PAPER

γ-Sultam-cored *N,N*-ligands in the ruthenium(II)-catalyzed asymmetric transfer hydrogenation of aryl ketones†

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The synthesis of new enantiopure *syn-* and *anti-*3-(α-aminobenzyl)-benzo-γ-sultam ligands **6** and their application in the ruthenium(II)-catalyzed asymmetric transfer hydrogenation (ATH) of ketones using formic acid/triethylamine is described. In particular, benzo-fused cyclic ketones afforded excellent enantioselectivities in reasonable time employing a low loading of the *syn* ligand-containing catalyst. A never-before-seen dynamic kinetic resolution (DKR) during reduction of a γ-keto carboxylic ester (**S7**) derivative of 1-indanone is realized leading as well to excellent induction.

Introduction

The efficient asymmetric transfer hydrogenation (ATH) of ketones employing a HCO_2H/Et_3N binary mixture can be currently achieved under mild conditions by three generations of RSO_2-DPEN-based chiral Ru(II) complexes (available in both enantiomeric forms, DPEN = *trans*-1,2-diphenylethyl-enediamine) (Fig. 1).[1–5] Noyori and co-workers' chiral [RuCl-(TsDPEN)(η⁶-arene)]-type complexes (1st generation) were the starting point of such catalyzed asymmetric transformation both on the applied and fundamental levels.[2,3] Then, intra-covalent tethering of the diamine and η⁶-arene ligand units (2nd and 3rd generations) led to an increased longevity of the catalytic species improving thus the turnover number.[4,5]

Exploring the origin of the stereocontrol by the structural stereoarray of the 1st generation ligands and aiming to enhance the enantioselectivity and catalyst activity, empirical modifications of the chiral elements were undertaken (Fig. 2). In particular, TsDPEN skeletal alteration at the level of its ethylene-bridge substituents on position 1 or 2 revealed the critical importance of their aromatic nature (and inherent
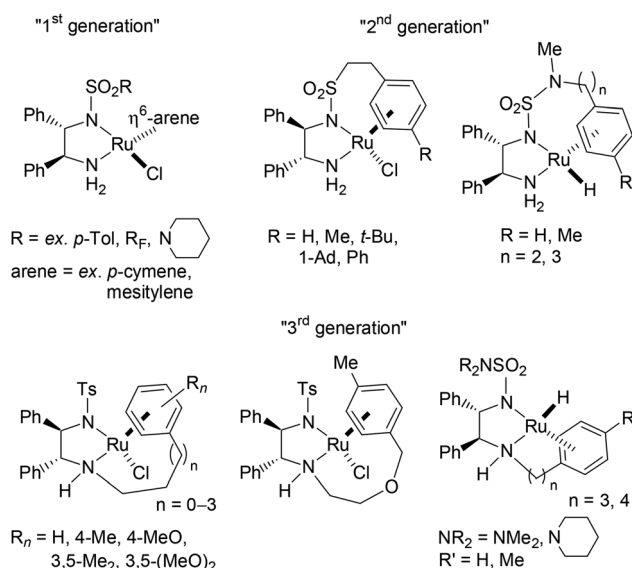
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†Electronic supplementary information (ESI) available: X-ray crystallographic data for racemic *trans*-**5**, [*syn*-(3*S*,1′*R*)-**6**]·(*S*)-CSA, [*anti*-(3*R*,1′*R*)-**6**]·(*S*)-CSA, and the **S7** ATH major reduction product, HPLC and GC chromatograms of ATH products, and ¹H, ¹³C NMR and HMBC spectra. CCDC 1436151–1436154. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c5ob02352a

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Fig. 1 "SO₂DPEN"-embedded ATH-efficient chiral Ru(II) complexes.

steric bulk) as well as the advantage of their *anti* disposition.[2a,6]

With our ongoing research interest in this area, we present hereafter the synthesis of 5-membered cyclic minimalist TsDPEN analogs (Fig. 3) and their investigation in the ATH of various classes of ketones. This new design possesses a partial degree of stereochemical rigidity, maintaining however TsDPEN structural elements of the *vic*-diaryls disposition and the mono *N*-sulfonyl group. Such a structure gives rise to two possible pairs of *syn* and *anti* diastereomers of which preparation was targeted.

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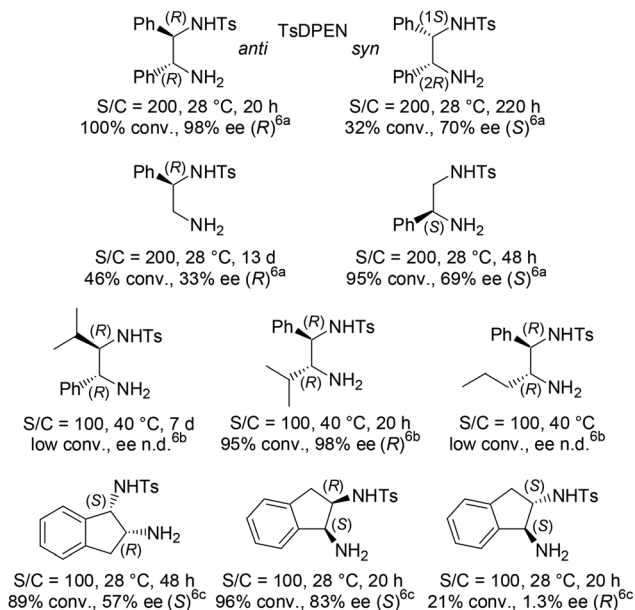This journal is © The Royal Society of Chemistry 2016

Fig. 2 Representative results of [RuCl(TsDPEN or "altered TsDPEN")(*p*-cymene)]-catalyzed ATH of acetophenone using HCO$_2$H/Et$_3$N 5 : 2.
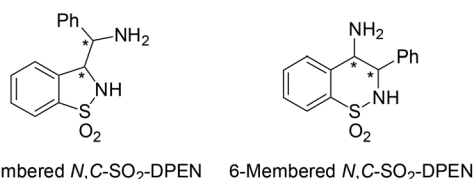

Fig. 3 Possible heterocyclic regioisomers of "structurally-simplified TsDPEN".

Results and discussion

Synthesis of the new 5-membered cyclic *N*,*C*-SO$_2$-DPEN ligands

In this study, we opted for a non-asymmetric synthetic strategy emphasizing on a convenient access to these ligands with a late-stage resolution. Thus, the NaOMe-mediated Wittig reaction of sodium *ortho*-formylbenzenesulfonate with benzyltriphenylphosphonium chloride afforded pure sodium (*E*)-β-styrylbenzenesulfonate [(*E*)-1] in 59% yield after recrystallization (Scheme 1). Conversion into the (*E*)-sulfonamide (*E*)-2 followed by epoxidation with *m*-CPBA and reaction with LiOMe in MeOH led to the regioselective formation of the 6-*endo*-tet-cyclized *trans*-δ-sultam *trans*-4 in high overall yield (82%). Such regioselectivity is supported by ^{1}H, ^{13}C-HMBC analysis from a correlation between the proximal aromatic hydrogen of the 1,1-dioxo-benzo-1,2-thiazinane core and the carbon atom bearing the hydroxyl group (see the ESI†).[7] Tandem *in situ* *O*-mesylation-intra-*N*-alkylation furnished in 76% yield the *trans*-configured aziridine-cored product *trans*-5 (for its X-ray structure showing the aromatic rings in *trans* and a chiral

angular N atom, see the ESI†).§ Alternatively to this circuitous approach, a straightforward single-step conversion of (*E*)-2 into *trans*-5 *via* Rh$_2$(OAc)$_4$-catalyzed aziridination using PhI(OAc)$_2$[8] was achieved in 57% yield. Further on, consecutive aziridine highly regioselective ring-opening with sodium azide in MeCN/H$_2$O (4 : 1) and Pd/C-catalyzed hydrogenation gave the *syn*-3-(α-aminobenzyl)-benzo-γ-sultam *syn*-6. The (3*S*,1′*R*)- and (3*R*,1′*S*)-configured enantiomeric ligands 6 were separated by preparative chiral HPLC in >99% ee and 78% combined yields. The absolute configuration of the 1st eluting enantiomer was determined by X-ray analysis of its (*S*)-CSA salt (Fig. 4).[9]

