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Investigation into the enantioselection mechanism of ruthenium–arene–diamine transfer hydrogenation catalysts using fluorinated substrates

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ABSTRACT

The effects of both steric and electronic properties of ketones on the selectivity in asymmetric transfer hydrogenation have been studied with aryl alkyl/fluoroalkyl ketones using four ruthenium based catalysts and two different media. The 1-arylethanones, 1-aryl-2-fluoroethanones and 2,2-difluoroacetophenones could be reduced with medium to high ee (86–99%), while the 1-aryl-2,2,2-trifluoroethanones were reduced with low selectivity in most systems. The change in enantioselectivity upon structural variation has been rationalised aided by regression analysis with substituent constants and the partial charge of the carbonyl carbon as predictors. The steric bulk of the alkyl/fluoroalkyl chain was found to be the major factor in determining selectivity in formic acid/triethylamine, while for reduction of a series of substituted 1-arylethanones and 1-aryl-2-fluoroethanones, the selectivity was found to depend on the electronic properties of the aromatic ring, supporting previous evidence that π–π interaction between the substrate and catalyst is important in determining the selectivity. For reductions in water using sodium formate as the hydrogen donor, altered and more complex selectivity mechanisms were observed. Experiments and regression focused on the variation of the alkyl/fluoroalkyl group of phenyl and 1-naphthyl ketones, showed that the selectivity correlated with the size of the substituent, but also the partial charge of the carbonyl carbon.

1. Introduction

Asymmetric transfer hydrogenation (ATH) has been recognised as a valuable method for obtaining enantioenriched alcohols and amines.[1,2] Considerable progress has been made in the areas of catalyst/ligand development[1–5] and in the understanding of the catalytic processes.[6–9] Despite the appearance of new catalysts, the systems developed by Noyori et al.,[10,11] are still attractive due to experimental simplicity and the availability of ligands in both enantiomeric forms. The enantioselection mechanisms of these catalysts have been investigated previously.[7,12–14] Aryl ketones are generally reduced with higher selectivity and rates than alkyl ketones. This has been rationalised by a favourable edge to face π–π interaction between the arene of the ligand and the substrate.[12,13] The more congested transition state is assumed favoured by these interactions, and could explain why a lower ee results when the aromatic moiety contains electron withdrawing substituents. In structurally related systems, the enantioselectivity has been found to originate primarily from unfavourable steric interactions between the substrate and the ligand part of the catalyst,[7] or to be the result of a complex interplay between steric, electrostatic, dispersion and solvation effects.[14]

With respect to fluorinated ketones our laboratory has previously investigated the ATH of 1-aryl-2-fluoroethanones[15] and 2,2,2-trifluoro-1-phenylethanone have also been reduced using the ATH concept in a low 33–38% ee.[16,17] Although useful protocols exist for the asymmetric reduction of 1-aryl-2,2-difluoroethanones and 1-aryl-2,2,2-trifluoroethanones,[18–22] asymmetric reduction of the such fluoroketones often gives the product alcohols in mediocre ee.[16–18,23,24] Thus, increased knowledge of the effects caused by fluorine in asymmetric processes is needed.

On this background we have undertaken the ATH of 1-aryl-1-alkanones and fluoroalkanones, with the aim of developing enantioselective reductions and gaining an increased understanding of the enantioselection mechanism of the ruthenium–arene–diamine catalysts.

2. Result and discussion

2.1. Substrates, catalyst and substituent constants

The ketones used in this study were purchased or prepared as described previously.[25–27] The substrates were subjected to ATH in two different media; formic acid/triethylamine (5/2 mol ratio) and

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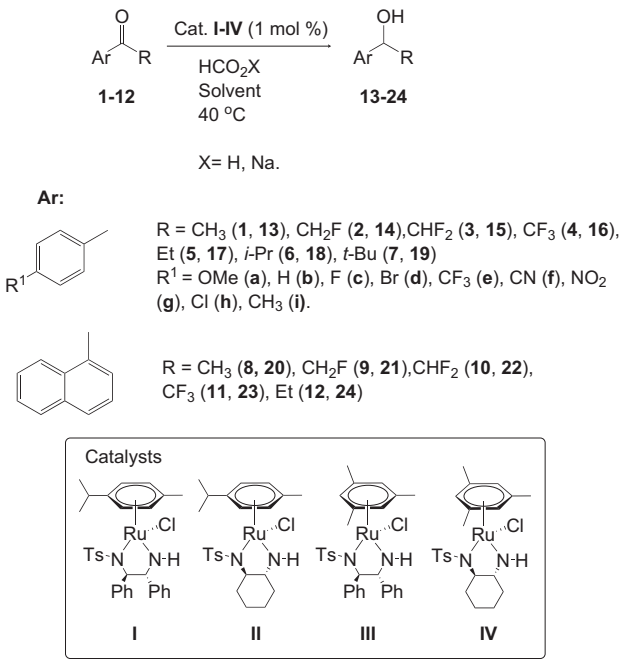
in water using sodium formate as hydrogen donor. Each reduction was performed using four different ruthenium based catalysts **I**–**IV**, see Scheme 1.



Scheme 1. Asymmetric reduction of **1**–**12** to **13**–**24** using catalyst **I**–**IV**.

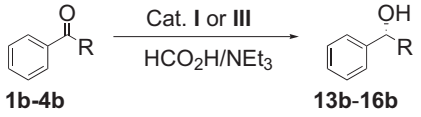
The catalysts were made in situ by mixing of $[RuCl_2(p\text{-cymene})_2]_2$ or $[RuCl_2(\text{mesitylene})_2]_2$ in combinations with each of the ligands (1*R*,2*R*)-*N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine ((*R*,*R*)-TsDPEN) and (1*R*,2*R*)-*N*-(*p*-toluenesulfonyl)-1,2-cyclohexanediamine ((*R*,*R*)-TsCYDN).

In order to reveal how structural variations affected the enantioselectivity, regression analysis was performed using the difference in Gibbs free energy for the reactions leading to the two enantiomers, $\Delta(\Delta G)$, calculated from the ee-values and substituent constants.[28] The substituent constant evaluated includes parameters for size of groups: Taft's Es (Es), Charton volume (ES–V), inductive parameters: σ-*para*, σ-*para*$^-$, σ-*para*$^+$, resonance: resonance effect (R), resonance delocalisation of negative charge (R^-), resonance delocalisation of positive charge (R^+), group dipole, hydrophobicity, group electronegativity and molar refractivity. As electronic substituents constants are less developed in the case of fluoroalkyl groups, the calculated Hückel and Mulliken charge for the carbonyl carbon and oxygen were also used as predictors. Regression was performed at a confidence level of 95%. The quality of various models was evaluated by comparing the correlation coefficient (r), the statistical significance (F) and the standard deviation (s), whereas the number of n denotes the number of experiments included in the model. The residuals (Res.) describe the deviation of the modelled difference in Gibbs free energy $\Delta(\Delta G_{mod.})$ as compared to each experimental value. A good model is characterised by having a r-value close to 1, a small s-value and a large F-value.

2.2. ATH in formic acid/triethylamine using catalyst I and III

Due to the structural similarity of catalysts **I** and **III**, their performance are often comparable in terms of rates and selectivity.[15] Therefore, a comparison is useful in rationalising their enantioselection mechanisms. In the following sub-chapters their efficiency as catalysts in ATH in formic acid/triethylamine are discussed.

*2.2.1. Effect of alkyl/fluoroalkyl side chain on enantioselectivity using catalyst **I** and **III**.* The introduction of aliphatic fluorines alters both the electronic and steric properties of the substrates. Catalysts **I** and **III** were therefore first employed in reduction of **1b**, **2b**, **3b** and **4b** (Scheme 2) to investigate how a modification of the alkyl/fluoroalkyl group affected selectivity and rate.



Scheme 2. ATH of **1b**, **2b**, **3b** and **4b** in formic acid/triethylamine using catalyst **I** and **III**, R=CH_3 (**1**, **13**), CH_2F (**2**, **14**), CHF_2 (**3**, **15**), CF_3 (**4**, **16**).

ATH of **1b** and **2b** proceeded with a high selectivity (97.0–97.5% ee), while reduction of **3b** gave **15b** in 90.0–93.0% ee. For both systems a lower ee was observed as the number of fluorines in the side chain increased, and ATH of 2,2,2-trifluoroacetophenone (**4b**) gave (*S*)-**16b** in a low 14.0–44.0% ee. In all cases hydride delivery occurred preferably from the same relative side leading to enantioenriched (*R*)-**13b** and (*S*)-**14b**, (*S*)-**15b** and (*S*)-**16b**.

Regression analysis with $\Delta(\Delta G)$ data for catalyst **I** with various predictors, gave the best fit with the steric bulk of the substituents as defined by Taft (Es), and slightly lower using the Charton volume (ES–V). Analysis of the performance of catalyst **III**, also including the compounds **5b** (R=Et) and **6b** (R=*i*-Pr),[11] gave a better regression using ES–V. Both cases suggest that the lower selectivity experienced upon exchanging hydrogens with fluorines are mainly a size effect. The ee-values, conversion data, the observed and modelled $\Delta(\Delta G)$, and residuals are compiled in Table 1 (Note that Es and ES–V parameters have different signs.).

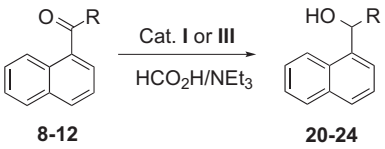
Table 1
ATH of the phenyl ketones **1b**, **2b**, **3b** and **4b** using catalyst **I** and **III** in formic acid/triethylamine: ee (%), conversion (Conv., %), reaction time in hours (h), $\Delta(\Delta G)$, model estimated $\Delta(\Delta G_{mod.})$ in kcal/mol and the residuals (Res.)

