Enantioselectivity in Noyori−Ikariya Asymmetric Transfer Hydrogenation of Ketones

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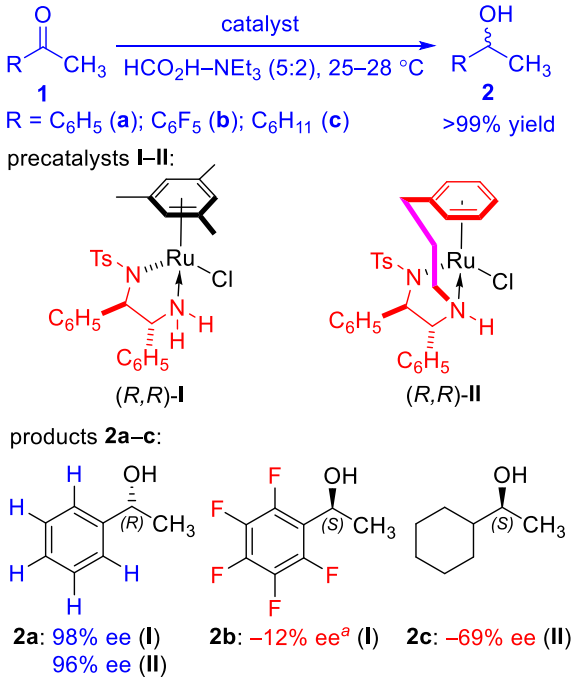
ABSTRACT: Asymmetric transfer hydrogenation (ATH) is an important catalytic process in the fragrance and pharmaceutical industries. The Noyori–Ikariya chiral molecular ruthenium complex has been the catalyst of choice for this reaction for over 25 years. The mechanism and origin of enantioselectivity has irked chemists ever since the catalyst conception. This work addresses important shortcomings in understanding the origin of enantioselectivity with the Noyori–Ikariya catalysts, traditionally associated with the CH–π interaction (Noyori, R. et al *Angew. Chem. Int. Ed*. **2001**, 40, 2818). Here we show that there are two spatial regions of the catalyst that simultaneously control the enantioselectivity for any arbitrary substrate: the region of the (tethered) η^6-arene ligand and the region of the SO_2 moiety. Dynamic equilibrium and interplay of attraction and repulsion via CH–π, C–H···H–C, lone pair–π, lone pair···H–C and other non-covalent interactions in each region leads to stabilization/destabilization of the corresponding diastereomeric transition state and, as such, determines the final percent enantiomeric excess (% ee).

1. INTRODUCTION

Asymmetric transfer hydrogenation (ATH) of ketones and imines represents a powerful alternative to asymmetric hydrogenation for the production of optically active alcohols and amines.[1] Specifically, the use of stable hydrogen donors such as propan-2-ol, HCO_2Na/H_2O, or azeotropic mixtures of $HCO_2H–NEt_3$ has operational advantage by avoiding flammable hydrogen gas and high-pressure equipment.[2] Because of its modularity, efficiency, stability and cost-effectiveness, the *N*-sulfonated diamine-η^6-arene Noyori–Ikariya ruthenium complex is one of the most common catalysts used in the fine chemical industry.[3] Since the publication of the first catalytic system in 1995,[4] several other variations have been developed.[5] In many cases the enantiomeric excess (ee) in the ATH (and related AH) of ketones frequently reach ~99%. However, such high levels of enantioselection are observed for electron-rich aromatic[4a] and alkynyl[6] ketones. In contrast, the use of perfluoroaromatic[7] and aliphatic[1a-c, 1e, 1f, 5e, 8] ketones leads to much smaller ee's and even reversal of the sense of the enantioselection; see Scheme 1 on the example of representative commercially available precatalysts (*R,R*)-**I** and (*R,R*)-**II**.

For a period of time,[9,10] CH–π interaction between the C−H proton(s) of the (η^6-arene) ligand and π electron density of the approaching electron-rich ketonic substrate have been associated with the major interaction that contributes to the high enantioselectivity.[11] However, an ee of 99% or higher usually suggests there is only one kinetically accessible mechanism of generation of chirality arising as a compromise of multiple attractive and repulsive (typically non-covalent) interactions between the substrate and the catalyst within the catalyst-substrate transition-state complex.[12] Specifically, lone pair(s) lp(s)–π repulsion originating from the SO_2 oxygen atom(s) of the catalyst and the electron-rich aromatic substrate was further identified as another equally important factor contributing to the high enantiomeric excess for electron-rich aromatic ketones with the

Scheme 1. Reported asymmetric transfer hydrogenation of acetophenone,[4a] 2',3',4',5',6'-pentafluoroacetophenone[7] and 1-cyclohexylethanone[5e] with precatalysts (*R,R*)-**I** and (*R,R*)-**II**. Ts = 4-$CH_3C_6H_4SO_2$.



