

Origin of Enantioselectivity in the Ru(arene)(amino alcohol)-Catalyzed Transfer Hydrogenation of Ketones

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The origin of the enantioselectivity in the ruthenium-catalyzed transfer hydrogenation has been studied by means of experiment and density functional theory calculations. The results clearly show that electrostatic effects are of importance, not only in the T-shaped arene-aryl interaction in the favored transition state but also between the aryl of the substrate and the amine ligand in the disfavored TS. In addition, the electrostatic interaction between the alkyl substituent of the substrate and the catalyst is of importance to the enantioselectivity. The major cause of enantioselection is found to be of nonelectrostatic origin. This inherent property of the catalytic system is discussed in terms of dispersion forces and solvent effects. Finally, a minor but well-characterized steric effect was identified. The success of this class of catalysts in the reduction of alkyl aryl ketones is based on the fact that all factors work in the same direction.

Introduction

The reduction of organic compounds is a subject of remarkable interest from both academic and industrial perspectives. Several viable methodologies have been established for this purpose, and most of them make use of a metal, in either stoichiometric or catalytic amounts, to promote the reaction between the reducing agent and the substrate. Transfer hydrogenation is a further one of these methodologies, and among the metal-catalyzed processes it is second only to hydrogenation with molecular hydrogen in its importance. Enantioselective transfer hydrogenation has been intensely studied during the past decade.¹ Noyori and co-workers reported on the use of monotosylated diamines as ligands (L) in the Ru-(arene)(L)-catalyzed transfer hydrogenation of aromatic ketones.² This important discovery led to the development of new chiral ligands by our group³ and by the groups of Wills,⁴ van Leeuwen,⁵ Knochel,⁶ and others.⁷

With this type of catalysts, aryl alkyl ketones are reduced with high enantiomeric excess using *i*-PrOH as reductant. The reaction mechanism has been investigated by quantum chemical methods by our group⁸ and by the groups of Noyori⁹ and van Leeuwen.¹⁰ In addition, intermediates in the catalytic cycle have been isolated, and the kinetic isotope effects have been determined.^{7h,11,12} These investigations support a mechanism with a concerted delivery of an N–H proton from the ligand and a hydride from ruthenium.

Stereoselectivity could arise from either attractive or repulsive forces between the substrate and the catalyst or a combination thereof. Enzymes, also recognized as excellent catalysts for enantioselective reactions, are

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known to use electrostatic interactions, hydrophobic interactions, hydrogen bonds, and dispersion interactions in combination with repulsive steric interactions to specifically bind and transform a substrate.¹³ In asymmetric catalysis a chiral ligand is commonly used in place of a protein to differentiate between two prochiral faces via *repulsive* steric interactions. In some cases though, enantioselection is realized by *stabilization* of one of the diastereomeric transition states by attractive interactions. One such well-known example is the Sharpless asymmetric dihydroxylation that partly relies on attractive interactions between aromatic moieties. This interaction could, according to the participating molecular fragments and the geometry of the transition state, be referred to as π -stacking.¹⁴ The importance of arene-arene interactions as well as alkyl-arene interactions is still a matter of debate.¹⁵

In the case of ruthenium-catalyzed asymmetric transfer hydrogenation Van Leeuwen et al.¹⁰ suggest that steric hindrance is the major factor determining the enantioselectivity. To the contrary, Noyori et al. earlier proposed that the selectivity is due to an attractive CH/ π interaction between the aryl of the substrate and the arene in the catalyst.^{11,16} On the basis of MP2 and B3LYP calculations, this interaction is suggested to be dominated by electrostatic forces together with a nonnegligible charge-transfer component. This proposal nicely rationalizes why aliphatic ketones are poor substrates and that electron-withdrawing substituents on acetophenone substrates decrease the enantiomeric excess. For the catalyst derived from an amino alcohol and [RuCl₂(hexamethylbenzene)]₂, a stabilizing electrostatic attraction between C(sp³)H/ π is proposed. Again quantum chemical calculations show that the hydrogens of the methyl groups of the hexamethylbenzene have net positive charge.