Entry	Substrate	R	Cat.	ee (%)	Conv.% (h.)	*R*/*S*	$\Delta(\Delta G)$	$\Delta(\Delta G_{mod.})$[f]	Res.[f]
1[a]	**1b**	CH_3	**I**	97.0	98 (24)	*R*	2.60	2.73	−0.12
2[b]	**2b**	CH_2F	**I**	97.0	>99 (2)	*S*	2.60	2.59	0.02
3	**3b**	CHF_2	**I**	90.0	>99 (6)	*S*	1.83	1.56	0.26
4	**4b**	CF_3	**I**	44.5	>99 (6)	*S*	0.59	0.74	−0.15
5[c]	**1b**	CH_3	**III**	97.5	89 (24)	*R*	2.72	2.94	−0.22
6	**2b**	CH_2F	**III**	97.0	>99 (2)	*S*	2.60	2.21	0.32
7	**3b**	CHF_2	**III**	93.0	78 (24)	*S*	2.06	1.89	0.17
8	**4b**	CF_3	**III**	14.0	>99 (24)	*S*	0.18	0.38	−0.20
9[d]	**5b**	Et	(*S*,*S*)-**III**	97.0	96 (60)	*S*	2.50	2.68	−0.17
10[e]	**6b**	*i*-Pr	(*S*,*S*)-**III**	83.0	41 (NR[e])	*S*	1.48	1.37	0.11
11[e]	**7b**	*t*-Bu	(*S*,*S*)-**III**	ND	<1 (NR[e])	—	—	—	—

[a] Previously done by Wu et al. in 97% ee.[29]
[b] Data from Ref. 15.
[c] Previously done by Fujii using (*S*,*S*)-**III**, 98% ee.[10]
[d] Data from Ref. 10 reaction at 28 °C.
[e] Taken from Ref. 11, reaction time not reported (NR).
[f] Regression: catalyst **I**: $\Delta(\Delta G_{mod.})=4.85+(1.72\times Es)$, $n=4$, $s=0.226$, $r=0.981$, $F=51.04$, catalyst **III**: $\Delta(\Delta G_{mod.})=6.36-(6.57\times ES-V)$, ($n=6$, $s=0.259$, $r=0.971$, $F=66.31$).

The size of a phenyl group is not that different to a trifluoromethyl group. Therefore, the lower selectivity observed in reductions moving from **1b** to **4b** could in principal be attributed to the minor size differences between the two substituents. Reductions were therefore performed using the larger naphthyl ketones **8**–**12**, Scheme 3.

As compared with their phenyl analogues, reductions of the 1-naphthyl ketones **8**–**10** proceeded to give products with lower ee-values. Catalyst **I** displayed a higher selectivity in reduction of **8**–**10** and **12** than catalyst **III**, giving the products **20**–**22** and **24** in



Scheme 3. ATH of the 1-naphthyl ketones **8**–**12** using catalyst **I** and **III**, R=CH_3 (**8**, **20**), CH_2F (**9**, **21**), CHF_2 (**10**, **22**), CF_3 (**11**, **23**), CH_2CH_3 (**12**, **24**).

77.0–94.0% ee. Reduction of the 2,2,2-trifluoroketone **11**, preferably occurred from the opposite side as compared to that of **8**–**10** and **12**. The change in selectivity was most pronounced using catalyst **III** (77.0% ee). The fluoro-containing substrates reacted with the highest rate.

The selectivity, Δ(Δ*G*) in the reduction correlated with the size of the R-substituent, and the best regression was found to be with the Charton volume. The ee-values, conversions, Δ(Δ*G*), regression equations and residuals are shown in connection to Table 2.

Table 2
ATH of the 1-naphthyl ketones **8**–**12** using catalyst **I** and **III** in formic acid/triethylamine: ee (%), conversion (Conv., %), reaction time in hours (h), Δ(Δ*G*), model estimated $\Delta(\Delta G_{mod.})$ in kcal/mol and the residuals (Res.)

Entry	Substrate	R	Cat.	ee (%)	Conv. % (h.)	*R*/*S*	ΔΔ*G*	$\Delta(\Delta G_{mod.})$[c,d]	Res.[c]
1[a]	**8**	CH_3	**I**	94.0	37 (22)	*R*	2.16	2.15	0.01
2	**9**	CH_2F	**I**	91.0	>99 (2)	*S*	1.90	1.58	0.33
3	**10**	CHF_2	**I**	77.0	>99 (2)	*S*	1.27	1.23	0.04
4	**11**	CF_3	**I**	12.5	>99 (2)	*R*	−0.16	−0.09	−0.07
5	**12**	Et	**I**	86.0	4 (20)	*R*	1.61	1.92	−0.31
6[b]	**8**	CH_3	**III**	78.5	18 (21)	*R*	1.32	1.43	−0.11
7	**9**	CH_2F	**III**	62.0	>99 (21)	*S*	0.90	0.78	0.12
8	**10**	CHF_2	**III**	28.0	>99 (2)	*S*	0.36	0.40	−0.04
9	**11**	CF_3	**III**	71.0	75 (2)	*R*	−1.10	−1.08	−0.02
10	**12**	Et	**III**	75.5	15 (21)	*R*	1.23	1.17	0.05

[a] Previously done by Liu et al., 95% ee.[30]
[b] Previously done by Fujii et al. with (*S*,*S*)-**III** at 28 °C, 83% ee.[10]
[c] Regression: catalyst **I**: $\Delta(\Delta G_{mod.})=5.13-(5.74\times ES-V)$, $n=5$, $r=0.967$, $s=0.263$, $F=44.59$, catalyst **III**: $\Delta(\Delta G_{mod.})=4.78-(6.45\times ES-V)$, $n=5$, $r=0.996$, $s=0.102$, $F=374.84$.

Apparently, the lower selectivity for the reduction of the di- and trifluoroketones **3b** and **4b**, is not related to the relative size of the aromatic/fluoroalkyl group, but rather to an increase in the size of the fluoroalkyl moiety. The cartoon drawing in Fig. 1 accounts for some of the observations.

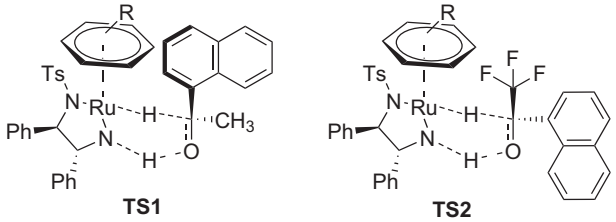


Fig. 1. Assumed orientation of the ketones in the transition states leading to product alcohols with opposite stereochemistry.

The lower ee-values for ATH of the naphthyl ketones as compared to the phenyl ketones might be related to less favourable π–π interactions due to steric effects. As the size of the fluoroalkyl group increases there could be unfavourable interactions with the ligand, causing a distortion of the normally favoured transition state (TS1). These repulsive interactions might be more pronounced in catalysis using the mesitylene-containing catalyst **III**.

*2.2.2. Effect of aromatic substituents using catalyst **I** and **III**.* The importance of the previously postulated edge to face π–π interaction between the arenes of the catalyst and the substrate in determining selectivity was then investigated. These intermolecular binding forces should be strengthened by increasing the donating properties in the aromatic part of the substrate ketone.[31,32] Previously reported data on reduction of 1-arylethanones and 1-aryl-2-fluoroethanones (**2a**–**g**)[15] were complemented by performing additional reactions with the *p*-substituted 1-arylethanones **1a**–**e** and 1-aryl-2,2,2-trifluoroethanones **4a**–**e**, for unreported substrate/catalyst/solvent combinations.

Reductions of **1a**–**g** and **2a**–**g** using catalyst **I** and **III** gave the product alcohols in 82.5–97.5% ee, and the highest selectivity and rates were observed using catalyst **III**. The 2,2,2-trifluoroketones **4a**–**e** were reduced in a low 0.5–44.5% ee. The selectivities and conversions obtained are shown in Table 3. Regression analysis performed for each substrate class-catalyst combination, revealed the best correlation when combining both inductive and resonance descriptors. For catalyst **I**/substrate **1b**–**g**, a statistically significant model was obtained by combining the inductive σ-*para*$^-$ parameter with the resonance term, R, Fig. 2. With the same predictors, a lower fit was obtained for the combination of catalyst **III**/substrate **1a**–**g**, (n=8, r=0.952, s=0.139, F=24.06).