Next, the complementary diastereomer *anti*-3-(α-amino-benzyl)-benzo-γ-sultam *anti*-6 was prepared analogously, however by resorting to NaHMDS as the base[10] in the Wittig step (Scheme 2). The resulting ~1 : 1 (*E*/*Z*)-isomeric mixture 1 was directly engaged in the further transformation (*via* the sulfonamide 2) into the aziridine 5 upon Rh$_2$(OAc)$_4$-catalyzed aziridination. The *cis* and *trans* diastereomers 5 were separated by silica gel chromatography at this stage of the sequence (28% yield for *cis*-5) and the former was converted as above into the corresponding racemic *anti*-3-(α-aminobenzyl)-benzo-γ-sultam *anti*-6. Its (3*R*,1′*R*)- and (3*S*,1′*S*)-configured enantiomers were separated by preparative chiral Supercritical Fluid Chromatography (SFC) affording the ligands in >99% ee and 44% combined yields. The absolute configuration of the 1st eluting enantiomer was equally determined by X-ray analysis of its (*S*)-CSA salt (Fig. 5).[11]
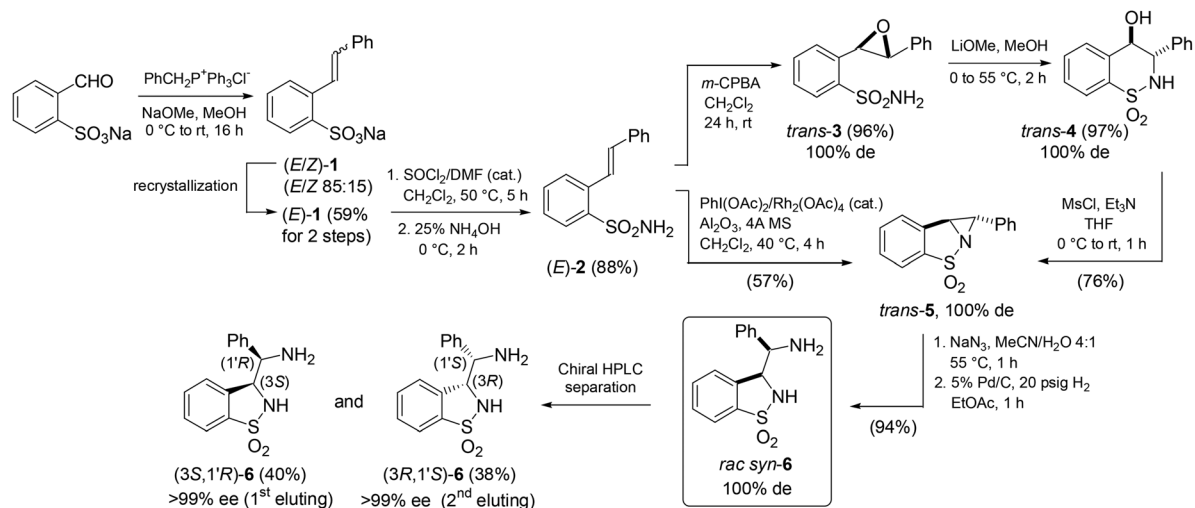
Evaluation of the new sulfonamido-amine ligands 6 in ATH

The assessment of the efficiency in ATH of the Ru(II) complexes incorporating the new 3-(α-aminobenzyl)-benzo-γ-sultam ligands was first conducted on the representative benchmark substrates acetophenone (**S1**), ethyl benzoylacetate (**S2**), 1-indanone (**S3**), and α-tetralone (**S4**) (Table 1). The Ru complexes were prepared from a [RuCl$_2$(η^6-arene)]$_2$ precursor and the enantiopure sulfonamido-amine ligand 6 (*syn* or *anti*; 1.1 equiv. to Ru atom) at 40 °C (1 h) in 1,2-dichloroethane. The catalysts' screening with an S/C = 200 was performed at 40 °C using HCO$_2$H/Et$_3$N 5 : 2.

The outcome of this exploratory profiling clearly revealed the faster reduction rate using the new sulfonamido-amine ligands 6 *versus* the more flexible TsDPEN and "altered TsDPEN" ligands, or Wills' conformationally locked indane-cored sulfonamido-amine ligands in Fig. 2. Also, it was noticed for TsDPEN that a supplemental amount of HCO$_2$H/Et$_3$N 5 : 2 was required in order to revitalize the reduction and drive it to completion. However, acetophenone (**S1**) and its α-ethoxycarbonyl-substituted derivative **S2** afforded lower enantioselectivities (up to 85% ee and 92% ee, respectively) than the ones with the TsDPEN reference. Noteworthily, as (*R*)-1-phenylethanol was the major resulting enantiomer, the sense of induction on acetophenone (**S1**) of the *syn*-(3*R*,1′*S*)-6 and *anti*-(3*R*,1′*R*)-6 revealed to be in line with the one expected

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Scheme 1 Preparation of the *syn*-3-(α-aminobenzyl)–benzo-γ-sultam ligand **6** enantiomers.

Fig. 4 ORTEP drawing of the (1*S*)-camphor-10-sulfonic acid ((*S*)-CSA) salt of the HPLC 1st eluting *syn*-**6** enantiomer at the 50% probability level ((*S*)-CSA was omitted for clarity; for full details, see the ESI†).
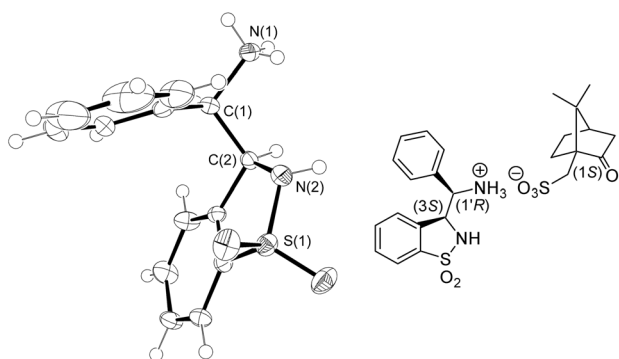

