI (10 mol%)	–	n.d.
6	AgOTf (5 mol%)	58	93 (*S*)
7	NaCl (10 mol%)	74	93 (*S*)
8	KCl (10 mol%)	76	93 (*S*)
9	LiCl (10 mol%)	85	95 (*S*)
10	LiBr (10 mol%)	84	94 (*S*)
11	LiI (10 mol%)	77	94 (*S*)
12	$LiClO_4$ (10 mol%)	77	95 (*S*)
13	LiOAc (10 mol%)	76	94 (*S*)

[a] Reaction conditions: acetophenone (1 equiv, 0.2 M in 2-propanol), [{$RuCl_2$(*p*-cymene)}$_2$] (0.5 mol%), ligand (1.1 mol%), NaO*i*Pr (5 mol%), room temperature. [b] The reaction mixtures were analyzed after 30 min to avoid erosion of *ee*, which can occur as the reaction equilibrium is approached; here, at 91–92% conversions. [c] Conversions and enantioselectivities were determined by GLC.

Table 2. Effect of lithium cations on the [{$RuCl_2$(*p*-cymene)}$_2$]–pseudo-dipeptide-catalyzed transfer hydrogenation of acetophenone.[a,b]

Entry	Ligand	Base ([mol%])	Additive ([mol%])	Conver. [%][c]	*ee* [%][c]
1	**1**	*i*PrONa (5)	–	83	92 (*S*)
2	**1**	*i*PrONa (5)	LiCl (10)	85	95 (*S*)
3	**1**	*i*PrOLi (10)	–	86	95 (*S*)
4	**2**	*i*PrONa (5)	–	41	94 (*R*)
5	**2**	*i*PrONa (5)	LiCl (10)	41	97 (*R*)
6	**3**	*i*PrONa (5)	–	76	97 (*S*)
7	**3**	*i*PrONa (5)	LiCl (10)	88	98 (*S*)
8	**3**	*i*PrOLi (5)	–	77	98 (*S*)
9	**4**	*i*PrONa (5)	–	23	61 (*S*)
10	**4**	*i*PrONa (5)	LiCl (10)	16	45 (*S*)
11	**5**	*i*PrONa (5)	–	81	95 (*R*)
12	**5**	*i*PrONa (5)	LiCl (10)	85	98 (*R*)
13	**6**	*i*PrONa (5)	–	31	7 (*R*)
14	**6**	*i*PrONa (5)	LiCl (10)	24	56 (*R*)
15	**7**	*i*PrONa (5)	–	87	92 (*S*)
16	**7**	*i*PrONa (5)	LiCl (10)	89	95 (*S*)
17	**8**	*i*PrONa (5)	–	24	61 (*R*)
18	**8**	*i*PrONa (5)	LiCl (10)	22	58 (*R*)

[a] Reaction conditions: acetophenone (1 equiv, 0.2 M in 2-propanol), [{$RuCl_2$(*p*-cymene)}$_2$] (0.5 mol%), ligand (1.1 mol%), base (see table), room temperature. [b] The reaction mixtures were analyzed after 30 min to avoid erosion of *ee*, which can occur as the reaction equilibrium is approached; here, at 91–92% conversions. [c] Conversions and enantioselectivities were determined by GLC.

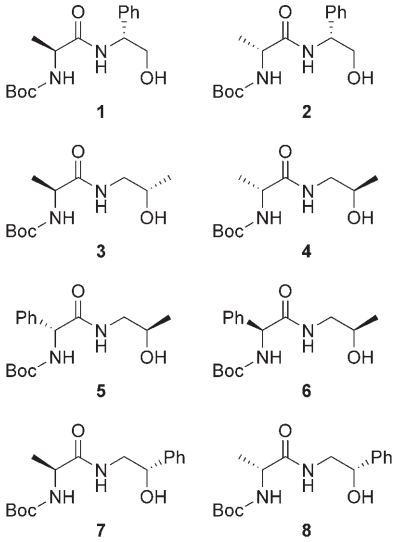


Figure 1. Pseudo-dipeptide ligands used in the study of cation effects on the [{$RuCl_2$(*p*-cymene)}$_2$]–pseudo-dipeptide-catalyzed transfer hydrogenation of acetophenone.