In the first published quantum chemical investigation of the reaction,⁸ we concluded that gas-phase density functional theory calculations (B3LYP) are not able to reproduce the degree of enantioselection experienced in the reaction. In this approach, two major forces are neglected, namely, the dispersion interaction between catalyst and substrate and the effect of the solvent. Taking this latter effect into account by performing

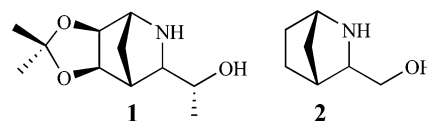


FIGURE 1. 2-Azanorbomnyl-3-methanol ligands **1** and **2**.

calculations using the polarized continuum model (PCM),¹⁷ a great improvement in the correlation between predicted and experimental enantioselectivity was achieved. Thus, we arrived at a conclusion very different from those of Van Leeuwen and Noyori, namely, that electrostatics and sterics, well taken care of by our DFT calculations, could not be the main contributors to the enantioselectivity. In this paper we have studied in detail the impact of electrostatics and sterics on enantioselectivity, trying to form a consensus picture of the origin of the enantioselectivity in the ruthenium-catalyzed transfer hydrogenation.

We have earlier reported that ligands **1** and **2** are excellent ligands in the ruthenium-catalyzed asymmetric transfer hydrogenation of aromatic ketones (Figure 1). Here, we present our conclusions on the origin of the enantioselectivities achieved in the reactions using these ligands.

Computational Methods

Geometries of all substrates were calculated using the Gaussian electronic structure program,¹⁸ using B3LYP,¹⁹ a density functional based on a hybrid functional, together with the double- ζ quality basis set LANL2DZ.²⁰ The basis set involve the use of d95 for C, N, O, and H. Atomic charge distributions were thereafter fitted to the electrostatic potential at points selected according to the CHelpG²¹ scheme using the procedure implemented in Gaussian 98. This was done using the B3LYP/6-311+G(d,p) wave functions at the B3LYP/LANL2DZ geometries. For the 3-substituted substrates, there are two alternative conformations relating to the position of the substituent relative to the acetyl group. In this work we report data from the *s-trans* conformations. The *s-cis* conformations were also investigated, but no significant differences were detected. The sum of the calculated charges of the six heavy atoms in the aromatic ring of the substrate were used as a measure of the charge distribution of the aromatic ring.

To assess the performance of B3LYP in terms of predicting relative enantioselectivities between substrates with different charge distribution, we performed transition state calculations using two different substrates, acetophenone and 2,3,4,5,6-

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TABLE 1. Transfer Hydrogenation of Substituted Acetophenones with Ru(*p*-cymene)(1) as Catalyst

entry	Ar	time (min)	conv (%) ^a	ee (%) ^b (config) ^c	Σ(<i>q</i>) ^d
1	3-NH ₂ -C ₆ H ₄	4	98	99(S)	−0.26
2	3-MeO-C ₆ H ₄	4	100	98(S)	−0.29
3	C ₆ H ₅	6	96	96(S)	−0.44
4	3-Me-C ₆ H ₄	4	99	96(S)	−0.39
5	4-Me-C ₆ H ₄	6	92	93(S)	−0.38
6	4-Cl-C ₆ H ₄	3	92	93(S)	−0.29
7	4-Br-C ₆ H ₄	3	98	91(S)	−0.28
8	4-pyridyl	3	97	91(S)	−0.26
9	3-NO ₂ -C ₆ H ₄	4	99	91(S)	−0.29
10	4-CF ₃ -C ₆ H ₄	3	97	89(S)	−0.35
11	3-pyridyl	4	98	89(S)	−0.27
12	4-NO ₂ -C ₆ H ₄	3	95	88(S)	−0.31
13	2,6-F ₂ -C ₆ H ₃	3	97	88(S)	−0.10
14	3,4,5-F ₃ -C ₆ H ₂	3	98	82(S)	0.15
15	2,3,4,5,6-F ₅ -C ₆	3	98	32(S)	0.56

^a Determined by ¹H NMR. ^b Determined by chiral GC. ^c Absolute configuration determined by comparison with reported optical rotation. ^d Σ(*q*) refers to the sum of the electrostatic potential derived atomic charges of the six heavy atoms in the aromatic ring of the substrate.

