(β-Amino alcohol)(arene)ruthenium(II)-Catalyzed Asymmetric Transfer Hydrogenation of Functionalized Ketones − Scope, Isolation of the Catalytic Intermediates, and Deactivation Processes

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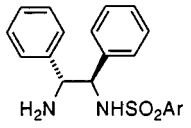
The asymmetric transfer hydrogenation of functionalized ketones with (β-amino alcohol)(arene)Ru^{II} catalysts using 2-propanol as the hydrogen source has been studied. The structure of the catalyst has been systematically screened using a wide variety of $[(\eta^6\text{-arene})RuCl_2]_2$ complexes and β-amino alcohols $R^1CH(OH)CHR^2NHR^3$, some of which were specifically designed for optimized performance, e.g. (1*S*,2*R*)-*N*-(4-biphenylmethyl)norephedrine (**9o**). The efficiencies of the catalytic combinations have been evaluated in the reduction of β-oxo esters and ketones bearing heteroatoms at the α-position. The catalyst precursor [{η^6-*p*-cymene}{η^2-*N*,*O*-(**9o**)}RuCl] (**35**), the 16-electron true catalyst [{η^6-*p*-cymene}{η^2-*N*,*O*-(**9o**$^{1-}$)}Ru] (**36**), and the hydride [{η^6-*p*-cymene}{η^2-*N*,*O*-(**9o**)}RuH] (**37**) involved in the reduction process have been isolated, characterized by NMR and ESI-MS, as well as by X-ray crystallography in the case of **35**, and their reactivities have been investigated. The results reveal two general trends regarding this catalytic process: (1) the apparent reaction rate and the enantioselectivity are largely controlled by the nature of the amine functionality of the chiral ligand and the arene ring of the Ru^{II} precursor; (2) side reactions occur between the ketone substrate and the active catalytic species that affect the concentration of the latter and consequently the apparent rate; the formation of inactive (β-diketonato)Ru^{II} complexes is demonstrated in the case of β-oxo esters.

Introduction

Catalytic asymmetric transfer hydrogenation of ketones using 2-propanol has recently emerged as a viable means of synthesizing chiral alcohols.[1] Owing to its operational simplicity, the many favourable properties of the reductant, and the high enantioselectivities achieved for certain substrates, this method may be considered as complementary or a useful alternative to catalytic reduction with molecular hydrogen for small- and medium-scale reactions. Of all the important developments made in this area in recent years, perhaps the most significant is the use of (arene)(chloro)ruthenium(II) compounds with monoarylsulfonylated-1,2-diamine or simple β-amino alcohol ligands, as reported by Noyori and co-workers.[2−5] The structurally well-defined (arene)(TsDPEN)Ru^{II} system [TsDPEN = (1*R*,2*R*)-*N*-(*p*-tolylsulfonyl)-1,2-diphenylethylenediamine, **1**, Figure 1] facilitates the highly effective reduction of a variety of ketones with greater than 90% *ee*.[2] Moreover, Noyori's systems based on β-amino alcohols give some of the very best results in terms of enantioselectivity and catalytic activities, the latter being among the highest yet reported for Ru^{II}-catalyzed transfer hydrogenation.[3] This key development has led to intense exploration of (β-amino alcohol)(arene)Ru^{II} systems by Wills,[6] Andersson,[7] van Leeuwen,[8] Knochel,[9] our own group,[10] and others[11,12] with a view to rationalize the enantioselectivity, designe more efficient ligands, and develope specific applications of asymmetric transfer hydrogenation.



1 (Ar = 4-$CH_3C_6H_4$)

Figure 1. TsDPEN ligand

The majority of these efforts have focused on the reduction of simple alkyl aryl ketones, although prochiral ketones of interest in the fine chemical industry most often contain functional groups. We[10] and others[2a][6b,9] have previously reported that functionalities such as an alkyloxycarbonyl, an alkyloxy, an amino, or a halo group strongly affect, and unfortunately generally decrease, both the activity and the enantioselectivity of the catalyst. In order to ultimately attain a high level of catalytic performance for these classes of functionalized ketones and to broaden the scope of Ru-

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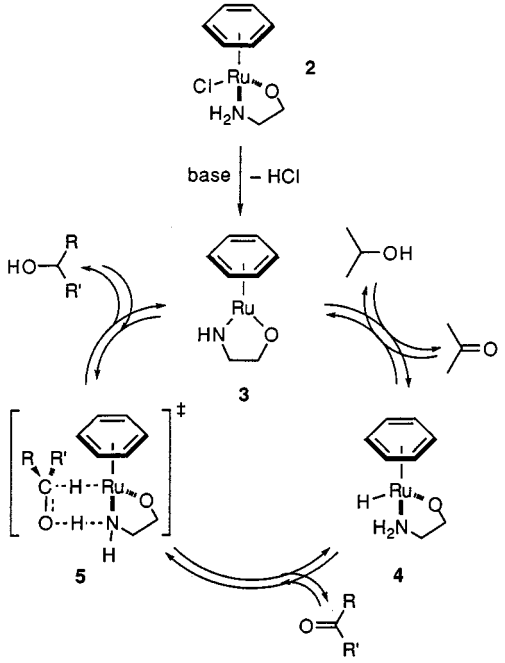
catalyzed transfer hydrogenation, it is necessary to gain a thorough understanding of the reaction mechanism and to determine the factors that might affect it. In this regard, knowledge of the mechanism of transfer hydrogenation with (amino alcohol)Ru^{II} catalysts is still poor, since the exact nature of the catalytic intermediates has not yet been fully elucidated. Andersson,[7b] Noyori,[5] and van Leeuwen[8b] have performed computational studies on simple putative (β-amino alcohol)(arene)Ru^{II} intermediates transposed from the (arene)(TsDPEN)Ru^{II}/*i*PrOH system, for which the catalytic intermediates have been characterized by X-ray crystallography.[2c] These three independent studies led to predictions consistent with a mechanism similar to that proposed by Noyori on the basis of experimental observations.[4] This mechanism, depicted in Scheme 1, involves the preliminary formation of the formal 18-electron Ru complex **2**, viz. the precatalyst, which, in the presence of a base, gives the 16-electron alkyloxyamido species **3**, i.e. the true catalyst. Addition of 2-propanol subsequently affords the 18-electron Ru hydride **4**, i.e. the reducing intermediate, from which hydrogen transfer to the ketone occurs in a concerted manner via the putative six-membered cyclic transition state **5**, which is stabilized by hydrogen bonding between Ru−N−H and the carbonyl oxygen atom. The intermediates **2**−**4** produced in situ from the (*cis*-1-amino-2-indanol)[(*p*-cymene)$RuCl_2$]$_2$/*i*PrOK/*i*PrOH system have recently been detected by mass spectrometry,[13] while the catalyst precursor **2**, [{η^6-*p*-cymene}{η^2-*N*,*O*-(1*S*,2*R*)-amino-1,2-diphenylethanolato}RuCl], has been isolated and its X-ray crystal structure determined.[12]



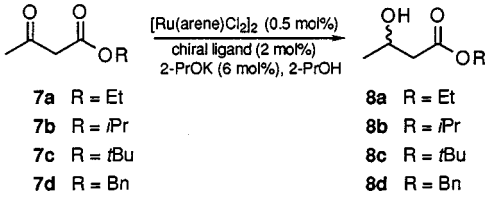
Scheme 1. Mechanism for the (β-amino alcohol)(arene)Ru^{II}-catalyzed transfer hydrogenation

We describe herein for the first time the preparation, NMR characterization, and reactivity of the true catalytically active species **3** and **4**. The isolated (arene)Ru^{II} complexes incorporate a β-amino alcohol derived from the norephedrine backbone, which constitutes a peculiar member of a new class of ligands developed for the asymmetric transfer hydrogenation of functionalized ketones. In this study, we have also investigated a wide variety of (β-amino alcohol)(arene)Ru^{II} systems to explore the resulting effects on the enantioselectivity and the catalytic activity.[10] Three parameters have been systematically studied: (i) the structure of the β-amino alcohol ligand, (ii) the structure of the arene ligand, and (iii) the influence of functional groups on the ketones. Our results show that the concomitant study of these parameters, together with reactivity data relating to isolated complexes, leads to essentially complementary information that enables the determination of general trends and gives a better insight into the factors that influence the outcome of these reactions.

Results

1. Preliminary Observations

In order to identify suitable β-amino alcohol ligands for the asymmetric transfer hydrogenation of functionalized ketones, a preliminary screening using readily available ligands was performed. Activities and selectivities were investigated under typical reaction conditions using either [(benzene)$RuCl_2$]$_2$ (**6a**) or [(*p*-cymene)$RuCl_2$]$_2$ (**6e**) as the precursor in the chosen model reaction of the reduction of ethyl acetoacetate (**7a**) to ethyl 3-hydroxybutyrate (**8a**) (Scheme 2). Representative results are reported in Table 1.



Scheme 2

Table 1. Asymmetric transfer hydrogenation of **7a**

Entry[a]	(arene)Ru^{II}	Ligand	Time[b] [h]	Conv.[c] [%]	TOF_{50}[d] [h^{-1}]	*ee*[e] [%]	Config.
1	**6e**	**9a**	3	> 99	67	3	(−)-(*R*)
2	**6e**	**9b**	2	> 99	60	15	(−)-(*R*)
3	**6a**	**9b**	0.5	> 99	300	36	(+)-(*S*)
4	**6a**	**9i**	0.5	> 99	300	56	(+)-(*S*)
5	**6e**	**11a**	5	> 99	60	13	(−)-(*R*)
6	**6e**	**12a**	5	> 99	20	10	(+)-(*S*)
7	**6e**	**13a**	1	> 99	107	2	(−)-(*R*)
8	**6e**	**16**	96	3	<<	ca. 0	−
9	**6e**	**14**	2[f]	40[f]	<	12	(+)-(*S*)
10	**6e**	**15**	96	5	<<	ca. 0	−
11	**6a**	**1**	3	> 99	43	15	(+)-(*S*)
12	**6e**	**1**	2	> 99	188	15	(−)-(*R*)
13	**6c**	**1**	36	> 99	3	12	(+)-(*S*)
14	**6i**	**1**	20	63	3	56	(+)-(*S*)

[a] The reaction was carried out at 50 °C using 2.0 mmol of **7a** in a 0.1 M 2-propanol solution with [**7a**]/[*i*PrOK]/[chiral ligand]/[Ru] = 100:6:2:1. − [b] Reaction time was not optimized. − [c] Conversions of **7a** were determined by quantitative GLC analysis using a BPX5 column. − [d] Catalyst turnover frequency at half-reaction determined by GLC monitoring and expressed in mol of product/(mol of Ru·h). − [e] Determined by chiral GLC analysis using a Chirasil-DEX CB column with H_2 as carrier gas. − [f] The reaction consistently stopped after 2 h.

For all of the ligands examined, GLC monitoring and ^{1}H NMR analyses established that the reaction invariably proceeds with total chemoselectivity to give β-hydroxy ester **8a**. This proved to be general for all of the functionalized ketones investigated in this study (except for methyl 2-acetylbenzoate, vide infra) and shows, in particular, that reduction of active methylene ketones under moderately basic conditions does not compete with aldolization side processes.[14] Virtually quantitative conversions were obtained at 50 °C within reasonably short times with a variety of amino alcohols (**9**−**13**) having a secondary hydroxy group. With these ligands, the reaction rate was relatively constant throughout most of the reaction, with *apparent* turnover frequencies at half reaction (TOF_{50}) in the range 20−300 h^{-1}. When (*S*)-2-(hydroxymethyl)pyrrolidine (**14**) was used, the reaction was frequently found to stop before reaching completion, most likely because of an irreversible catalyst deactivation process (Entry 9). A similar observation was made by Andersson et al. in relation to the transfer hydrogenation of acetophenone.[7a] β-Amino alcohols **15**−**17**, having a tertiary hydroxy group, reacted only very slowly; it is still unclear as to whether such a negative effect upon increasing the steric hindrance around the alcohol moiety of the ligand can be attributed to the sluggish activity of the resulting Ru catalyst and/or to a much less efficient formation of the active catalytic Ru species from its precursors. As a concept that is developed in more detail later in this paper, it should be pointed out that *apparent* reaction rates do *not* necessarily reflect the *intrinsic* activity of the catalytic species, but may stem from more complex phenomena. On the other hand, the enantioselectivities of all of the catalytic reactions performed in this study with functionalized ketones (including 2-acetylpyridine) proved to be constant with time; this means that there is no significant racemization in these processes due to reaction reversibility, in contrast to most reactions with alkyl aryl ketones.[4] Hence, the *ee* values are representative of the intrinsic discriminating abilities of the catalytic species, which was confirmed by carrying out reactions with isolated catalytic intermediates (vide infra). The enantioface differentiation abilities of the simple (β-amino alcohol)Ru systems are low to moderate as the maximum *ee* value achieved was a modest 56%. Catalyst systems based on chiral derivatives of (1*R*,2*R*)-1,2-diphenyl-1,2-diaminoethane such as **1**[15] also gave low enantioselectivities and/or very low reaction rates, irrespective of the (arene)Ru^{II} precursor used.

A more systematic investigation of the use of (β-amino alcohol)(arene)Ru^{II} systems in the asymmetric transfer hydrogenation of β-oxo esters was prompted by two observations.[16] (i) As exemplified with ephedrine (**9b**) as the ligand, the use of the (benzene)(chloro)ruthenium dimer (**6a**) as the catalyst precursor leads to significantly higher reaction rates and a reversed product configuration as compared to the *p*-cymene analogue **6e** (Entries 2 and 3). (ii) The catalytic performance of a given system, above all the *apparent* catalytic activity, varies with the steric bulk of the alkyloxycarbonyl group of the β-oxo ester. For the [**6a**/**9b**] system, the bulkier the COOR moiety, the higher the apparent catalyst turnover frequency, the most significant improvement being observed with the *t*Bu ester (Figure 2). The increase in the enantioselectivity on going from **7a** (R = Et) to **7c** (R = *t*Bu), though noticeable, is much more limited. Comparable trends in reaction rates and enantioselectivities were observed in most other (amino alcohol)(β-oxo ester)Ru systems (vide infra). Accordingly, a systematic study was conducted on the transfer hydrogenation of **7c**.