The stereochemical outcome of the transfer-hydrogenation reactions performed with ruthenium–pseudo-dipeptide catalysts is determined predominantly by the stereocenter present in the amino acid moiety.[11,12] Therefore, it is possible to predict the absolute configuration of the product of a given reaction by choosing an appropriate ligand; pseudo-dipeptides based on natural L-amino acids induce *S*-product formation and ligands based on D-amino acids give the *R* product. However, the addition of lithium salts revealed that alkyl substituents have a larger effect on enantioselectivity than phenyl groups. This effect is particularly pronounced with the second-generation pseudo-dipeptides **5** and **6**, in which the hydroxy group is adjacent to one of the stereogenic centers. In these cases, the effect of the alkyl substituent of the amino alcohol moiety is more dominant than the effect of the phenyl group of the amino acid. As seen in entry 13 of Table 2, the *R*-configured product was formed as the major isomer even though an L-amino acid based ligand was used. The addition of LiCl increased the enantioselectivity to 56% *ee* (entry 14, Table 2), but still the *R* alcohol was favored. Apparently, the presence of lithium cations amplifies the importance of the alcohol stereogenic center in the enantiodifferentiating step. However, in general, a decrease in product *ee* can be expected upon addition of lithium salts to reduction reactions catalyzed by ruthenium complexes containing mismatched second-generation ligands, unless these ligands are based on phenylglycine (e.g., ligand **6**).

Effect of lithium additives on other transfer-hydrogenation systems: To investigate whether the addition of lithium salts could influence other typical transfer-hydrogenation systems we performed reactions with ruthenium catalysts derived from some commonly used ligands (Figure 2).[2,4] In contrast

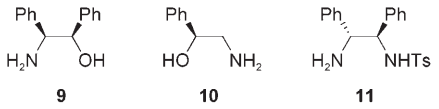


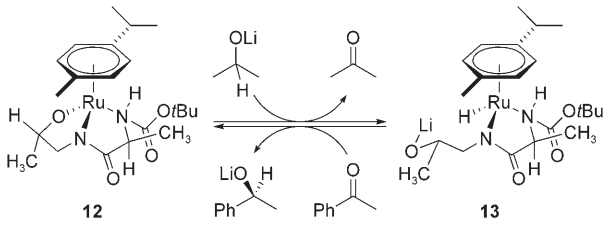
Figure 2. Amino alcohol and diamine ligands used in the ruthenium-catalyzed transfer hydrogenation of ketones.

to the pseudo-dipeptide systems, we observed no effect of adding LiCl to catalytic reactions in which the amino alcohols **9** and **10** or (*R*,*R*)-TsDPEN (**11**) were employed as ligands (see Supporting Information). The absence of an alkali-cation effect on these systems suggests that the hydride transfer may occur by a different mechanism to that operating when catalysts based on pseudo-dipeptides are used in the ketone reduction.

The importance of alkali-metal cations in the hydrogenation of ketones employing molecular hydrogen and the *trans*-[$RuCl_2${(*S*)-binap}{(*S*,*S*)-dpen}][15] catalyst has been demonstrated previously (binap = 1,1′-binaphthalene-2,2′-diylbis(diphenylphosphane), dpen = 1,2-diphenylethylenediamine).[16] In this system, a decrease in activity in the order K > Na ~ Rb > Li was observed. This was attributed to the formation of a potassium-specific binding site, formed with the aid of the two phenyl rings of the ligand, which helps to position better the *t*BuOK molecules in the transition state, leading to the deprotonation of the intermediate dihydrogen complex. Previously, secondary interactions with ancillary ligand functionalities were shown to play an important role in some catalytic asymmetric processes, including hydrogenation.[17–19] However, in our case these interactions appear

to be truly critical for catalytic activity, as demonstrated below.