[a]*p*-cymene version of the catalyst 1 and propan-2-ol as reagent/solvent were used, respectively.

Noyori–Ikariya complex.[13] Up to now, however, there is no general understanding on what determines the enantioselectivity for an arbitrary prochiral ketone and/or any *N*-sulfonated diamine derivatives of the Noyori–Ikariya ruthenium catalyst. Here, based on hybrid dispersion-corrected Density Functional Theory (DFT)[14] calibrated against experimental data, we eliminate these important shortcomings in understanding the origin of enantioselectivity with the Noyori–Ikariya catalyst. Our results explain the experimentally observed drop and further reverse of the sense of the enantioselection for "challenging" perfluoroaromatic and aliphatic ketones and, more-importantly, provide insights for next-generation catalyst design.

2. RESULTS AND DISCUSSION

2.1. Comparative asymmetric transfer hydrogenation of 1a–c with precatalysts (*R,R*)-I and (*R,R*)-II. To calibrate the computational results presented in this work, we performed the ATH of acetophenone (**1a**), 2',3',4',5',6'-pentafluoroacetophenone (**1b**) and 1-cyclohexylethanone (**1c**) with chiral precatalysts (*R,R*)-**I** and (*R,R*)-**II** under identical conditions in propan-2-ol, Table 1.

Table 1. Comparative ATH of acetophenone, 2',3',4',5',6'-pentafluoroacetophenone and 1-cyclohexylethanone with chiral precatalysts (*R,R*)-**I** and (*R,R*)-**II**, isopropanol, 2 mol% KOH, 25 °C, 1 mol% precatalyst loading. [substrate] = 0.1 M, 0.5 mmol scale.

Run	substrate	pre catalyst	conversion, %[a]	% ee[a]	*R/S*
1	**1a**	(*R,R*)-**I**	~99	97 ± 1	*R*
2	**1a**	(*R,R*)-**II**	~95	96 ± 1	*R*
3	**1b**	(*R,R*)-**I**	>99	–16 ± 2	*S*
4	**1b**	(*R,R*)-**II**	>99	–90 ± 0	*S*
5	**1c**	(*R,R*)-**I**	~13	–72 ± 2	*S*
6	**1c**	(*R,R*)-**II**	~40	–73 ± 4	*S*

[a]In 24h, based on withdrawn aliquot, chiral GC (average of 2 runs).

In line with the previous results where HCO_2H–NEt_3 was used as a source of hydrogen atoms and reaction media,[4a, 5e] both precatalysts (*R,R*)-**I** and (*R,R*)-**II** produced (*R*)-1-phenylethanol (**2a**) with excellent enantiomeric excess of ~97-98% in the ATH of acetophenone (**1a**), runs 1–2 (Table 1). Switching to 2',3',4',5',6'-pentafluoroacetophenone (**1b**) resulted in the reverse of the sense of the enantioselection, producing (*S*)-configuration 1-(pentafluorophenyl)ethanol (**2b**) with 15% and 90% ee for precatalysts (*R,R*)-**I** and (*R,R*)-**II**, respectively (runs 3–4, Table 1). The sense and level of enantioselectivity of 15% observed with mesitylene precatalyst (*R,R*)-**I** is comparable to that of 12% reported for the similar *p*-cymene analog.[7b] However, we note here an appreciably high level of percent enantiomeric excess of ~90% for (*S*)-1-(pentafluorophenyl)ethanol (**2b**) achieved with catalyst (*R,R*)-**II** in this reaction, which is a significant improvement over most existing catalytic ATH approaches[15] developed to replace classical synthetic methods.[16] The use of 1-cyclohexylethanone (**1c**) similarly results in the reverse of the sense of the enantioselection, delivering (*S*)-1-cyclohexylethanol (**2c**) with similar (assuming exponential behavior) ~69% ee and ~78% ee for (*R,R*)-**I** and (*R,R*)-**II**, respectively (runs 5–6, Table 1). The sense of the enantioface selection (*S*-product) and the value of ~78% ee for (*R,R*)-**II** is well-comparable to the value of ~69% ee reported in HCO_2H–NEt_3.[5e]