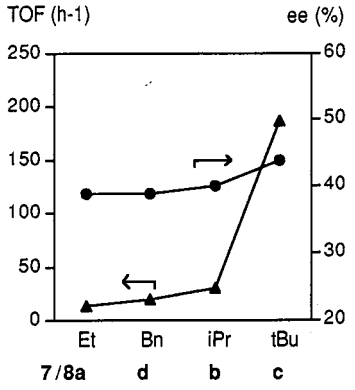


Figure 2. Transfer hydrogenation of β-oxo esters **7a**−**d** with [**6a**/**9b**] catalytic combinations [see Table 2 for reaction conditions; the configuration of the major enantiomer of **8a**−**d** is (3*S*)]

2. Structure of the β-Amino Alcohol Ligand

The effect of the β-amino alcohol structure, $R^1CH(OH)CHR^2NHR^3$, was addressed by varying the nature of substituents R^1, R^2, and R^3. The effect of varying the R^3 substituent was first investigated by the use of *N*-substituted (1*S*,2*R*)-norephedrine amino alcohols **9a**−**w** (Figure 3), which generally gave the best performances (Table 2). *N*-Alkylated derivatives **9c**−**s** were most readily prepared by the two-step one-pot procedure of Saavedra using a variety of aldehydes and ketones (Scheme 3).[18] Sulfonyl, acyl, and ethyloxycarbonyl groups (**9t**−**w**) were introduced by substitution of the primary amine functionality with the corresponding chloride reagents. No ligand having a tertiary amino group was investigated since the presence of an N−H moiety has previously been shown to be of crucial importance for catalytic activity.[3,5]

Systems based on *N*-alkyl-substituted ligands (**9b**−**h**; Entries 16−22) gave *ee* values comparable to that achieved with the primary amine, in the range 30−50%, which corresponds to a difference in the Gibbs' free energy of activation for the (*S*) and (*R*) products, $\Delta(\Delta G^{\neq})$ of 0.4−0.7 kcal mol^{-1}. The highest apparent reaction rate was observed with ephedrine. The use of catalysts derived from the corresponding primary amine (R^3 = H) or from substrates bearing higher R^3 substituents resulted in a significant drop in the reaction rate, as is clearly evident in the case of the bulky ligand **9f**. The introduction of a benzylic substituent led to an increase in the enantioselectivity to 60−68%, corresponding to a $\Delta(\Delta G^{\neq})$ of ca. 0.8−1.0 kcal mol^{-1} (Entries 23−34). The incorporation of additional substituents at the benzyl ring proved to have a much greater effect on the reaction rate than on the enantioselectivity. Very slow ap-

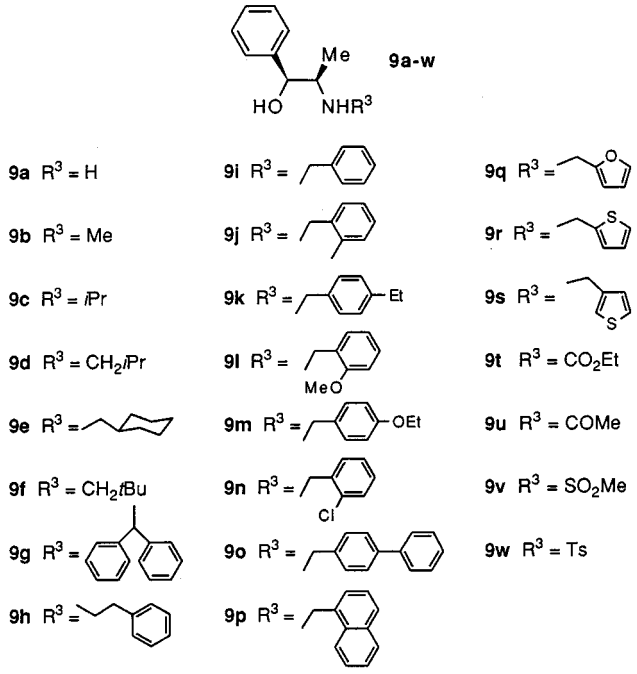


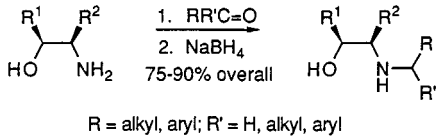
Figure 3. Amino alcohols based on (1*S*,2*R*)-norephedrine used in this study

Table 2. Asymmetric transfer hydrogenation of **7c** using [**6a**/**9a**−**w**] catalytic combinations

Entry[a]	Ligand	Time[b] [h]	Conv.[c] [%]	TOF_{50}[d] [h^{-1}]	*ee* [e] [f] [%]
15	**9a**	16	> 99	9	32
16	**9b**	1	98	190	44
17	**9c**	16	> 99	12	29
18	**9d**	16	> 99	10	49
19	**9e**	14	> 99	12	51
20	**9f**	17	13	<<	35
21	**9g**	16	51	3	32
22	**9h**	16	> 99	12	36
23	**9i**	5	> 99	22	68
24[g]	**9i**	14	> 99	10	68
25	**9j**	19	43	<<	62
26	**9k**	8	> 99	23	60
27	**9l**	16	70	5	64
28	**9m**	3	> 99	46	61
29	**9n**	13	38	<<	63
30	**9o**	2.5	> 99	46	67
31	**9p**	6	4	<<	n. d.
32	**9q**	4	> 99	50	56
33	**9r**	6	> 99	27	59
34	**9s**	5	> 99	25	61
35	**9t**	16	8	<<	12
36	**9u**	21	1	<<	n. d.
37[h]	**9v**	6	12	<<	7
38[h]	**9w**	50	20	<<	22

[a] The reaction was carried out at 20 °C as described in Table 1. − [b] Reaction time was not optimized. − [c] Conversions of **7c** were determined by quantitative GLC analysis using a BPX5 column. − [d] Catalyst turnover frequency at half-reaction determined by GLC monitoring and expressed in mol of product/(mol of Ru·h). − [e] Determined by chiral GLC analysis using a Chirasil-DEX CB column with H_2 as carrier gas. − [f] The configuration of the major isomer of **8c** is (+)-(*S*). − [g] T = 0 °C. − [h] T = 83 °C.

parent reduction rates were observed with the *ortho*-substituted ligands **9j**, **9l**, **9n**, and **9p**. Considering the differences in the electronic properties of the investigated substituents



Scheme 3. *N*-Alkylation of amino alcohols

(Me, OMe, Cl, Ph), it would seem that the observed retardation is wholly due to steric factors. Quite surprisingly, however, *ee* values for this series were just marginally lower compared to that with the unsubstituted system **9i**, corresponding to a difference of $\Delta(\Delta G^{\neq})$ of 0.12 kcal mol^{-1}. Conversely, ligands **9k**, **9m**, and **9o**, bearing *para*-substituted benzyl groups, gave rise to improved reaction rates, again with only minimal effects on the selectivity. Transformation of the primary amine functionality of **9a** to give the carbamate, amide, and sulfonamide derivatives **9t**−**w** led to dramatically reduced catalytic efficiencies (Entries 35−38) comparable to those of related diamino systems such as **1** (Entries 11−14). These results suggested the system derived from (4-biphenylmethyl)norephedrine (**9o**; the X-ray crystal structure of this ligand is presented in the Supporting Information) to be the optimal catalyst in terms of both selectivity and reactivity.

The effect of the substituent at the 2-position was first studied using the series of β-amino alcohols **10a**−**h** (Figure 4, Table 3). 1,2-Disubstituted β-amino alcohols **10d**−**g** were prepared by the addition of a Grignard reagent to the *O*-protected chiral cyanohydrins followed by reduction of the intermediate imine, as reported previously.[19] Surprisingly, changing R^2 from methyl to H led to a dramatic decrease in the reaction rate, the *N*-benzyl derivative **10c** consistently leading to ineffective catalysts (Entries 39−41). Much smaller decreases in the reaction rate were observed on replacing the methyl R^2 group by an ethyl, a benzyl, or a phenyl group (**10d**−**h**). Catalysts derived from ligands **10d**−**f** afforded *ee* values identical, within the limits of experimental uncertainty, to those seen with their analogues with R^2 = Me, i.e. **9b** and **9o**. This suggests that the selectivities of the catalytic species in this series are independent of the 2-substituent. However, systems derived from ligands **10g** and **10h** did not conform to this trend and gave rise to lower *ee* values (34%) than their analogues with R^2 = Me, i.e. **9o** and **9i** (68%), which corresponds to a difference of $\Delta(\Delta G^{\neq})$ of 0.57 kcal mol^{-1}. Computed molecular models showed, however, that π−π stacking occurs between the aryl groups at C-2 and the NH-benzyl moieties of these ligands, which can be expected to affect the conformations and consequently the selectivities of the catalysts. The close similarity of the activity and selectivity data for these systems, despite the differences in steric and electronic properties between a benzyl group and a phenyl group (Entries 45 and 46), lends support to this hypothesis.

The effect of varying the R^1 substituent and further effects of the substituents at the 2- and 3-positions were investigated using the series of β-amino alcohols **11**−**17** (Figure 5 and Figure 6, Table 3). Replacing the 1-phenyl group by a methyl R^1 substituent in the case of R^2 = H, i.e.

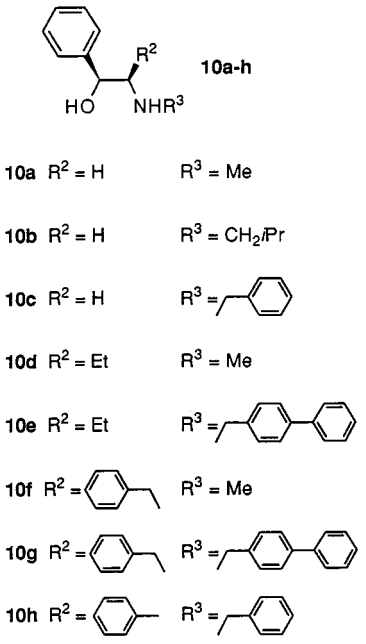


Figure 4. Chiral amino alcohols **10a−h**

Table 3. Asymmetric transfer hydrogenation of **7c** using [**6a/10−13**] and [**6a/17**] catalytic combinations

Entry[a]	Ligand	Time[b] [h]	Conv.[c] [%]	TOF_{50}[d] [h^{-1}]	*ee*[e] [f] [%]
39	**10a**	5	> 99	28	39
40	**10b**	24	29	<<	13
41	**10c**	24	< 1	0	−
42	**10d**	6	> 99	23	44
43	**10e**	14	> 99	10	64
44	**10f**	4.5	99	25	47
45	**10g**	16	98	8	34
46	**10h**	14	> 99	10	36
47	**11a**	5	> 99	23	35
48	**11b**	13	99	11	43
49[g]	**11c**	3	> 99	30	53[g]
50	**11d**	4.5	98	25	45
51	**12b**	40	> 99	3	46
52	**13b**	4	> 99	30	20
53	**17**	22	3	<<	n. d.
54	**1**	17	21	<<	4

[a] The reaction was carried out at 20 °C as described in Table 1. − [b] Reaction time was not optimized. − [c] Conversions of **7c** were determined by quantitative GLC analysis using a BPX5 column. − [d] Catalyst turnover frequency at half-reaction determined by GLC monitoring and expressed in mol of product/(mol of Ru·h). − [e] Determined by chiral GLC analysis using a Chirasil-DEX CB column with H_2 as carrier gas. − [f] The configuration of the major isomer of **8c** is (+)-(*S*). − [g] Ligand **11c** is an 87:13 mixture of the (1*S*,2*R*) and (1*S*,2*S*) stereoisomers.

switching from **10a** to **11a**, had virtually no effect on the results (Entries 39/47). Similarly, systems based on ligands bearing a somewhat bulkier *p*-methoxyphenyl group instead of a phenyl group at the 1-position, such as **9o/11c** (R^2 = Me) and **10f/11d** (R^2 = Bn),[19] gave nearly identical performances (Entries 30/49 and 44/50, respectively). Hence, a small group at C-1 is sufficient for attaining the maximal enantioselectivity yet achieved for the reduction of *tert*-butyl acetoacetate. Nonetheless, chirality at the 1-position proved to be a crucial factor. In fact, loss of the chirality, either by removing the substituent from **9o** (**11b**, R^1 = H) or by symmetrical disubstitution of **9i** (**17**, R^1 = Ph,Ph), turned out to be detrimental both in terms of selectivity and reaction rate (compare Entries 30/48 and 23/53).[11] Moreover, systems based on pseudoephedrine derivatives (**13a**, **13b**) afforded lower selectivities than those based on the corresponding ephedrine analogues (**9b**, **9i**, respectively) (compare, for instance, Entries 2/7 and 23/52), which highlights the effect of the relative C-1/C-2 configuration.

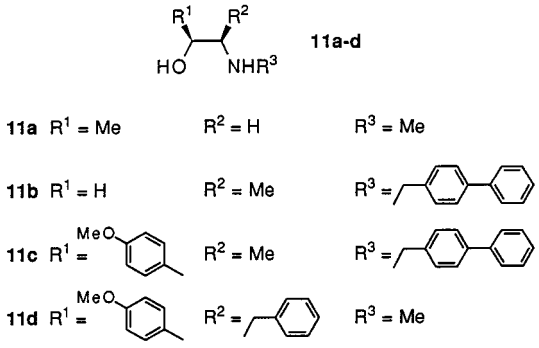


Figure 5. Chiral amino alcohols **11a−d**

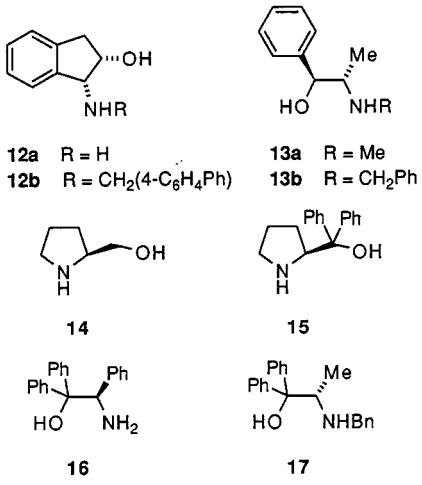


Figure 6. Other chiral amino alcohols used in this study

3. Structure of the Arene Ligand

Preliminary observations revealed that substituents on the Ru−arene ring may also have a significant influence on the performance of the catalyst system. This effect was investigated by evaluating in situ combinations of two relevant β-amino alcohols and (arene)(chloro)Ru^{II} precursors **6a−i** (Figure 7) in the transfer reduction of **7c** (Table 4). Most of the (arene)(chloro)Ru^{II} dimers were prepared by reaction of $RuCl_3 \cdot 3\,H_2O$ with 1,4-dienes,[20] which are available by Birch reduction of the corresponding arenes.

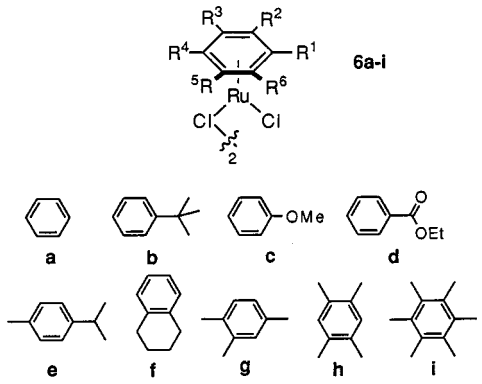


Figure 7. (Arene)ruthenium(II) precursors **6a−i**

Table 4. Asymmetric transfer hydrogenation of **7c**; effect of the arene ligand

Entry[a]	(arene)Ru^{II}	Ligand	Time[b] [h]	Conv.[c] [%]	TOF_{50}[d] [h^{-1}]	*ee*[e] [f] [%]
55	**6a**	**9b**	1	98	187	44
56	**6b**	"	48	> 99	5	18
57	**6c**	"	2	> 99	250	42
58	**6d**	"	24	0	0	−
59	**6e**	"	3	> 99	33	5[g]
60	**6f**	"	14	> 99	12	15
61	**6g**	"	14	> 99	20	17
62	**6h**	"	48	70	3	12[g]
63	**6i**	"	24	5	<<	3[g]
64	**6a**	**9i**	5	> 99	22	68
65	**6c**	"	6	> 99	18	65
66	**6e**	"	23	98	6	30
67	**6f**	"	14	> 99	20	51
68	**6g**	"	16	> 99	10	46

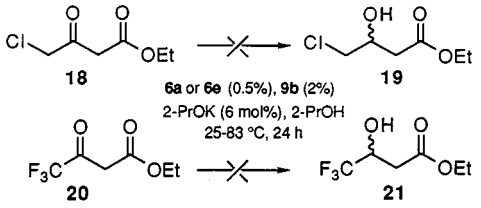
[a] The reaction was carried out at 20 °C as described in Table 1. − [b] Reaction time was not optimized. − [c] Conversions of **7c** were determined by quantitative GLC analysis using a BPX5 column. − [d] Catalyst turnover frequency at half-reaction determined by GLC monitoring and expressed in mol of product/(mol of Ru·h). − [e] Determined by chiral GLC analysis using a Chirasil-DEX CB column with H_2 as carrier gas. − [f] The configuration of the major isomer of **8c** is (+)-(*S*). − [g] The configuration of the major isomer of **8c** is (−)-(*R*).