Table 3
ATH of **1a**–**g**, **2a**–**g** and **4a**–**e** to the alcohols **13a**–**g**, **14a**–**g** and **16a**–**e** using catalyst **I** and **III** in formic acid/triethylamine: ee (%), conversion (conv.) and reaction time in hours (h)

Entry	R_1	Cat.	CH_3 (**13**)		CH_2F (**14**)		CF_3 (**16**)		
			ee, %[a]	Conv. %, (h)	ee, %[b]	Conv. %, (2 h)	ee, %	Conv. %, (h)	*R*/*S*
1	MeO (**a**)	**I**	—	<1 (24)	95.5	>99	41.0	>99 (6)	*S*
2	H (**b**)	**I**	97.0	69 (24)	97.0	>99	44.5	>99 (6)	*S*
3	F (**c**)	**I**	92.5	67 (24)	92.0	>99	2.5	>99 (2)	*S*
4	Br (**d**)	**I**	93.0	64 (24)	90.5	>99	0.5	>99 (2)	*R*
5	CF_3 (**e**)	**I**	93.0	>99 (24)	91.0	>99	1.0	>99 (2)	*S*
6	CN (**f**)	**I**	[c]	—	84.5	>99	[c]	—	—
7	NO_2 (**g**)	**I**	82.5[d]	>99 (4)	85.0	>99	[c]	—	—
8	MeO (**a**)	**III**	96.5	23 (24)	96.0	>99	27.5	92 (24)	*S*
9	H (**b**)	**III**	97.5	89 (24)	97.0	>99	14.0	>99 (6)	*S*
10	F (**c**)	**III**	94.0	96 (24)	93.5	>99	11.5	>99 (2)	*R*
11	Br (**d**)	**III**	95.5	100 (24)	91.0	>99	12.5	>98 (2)	*R*
12	CF_3 (**e**)	**III**	95.5	100 (24)	90.5	>99	3.5	>99 (6)	*R*
13	CN (**f**)	**III**	90.0[e]	99 (14)	88.0	>99	[c]	—	—
14	NO_2 (**g**)	**III**	86.0[e]	99 (24)	84.5	>99	[c]	—	—

[a] All products had the (*R*)-configuration.
[b] Data from Ref. 15, all products had the *S*-configuration.
[c] Data not obtained.
[d] Data from Ref. 30.
[e] Data from Ref. 11.

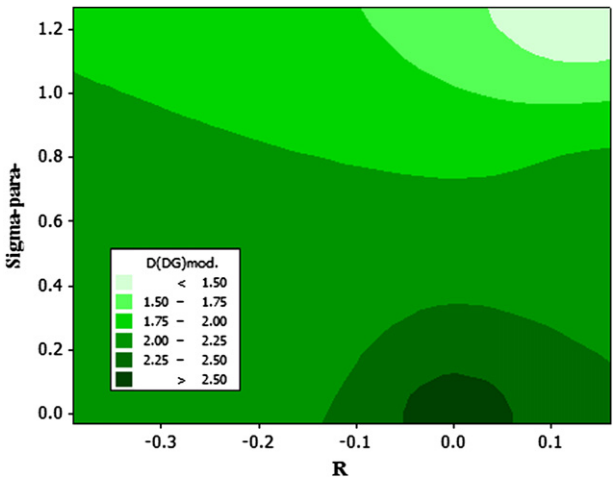


Fig. 2. ATH of **1b**–**f** using catalyst **I** in formic acid/triethylamine. The selectivity model plotted as a function of the σ-*para*$^-$ and resonance (R). Regression equation: $\Delta(\Delta G_{mod.})=2.56-(1.07\times\sigma\text{-}para^-)+(1.30\times R)$, n=5, r=0.996, s=0.054, F=122.43.

Analysis of the data for the combinations of catalyst **I**/substrate **2a**–**g** and of catalyst **III**/substrate **2a**–**g** (Fig. 3) gave a better fit when using the inductive term σ-*para* and the resonance term (R) as predictors.

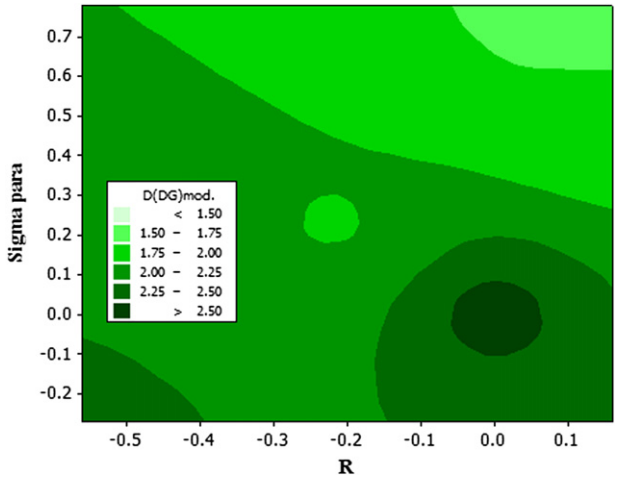
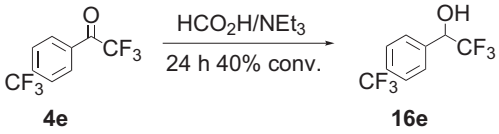


Fig. 3. ATH of **2a**–**g** in formic acid/triethylamine using catalyst **III**. The selectivity model plotted as a function of the inductive σ-*para* and resonance (R). Regression equation: $\Delta(\Delta G_{mod.})=2.58-(1.57\times\sigma\text{-}para)-(1.06\times R)$, $n=7$, $r=0.992$, $s=0.057$, $F=131.42$.

Although the effect is slightly different in the systems studied, the results strongly suggest that the electron density of the aromatic ring, expressed as a combination of inductive and resonance contributions, affects enantioselectivity in formic acid/triethylamine. This is most likely due to more favourable π–π interaction between some substrates and the arene part of the catalyst.

Low ee-values were obtained in reduction of **4a**–**c** and especially so in reduction of **4d** and **4e**. A background reaction was observed for **4d** and **4e** (Scheme 4), however at such a low rate that this alone could not alone account for the low selectivity. More likely, formic acid delivers a hydride to the ruthenium-complexed ketone, efficiently competing with the intramolecular hydride transfer reaction.



Scheme 4. Reduction of **4e** in formic acid/triethylamine.

2.3. ATH in formic acid/triethylamine using catalyst II and IV

ATH of **1a**–**e**, **2a**–**g**, **3b**, **4a**–**4e** and **8**–**12** in formic acid/triethylamine using catalyst **II** gave products with mediocre ee-values and with a low turnover. Catalyst **IV** appeared even worse and can be regarded as useless in this solvent system. Data for the reduction of the 1-aryl-2-fluoroethanones **2a**–**g** have been reported previously,[15] while data for reduction of the other compounds using catalyst **II** is shown in Table 4.

2.4. ATH in water using catalyst I–IV

ATH can also be performed in water using sodium formate as hydrogen donor. This system is attractive due to the higher rate observed in reduction of less activated ketones,[5,29] In contrast to the formic acid/triethylamine system, reactions in water also gave acceptable rate of reactions using the TsCYDN based catalysts **II** and **IV**. The use of all catalyst is therefore discussed, and their selectivity has been correlated with substituent constants and the partial charge of the carbonyl carbon.

Table 4
ATH of 1-aryl-2-ethanones in formic acid/triethylamine using catalyst **II**: ee (%), conversion (conv. %) and reaction time in hours (h). The data for reduction of **2a**–**g** can be found in Ref. 15

Entry	Substrate	R_1/Ar	R	ee %	Conv. % (h)	Product
1	**1a**	MeO	CH_3	—	<1 (24)	—
2	**1b**	H	CH_3	83	11 (24)	(*R*)-**13b**
3	**1c**	F	CH_3	86	53 (24)	(*R*)-**13c**
4	**1d**	Br	CH_3	—	<1 (24)	—
5	**1e**	CF_3	CH_3	86	61 (24)	(*R*)-**13f**
6	**3d**	H	CHF_2	61	77 (24)	(*S*)-**15b**
7	**4a**	MeO	CF_3	40	94 (24)	(*S*)-**16a**
8	**4b**	H	CF_3	39	99 (24)	(*S*)-**16b**
9	**4c**	F	CF_3	17	99 (24)	(*S*)-**16c**
10	**4d**	Br	CF_3	14	>99 (24)	(*S*)-**16d**
11	**4e**	CF_3	CF_3	18	>99 (6)	(*S*)-**16e**
12	**8**	1-Naphthyl	CH_3	79	11 (23)	(*R*)-**20**
13	**9**	1-Naphthyl	CH_2F	76	22 (23)	(*S*)-**21**
14	**10**	1-Naphthyl	CHF_2	53	>99 (23)	(*S*)-**22**
15	**11**	1-Naphthyl	CF_3	21	>99 (22)	(*R*)-**23**
16	**12**	1-Naphthyl	Et	—	<1 (24)	—

2.4.1. Effect of alkyl/fluoroalkyl side chain on enantioselectivity using catalyst I–IV. The ee of the products for the ATH of **1b**, **2b**, **3b** and **4b** in water, depended on the catalyst and substrate structure, see Fig. 4. A decrease in selectivity was again observed when increasing the number of aliphatic fluorines. In all cases the hydride was delivered preferably from the same side providing an excess of (*R*)-**13b**, (*S*)-**14b**, (*S*)-**15b** and (*S*)-**16b**, respectively. Transfer hydrogenations catalysed by **III** gave the highest selectivity for all substrates. The

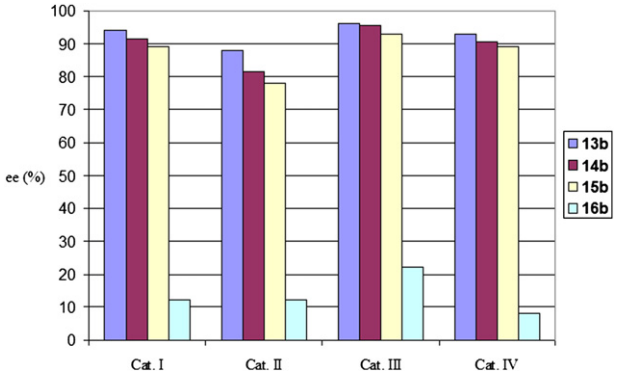


Fig. 4. Enantiomeric excess (ee, %) of products after ATH of **1b**, **2b**, **3b** and **4b** using cat. **I**–**IV** in water with sodium formate as hydrogen donor.