TABLE 2. Transfer Hydrogenation of Substituted Acetophenones with Ru(HMB)(1) as Catalyst

entry	Ar	time (min)	conv (%) ^a	ee (%) ^b (config) ^c
1	C ₆ H ₅	60	93	97(S)
2	2,6-F ₂ -C ₆ H ₃	60	98	94(S)
3	4-Br-C ₆ H ₄	60	98	92(S)
4	4-CF ₃ -C ₆ H ₄	60	97	91(S)
5	3,4,5-F ₃ -C ₆ H ₂	60	92	84(S)
6	2,3,4,5,6-F ₅ -C ₆	120	99	78(S)

^a Determined by ¹H NMR. ^b Determined by chiral GC. ^c Absolute configuration determined by comparison with reported optical rotations.

pentafluoroacetophenone. These calculations were performed in the Jaguar program.²² The transition state structures were located using the quadratic synchronous transit (QST) method and the B3LYP functional together with the LACVP ECP and basis set. Normal-mode analysis revealed one imaginary frequency for each structure. LACVP in Jaguar defines a combination of the LANL2DZ basis set for ruthenium²⁰ and the 6-31G basis set for other atoms. LACVP implies the use of an effective core potential for 28 core electrons of ruthenium and a (5s,6p,4d) primitive basis contracted to [3s,3p,2d]. Final energies were retrieved from single point calculations at B3LYP/LACV3p+**, LACV3p+** differs from LACVP by using the 6-311+G** basis set in place of 6-31G.

Results

Four different studies were performed to obtain an understanding of what is important for the enantiofacial discrimination observed in the reduction of alkyl aryl ketones. The variations studied were (1) substituents on the aryl of the substrate using Ru(*p*-cymene)(1) as catalyst, (2) substituents on the aryl of the substrate using Ru(hexamethylbenzene)(1) as catalyst, (3) changes of the substituents of the arene in the catalyst using acetophenone as substrate and finally, (4) a study of how the alkyl part of the substrate influences the enantioselectivity. The results are summarized in Tables 1–5.

TABLE 3. Variation of the Ru(arene) in Transfer Hydrogenation of Acetophenone Using Amino Alcohol 1

entry	Ru(arene)	time (min)	conv (%) ^a	ee (%) ^b (config)
1	Ru(HMB) ^c	60	92	97(S)
2	Ru(<i>p</i> -cymene)	10	90	96(S)
3	Ru(PhCO ₂ Et)	6	96	88(S)
4	Ru(benzene)	4	94	81(S)

^a Determined by ¹H NMR. ^b Determined by chiral GC. ^c HMB = hexamethylbenzene.

TABLE 4. Transfer Hydrogenation of Ketones with Variation of Aliphatic Substituent Using Ru(*p*-cymene)(2) as Catalyst^{3b}

entry	R	conv (%) ^a	ee (%) ^b (config) ^c	STERIMOL B1 parameter
1	Me	91	94(S)	1.52
2	Et	81	93(S)	1.52
3	<i>n</i> -Pr	90	92(S)	1.55
4	<i>n</i> -Bu	78	95(S)	1.52
5	<i>n</i> -hexyl	85	95(S)	1.52
6	<i>i</i> -Pr	76	90(S)	1.90
7	<i>i</i> -Bu	93	90(S)	1.90
8	<i>t</i> -Bu	46	64(S)	2.60

^a Determined by ¹H NMR. ^b Determined by chiral GC. ^c Absolute configuration determined by comparison with reported optical rotations.