2.2. Dispersion-corrected DFT identification of stereoselectivity determining transition states. Dispersion-corrected DFT calculations were further used to estimate percent enantiomeric excesses and identify non-covalent interactions involved in four representative enantioselective reactions of (*R,R*)-**I**/**1a**, (*R,R*)-**I**/**1b**, (*R,R*)-**II**/**1b** and (*R,R*)-**II**/**1c**. The mechanism of ATH of ketones with the Noyori–Ikariya catalyst is understood to an appreciable degree.[1b, 17] The experimental and theoretical data accumulated for the asymmetric transfer hydrogenation of ketones points to two plausible catalytic cycles, which differ only in their second proton (H^+) transfer step.[13] The relative contribution of the pathway in which the N–H functionality remains intact is difficult to assess from the static[13] DFT computations, whereas dynamic[18] DFT computations point to propan-2-ol as the predominant source of the proton, *i.e*. the catalytic reaction coordinate does not asymptotically include the 16e$^-$ amido Ru complex[19] on the potential energy surface. Regardless, both reaction channels are identical by the first hydride (H^-) step, which is rate- and enantiodetermining.[20] The composition of the enantiomers (% ee) therefore is (classically) expected to be determined by the free energy difference ($\Delta G_{298K}°$) between two diastereomeric transition states leading to the opposite enantiomers of the product. The stereoselectivity determining transition states can be accessed via geometry optimization using common quantum chemical methodologies.[12]

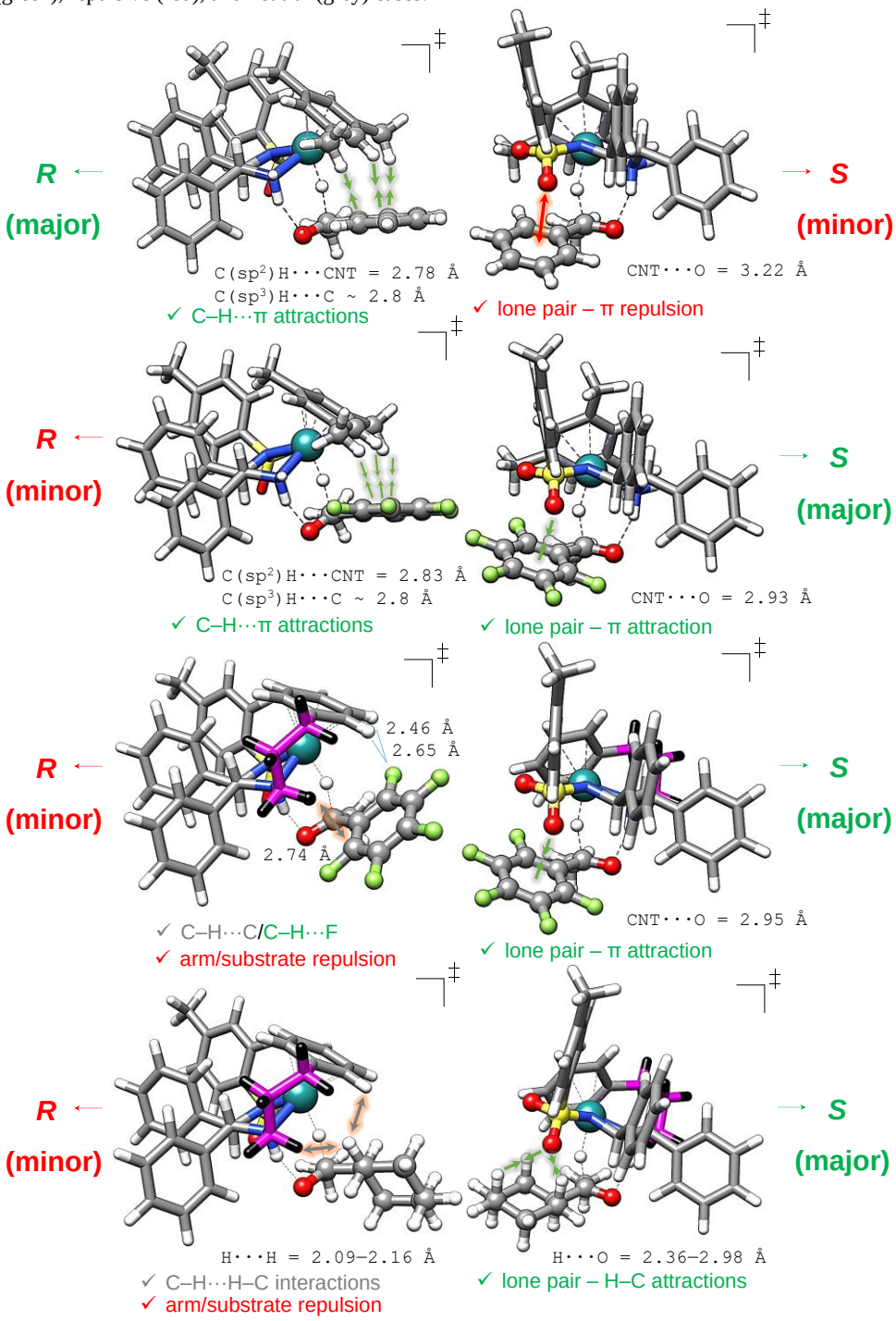
Three popular hybrid DFT exchange-correlation kernels[21] coupled with extended def2-TZVP basis set[22] were then used to model stereoselectivity determining transition states, namely B3LYP[23] (with global 20% orbital exchange fraction), range-separated ωB97X-D[24] (with 100 and 22% exchange at long and short ranges, respectively) and M06-2X[25] (with global 54% exchange) functionals. The use of dispersion-corrected models is mandatory for improved description of non-covalent interactions (specifically van der Waals forces).[26] As such, utilized B3LYP and M06-2X functionals were parametrized via D3 dispersion model,[27] whereas ωB97X-D implements built-in D2 correction term.[28] Furthermore, to introduce non-specific solvent effects of propan-2-ol in the geometry optimization steps, we employed the Solvation Model based on Density (SMD),[29] a popular version of a polarizable continuum model. All simulations were performed with Gaussian 16 (rev. C01) software.[30] Additional computational details and optimized geometries are provided in SI. The results for the free energy difference ($\Delta G_{298K}°$) in kcal·mol^{-1} between the transition states leading to *S*- and *R*-product as well as calculated from it percent enantiomeric excess[31] are presented in Table 2.