The use of the (benzene)Ru^{II} precursor **6a** in combination with ephedrine (**9b**) or *N*-benzylnorephedrine (**9i**) led to higher apparent reaction rates and improved enantioselectivities than the corresponding combinations with the *p*-cymene precursor **6e** (Entries 55/59 and 64/66; cf. also Entries 2/3). With ephedrine as the ligand, a reversal of the configuration of the major reduction product was observed [44% (*S*) and 5% (*R*), respectively] as compared to that obtained with *N*-benzylnorephedrine [68% (*S*) and 30% (*S*)]. However, both variations correspond to the same difference in the Gibbs' free energies [$\Delta(\Delta G^{\neq})_{\mathbf{6a/6e}} = 0.62$ kcal mol^{-1}]. In the same way, the systems with 1,2,4-trimethylbenzene (**6g**) are less selective than the corresponding systems based on **6a**, giving rise to nearly identical energy differences [$\Delta(\Delta G^{\neq})_{\mathbf{6a/6g}} = 0.35$ kcal mol^{-1} with **9b**; $\Delta(\Delta G^{\neq})_{\mathbf{6a/6g}} = 0.39$ kcal mol^{-1} with **9i**]. The same trend was found for the tetrahydronaphthalene systems [$\Delta(\Delta G^{\neq})_{\mathbf{6a/6f}} = 0.38$ kcal mol^{-1} with **9b**; $\Delta(\Delta G^{\neq})_{\mathbf{6a/6f}} = 0.32$ kcal mol^{-1} with **9i**]. Undoubtedly, steric interactions between substituents on the arene ring and the substrate do exist in the transition state. Considering the similarity in the values of $\Delta(\Delta G^{\neq})$ on going from the simple (benzene)Ru^{II} precursor to arene-substituted precursors, despite the difference in the steric bulk of **9b** and **9i** (R^3 = Me vs. Bn), there is apparently no significant steric interaction between the substituents on the arene ring and the R^3 substituent on the ligand. In line with these results, the introduction of a bulky *tert*-butyl group (**6b**) or four or more methyl substituents (**6h**, **6i**) on the arene ring caused both the reaction rate and the selectivity to decrease compared to the results achieved with the unsubstituted system (**6a**). The (anisole)Ru^{II} system **6c** exhibited comparable properties to those of **6a**, but no activity was observed with the (benzoate)Ru^{II} system **6d**. This indicates that, besides steric considerations, electronic factors must also contribute to the outcome of the reaction, and that a minimal electron density on the arene ring may be required.

4. Influence of Functional Groups on the Ketone

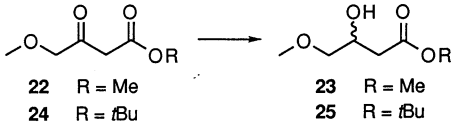
In order to assess the generality of the trends found for the reduction of *tert*-butyl acetoacetate, the reactivities of other β-oxo esters and functionalized ketones were investigated. We have recently reported that transfer hydrogenation of β-aroyl acetate esters bearing various (hetero)substituents on the aryl ring using the catalytic combination [**6e/9b**] proceeds to give the corresponding β-hydroxy esters in high yields and with good selectivities up to 94% *ee* (vide infra).[21] Similar investigations were performed in the present study on β-oxo esters having an $XC_{sp^3}-CO$ functionality. It was found that ethyl 4-chloroacetoacetate (**18**) and ethyl 4,4,4-trifluoroacetoacetate (**20**) could not be reduced with the various catalytic systems, even under drastic conditions (Scheme 4). This was surprising since the presence of an electron-withdrawing group was expected to lower the oxidation potential of the ketone and thus facilitate its reduction.[4] Experiments conducted on 1:1 mixtures of **18**/**7c** and **20**/**7c** using the catalytic combination [**6e/9b**] revealed that the presence of **18** or **20** inhibits the reduction of **7c**. On the other hand, the transfer hydrogenation of **7c** was not affected by adding 10 equiv. (with respect to Ru) of **21**. These results demonstrate that it is the functionalized β-oxo esters **18** and **20** that deactivate the catalytic species and not their reduction products (**19** and **21**). In line with our observations, Wills and co-workers have reported that substituted alkyl aryl ketones of the type $PhCOCH_2X$ (X = Cl, OMe, NMe_2) are resistant to reduction under usual transfer hydrogenation conditions and also inhibit the reaction of ketones that are normally reduced such as acetophenone.[6b]

We found, however, that 4-methoxyacetoacetate esters **22** and **24** are quite easily reduced (Scheme 5, Table 5). As observed with simple acetoacetates **7a−d** (Figure 3) and β-aroyl acetate esters,[21] the reduction of *tert*-butyl ester **24** proceeded more rapidly than that of methyl ester **22**. This allowed the reduction of the former to be carried out at 50 °C, but apparent reaction rates were significantly decreased



Scheme 4

compared to those for the reduction of **7c**. The presence of the 4-methoxy substituent also had a marked effect on the selectivity. Systems based on β-amino alcohol **9o** led to lower *ee* values and much reduced activities compared to those derived from simple ephedrine. The best results were achieved with the [**6e**/**9b**] combination instead of [**6a**/**9o**] (#[**6a**/**9i**]) for **7c**.



Scheme 5

Table 5. Asymmetric transfer hydrogenation of β-oxo esters **22** and **24**

Entry[a]	Subst.	(arene)Ru^{II}	Ligand	Time[b] [h]	Conv.[c] [%]	TOF_{50}[d] [h^{-1}]	*ee*[e] [f] [%]
69	**22**[g]	**6a**	**9b**	0.25	> 99	600	11
70	**22**[g]	**6e**	**9b**	40	49	22	30
71	**22**[g]	**6i**	**9b**	20	13	<<	6
72	**24**[h]	**6a**	**9b**	1	> 99	200	25
73	**24**[h]	**6a**	**9o**	22	21	<<	7
74	**24**[h]	**6e**	**9b**	5	> 99	32	50
75	**24**[h]	**6e**	**9o**	15	22	<<	33

[a] The reaction was carried out at 20 °C as described in Table 1. – [b] Reaction time was not optimized. – [c] Conversions of **22** and **24** were determined by quantitative GLC analysis using a BPX5 column. – [d] Catalyst turnover frequency at half-reaction determined by GLC monitoring and expressed in mol of product/(mol of Ru h). – [e] Determined by chiral GLC analysis using a Chirasil-DEX CB column with H_2 as carrier gas. – [f] The configuration of the major isomer of **23** and **25** is (−)-(*S*). – [g] T = 83 °C. – [h] T = 50 °C.

The effect of the methoxy group was probed using methoxyacetone (**26**) (Scheme 6, Table 6). Ketone **26** was reduced very rapidly with most of the (β-amino alcohol)(arene)Ru^{II} systems, so that only limited informative reactivity data for comparison purposes could be obtained. Transfer hydrogenation of **26** follows the same trends as those observed for **7c**. In fact, the combination of the (benzene)Ru^{II} precursor **6a** with *N*-benzylnorephedrine-type ligands, in particular **9i** and **9o**, afforded the highest enantioselectivity yet achieved (66%) (Entries 78−80). As regards the structure of the ligand backbone, no significant variation in selectivity was seen on changing the 2-methyl substituent of **9b** and **9o** to R^2 = ethyl, i.e. using **10d** and **10e** (compare Entries 76/84 and 80/85). Also, replacing the 1-phenyl substituent of ephedrine by the somewhat more bulky *p*-methoxyphenyl moiety had no effect on the catalyst performance (Entries 76/88). Finally, the use of substituted (arene)Ru^{II} precursors (**6b**, **6e**, **6f**) led to decreased performances as compared to **6a**, an exception being the anisole precursor (**6c**) which gave a comparable selectivity. It is noteworthy that (TsDPEN)Ru systems proved to be totally ineffective in this case (Entry 89).

Scheme 6

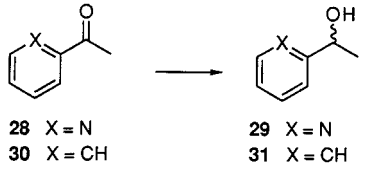
Table 6. Asymmetric transfer hydrogenation of methoxyacetone (**26**)

Entry[a]	(arene)Ru^{II}	Ligand	Time[b] [h]	Conv.[c] [%]	TOF_{50}[d] [h^{-1}]	*ee*[e] [f] [%]
76	**6a**	**9b**	0.33	> 99	> 600	54
77	**6e**	**9b**	0.33	> 99	> 600	36
78	**6a**	**9i**	0.33	> 99	> 600	66
79	**6a**	**9k**	0.33	> 99	> 600	63
80	**6a**	**9o**	0.33	> 99	> 600	66
81[g]	**6b**	**9o**	1	> 99	120[g]	46
82	**6c**	**9o**	0.33	> 99	> 600	61
83	**6f**	**9o**	0.33	> 99	> 600	52
84	**6a**	**10d**	1	> 99	120	54
85	**6a**	**10e**	0.33	> 99	375	60
86	**6a**	**10f**	0.5	> 99	300	46
87	**6a**	**10g**	0.5	> 99	300	32
88	**6a**	**11d**	0.33	> 99	> 600	56
89	**6a**	**1**	16	39	<<	n. d.

[a] The reaction was carried out at 20 °C as described in Table 1. – [b] Reaction time was not optimized. – [c] Conversions of **26** were determined by quantitative GLC analysis using a BPX5 column. – [d] Catalyst turnover frequency at half-reaction determined by GLC monitoring and expressed in mol of product/(mol of Ru·h). – [e] Determined by chiral GLC analysis using a Chirasil-DEX CB column with H_2 as carrier gas. – [f] The configuration of the major isomer of **27** is (+)-(*S*). – [g] T = 50 °C.

A question that arose at this stage was whether or not the reactivity and selectivity trends observed for the above ketones having an $XC_{sp^3}-CO$ functionality could be extended to functionalized aryl ketones and related to previous work on simple alkyl aryl ketones.[1−9] To this end, the transfer hydrogenation of 2-acetylpyridine (**28**) was investigated and the results were compared to those obtained in the case of acetophenone (**30**) (Scheme 7, Table 7). As expected from the presence of an sp^2 carbon atom α to the oxo function,[2−4] the level of selectivity achieved for **28** was much higher, with *ee* values up to 89%, corresponding to $\Delta(\Delta G^{\neq})$ values of up to 1.7 kcal mol^{-1}. However, the pyridyl ring caused a systematic decrease in the enantioselectivity as compared to the case of acetophenone, with corresponding $\Delta(\Delta G^{\neq})_{\mathbf{28/30}}$ values in the range 0.1−0.45 kcal mol^{-1}. This was typically accompanied by a decrease in the reaction rate. Nonetheless, transfer hydrogenation of both **28** and **30** followed the same trends. As consistently found with all the other ketone substrates, a decrease in reactivity was observed upon increasing the steric bulk of the arene ligand. The best results in terms of enantioselectivity were obtained with the catalytic combinations [**6e**/**9i**]

(#[**6e/9o**]). Contrary to the previously studied ketones, the nature of the R^2 substituent on the β-amino alcohol backbone was found to have a significant effect on the catalyst efficiency, above all on the reaction rate. In fact, changing the 2-methyl substituent to R^2 = ethyl or benzyl, i.e. using ligands **10d**−**g**, resulted in very slow reaction rates, even at 50 °C (Entries 97−100). An experiment conducted on a 1:1 mixture of **28/30** using the **6e/10d** catalytic combination showed that transfer hydrogenation of both ketones proceeded very sluggishly (less than 2% after 30 min at 20 °C), which suggests that **28** deactivates the catalytic species. This (partial) deactivation is much more surprising than in the case of **18** and **20** since the interaction of 2-acetylpyridine with the active species is specific to ligands of the type **10d**−**g**.



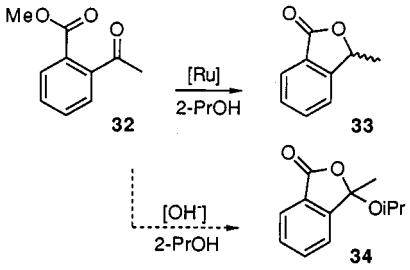
Scheme 7

Table 7. Asymmetric transfer hydrogenation of 2-acetylpyridine (**28**) and acetophenone (**30**)

Entry[a]	(arene)Ru^{II}	Ligand	Time[b] [h]	Conv.[c] [%]	TOF_{50}[d] [h^{-1}][g]	*ee*[e] [f] [%][g]
90	**6a**	**9b**	0.5	> 99	450	68
91	**6c**	**9b**	0.5	> 99	375	66
92	**6e**	**9b**	0.5	> 99	375 (120)	83 (91)
93	**6a**	**9i**	2	> 99	200 (250)	79 (82)
94	**6b**	**9i**	15	> 99	17	83
95	**6c**	**9i**	1	98	300	78
96	**6e**	**9i**	16	> 99	7 (120)	89 (91)
97[h]	**6e**	**10d**	24	40	<< (460)	70 (90)
98[h]	**6e**	**10e**	20	16	<< (75)	65 (84)
99[h]	**6e**	**10f**	24	36	<< (400)	66 (89)
100[h]	**6e**	**10g**	22	36	<< (300)	52 (74)
101	**6a**	**1**	21	40	<<	88[i]

[a] The reaction was carried out at 20 °C as described in Table 1. − [b] Reaction time was not optimized. − [c] Conversions of **28** and **30** were determined by quantitative GLC analysis using a BPX5 column. − [d] Catalyst turnover frequency at half-reaction determined by GLC monitoring and expressed in mol of product/(mol of Ru·h). − [e] Determined by chiral GLC analysis using a Chirasil-DEX CB column with H_2 as carrier gas. − [f] The configuration of the major isomer of **29** and **31** is (−)-(*S*). − [g] Values in brackets refer to acetophenone (**30**); conversions of 92−96% into **31** were obtained within 3 h. − [h] Transfer hydrogenation of **28** was carried out at 50 °C. − [i] The configuration of the major isomer of **29** is (+)-(*R*).