Table 5
ATH of the phenyl ketones **1b**, **2b**, **3b** and **4b** using catalyst **I** and **III** in water: ee (%), conversion (Conv.), reaction time in hours (h), Δ(Δ*G*), model estimated $\Delta(\Delta G_{mod.})$ in kcal/mol and the residuals (Res.)

Entry	Substrate	R	Cat.	ee (%)	Conv.% (h.)	*R*/*S*	Δ(Δ*G*)	Δ(Δ*G* mod.)[c]	Res.[c]
1[a]	**1b**	CH_3	**I**	94.0	>99 (2)	*R*	2.16	2.19	−0.03
2	**2b**	CH_2F	**I**	91.5	>99 (2)	*S*	1.94	1.94	0.00
3	**3b**	CHF_2	**I**	89.0	>99 (6)	*S*	1.77	1.75	0.02
4	**4b**	CF_3	**I**	12.0	>99 (2)	*S*	0.15	0.16	−0.01
5[b]	**5b**	Et	**I**	86.0	>99 (2)	*R*	1.61	1.59	0.02
6	**1b**	CH_3	**III**	96.0	>99 (6)	*R*	2.42	2.44	−0.02
7	**2b**	CH_2F	**III**	95.5	>99 (2)	*S*	2.35	2.28	0.07
8	**3b**	CHF_2	**III**	93.0	>99 (6)	*S*	2.06	2.11	−0.05
9	**4b**	CF_3	**III**	22.0	>99 (6)	*S*	0.28	0.28	0.00

[a] Data corresponds with that obtained by Wu et al.[29]
[b] Reported by Wu Ref. 29.
[c] Regression equations: catalyst. **I**: $\Delta(\Delta G_{mod.})=9.94-(7.44\times ES-V)-(6.82\times Mul.C)$, $n=5$, $r=0.999$, $s=0.030$, $F=1220.77$, catalyst **III**: $\Delta(\Delta G_{mod.})=12.6-(8.78\times ES-V)-(9.84\times Mul.C)$, $n=4$, $r=0.999$, $s=0.087$, $F=200.75$.

data obtained using catalysts **I** and **III** are compiled in Table 5, and the results using catalyst **II** and **IV** are shown in Table 6.

Table 6
ATH of the phenyl ketones **1b**, **2b**, **3b** and **4b** using catalyst using catalyst **II** and **IV** in water: ee (%), conversion (Conv.), reaction time in hours (h), $\Delta(\Delta G)$, model estimated $\Delta(\Delta G_{mod.})$ in kcal/mol and the residuals (Res.)

Entry	Substrate	R	Cat.	ee (%)	Conv.% (h.)	*R*/*S*	$\Delta(\Delta G)$	$\Delta(\Delta G_{mod.})$[b]	Res.[b]
1[a]	**1b**	CH_3	**II**	88.0	78 (24)	*R*	1.71	1.72	−0.01
2	**2b**	CH_2F	**II**	81.5	>99 (24)	*S*	1.42	1.34	0.02
3	**3b**	CHF_2	**II**	78.0	>99 (6)	*S*	1.30	1.31	−0.01
4	**4b**	CF_3	**II**	12.0	99 (24)	*S*	0.15	0.15	−0.00
5	**1b**	CH_3	**IV**	93.0	99 (24)	*R*	2.06	2.11	−0.05
6	**2b**	CH_2F	**IV**	90.5	>99 (2)	*S*	1.87	1.77	0.09
7	**3b**	CHF_2	**IV**	89.0	99 (6)	*S*	1.77	1.80	−0.03
8	**4b**	CF_3	**IV**	8.0	92 (24)	*S*	0.10	0.11	−0.01

[a] Performed previously in 85% ee.[33]
[b] Regression equations: Cat. **II**: $\Delta(\Delta G_{mod.})=10.5-(6.73\times ES-V)-(11.2\times Huc.C)$, $n=4$, $r=0.999$, $s=0.026$, $F=1071.55$. Cat. **IV**: $\Delta(\Delta G_{mod.})=19.7-(11.1\times ES-V)-(25.0\times Huc.C)$, $n=4$, $r=0.997$, $s=0.109$. $F=103.32$.

Regression analysis for each catalyst gave an acceptable correlation of $\Delta(\Delta G)$ with the size of the alkyl/fluoroalkyl group as defined by the Charton volume (ES−V). Further, when including the Mulliken charge (catalyst **I** and **III**) or the Hückel charge (catalyst **II** and **IV**) of the carbonyl carbon as predictor, improved models of the $\Delta(\Delta G)$ were obtained, see Figs. 5 and 6.

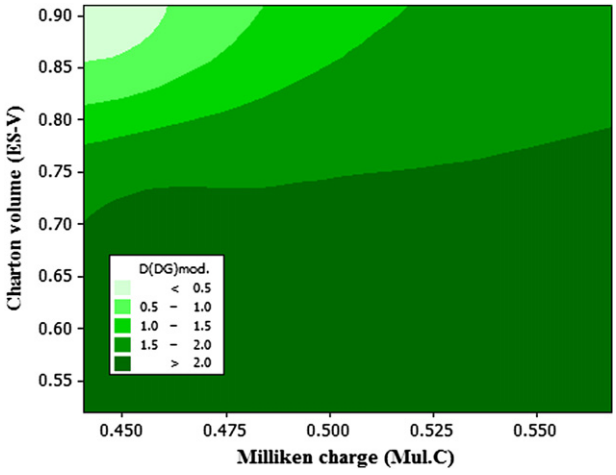


Fig. 5. ATH of **1b**, **2b**, **3b** and **4b** using catalyst **III** in water with sodium formate as hydrogen donor. The selectivity model plotted as a function of the predictors Charton volume (ES−V) and the Mulliken charge of the carbonyl carbon (Mul.C). Regression equation: $\Delta(\Delta G_{mod.})=12.6-(8.78\times ES-V)-(9.84\times Mul.C)$, $n=4$, $r=0.999$, $s=0.087$, $F=200.75$.

Although the number of data points is limited, the selectivity displayed by the catalysts **I**–**IV** seems to be affected by the size of the fluoroalkyl chain, but also by an electronic component, which is related to the charge density of the carbonyl carbon. Moreover, according to the model, the increase in partial charge upon fluorination affects the selectivity in the opposite direction to the size effect. This might explain the low selectivity for the trifluoroketones.

Turning to the ATH of the 1-naphthyl ketones, **8**–**12** (Table 7), the use of water in general gave a lower selectivity as compared to the use of formic acid/triethylamine as reaction medium. The selectivities obtained with the catalysts **I**–**IV** are visualised in Fig. 7.

Interestingly, reduction of the trifluoroketone **11** by catalyst **IV** gave a product originating from reduction from the opposite face,

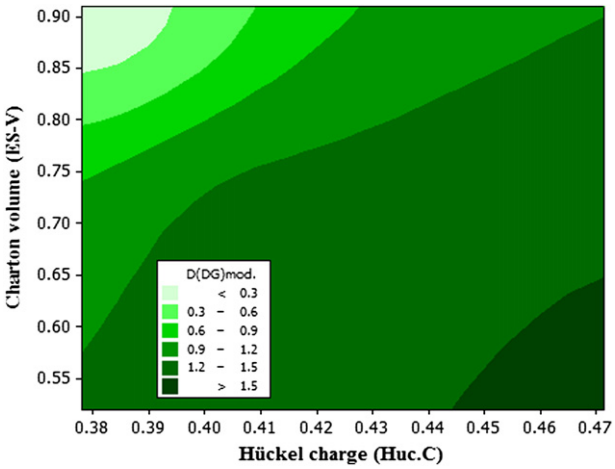


Fig. 6. ATH of **1b**, **2b**, **3b** and **4b** using catalyst **II** in water with sodium formate as hydrogen donor. The selectivity model $\Delta(\Delta G)$ plotted as a function of the Charton volume (ES−V) and the Hückel charge of the carbonyl carbon (Huc.C).

Table 7
ATH of **8**–**12** in water using sodium formate using catalyst **I**–**IV**: ee (%), conversion (conv.), reaction time in hours (h), $\Delta(\Delta G)$, model estimated $\Delta(\Delta G_{mod.})$ in kcal/mol and residuals (Res.)

