Ruthenium(II)-Catalyzed Asymmetric Transfer Hydrogenation of Carbonyl Compounds with 2-Propanol and Ephedrine-Type Ligands

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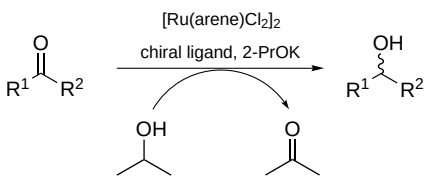
Abstract: This account describes the development and application of Noyori's type catalysts based on ruthenium-arene complexes and simple chiral β-amino alcohols derived from ephedrine, for the asymmetric transfer hydrogenation of 2-propanol to carbonyl substrates. The influence of key parameters of the catalyst system has been studied systematically, resulting in particular in the design of the novel ligand (4-biphenylmethyl)norephedrine. Thanks to the latter, the catalytic precursors and true active species could be isolated for the first time, enabling a complete structural description of the catalytic cycle and of probable deactivation pathways. Highly effective applications of those catalysts systems, i.e., the asymmetric reductions of simple aryl ketones and aryl β-keto esters, the synthesis of chiral phthalides and *syn*-β,δ-dihydroxy esters, are described.

Keywords: amino alcohols; asymmetric catalysis; chiral alcohols, ephedrine; hydrogen transfer; *N,O* ligand; ruthenium

1 Introduction

Catalytic asymmetric reduction of C=O bonds is a pivotal transformation in organic chemistry to create new stereocenters. Very successful developments in this field have been reported in recent years and a large number of catalytic methods are now available to achieve this goal.[1] Among these, transfer hydrogenation of 2-propanol to prochiral ketones has emerged as a highly efficient technique (Scheme 1).[2]

In this reversible process, referred to as the Meerwein–Pondorf–Verley reduction, 2-propanol acts simultaneously as a safe, inexpensive, easy to handle solvent and reductant that is transformed into acetone, which can be readily removed from the reaction mixture. The resulting operational simplicity and high product yields in high enantiomeric excess for some specific ketones make catalytic transfer hydrogenation a useful complement/alternative to hydrogenation using molecular hydrogen, particularly for small- to medium-scale reactions. After a rather long and quite primitive stage, several advances have been accomplished in the last decade for designing efficient hydrogen transfer catalyst systems with some transition metal and lanthanide complexes.[2] Undoubtedly, one of the most significant breakthroughs, reported by Noyori et al., is the use of chlororuthenium(II)arene precursors with chiral monoarylsulfonylated-1,2-diamine or β-amino alcohol ligands (Scheme 1).[3,4] The structurally well-defined [Ru^{II}(arene)(TsDPEN)] [TsDPEN = (1*R*,2*R*)-*N*-(*p*-tolylsulfonyl)-1,2-diphenylethylene-diamine, **1**] system enables the highly effective reduction of a variety of aryl alkyl and related ketones in above 90% ee.[3]



Scheme 1.

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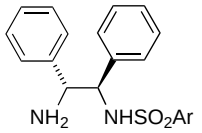
Kathelyne Everaere was born in Béthune, France, in 1973. She studied chemistry at the Graduate Engineering School in Lille and earned her Ph. D. degree in organic chemistry in 2000 from the University of Lille, under the direction of Professor André Mortreux and Dr. Jean-François Carpentier, with a thesis on the topic of this account. After 15 months post-doctoral research at the ATOFINA research center of King of Prussia, USA, she recently joined CEREXAGRI where she works on pesticides formulation.

André Mortreux was born in Libercourt, France, in 1943. He received his Ph. D. from the University of Poitiers working with Professor M. Blanchard on catalytic reactions of alkynes, where he discovered in 1973 the first homogeneous catalytic system for alkyne metathesis. After post-doctoral research in 1976 with Professor F. G. A. Stone in Bristol, U. K., he moved to the University of Lille to join Professor F. Petit who had just set up a research team devoted to homogeneous catalysis. He was promoted to Professor of Chemistry in 1983 and Professor at the Institut Universitaire de France in 2001. In the same year, he received the Clavel-Lespiau award from the French Academy of Sciences. He his now head of the homogeneous catalysis team of the Laboratoire de Catalyse of Lille University. His current research interests include the development of new catalysts for transition metal-catalyzed processes involving asymmetric catalysis, carbonylation, oligomerization and polymerization reactions. He is the author and co-author of more than 200 research papers and holds 30 patents.

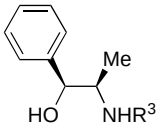
Jean-François Carpentier was born in Lille, France, in 1967. He graduated from the Engineering School of Chemistry of Lille in 1989. He earned his Ph. D. in chemistry from the University of Lille in 1992, working with Professors A. Mortreux and F. Petit on palladium-catalyzed carbonylation of organic halides with alkyl formates. After a 12-month period of post-doctoral research at the French Nuclear Agency in Tours, he was appointed as a CNRS research fellow at the University of Lille where he prepared his habilitation working on a wide variety of homogeneously-catalyzed processes, mostly asymmetric hydrogenation of carbonyl compounds and nucleophilic allylic substitution. In 1997, Carpentier was a visiting scientist at the University of Iowa where he worked with Professor R. F. Jordan on mechanistic issues related to the interaction of olefins with alkyl cationic group 4 metallocenes. Returning to Lille, he pursued his studies on olefin polymerization using organolanthanide catalysts. Carpentier joined the University of Rennes in 2001 as Professor of Chemistry. His current research interests include the design of new ligands, organometallic chemistry of early transition metals, and application of these complexes as homogeneous single-site catalysts for olefin polymerization and fine chemicals synthesis.