Transfer hydrogenation of methyl 2-acetylbenzoate (**32**) to give the phthalide **33**[22] was found to follow the same activity and enantioselectivity trends as those found for **28** (Scheme 8, Table 8). The level of enantioselectivity achieved for **33** with a given catalyst proved to be systematically lower than that for **29** (Entries 90 and 102). Catalytic combinations of the bulky arene precursor **6i** with either **9b** or **9o** afforded **33** with 82−84% *ee*, while up to 91% *ee* could be attained using a TsDPEN catalyst. However, the potential synthetic application of this process is hampered by the formation of **34**, a side-product that most probably arises from lactonization of the hemiacetal of **32** under basic conditions.[23] Slightly better chemoselectivities in favour of **33** were obtained by carrying out the reaction at 50 °C, but this resulted in somewhat lower *ee* values.



Scheme 8

Table 8. Asymmetric transfer hydrogenation of methyl 2-acetylbenzoate (**32**)

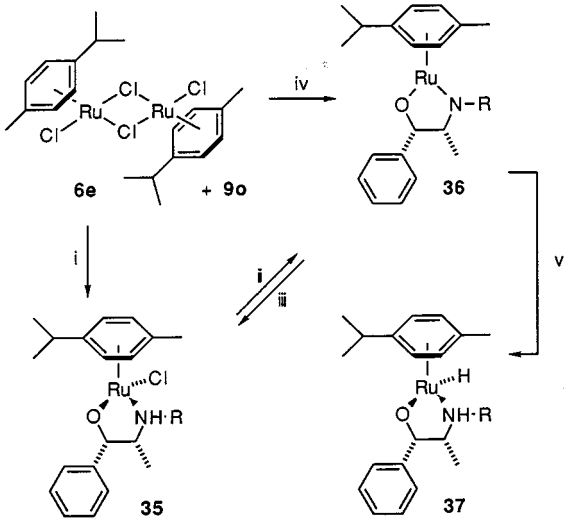
Entry[a]	(arene)Ru^{II}	Ligand	Time[b] [h]	Conv.[c] [%]	Sel. **33**[d] [%]	TOF_{50}[e] [h^{-1}]	*ee*[f] [g] [%]
102	**6a**	**9b**	5	> 99	81	50	25
103	**6e**	**9b**	17	> 99	50	20	69
104[h]	**6e**	**9b**	3	> 99	64	75	59
105	**6i**	**9b**	20	80	54	<<	82
106[h]	**6i**	**9b**	20	87	69	50	70
107	**6i**	**9o**	16	65	41	<<	84
108[h]	**6i**	**9o**	16	75	47	<<	73
109	**6a**	**1**	17	> 99	29	<<	91[i]
110[h]	**6a**	**1**	17	> 99	52	ca. 5	88[i]

[a] The reaction was carried out at 20 °C as described in Table 1. − [b] Reaction time was not optimized. − [c] Conversions of **32** were determined by quantitative GLC analysis using a BPX5 column. − [d] Compound **34** accounts for the balance. − [e] Catalyst turnover frequency at half-reaction determined by GLC monitoring and expressed in mol of product/(mol of Ru·h). − [f] Determined by chiral GLC analysis using a Chirasil-DEX CB column with H_2 as carrier gas. − [g] The configuration of the major isomer of **33** is (−)-(*S*). − [h] T = 50 °C. − [i] The configuration of the major isomer of **33** is (+)-(*R*).

5. Preparation, Characterization, and Reactivity of Catalytic Intermediates

In order to gain a better insight into the structure of the species formed from the precursors, stoichiometric reactions were attempted using the most efficient in situ combinations. We have so far succeeded in preparing the three postulated intermediates derived from the [(*p*-cymene)$RuCl_2]_2$/(1*S*,2*R*)-(4-biphenylmethyl)norephedrine [**6e/9o**] combination.[24] The synthetic methodology used was similar to that reported by Noyori and co-workers for the preparation of the diamine variants from the [**6e/1**] combination (Scheme 9).[2c]

The catalyst precursor **35** was prepared as a virtually pure brown powder by reacting **6e**, **9o**, and NEt_3 (Ru/amino alcohol/NEt_3 = 1:1:2 molar ratio) in refluxing 2-propanol (i, Scheme 9). The ESI mass spectrum of **35** in CH_2Cl_2 solution showed an isotope cluster centred at m/z = 588.1. The mass peaks observed for this cluster and the intensity ratio of the various isotope peaks were in excellent agreement with the calculated pattern for the protonated expected mo-



Scheme 9. Preparation of catalytic intermediates **35**−**37** from **6e** and **9o** [R = (4-biphenyl)methyl]: (i) NEt_3 (2 equiv. vs. Ru), 2-PrOH, reflux, 2 h; (ii) KOH (1 equiv.), CH_2Cl_2, 40 °C, 20 min; (iii) $CHCl_3$, 20 °C, 30 min; (iv) KOH (7 equiv.), CH_2Cl_2, 40 °C, 20 min; (v) 2-PrOH, 20 °C, 5 min

lecule $C_{32}H_{37}ClNORu$. NMR-spectroscopic data confirmed that the amino alcohol is chelated to Ru in $CDCl_3$ and C_6D_6 solutions and that **35** exists as a single diastereomer. All the ^1H and ^{13}C resonances of nuclei in the vicinity of the oxygen and nitrogen atoms in **35** are shifted compared to those of the free ligand **9o**. As expected for the chelated structure, the ^1H NMR spectrum of **35** features two doublets due to the diastereotopic $CH(CH_3)_2$ groups and four doublets due to the diastereotopic protons of the arene.[12] Similarly, the ^{13}C NMR spectrum features two $CH(CH_3)_2$ signals and four *C*H signals due to the *p*-cymene ring.[24] The NH resonance underwent a slow H/D exchange in CD_3OD at room temperature. Crystallization of the crude product from methanol/diethyl ether afforded the methanol adduct of **35**. The molecular structure of **35**·MeOH is depicted in Figure 8, which shows a distorted "piano stool" structure. Both the Ru−N [2.080(18) Å] and Ru−Cl [2.432(9) Å] bond lengths, as well as the Ru−C(arene) distances (range 2.13−2.30 Å) are comparable with those found in the related complexes [{η^2-*N*,*O*-(1*S*,2*R*)-amino-1,2-diphenylethanolato}{η^6-*p*-cymene}RuCl][12] and [(η^6-*p*-cymene){η^2-*N*,*N*-(1*S*,2*S*)-TsDPEN^{-1}}RuCl].[2c] Moreover, the N−Ru−O [80.6(8)°], N−Ru−Cl [80.1(7)°], and O−Ru−Cl [87.4(5)°] bond angles in **35** closely resemble those found in the former analogue [78.3(2), 81.28(14), and 89.19(12)°, respectively].[12] Interestingly, the aryl rings of the biphenyl moiety, which were found to be strictly coplanar in the free ligand **9o**, are twisted in **35**·MeOH (dihedral angle between the two mean planes: 27.2°).

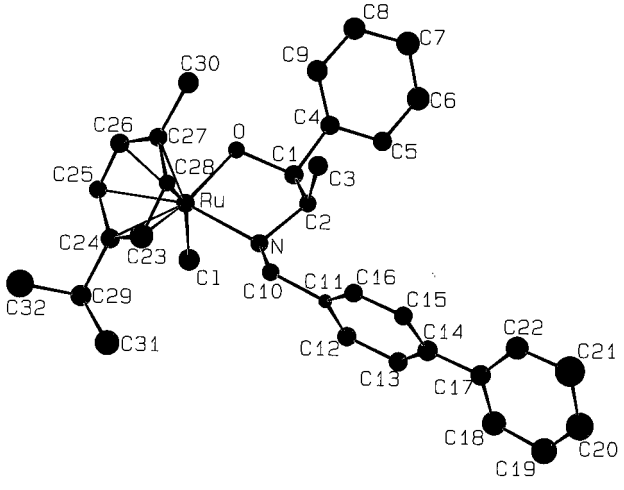


Figure 8. Molecular structure of **35**·MeOH (the solvate molecule and hydrogen atoms have been omitted for clarity); selected bond lengths [Å] and angles [°]: Ru−O 2.035(19), Ru−N 2.080(18), Ru−Cl 2.432(9), O−C(1) 1.54(3), N−C(2) 1.54(3), N−C(10) 1.48(3); N−Ru−O 80.6(8), N−Ru−Cl 80.1(7), O−Ru−Cl 87.4(5)

Complex **35** catalyzes the asymmetric transfer hydrogenation of *tert*-butyl acetoacetate (**7c**) in 2-propanol with the same enantioselectivity and activity as observed with the complex formed in situ only upon addition of *i*PrOK.

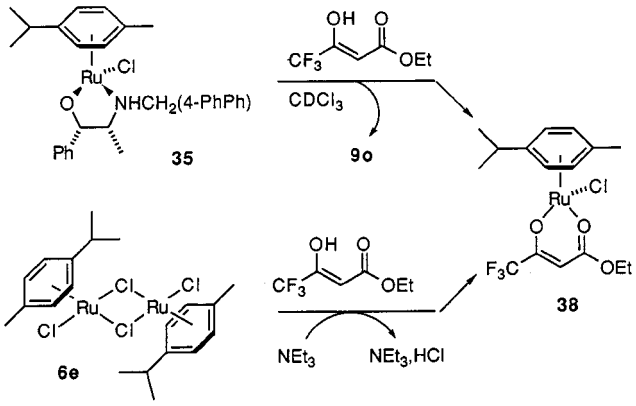
Upon treatment with one equivalent of KOH, complex **35** undergoes facile elimination of HCl to give the formally 16-electron complex **36** as a deep-purple solid (ii, Scheme 9). This compound is most easily prepared in > 80% yield by direct reaction of a **6e/9o** mixture (Ru/amino alcohol = 1:1) with excess KOH (7 equiv.) in CH_2Cl_2 at 40 °C (iv, Scheme 9). It is sensitive, however, and significant degradation was observed after a few days in the solid state or within 1−2 h in hydrocarbon or dichloromethane solutions at room temperature. The complex reacts rapidly at room temperature in chloroform solution through capture of HCl to give back **35** in quantitative yield and with high spectroscopic purity (iii, Scheme 9). The unexpected instability of **36** compared to the TsDPEN analogues limited its analysis to NMR, IR spectroscopy, and ESI-MS. The ESI mass spectrum of **36** in CH_2Cl_2 solution shows an isotope cluster centred at *m*/*z* = 552.1, with a pattern in excellent agreement with that calculated for the protonated expected molecule $C_{32}H_{36}NORu$. As expected, the ^1H NMR resonances (in $C_6D_5CD_3$ at −20 °C or C_6D_6 at 20 °C) of the nuclei in the vicinity of the oxygen atom in **36** [e.g. 1-H, δ = 5.06] are unchanged from those of **35**, whereas those due to nuclei in the vicinity of the nitrogen atom are shifted. In particular, the 2-H resonance (δ = 2.70) and the NCH_2Ar resonances (δ = 4.17 and 5.00) are downfield shifted from the corresponding resonances in **35** (δ = 2.39, 3.82, and 4.34). The $CH(CH_3)_2$ resonance of the *p*-cymene ring is upfield shifted from δ = 2.82 in **35** to δ = 2.43 in **36**. A similar trend in the chemical shifts on going from the 18-electron catalyst precursor to the 16-electron catalyst was observed by Noyori et al. for TsDPEN variants.[2c] The IR spectrum of **36** lacks the band due to the N−H vibration ($\tilde{\nu}$ = 3195 cm^{-1}) observed for **35**. Despite repeated efforts, no crystalline material suitable for X-ray diffraction analysis has yet been obtained for complex **36**, nor for the intermediate **37** derived therefrom.

After various attempts, it was found that complex **37** could best be prepared by treatment of the purple complex **36** with a large excess of 2-propanol at room temperature, followed immediately by removal of the volatiles in vacuo at 0 °C (v, Scheme 9). In this way, **37** was obtained as a

brown-red solid in > 95% purity on the basis of ^{1}H NMR. The ^{1}H NMR monitoring of the variable-temperature reaction of **36** with ca. 50 equiv. of 2-propanol in $C_6D_5CD_3$ showed the appearance at −25 °C of an Ru−H resonance at δ = −5.20, which remained unique (≥ 95%) up to 0 °C. The presence of this single hydride signal was attributed, in the light of Noyori's results,[2c] to the kinetically controlled formation of complex **37** as a single (major) diastereomer. This species is unstable at room temperature and is rapidly converted to other species, most notably another Ru hydride species (δ = −4.80) which accounts for 20% of the hydride products after 10 min and for 60% after 1 h. No evidence has yet been obtained as regards whether the hydride species giving rise to the signal at δ = −4.80 is the opposite (thermodynamically favoured) stereoisomer of **37** or another species. In addition to the hydride resonance, the ^{1}H NMR spectrum of **37** ($C_6D_5CD_3$, −20 °C) features a set of resonances, including two doublets due to the $CH(CH_3)_2$ groups and four doublets due to the protons of the arene, that establishes the formation of a major diastereomer (≥ 95% according to NMR). In line with this, the ^{13}C NMR spectrum of **37** features four CH signals due to the *p*-cymene ring.

Both complexes **36** and **37** catalyze the asymmetric transfer hydrogenation of **7c** and **30** in 2-propanol without the need for addition of a base, to give **8c** and **31** with the same stereoselectivity and catalytic activity as observed using the complex formed in situ. Because of their relative instabilities in solution, the reactivities of **36** and **37** could not be conveniently investigated. In particular, this hampered careful investigation of the kinetics of the reaction between **36** and 2-propanol and of the reverse reaction between **37** and acetone. Such data would have unambiguously established the turnover-limiting step of the (β-amino alcohol)(arene)Ru^{II}-catalyzed transfer hydrogenation,[2c] which remains an open issue.