Entry	Substrate	R	Cat.	ee (%)	Conv. % (h)	*R*/*S*	$\Delta(\Delta G)$	$\Delta(\Delta G_{mod.})$[a]	Res.[a]
1[b]	**8**	CH_3	**I**	87.5	85 (168)	*R*	1.69	1.74	−0.06
2	**9**	CH_2F	**I**	77.0	>99 (4)	*S*	1.27	1.19	0.08
3	**10**	CHF_2	**I**	70.0	>99 (4)	*S*	1.08	0.85	0.23
4	**11**	CF_3	**I**	40.5	>99 (9)	*R*	−0.53	−0.43	−0.10
5[b]	**12**	Et	**I**	80.0	28 (168)	*R*	1.37	1.52	−0.15
6[b]	**8**	CH_3	**II**	73.5	23 (166)	*R*	1.17	1.15	0.02
7	**9**	CH_2F	**II**	58.0	>99 (27)	*S*	0.82	0.74	0.09
8	**10**	CHF_2	**II**	50.0	97 (28)	*S*	0.68	0.49	0.20
9	**11**	CF_3	**II**	41.5	>99 (21)	*R*	−0.55	−0.47	−0.08
10[b]	**12**	Et	**II**	54.5	3 (167)	*R*	0.76	0.98	−0.22
11[b]	**8**	CH_3	**III**	80.0	74 (167)	*R*	1.37	1.54	−0.17
12	**9**	CH_2F	**III**	51.5	>99 (23)	*S*	0.71	0.84	−0.13
13	**10**	CHF_2	**III**	47.0	>99 (7)	*S*	0.63	0.42	0.22
14	**11**	CF_3	**III**	77.0	>99 (7)	*R*	−1.27	−1.20	−0.07
15[b]	**12**	Et	**III**	81.5	24 (167)	*R*	1.42	1.26	0.16
16[b]	**8**	CH_3	**IV**	67.5	38 (161)	*R*	1.02	1.21	−0.19
17	**9**	CH_2F	**IV**	34.5	>99 (16)	*S*	0.45	0.49	−0.04
18	**10**	CHF_2	**IV**	23.0	>99 (16)	*S*	0.29	0.05	0.24
19	**11**	CF_3	**IV**	88.0	86.0 (6)	*R*	−1.71	−1.61	−0.10
20[b]	**12**	Et	**IV**	67.0	20 (161)	*R*	1.01	0.92	0.09

[a] Regression equations: catalyst **I**: $\Delta(\Delta G_{mod.})=4.65-(5.59\times ES-V)$, $n=5$, $r=0.983$, $s=0.179$, $F=91.23$, catalyst **II**: $\Delta(\Delta G_{mod.})=3.31-(4.15\times ES-V)$, $n=5$, $r=0.970$, $s=0.186$, $F=46.86$, catalyst **III**: $\Delta(\Delta G_{mod.})=5.19-(7.02\times ES-V)$, $n=5$, $r=0.987$, $s=0.204$, $F=111.07$, catalyst **IV**: $\Delta(\Delta G_{mod.})=4.98-(7.25\times ES-V)$, $n=5$, $r=0.989$, $s=0.193$, $F=131.72$.
[b] The long reaction time in case of substrate **8** and especially **12** might lead to change in catalyst structure over time, thus possibly changing the selectivity.

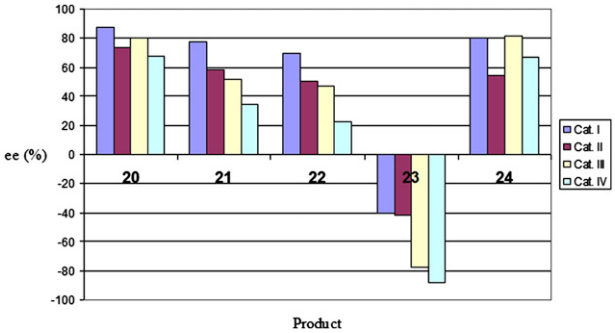


Fig. 7. Enantiomeric excess (ee, %) of products in asymmetric reduction of **8**–**12** using catalyst **I**–**IV** in water with sodium formate as hydrogen donor. Negative ee-values are assigned for products were hydride delivery occurred from the opposite face.

giving as high as 86% ee. Thus, the combination of the bulky trifluoromethyl group in the substrate, the mesitylene–TsCYDN catalyst and water as reaction medium, favours reduction from the opposite face of the ketone, as compared to a methyl substituent, *p*-cymene-TsDPEN based catalyst and formic acid/triethylamine as solvent.

Regression analysis revealed a fairly good correlation between $\Delta(\Delta G)$ and the Charton volume, again indicating size as the major factor in enantioselection. However, better models were also for catalyst **I** and **II** obtained by including the Mulliken charge as predictor.

2.4.2. Effect of aromatic substituents (water). The selectivity in reduction of the 1-aryl-2-fluoroethanones **2a**–**g** using water as solvent was governed by different factors than in formic acid/triethylamine.[15] Therefore, reduction of **1a**–**e** and **4a**–**e** were also undertaken to complement previous reported data. The experimental results for reduction of the 1-arylethanones, **1a**–**e** and 1-aryl-2,2,2-trifluoroethanones **4a**–**e** using catalyst **I** and **III** are compiled in Table 8.

Table 8
ATH of **1a**–**e** and **4a**–**e** in water using catalysts **I** and **III**: ee (%), conversions (conv.) and reaction time in hours (h)

Entry	R_1	Cat.	CH_3, **13**		CF_3, **16**		
			ee (%)[a]	Conv. % (h)	ee (%)	Conv. % (h)	*R*/*S*
1[b]	MeO (**a**)	I	94.5	77 (24)	5.0	99 (6)	*S*
2[b]	H (**b**)	I	94.0	100 (2)	11.5	>99 (2)	*S*
3	F (**c**)	I	91.0	100 (2)	22.0	99 (24)	*R*
4[b]	Br (**d**)	I	89.0	98 (24)	11.0	90 (24)	*R*
5[b]	CF_3 (**e**)	I	92.5	100 (2)	3.5	>99 (2)	*R*
6[c]	Cl (**h**)	I	91.0	>99 (2)	[d]	[d]	—
7[c]	CH_3 (**i**)	I	90.0	98 (2)	[d]	[d]	—
8	MeO (**a**)	III	95.5	96 (24)	5.0	>99 (6)	*S*
9	H (**b**)	III	95.5	>99 (6)	22.5	>99 (6)	*S*
10	F (**c**)	III	95.0	>99 (6)	21.5	>99 (24)	*R*
11	Br (**d**)	III	98.0	>99 (24)	15.0	>99 (24)	*R*
12	CF_3 (**e**)	III	95.0	>99 (24)	2.0	>99 (2)	*R*

[a] (*R*)-Stereochemistry.
[b] Previously reported in ee of 95% (R=OMe), 94% (R=H), 93% (R=Br), 94% ($R=CF_3$).[29]
[c] Data from Ref. 29.
[d] Not performed.

The ATH of **1a**–**e** with catalyst **I** gave products with ee-values ranging from 89.0 to 94.5%. Even higher enantioselectivity was obtained with the less commonly used mesitylene based catalyst **III** (95.0–98.0% ee).

The 1-aryl-2,2,2-trifluoroethanones, **4a**–**e**, were all reduced in low ee, with the stereochemistry varying depending on the R^1-group. No background reduction was observed in water and the modest enantioselectivity is assumed to be due to comparable rates for the two possible transition states.

The use of catalyst **II** and **IV** (Table 9) in the reduction of the 1-arylethanones **1a**–**e** resulted in decent selectivity (84.5–93.0% ee), and rate in contrast to that observed using formic acid/triethylamine as solvent. However, the 1-aryl-2,2,2-trifluoroethanones, **4a**–**e** were reduced in low 0–20.5% ee. Attempts to correlate the $\Delta(\Delta G)$ with a number of substituent constants did not lead to any trustworthy models. Possibly, in water, additional hydrophobic and solvation effects are operating disguising electronic effects exerted by the *para*-substituent.

2.5. Determination of absolute stereochemistry of compounds 9 and 10

The absolute configuration of the alcohols **9** and **10** was determined by circular dichroism spectroscopy (CD) using the exciton chirality method.[15,34–37] The exciton chirality method depends on two interaction chromophores and the alcohols were therefore derivatised to their benzoate esters **25**–**27** (Fig. 8) by standard benzoylation.

Table 9
ATH of **1a**–**e** and **4a**–**e** in water using catalyst **II** and **IV**: ee (%), conversion (conv. %) and reaction time in hours (h)

Entry	R	Cat.	CH_3, **13**		CF_3, **16**		
			ee (%)[a]	Conv. (h)	ee (%)	Conv. (h)	*R*/*S*
1	MeO (**a**)	II	88.5	9 (24)	1.0	97 (24)	*R*
2[b]	H (**b**)	II	88.0	78 (24)	12.0	99 (24)	*S*
3	F (**c**)	II	84.5	100 (2)	19.5	>99 (6)	*R*
4	Br (**d**)	II	87.5	86 (24)	10.0	90 (24)	*R*
5	CF_3 (**e**)	II	90.0	99 (2)	0.0	>99 (2)	*ND*
6	MeO (**a**)	IV	93.0	31 (24)	0.5	>99 (6)	*ND*
7	H (**b**)	IV	93.0	99 (24)	14.0	92 (24)	*S*
8	F (**c**)	IV	90.6	98 (24)	20.5	>99 (24)	*R*
9	Br (**d**)	IV	95.5	96 (24)	9.5	86 (24)	*R*
10	CF_3 (**e**)	IV	92.5	99 (24)	3.5	>99 (2)	*R*

[a] (*R*)-Stereochemistry.
[b] Previously reported in 85% ee.[33]

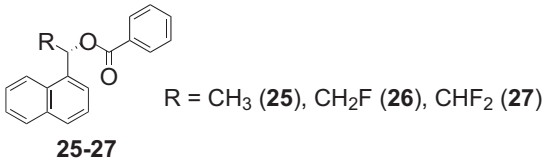


Fig. 8. Structure of the benzoates **25**–**27**.

An energy minimisation using Molecular Modelling Pro (MM2) showed that the benzoates, **25**–**27**, had similar preferred conformations. A negative first cotton effect was predicted and later confirmed by CD measurements.