TABLE 5. Transfer Hydrogenation of Ketones with Variation of the Aliphatic Substituent Using Ru(*p*-cymene)(1) as Catalyst

entry	R	time (min)	conv (%) ^a	ee ^b (%) (config) ^c	STERIMOL B1 parameter
1	Me	6	96	96(S)	1.52
2	<i>n</i> -Pr	20	91	93(S)	1.55
3	<i>i</i> -Pr	30	92	90(S)	1.90
4	<i>i</i> -Bu	30	93	90(S)	1.90
5	<i>t</i> -Bu	30	83	85(S)	2.60

^a Determined by ¹H NMR. ^b Determined by chiral GC. ^c Absolute configuration determined by comparison with reported optical rotations.

Discussion

We have earlier discovered that electrostatics is important for the overall rate of the ruthenium-catalyzed transfer hydrogenation of aromatic ketones.^{3a} Therefore, it is not far-fetched that electrostatics could be of importance also for the enantioselectivity. However, the interaction that was found to increase the rate was a dipole–dipole stabilization of the transition state, whereas the interaction that is expected to influence the enantioselectivity is a quadrupole–quadrupole interaction. This latter interaction is generally weaker and more dependent on the distance between the interacting partners. Fortunately, the arene of the catalyst is in direct contact with the aryl of the reacting substrate. Thus, a significant contribution could be expected as suggested by Noyori et al.^{11,16}

However, could this agreeably weak interaction really be the main contributor to the enantioselectivity as suggested by the same authors? This skepticism is based on several publications of studies of T-shaped arene–arene interactions, claiming that, at least for the generic system consisting of two interacting benzene rings, the main contribution to the stability of the molecular complex is

(22) Jaguar 4.2; Schrödinger, Inc., Portland, OR, 1991–2000.

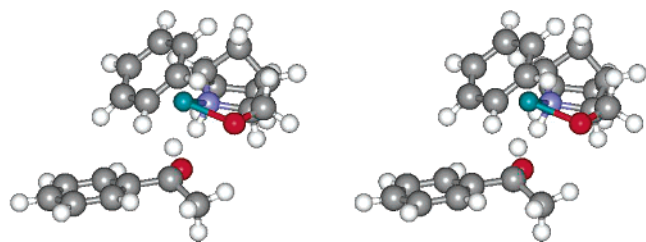


FIGURE 2. Favored TS showing a close contact between the methyl of the substrate and the amino alcohol oxygen and a tilted T-shaped arene-aryl interaction between catalyst and the phenyl group of the substrate (stereoimage).

the dispersion energy.^{15a–c,23} The consensus that can be extracted from the literature is that dispersion interactions dominate the interaction energy, whereas the electrostatic interactions generally determine the geometrical preference. To shed light on the origin of the enantioselectivity, we decided to reinvestigate the current reaction with a combination of experiments and calculations.

A primary study investigated the efficiency of the catalyst Ru(*p*-cymene)(**1**) in the enantioselective reduction of a wide range of substituted acetophenones. To describe the electrostatic properties of the aromatic rings of the substrates, the electrostatic potential based atomic charges of the substrates were calculated using the hybrid density functional method B3LYP and the ChelpG method. The results are summarized in Table 1.

For simplicity, we used the sum of the atomic charges of the atoms in the aromatic ring of the substrate ($\Sigma(q)$) as an electrostatic measure. Plotting the observed difference in transition state energies ($\Delta\Delta G^\ddagger_{\text{Exp}}(R-S)$ kcal/mol) against $\Sigma(q)$, Figure 3, a reasonable correlation is found. This crude model, neglecting conformational effects as well as the effect of the relative orientation of the substrate and the catalyst, indeed supports the conclusion made by Noyori that the electrostatic interactions are important. Apart from two obvious outliers (*m*-MeO and *m*-NH₂, both substituents interacting directly with the arene ligand), the correlation is fair for such a rudimentary model.²⁴

If the columbic attraction between the hydrogens of the arene ligand and the aryl carbons of the substrate (Figure 2) would be the main contributor to the selectivity, then reverting the charge distribution of the aryl should lead to the opposite enantiomer of the product. The best way to do this is to replace the hydrogens by fluorines, as in 2,3,4,5,6-pentafluoroacetophenone. Using Ru(*p*-cymene)(**1**) as catalyst, this substrate is reduced in 32% ee with the same asymmetric induction as observed with the other acetophenone derivatives. Evidently, there is more to the enantioface discrimination than simply the charge distribution in the aromatic ring.