To obtain a better understanding of the catalyst deactivation processes, the interaction between β-oxo ester **20** and complex **35**, a non-reducing analogue of **37**, was investigated by NMR spectroscopy. The addition of **20** (1.2 equiv.) to a $CDCl_3$ solution of **35** at 40 °C led, within 30 min, to the formation of the new β-diketonato complex **38** in ca. 90% yield (by NMR), with concomitant release of the β-amino alcohol **9o** (Scheme 10). The reaction in C_6D_6 proceeded analogously, but was somewhat less selective, another unidentified species being formed in ca. 20% yield (by NMR). The synthesis of (β-diketonato)Ru complexes from (alkyloxy)Ru precursors and β-diketones or acetoacetate esters, akin to the formation of **38** from **35**, has been reported.[25] Complex **38** was independently prepared by the reaction of the (chloro)(*p*-cymene)Ru dimer **6e** with **20** in the presence of triethylamine in refluxing ethanol (Scheme 10). The ^{1}H and ^{13}C NMR spectra of this complex exhibit new sets of resonances due to the arene and β-diketonato ligands, which were assigned with the aid of ^{1}H,^{1}H-COSY, ^{13}C-APT, and ^{13}C,^{1}H-HETCOR experiments. In particular, the ^{1}H NMR spectra display a singlet resonance (δ = 5.01 in $CDCl_3$, δ = 5.36 in C_6D_6, 1 H), which is



Scheme 10. Formation of β-diketonato complex **38**

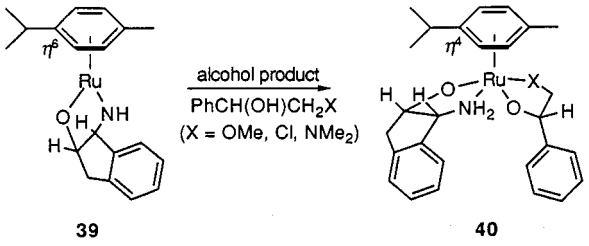
slightly shifted from that in the free β-oxo ester **20** [δ = 5.60 in $CDCl_3$, δ = 5.28 in C_6D_6, $CF_3C(OH)=CHCO_2R$] due to the incorporation of **20** into the coordination sphere of Ru. The ^{13}C resonances ($CDCl_3$) of the β-oxo ester residue in **38** are also shifted from those of free **20**, i.e. C=O (δ = 169.2, q, J_{CF} = 33 Hz vs. δ = 159.8, *J* = 36 Hz in **20**), CH (δ = 83.05, s vs. δ = 92.7, q, J_{CF} = 4 Hz in **20**), and COO (δ = 172.6 vs. δ = 171.4 in **20**). Similar ^{1}H chemical shifts have been reported for the acac hydrogen in comparable (acac)Ru^{II} complexes such as $[(\eta^5\text{-}C_5Me_5)\{\eta^2\text{-}OC(R^1)CHC(R^2)O\}Ru]_n$ (e.g. R^1 = Me, R^2 = OEt, δ = 5.07; R^1 = Me, R^2 = CF_3, δ = 5.65; R^1 = R^2 = Me, δ = 5.11; C_6D_6 throughout),[25] $[(acac)_2(\eta^2\text{-}C_8H_{14})_2Ru]$ (δ = 5.20; C_6D_6),[26] and $[(Cl)(CO)\{\eta^2\text{-}OC(R^1)CHC(R^2)O\}(PPh_3)Ru]$ (e.g. R^1 = R^2 = CF_3, δ = 5.45; R^1 = Me, R^2 = CF_3, δ = 5.15; $CDCl_3$ throughout).[27] β-Diketonato complex **38** showed no activity as a catalyst precursor in the transfer hydrogenation of **7c**.

The true catalyst **36** and the reducing species **38** were found to react rapidly with enol **20** in C_6D_6 and CD_2Cl_2 solutions. This was particularly well evidenced by the immediate change in coloration of complex **36** from deep-purple to brown upon addition of the β-oxo ester. However, both reactions proved to be unselective and the precise nature of the products could not be established. Addition of **20** to complex **38**, even at low temperatures, resulted in the rapid disappearance of the hydride resonances.

Discussion

The most striking feature of these catalysis results is the strong influence of the substrate structure on the apparent reaction rate of transfer hydrogenation. Single and mixed-substrate experiments give evidence that the presence of functional groups on the ketone induces total or partial inactivation of the active species. Wills and co-workers have proposed a mechanism for the inactivation of the (*cis*-1-amino-2-indanol)(*p*-cymene)Ru^{II} catalyst by α-substituted acetophenone derivatives (Scheme 11).[6b] It involves the reaction of the formal 16-electron intermediate **39** with the alcohol product to give the inactive bis-chelated (η^4-arene)ruthenium species **40**. Support for an inactivation pro-

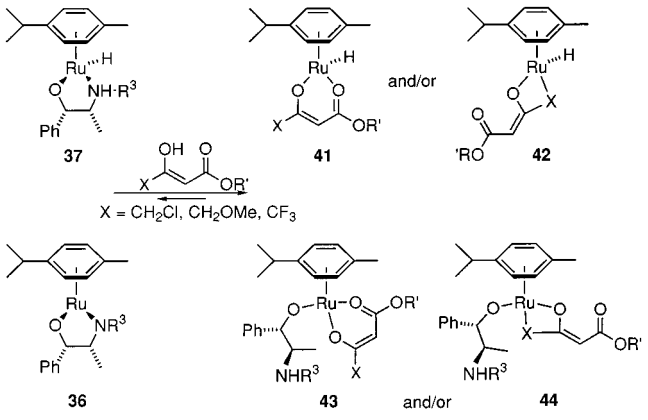
cess involving chelated species is provided by the fact that incorporation of a longer chain between the ketone and the coordinating group, as in $PhCO(CH_2)_nX$ (n = 2, 3; X = OMe), furnishes substrates more compatible with the reduction reaction.[6b] The addition of a protic compound across the polar Ru−N bond in the formal 16-electron complex to give the corresponding 18-electron complex has been experimentally observed using, e.g., an HCl donor (Scheme 9, iii). However, no experimental evidence for such an irreversible linkage with the alcohol has yet been obtained (vide infra).[5] In fact, we have shown that the presence of reduction product **21**, a rather acidic alcohol, does not account for the inhibition observed in the reduction of **20**. The η^6-to-η^4 structural change of the arene ligand, as proposed in Scheme 11 is, moreover, an unfavourable step according to computational studies.[5,7b]



39 **40**

Scheme 11. Wills' proposed intermediate leading to catalyst inactivation by a chelating product

Our results are best explained in terms of non-productive interactions between the active species and the ketone substrates. Considering the six-membered pericyclic transition state **5**, we reasoned that any removal of the amino group from the Ru coordination sphere in the 18-electron reducing species, e.g. **37**, must block the reduction process. This could arise from side reactions of the reducing species **37** itself and/or of the 16-electron true catalyst, e.g. **36**. Although the exact nature of the products arising from the reactions between β-oxo ester **20** and the intermediates **36** and **37** has not yet been established, there is strong evidence for inactivation of the catalytic species through the formation of (β-diketonato)Ru species. Scheme 12 depicts several such possibilities involving functionalities of the ketone substrates.



37 **41** **42**

36 **43** **44**

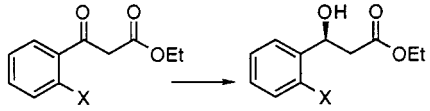
Scheme 12. Possible deactivation pathways of the true catalyst **36** and the reducing species **37**

Despite the fundamental differences in the mechanism, it is worth recalling that Meerwein−Ponndorf−Verley (MPV) reductions cannot be applied to easily enolizable substrates such as β-diketones and β-oxo esters, since these compounds form stable, inactive β-enolate chelate complexes with metal (Al) alkoxides.[28] Moreover, coordination of the enol form of acetophenone and acetylacetone has been proposed to account for the inactivation of rhodium and iridium hydrogen-transfer catalysts.[29] Experimental evidence regarding the present Ru-catalyzed process can be summarized as follows: (i) The increase in the *apparent* transfer hydrogenation rate with the steric bulk of the alkyloxycarbonyl group of the β-oxo ester, a common trend seen with simple acetoacetates **7a**−**d** (Figure 2), 4-methoxyacetoacetates **22**/**24**, and β-aroyl acetates,[21] demonstrates the detrimental coordination of the ester group; hence, the advantageous use of *tert*-butyl esters can be understood in terms of the prevention of the formation of inactive species. (ii) Displacement of an alkyloxy ligand from Ru^{II} with β-diketones or acetoacetate esters to form (β-diketonato)Ru complexes is a facile process.[25] (iii) The reaction of **35**, a non-reducing analogue of **37**, with β-oxo ester **20** leads to complex **38**, a species related to **43**. Though the irreversible addition of an alcohol across the polar Ru−N bond in the formal 16-electron complex has not yet been observed, the formation of a β-diketonato species such as **43** is an obvious driving force for such a linkage by the enol substrate (Scheme 11). It is noteworthy that among the ketones studied, those having an acidic enol tautomer caused complete catalyst poisoning, e.g. 4-chloroacetoacetate (**18**) and 4,4,4-trifluoroacetoacetate (**20**) esters,[30] as well as α-chloroacetophenone.[6b] Strongly electron-withdrawing atoms (Cl, F) enhance the acidity of the enol form, thus favouring the formation of (β-diketonato)ruthenium species such as **41** and **43**. Only partial deactivation was observed for β-oxo esters **22** and **24**, having a slightly electron-withdrawing methoxy group. The high reaction rates for the transfer hydrogenation of methoxyacetone (**26**, Table 6) are consistent with limited effectiveness of the methoxy group as a coordinating functionality.[31]

A direct consequence of these deactivation processes is that the *apparent* reaction rates do not necessarily reflect the *intrinsic* activity of the catalytic species. We reasonably believe that they affect the bulk of the active species in the reaction medium. It is therefore questionable in which terms the influence of other parameters, such as the structure of the chiral ligand or of the ruthenium precursor, should be discussed, i.e. do they enhance the intrinsic activity of the active species and/or prevent the formation of non-productive species? Only the reactivity of isolated ruthenium complexes such as **36** and **37** bearing various β-amino alcohol and arene ligands can provide a clear answer. However, this would clearly pose a considerable challenge.

Other relevant kinetic information has been obtained from the reaction of β-aroylacetates (Scheme 13).[21] Transfer hydrogenations of ethyl benzoylacetate (**45**) and its *ortho*-methyl derivative **47** using the catalytic combination [**6e**/**9b**] proceeded with the same apparent turnover frequency

(TOF_{50} = 10 h^{-1} at 50 °C) in each case, to give the corresponding β-hydroxy esters **46** and **48** with 94% and 75% *ee*, respectively. This shows that non-productive interactions of ketones **45** and **47** with the catalytic species are equivalent. Most interestingly, when transfer hydrogenation of a 1:1 mixture of **45** and **47** was carried out under the same conditions, a kinetic resolution was observed. In fact, the reduction of **47** only proceeded after that of **45** had almost reached completion (k_{45}/k_{47} = 40 at 80% conv. of **45**; k_{45}/k_{47} = 10 at 95% conv. of **45**), the β-hydroxy esters **46** and **48** finally being recovered with the same *ee* values as in the individual experiments. Considering Noyori's mechanism (Scheme 1), this kinetic resolution may reflect a difference in the ease of approach of the ketone substrate (one preferred enantioface) at the formal 18-electron hydrido complex **4** to form the six-membered transition state **5** for hydrogen transfer. Indeed, as compared to **45**, the *ortho*-methyl group in **47** significantly increases the steric hindrance around the C=O bond.



45 X = H
47 X = Me
46 X = H
48 X = Me

Scheme 13

Finally, it should be pointed out that because of these kinetic resolution and deactivation phenomena, no fully reliable information about the *relative* rates of transfer hydrogenation can be obtained from the use of combinatorial mixtures of substrates.[17a] Useful information concerning enantioselectivity is nevertheless expected to be provided by such robotic techniques,[32] in view of the comparable *ee* values found for the conventional single substrate reactions with the individual ketones **45** and **47** and the aforementioned parallel reaction.

The enantioselectivity in asymmetric hydrogen transfer has not yet been satisfactorily rationalized, although a considerable number of ligands and catalytic systems have been investigated to date. On the basis of computational studies, two different steps have been suggested for the enantioselection:[5,7b,8b] (i) the generation of an enantiopure Ru centre, as observed experimentally for the (TsDPEN)Ru systems[2c] and the (β-amino alcohol)Ru systems of the present study; (ii) differentiation of the two enantiofaces of the ketone substrate, as presumably governed by the chirality of the nitrogen-based, five-membered chelate ring in TS **5**. To achieve high asymmetric inductions, an adequate combination of not only chiral auxiliaries and arene ligands at the Ru centre but also of substituents on the carbonyl substrates is essential. Because cooperative steric effects are clearly involved, no general directives for the rational design of catalysts can be drawn. Nevertheless, some useful trends emerge from our results. Tuning of the β-amino alcohol structure through substitution at the carbon atoms in the 1- and 2-positions has a limited effect. Indeed, optimization of the catalyst structure for a given substrate can most effectively be achieved through modifications at the amine functionality and on the arene ring. The large differences in catalyst efficiency observed with the various (arene)Ru^{II} precursors investigated here strongly suggest that future work should be focused in this direction, although as yet the chemistry of these complexes has a somewhat limited versatility.

Conclusion

We have investigated the application of asymmetric hydrogen transfer to ketone substrates of potential industrial interest. A systematic investigation of the factors that affect the activity and enantioselective outcome of the reaction has led to the emergence of several general trends. Based on these results, we have developed a series of new, easily accessible β-amino alcohol ligands that offer the most effective performances for the transfer hydrogenation of a variety of functionalized ketones achieved to date. With these ligands, the two catalytic intermediates involved in the reduction process could be isolated and characterized by NMR for the first time. This allowed confirmation of the mechanistic pathway hitherto envisaged on the basis of computational studies. The importance of inhibition processes of the active Ru species during the course of the reaction has been highlighted. Deactivation of the catalytic species by β-dicarbonyl compounds represents an intrinsic limitation of the Ru-catalyzed transfer hydrogenation process. Its detrimental impact seemingly varies with the acidity of the substrate and can, in some cases, be modulated by the use of bulky *tert*-butyloxycarbonyl derivatives.

Experimental Section

General: Catalytic reactions and syntheses of the catalysts were performed under nitrogen using standard Schlenk techniques. 2-Propanol was freshly distilled from CaH_2 and degassed prior to use. GLC analyses were performed with a Chrompack CP 9001 apparatus equipped with a flame ionization detector and either a BPX5 (25 m × 0.32 mm, SGE) or a chiral Chirasil-DEX CB (25 m × 0.25 mm, Chrompack) column. – ^1H and ^{13}C NMR spectra were recorded with a Bruker AC-300 spectrometer at 23 °C unless otherwise indicated. Chemical shifts are reported in ppm downfield from TMS and were determined by reference to the residual ^1H and ^{13}C solvent peaks. All coupling constants are reported in Hz. – MS and HR-MS of organic compounds were performed with a JEOL JMS-700 M Station mass spectrometer operating in either electron impact (70 eV) or chemical (NH_3) ionization mode. ESI-MS of Ru complexes was performed with a Perkin–Elmer Sciex API-I single quadrupole spectrometer. The instrument was operated at atmospheric pressure in the positive-ion mode (5 kV) and samples were introduced by loop injection at a concentration of ca. 20–30 mM; 10 spectra were acquired using an increment of 0.1 Da and a dwell time of 2 ms. The spectrometer was calibrated with polypropylene glycol. – Microanalyses (C, H, N) were performed with a LECO-CHNS 932 apparatus. – Optical rotations were measured with a Perkin–Elmer 343 polarimeter at 25 °C with solutions in a 1-dm cell. – IR spectra were recorded with a Nicolet 510 FT-IR spectro-

photometer and band positions are given in wavenumbers (cm^{-1}). − Melting points are uncorrected.

Di-μ-chlorobis[(η⁶-1,2,4-trimethylbenzene)chlororuthenium(II)] (6g): Compound **6g** was synthesized in analogy to a literature procedure.[20] Yield: 233 mg, 72%; red powder. − ^{1}H NMR ($CDCl_3$): δ = 2.09, 2.10, 2.15 (each s, 3 H, CH_3), 4.98 (s, 1 H, H_{arom}), 5.25 (m, 1 H, H_{arom}), 5.32 (m, 1 H, H_{arom}). − ^{13}C NMR ($CDCl_3$): δ = 16.8, 17.3, 18.8 (3 CH_3), 79.2, 80.5, 84.2 (3 CH_{arom}), 90.4, 95.3, 96.5 (3 C_q).