Mechanistic considerations: We previously reported that the presence of a base-stable carbamoyl group at the N terminal and a free hydroxy functionality at the C terminal is crucial for efficient catalysis.[11] From these observations it is evident that the Boc-NH and OH functionalities act in a highly cooperative fashion. Complexes based on ligands lacking either of these groups were completely ineffective in the transfer-hydrogenation reaction. For instance, no conversion was observed when the *N*-tosyl analogue of **1** was employed as a ligand of ruthenium. Similarly poor results were obtained by using the *O*-methylated derivative of ligand **1**.[11] In addition, when the reduction was performed with ligands lacking a central amide functionality (no peptide bond) or when this amide was *N*-alkylated, we observed no product formation. Another factor that has a huge effect on these reductions is the amount of base added to generate the active catalyst and to start the reaction. We observed that more than three equivalents of base (isopropoxide) are typically needed for the reaction to occur. If the reduction was performed with less than three equivalents, we observed poor conversion to the alcohol. The pseudo-dipeptides have three acidic positions that can undergo deprotonation relatively easily. However, the acidities of the hydroxy and amide NH functionalities are several orders of magnitude higher than that of the carbamate NH. Under the reaction conditions employed (5 mol% base), the hydroxy and amide NH functionalities are the most likely to undergo deprotonation readily. In fact, Beck and co-workers demonstrated that treatment of a Boc-protected dipeptide with NaOMe in the presence of $[\{RuCl_2(p\text{-cymene})\}_2]$ results in the formation of a Ru–arene–dipeptide complex in which no carbamate deprotonation occurs.[20] In accordance with this result, we assume that only two equivalents of base are consumed in the ligand-deprotonation reactions. Consequently, the required third equivalent of base must be involved in a different process. If three equivalents of isopropoxide were consumed in the formation of the catalyst, we would obtain inactive anionic ruthenium complexes. As previously demonstrated, the use of ligands containing three equally acidic sites (e.g., the *N*-tosyl analogue of **1**) resulted in ruthenium complexes with no catalytic activity. To study further the nature of the catalyst, we performed reduction reactions using mixtures of ligands **2** and ***ent*-2**. The absence of a nonlinear relationship between the enantiomeric purities of the ligand and product in the transfer hydrogenation of acetophenone by using ligands **2**/***ent*-2** (see Supporting Information) is in favor of a monoligated ruthenium catalyst. Based on these facts, we propose that a ruthenium complex with structure **12** is formed under the reaction conditions (Scheme 1).[21]



Scheme 1. Proposed catalytic intermediates in the reduction of acetophenone under hydrogen-transfer conditions.

This 18-electron complex must release one of its donor atoms to form the reducing ruthenium–hydride species. Release of the weakly coordinated carbamate followed by subsequent hydride formation would again generate a formally negatively charged, catalytically inactive ruthenium complex. Instead, in line with the significant effect imposed by the alkali cation, it can be proposed that ruthenium complex **12** reacts with *i*PrOLi to form hydride complex **13**. The substrate reacts with the hydride complex **13** to generate the desired secondary alcohol. The role of the lithium ion present in complex **13** is to activate and direct the incoming ketone prior to hydride transfer from the ruthenium center. We suggest that the transfer of the hydride and alkali ion to the substrate proceeds via a six-membered transition state, analogous with the aluminium alkoxide mediated Meerwein–Pondorff–Verley reduction[22] (Figure 3a and b). Lewis acid activation and orientation of the ketone by lithium (or other alkali-metal)-ion coordination[23] are important for the selective reduction process employing the $[\{RuCl_2(p\text{-cymene})\}_2]$–pseudo-dipeptide catalytic system. The increased selectivity obtained in the presence of lithium salts compared to other alkali cations can be explained in terms of the formation of a tighter transition state with the smaller lithium ion (Figure 3c). Consequently, the close participation of larger-sized alkali cations in the transition state should be limited, leading to lower reactivity and selectivity. The observation that the product configuration is predominantly determined by the stereogenic center in the amino