The energetic contribution of this nonelectrostatic contributor to the enantioselection could be estimated to ca. 1.4 kcal/mol for this catalyst, as calculated from the intercept in Figure 3. This is slightly more than the electrostatic contribution to the enantioselectivity in, for example, acetophenone where the electrostatic contribu-

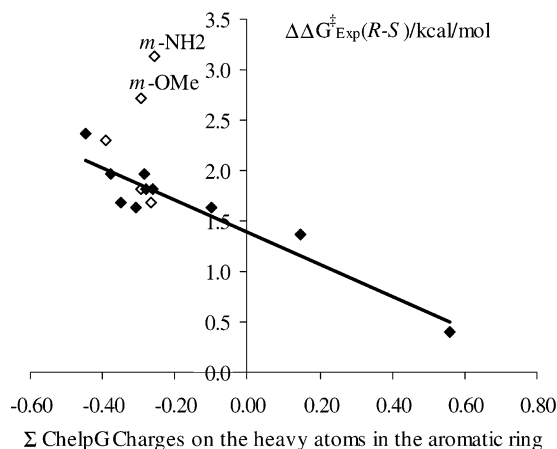


FIGURE 3. Linear correlation between the sum of charges of the atoms in the aromatic ring and the difference in transition state energy $\Delta\Delta G^\ddagger_{\text{Exp}}(R-S)$ (kcal/mol) using Ru(*p*-cymene)(**1**) as catalyst. Excluding the *m*-substituted substrates (◇) gives slope = -1.60 , intercept = 1.39 , $R^2 = 0.883$.

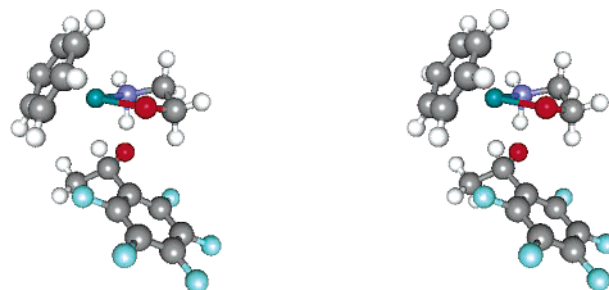
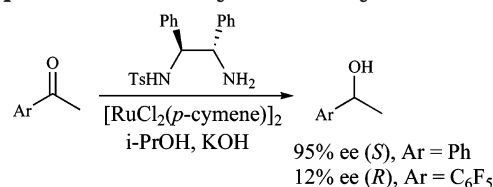


FIGURE 4. (*S*)-Transition state for reduction of 2,3,4,5,6-pentafluoroacetophenone showing a close contact between the methyl of the substrate and the arene ligand and a possible electrostatic interaction between the phenyl group of the substrate and the amino alcohol oxygen of the ligand (stereoimage).

SCHEME 1. Transfer Hydrogenation of Acetophenone with Noyori's Catalyst



tion of the arene-phenyl interaction could be estimated to ca. 1 kcal/mol.

Although we have discussed the electrostatic effects in terms of an arene-aryl interaction, it is far from certain at this point that the interaction is only attractive. Another plausible explanation could be that there is an electrostatic repulsion (Figure 4) between the aryl of the substrate and the alkoxy substituent (or sulfonamide with the amino sulfonamide ligands) of the ligand in the disfavored diastereomer of the transition state. Accordingly, reduction of acetophenone with Noyori's monotosylated diamine gives 95% ee (*S*), whereas 2,3,4,5,6-pentafluoroacetophenone is reduced in 12% ee with the opposite absolute configuration (*R*) (Scheme 1). Thus, this system is slightly more sensitive to changes in the electrostatics of the substrate and is also expected to be