Fig. 5 ORTEP drawing of the (1*S*)-camphor-10-sulfonic acid ((*S*)-CSA) salt of the SFC 1st eluting *anti*-**6** enantiomer at the 50% probability level ((*S*)-CSA was omitted for clarity; for full details, see the ESI†).
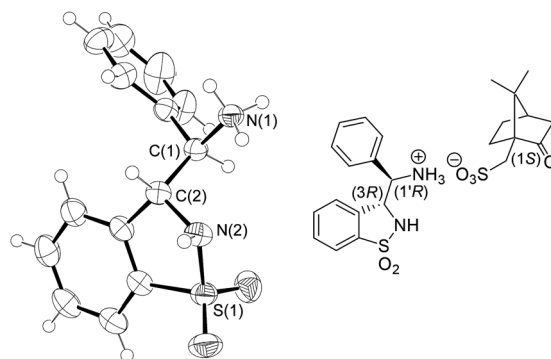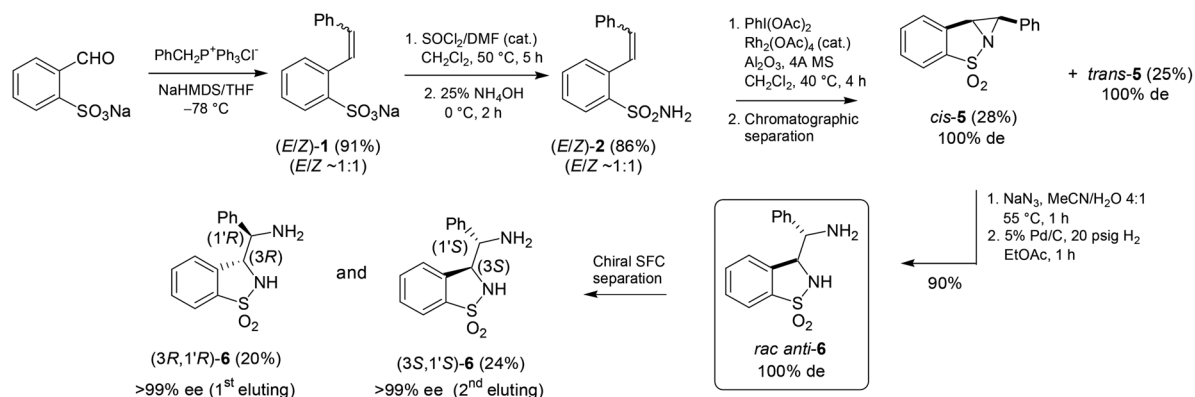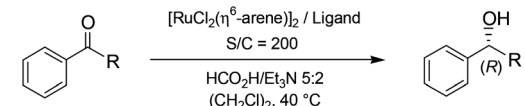

Scheme 2 Preparation of the *anti*-3-(α-aminobenzyl)–benzo-γ-sultam ligand **6** enantiomers.

Table 1 Ru(II)-catalyzed ATH of benchmark ketones with the enantio-pure ligands *syn*-(3R,1'S)-**6** (HPLC 2nd eluting) and *anti*-(3R,1'R)-**6** (SFC 1st eluting)[a]

$$\text{PhCOR} \xrightarrow[\substack{\text{HCO}_2\text{H/Et}_3\text{N } 5:2 \\ (\text{CH}_2\text{Cl})_2,\ 40\ °C}]{\substack{[\text{RuCl}_2(\eta^6\text{-arene})]_2 / \text{Ligand} \\ \text{S/C} = 200}} \text{PhCH(OH)R}$$

Ketone	Ligand	η6-Arene	t (h)	Conv. (%)	ee (%)
S1	*syn*-**6**	*p*-Cymene	4	>99	78
			3[b]	100	85
	syn-**6**	Mesitylene	7	80	72
	anti-**6**	*p*-Cymene	4	>99	58
	anti-**6**	Mesitylene	7	90	72
	TsDPEN	*p*-Cymene	4	25	97
			4[b]	25	97
			20[b]	99	97
S2	*syn*-**6**	*p*-Cymene	3	100	92
	syn-**6**	Mesitylene	3	100	86
	anti-**6**	*p*-Cymene	3	100	54
	anti-**6**	Mesitylene	3	100	82
	TsDPEN	*p*-Cymene	7	85	98
			7[b]	>99	98
S3	*syn*-**6**	*p*-Cymene	4	100	99
	anti-**6**	*p*-Cymene	5	>99	95
	anti-**6**	Mesitylene	7	90	95
	TsDPEN	*p*-Cymene	4[b]	50	-
			20[b]	>99	99
S4	*syn*-**6**	*p*-Cymene	3	100	99
	syn-**6**	Mesitylene	7	80	98
	anti-**6**	*p*-Cymene	7	95	>99
	anti-**6**	Mesitylene	7	85	>99
	TsDPEN	*p*-Cymene	3	25	99
			3[b]	40	99
			20[b]	98	98

[a] Reaction conditions: S/C = 200, ketone (1.0 mmol), 1,2-dichloroethane (1 mL), HCO₂H/Et₃N 5:2 (250 μL), 40 °C. Conversion was determined by ¹H NMR of the extracted crude. Isolated yields were 96–98%. ees were determined by chiral GC or HPLC. (R)-Configured alcohols were obtained [(R,R)-TsDPEN used]. For further details, see the Experimental section. [b] Reaction in neat HCO₂H/Et₃N 5:2 (500 μL).

Table 2 Ru(II)-catalyzed ATH of benzo-fused cyclic ketones with the *syn*-(3R,1'S)-**6** (HPLC 2nd eluting) ligand[a]

Ketone	S/C	t (h)	Conv. (%)	Product cis/trans	ee (%)
S3	1000	16	95	—	99
S4	1000	16	>99	—	99
S5	1000	12	100	—	99
S6	200	4	100	97:3	>99 (cis)
S7	200	6	100	95:5	99 (cis) >99 (trans)
S8	200	6	>99	98:2	>99 (cis)
S9	100	6	>99	50:50	99 (cis)[b]
S10	200	3	100	50:50	>99 (cis) >99 (trans)

[a] Reaction conditions: [RuCl₂(*p*-cymene)]₂/(3R,1'S)-**6**, ketone (1.0 mmol), 1,2-dichloroethane (1 mL), HCO₂H/Et₃N 5:2 (250 μL), 40 °C. Conversion and *cis/trans* ratio (dr) were determined by ¹H NMR of the extracted crude. Isolated yields were 94–99%. ees were determined by chiral GC or HPLC. (R)-Configured alcohols were obtained in all the cases. For further details, see the Experimental section. [b] Determined by ¹⁹F NMR of the (R)-Mosher ester; *trans*-stereoisomers were not separated.

with the *syn*-(1R,2S)-TsDPEN (as its *syn*-(1S,2R)-enantiomer led to (S)-1-phenylethanol) or observed with *anti*-(R,R)-TsDPEN (Fig. 2).

Noticeably, the performance of *syn*-(3R,1'S)-**6** was particularly good against the benzo-fused ketones, 1-indanone (**S3**) and α-tetralone (**S4**), as up to 99% ee with full conversion was obtained in reasonable times leading as well to (R)-configured alcohols.[2a] Also, (R)-configured products (95 to >99% ee) were formed employing the *anti*-(3R,1'R)-**6** demonstrating hence that the chirality on the C(3) atom (bearing the sulfonamido group) predominantly determines the enantiofacial discrimination.