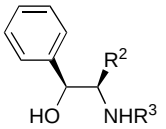
1 (Ar = 4-$CH_3C_6H_4$)

Initial systems designed by Noyori et al. that employ simple β-amino alcohols, e.g., ephedrine, gave also very good results in terms of enantioselectivity and catalytic activities, the latter being among the highest reported at this time for Ru^{II}-catalyzed transfer hydrogenation.[4] Since chiral diamines are notoriously complicated to synthesize in contrast to the large variety and ready availability of chiral amino alcohols, this step-change has led to intense exploration of [Ru^{II}(arene)(β-amino alcohol)] systems for rationalizing the enantioselectivity, designing more efficient ligands, improving catalyst activity and broadening the scope of asymmetric hydrogen transfer of 2-propanol to functionalized carbonyl compounds.[5–7]

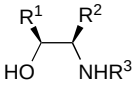
In this account we summarize our own efforts toward these objectives using ephedrine-type ligands.[6] Three essential parameters of these asymmetric hydrogen transfer systems, i.e., (i) structure of the β-amino alcohol ligand, (ii) structure of the arene ligand in the ruthenium precursor, and (iii) influence of functional groups of ketones to be reduced, have been studied systematically. The complementary information thus collected, together with reactivity data of unique isolated [Ru^{II}(arene)(*β*-amino alcohol)] complexes, have led to a better understanding of the process with a complete structural



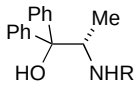
2a R^3 = H
2b R^3 = Me
2c R^3 = ^{i}Pr
2d R^3 = CH_2Bn
2e R^3 = Bn
2f R^3 = $CH_2C_6H_4$-(4-Ph)
2g R^3 = CO_2Et, COMe, CO_2Me, Ts



3a R^2 = H R^3 = Me
3b R^2 = H R^3 = Bn
3c R^2 = Et R^3 = Me
3d R^2 = Et R^3 = $CH_2C_6H_4$-(4-Ph)
3e R^2 = Bn R^3 = Me
3f R^2 = Bn R^3 = $CH_2C_6H_4$-(4-Ph)
3g R^2 = Ph R^3 = Bn



4a R^1 = Me R^2 = H R^3 = Me
4b R^1 = H R^2 = Me R^3 = $CH_2C_6H_4$-(4-Ph)
4c R^1 = 4-MeOC H R^2 = Bn R^3 = Me



5a R = H
5b R = Bn

Table 1. Influence of the ligand structure on the asymmetric transfer hydrogenation of *tert*-butyl acetoacetate (**K1**).[a]

Entry	Ligand	Time[b] [h]	Conversion[c] [%]	TOF_{50} [h^{-1}][d]	ee[e] [%, (*S*)]
1	**1**	17	21	≪	4
2	**2a**	16	>99	9	32
3	**2b**	1	98	190	44
4	**2c**	16	>99	12	29
5	**2d**	16	>99	12	36
6	**2e**	5	>99	22	68
7	**2f**	2.5	>99	46	67
8	**2g**	16–50	8–10	≪	7–22
9	**3a**	5	>99	28	39
10	**3b**	24	>1	0	–
11	**3c**	6	>99	23	44
12	**3d**	14	>99	10	64
13	**3e**	4.5	99	25	47
14	**3f**	16	98	8	34
15	**3g**	14	>99	10	36
16	**4a**	5	>99	23	35
17	**4b**	13	99	11	43
18	**4c**	4.5	98	25	45
19	**5b**	22	3	≪	nd

[a] Reactions were carried out at 20 °C using 2.0 mmol of **K1** in a 0.1 M 2-propanol solution with [**K1**]/[*i*-PrOK]/[chiral ligand]/[Ru(benzene)] = 100:6:2:1.
[b] Reaction time not optimized.
[c] Conversions of **K1** determined by GLC.
[d] Catalyst turnover frequency at half-reaction determined by GLC monitoring, in mole of product/(mole of Ru · h).
[e] Determined by chiral GLC analysis.

description of the intermediates involved in the catalytic cycle. Valuable synthetic applications that have been developed from these catalysts will be described.

2 Development of [Ru(arene)-(β-Amino Alcohol)] Catalysts

2.1 Effect of the β-Amino Alcohol Ligand

The effect of the β-amino alcohol structure on the performance of *in situ* generated catalysts was addressed by varying the nature of substituents R^1, R^2, and R^3 in $R^1CH(OH)CHR^2NHR^3$ ligands. No ligand having a tertiary amino group was investigated since the presence of an N-H moiety was shown previously to have a crucial importance for catalytic activity.[4] About 50 different chiral ligands, related to ephedrine, were prepared using various synthetic procedures and evaluated systematically in the reduction of ketone substrates. Noteworthy, similar trends in reaction rates and enantioselectivities* were observed with different $[Ru(arene)Cl_2]_2$ precursors and ketones, thus allowing us to draw some general conclusions. Representative results for the transfer hydrogenation of model substrate *tert*-butyl acetoacetate (**K1**) using $[Ru(benzene)Cl_2]_2$ (**6a**) as catalyst precursor are summarized in Table 1.

The influence of the R^3 substituent proved to be the most important and was addressed from *N*-substituted (1*S*,2*R*)-norephedrine amino alcohols (**2a–h**). The highest apparent reaction rate was observed with ephedrine (**2b**). Use of the corresponding primary amine (**2a**) or of any other *N*-alkyl-substituted ligand (e.g., **2c, d**), or even worse of the *N*-carbamate, amide and sulfonamide derivatives (**2g**), resulted in reduced reaction rates and ees. The sole but remarkable exception was found with benzyl-type substituents (**2e, f**) that caused the enantioselectivity to increase up to 68%. The influence of additional substituents at the benzyl ring proved to be sensitive in terms of reaction rate but with minimal effects on the selectivity. While *ortho*-substituted ligands [*N*-CH_2(2-XC_6H_4); X = Me, OMe, Cl, Ph] led to very low reduction rates, most likely

* The enantioselectivities of the catalytic reactions performed with the systems described in this paper were found to be constant in time. Hence, these values are representative of the intrinsic discriminating abilities of the catalytic species, which was confirmed from the reactions carried out with isolated catalytic intermediates.

because of steric reasons, ligands having *para*-substituted benzyl groups [N-CH_2(4-XC_6H_4); X = Me, OEt, Ph] gave rise to slightly improved reaction rates. As will be exemplified below, these results implicated the system derived from (4-biphenylmethyl)norephedrine (**2f**) to be the most efficient for the transfer hydrogenation of many non-aromatic ketones.