Table 2. Calculated free energy difference ($\Delta G_{298K}°$) in kcal·mol^{-1} between the transition states leading to *S*- and *R*-product and percent enantiomeric excess (% ee) as a function of a DFT model combined with Def2-TZVP basis and SMD(propan-2-ol) solvent model.

Substrate	catalyst	$\Delta G_{298K}°$ (ee) B3LYP-D3	$\Delta G_{298K}°$ (ee) ωB97X-D	$\Delta G_{298K}°$ (ee) M06-2X-D3
1a	(*R,R*)-**I**	0.9 (65%)	0.7 (51%)	2.1 (94%)
1b	(*R,R*)-**I**	–0.3 (–27%)	–2.1 (–95%)	–1.0 (–70%)
1b	(*R,R*)-**II**	–2.7 (–98%)	–4.2 (–99.8%)	–4.0 (–99.8%)
1c$_{(eq)}$	(*R,R*)-**II**	1.6 (88%)	1.1 (73%)	–0.9 (–66%)

The following conclusions can be made from Table 2: 1) regardless the functional use, calculations consistently qualitatively predict[13] the correct sense of the enantioface selection for substrates **1a** and **1b**;

Figure 1. Optimized transition states at the M06-2X-D3/def2-TZVP/SMD(propan-2-ol) level leading to enantiomers of 1-phenylethanol (catalyst *(R,R)*-**I**, top), 1-(2,3,4,5,6-pentafluorophenyl)ethanol (catalysts *(R,R)*-**I** and (*R,R*)-**II**, middle) and 1-cyclohexane-1-ethanol (catalyst *(R,R)*-**II**, bottom). For (*R,R*)-**II**, the tethering arm is highlighted by violet. The color for various non-covalent interactions identified by finding close contacts between atoms (separation that is less than the sum of the van der Waals radii of the respective atoms) represents relative attractive (green), repulsive (red), and neutral (grey) cases.



2) only highly advanced specifically designed to describe noncovalent interactions M06-2X-D3 functional predicts the correct sense of the enantioface selection for substrate **1c**[32,33]; 3) on average, M06-2X-D3 being one of the most efficient dispersion-corrected hybrid according to GMTKN30 database,[34] works more effectively in terms of the sense of enantioselection and % ee prediction compared to that of B3LYP-D3 and ωB97X-D.[26d, 35] However, the results are only qualitative as expected due to non-universal nature of the functional. In addition, the discrepancy between experimental and theoretically predicted % ee might be affected by the additional mechanisms of the generation of chirality caused by energetically accessible conformers of the catalyst-substrate complex, possible involvement of Ru*R*-pathway, specific solvation of propan-2-ol. These pathways, however, seem to play a minor role as discussed elsewhere.[17] Optimized M06-2X-D3 geometries for the transition states are shown in Figure 1.