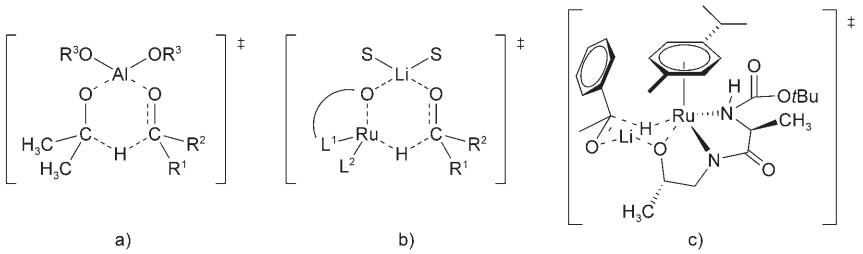


Figure 3. a) Cyclic transition state for the aluminium alkoxide mediated reduction of ketones by 2-propanol (Meerwein–Pondorff–Verley reduction). b) Proposed schematic cyclic transition state involved in the Ru^{II}-(arene)–pseudo-dipeptide-catalyzed reduction of ketones in the presence of lithium salts. c) Possible geometry of the transition state showing the important interactions between the ruthenium hydride, the lithium cation, and the substrate.

acid moiety of the ligand is explained by the presence of this center in the *N*,*N*-chelate of **13**. In addition, the chirality of the amino acid certainly has a strong influence on the configuration of the ruthenium stereogenic center.

Computational results: To further our understanding of the effect of different-sized alkali cations on the transition-state geometry of the hydrogen-transfer reaction, we performed gas-phase DFT computations on the reaction systems. We decided to perform these calculations because our recent studies[24] demonstrated that the intimate details of complex reaction mechanisms could be treated well by computational methods. The computational details are described in the Experimental Section. A comprehensive account of solvent effects in the model with explicit solvent molecules and a polarizable continuum medium will be discussed elsewhere. Here, we present gas-phase calculations that enable comparative estimation of the geometrical parameters of the transition states involving Li^+, Na^+, and K^+ complexes. The calculated transition-state (TS) structures are presented in Figure 4.[25]

As illustrated in Figure 4, the TS structure is looser for ions with a larger ionic radius. The Ru–C and Ru–ion distances increase as the alkali-ion radii increase,[26] resulting in a larger Ru–H–C–O–ion–O ring motif. In addition, in contrast to the results of theoretical studies by Noyori and coworkers on the ruthenium–TsDPEN catalyst,[27] aryl–aryl (CH–π)-directing interactions between the η^6-arene ligand and the substrate do not appear to be crucial for hydride transfer using the ruthenium–pseudo-dipeptide catalyst.[29]

Addition of crown ethers and cryptands: The observed loosening of the TS with larger alkali cations is likely to be responsible for the lower enantiocontrol observed in systems using *i*PrONa or *i*PrOK as base. If this assumption is true, a further increase in cation size may lead to an additional drop in the enantioselectivity of the transfer-hydrogenation process in the pseudo-dipeptide-based catalytic system. Indeed, reduction reactions performed with $[BnNMe_3]OH$ as base resulted in poor conversion and enantioselectivity of the alcohol formed (entries 7 and 13, Table 3), however, upon addition of LiCl the *ee* was dramatically improved (entries 8 and 14, Table 3). Furthermore, the addition of macrocyclic ethers [15]crown-5 or [18]crown-6, which selectively complex alkali cations and increase their effective size, to reaction mixtures containing the bases *i*PrONa or *t*BuOK, respectively, led to a noticeable decrease in both the conversion and enantioselectivity of 1-phenylethanol (entries 2, 4,

Table 3. Effect of cation size on the $[\{RuCl_2(p\text{-cymene})\}_2]$–pseudo-dipeptide-catalyzed transfer hydrogenation of acetophenone.[a,b]