The effect of the substituent at the 2-position was studied using β-amino alcohols **3a – g** and was shown to be moderate in most cases. Thus, replacing of the methyl R^2 group of ephedrine by an ethyl, a benzyl or a phenyl group (**3c – g**) had almost no effect on the reaction rate. Also, in most cases, the selectivity abilities of catalytic species in this series are not affected by the 2-substituent. However, two exceptions were found to these trends: (i) surprisingly, changing R^2 from a methyl to an H atom (**3a, b**) caused a dramatic decrease in the reaction rate. (ii) Systems derived from ligands bearing phenyl rings at both the R^2 and R^3 substituents, gave rise to lower ees than their analogues with R^2 = Me, (e.g., compare **3g**, 34% ee, vs. **2e**, 68%); computed molecular models suggested that such decreased selectivity ability may originate from π-π-stacking between the aryl groups at C-2 and the NH-benzyl moieties.

The influence of the R^1 substituent was addressed with a variety of β-amino alcohols and proved also to be variable. Systems based on ligands containing the relatively more bulky *para*-methoxyphenyl group instead of a phenyl group at the 1-position gave nearly identical performances (R^2 = Me, Bn; **4c** vs. **3e**). Also, changing the 1-phenyl group by a methyl R^1 substituent in the case R^2 = H (**4a** vs. **3a**) almost did not affect the results. Hence, a small group at C-1 apparently suffices to reach the maximal enantioselectivity. On the other hand, non-substitution (**4b**, R^1 = H) or disubstitution (**5**, R^1 = Ph,Ph) turned out to be detrimental in terms of selectivity and reaction rate, respectively. Also, systems based on pseudoephedrine derivatives led to lower selectivities than those based on the corresponding ephedrine analogues, highlighting the importance of relative 1*S*,2*R*/1*R*,2*S* stereoselectivity.

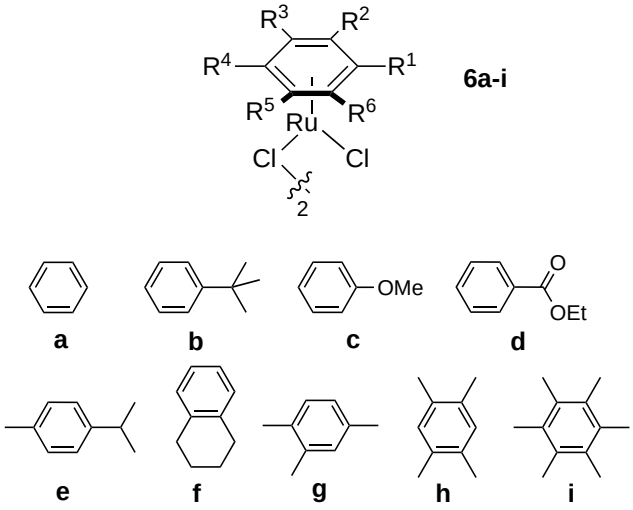
Table 2. Influence of the arene structure on the asymmetric transfer hydrogenation of *tert*-butyl acetoacetate (**K1**).[a]

Entry	Ru(II)-arene	Ligand	Time[b] [h]	Conversion[c] [%]	TOF_{50} [h^{-1}][d]	ee[e] [%, (S)]
1	**6a**	**2b**	1	98	190	44
20	**6b**	**2b**	48	>99	5	18
21	**6c**	**2b**	2	>99	250	42
22	**6d**	**2b**	24	0	0	–
23	**6e**	**2b**	3	>99	33	5[f]
24	**6f**	**2b**	14	>99	12	15
25	**6g**	**2b**	14	>99	20	17
26	**6h**	**2b**	48	70	3	12[f]
27	**6i**	**2b**	24	5	≪	3[f]
6	**6a**	**2e**	5	>99	22	68
28	**6c**	**2e**	6	>99	18	65
29	**6e**	**2e**	23	98	6	30
30	**6f**	**2e**	14	>99	20	51
31	**6g**	**2e**	16	>99	10	46

[a–e] See Table 1.
[f] The configuration of the major isomer of **A1** is *R*-(–).

2.2 Effect of the Arene Ligand

Most of the work reported in the field of Ru-catalyzed asymmetric transfer hydrogenation has focused on commercially available $[Ru(arene)Cl_2]_2$ precursors such as the *para*-cymene and benzene complexes. Preliminary observations by Noyori et al. revealed, however, that substituents on the Ru-arene ring also play a significant role in the performances of the catalyst system.[4] To get a better insight in this effect, we have evaluated *in situ* combinations generated from a set of chloroRu^{II}(arene) precursors (**6a – i**) in the transfer reduction of **K1** (Table 2). These chloroRu^{II}(arene) dimers were prepared *via* reaction of $RuCl_3 \cdot 3\ H_2O$ with 1,4-dienes,[7] which are available through the Birch reduction of the corresponding arene.