Figure 2. Non-covalent interaction (NCI) plots of transition states leading to enantiomers of 1-phenylethanol (catalyst *(R,R)*-**I**, left), 1-(2,3,4,5,6-pentafluorophenyl)ethanol (catalysts *(R,R)*-**I** and (*R,R*)-**II**, middle) and 1-cyclohexane-1-ethanol (catalyst *(R,R)*-**II**, right), reduced gradient of the electron density (*s*) = 0.6 a.u.

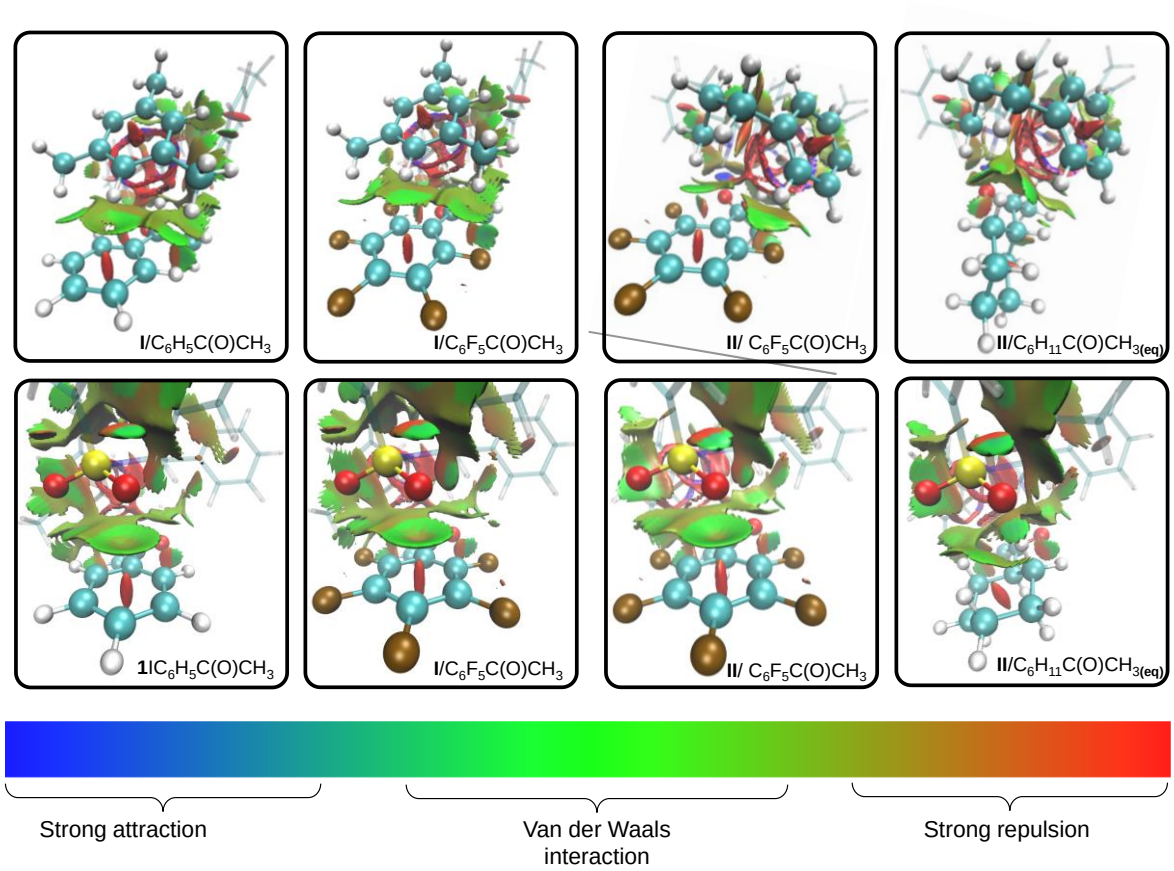
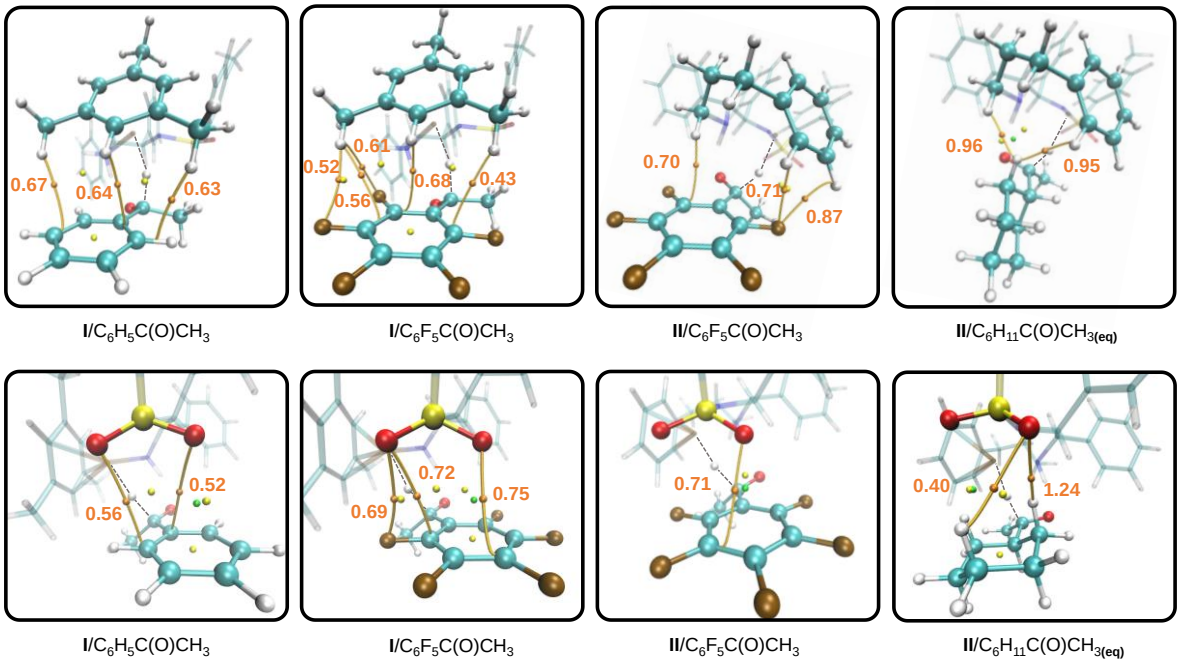