Therefore, the [RuCl₂(*p*-cymene)]₂/(3R,1'S)-**6** complex was further screened on a series of methoxycarbonyl-substituted 1-indanones (**S6–S7**) and methoxycarbonyl-substituted α-tetralones (**S8–S10**) (Table 2).

Employing an S/C = 1000, a 99% ee coupled with a high conversion was obtained within 16 h for 1-indanone (**S3**), α-tetralone (**S4**), and 4-chromanone (**S5**).

Shifting to functionalized variants, ATH of racemic 2- or 3-methoxycarbonyl-1-indanone (**S6** and **S7**) using an S/C = 200 resulted in high diastereoselectivities (*cis/trans* 97:3 and 95:5, respectively) and 99% enantioselectivity indicating a dynamic kinetic resolution (DKR)[12,13] occurring during their reduction. Regioisomeric methoxycarbonyl-α-tetralones **S8–S10** displayed as well an excellent ATH outcome. A high enantioselectivity (>99% ee) was attained in all the cases, with **S8** undergoing DKR[12] in 98:2 *cis/trans* ratio. Noteworthily, **S9** exhibited some kinetic resolution (KR) during ATH as, at ~75% conversion, ¹H NMR indicated a 60:40 *cis/trans* ratio.[14]

Most interestingly, in a related fashion to the reported DKR during ATH of readily enolizable β-keto esters (such as **S6** and **S8**),[12] a first-time DKR during reduction of a γ-keto ester as *rac*-3-methoxycarbonyl-1-indanone[15] (**S7**) was encountered (Scheme 3). We hypothesize that this DKR occurs by keto–enol tautomerization of this 5-membered cyclic γ-keto ester *via* the racemization-prone dual benzylic and allylic carbon. This stereolability could be accentuated in the transition state (TS) influenced by the electrostatic interaction as shown in

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Privileged *Si*-face attack of Ru(II)-[*syn*-(3R,1'S)-**6**] hydride on **S7** enantiomer giving rise to a *cis*-product
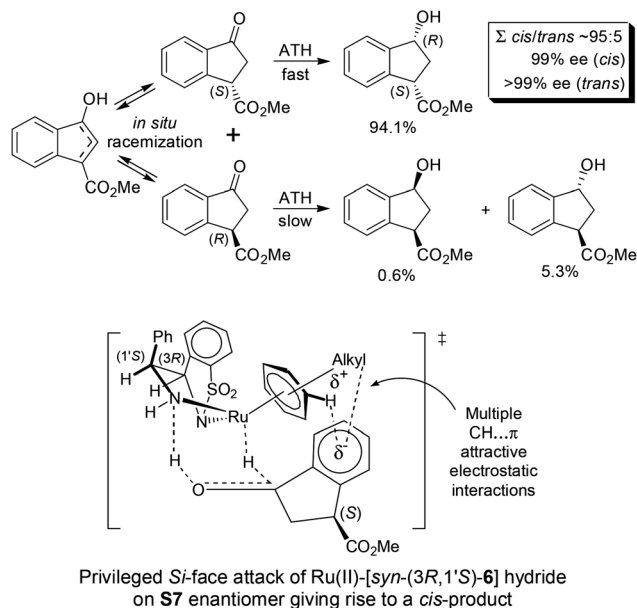
Scheme 3 DKR of *rac*-3-methoxycarbonyl-1-indanone (**S7**) during ATH (Table 2).

Scheme 3. We assume that the configuration of the GC-detected *trans*-product (5.3%) is as depicted supported by the 99% ee obtained with 1-indanone (**S3**). By contrast, the 6-membered δ-keto ester higher homolog **S10** is unable to undergo racemization (under the test conditions) of its methoxycarbonyl-borne benzylic carbon precluding thus DKR.

The [Ru(TsDPEN)(η⁶-arene)]-catalyzed ATH mechanism was established by Noyori, Ikariya and co-workers who considered multiple CH···π attractive electrostatic interactions in the Ru(II)-hydride-ketone TS.[16] In the case of racemic ketone **S7**, a more facile reduction of the (*S*)-enantiomer (*vs.* the (*R*)-enantiomer) is attributable to the CO₂Me group outwards orientation minimizing the steric interference in the TS.

Conclusions

We have successfully prepared diastereo- and enantiopure *syn*- and *anti*-(α-aminobenzyl)-benzo-γ-sultam ligands **6** and explored them in Ru(II)-catalyzed ATH of conventional ketones in the presence of formic acid/triethylamine 5 : 2. The ATH rate and enantioselectivity using the *syn* isomer ligand were better than with the *anti* isomer. High enantioselectivities (99 to >99% ee) were obtained for the benzo-fused cyclic ketones **S3**–**S10** based on 1-indanone or α-tetralone. Namely, a first-time ever DKR of a γ-keto carboxylic ester occurred during reduction. In fact, ketone **S7** derived from 1-indanone afforded the corresponding γ-hydroxy ester in a high *cis/trans* ratio (95 : 5) and excellent ee (99% ee for *cis*, >99% ee for *trans*).

Finally, this study is yet another example of how skeletal changes in a chiral ligand design can translate into unpredictable catalyst properties.

Experimental section

Materials and methods

The following non-commercial ketones were prepared according to literature procedures: 2-methoxycarbonyl-1-indanone[17] and 2-methoxycarbonyl-1-tetralone[18] from 1-indanone and α-tetralone, respectively, using dimethyl carbonate; 3-methoxycarbonyl-1-indanone[19] by esterification of 3-oxo-1-indane-carboxylic acid; 3-methoxycarbonyl-1-tetralone[20] starting by a Stobbe condensation of benzaldehyde with dimethyl succinate; 4-methoxycarbonyl-1-tetralone[19] from 2-phenyl-glutaric anhydride.

All reactions were conducted under an inert atmosphere (nitrogen or argon) using anhydrous solvents. HCO₂H/Et₃N 5 : 2 (azeotrope) was prepared by adding Et₃N (280 mL, 2 mol) to HCO₂H (190 mL, 5 mol) at 0 °C under a nitrogen atmosphere and used as such. Analytical thin-layer chromatography (TLC) was performed using Silica Gel 60 F254 pre-coated plates (0.25 mm thickness); R_f values are reported and visualization was accomplished by irradiation with an UV lamp (254 nm) and/or staining with KMnO₄ solution. Silica gel 60 (40–63 μm) was used for flash column chromatography. ¹H (299.9 MHz; internal Me₄Si) and ¹³C (75.4 MHz; internal CDCl₃, δ 77.00) spectra were recorded for solutions in CDCl₃ if not stated otherwise. HRMS measurements were obtained on a Q-TOF instrument equipped with an orthogonal Z-spray ESI interface.