(1*S*,2*R*)-*N*-(Cyclohexylmethyl)norephedrine (9e): A mixture of (1*S*,2*R*)-norephedrine (1.0 g, 6.7 mmol) and cyclohexylcarboxaldehyde (0.75 g, 6.7 mmol) in absolute ethanol (15 mL) was stirred at room temperature for 30 min. It was then cooled to 0 °C, whereupon sodium borohydride (450 mg, 12 mmol) was added in small portions. The resulting mixture was stirred for 20 min at 0 °C, then quenched with water (2.5 mL), diluted with CH_2Cl_2 (10 mL), and filtered. The filtrate was concentrated in vacuo and the residue was extracted with diethyl ether. Drying of the organic layer with $MgSO_4$ and evaporation of the solvent provided **9e**. Yield: 1.32 g, 80%; colourless needles; m.p. 90 °C. − ^{1}H NMR ($CDCl_3$): δ = 0.79 (d, 3 H, *J* = 6.5, CH_3), 0.83−0.99 (m, 2 H, Cy), 1.10−1.32 (m, 3 H, Cy), 1.34−1.48 (m, 1 H, Cy), 1.63−1.84 (m, 5 H, Cy), 2.47 (dd, 1 H, *J* = 6.9, *J* = 11.5, C*H*HNH), 2.57 (dd, 1 H, *J* = 6.3, *J* = 11.5, CH*H*NH), 2.90 (dq, 1 H, *J* = 3.9, *J* = 6.5, CH_3C*H*), 4.72 (d, 1 H, *J* = 3.9, C*H*OH), 7.20−7.35 (m, 5 H, H_{arom}). − ^{13}C NMR ($CDCl_3$): δ = 14.8 (CH_3), 26.0, 26.6, 31.5 (5 CH_2, Cy), 38.3 (CH, Cy), 54.0 (CH_2NH), 58.4 (CHNH), 72.7 (CHOH), 126.0, 126.8, 128.0 (5 CH_{arom}), 141.4 (1 C_q). − $[\alpha]_D^{25}$ = +5.0 (*c* = 1.0, CH_2Cl_2). − $C_{16}H_{25}NO$ (247.38): calcd. C 77.68, H 10.19, N 5.66; found C 77.51, H 9.83, N 5.79.

The following ligands were prepared analogously to **9e**. When 4-biphenylcarboxaldehyde was used (**9o**, **10e**, **10g**, **11b**, **11c**, and **12b**), it was necessary to heat the ethanolic solution to 80 °C.

(1*S*,2*R*)-*N*-Benzylnorephedrine (9i): Yield: 1.44 g, 90%; colourless crystals; m.p. 54 °C. − ^{1}H NMR ($CDCl_3$): δ = 0.87 (d, 3 H, *J* = 6.7, CH_3), 3.00 (dq, 1 H, *J* = 3.8, *J* = 6.7, C*H*NH), 3.89 (s, 2 H, CH_2), 4.80 (d, 1 H, *J* = 3.8, C*H*OH), 7.2−7.4 (m, 10 H, H_{arom}). − ^{13}C NMR ($CDCl_3$): δ = 14.7 (CH_3), 51.3 (CH_2), 57.8 (CHNH), 73.1 (CHOH), 126.1, 127.0, 127.2, 128.1, 128.5 (10 CH_{arom}), 140.1, 141.3 (2 C_q). − $[\alpha]_D^{25}$ = +14.6 (*c* = 1.0, CH_2Cl_2) (ref.[8a] −16, *c* = 0.70, EtOH). − $C_{16}H_{19}NO$ (241.33): calcd. C 79.63, H 7.94, N 5.80; found C 79.48, H 7.85, N 5.66.

(1*S*,2*R*)-*N*-(2-Methylbenzyl)norephedrine (9j): Yield: 1.44 g, 85%; colourless oil. − ^{1}H NMR ($CDCl_3$): δ = 0.90 (d, 3 H, *J* = 6.5, CH_3CH), 2.37 (s, 3 H, CH_3Ph), 3.04 (dq, 1 H, *J* = 3.9, *J* = 6.5, C*H*NH), 3.87 (s, 2 H, CH_2NH), 4.82 (d, 1 H, *J* = 3.9, C*H*OH), 7.15−7.25 (m, 9 H, H_{arom}). − ^{13}C NMR ($CDCl_3$): δ = 14.7 (*C*H_3CH), 19.0 (*C*H_3Ph), 49.4 (CH_2NH), 58.4 (CHNH), 73.1 (CHOH), 126.1, 127.0, 127.3, 128.1, 128.6, 130.4 (9 CH_{arom}), 136.4, 137.8, 141.2 (3 C_q). − $[\alpha]_D^{25}$ = +20.6 (*c* = 1.0, CH_2Cl_2). − $C_{17}H_{21}NO$ (255.36): calcd. C 79.96, H 8.29, N 5.49; found C 79.86, H 8.40, N 5.38.

(1*S*,2*R*)-*N*-(4-Ethylbenzyl)norephedrine (9k): Yield: 1.57 g, 88%; white powder; m.p. 66 °C. − ^{1}H NMR ($CDCl_3$): δ = 0.84 (d, 3 H, *J* = 6.6, CH_3), 1.24 (t, 3 H, *J* = 7.6, CH_3CH_2), 1.55 (br. s, 2 H, OH, NH), 2.65 (q, 2 H, *J* = 7.6, CH_3CH_2), 3.00 (dq, 1 H, *J* = 3.8, *J* = 6.6, C*H*NH), 3.85 (s, 2 H, CH_2NH), 4.80 (d, 1 H, *J* = 3.8, C*H*OH), 7.15−7.33 (m, 9 H, H_{arom}). − ^{13}C NMR ($CDCl_3$): δ = 14.6, 15.6 (2 CH_3), 28.5 (*C*H_2CH$_3$), 51.0 (CH_2NH), 57.7 (CHNH), 73.0 (CHOH), 126.1, 127.0, 128.0 (9 CH_{arom}), 137.3, 141.3, 143.2 (3 C_q). − $[\alpha]_D^{25}$ = +18.6 (*c* = 1.0, CH_2Cl_2). − HRMS; *m*/*z*: calcd. for $C_{18}H_{24}NO$ $[M + H]^+$ 270.1858; found 270.1852.

(1*S*,2*R*)-*N*-(2-Methoxybenzyl)norephedrine (9l): Yield: 1.38 g, 77%; white powder; m.p. 94 °C. − ^{1}H NMR ($CDCl_3$): δ = 0.81 (d, 3 H, *J* = 6.7, C*H*$_3$CH), 2.94 (dq, 1 H, *J* = 3.8, *J* = 6.7, C*H*NH), 3.82 (s, 3 H, CH_3O), 3.89 (s, 2 H, CH_2NH), 4.84 (d, 1 H, *J* = 3.8, C*H*OH), 6.86−6.99 (m, 2 H, H_{arom}), 7.20−7.33 (m, 7 H, H_{arom}). − ^{13}C NMR ($CDCl_3$): δ = 14.7 (*C*H_3CH), 46.6 (CH_2NH), 55.1 (CH_3O), 57.1 (CHNH), 72.7 (CHOH), 110.2, 120.4, 126.0, 126.8, 127.9 (7 CH_{arom}), 128.0 (C_q), 128.4, 129.8 (2 CH_{arom}), 141.6, 157.6 (2 C_q). − $[\alpha]_D^{25}$ = +21.5 (*c* = 1.0, CH_2Cl_2).

(1*S*,2*R*)-*N*-(4-Ethyloxybenzyl)norephedrine (9m): Yield: 1.42 g, 75%; yellowish powder; m.p. 59 °C. − ^{1}H NMR ($CDCl_3$): δ = 0.86 (d, 3 H, *J* = 6.7, CH_3), 1.42 (t, 3 H, *J* = 7.0, CH_3CH$_2$), 2.98 (dq, 1 H, *J* = 3.8, *J* = 6.7, C*H*NH), 3.91 (s, 2 H, CH_2NH), 4.05 (q, 2 H, *J* = 7.0, CH_3CH_2), 4.78 (d, 1 H, *J* = 3.8, C*H*OH), 6.85−6.89 (m, 2 H, H_{arom}), 7.20−7.31 (m, 7 H, H_{arom}). − ^{13}C NMR ($CDCl_3$): δ = 14.5, 14.8 (2 CH_3), 50.5 (CH_2NH), 57.5 (CHNH), 63.3 (*C*H_2CH$_3$), 73.1 (CHOH), 114.4, 126.0, 126.9, 128.0, 129.1 (9 CH_{arom}), 131.9, 141.4, 158.0 (3 C_q). − $[\alpha]_D^{25}$ = +15.4 (*c* = 1.0, CH_2Cl_2). − HRMS; *m*/*z*: calcd. for $C_{18}H_{24}NO_2$ $[M + H]^+$ 286.1807; found 286.1802.

(1*S*,2*R*)-*N*-(4-Biphenylmethyl)norephedrine (9o): Yield: 1.79 g, 85%; white powder; m.p. 81 °C. − ^{1}H NMR ($CDCl_3$): δ = 0.88 (d, 3 H, *J* = 6.5, CH_3), 3.03 (dq, 1 H, *J* = 3.8, *J* = 6.5, C*H*NH), 3.93 (s, 2 H, CH_2), 4.83 (d, 1 H, *J* = 3.8, C*H*OH), 7.22−7.65 (m, 14 H, H_{arom}). − ^{13}C NMR ($CDCl_3$): δ = 14.7 (CH_3), 51.0 (CH_2), 57.8 (CHNH), 73.3 (CHOH), 126.2, 127.1, 127.3, 127.5, 128.1, 128.5, 128.8 (14 CH_{arom}), 139.2, 140.2, 140.9, 141.3 (4 C_q). − $[\alpha]_D^{25}$ = +16.6 (*c* = 1.0, CH_2Cl_2). − MS (CI, NH_3); *m*/*z*: 318 $[MH]^+$. − MS (EI); *m*/*z* (%): 167 (100) $[CH_2PhPh]$. − $C_{22}H_{23}NO$ (317.43): calcd. C 83.24, H 7.30, N 4.41; found C 83.41, H 7.16, N 4.52.

(1*S*,2*R*)-2-(4-Biphenylmethylamino)-1-phenyl-1-butanol (10e): Yield: 1.96 g, 89%; white powder; m.p. 62 °C. − ^{1}H NMR ($CDCl_3$): δ = 0.85 (t, 3 H, *J* = 7.4, CH_3), 1.15−1.40 (m, 2 H, CH_2CH$_3$), 2.78 (quint, 1 H, *J* = 4.0, C*H*NH), 3.90 (d, 1 H, *J* = 13.1, C*H*HNH), 3.97 (d, 1 H, *J* = 13.1, CH*H*NH), 4.89 (d, 1 H, *J* = 4.0, C*H*OH), 7.20−7.65 (m, 14 H, H_{arom}). − ^{13}C NMR ($CDCl_3$): δ = 10.9 (CH_3), 21.4 (*C*H_2CH$_3$), 51.5 (CH_2NH), 64.3 (CHNH), 72.2 (CHOH), 126.2, 127.0, 127.3, 128.1, 128.6, 128.8 (14 CH_{arom}), 139.3, 140.2, 140.8, 141.3 (4 C_q). − $[\alpha]_D^{25}$ = +38.2 (*c* = 1.0, CH_2Cl_2). − HRMS; *m*/*z*: calcd. for $C_{23}H_{26}NO$ $[M + H]^+$ 332.2014; found 332.2011.

(1*S*,2*R*)-2-(4-Biphenylmethylamino)-1,3-diphenyl-1-propanol (10g): Yield: 1.99 g, 76%; white powder; m.p. 70 °C. − ^{1}H NMR ($CDCl_3$): δ = 1.57 (br. s, 2 H, OH, NH), 2.45 (m, 2 H, CH_2CH), 3.10 (m, 1 H, C*H*NH), 3.70 (d, 1 H, *J* = 13.5, C*H*HNH), 3.89 (d, 1 H, *J* = 13.5, CH*H*NH), 4.99 (d, 1 H, *J* = 3.5, C*H*OH), 6.95−7.65 (m, 19 H, H_{arom}). − ^{1}H NMR ($C_6D_5CD_3$): δ = 2.40 (dd, 1 H, *J* = 10.5, *J* = 14.0, C*H*HCHNH), 2.49 (dd, 1 H, *J* = 3.6, *J* = 14.0, CH*H*CHNH), 2.98 (dt, 1 H, *J* = 3.6, *J* = 10.5, C*H*NH), 3.40 (d, 1 H, *J* = 13.6, C*H*HNH), 3.59 (d, 1 H, *J* = 13.6, CH*H*NH), 4.93 (d, 1 H, *J* = 3.6, C*H*OH), 6.7−7.5 (m, 19 H, H_{arom}). − ^{13}C NMR ($CDCl_3$): δ = 34.3 (*C*H_2CH), 51.0 (CH_2NH), 63.4 (CHNH), 71.4 (CHOH), 125.9, 127.0, 127.1, 127.2, 128.3, 128.3, 128.6, 128.8, 129.0 (19 CH_{arom}), 138.7, 138.8, 140.0, 140.8, 140.9 (5 C_q). − $[\alpha]_D^{25}$ = +21.9 (*c* = 1.0, CH_2Cl_2). − HRMS; *m*/*z*: calcd. for $C_{28}H_{28}NO$ $[M + H]^+$ 394.2171; found 394.2166.

(1*S*,2*R*)-2-(*N*-Benzylamino)-1,2-diphenylethanol (10h): Yield: 1.51 g, 75%; white powder; m.p. 155 °C. − ^{1}H NMR ($CDCl_3$): δ = 1.65 (br. s, 2 H, OH, NH), 3.53 (d, 1 H, *J* = 13.4, C*H*HNH), 3.70 (d,

1 H, J = 13.4, CH*H*NH), 3.92 (d, 1 H, J = 6.0, C*H*NH), 4.81 (d, 1 H, J = 6.0, C*H*OH), 7.05−7.4 (m, 15 H, H_{arom}). − ^{13}C NMR ($CDCl_3$): δ = 51.1 (CH_2NH), 67.9 (CHNH), 76.8 (CHOH), 126.9, 127.0, 127.7, 128.0, 128.3, 128.4, 128.5, 128.6 (15 CH_{arom}), 139.2, 139.9, 140.4 (3 C_q). − $[\alpha]_D^{25}$ = −6.2 (c = 1.0, CH_2Cl_2). − $C_{21}H_{21}NO$ (303.40): calcd. C 83.13, H 6.98, N 4.62; found C 83.02, H 6.86, N 4.51.

(*R*)-*N*-(4-Biphenylmethyl)-alaninol (11b): Yield: 1.44 g, 90%; white powder; m.p. 107 °C. − ^1H NMR ($CDCl_3$): δ = 1.09 (d, 3 H, J = 6.4, CH_3), 1.95 (br. s, 2 H, OH, NH), 2.88 (m, 1 H, C*H*NH), 3.30 (dd, 1 H, J = 7.0, J = 10.6, C*H*HOH), 3.63 (dd, 1 H, J = 4.0, J = 10.6, CH*H*OH), 3.78 (d, 1 H, J = 13.0, C*H*HNH), 3.91 (d, 1 H, J = 13.0, CH*H*NH), 7.30−7.65 (m, 9 H, H_{arom}). − ^{13}C NMR ($CDCl_3$): δ = 17.2 (CH_3), 50.7 (CH_2NH), 53.8 (CHNH), 65.5 (CH_2OH), 127.0, 127.2, 128.5, 128.7 (9 CH_{arom}), 139.4, 140.0, 140.9 (3 C_q). − $[\alpha]_D^{25}$ = −41.3 (c = 1.0, CH_2Cl_2). − $C_{16}H_{19}NO$ (241.33): calcd. C 79.63, H 7.94, N 5.80; found C 79.77, H 7.86, N 5.91.