Figure 3. Quantum theory of atoms in molecules (QTAIM) plots of transition states leading to enantiomers of 1-phenylethanol (catalyst *(R,R)*-**I**, left), 1-(2,3,4,5,6-pentafluorophenyl)ethanol (catalysts *(R,R)*-**I** and (*R,R*)-**II**, middle) and 1-cyclohexane-1-ethanol (catalyst *(R,R)*-**II**, right). Bond paths (orange lines), bond critical points (orange small dots), ring critical points (yellow small dots), and cage critical points (green small dots). Values of electron densities (ρ) for bond critical points are given in [10^{-2} × a.u.] units.



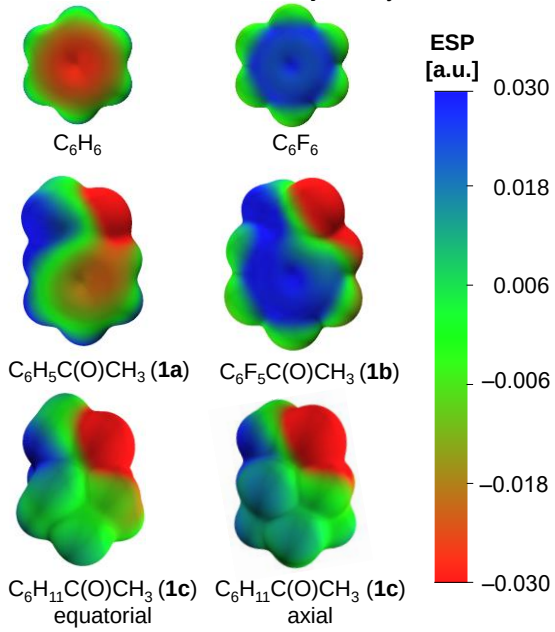
By inspecting optimized geometries which are first-order saddle-points on the potential energy surface, multiple close contacts defined as a separation that is less than the sum of the van der Waals radii of the respective atoms could be identified in the region of (tethered) η^6-arene ligand and the region of SO_2 moiety. These contacts include not only known CH–π,[36] lone pair (lp)–π,[37] and C–H···H–C interactions,[38] but also apparently a novel[39] lp···H–C non-covalent interaction ($d_{H\cdots O}$ = 2.36 Å, *cf.* 2.70 Å for the sum of van der Waals radii[40]). In addition, we also note several short C–H···F proximities of 2.64-2.71 Å observed for transition states leading to *R*-product of **2b** (Figure 1). To visualize non-covalent interactions present in these geometries, Non-Covalent Interaction (NCI)[41] plots, which are based on M06-2X-D3 electron density and its derivative analysis, were adapted (Figure 2). In all cases (i.e., eight transition states), the (green) isosurfaces confirm the presence of delocalized weak non-covalent interactions in the region of (tethered) η^6-arene ligand and the region of SO_2 moiety of the catalyst. The topological features of electron density in these regions were further analyzed with well-established Quantum Theory of Atoms in Molecules (QTAIM) analysis (Figure 3).[42] The presence of non-covalent interactions is confirmed by the presence of bond critical points (BCPs) of molecular electron density. Furthermore, cage critical points (CCPs) are observed in the regions of O=S=O/arene in all three studied cases of **1a** and **1b** and are characteristic for lp–π interactions.[43]