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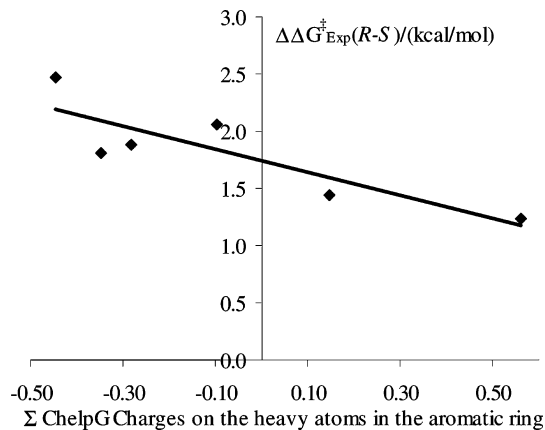


FIGURE 5. Linear correlation between the sum of charges of the heavy atoms in the aromatic ring and the difference in transition state energy $\Delta\Delta G_{\text{Exp}}^{\ddagger}(R-S)$ (kcal/mol) using Ru-(HMB)(1) as catalyst; slope = -1.0 , intercept = 1.74 , $R^2 = 0.74$.

less dependent on nonelectrostatic contributions to the enantioselectivity.

To examine the enantioselection further, we changed the arene of the catalyst from *p*-cymene to the less polar and more lipophilic hexamethylbenzene ligand. This change is known to be beneficial for the enantioselectivity in many cases. Thus, if electrostatics would be the major cause of the enantioselectivity, the plot of $\Delta\Delta G_{\text{Exp}}^{\ddagger}(R-S)$ versus the sum of the charges of the atoms in the aromatic rings of the substrates tested would reveal a steeper slope. If, on the other hand, the electrostatic repulsion between the amino alcohol ligand and the aryl of the substrate would be dominating (Figure 4) the slope should probably be as steep or even steeper as the result of a tighter substrate-catalyst interaction in the transition state. As a third alternative, the electrostatic contribution to the enantioselectivity will be decreased as a result of the less polar arene of the catalyst, and some other property such as dispersion or solvation effects give rise to the increased enantioselectivity. This last alternative should result in an enantioselectivity that is less sensitive to the electrostatic properties of the substrate.

Figure 5 depicts the calculated results, with the gradient dramatically reduced and the intercept increased slightly. This indicates that the relative contribution from the electrostatics is reduced and that what could be called the intrinsic selectivity is increased. To conclude, the interaction between the arene of the catalyst and the aryl of the substrate seems to be the major electrostatic interaction present in the amino alcohol system.

Having identified this difference between *p*-cymene and hexamethylbenzene, it was of interest to expand this study to other arenes. To get some reference data points, we determined the enantiomeric excess by using benzene and ethylbenzoate as ligands to ruthenium in the reduction of acetophenone. Ru(benzene)(1) gave only 81% ee, and the corresponding ethylbenzoate catalyst gave 88% ee. These results can be rationalized by means of a decreased dispersion/solvophobic effect rather of suggesting that these two arenes have less positively charged hydrogens. Any rationalization based on steric interactions would give the opposite result because of the smaller size of benzene compared to hexamethylbenzene.

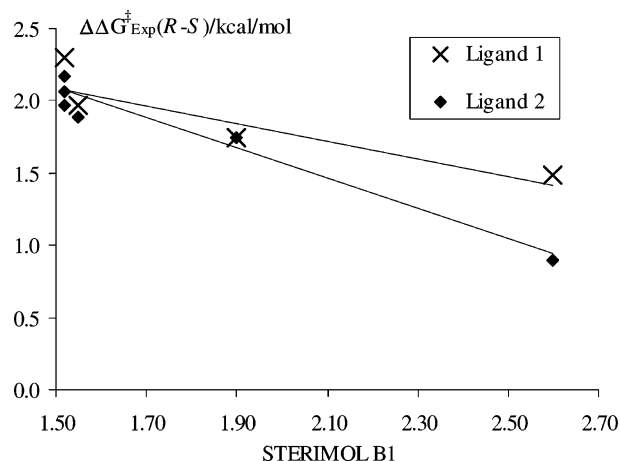


FIGURE 6. Correlation between $\Delta\Delta G_{\text{Exp}}^{\ddagger}(R-S)$ (kcal/mol) and the STERIMOL B1 parameter of the alkyl group of the alkyl phenyl ketones Ru(*p*-cymene)(L). (L = 1: slope = -0.6 , $R^2 = 0.77$. L = 2: slope = -1.05 , $R^2 = 0.94$).