Sodium (*E*)-2-β-styrylbenzenesulfonate (= sodium *trans-o*-stilbenesulfonate) [(*E*)-1]. To a freshly prepared solution of NaOMe in MeOH (80 mL, 54 mmol) was added 2-formylbenzenesulfonic acid sodium salt (10.20 g, 49.0 mmol) and the mixture was cooled on an ice-bath. Then, benzyltriphenylphosphonium chloride (19.05 g, 49.0 mmol) in MeOH (50 mL) was added dropwise. The resulting pale yellow mixture was allowed to reach rt in 1 h and left to stir for 16 h. The mixture was concentrated and the residue was suspended in cold H₂O (50 mL). The solid was filtered, and washed with cold H₂O (20 mL) and CH₂Cl₂ until TLC showed that no triphenylphosphine oxide is present. After drying, a white powder (12.5 g) was obtained as an (*E*/*Z*)-isomeric mixture in 85 : 15 ratio [by ¹H NMR in DMSO-d_6; δ 6.54 (d, *J* = 12.3 Hz) is the characteristic signal for the (*Z*)-isomer and δ 8.25 (d, *J* = 16.6 Hz) for the (*E*)-isomer]. Recrystallization from MeCN led to the title product as a white powder (8.14 g, 59% yield). ¹H NMR (300 MHz, DMSO-d_6): δ = 7.13 (d, 16.6 Hz, 1 H), 7.18–7.41 (m, 5 H), 7.50–7.53 (m, 2 H), 7.75–7.81 (m, 2 H), 8.25 (d, *J* = 16.6 Hz, 1 H). ¹³C NMR (76 MHz, DMSO-d_6): δ = 125.3, 126.52, 126.58, 127.1, 127.5, 128.1, 128.3, 128.7, 128.9, 134.3, 137.8, 145.7. HRMS-ESI (*m/z*): [M]⁺ calcd for C₁₄H₁₁²³NaO₃S, 282.0327; found, 282.0326.

Sodium (*E*/*Z*)-2-β-styrylbenzenesulfonate [(*E*/*Z*)-1]. To a cold (0 °C) suspension of benzyltriphenylphosphonium chloride (11.67 g, 30 mmol) in THF (250 mL) was added dropwise under stirring NaHMDS (2 M in THF, 15 mL, 30 mmol). After stirring for 3 h at rt, the reaction mixture was cooled to −78 °C and a solution of 2-formylbenzenesulfonic acid sodium salt (6.25 g, 30 mmol) in MeOH (70 mL) was added dropwise. After 2 h, the mixture was allowed to reach rt and then concentrated.

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The residue was suspended in EtOAc/2-PrOH (200 mL), filtered, and purified by column chromatography eluting with hexane/EtOAc/MeOH (7 : 2 : 1) and then EtOAc/MeOH (4 : 1). Fractions containing the product/triphenylphosphine oxide were concentrated, and the solid suspended in H_2O (400 mL) and stirred at rt for 3 h. The insoluble matter was filtered off and the filtrate concentrated and dried under high vacuum at 60 °C affording the title product with a ~1 : 1 E/Z ratio [by ^1H NMR in DMSO-d_6; δ 6.54 (d, J = 12.3 Hz) is the characteristic signal for the (Z)-isomer and δ 8.25 (d, J = 16.6 Hz) for the (E)-isomer] (7.70 g, 91% yield) as a pale yellow powder.

(E)-2-β-Styrylbenzenesulfonamide [(E)-2]. To a cold (0 °C) suspension of (E)-1 (6.40 g, 22.68 mmol) in CH_2Cl_2 (160 mL) was added under stirring thionyl chloride (6.5 mL, 90 mmol) followed by DMF (50 µL). After heating at 50 °C for 5 h, the resulting solution was cooled to 0 °C and added dropwise to a cold (0 °C) solution of NH_4OH (25%, 100 mL)/acetone (50 mL) keeping the internal temperature below 5 °C. Then, the mixture was stirred at 0 °C for 2 h, and CH_2Cl_2 (100 mL) and brine (50 mL) were added. The aqueous layer was re-extracted with CH_2Cl_2 (2 × 100 mL), and the combined organic layers were dried (Na_2SO_4) and concentrated. The crude was filtered through a bed of silica gel eluting with CH_2Cl_2/EtOAc (4 : 1). After concentration and trituration with iPr$_2$O, the title product (5.17 g, 88%) was obtained as colorless crystals; mp 145–146 °C. ^1H NMR (300 MHz, CDCl$_3$): δ = 4.72 (s, 2 H), 7.07 (d, J = 16 Hz, 1 H), 7.28–7.51 (m, 4 H), 7.50–7.65 (m, 3 H), 7.73 (d, J = 8 Hz, 1 H), 7.97 (d, J = 16 Hz, 1 H), 8.07 (dd, J = 8, 1 Hz, 1 H). ^{13}C NMR (76 MHz, CDCl$_3$): δ = 124.4, 127.1, 127.5, 128.0, 128.2, 128.7, 128.9, 133.0, 134.6, 136.3, 136.5, 138.9. HRMS-ESI (m/z): [M + H]$^+$ calcd for $C_{14}H_{14}NO_2S$, 260.0745; found, 260.0748.

(E/Z)-2-β-Styrylbenzenesulfonamide [(E/Z)-2]. Prepared from (E/Z)-1 (~1 : 1) (4.00 g, 14.18 mmol) following a similar procedure to that for (E)-2. The title product (3.17 g, 86% yield; E/Z ~1 : 1) was obtained as an amber-colored oil.

trans-o-Sulfamoyl-stilbene oxide (trans-3). To a solution of (E)-2 (4.50 g, 17.36 mmol) in CH_2Cl_2 (50 mL) was added at rt a solution of m-CPBA (5.00 g, 77%; dried over MgSO$_4$) in CH_2Cl_2 (50 mL). After stirring for 16 h, the mixture was washed with sat. aq. NaHCO$_3$ (2 × 100 mL). The organic phase was filtered through a bed of silica gel/Na$_2$SO$_4$ and concentrated affording the title product (4.59 g, 96% yield) as a slightly yellowish syrup which crystallized upon standing; mp 86–89 °C. ^1H NMR (300 MHz, CDCl$_3$): δ = 3.88 (d, J = 2 Hz, 1 H), 4.62 (d, J = 2 Hz, 1 H), 4.87 (br s, 2 H), 7.34–7.51 (m, 6 H), 7.57–7.71 (m, 2 H), 8.04 (d, J = 8 Hz, 1 H). ^{13}C NMR (76 MHz, CDCl$_3$): δ = 59.9, 62.3, 125.7, 126.8, 128.0, 128.2, 128.8, 133.1, 135.5, 136.0, 140.0. HRMS-ESI (m/z): [M + H]$^+$ calcd for $C_{14}H_{14}NO_3S$, 276.0694; found, 276.0689.