What causes the reverse of the sense of enantioselection when going from **1a** to **1b** with catalyst (*R*,*R*)-**I**? The analysis presented above indicates that transition states leading to *R*-product are comparably somewhat equally stabilized via CH–π interactions (Figure 1, two top left structures). However, the large difference is observed for transition states leading to *S*-product in the region of lp–π interactions (Figure 1, two top right structures). Although any chemical bond is a dynamic equilibrium between attractive and repulsive forces,[44] there is apparently more attraction between lone pair of (SO)O oxygen of the catalyst and π-electron density of 2',3',4',5',6'-pentafluoroacetophenone (**1b**) vs π-electron density of acetophenone (**1a**). This is evidenced by a much shorter centroid (CNT)···O bond distance present in the case of **1b** with respect to **1a** (Δ = –0.29 Å, Figure 1), as well as greater values of electron densities (ρ) for bond critical points in the corresponding transition state structures (Δ ~ 0.16 × 10^{-2} a.u. on average, Figure 3). More attraction implies more exergonic stabilization of the corresponding transition state, e.g. a kinetical deblockage to accumulate the *S*-enantiomer through lowering the position of the first-order saddle-point on the potential energy surface. Purely electrostatic component of these lp–π interactions can be further understood by examining electrostatic potential (ESP)[45] maps of **1a** and **1b** as shown in Figure 4.

The π cloud of benzene (shown for comparison) and to some extent acetophenone (**1a**) creates a negative region of ESP, called the heap, above and below the molecular plane leading to a negative sign of quadrupole moment tensor Q_{zz} (*z*-direction is normal to the molecular plane), see SI.[46] In contrast, the similar region ("hole") of ESP is positive for hexafluorobenzene (shown for comparison) and 2',3',4',5',6'-pentafluoroacetophenone (**1b**), leading to a positive sign of quadrupole moment tensor Q_{zz}. One therefore should expect that the aromatic ring of **1a** will repel the negative oxygen atom of SO_2 moiety of the catalyst, whereas the one of **1b** will attract it. To conclude, lp–π interaction in the region of SO_2 moiety of the catalyst seems to be the major driving force which causes the reverse of the sense of enantioselection when going from **1a** to **1b** with catalyst (*R*,*R*)-**I**.

What makes a further dramatic improvement of the % ee for **1b** when going from catalyst (*R*,*R*)-**I** to (*R*,*R*)-**II**? The transition states leading to the major *S*-product seems to be stabilized by lp–π interaction on an equal footing ("identical" CNT···O bond distance of ~2.94 Å as well as ρ of ~0.70 × 10^{-2} a.u.).

Figure 4. Calculated M06-2X-D3/def2-TZVP/SMD(pronan-2-ol) electrostatic potential (ESP) surfaces (ρ = 0.001 a.u.) of benzene, hexafluorobenzene, acetophenone, 2',3',4',5',6'-pentafluoroacetophenone, and two conformers of 1-cyclohexylethanone.



In contrast, there seems to be more destabilization present for the diastereomeric transition state leading to a minor *R*-product with (*R*,*R*)-**II** (Figure 1, second structure from bottom right), thus kinetically blocking its accumulation. The origin of this destabilization is the "tethered" arm, which increases steric bulkiness. As a result, the aromatic ring of **1b** experiences forced rotation around C(sp^2)–C(sp^3) bond. Even though the resultant structure is stabilized by C–H···X (X = C, F) interactions, the overall destabilization plays a major role. Therefore, the reason why (*R*,*R*)-**II** gives **2b** with much improved % ee than (*R*,*R*)-**I** relies in the kinetical blockage of the pathway leading to a minor *R*-product through significant destabilization of the corresponding diastereomeric transition state in the region of (tethered) η^6-arene ligand.