2-(4-Biphenylmethylamino)-1-(4-methoxyphenyl)-1-propanol (11c): This compound was prepared from an 87:13 mixture of the (1*S*,2*R*)-*erythro* and (1*S*,2*S*)-*threo* diastereomers of 2-amino-1-(4-methoxyphenyl)-1-propanol. Total yield: 1.88 g, 82%; white powder.

(1*S*,2*R*)-2-(4-Biphenylmethylamino)-1-(4-methoxyphenyl)-1-propanol (*erythro*-11c) (87%)**:** ^1H NMR ($CDCl_3$): δ = 0.90 (d, 3 H, J = 6.3, C*H*$_3$CH), 2.99 (dq, 1 H, J = 3.8, J = 6.3, C*H*NH), 3.80 (s, 3 H, CH_3O), 3.91 (s, 2 H, C*H*$_2$NH), 4.75 (d, 1 H, J = 3.8, C*H*OH), 6.88 (d, 2 H, J = 8.9, H_{arom}), 7.2−7.68 (m, 11 H, H_{arom}). − ^{13}C NMR ($CDCl_3$): δ = 14.8 (*C*H$_3$CH), 50.9 (CH_2NH), 55.3 (CH_3O), 57.8 (CHNH), 73.1 (CHOH), 113.6, 127.1, 127.3, 128.5, 128.8 (13 CH_{arom}), 133.3, 139.2, 140.2, 140.3, 158.2 (all C_q).

(1*S*,2*S*)-2-(4-Biphenylmethylamino)-1-(4-methoxyphenyl)-1-propanol (*threo*-11c) (13%)**:** ^1H NMR ($CDCl_3$): δ = 1.01 (d, 3 H, J = 6.4, C*H*$_3$CH), 2.79 (dq, 1 H, J = 8.6, J = 6.4, C*H*NH), 3.80 (s, 3 H, CH_3O), 3.91 (s, 2 H, C*H*$_2$NH), 4.19 (d, 1 H, J = 8.6, C*H*OH), 6.88 (d, 2 H, J = 8.9, H_{arom}), 7.2−7.68 (m, 11 H, H_{arom}).

(1*R*,2*S*)-*cis*-1-(4-Biphenylmethylamino)-2-indanol (12b): Yield: 1.86 g, 89%; white powder; m.p. 118 °C. − ^1H NMR ($CDCl_3$): δ = 2.97 (dd, 1 H, J = 2.9, J = 15.8, C*H*HCHOH), 3.08 (dd, 1 H, J = 5.1, J = 15.8, CH*H*CHOH), 4.02 (d, 1 H, J = 12.0, C*H*HNH), 4.07 (d, 1 H, J = 12.0, CH*H*NH), 4.18 (d, 1 H, J = 5.2, C*H*NH), 4.43 (m, 1 H, C*H*OH), 7.15−7.55 (m, 13 H, H_{arom}). − ^{13}C NMR ($CDCl_3$): δ = 39.7 (*C*H$_2$CHOH), 52.3 (CH_2NH), 65.2 (CHNH), 70.7 (CHOH), 123.7, 125.7, 126.7, 127.1, 127.3, 127.3, 128.1, 128.6, 128.8 (13 CH_{arom}), 138.8, 140.4, 140.8, 141.1, 142.2 (5 C_q). − $[\alpha]_D^{25}$ = −18.7 (c = 1.0, CH_2Cl_2). − $C_{22}H_{21}NO$ (315.41): calcd. C 83.78, H 6.71, N 4.44; found C 83.65, H 6.78, N 4.51.

(*R*)-2-(*N*-Benzylamino)-1,1-diphenyl-1-propanol (17): Yield: 1.79 g, 82%; yellowish powder; m.p. 75 °C. − ^1H NMR ($CDCl_3$): δ = 1.03 (d, 3 H, J = 6.3, CH_3), 3.62 (d, 1 H, J = 13.5, C*H*HNH), 3.79 (q, 1 H, J = 6.3, CH), 3.82 (d, 1 H, J = 13.5, CH*H*NH), 7.1−7.8 (m, 15 H, H_{arom}). − ^{13}C NMR ($CDCl_3$): δ = 14.3 (CH_3), 50.9 (CH_2), 57.5 (CHNH), 78.9 (COH), 125.4, 126.0, 127.9, 128.1, 128.4, 128.5 (15 CH_{arom}), 139.3, 144.6, 146.2 (3 C_q). − $[\alpha]_D^{25}$ = −70.5 (c = 1.0, CH_2Cl_2). − $C_{23}H_{23}NO$ (329.44): calcd. C 83.86, H 7.04, N 4.25; found C 83.92, H 6.97, N 4.36.

3-Isopropyloxy-3-methyl-3*H*-isobenzofuran-1-one (34): ^1H NMR ($CDCl_3$): δ = 0.92, 1.12 [each d, 3 H, J = 6.1, CH(C*H*$_3$)$_2$], 1.73 (s, 3 H, CH_3C), 3.41 [m, 1 H, C*H*(CH$_3$)$_2$], 7.25−7.85 (m, 4 H, H_{arom}). − ^{13}C NMR ($CDCl_3$): δ = 23.41, 24.0 [CH(*C*H$_3$)$_2$], 26.2 (CH_3), 67.8 [*C*H(CH$_3$)$_2$], 109.0 (C_q, sp^3), 122.2, 125.2 (CH_{arom}), 127.4 (Cq), 130.3, 134.3 (CH_{arom}), 148.4 (C_q), 168.1 (COO). − MS (EI); m/z (%): 43 (29) [*i*Pr], 76 (16) [Ph], 147 (100) [M^+ − O*i*Pr], 191 (13) [M^+ − CH_3].

[{η²-*N*,*O*-(1*S*,2*R*)-*N*-(4-biphenylmethyl)norephedrine^{-1}}{η⁶-*p*-cymene}RuCl] (35): A mixture of [(η⁶-*p*-cymene)$RuCl_2$]$_2$ (**6e**, 612.5 mg, 1.0 mmol), (1*S*,2*R*)-*N*-(4-biphenylmethyl)norephedrine (**9o**, 634 mg, 2.0 mmol), and triethylamine (0.56 mL, 4.0 mmol) in 2-propanol (20 mL) was heated at 80 °C for 2 h. The orange solution was then concentrated to dryness, and the residue was washed with water (2 × 4 mL) and dried under reduced pressure to afford **35** as a brown powder. Yield: 775 mg, 66%. The same complex was obtained by stirring compound **36** (vide infra) in chloroform for 30 min and then drying in vacuo. Yield: 585 mg, 100%. − IR (KBr): $\tilde{\nu}$ = 3195 cm^{-1} (H−N). − ^1H NMR (C_6D_6): δ = 0.56 (d, 3 H, J = 6.3, C*H*$_3$CHN), 1.17, 1.20 [each d, 3 H, J = 7.1, CH(C*H*$_3$)$_2$], 2.02 (s, 3 H, CH_3 of *p*-cymene), 2.39 (m, 1 H, C*H*NH), 2.82 [m, 1 H, C*H*(CH$_3$)$_2$], 3.82 (dd, 1 H, J = 11.0, J = 13.6, C*H*HNH), 4.34 (dd, 1 H, J = 4.2, J = 13.6, CH*H*NH), 4.54, 4.64 (each d, 1 H, J = 5.5, H_{arom} of *p*-cymene), 4.87 (br. d, 1 H, J = 10.5, NH), 5.06 (d, 1 H, J = 2.6, PhC*H*), 5.12, 5.20 (each d, 1 H, J = 5.8, H_{arom} of *p*-cymene), 7.0−7.65 (m, 14 H, H_{arom}). − ^{13}C NMR (C_6D_6): δ = 8.7 (*C*H$_3$CHN), 17.0 (CH_3 of *p*-cymene), 21.6, 23.7 [CH(*C*H$_3$)$_2$], 31.1 [*C*H(CH$_3$)$_2$], 56.2 (CH_2NH), 60.2 (CHNH), 77.3, 78.0, 80.2 (3 CH_{arom} of *p*-cymene), 81.6 (Ph*C*H), 82.3 (CH_{arom} of *p*-cymene), 94.6, 101.0 (2 C_q of *p*-cymene), 126.1, 127.3, 127.5, 129.2 (14 CH_{arom}), 137.9, 140.2, 141.3, 142.4 (4 C_q). − ^1H NMR ($C_6D_5CD_3$): δ = 0.58 (d, 3 H, J = 6.3, C*H*$_3$CHN), 1.21, 1.23 [each d, 3 H, J = 7.2, CH(C*H*$_3$)$_2$], 2.08 (s, 3 H, CH_3 of *p*-cymene), 2.37 (m, 1 H, C*H*NH), 2.86 [m, 1 H, C*H*(CH$_3$)$_2$], 3.87 (dd, 1 H, J = 11.3, J = 13.6, C*H*HNH), 4.38 (dd, 1 H, J = 3.8, J = 13.6, CH*H*NH), 4.60, 4.68 (each d, 1 H, J = 5.3, H_{arom} of *p*-cymene), 4.89 (br. d, 1 H, J = 10.6, NH), 5.01 (d, 1 H, J = 2.9, PhC*H*), 5.25, 5.33 (each d, 1 H, J = 5.6, H_{arom} of *p*-cymene), 6.95−7.5 (m, 14 H, H_{arom}). − ^1H NMR ($CDCl_3$): δ = 0.65 (d, 3 H, J = 6.2, C*H*$_3$CHN), 1.32, 1.35 [each d, 3 H, J = 7.2, CH(C*H*$_3$)$_2$], 2.29 (m, 4 H, C*H*NH + CH_3 of *p*-cymene), 2.94 [m, 1 H, C*H*(CH$_3$)$_2$], 4.30 (dd, 1 H, J = 11.8, J = 13.5, C*H*HNH), 4.55 (m, 2 H, PhC*H* + NH), 4.70 (dd, 1 H, J = 3.2 and 13.5, CH*H*NH), 5.14, 5.22 (each d, 1 H, J = 5.3, H_{arom} of *p*-cymene), 5.30, 5.41 (each d, 1 H, J = 5.8, H_{arom} of *p*-cymene), 7.0−7.7 (m, 14 H, H_{arom}). − ^{13}C NMR ($CDCl_3$): δ = 8.2 (*C*H$_3$CHN), 17.0 (CH_3 in *p*-cymene), 21.5, 23.8 [CH(*C*H$_3$)$_2$], 30.7 [*C*H(CH$_3$)$_2$], 56.2 (CH_2NH), 59.7 (CHNH), 76.7, 78.3, 79.6 (3 CH_{arom} of *p*-cymene), 81.1 (Ph*C*H), 82.6 (CH_{arom} of *p*-cymene), 95.3, 101.3 (2 C_q of *p*-cymene), 125.9, 126.9, 127.0, 127.2, 127.6, 127.7, 128.7, 128.8 (CH_{arom}), 137.9, 140.2, 141.3, 142.4 (4 C_q). − ESI-MS; m/z: 588.1 $[MH]^+$; masses and intensity ratio in excellent agreement with the calculated pattern for the protonated expected molecule $C_{32}H_{37}ClNORu$. − Recrystallization of a crude sample from methanol/diethyl ether at −20 °C afforded analytically pure orange crystals of **35**·MeOH suitable for X-ray diffraction analysis. − $C_{33}H_{40}ClNO_2Ru$ (619.21): calcd. C 64.01, H 6.51, N 2.26; found C 64.11, H 6.48, N 2.33.

[{η⁶-*p*-cymene}{η²-*N*,*O*-(1*S*,2*R*)-ephedrine^{-1}}RuCl] (35b): This compound was synthesized analogously to **35** and was obtained as a brown powder. Yield: 696 mg, 80%. − ^1H NMR (C_6D_6): δ = 0.31 (d, 3 H, J = 6.6, C*H*$_3$CHN), 1.14, 1.22 [each d, 3 H, J = 6.9, CH(C*H*$_3$)$_2$], 2.03 (s, 3 H, CH_3 of *p*-cymene), 2.09 (m, 1 H, C*H*NH), 2.17 (d, 3 H, J = 6.4, C*H*$_3$NH), 2.88 [m, 1 H, C*H*(CH$_3$)$_2$], 4.03 (br. m, 1 H, NH), 4.27, 4.48 (each d, 1 H, J = 5.4, H_{arom} of *p*-cymene), 5.03 (d, 1 H, J = 3.1, PhC*H*), 5.27, 5.34 (each d, 1 H, J = 6.0, H_{arom} of *p*-cymene), 7.17 (d, 1 H, J = 7.5, H_{arom}), 7.33 (t, 2 H, J =

7.5, H_{arom}), 7.68 (d, 2 H, J = 7.5, H_{arom}). − ^{13}C NMR (C_6D_6): δ = 8.2 (CH_3CHN), 16.8 (CH_3 of *p*-cymene), 21.3, 24.0 [CH(CH_3)$_2$], 31.0 [CH(CH$_3$)$_2$], 39.7 (CH_3NH), 64.4 (CHNH), 76.5, 77.5, 79.5 (3 CH_{arom} of *p*-cymene), 81.2 (PhCH), 82.9 (CH_{arom} of *p*-cymene), 94.7, 100.1 (2 C_q of *p*-cymene), 126.1, 127.4, 127.8 (5 CH_{arom}), 144.6 (C_q).

[{η²-*N*,*O*-(1*S*,2*R*)-*N*-benzylnorephedrine⁻¹}{η⁶-*p*-cymene}RuCl] (35c): This compound was synthesized analogously to **35**. Yield: 766 mg, 75%; brown powder. − ^{1}H NMR ($CDCl_3$): δ = 0.62 (d, 3 H, J = 6.4, CH_3CHN), 1.33, 1.36 [each d, 3 H, J = 7.4, CH(CH_3)$_2$], 2.24 (m, 1 H, CHNH), 2.30 (s, 3 H, CH_3 of *p*-cymene), 2.96 [m, 1 H, CH(CH$_3$)$_2$], 4.24 (dd, 1 H, J = 11.3, J = 13.4, CHHNH), 4.51 (m, 1 H, NH), 4.56 (d, 1 H, J = 3.1, PhCH), 4.68 (dd, 1 H, J = 3.7, J = 13.4, CHHNH), 5.13, 5.23 (each d, 1 H, J = 5.6, H_{arom} of *p*-cymene), 5.30, 5.45 (each d, 1 H, J = 6.2, H_{arom} of *p*-cymene), 7.05−7.45 (m, 10 H, H_{arom}). − ^{13}C NMR ($CDCl_3$): δ = 8.0 (CH_3CHN), 16.8 (CH_3 of *p*-cymene), 21.4, 23.6 [CH(CH_3)$_2$], 30.6 [CH(CH$_3$)$_2$], 56.2 (CH_2NH), 59.4 (CHNH), 77.2, 78.3, 79.4 (3 CH_{arom} of *p*-cymene), 80.9 (PhCH), 82.4 (CH_{arom} of *p*-cymene), 95.1, 101.0 (2 C_q of *p*-cymene), 125.7, 126.8, 127.0, 128.1, 128.2, 128.9 (10 CH_{arom}), 135.8, 142.4 (2 C_q).