3. Conclusion

The scope and limitations for the use of the Noyori type ruthenium–arene–diamine catalysts in ATH of fluorinated ketones have been investigated in two different solvent systems. Generally, good rates and high selectivity were obtained in reduction of 1-aryl-2-fluoroethanones and 2,2-difluoroacetophenone using ruthenium *p*-cymene or mesitylene in combination with the TsDPEN ligand and formic acid/triethylamine as reaction medium. ATH with the Ru–mesitylene complex in most cases gave the highest selectivity. This catalyst was also found to be highly selective for reductions of 1-arylethanones in water (95.0–98.0% ee). Reduction of the trifluoroketones **4a**–**e** gave the products in a low ee. However, the ruthenium–mesitylene–TsCYDN catalyst, unsuited in ATH of 1-acetonaphthone, in water reduced the trifluorinated analogue in 86% ee. Thus, suitable conditions for enantioselective ATH of trifluoroketones cannot be found by employing the aryl methyl ketones as model systems.

In formic acid/triethylamine the enantioselection mechanism was found to depend mainly on the size of the fluoroalkyl group. However, within series of 1-arylethanones and 1-aryl-2-fluoroethanones, regression analysis identified electronic properties of the aromatic group to be a determinating factor for the selectivity. This is most likely due to π–π interaction between the catalyst and the substrate.

Also in water, the steric bulk of the alkyl/fluoroalkyl substituent was found to be a major factor in determining selectivity. However, an electronic effect related to the partial charge of the carbonyl

carbon, was also found to be of significance. The regression analysis indicated this effect to operate in the opposite direction to the size effect, in part explaining the low selectivity obtained in reduction of the trifluoroketones. The enantioselection mechanism for ATH in water within a series of 1-arylethanones and 1-aryl-2-fluor4oethanones, seemed more complex and could not be revealed by the present study.

4. Experimental

4.1. Chemical and equipment

The solvents and reagents were used as received from the suppliers. $[RuCl_2(p\text{-cymene})]_2$, (*R*,*R*)-TsDPEN, (*R*,*R*)-TsCYDN, ruthenium(III) chloride hydrate, acetophenones (**1a**–**e**), 1-acetonaphthone (**8**) 2,2,2-trifluoro-1-phenylethanone (**4b**) and 2,2,2-trifluoro-1-(4-(trifluoromethyl)phenyl)ethanone (**4e**) were from Aldrich, 1,3,5-trimethyl-1,4-cyclohexadiene was from Alfa Aesar, **4a** was from Fluchem, **4c** and **4d** were from Apollo. The 1-aryl-2-fluoroethanones, **2a**–**g**,[25,26] the 1-naphthyl ketones **9**–**12**,[38] 2,2-difluoro-1-phenylethanone (**3b**)[39] and $[RuCl_2(mesitylene)]_2$,[40,41] were all synthesised as described previously. Asymmetric transfer hydrogenations were performed in an incubator shaker from Brunswic Scientific Co Inc. The Hückel and Mulliken partial charge was estimated starting with MM2 minimised structure using ChemBio3D, Version 12.0. The Mulliken charges were obtained via the Games interface (RHF/3-21G). The used values are shown in Table 10. Regression analysis was performed using Minitab 15 from Minitab Inc. at a confidence level of 95%.

Table 10
Estimated values for the partial charge of the carbonyl oxygen and carbon: Hückel charge of carbon (Huc.C), Hückel charge of oxygen (Huc.O), Mulliken charge of carbon (Mul.C), Mulliken charge of oxygen (Mul.O)

Compound	Ar	R_1	Huc.C	Huc.O	Mul.C	Mul.O
1b	Ph	CH_3	0.471	−0.552	0.568	−0.587
2b	Ph	CH_2F	0.440	−0.552	0.496	−0.553
3b	Ph	CHF_2	0.413	−0.538	0.459	−0.541
4b	Ph	CF_3	0.378	−0.526	0.440	−0.535
5b	Ph	Et	0.464	−0.553	0.613	−0.587
6b	Ph	*i*-Pr	0.462	−0.562	0.645	−0.590
8	Naphthyl	CH_3	0.452	−0.557	0.583	−0.588
9	Naphthyl	CH_2F	0.424	−0.547	0.533	−0.581
10	Naphthyl	CHF_2	0.390	−0.544	0.463	−0.556
11	Naphthyl	CF_3	0.353	−0.534	0.448	−0.554
12	Naphthyl	Et	0.448	−0.565	0.605	−0.594

4.2. Analyses

NMR spectra were recorded with Bruker Avance DPX 400 or 300 MHz ^1H and ^{13}C NMR chemical shifts are in parts per million relative to TMS, while for ^{19}F NMR the shift values are relative to hexafluorobenzene. Coupling constants are in hertz. High resolution MS (EI/70 eV) was performed using a Finnigan MAT 95 XL. FTIR spectra were recorded on a Thermo Nicolet Avatar 330 infrared spectrophotometer. All melting points are uncorrected and measured by a Büchi melting point instrument. HPLC was performed using an Agilent 1100 series system with a DAD detector. GC was performed using a Varian 3380. CD spectra were recorded on an OLIS DSM 1000 spectrophotometer in a 1 cm cell, at concentration 0.01 mg/mL in MeCN.

The ee of **13a** was determined using HPLC on a Chiracel OD column (0.46 cm×25 cm), mobile phase: hexane/2-propanol (99/1), flow rate 1.0 mL/min, (*R*)-**13a**: 23.7 min, (*S*)-**13a**: 27.3 min. Determination of the ee of **13b**–**e** was performed using GC and a CP-Chirasil-Dex CB column, column pressure: 10 psi, split flow: 30 mL/min, isothermal programs, **13b** (100 °C): (*R*)-**13b**: 18.3 min, (*S*)-**13b**: 21.2 min, **13c** (125 °C): (*R*)-**13c**: 6.3 min, (*S*)-**13c**: 7.1 min, **13d** (145 °C): (*R*)-**13d**: 10.7 min, (*S*)-**13d**: 12.0 min; **13e** (115 °C): (*R*)-**13e**: 13.1 min, (*S*)-**13e**: 16.5 min. The ee of the fluoroalcohols **14a**–**g** was determined by HPLC using a Chiracel OD column (0.46 cm×25 cm), mobile phase: hexane/2-propanol, 98/2, flow rate 1.0 mL/min[42] 2,2-Difluoro-1-phenylethanol (**15b)** was analysed using HPLC and a Chiracel OD column (0.46 cm×25 cm), mobile phase: hexane/2-propanol (95/5), flow rate 1.0 mL/min, (*S*)-**15b**: 12.7 min, (*R*)-**15a**: 13.7 min.

The trifluoroalcohols **16a**–**e** were analysed using HPLC and a Chiralcel OD column with a flow rate of 1 mL/min **16a**,**b**: mobile phase: hexane/2-propanol (99/1): (*S*)-**16a**: 45.7 min, (*S*)-**16a:** 52.4 min, (*S*)-**16b**: 37.5 min, (*R*)-**16b:** 41.4 min **16c**–**e**: mobile phase: hexane/2-propanol (95/5): (*R*)-**16c:** 7.2 min, (*S*)-**16c**: 8.8 min, (*R*)-**16d**: 8.2 min, (*S*)-**16d**: 10.4 min, (*R*)-**16e**: 6.8 min, (*S*)-**16e**: 7.7 min. The trifluoroalcohol **16a** was also analysed using GC and a CP-Chirasil-Dex CB column, 80–200 °C, 10 °C/min, column pressure: 10 psi, split flow: 30 mL/min. Retention times: (*R*)-**16a**: 8.2 min, (*S*)-**16a**: 8.4 min.

The 1-naphthylalkanols **20**–**24** were analysed using HPLC and a Chiralcel OD column eluting with hexane/2-propanol (87/13), flow rate of 1 mL/min. Retention times: (*S*)-**20**: 8.10 min, (*R*)-**20**: 12.1 min, (*R*)-**21**: 8.9 min, (*S*)-**21**: 13.5 min, (*R*)-**22**: 8.9 min, (*S*)-**22**: 17.6 min, (*R*)-**23**: 7.3 min, (*S*)-**23**: 21.9 min, (*S*)-**24**: 6.9 min, (*R*)-**24**: 11.7 min.

4.3. Asymmetric transfer hydrogenation in formic acid/triethylamine (Investigation scale)

A suspension of the $[RuCl_2(arene)]_2$ (0.001 mmol) and ligand (0.0027 mmol) in CH_2Cl_2 (0.5 mL) was stirred at 20 °C for 30 min. After removal of CH_2Cl_2 by a stream of N_2, the ketone (0.1 mmol) in a physical mixture of HCO_2H/Et_3N (5/2 mol ratio, 0.25 mL) was added. The reaction mixture was stirred vigorously at 40 °C for the specified number of hours. Samples were withdrawn from the reaction mixture and the solvent was removed under a stream of N_2. The samples were then dissolved in the HPLC eluent, filtered through silica and analysed by HPLC for determination of conversion and ee. *Note*: *on scale-up the pressure built-up of CO_2 must be taken into account.*

4.4. Asymmetric transfer hydrogenation in water (Investigation scale)

A suspension of $[RuCl_2(arene)]_2$ (0.001 mmol) and the ligand (0.0027 mmol) in H_2O (0.5 mL) were stirred at 40 °C for 1 h. Sodium formate (34 mg, 0.5 mmol) and the ketone (0.1 mmol) were then added and the mixture was stirred vigorously at 40 °C for the specified number of hours. Samples were withdrawn from the reaction mixture, extracted with Et_2O and filtered through silica before analysis by HPLC for determination of conversion and ee.