trans-4-Hydroxy-3-phenyl-1,1-dioxo-benzo-1,2-thiazinane (trans-4). To a cold (0 °C) solution of trans-3 (2.00 g, 7.26 mmol) in MeOH (30 mL) was added a freshly prepared solution of LiOMe in MeOH (0.5 M, 14.8 mL, 7.4 mmol) and the resulting solution was allowed to reach rt. After heating at 55 °C for 2 h, it was brought to rt and the concentrated residue was parti-

tioned between CH_2Cl_2 (100 mL) and 0.5 M HCl (40 mL). The aq. layer was re-extracted with CH_2Cl_2 (20 mL), and the combined organic layers were filtered through a bed of silica gel/Na$_2$SO$_4$ and concentrated affording the title product (1.94 g, 97% yield) as a white crispy foam. The structure is supported by ^1H, ^{13}C-HMBC analysis from a correlation between the proximal aromatic hydrogen of the 1,1-dioxo-benzo-1,2-thiazinane core and the carbon atom bearing the hydroxyl group (see the ESI†). ^1H NMR (300 MHz, CDCl$_3$): δ = 2.30 (d, J = 6 Hz, 1 H), 4.56–4.68 (m, 1 H), 4.92 (d, J = 9 Hz, 1 H), 5.12 (dd, J = 10 and 5 Hz, 1 H), 7.41–7.55 (m, 6 H), 7.60–7.70 (m, 1 H), 7.77–7.83 (m, 1 H), 7.86 (dd, J = 8 and 1 Hz, 1 H). ^{13}C NMR (76 MHz, CDCl$_3$): δ = 63.7, 69.8, 123.0, 126.8, 127.7, 128.4, 129.1, 129.2, 132.6, 137.1, 137.3, 137.4. HRMS-ESI (m/z): [M + H]$^+$ calcd for $C_{14}H_{14}NO_3S$, 276.0694; found, 276.0690.

trans-2,3-Benzylidene-1,1-dioxo-benzo-1,2-thiazolidine (trans-5). To a cold (0 °C) solution of trans-4 (1.50 g, 5.45 mmol) in THF (30 mL) was added Et$_3$N (1.7 mL, 12 mmol) followed by dropwise addition of methanesulfonyl chloride (0.69 g, 6.0 mmol). The resulting white suspension was left to stir at 0 °C for 0.5 h then at rt for 1 h. The mixture was quenched at 0 °C with H_2O (20 mL), EtOAc (20 mL) was added and layers were separated. The aq. layer was re-extracted with EtOAc (2 × 20 mL) and the combined organic layers were washed with brine (20 mL), dried (Na$_2$SO$_4$) and concentrated. The crude was purified on silica gel eluting with petroleum ether (40–60)/EtOAc (9 : 1, 8 : 2, 7 : 3 then 6 : 4) affording the title product (1.07 g, 76% yield) as colorless crystals. Its structure was determined by X-ray analysis (see the ESI†). ^1H NMR (300 MHz, CDCl$_3$): δ = 3.48 (d, J = 3 Hz, 1 H), 4.18 (d, J = 3 Hz, 1 H), 7.39 (m, 5 H), 7.54–7.70 (m, 3 H), 7.74–7.81 (m, 1 H). ^{13}C NMR (76 MHz, CDCl$_3$): δ = 51.2, 57.5, 123.4, 125.5, 126.4, 128.7, 129.0, 130.3, 133.5, 133.6, 134.0, 136.0. HRMS-ESI (m/z): [M + H]$^+$ calcd for $C_{14}H_{12}NO_2S$, 258.0589; found, 258.0586.

cis-2,3-Benzylidene-1,1-dioxo-benzo-1,2-thiazolidine (cis-5). To a degassed solution of (E/Z)-2 (~1 : 1) (4.00 g, 15.4 mmol) in CH_2Cl_2 (160 mL) were successively added at rt Al$_2$O$_3$ (3.9 g, 38.6 mmol), molecular sieves 4 Å (4 g), Rh$_2$(OAc)$_4$ (341 mg, 0.77 mmol) and PhI(OAc)$_2$ (7.46 g, 23.17 mmol). The resulting mixture was stirred at 40 °C for 4 h, brought to rt and filtered through a plug of silica gel eluting with CH_2Cl_2. The crude was purified on silica gel eluting with toluene/EtOAc (24 : 1) affording trans-5 (0.97 g, 25% yield) and cis-5 (1.1 g, 28% yield) as an oil. cis-5: ^1H NMR (300 MHz, CDCl$_3$): δ = 4.31 (d, J = 5 Hz, 1 H), 4.62 (d, J = 5 Hz, 1 H), 6.92–7.02 (m, 2 H), 7.03–7.21 (m, 3 H), 7.35–7.52 (m, 2 H), 7.61–7.70 (m, 1 H), 7.71–7.82 (m, 1 H). ^{13}C NMR (76 MHz, CDCl$_3$): δ = 47.3, 55.8, 122.5, 126.4, 127.2, 127.8, 128.5, 130.3, 131.0, 133.2, 134.1, 137.1. HRMS-ESI (m/z): [M + H]$^+$ calcd for $C_{14}H_{12}NO_2S$, 258.0589; found, 258.0588.

syn-3-(α-Aminobenzyl)-1,1-dioxo-benzo-1,2-thiazolidine (syn-6). A solution of trans-5 (910 mg, 3.53 mmol) and NaN$_3$ (0.56 g, 8.56 mmol) in MeCN/H$_2$O (4 : 1, 30 mL) was heated at 55 °C for 1 h, then brought to rt and concentrated. The residue was partitioned between H_2O (pH 4.5) and CH_2Cl_2, and the combined organic layers were dried (Na$_2$SO$_4$) and concentrated. To

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the resulting oil (1.3 g) in EtOAc (30 mL), 5% Pd/C (130 mg) was added and the mixture was hydrogenated using Parr apparatus at 20 psig H_2 for 1 h. After filtration through Celite and concentration, the residue was purified on silica gel eluting successively with CH_2Cl_2, CH_2Cl_2/EtOAc (4 : 1 then 1 : 2) and EtOAc/EtOH (4 : 1), affording *syn*-6 (910 mg, 94% yield) as a yellowish syrup. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.11 (br s, 3 H), 4.36 (d, *J* = 6 Hz, 1 H), 4.90 (d, *J* = 6 Hz, 1 H), 7.02–7.19 (m, 1 H), 7.28–7.62 (m, 7 H), 7.66–7.86 (m, 1 H). ^{13}C NMR (76 MHz, $CDCl_3$): δ = 59.0, 63.1, 121.4, 125.8, 127.1, 128.2, 128.9, 129.6, 132.5, 136.6, 137.0, 140.6. HRMS-ESI (*m/z*): $[M + H]^+$ calcd for $C_{14}H_{15}N_2O_2S$, 275.0854; found, 275.0849. The *syn*-6 enantiomers were separated by preparative HPLC on ChiralPak IC (5 μm, 250 × 30 mm), mobile phase CH_2Cl_2/EtOH (98 : 2), flow rate 42.5 mL min^{-1}, 25 °C, UV detection at 260 nm. Analytical HPLC conditions: ChiralPak IC (5 μm, 250 × 4.6 mm), mobile phase: CH_2Cl_2/EtOH (98 : 2), flow rate: 1 mL min^{-1}, 25 °C, UV detection at 230 nm.[21]

1st eluting *syn* enantiomer (3S,1′R)-6. Beige-colored powder, 374 mg (40%); t_R 15.9 min; >99% ee; $[\alpha]_D^{32}$ −11.5 (*c* 1.0 in $CHCl_3$); chemical purity (area at 230 nm) = 96.9%. The indicated absolute configuration was determined by X-ray analysis of the (1S)-camphor-10-sulfonic acid salt (colorless plates from MeOH).

2nd eluting *syn* enantiomer (3R,1′S)-6. Beige-colored powder, 373 mg (38%); t_R 26.9 min; >99% ee; $[\alpha]_D^{25}$ +11.6 (*c* 1.0 in $CHCl_3$); chemical purity (area at 230 nm) = 93.3%.