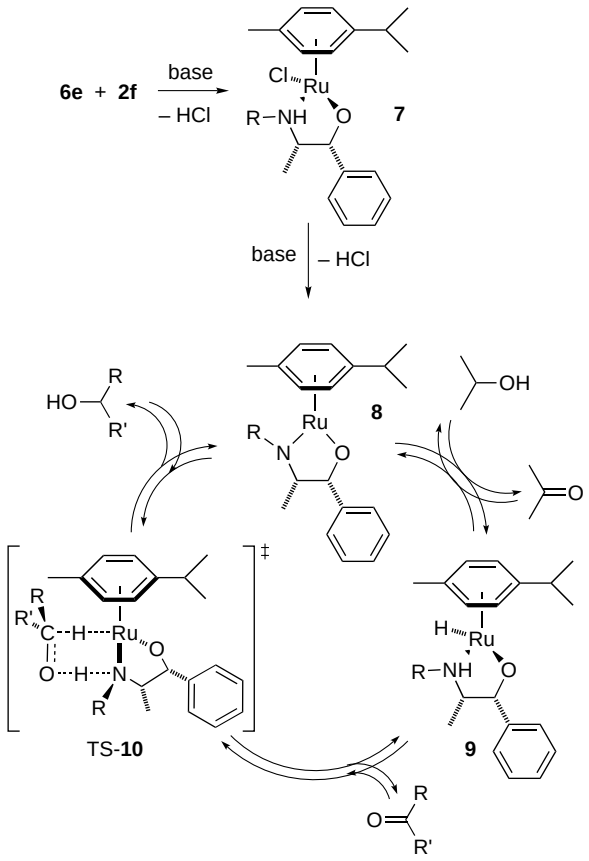
As anticipated, introduction of alkyl substituents on the arene ring logically resulted in a concomitant decrease of the apparent reaction rate with increased steric hindrance; thus, the Ru^{II}(benzene) (**6a**) and the Ru^{II}(hexamethylbenzene) (**6i**) systems feature extreme positions, the former system being the most active among those investigated. On the other hand, the ephedrine-Ru^{II}(anisole) system (**6c**) led to similar kinetics to the one based on Ru^{II}(benzene) (**6a**), but no activity was observed with the Ru^{II}(benzoate) system (**6d**). This indicates that, besides steric considerations, electronic factors contribute also to the reaction outcome and that a minimal electron density on the arene ring may be required for the reaction to proceed. It is, however, still an

open question whether these steric and electronic factors affect the intrinsic activity of the active ruthenium species in the rate-determining-step of the process or the efficiency of its *in situ* generation from the catalyst precursors, i.e., the amount of active species (*vide infra*).

Significant and subtle influence of the arene ligand on enantioselectivity was also observed. Contrary to reaction rates, but not surprisingly, the relative efficiency of Ru^{II}(arene) precursors in this matter depends strictly on the nature of the ketone to be reduced. In the case of *tert*-butyl acetoacetate (**K1**), the use of the benzene precursor (**6a**) in combination with ephedrine (**2b**) or *N*-benzylnorephedrine (**2e**) leads to improved enantioselectivities with respect to corresponding combinations based on the *p*-cymene precursor (**6e**). A reversal in the configuration of the major reduction product **A1** is observed with ephedrine as the ligand [44% (*S*) and 5% (*R*), respectively] in contrast with *N*-benzylnorephedrine [68% (*S*) and 30% (*S*)]; however, both variations of ees correspond to the same difference in the Gibbs energies [$\Delta(\Delta G^{\neq})_{\mathbf{6a/6e}} = 0.62$ kcal · mol^{-1}). In the same way, the 1,2,4-trimethylbenzene systems (**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 **2b**; $\Delta(\Delta G^{\neq})_{\mathbf{6a/6g}} =$ 0.39 kcal · mol^{-1} with **2e**]. The same trend was found for the tetrahydronaphthalene systems [$\Delta(\Delta G^{\neq})_{\mathbf{6a/6f}} =$ 0.38 kcal · mol^{-1} with **2b**; $\Delta(\Delta G^{\neq})_{\mathbf{6a/6f}} = 0.32$ kcal · mol^{-1} with **2e**]. As pointed out above, it is obvious that steric interactions between substituents on the arene ring and the substrate do exist in the transition state. Nonetheless, considering the similarity in the differences in the $\Delta(\Delta G^{\neq})$ values going from the "naked" Ru^{II}(benzene) precursor to arene-substituted precursors, despite the difference in the steric bulk of **2b** and **2e** (R^3 = Me vs. Bn), there is apparently no significant steric interaction between substituents on the arene ring and the R^3 substituent on the ligand.

3 Isolation and Reactivity of Catalytic Intermediates

Since Noyori et al. established the identity of the catalyst precursors and true active species involved in the transfer hydrogenation process promoted by [Ru(arene)(TsDPEN)] catalysts,[3c] the nature of the corresponding [Ru(arene)(β-amino alcohol)] intermediates was speculated to be analogous.[3g] Repeated attempts to isolate intermediates from the [Ru(*p*-cymene)$Cl_2]_2$/ephedrine system using a synthetic methodology similar to that reported by Noyori for TsDPEN led, however, to mixtures of products. Fortunately, thanks to the new ligand (1*S*,2*R*)-(4-biphenylmethyl)norephedrine (**2f**), we were able to prepare for the first time the three speculated intermediates and to establish formally the mechanism pathway (Scheme 2).[6d]



Scheme 2.

The formally 18-electron *catalyst precursor* **7** was prepared readily by reacting the Ru^{II}-*p*-cymene complex (**6e**) and ligand (**2f**) with 2 equivalents of NEt_3 in refluxing 2-propanol. Complex **7** was fully characterized by elemental analysis, ESI-MS, and an X-ray diffraction study of its methanol adduct, which revealed a distorted "piano stool" structure in the solid state. The ^{1}H and ^{13}C NMR data confirmed that the amino alcohol chelates to Ru in $CDCl_3$ and C_6D_6 solutions and that **7** exists as a single diastereomer. Complex **7** catalyzes the asymmetric transfer hydrogenation of *tert*-butyl acetoacetate (**K1**) in 2-propanol *only* upon addition of *i*-PrOK, with the same enantioselectivity and activity as those observed with the complex formed *in situ*.