Entry	Ligand	Base ([mol%])	Additive ([mol%])	Conver. [%][c]	*ee* [%][c]
1	**1**	*i*PrONa (5)	–	83	92 (*S*)
2	**1**	*i*PrONa (5)	[15]crown-5 (30)	68	83 (*S*)
3	**1**	*t*BuOK (5)	–	70	91 (*S*)
4	**1**	*t*BuOK (5)	[18]crown-6 (30)	40	64 (*S*)
5	**1**	*i*PrOLi (10)	–	86	95 (*S*)
6[d]	**1**	*i*PrOLi (10)	cryptand 2.1.1 (30)	22	64 (*S*)
7[e]	**1**	$[BnNMe_3]OH$	–	21	78 (*S*)
8[e]	**1**	$[BnNMe_3]OH$	LiCl (10)	21	92 (*S*)
9	**3**	*i*PrONa (5)	–	76	97 (*S*)
10	**3**	*i*PrONa (5)	[15]crown-5 (30)	52	92 (*S*)
11	**3**	*i*PrOLi (5)	–	77	98 (*S*)
12[d]	**3**	*i*PrOLi (5)	cryptand 2.1.1(30)	6	14 (*S*)
13[e]	**3**	$[BnNMe_3]OH$	–	10	73 (*S*)
14[e]	**3**	$[BnNMe_3]OH$	LiCl (10)	40	98 (*S*)
15	**8**	*i*PrONa (5)	–	24	61 (*R*)
16	**8**	*i*PrONa (5)	[15]crown-5 (30)	17	48 (*R*)

[a] Reaction conditions: acetophenone (1 equiv, 0.2 M in 2-propanol), $[\{RuCl_2(p\text{-cymene})\}_2]$ (0.5 mol%), ligand (1.1 mol%), base (see table), room temperature. [b] The reaction mixtures were analyzed after 30 min to avoid erosion of *ee*, which can occur as the reaction equilibrium is approached; here, at 91–92% conversions. [c] Conversions and enantioselectivities were determined by GLC. [d] Cryptand 2.1.1 = 4,7,13,18-tetraoxa-1,10-diazabicyclo[8.5.5]eicosane. [e] $[BnNMe_3]OH$ was employed as a 40% aqueous solution.