***anti*-3-(α-Aminobenzyl)-1,1-dioxo-benzo-1,2-thiazolidine (*anti*-6).** Prepared from *cis*-5 (1.10 g, 4.27 mol) following a similar procedure to that for *syn*-6. The title compound (1.06 g, 90% yield) was obtained as a yellowish crispy foam. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.25 (d, *J* = 6 Hz, 1 H), 4.79 (d, *J* = 6 Hz, 1 H), 5.51 (br s, 1 H), 6.58–6.95 (m, 1 H), 7.29–7.63 (m, 7 H), 7.68–7.99 (m, 1 H). ^{13}C NMR (76 MHz, $CDCl_3$): δ = 59.3, 63.7, 121.4, 124.9, 127.2, 128.4, 129.0, 129.6, 132.7, 136.5, 137.5, 141.2. HRMS-ESI (*m/z*): $[M + H]^+$ calcd for $C_{14}H_{15}N_2O_2S$, 275.0854; found, 275.0858. The *anti*-6 enantiomers were separated by preparative SFC on ChiralPak AY (20 μm, 300 × 30 mm), mobile phase 'A' for CO_2 and 'B' for 2-PrOH (0.1% NH_3 in H_2O), gradient 'B' 40%; flow rate 70 mL min^{-1}, back pressure 100 bar, 38 °C, UV detection at 220 nm. Analytical SFC conditions: ChiralPak AY (150 × 4.6 mm), mobile phase 'A' for CO_2 and 'B' for EtOH (0.05% Et_2NH), gradient 'B' 40%, flow rate 2.4 mL min^{-1}, UV detection at 210 nm.[22]

1st eluting *anti* enantiomer (3R,1′R)-6. Slightly greenish powder, 177 mg (20%); t_R 1.82 min; >99% ee; $[\alpha]_D^{23}$ −7.9 (*c* 1.0 in $CHCl_3$); chemical purity (area at 210 nm) = 100%. The indicated absolute configuration was determined by X-ray analysis of the (1S)-camphor-10-sulfonic acid salt (colorless needles from EtOAc/MeOH).

2nd eluting *anti* enantiomer (3S,1′S)-6. Slightly greenish powder, 215 mg (24%); t_R 2.87 min; >99% ee; $[\alpha]_D^{23}$ +7.7 (*c* 1.0 in $CHCl_3$); chemical purity (area at 210 nm) = 100%.

General ATH procedure for ketones listed in Tables 1 and 2

Catalyst preparation. A mixture of the enantiopure ligand 6 (1.1 equiv. to Ru atom) and $[RuCl_2(\eta^6\text{-arene})]_2$ in 1,2-dichloro-

ethane (1 mL/1.0 mmol of ketone) was degassed with N_2 back-filling and stirred at 40 °C for 1 h. The resulting orange-colored solution of the catalyst was used directly in ATH or was concentrated to dryness when the ATH was performed in neat HCO_2H/Et_3N 5 : 2.

ATH of ketones. To the above preformed solution of the $[RuCl(ligand\ 6)(\eta^6\text{-arene})]$ complex (1 mL; with S/C = 100 : 0.01 mmol Ru atom; with S/C = 200 : 0.005 mmol Ru atom; with S/C = 1000 : 0.001 mmol Ru atom) was added HCO_2H/Et_3N 5 : 2 (250 μL; 500 μL when no cosolvent was used) followed by the ketone (1.0 mmol). This mixture was stirred at 40 °C with continuous mild N_2 sweeping. The reaction progress was monitored by ^{1}H NMR. Workup: the reaction mixture was partitioned between Et_2O (5 mL) and H_2O (5 mL). The aq. layer was re-extracted with Et_2O (5 mL) and the combined organic layers were filtered through a bed of silica gel/ Na_2SO_4 and concentrated.

Preparation of racemic alcohol standards. Samples of the racemic alcohols were prepared by reduction of the corresponding ketones with $NaBH_4$ (3 equiv.) in MeOH (EtOH in the case of ethyl benzoylacetate) at 0 °C to rt. Workup: H_2O was added, the mixture was neutralized with aq. HCl, and the product was extracted with Et_2O. The Et_2O layer was successively washed with H_2O and brine, filtered through a bed of silica gel/Na_2SO_4, and concentrated.

Characterization and ee determination of the ATH prepared chiral alcohols

(*R*)-1-Phenylethanol. Colorless oil (117 mg, 96% yield); 78% ee. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.47 (d, *J* = 6.4 Hz, 3 H), 2.04 (br s, 1 H), 4.86 (q, *J* = 6.4 Hz, 1 H), 7.35–7.33 (m, 5 H). ee was determined by chiral GC analysis[23a] on a Chiralsil-DEX CB column (25 m × 0.25 mm), 120 °C (isothermal), t_R 4.6 min (*R*), 4.8 min (*S*).

Ethyl (*R*)-3-hydroxy-3-phenylpropionate. Colorless oil (190 mg, 98% yield); 92% ee. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.27 (t, *J* = 7.2 Hz, 3 H), 2.65–2.83 (m, 2 H), 3.00 (q, *J* = 7.2 Hz, 1 H), 4.19 (q, *J* = 7.1 Hz, 2 H), 5.14 (dd, *J* = 8.3 and 4.5 Hz, 1 H), 7.28–7.42 (m, 5 H). ee was determined by chiral GC analysis[23b] on a Chiralsil-DEX CB (25 m × 0.25 mm), 140 °C (isothermal); t_R 14.6 min (*S*), 14.9 min (*R*).

(*R*)-1-Indanol. Colorless oil which crystallized upon standing (130 mg, 97% yield); 99% ee. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.75 (br s, 1 H), 1.86–2.02 (m, 1 H), 2.41–2.58 (m, 1 H), 2.74–2.91 (m, 1 H), 3.06 (m, *J* = 15.9, 8.5, 4.8 Hz, 1 H), 5.25 (t, *J* = 6.0 Hz, 1 H), 7.17–7.26 (m, 3 H), 7.33–7.47 (m, 1 H). ee was determined by chiral HPLC analysis[23a] on a Chiralcel OD column (25 cm). Eluent hexane/2-PrOH (98 : 2), flow rate 1.0 mL min^{-1}, UV detection at 254 nm; racemate: t_R 22.6 min (*S*), 26.2 min (*R*).

(*R*)-1-Tetralol. Colorless oil (194 mg, 96% yield); 99% ee. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.70 (br s, 1 H), 1.74–2.06 (m, 4 H), 2.66–2.89 (m, 2 H), 4.66–4.90 (m, 1 H), 7.05–7.15 (m, 1 H), 7.15–7.24 (m, 2 H), 7.43 (dd, *J* = 5.1, 3.9 Hz, 1 H). ee was determined by chiral GC analysis[23a] on a Chiralsil-DEX CB

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column (25 m × 0.25 mm), 130 °C (isothermal); racemate: t_R 13.3 min (S), 13.8 min (R).