Upon treatment with one equivalent of KOH, complex **7** undergoes facile elimination of HCl to give the formally 16-electron complex **8** as a very air-sensitive deep purple solid. This compound is most easily prepared in > 80% yield *via* the direct reaction of a 1:1 mixture of **6e**/**2e** with excess KOH (7 equivalents) in CH_2Cl_2. It reacts rapidly at room temperature in chloroform solution through capture of HCl to give back **7** in quantitative yield. The identity of **8** was unambiguously established from NMR, IR spectroscopy and ESI-MS. In particular, the ^{1}H NMR resonances in **8** around the oxygen atom are unchanged from those of **7**, whilst those

Table 3. Asymmetric transfer hydrogenation of acetophenone (**K2**) and 2-acetylpyridine (**K3**).[a]

Entry	Ru(II)-arene	Ligand	Ketone	Time[b] [h]	Conversion[c] [%]	TOF_{50} [h^{-1}][d]	ee[e] [%, (*S*)]
32	**6a**	**2e**	**K2**	2	>99	250	82
33	**6e**	**2b**	**K2**	0.5	>99	120	91
34	**6e**	**2e/2f**	**K2**	2	>99	120	91
35	**6e**	**2h**[f]	**K2**	2	>99	120	95
36	**6a**	**2b**	**K2**	0.5	>99	450	68
37	**6e**	**2b**	**K2**	0.5	>99	375	83
38	**6e**	**2e/2f**	**K3**	16	>99	7	89
39	**6a**	**1**	**K3**	21	40	≪	88[g]

[a–e] See Table 1.
[f] **2h** = (1*S*,2*R*)-*N*-(cyclohexylmethyl)-norephedrine.
[g] The configuration of the major isomer of **A3** is *R*-(+).

Table 4. Asymmetric transfer hydrogenation of 2-acylarylcarboxylates **K4**.[a]

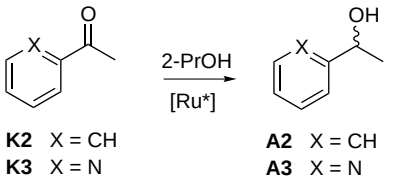
Entry	Ketone	Catalyst	Temperature [°C]	Time[b] [h]	Conversion[c] [%]	Selectivity **A4**[d] [%]	ee[e] [%]
40	**K4a**	Ru-**1** *in situ*	20	18	92	32[f]	97 (*S*)
41	**K4a**	Ru-**1** preformed	"	23	93	99	97 (*S*)
42	**K4a**	Ru-**1** preformed	50	3.5	96	>99	94 (*S*)
43	**K4a**	Ru-**2f** *in situ*	20	16	65	41[f]	84 (*S*)
44	**K4a**	Ru-**2f** preformed (**8**)	20	3	96	>99	83 (*S*)
45	**K4b**	Ru-**1** *in situ*	50	2	65	96	94 (−)
46	**K4b**	Ru-**1** preformed	"	1	100	>99	96 (−)
47	**K4b**	Ru-**2f** preformed (**8**)	20	3	99	>99	23 (−)
48	**K4c**	Ru-**1** preformed	"	18	80	98	92 (*S*)
49	**K4c**	Ru-**1** preformed	50	22	91	98	80 (*S*)
50	**K4c**	Ru-**2f** preformed (**8**)	20	18	99	>99	72 (*S*)

[a–c] See Table 1.
[d] Selectivities for **A4** determined by GLC and ^{1}H NMR analysis; corresponding compound **B4** accounts for the balance.
[e] Determined by chiral GLC analysis.
[f] Compound **B4** accounts for the balance.

around the nitrogen atom are shifted, as expected from the transformation of the amino to amido functionality.

Treatment of the purple complex **8** with a large excess of 2-propanol at room temperature gave the subsequent intermediate, the *true catalytically active* hydrido species **9**, as a brown red solid. The variable temperature ^{1}H NMR monitoring of this reaction showed the appearance at −25 °C of one set of resonances, including a single Ru-H resonance at δ = −5.20, that remained unique (⩾95%) till 0 °C. In light of Noyori's results,[3c] this is consistent with the kinetically controlled formation of a major diastereomer.

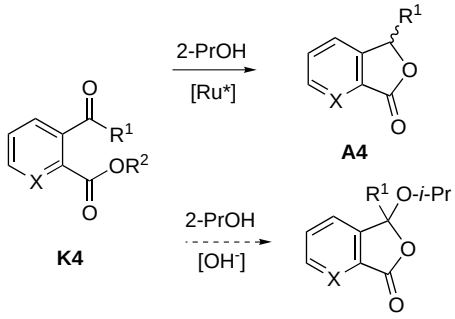
Both complexes **8** and **9** catalyze the asymmetric transfer hydrogenation of β-keto ester **K1** and acetophenone (**K2**) in 2-propanol *without addition of a base* to give the corresponding alcohols in the same stereoselectivity and catalytic activity as those observed with the complex formed *in situ*. As shown in the next section, the possibility to achieve hydrogen transfer under *neutral* conditions turned to be of major interest for the reduction of sensitive ketone substrates.



K2 X = CH
K3 X = N

A2 X = CH
A3 X = N

Scheme 3.



a: X = CH, R^1 = Me, R^2 = Me
b: X = N, R^1 = Me, R^2 = *i*-Pr
c: X = CH, R^1 = *n*-Bu, R^2 = Me

Scheme 4.