4.5. Reference materials

The identity of the (*R*)-1-aryl-2-ethanols was confirmed by co-injection of the (*S*)-1-aryl-2-ethanols, **13a**–**e**, prepared by enzyme catalysed resolution using lipase B from *Candida antarctica* and vinyl acetate as acyl donor. ^1H NMR and optical rotation corresponded with that reported previously. The enantioenriched 2-fluoro-1-arylethanols **14a**–**g** have been described previously.[15,27]

*4.5.1. (S)-2,2-Difluoro-1-phenylethanol (**15b**)*[21,23]. The reaction was performed starting with $[RuCl_2(mesitylene)]_2$ (12 mg, 0.02 mmol), TsDPEN (22 mg, 0.06 mmol) and 2,2,-difluoro-1-phenylethanone (**3b**) (312 mg, 2.00 mmol) in formic acid/NEt_3 (5/2 mol ratio,

5 mL) at 40 °C. Full conversion was obtained after 2.5 h. The mixture was diluted with CH_2Cl_2 (50 mL) and extracted with water (4×25 mL) and brine (25 mL) and dried over Na_2SO_4 The crude product was purified by silica-gel column chromatography (hexane/EtOAc, 8/2, R_f=0.27) and gave 290 mg (1.84 mmol, 92%) of a clear oil, ee=90.0%, $[\alpha]_D^{24}$ +16.5 (*c* 1.00, CH_2Cl_2), lit.[21] ee=99%, $[\alpha]_D^{24}$ +19.4 (*c* 0.96, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.45–7.37 (m, 5H), 5.77 (dt, *J*=56.0, 4.8, 1H), 4.84 (m, 1H), 2.37 (d, *J*=3.9, 1H, OH).

*4.5.2. (S)-2,2,2-Trifluoro-1-(4-methoxyphenyl)ethanol (**16a**)*[43]. The reaction was performed starting with $[RuCl_2(cymene)]_2$ (7.3 mg, 0.012 mmol), TsDPEN (11.8 mg, 0.032 mmol) and 2,2,2-trifluoro-1-(4-methoxyphenyl)ethanone (**4a**) (241 mg, 1.18 mmol) in formic acid/NEt_3 (5/2 mol ratio, 3 mL) at 40 °C. Full conversion was obtained after 2.5 h. The mixture was diluted with CH_2Cl_2 (50 mL) and extracted with water (4×25 mL) brine (25 mL) and dried over Na_2SO_4 The crude product was purified by silica-gel column chromatography (hexane/EtOAc, 8/2, R_f=0.36) and gave 112 mg (0.54 mmol, 46%) of a clear oil, ee=42.0%, $[\alpha]_D^{20}$ +13.5 (*c* 1.00, CH_2Cl_2), lit.[44] (*R*)-**4a**, ee=41.0%, $[\alpha]_D^{20}$ −8.9 (*c* 1.00, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.42 (d, *J*=8.9, 2H), 6.96 (d, *J*=8.9, 2H), 4.99 (m, 1H, CH), 3.85 (s, 3H), 2.56 (d, *J*=4.4, 1H, OH).

*4.5.3. (S)-2,2,2-Trifluoro-1-phenylethanol (**16b**)*[44]. The reaction was performed as described for **16a** starting with 2,2,2-trifluoro-1-phenylethanone (**4b**) (205 mg, 1.18 mmol). The crude product was purified by silica-gel column chromatography (CH_2Cl_2, R_f=0.77) and gave 91 mg (0.52 mmol, 44%) of a clear oil, ee=49%, $[\alpha]_D^{20}$ +12.7 (*c* 0.40, CH_2Cl_2), lit.[44] (*R*)-**4b**: ee=56%, $[\alpha]_D^{20}$ −12.5 (*c* 0.40, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.47–7.40 (m, 5H), 5.00 (m, 1H), 2.63 (d, *J*=4.6, 1H, OH).

*4.5.4. (R)-2,2,2-Trifluoro-1-(4-fluorophenyl)ethanol (**16c**)*[44]. $[RuCl_2(mesitylene)]_2$ (6.7 mg, 0.012 mmol) and TsDPEN (11.8 mg, 0.032 mmol) were suspended in H_2O (6.0 mL) and stirred at 40 °C for 1 h. To this mixture was added $NaHCO_3$ (400 mg, 6 mmol) and 2,2,2-trifluoro-1-(4-fluorophenyl)ethanone (**4c**) (226 mg, 1.18 mmol) and the mixture was allowed to react at 40 °C for 24 h. Work up as described for **16a** and purification using silica-gel column chromatography (CH_2Cl_2, R_f=0.41) gave 146 mg (0.75 mmol, 64%), of an oil, ee=27.0%, $[\alpha]_D^{20}$ −5.7 (*c* 1.05, CH_2Cl_2), lit.[44] ee=57%, $[\alpha]_D^{20}$ −20.0 (*c* 0.02, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.45 (m, 2H), 7.09 (m, 2H), 5.00 (m, 1H), 2.56 (s, 1H, OH).

*4.5.5. (R)- and (S)-1-(4-Bromophenyl)-2,2,2-trifluoroethanol (**16d**)*[45]. The compound was prepared as described for **16c** using 1-(4-bromophenyl)-2,2,2-trifluoroethanone (**4d**) (300 mg, 1.19 mmol), and the mixture was allowed to react for 2.5 h. Work up as described for **16a** and purification using silica-gel column chromatography (CH_2Cl_2, R_f=0.30) gave a 174 mg (0.68 mmol, 57%), of a white solid, mp 54–56 °C, lit.[45] 55–56 °C, ee=12.0%, $[\alpha]_D^{20}$ −1.3 (*c* 1.04, EtOH), lit.[45] ee=92.5%, $[\alpha]_D^{20}$ −27.5 (*c* 1.06, EtOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.55 (m, 2H), 7.36 (m, 2H), 5.00 (m, 1H), 2.78 (d, *J*=4.6, 1H, OH).

Due to the low ee and the low optical rotation, a sample of the (*S*)-enantiomer was prepared by reduction using *Geotrichum candidum* acetone powder as described by Nakamura et al.[46] Starting with **4d** (100 mg, 0.40 mmol) this gave 21 mg (0.08 mmol, 21%) of a white solid, mp 54–56 °C, ee=98%, $[\alpha]_D^{20}$ +28.0 (*c* 1.00, EtOH), lit.[21] $[\alpha]_D^{24}$ +30.25 (*c* 0.862, EtOH). ^{1}H NMR was identical to that described for (*R*)-**16d**.

*4.5.6. (S)-2,2,2-Trifluoro-1-(4-(trifluoromethyl)phenyl)ethanol (**16e**)*[47]. $[RuCl_2(cymene)]_2$ (7.3 mg, 0.012 mmol) and TsCYDN (8.7 mg, 0.032 mmol) in CH_2Cl_2 (6.0 mL) were stirred vigorously for 30 min. After removal of the solvent by using N_2 gas, HCO_2H/NEt_3 (5/2 mol ratio, 3.0 mL) and 2,2,2-trifluoro-1-(4-(trifluoromethyl) phenyl)ethanone (**4e**) (287 mg, 1.19 mmol) were added and the mixture was stirred vigorously at 40 °C for 18 h. Work up as described for **16a** gave after silica-gel column chromatography (CH_2Cl_2, R_f=0.55) 168 mg (0.69 mmol, 58%) of a clear oil, ee=13%, $[\alpha]_D^{20}$ +4.6 (*c* 1.06, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.68 (m, 2H), 7.63 (m, 2H), 5.12 (m, 1H), 3.17 (d, *J*=4.5, 1H, OH).

*4.5.7. (R)-1-(Naphthalen-1-yl)ethanol (**20**)*[48]. Due to a low rate in formic acid/triethylamine the following protocol was used to provide a reference compound: a suspension of $[RuCl_2(cymene)]_2$, (7.3 mg, 0.012 mmol) and TsDPEN (12.7 mg, 0.035 mmol) in water (2.0 mL) was stirred for 1 h at 40 °C. Formic acid (68 mg, 1.48 mmol), NEt_3 (124 mg, 1.23 mmol) and 1-(1-naphthalen-1-yl) ethanone (**8**) (210 mg, 1.23 mmol) were added and the mixture was stirred for 18 h at 40 °C. Work-up was performed as described for **16a** and silica-gel column chromatography (hexane/EtOAc, 2/1, R_f=0.21) gave 150 mg (0.87 mmol, 71%) of a white solid, mp 62–63 °C, lit.[48] 66–67 °C, ee=89.5%, $[\alpha]_D^{20}$ +76.6 (*c* 1.13, Et_2O), lit.[48] ee>99.5%, $[\alpha]_D^{25}$ +82.1 (*c* 1.00, Et_2O). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.15 (d, *J*=8.1, 1H), 7.86 (m, 1H), 7.77 (d, *J*=8.1, 1H), 7.67 (d, *J*=7.2, 1H), 7.54–7.46 (m, 3H), 5.71 (dq, *J*=6.5, 3.6, 1H), 1.9 (d, *J*=3.6, 1H, OH), 1.69 (d, *J*=6.5, 3H).