(R)-4-Chromanol. White crystals (145 mg, 97% yield); 99% ee. ^{1}H NMR (300 MHz, CDCl$_3$): δ = 1.72 (br s, 1 H), 1.95–2.22 (m, 2 H), 4.19–4.40 (m, 2 H), 4.80 (t, J = 4.0 Hz, 1 H), 6.77–7.02 (m, 2 H), 7.17–7.24 (m, 1 H), 7.31 (dd, J = 7.6, 1.4 Hz, 1 H). ee was determined by chiral HPLC analysis[23a] on a Chiralcel OD-H column (25 cm). Eluent hexane/2-PrOH (95 : 5), flow rate 1.0 mL min^{-1}, UV detection at 220 nm; racemate: t_R 10.0 min (S), 11.7 min (R).

(1R,2R)-2-Methoxycarbonyl-1-indanol. Yellowish oil which crystallized upon standing (186 mg, 97% yield); cis/trans 97 : 3 by ^{1}H NMR; >99% ee (cis). ^{1}H NMR (300 MHz, CDCl$_3$): δ = 2.77 (d, J = 6.1 Hz, 1 H), 2.97–3.21 (m, 1 H), 3.34–3.53 (m, 2 H), 3.79 (s, 3 H), 5.35 (t, J = 5.9 Hz, 1 H), 7.23–7.32 (m, 3 H), 7.39–7.48 (m, 1 H). ee was determined by chiral GC analysis[12,23a] on a Chiralsil-DEX CB column (25 m × 0.25 mm), 130 °C (isothermal); racemates (cis/trans = 55 : 45): t_R 33.7 min [cis-(R,R)], 34.8 min [cis-(S,S)], 45.0 min (trans-1), 50.0 min (trans-2).

(1R,3S)-3-Methoxycarbonyl-1-indanol. Slightly yellowish powder (184 mg, 96% yield); cis/trans 95 : 5 by ^{1}H NMR; 98.8% ee (cis), >99% ee (trans); mp 105–108 °C; $[\alpha]_D^{20}$ –37.5 (c 1.15 in CHCl$_3$). ^{1}H NMR (CDCl$_3$): δ = 2.20 (m, 0.05 H, trans), 2.33 (app t, J = 14.5, 8.0 and 6.8 Hz, 1 H), 2.59 (ddd, J = 14.5, 8.0 and 6.8 Hz, 1 H), 2.84 (m, 0.05 H, trans), 3.14 (br s, 1 H), 3.72 (s, 0.15 H, trans), 3.76 (s, 3 H), 4.02 (dd, J = 8.0 and 2.8 Hz, 1 H), 4.24 (dd, 0.05 H, trans), 5.16 (m, 1 H), 5.46 (t, 0.05 H, trans), 7.30–7.39 (m, 3 H), 7.50–7.53 (m, 1 H). ^{13}C NMR (CDCl$_3$): δ = 38.5, 48.4, 52.6, 75.2, 124.8, 125.4, 128.6, 128.9, 140.3, 145.4, 175.8. HRMS-ESI (m/z): [M + Na]$^+$ calcd for C$_{11}$H$_{12}$O$_3$^{23}Na, 215.0684; found, 215.0686. ees were determined by chiral GC analysis on a Chiralsil-DEX CB column (25 m × 0.25 mm), 130 °C (isothermal); racemates (cis/trans = 97 : 3): t_R 16.8 min [cis-(1S,3R)], 18.6 min [cis-(1R,3S)], 24.1 min (trans-1), 25.2 min (trans-2). Recrystallization from hexane/CH$_2$Cl$_2$ afforded colorless needles (162 mg, 84% yield, >99.9% de, >99.9% ee) which were used for absolute configuration determination by X-ray analysis (see the ESI†).

(1R,2R)-2-Methoxycarbonyl-1-tetralol. Colorless oil (202 mg, 98% yield); cis/trans = 97.6 : 2.4 by ^{1}H NMR; 99.4% ee (cis). ^{1}H NMR (300 MHz, CDCl$_3$): δ = 2.07–2.31 (m, 2 H), 2.75–2.99 (m, 4 H), 3.70 (s, 3 H), 4.80 (d, J = 9.0 Hz; CH, trans diastereomer), 5.05 (m, 1 H), 7.12–7.14 (m, 1 H), 7.19–7.25 (m, 2 H), 7.37–7.42 (m, 1 H). ee was determined by chiral HPLC analysis on a Chiralpak IB-3 column (25 cm). Eluent hexane/2-PrOH (97 : 3), flow rate 1.0 mL min^{-1}, UV detection at 220 nm; racemates (a mixture prepared by weighing both the corresponding ATH products derived from enantiomeric catalysts): t_R 15.4 min (trans-1), 17.4 min [cis-(R,R)], 19.7 min (trans-2), 32.7 min [cis-(S,S)].[12]

(1R,3RS)-3-Methoxycarbonyl-1-tetralol. Light violet-colored syrup (204 mg, 99% yield); cis/trans = 50 : 50 by ^{1}H NMR; 99% ee (cis). ^{1}H NMR (300 MHz, CDCl$_3$): δ = 1.70–1.71 (m, 1 H), 1.92–2.04 (m, 2 H), 2.22 (d, J = 8.1 Hz, 1 H), 2.35–2.42 (m, 1 H), 2.44–2.52 (m, 1 H), 2.85–3.19 (m, 6 H), 3.73 and 3.75 (2s, 2 × 3 H), 4.82–4.91 (m, 2 H), 7.10–7.28 (m, 6 H), 7.32–7.37 (m, 1 H),

7.54–7.56 (m, 1 H). HRMS-ESI (m/z): [M + Na]$^+$ calcd for C$_{12}$H$_{14}$O$_3$^{23}Na, 229.0841; found, 229.0846. Racemates (cis/trans = 96 : 4). ee was determined by ^{19}F NMR (CDCl$_3$) of the (R)-Mosher ester (prepared from (S)-Mosher's acid chloride): δ 71.95 [cis-(1R,3R)], 72.00 [cis-(1S,3S)], 72.24 (trans; stereoisomers not separated). The absolute configuration was assigned based on the general observed trend of enantioselectivity.

(1R,4RS)-4-Methoxycarbonyl-1-tetralol. Colorless syrup (202 mg, 98% yield); cis/trans = 50 : 50 by ^{1}H NMR; >99% ee (cis), >99% ee (trans). ^{1}H NMR (300 MHz, CDCl$_3$): δ = 1.72–1.80 (m, 1 H), 2.31–1.88 (m, 7 H), 2.62 (br s, 2 H), 3.67 and 3.69 (2s, 2 × 3 H), 3.75–3.83 (m, 2 H), 4.65–4.73 (m, 2 H), 7.23–7.27 (m, 6 H), 7.39–7.47 (m, 2 H). HRMS-ESI (m/z): [M + Na]$^+$ calcd for C$_{12}$H$_{14}$O$_3$^{23}Na, 229.0841; found, 229.0845. ees were determined by chiral GC analysis on a Chiralsil-DEX CB column (25 m × 0.25 mm), 150 °C (isothermal); racemates (cis/trans = 72 : 28): t_R 21.1 min [cis-(1R,4S)], 21.9 min [trans-(1R,4R)], 22.7 min [cis-(1S,4R)], 24.4 min [trans-(1S,4S)]. The absolute configuration was assigned based on the general observed trend of enantioselectivity.

Acknowledgements

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