Table 5. Asymmetric transfer hydrogenation of 2-aroylacetates **K5**.[a]

Entry	Ketone	Ru(II)-arene	Time[b] [h]	Conversion[c] [%]	TOF_{50}[d] [h^{-1}]	ee[e] [%]
51	**K5a**	**6a**	2.5	99	136	40 (*S*) (−)
52	**K5a**	**6e**	15	>99	10	94 (*S*) (−)
53	**K5b**	**6e**	1	>99	120	89 (*S*) (−)
54	**K5c**	**6e**	2[f]	95	10	75 (−)
55	**K5d**	**6e**	1	>99	>100	82 (−)
56	**K5e**	**6e**	16	>99	nd	82 (*S*) (−)
57	**K5f**	**6e**	14[f]	>99	nd	72 (−)
58	**K5g**	**6e**	1[f]	>99	25	81 (−)
59	**K5h**	**6e**	1[f]	>99	30	84 (−)

[a–e] See Table 1 except $T = 50$ °C ; ligand used: **2b**.
[f] [**K5**]/[Ru] = 20.

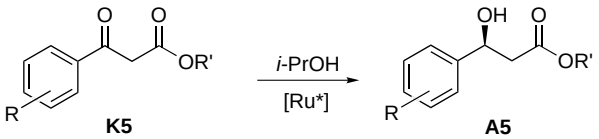
4 Applications of [Ru(arene)(β-Amino Alcohol)]-Catalyzed Transfer Hydrogenation

4.1 Aromatic Ketones and Keto Esters

Carbonyl compounds having one sp^2-carbon atom α to the keto function belong to the most favorable class of substrates for asymmetric transfer hydrogenation with [Ru(arene)(β-amino alcohol)] catalysts. High enantioselectivities have been readily achieved for a number of aromatic ketones and keto esters.

Acetophenone (**K2**), the usual model substrate, and 2-acetylpyridine (**K3**) are reduced with high turnover frequencies and ees up 91% with *N*-benzylnorephedrine-type ligands such as **2e** and **2f** (Scheme 3, Table 3). The use of *N*-(cyclohexylmethyl)-norephedrine (**2h**), prepared readily from norephedrine and cyclohexylcarbaldehyde, afforded **A3** in up to 95% ee.[6d, g] Consistent with all the other ketone substrates, a decrease in reactivity was observed upon increasing the steric bulk on the arene ligand. Nonetheless, the best enantioselectivities for the reduction of **K2** and **K3** were obtained with catalytic combinations based on the *para*-cymene precursor (**6e**). With respect to acetophenone, the pyridyl ring caused a systematic decrease in enantioselectivity with corresponding differences in $\Delta(\Delta G^{\neq})_{K3/K2}$ in the range 0.1 – 0.45 kcal · mol^{-1}, as well as in the reaction rate.

Catalytic asymmetric reduction of 2-acylbenzoates (**K4**) is a process of high interest to prepare chiral phthalides (**A4**).[8] Such molecules, almost all of them having an *S* configured chiral center, feature an impressive list of applications due to their pharmacological effects and are also key intermediates for the synthesis of several alkaloids.[9] The transfer hydrogenation of 2-acylbenzoates and 3-acetylpyridine-2-carboxylate, e.g., **K4a – c**, using *in situ* combinations of $[RuCl_2(p\text{-cymene})]_2$ with either TsDPEN (**1**) or β-amino alcohols **2** as ligands, in the presence of a base promoter (6 equiv. *i*-PrOK vs. Ru), gave the expected phthalides **A4** in up to 91 – 97% ee (Scheme 4, Table 4).[6e] The synthetic efficiency of this procedure is, however, hampered by the formation of large amounts of side-products **B4**, which arise from lactonization of the hemiacetal of **K4** formed under basic conditions. This could be efficiently prevented by performing asymmetric transfer hydrogenation *in the absence of base*, under neutral conditions, with the presynthesized true catalysts [Ru(*p*-cymene)(β-amino alcohol)] (**8**) or its analogue [Ru(*p*-cymene)(TsDPEN)] (Ru-**1**). Thus, 3-alkylphthalides were recovered in virtually quantitative yields and the same enantioselectivity. As a general trend, the β-amino alcohol catalyst **8** was found to be more active, although significantly less enantioselective than the TsDPEN catalyst Ru-**1**, especially for the pyridyl derivative **K4b**.



a	R = H	R' = Et		**e**	R = 4-OMe	R' = Et
b	H	*t*-Bu		**f**	2-Cl	Et
c	2-Me	Et		**g**	4-Cl	Et
d	2-OMe	Et		**h**	4-F	Et

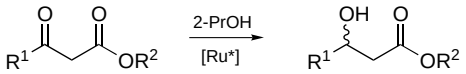
Scheme 5.

Another valuable class of carbonyl substrates is β-keto esters. Benzoylacetate esters and aryl-substituted analogues **K5** are efficiently reduced in 2-propanol using the simple catalytic combination of (1*S*,2*R*)-ephedrine (**2b**) with $[RuCl_2(p\text{-cymene})]_2$ (**6e**) to give the corresponding β-hydroxy esters **A5** in high yields and valuable enantioselectivities up to 94% ee (Scheme 5, Table 5).[6c] Introduction of a variety of *ortho* substituents on the phenyl ring systematically resulted in lower ees, probably reflecting steric factors. The reduction of

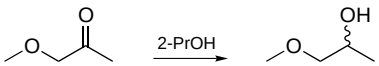
Table 6. Asymmetric transfer hydrogenation of β-keto esters and methoxyacetone (**K10**).[a]

Entry	Ketone	Ru(II)-arene	Ligand	Temperature [°C]	Time[b] [h]	Conversion[c] [%]	TOF_{50} [h^{-1}][d]	ee[e] [%, (*S*)]
1	**K1**	**6a**	**2b**	20	1	98	190	44
6	**K1**	**6a**	**2e**	20	5	>99	22	68
60	**K6**	**6a**	**2b**	50	0.5	>99	300	36
61	**K6**	**6a**	**2e**		0.5	>99	300	56
62	**K9**	**6a**	**2b**	50	1	>99	200	25
63	**K9**	**6e**	**2b**	50	5	>99	32	50
64	**K10**	**6a**	**2b**	20	0.33	>99	>600	54
65	**K10**	**6e**	**2b**	20	0.33	>99	>600	36
66	**K10**	**6a**	**2i/2o**	20	0.33	>99	>600	66
67	**K10**	**6a**	**1**	20	16	39	≪	nd

[a–e] See Table 1 except for temperatures.