*4.5.8. (S)-2-Fluoro-1-(naphthalen-1-yl)ethanol (**21**).* The reaction was performed as described for **16a** starting with 2-fluoro-1-(naphthalen-1-yl)ethanone (**9**) (200 mg, 1.06 mmol). The reaction time was 2 h. The crude product was purified by silica-gel column chromatography (CH_2Cl_2, R_f=0.27) and gave 170 mg (0.89 mmol, 84%) of a white solid, mp 66–67 °C, ee=89.0%, $[\alpha]_D^{20}$ +52.9 (*c* 1.07, EtOH). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.04 (d, *J*=8.4, 1H), 7.88 (m, 1H), 7.82 (d, *J*=8.0, 1H), 7.73 (m, 1H), 7.57–7.48 (m, 3H), 5.84 (m, 1H), 4.73 (ddd, *J*=46.7, 9.8, 2.9, 1H), 4.54 (ddd, *J*=48.7, 9.8, 8.4, 1H), 2.65 (s, 1H, OH). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 133.7, 133.6, 130.4, 129.1, 128.9, 126.5, 125.8, 125.5, 124.2 (d, *J*=2.0), 122.4, 87.7 (d, *J*=175.1), 70.1 (d, *J*=19.1). ^{19}F NMR (376 MHz, $CDCl_3$) δ: −219.5 (dt, *J*=46.6, 14.4, 1F). HRMS (EI): 190.0790 (calcd 190.0788, M^+). IR (KBr, cm^{-1}): 3388, 2954, 1103.

*4.5.9. (S)-2,2-Difluoro-1-(naphthalen-1-yl)ethanol (**22**).* The reaction was performed as described for **16a** starting with 2,2-difluoro-1-(naphthalen-1-yl)ethanone (**10**) (210 mg, 1.02 mmol). The reaction time was 2 h. Purification by silica-gel column chromatography (CH_2Cl_2, R_f=0.47) gave 170 mg (0.82 mmol, 80%) of a white solid, mp 48–50 °C, ee=76.5%, $[\alpha]_D^{20}$ +17.1 (*c* 1.00, EtOH). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.08 (d, *J*=8.4, 1H), 7.92–7.87 (m, 2H), 7.72 (d, *J*=7.0, 1H), 7.58–7.50 (m, 3H), 6.02 (ddd, *J*=55.1, 55.1, 4.7, 1H), 5.66 (m, 1H), 2.53 (s, 1H, OH). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 133.8, 131.7 (dd, *J*=2.5, 2.5), 131.0, 129.6, 129.0, 126.6, 125.9, 125.3, 125.2, 122.9 (d, *J*=1.5), 115.8 (t, *J*=246.5), 70.8 (dd, *J*=23.0, 23.0). ^{19}F NMR (376 MHz, $CDCl_3$) δ: ABMX-spin system −125.8 (ddd, J_{AB}=282.5, J_{AM}=54.9, J_{AX}=7.1, 1F), −127.3 (ddd, J_{AB}=282.5, J_{AM}=56.4, J_{AX}=12.4, 1F). HRMS (EI): 208.0703 (calcd 208.0694, M^+). IR (KBr, cm^{-1}): 3402, 1139.

*4.5.10. (R)-2,2,2-Trifluoro-1-(naphthalen-1-yl)ethanol (**23**)*[43,49]. A suspension of $[RuCl_2(mesitylene)]_2$ (5.6 mg, 0.01 mmol) and (*R*,*R*)-TsCYDN (6.7 mg, 0.025 mmol) in water (4.5 mL) was stirred for 1 h at 40 °C. To this mixture was added sodium formate (0.30 g, 4.48 mmol) and 2,2,2-trifluoro-1-(naphthalen-1-yl)ethanone (**11**) (200 mg, 0.89 mmol). Reaction for 24 h at 40 °C, work up as described for **16a**, and silica-gel column chromatography (hexane/EtOAc, 5/1, R_f=0.18) gave 113 mg (0.50 mmol, 56%) of a white solid, mp 44–46 °C, lit.[49] 51.6–53.2 °C, ee=85.0%, $[\alpha]_D^{20}$ −20.8 (*c* 1.05, EtOH), lit.,[49] $[\alpha]_D^{25}$ −25.8 (*c* 5.1 EtOH). ^{1}H NMR (300 MHz, $CDCl_3$) δ:

8.06 (d, *J*=8.4, 1H), 7.94–7.89 (m, 2H), 7.83 (d, *J*=7.1, 1H), 7.59–7.52 (m, 3H), 5.90 (m, 1H), 2.61 (d, *J*=4.8, 1H, OH).

*4.5.11. (R)-1-(Naphthalen-1-yl)propan-1-ol (**24**)*[50]. A reference compound was prepared as described for **20** starting with 1-(naphthalen-1-yl)propan-1-one (**12**) (230 mg, 1.25 mmol). This gave after silica-gel column chromatography (hexane/EtOAc, 2/1, R_f=0.28) (*R*)-**24** as an oil, 60 mg (0.32 mmol, 26%), ee=78.0%, $[\alpha]_D^{20}$ +61.6 (*c* 0.50, benzene), lit.[51] ee=77%, $[\alpha]_D^{18}$ +61.1 (*c* 0.44, benzene). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.11 (d, *J*=9.3, 1H), 7.86 (d, *J*=7.2, 1H), 7.77 (d, *J*=8.1, 1H), 7.63 (d, *J*=7.1, 1H), 7.53–7.46 (m, 3H), 5.42 (m, 1H), 2.04–1.91 (m, 3H), 1.04 (t, *J*=7.4, 3H).

*4.5.12. (R)-1-(Naphthalen-1-yl)ethyl benzoate (**25**)*[52]. To a mixture of (*R*)-1-(naphthalen-1-yl)ethanol (**20**) (517 mg, 3.00 mmol) and NEt_3 (1.37 g, 13.53 mmol) in CH_2Cl_2 (20 mL) at 0 °C was added benzoyl chloride (0.67 g, 4.77 mmol). After stirring for 12 h at room temperature, brine (25 mL) was added, and the mixture was extracted with diethyl ether (3×25 mL). The combined organic fraction was washed with aq HCl soln (5%, 3×15 mL), brine (25 mL) and satd aq $NaHCO_3$ (25 mL). Drying over Na_2SO_4, concentration in vacuum, and silica-gel column chromatography (hexane/EtOAc, 4/1, R_f=0.47), gave 334 mg (1.21 mmol, 40%) of a clear oil, ee=98%, $[\alpha]_D^{25}$ −101.8 (*c* 1.00, EtOH). CD (MeCN): $\Delta\varepsilon$=−12.6 (223 nm). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.18 (d, *J*=8.2, 1H), 8.10 (m, 2H), 7.87 (m, 1H), 7.80 (d, *J*=8.3, 1H), 7.70 (d, *J*=7.1, 1H), 7.60–7.42 (m, 6H), 6.90 (q, *J*=6.6, 1H), 1.85 (d, *J*=6.6, 3H).

*4.5.13. (S)-2-Fluoro-1-(naphthalen-1-yl)ethyl benzoate (**26**).* The synthesis was performed as described for **25**, starting with (*S*)-**21** (105 mg, 0.55 mmol). This gave 120 mg (0.41 mmol, 74%) of a white solid, mp 74–75 °C, R_f=0.41, ee=89.0%, $[\alpha]_D^{20}$ −171.6 (*c* 1.00, EtOH), CD (MeCN): $\Delta\varepsilon$=−28.8 (227 nm). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.25 (d, *J*=8.8, 1H), 8.16 (m, 2H), 7.89 (d, *J*=8.4, 1H), 7.85 (d, *J*=8.0, 1H), 7.69 (d, *J*=6.8, 1H), 7.64–7.58 (m, 2H), 7.54 (m, 1H), 7.51–7.46 (m, 3H), 7.14–7.07 (m, 1H), 4.90 (ddd, *J*=48.1, 10.5, 7.8, 1H), 4.83 (ddd, *J*=46.6, 10.5, 3.0, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.6, 133.8, 133.3, 131.0, 130.4, 129.8 (2C), 129.8, 129.4, 129.1, 128.5 (2C), 126.9, 126.0, 125.3, 124.7, 122.6, 84.8 (d, *J*=180.1), 72.1 (d, *J*=21.1). ^{19}F NMR (376 MHz, $CDCl_3$) δ: −220.2 (dt, *J*=47.4, 15.9, 1F). HRMS (EI): 294.1059 (calcd 294.1051, M^+). IR (KBr, cm^{-1}): 3062, 1717, 1287, 1104.

*4.5.14. (S)-2,2-Difluoro-1-(naphthalen-1-yl)ethyl benzoate (**27**).* The synthesis was performed as described for **25**, starting with (*S*)-**22** (110 mg, 0.53 mmol). Work up and purification by silica-gel column chromatography (CH_2Cl_2/hexane, 4/1, R_f=0.56) gave 140 mg (0.45 mmol, 85%) of a white solid, mp 86–88 °C, ee=76.5% (based on **22**), $[\alpha]_D^{25}$ −178.6 (*c* 1.09, EtOH), CD (MeCN): $\Delta\varepsilon$=−28.0 (225). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.24 (d, *J*=8.4, 1H), 8.14 (m, 2H), 7.90 (d, *J*=7.6, 2H), 7.76 (d, *J*=7.2, 1H), 7.65–7.59 (m, 2H), 7.57–7.47 (m, 4H), 7.00 (dt, 1H, *J*=10.9, 4.2, 1H), 6.26 (dt, *J*=55.2, 4.2, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.9, 133.8, 133.6, 131.1, 130.0, 129.9 (2C), 129.2, 129.0, 128.9 (t, *J*=2.5), 128.5 (2C), 127.0, 126.2, 126.0, 125.2, 122.9, 114.1 (t, *J*=246.3), 71.0 (t, *J*=26.2). ^{19}F NMR (376 MHz, $CDCl_3$) δ: −126.2 (dd, *J*=55.5, 11.3, 1F), −126.4 (dd, *J*=55.0, 10.2, 1F). HRMS (EI): 312.0958 (calcd 312.0956, M^+) IR (KBr, cm^{-1}): 3058, 1719, 1284, 1110.

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