As mentioned earlier, dispersion forces and solvation and steric effects could, in addition to the electrostatic effects, be of importance to the enantioselectivity. Gas-phase B3LYP calculations that only take steric and electrostatic effects²⁵ into account are in agreement with the drop in enantioselectivity of 2,3,4,5,6-pentafluoroacetophenone compared to acetophenone using Ru(benzene)(1) as model for the real catalyst Ru(*p*-cymene)(2), $\Delta\Delta E_{\text{Calc}}^{\ddagger} = 1.3$, $\Delta\Delta E_{\text{Exp}}^{\ddagger} = 2.0$ kcal/mol. Thus, the decreased enantioselectivity is probably, to a large extent, governed by the change in the electrostatic potential of the substrate. Conversely, these gas-phase calculations are not able to reproduce the extent of enantioselection displayed experimentally; instead, the enantiomeric excess is underestimated.⁸ This result is in agreement with the conclusions drawn above. Thus, there are clear indications that some additional parameters are involved, such as dispersion forces and solvation effects.

As a final part of the investigation, we examined how steric effects influence the enantioselectivity. As noted above, Ru(benzene) catalysts generally give rise to lower selectivities when compared to the sterically more demanding Ru(HMB) catalysts. Considering the larger size of the phenyl group compared to the methyl group in acetophenone derivatives, it would be logic to state that steric factors therefore must be of minor importance. Otherwise, the enantioselectivity should increase instead of decrease. However, Because in this example the cause of the reduction in enantioselectivity is more likely to be the result of a reduction in dispersion forces or a decrease in the solvation effect, there is still room for steric impacts on the enantioselectivity.

Figure 6 displays the plot of $\Delta\Delta E^{\ddagger}(R-S)_{\text{Exp}}$ in experiments using Ru(*p*-cymene)(2) as catalyst versus a steric descriptor of the width of the alkyl substituent of the substrate. The parameter used to describe this

(24) More elaborate methods such as cross validated partial least squares (PLS) using the individual electrostatic potential fitted atomic charges gave improved results. However, as the purpose of this study is to illustrate the relative contribution of different forces rather than developing predictive models, we did not include these models.

(25) Charge transfer is also included but not likely to be of importance for these systems.

property is the STERIMOL B1 parameter.²⁶ As illustrated by the plot, the enantiomeric excess is nicely correlated with B1, and bulkier alkyl groups tend to decrease the enantioselectivity. Thus, as B1 of a phenyl group is slightly larger than that of a methyl group, there is an intrinsic steric factor that enhances the enantioselectivity in the reduction of acetophenone and other linear chain aliphatic phenyl ketones. A limited study using the Ru(*p*-cymene)(1) indicates slightly weaker steric effects for this catalyst (Table 5).

An example where steric discrimination could be of importance to the enantioselectivity is the dialkyl substrate cyclohexylmethyl ketone, which is reduced in 23% ee with the expected absolute configuration of the product alcohol (*S*) and 90% conversion after 2 h with the Ru(*p*-cymene)(1) catalyst. On the other hand, transfer hydrogenation effected by the Ru(HMB)(1) catalyst is slightly more selective and yields (*S*)-1-cyclohexylethanol in 30% ee and 66% conversion after 2 h. Thus, again the steric effect is less important than other factors.