K1 $R^1 = CH_3$ $R^2 = t$-Bu **A1**
K6 $R^1 = CH_3$ $R^2 = Et$ **A6**
K7 $R^1 = CH_2Cl$ $R^2 = Et$ **A7**
K8 $R^1 = CF_3$ $R^2 = Et$ **A8**
K9 $R^1 = CH_2OCH_3$ $R^2 = t$-Bu **A9**



K10 **A10**

Scheme 6.

tert-butyl esters, e.g., **K5b**, proceeded somewhat less enantioselectively but much faster than that of the ethyl equivalents. This increase in the apparent rate going from ethyl to *tert*-butyl esters was related to the bulkiness of the *tert*-butoxy group, which possibly prevents the formation of less or non reactive species (*vide infra*). Another relevant information is the kinetic resolution that was observed in the transfer hydrogenation of a 1:1 mixture of ethyl benzoylacetate (**K5a**) and of its *ortho*-methyl derivative (**K5c**). In fact, though transfer hydrogenation of **K5a** and **K5c** proceeded in individual experiments both with the same apparent turnover frequency ($TOF_{50} = 10\ h^{-1}$ at 50 °C), the reduction of **K5c** in the mixture proceeded after that of **K5a** was almost completed ($k_{\mathbf{K5a}}/k_{\mathbf{K5c}} = 40$ at 80% conversion of **K5a**; $k_{\mathbf{K5a}}/k_{\mathbf{K5c}} = 10$ at 95% conversion of **K5a**).[6c] In light of the mechanism depicted in Scheme 2, this kinetic resolution may correspond to the difference in easiness of approach of the ketone [one preferred enantioface] toward hydrido complex **9** to form the six-membered transition state **10** for hydrogen transfer.

4.2 Simple and Functionalized Aliphatic Ketones and Keto Esters

In view of the literature published over the last decade, asymmetric transfer hydrogenation of keto compounds in which the carbonyl function is surrounded by two α sp^3-carbon atoms, i.e., aliphatic ketones, has received much less attention than the previous class of substrates.[2–7] Obviously, this can be explained by the difficulty to achieve highly selective reduction of these carbonyl derivatives.

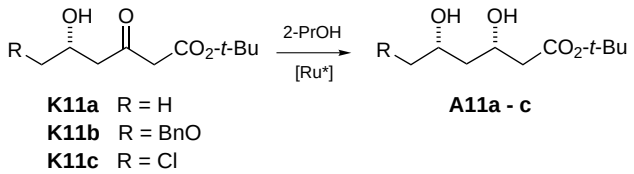
Transfer hydrogenation of simple β-keto esters such as **K1** and **K6** with catalysts generated *in situ*, in the presence of a base promoter, proceeds with high chemoselectivity but rather poor enantioselectivity. Best but still modest ees up to 67% could be reached using *N*-benzylnorephedrine-type ligands such as **2e** and **2f** (Scheme 6, Table 6). Interestingly, the *apparent* catalytic activity of a given catalyst system varies with the steric bulk of the alkoxycarbonyl group of the β-keto ester; the bulkier the COOR moiety, the higher the apparent catalyst turnover frequency. As a general trend, most significant improvements were observed with *tert*-butyl esters (*vide supra*). The increase in the enantioselectivity going from ethyl to *tert*-butyl esters, though noticeable, is much more limited.

Ethyl 4-chloroacetoacetate (**K7**) and ethyl 4,4,4-trifluoroacetoacetate (**K8**) failed to be reduced with various catalytic systems, even under drastic conditions. Cross-experiments established that those functionalized β-keto esters and not their reduction products (**A7** and **A8**) deactivate the catalytic species. On the other hand, we found that 4-methoxy-acetoacetate esters are reducible, especially the *tert*-butyl ester **K9**, but apparent reaction rates were significantly decreased compared to those for the reduction of **K1**. The presence of the 4-methoxy substituent affected also strongly the selectivity and only poor ees up to 50% were obtained for **A9**. The effect of the methoxy group was probed individually using methoxyacetone (**K10**) (Scheme 6, Table 6). Quite surprisingly, this ketone is reduced in very high

Table 7. Asymmetric transfer hydrogenation of chiral aldols **K11**.[a]

Entry	Aldol	Ru(II)-arene	Ligand	Temperature [°C]	Time[b] [h]	Conversion[c] **K11** [%]	de **A11**[c] [%]
68	(*S*)-**K11a**	**6a**	(1*R*,2*S*)-**2a**	50	0.33	99	25 *anti*
69	(*S*)-**K11a**	**6a**	(1*S*,2*R*)-**2a**	50	0.16	75	66 *syn*
70	(*S*)-**K11a**	**6a**	(1*S*,2*R*)-**2a**	20	20	85	70 *syn*
71	(*S*)-**K11a**	**6e**	(1*S*,2*R*)-**2a**	50	1	96	71 *syn*
72	(*S*)-**K11a**	**6e**	(1*S*,2*R*)-**2a**	20	30	79	79 *syn*
73	(*S*)-**K11a**	**6e**	(1*S*,2*R*)-**2f**	50	1	29	80 *syn*
74	(*S*)-**K11a**	(1*S*,2*R*)-Ru **8**[d]		20	1.5	86	75 *syn*
75	(*R*)-**K11b**	**6e**	(1*S*,2*R*)-**2a**	30	2	50	72 *syn*

[a] The reaction was carried out using 2.0 mmol of **K11** and 0.02 mmol of Ru in a 0.1 M 2-propanol solution as in Table 1.
[b] Optimized reaction time for >98% chemoselectivity to **A11**.
[c] Conversion and selectivities determined by GLC and NMR analysis.
[d] Reaction carried out with isolated catalyst under neutral conditions.