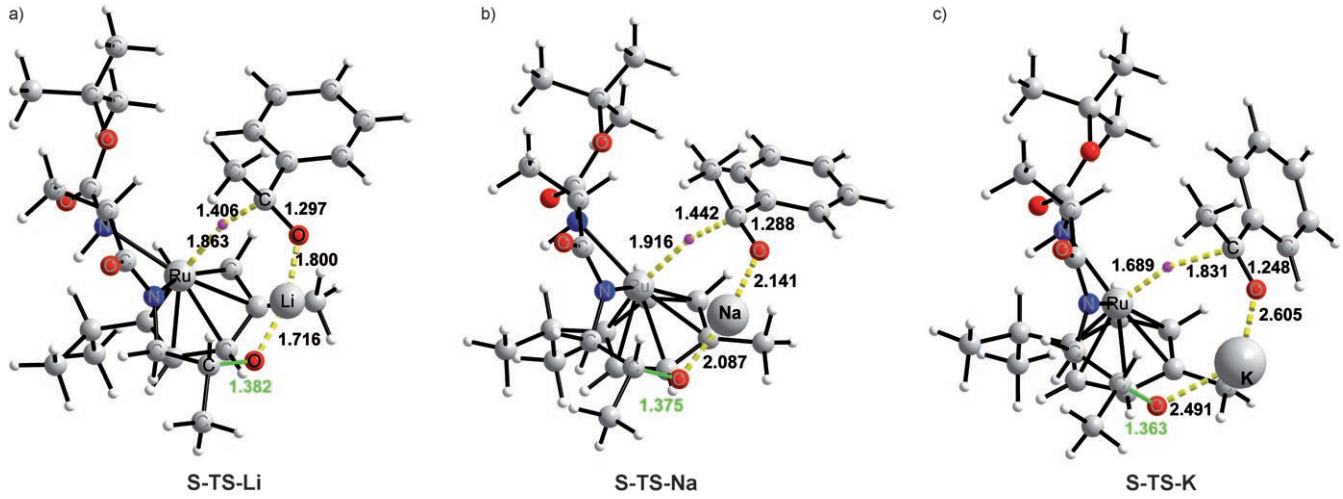


Figure 4. DFT-optimized TS structures involving a) Li^+, b) Na^+, and c) K^+ ions. All distances are in Å. The TS structures were characterized by one imaginary frequency along the appropriate normal mode. The key geometrical parameters [Å] are: **S-TS-Li**: Ru–C 3.231, Ru–Li 3.768, O–O 3.388; **S-TS-Na**: Ru–C 3.327, Ru–Na 3.997, O–O 3.903; **S-TS-K**: Ru–C 3.474, Ru–K 4.833, O–O 3.987.

10, and 16, Table 3). Addition of [12]crown-4 to the system containing *i*PrOLi did not affect the reaction outcome significantly.[30] However, performing the reaction under the same conditions in the presence of cryptand 2.1.1 led to a drastic decrease in conversion and enantioselectivity (entry 12, Table 3), which is most likely due to the increased size of the cation upon coordination to the crown ethers or the cryptand. This coordination inhibits participation of the cations in any preorganization of the reaction partners that lead to the product, and consequently, lower activity and scrambling of the enantioselectivity are observed. These results provide additional evidence that the alkali cation must play a significant intimate role in the hydride-transfer step of the reaction when pseudo-dipeptides are used as ligands. The use of triethylamine as base resulted in a low conversion (<2%) and selectivity (<2%), and this result was not improved by the addition of LiCl, indicating that high base strength is important for promoting the reaction.

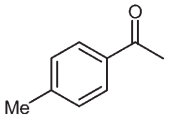
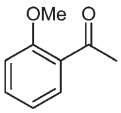
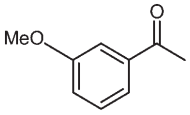
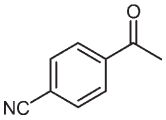
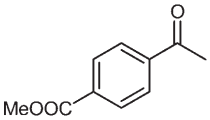
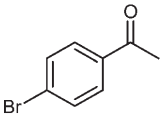
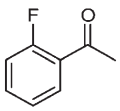
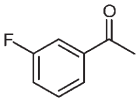
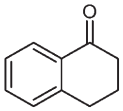
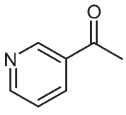
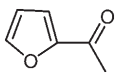
Effect of lithium chloride on the reduction of other ketones: To investigate the scope of the lithium salt effect, we studied the effect of lithium chloride on the transfer hydrogenation of different aromatic and heteroaromatic ketones by using ligands **1** (Table 4) and **3** (see Supporting Information) as matching ligands of the first- and second-generation pseudo-dipeptides, respectively. The data presented in the tables show that the magnitude of the effect is dependent on the nature of the substrate. Surprisingly, an increase in *ee* of up to 47% could be obtained for the transfer hydrogenation of 4-cyanoacetophenone by using ligand **1** upon addition of LiCl (entry 8, Table 4).

Thus, the addition of lithium salts to hydrogen-transfer catalytic systems based on pseudo-dipeptides is generally useful for enhancing the reduction of different aromatic and heteroaromatic ketones.

Conclusion

We have demonstrated that the transfer hydrogenation of ketones catalyzed by the [{$RuCl_2$(*p*-cymene)}$_2$]–pseudo-dipeptide system is highly dependent on the presence of alkali cations. The addition of crown ethers or cryptands significantly reduces the activity and selectivity of the reduction reaction, which implies that the alkali ion is part of the reducing catalyst and that a different reaction mechanism must operate. Furthermore, increased enantioselectivity was observed upon addition of lithium salts to the system. By employing DFT computations we could illustrate and validate key mechanistic findings, and the lithium effect is explained in terms of a significant tightening of the transition state that leads to the product alcohol. No alkali-ion effect has been observed in "traditional" transfer-hydrogenation systems (e.g., Ru–arene complexes of 1,2-amino alcohols), revealing the uniqueness of these modular pseudo-dipeptides with functional groups operating in a highly cooperative enzymelike mode.