[{η²-*N*,*O*-(1*S*,2*R*)-*N*-(4-biphenylmethyl)norephedrine⁻²}{η⁶-*p*-cymene}Ru] (36): A mixture of [(η⁶-*p*-cymene)RuCl$_2$]$_2$ (**6e**, 612 mg, 1.0 mmol), (1*S*,2*R*)-*N*-(4-biphenylmethyl)norephedrine (**9o**, 634 mg, 2.0 mmol), and KOH (800 mg, 14.3 mmol) in CH_2Cl_2 (14 mL) was heated at 40 °C for 20 min. Water (14 mL) was then added to the orange solution, which was stirred at 40 °C for a further 20 min. The dark-brown organic layer was subsequently washed with water (14 mL), dried with CaH_2, filtered, and concentrated to dryness to give **36** as a purple powder. Yield: 826 mg, 75%. The same compound was prepared by treating **35** with 1 equiv. of KOH in CH_2Cl_2 at 40 °C for 20 min and then proceeding with the workup as described above. Yield: 370 mg, 70%. − ^{1}H NMR ($C_6D_5CD_3$, −20 °C): δ = 0.70 (d, 3 H, J = 6.0, CH_3CHN), 1.26, 1.30 [each d, 3 H, J = 6.8, CH(CH_3)$_2$], 1.92 (s, 3 H, CH_3 of *p*-cymene), 2.44 [m, 1 H, CH(CH$_3$)$_2$], 2.67 (m, 1 H, CHNH), 4.14 (d, 1 H, J = 15.4, CHHNH), 4.49, 4.83 (each d, 1 H, J = 5.2, H_{arom} of *p*-cymene), 4.9−5.1 (m, 4 H, PhCH + CHHNH + 2 H_{arom} of *p*-cymene), 6.9−7.7 (m, 14 H, H_{arom}). − ^{1}H NMR (C_6D_6, +20 °C): δ = 0.70 (d, 3 H, J = 6.2, CH_3CHN), 1.23, 1.25 [each d, 3 H, J = 6.9, CH(CH_3)$_2$], 1.82 (s, 3 H, CH_3 of *p*-cymene), 2.43 [m, 1 H, CH(CH$_3$)$_2$], 2.70 (m, 1 H, CHNH), 4.17 (d, 1 H, J = 14.4, CHHNH), 4.54, 4.89 (each d, 1 H, J = 5.4, H_{arom} of *p*-cymene), 4.9−5.1 (m, 4 H, PhCH + CHHNH + 2 H_{arom} of *p*-cymene), 7.0−7.7 (m, 14 H, H_{arom}). − ^{13}C NMR ($C_6D_5CD_3$, −20 °C): δ = 9.7 (CH_3CHN), 16.1 (CH_3 of *p*-cymene), 23.9, 24.2 [CH(CH_3)$_2$], 32.5 [CH(CH$_3$)$_2$], 68.6 (CH_2NH), 73.1, 76.4, 77.6, 79.0 (4 CH_{arom}), 79.7 (1 CH_{arom} + 1 C_q of *p*-cymene), 96.4 (C_q of *p*-cymene), 126.1, 127.4, 127.6 (CH_{arom}), 140.2, 140.9, 141.6, 146.1 (4 C_q). − ESI-MS; *m*/*z*: 552.1 [MH]$^+$; masses and intensity ratio in excellent agreement with the calculated pattern for the protonated expected molecule $C_{32}H_{36}NORu$.

[{η²-*N*,*O*-(1*S*,2*R*)-*N*-(4-biphenylmethyl)norephedrine⁻¹}{η⁶-*p*-cymene}RuH] (37): The purple complex **36** (220 mg, 0.4 mmol) was stirred in 2-propanol (7 mL) for 5 min at room temperature. The resulting red solution was immediately concentrated to dryness at −10 °C to afford **37** as a brown-red powder. Yield: 221 mg, 100%. − ^{1}H NMR ($C_6D_5CD_3$, −20 °C): δ = −5.20 (s, 1 H, RuH), 0.87 (d, 3 H, J = 6.2, CH_3CHN), 1.19, 1.35 [each d, 3 H, J = 6.8, CH(CH_3)$_2$], 2.17 (s, 3 H, CH_3 of *p*-cymene), 2.27 [m, 1 H, CH(CH$_3$)$_2$], 2.33 (m, 1 H, CHNH), 3.58 (dd, 1 H, J = 10.5, J = 14.3, CHHNH), 3.71 (dd, 1 H, J = 3.8, J = 14.3, CHHNH), 3.90 (d, 1 H, J = 5.3 Hz, H_{arom} of *p*-cymene), 4.36 (m, 1 H, PhCH), 4.72 (d, 1 H, J = 5.6 Hz, H_{arom} of *p*-cymene), 4.81 (m, 1 H, NH), 5.17 (d, 1 H, J = 5.3 Hz, H_{arom} of *p*-cymene), 5.46 (d, 1 H, J = 5.6 Hz, H_{arom} of *p*-cymene), 6.8−7.6 (m, 14 H, H_{arom}). − ^{1}H NMR (C_6D_6, +20 °C): δ = −5.11 (s, 1 H, RuH), 0.90 (d, 3 H, J = 6.2, CH_3CHN), 1.20, 1.33 [each d, 3 H, J = 6.9, CH(CH_3)$_2$], 2.11 (s, 3 H, CH_3 of *p*-cymene), 2.35 [m, 2 H, CHNH + CH(CH$_3$)$_2$], 3.76 (m, 2 H, CH_2NH), 4.04 (d, 1 H, J = 5.3, H_{arom} of *p*-cymene), 4.43 (m, 1 H, PhCH), 4.54 (d, 1 H, J = 5.3, H_{arom} of *p*-cymene), 4.69 (m, 1 H, NH), 5.16, 5.38 (each d, 1 H, J = 5.3, H_{arom} of *p*-cymene), 6.8−7.7 (m, 14 H, H_{arom}). − ^{13}C NMR ($C_6D_5CD_3$, −40 °C): δ = 8.2 (CH_3CHN), 19.1 (CH_3 of *p*-cymene), 24.7 [CH(CH_3)$_2$], 33.4 [CH(CH$_3$)$_2$], 58.5 (CH_2NH), 60.9 (CHNH), 75.2, 76.2, 78.6 (3 CH_{arom} of *p*-cymene), 85.2 (PhCH), 88.7 (CH_{arom} of *p*-cymene), 97.6, 104.4 (2 C_q of *p*-cymene), 127.4, 128.2, 128.3 (CH_{arom}), 136.9, 141.7, 141.9, 145.2 (4 C_q).

[{η⁶-*p*-cymene}{η²-OC(CF$_3$)CHC(CO$_2$Et)O}RuCl] (38): A mixture of [(η⁶-*p*-cymene)RuCl$_2$]$_2$ (**6e**, 306 mg, 0.5 mmol), β-oxo ester **20** (184 mg, 1.0 mmol), and triethylamine (0.28 mL, 2.0 mmol) in ethanol (20 mL) was heated under reflux for 2 h. The orange solution was then concentrated to dryness, the residue was washed with water (2 × 4 mL), and extracted with benzene (10 mL). The benzene layer was concentrated under reduced pressure to afford **38** as an orange-brown powder. Yield: 386 mg, 85%. − ^{1}H NMR ($CDCl_3$): δ = 1.27 (t, 3 H, J = 7.1, OCH$_2$CH_3), 1.34, 1.35 [each d, 3 H, J = 6.9, CH(CH_3)$_2$], 2.22 (s, 3 H, CH_3 of *p*-cymene), 2.92 [sept., 1 H, J = 6.9, CH(CH$_3$)$_2$], 4.21, 4.23 (each dq, 1 H, J = 7.1 and 10.7, OCHHCH$_3$), 5.01 (s, 1 H, CH acac), 5.27, 5.29, 5.54, 5.56 (each d, 1 H, J = 5.9, H_{arom} of *p*-cymene). − ^{13}C NMR ($CDCl_3$): δ = 14.3 (OCH$_2$CH_3), 17.8 (CH_3 of *p*-cymene), 22.1, 22.2 [CH(CH_3)$_2$], 30.9 [CH(CH$_3$)$_2$], 61.8 (OCH_2CH$_3$), 78.0, 79.1, 81.7, 82.9 (4 CH_{arom} of *p*-cymene), 83.1 (CH acac), 96.8, 99.3 (2 C_q of *p*-cymene), 118.0 (q, J_{CF} = 283, CF_3), 169.2 (q, J_{CF} = 33, CF_3C=O), 172.6 (COO). − ^{1}H NMR (C_6D_6): δ = 0.93 (t, 3 H, J = 7.1, OCH$_2$CH_3), 1.09, 1.10 [each d, 3 H, J = 6.9, CH(CH_3)$_2$], 1.77 (s, 3 H, CH_3 of *p*-cymene), 2.64 [sept, 1 H, J = 6.9, CH(CH$_3$)$_2$], 3.88 and 3.91 (each dq, 1 H, J = 7.1 and 10.7, OCHHCH$_3$), 4.64 (d, 2 H, J = 6.1, H_{arom} of *p*-cymene), 4.94, 5.11 (each d, 1 H, J = 6.0, H_{arom} of *p*-cymene), 5.36 (s, 1 H, CH acac). − $C_{16}H_{20}ClF_3O_3Ru$ (453.85): calcd. C 42.34, H 4.44; found C 42.91, H 4.68.

Reaction of Complex 35 with β-Oxo Ester 20: In a glove box, β-oxo ester **20** (10 μL, 0.07 mmol) was added by means of a microsyringe to a brown solution of complex **35** (30 mg, 0.05 mmol) in $CDCl_3$ (ca. 2 mL) in an NMR tube. The tube was then shaken and placed in an oil bath at 40 °C for 30 min. No significant change in the coloration of the solution was observed. The reaction mixture was then analyzed by NMR spectroscopy (^{1}H, ^{13}C-APT, ^{1}H,^{1}H-COSY, ^{13}C,^{1}H-HETCOR) at room temperature, which showed the selective (> 90% according to ^{1}H NMR) formation of **38** with concomitant release of β-amino alcohol **9o**.

X-ray Crystal Structure of 9o·HCl: $C_{22}H_{24}ClNO$, M_r = 353.87; colourless platelet (0.25 × 0.30 × 0.050 mm); orthorhombic, space group $P2_12_12_1$ (no. 19); a = 5.4230(11), b = 11.838(2), c = 29.078(4) Å, V = 1866.7(6) Å^3; Z = 4, $\rho_{calcd.}$ = 1.259 g·cm^{-3}, μ(Mo-K_α) = 0.214 mm^{-1}; T = 293(2) K; Θ range = 1.86−23.31°. 8793 reflections were measured, of which 2385 were found to be independent and unique, and 1898 with $I > 2\sigma(I)$ were used for the structure solution; 323 parameters. All hydrogen atoms were located on a Fourier difference map and their positions were refined isotropically; R = 0.0554, Rw = 0.0840.

X-ray Crystal Structure of 35·MeOH: $C_{33}H_{40}ClNO_2Ru$, M_r = 619.18; orange platelet (0.30 × 0.20 × 0.08 mm); monoclinic, space

group $P2_1$ (no. 4); a = 7.563(5), b = 13.395(8), c = 16.617(11) Å, β = 96.581(12)°, V = 1672.4(19) Å^3; Z = 2, $\rho_{calcd.}$ = 1.230 g·cm^{-3}, μ(Mo-K_α) = 0.575 mm^{-1}; T = 293(2) K; Θ range = 1.96−23.41°. Due to slow degradation of the complex, data were collected using a quick procedure (240 frames of 1.5° width, 20 s exposure time). 4222 reflections were measured, of which 2635 were found to be independent and unique, and 1880 with $I > 2\sigma(I)$ were used for the structure solution. The Ru and Cl atoms were refined anisotropically, the O, N, and C atoms isotropically; R = 0.1125, Rw = 0.2824. The precision of this analysis was limited but was sufficient to confirm the connectivity and the geometrical features of the complex.

All the X-ray diffraction measurements were performed with a Bruker SMART diffractometer (Mo-K_α radiation, λ = 0.71069 Å, graphite monochromator). The structures were solved by direct methods (SHELX-97 package). Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-147146 and -147147. Copies of the data can be obtained free of charge on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ, U.K. [Fax: (internat.) + 44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].

General Procedure for Transfer Hydrogenation of Ketones: A solution of [(η^6-*p*-cymene)RuCl$_2$]$_2$ (**6e**, 6.2 mg, 0.01 mmol, 0.5 mol-% with respect to the ketone substrate) and (1*S*,2*R*)-*N*-(4-biphenylmethyl)norephedrine (**9o**, 12.7 mg, 0.04 mmol) in dry freshly distilled 2-propanol (5 mL) was heated under nitrogen at 80 °C for 20 min. After allowing the orange solution to cool to room temperature, a solution of *tert*-butyl acetoacetate (**7c**, 316 mg, 2.0 mmol) in 2-propanol (14 mL) and *i*PrOK (1.0 mL, 0.12 M in 2-propanol, 0.12 mmol) were added. The resulting solution was stirred at 20 °C and the reaction was monitored by GLC.

Supporting Information Available: GLC analytical procedures for the transfer hydrogenation products, NMR spectra of Ru complexes **35**, **36**, **37**, and **38**, and ESI-MS of Ru complexes **35** and **36** (see also footnote on the first page of this article).

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logously to **35** following sequences iv + iii as brown powders in 80% and 75% overall yields, respectively. The ^{1}H and ^{13}C NMR spectra of **35b** and **35c** in C_6D_6 are similar to those of **35** (see Exp. Sect.), and are consistent with the highly stereoselective formation of a major diastereomer. Attempted preparations of the active species derived from ephedrine, i.e. **36b** and **37b**, have so far yielded only mixtures of products.

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[30] Transfer hydrogenation is also inhibited in the presence of 3,5-dioxohexanoate esters, which exist in solution as the enols $CH_3COCH=C(OH)CH_2CO_2R$. The reduction of β-aroyl acetates requires the use of 1 to 5 mol-% of the (β-amino alcohol)(-arene)ruthenium catalyst to reach completion.[21]

[31] As remarked pertinently by a referee, the deactivation process of catalytic species by functionalized ketones discussed in this section do not account for the gradual deactivation of the catalytic systems based on (2-hydroxymethyl)pyrrolidine (**14**), which takes place even with acetophenone. In this case, it is possible that deactivation is due to a low, inherent stability of in situ formed Ru species.

[32] [32a] For a review on developments in combinatorial and rapid screening in homogeneous catalysis, see: R. H. Crabtree, *Chem. Commun.* **1999**, 1611–1616. – [32b] For an application to the asymmetric reduction of ketones, see: H. B. Kagan, *J. Organomet. Chem.* **1998**, *567*, 3. – [32c] For a recent development in transfer hydrogenation, see: D. G. I. Petra, J. N. H. Reek, P. C. J. Kamer, H. E. Schoemaker, P. W. M. N. van Leeuwen, *Chem. Commun.* **2000**, 683–684.

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