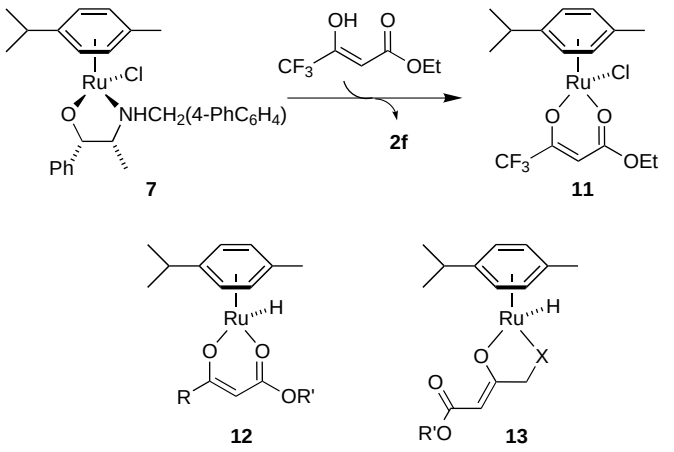
K11a R = H
K11b R = BnO
K11c R = Cl

A11a - c

Scheme 7.

reaction rates with most of [Ru^{II}(arene)(β-amino alcohol)] systems, which suggests a limited impact of the methoxy group as a coordinating functionality. Enantioselectivity of the transfer hydrogenation of **K10** follows the same trends as those observed for **K1**; the combination of the Ru^{II}(benzene) precursor **6a** with the *N*-benzylnorephedrine-type ligands **2e** and **2f** afforded the highest enantioselectivity so far (66%). Noteworthy, Ru-TsDPEN systems proved totally inefficient in reducing **K10**.

We have shown recently that asymmetric transfer hydrogenation of 2-propanol to chiral 5-hydroxy-3-oxohexanoates **K11** provides a promising catalytic alternative to traditional reduction with borane reagents to prepare *syn*-3,5-dihydroxyesters **A11** (Scheme 7, Table 7). *syn*-3,5-Dihydroxy esters **A11** are advanced building blocks for the preparation of HMG-CoA reductase inhibitors of industrial interest.[10] Preliminary investigations on model substrate (*S*)-**K11a** indicated that chirality of the catalyst are necessary to control the diastereoselectivity of the reduction. The best compromise between activity and stereoselectivity for the *syn*-diol was obtained with the **6e**/(1*S*,2*R*)-**2b** combination. High yields and promising diastereoselectivity up to 80% were obtained under smooth conditions. Usual systems based on TsDPEN (**1**) did not allow control of the stereoselectivity, irrespective of the ligand configuration. The reduction of *tert*-butyl (*R*)-6-benzyloxy-5-hydroxy-3-oxohexanoate (**K11b**), an adequately substituted molecule for further functionalization, proceeded in similar de for the *syn*-diol but was much faster and also more sensitive in terms of chemoselectivity. No reduction took place with *tert*-butyl (*R*)-6-chloro-5-hydroxy-3-oxohexanoate (**1c**), most likely because of catalyst poisoning by the chloro group as with other chloro-containing substrates.



Scheme 8.

4.3 Catalyst Deactivation Pathways

The above examples show that the efficiency of [ruthenium-{amino alcohol}] systems for transfer hydrogenation is sometimes annihilated by the presence of some functional groups in the ketone substrate. To get a better understanding of these catalyst deactivation processes, model reactions between the isolated catalytic intermediates and "reluctant" ketone substrates were undertaken. Thus, it was shown that Ru-chloro complex **7**, a non-reducing analogue of Ru-hydride **9**, reacts rapidly with β-keto ester **K8** to yield a new β-diketonato complex **11**, with concomitant release of the β-amino alcohol **2f** (Scheme 8). Consistent with the mechanism depicted in Scheme 2, which implies an active role of the

amino alcohol N-H moiety, β-diketonato complex **11** showed no activity as catalyst precursor in the transfer hydrogenation of **K1**. The 16-electron true catalyst **8** and the reducing species **9** react also rapidly with enol **K8**, with disappearance of the hydride resonances in the case of **9**; although the exact nature of the products could not be established, formation of analogous β-diketonato species was strongly suspected. On the basis of these elementary reactions and of the results of catalytic tests, we have proposed that catalyst deactivation proceeds *via* removal of the amino group from the Ru coordination sphere to form inactive species such as **12** and **13** (X = Cl) (Scheme 8).[11]

An important consequence of the deactivation processes is that the *apparent* reaction rates do not necessarily reflect the *intrinsic* activity of the catalytic species, but rather the amount of active species. Therefore, it is questionable in which terms the influence of the structure of the chiral ligand and of the ruthenium precursor on reaction rate should be discussed: enhancing the intrinsic activity of the active species and/or preventing the formation of non-productive species?

5 Conclusions

Factors that govern the activity and enantioselective outcome of asymmetric hydrogen transfer of 2-propanol to ketone substrates promoted by ruthenium catalysts based on simple ephedrine-type ligands reaction are nowadays reasonably well-understood. Thanks to a modified norephedrine ligand, the two catalytic key intermediates involved in the reduction process could be isolated, which has allowed confirmation of the mechanistic pathway so far envisioned from intuitive sense and computational studies. Concerning catalytic applications, high performances have been reached for the reduction of a variety of aryl ketone substrates while aliphatic functionalized ketones still remain more problematic. In particular, the deactivation of catalytic species by β-dicarbonyl compounds constitutes an intrinsic limitation of the Ru-catalyzed transfer hydrogenation process, which so far cannot compete, in this case, with classical hydrogenation.

Acknowledgements

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