Table 4. Effect of lithium chloride on the reduction of different aromatic and heteroaromatic ketones by using ligand **1**.[a]

Entry	Substrate	LiCl [mol%]	Time [min]	Conver. [%][b]	*ee* [%][b]
1		–	30	64	93 (*S*)
2		10	30	79	92 (*S*)
3		–	120	20	82 (*S*)
4		10	120	32	83 (*S*)
5		–	30	86	90 (*S*)
6		10	30	88	90 (*S*)
7		–	120	8	16 (*S*)
8		10	120	13	63 (*S*)
9		–	30	97[c]	92 (*S*)
10		10	30	99[c]	96 (*S*)
11		–	120	96	89 (*S*)
12		10	120	99	94 (*S*)
13		–	120	81	82 (*S*)
14		10	120	95	84 (*S*)
15		–	30	97	91 (*S*)
16		10	30	97	95 (*S*)
17		–	30	3	87 (*S*)
18		10	30	31	91 (*S*)
19		–	120	11	82 (*S*)
20		10	120	20	89 (*S*)
21		–	30	89	63 (*S*)
22		10	30	91	70 (*S*)

[a] Reaction conditions: acetophenone (1 equiv, 0.2 M in 2-propanol), [{$RuCl_2$(*p*-cymene)}$_2$] (0.5 mol%), ligand (1.1 mol%), *i*PrONa (5 mol%), room temperature. [b] Conversions and enantioselectivities were determined by GLC. [c] Partial transesterification of the methoxycarbonyl group with isopropanol was observed.

Experimental Section

Computational methods—technical details: Geometry optimizations of transition states and stable intermediates were carried out by using the B3LYP functional[31] with the lacvp*/6-31G(d,p) basis set.[32,33] All degrees of freedom were optimized, and only positive vibrational frequencies were obtained for the optimized geometries of the intermediates. The transition states were characterized by the presence of only one imaginary vibrational frequency along the appropriate normal mode. In the second step, B3LYP energies were evaluated for the optimized geometry by using the much larger triple-ζ basis set, lacv3p**+/6-311+G(d,p) with additional diffuse and polarization functions. Control calculations with respect to energy minimization and TS search were performed by using the BP86 functional. No discrepancy between the results of the two functionals was found for identical basis sets.

All computations were performed by using the Jaguar v4.0 and v6.0 suite of ab initio quantum chemistry programs.[34] Frequency analysis of the TS structures was performed by using Jaguar v6.0.

General procedure for the transfer hydrogenation of ketones by using ligands 1–8: Ligand (0.011 mmol), $[RuCl_2(p\text{-cymene})]_2$ (0.005 mmol), and LiCl (0.1 mmol) (or other additives; see details in the tables) were dried under vacuum in a dry Schlenk tube for 15 min. 2-Propanol (4.5 mL) and a 0.01 M solution of *i*PrONa (0.5 mL, 5 mol%) in *i*PrOH was added under nitrogen. The solution was stirred for 5 min and then the ketone (1 mmol) was added. The reaction mixture was stirred at ambient temperature. Aliquots were taken after the reaction times indicated in the tables and were then passed through a pad of silica with EtOAc as the eluent. The resulting solutions were analyzed by GLC (CP Chirasil DEXCB). For analytical data, see Supporting Information.

Acknowledgements

We thank Professor Masakatsu Shibasaki of the University of Tokyo and Professors Lena Mäler and Armando Córdova of the Stockholm University for valuable discussions. The Swedish Research Council and the Wenner-Gren Foundation are thanked for financial support and a postdoctoral fellowship (A.B.Z.), respectively.

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Received: November 7, 2005
Published online: January 27, 2006