Conclusions

Our results can be summarized as follows. Aliphatic substrates are reduced with low enantioselectivity compared to aromatic substrates, indicating that interactions between the substrate phenyl ring and the catalyst are important. The correlation between the sum of charges on the atoms in the aryl ring of the substrate and the enantiomeric excess of the product alcohol is to some extent due to an electrostatic interaction. Most likely, there is a similar but smaller contribution from the alkyl substituent of the substrate since electron-withdrawing substituents on the aryl of the substrate effect a change in net charge flux in the substrates. However, the electrostatic interaction between the substrate and catalyst is not the major contributor to the enantioselectivity for the Ru(*p*-cymene)(1)-catalyzed transfer hydrogenation.

Another, more important contribution originates from a mixture of solvation effects and dispersion interactions. The balance between these two factors and the former was found to be affected both by the choice of arene ligand on the catalyst and by the amine ligand.

A final smaller contribution was identified as a steric effect that, in the case of acetophenone, works in the same direction as the more significant factors described above.

(26) For use of STERIMOL parameters in QSAR, see: Högborg, T.; Norinder, U. In *A Textbook of Drug Design and Development*, 2nd ed.; Krogsgaard-Larsen, P.; Liljefors, T.; Madsen, U., Eds.; Harwood Academic Publishers, Amsterdam, 1996.

To conclude, the enantioselectivity in the ruthenium-catalyzed transfer hydrogenation of ketones is governed by the cooperative action of steric, electrostatic, dispersion, and solvent effects. The understanding of the delicate balance between different effects can be used in the design of new, even more selective catalysts, not only in the field of hydrogenation but also for all other types of catalysts where the selectivity is determined by an interaction between the substrate and the organic part of the catalyst.

Experimental Section

Commercially available ketones were used without further purification. The [RuCl₂(HMB)]₂ and [RuCl₂(*p*-cymene)]₂ complexes were prepared according to the literature.²⁷ All transfer hydrogenations were performed in a 0.1 M solution of the substrate in *i*-PrOH (freshly distilled over CaH₂). ¹H and ¹³C NMR spectra were measured in CDCl₃ (400 MHz for proton and 100.4 MHz for carbon). The residual solvent peak of CDCl₃ was used as reference (7.26 and 77.0 ppm). The absolute configuration of the products was determined from the sign of the optical rotation, and all products were identified by ¹H NMR analysis and by comparison with literature data.²⁸

General Procedure for Reduction of Ketones. To a dry 25-mL Schlenk flask was added amino alcohol 1 (4.3 mg, 0.02 mmol) and [RuCl₂(*p*-cymene)]₂ (1.5 mg, 0.0025 mmol) followed by 2 mL of *i*-PrOH, and the reaction was stirred for 15 min. *i*-PrOH (8 mL) and the ketone (1.0 mmol) were added followed by *i*-PrOK (0.025 mmol, 25 μL, from a 1 M solution in *i*-PrOH), and the solution was stirred at room temperature until completion according to GC. The reaction was quenched by the addition of 10 μL of 1 M HCl, and the solvent was evaporated under reduced pressure. The crude product was flashed through a short column of SiO₂ (1 g) with pentane/Et₂O as eluent to yield the pure alcohol. The enantiomeric excess was determined with chiral GC (CP-Chirasil-DEX CB) 25 m × 0.25 mm i.d. with N₂ (12 psi) as carrier gas. [RuCl₂(HMB)]₂, [RuCl₂(benzene)]₂, and [RuCl₂(PhCO₂Et)]₂ were stirred with the amino alcohol 1 at 80 °C for 30 min in 2 mL of *i*-PrOH to form the corresponding precatalysts.

(*S*)-(–)-1-(3,4,5-Trifluorophenyl)ethanol: ¹H NMR (400 MHz, CDCl₃) δ 1.44 (3H, d, *J* = 6.4 Hz), 2.19 (1H, bs), 4.82 (1H, q, *J* = 6.4 Hz) and 6.94–7.01 (2H, m); IR (neat) (cm^{–1}) 3350, 2981, 1620, 1532 and 1042; (EI) *m/z* (rel intensity) 176 (8), 159 (100) and 133 (13). The absolute configuration was determined after MTPA ester formation.²⁹

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