Finally, computational analysis provides insights on why (*R*,*R*)-**II** reduces **3a** with the reverse of the sense of enantioselection and moderate enantioselectivity. Here the transition state that leads to *S*-product, is stabilized by lp···H–C interactions, whereas its diastereomeric counterpart that leads to *R*-product, is stabilized by C–H···H–C interactions. Since these interactions seem to be comparable by force (see ESP surfaces in Figure 4), but with the non-negligable preference for *S*-pathway (ρ of ~1.24 × 10^{-2} vs 0.95 × 10^{-2} a.u., respectively), the final product is accumulated as *S*-enantiomer with moderate ee of 78%.

3. CONCLUSION

The field of molecular asymmetric catalysis is of great research interest in modern catalysis science. The elucidation of the mechanism of the generation of chirality in catalytic asymmetric reactions, is a central task aimed at improved catalyst design. This task is seemingly much more complex than is commonly accepted. For example, it is known that increasing the size of the catalyst often results in a higher percent enantiomeric excess.[12] However, at the moment it is impossible to attribute this effect to any particular dominating type of intramolecular interactions, because along with an evident increase of steric bulkiness, the network of possible non-

covalent interactions is also increasing.[39] Hence, mechanistic studies of the chiral catalytic reactions should preferably pursue the task of accumulating and calibrating data describing the weak non-covalent interactions.[12] This work attempts to provide a comprehensive understanding for the mechanism of generation of chirality in the ATH of arbitrary prochiral ketones with the Noyori–Ikariya ruthenium catalyst, being one of the most appealing examples of the use of molecular catalysts in the fine chemicals industry. Thus far, CH–π interaction in the region of (η^6-arene) ligand of the catalyst has been thought to be a major stereoregulating factor.[11] This work shows that there are actually two spatial regions of the catalyst that simultaneously control the enantioselectivity for any arbitrary substrate: the region of (tethered) η^6-arene ligand and the region of the SO_2 moiety. Dynamical equilibrium & interplay of attraction and repulsion via various non-covalent interactions in each region leads to stabilization/destabilization of the corresponding diastereomeric transition state and, as such, determines the final percent enantiomeric excess (% ee).

The newly established mechanism of generation of chirality with the Noyori–Ikariya catalyst explains the experimental drop and further reverse of the sense of the enantioselection for "challenging" perfluoroaromatic and aliphatic ketones. For the aromatic and perfluoroaromatic ketones in particular, the enantioselectivity is largely controlled by the catalyst region of the SO_2 moiety, in which repulsive-to-attractive repolarization of lp–π interactions leads to the inversion in the sense of enantioselection.

It is our hope that the results of this work will inspire next-generation catalyst design, which still traditionally relies on experimental trial-and-error approach. Although to our knowledge no explicit examples exist of rational catalyst design using lessons from studies of lp–π interactions in particular, we note that this interaction within catalyst-substrate complex was recently used to rationalize an inversion in the sense of enantioselection in another interesting asymmetric catalytic reaction, an asymmetric fluorination of allylic alcohols.[47]

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsorganomet.xxx. Detailed experimental procedures, characterization data, and computational details (PDF).

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Notes

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31. ee = [exp(–$\Delta G_{298K}°$/*RT*) – 1]/[exp(–$\Delta G_{298K}°$/RT) + 1], where $\Delta G_{298K}°$ is the free energy difference in kcal·mol^{-1} between the transition states leading to *S*- and *R*-product, *RT* = 0.59 kcal·mol^{-1}.
32. 1-cyclohexylethanone undergoes a conformational interconversion known as a chair flip [33]. In this chair flip, all axial groups become equatorial, and all equatorial groups become axial. Both chair forms of 1-cyclohexylethanone were considered in our calculations, see SI. Transition states leading to 1-cyclohexylethanol were found to be uniformly ~2–7 few kcal·mol–1 more stable for the chair conformation of 1-cyclohexylethanone which has an equatorial C(O)CH_3 group, in line with the stability of this conformer relative to the axial configuration by –0.58 kcal·mol^{-1} (M06-2X-D3), see SI.
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