Personal Account

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THE CHEMICAL RECORD

The Development of Phosphine-Free Tethered Ruthenium(II) Catalysts for the Asymmetric Reduction of Ketones and Imines

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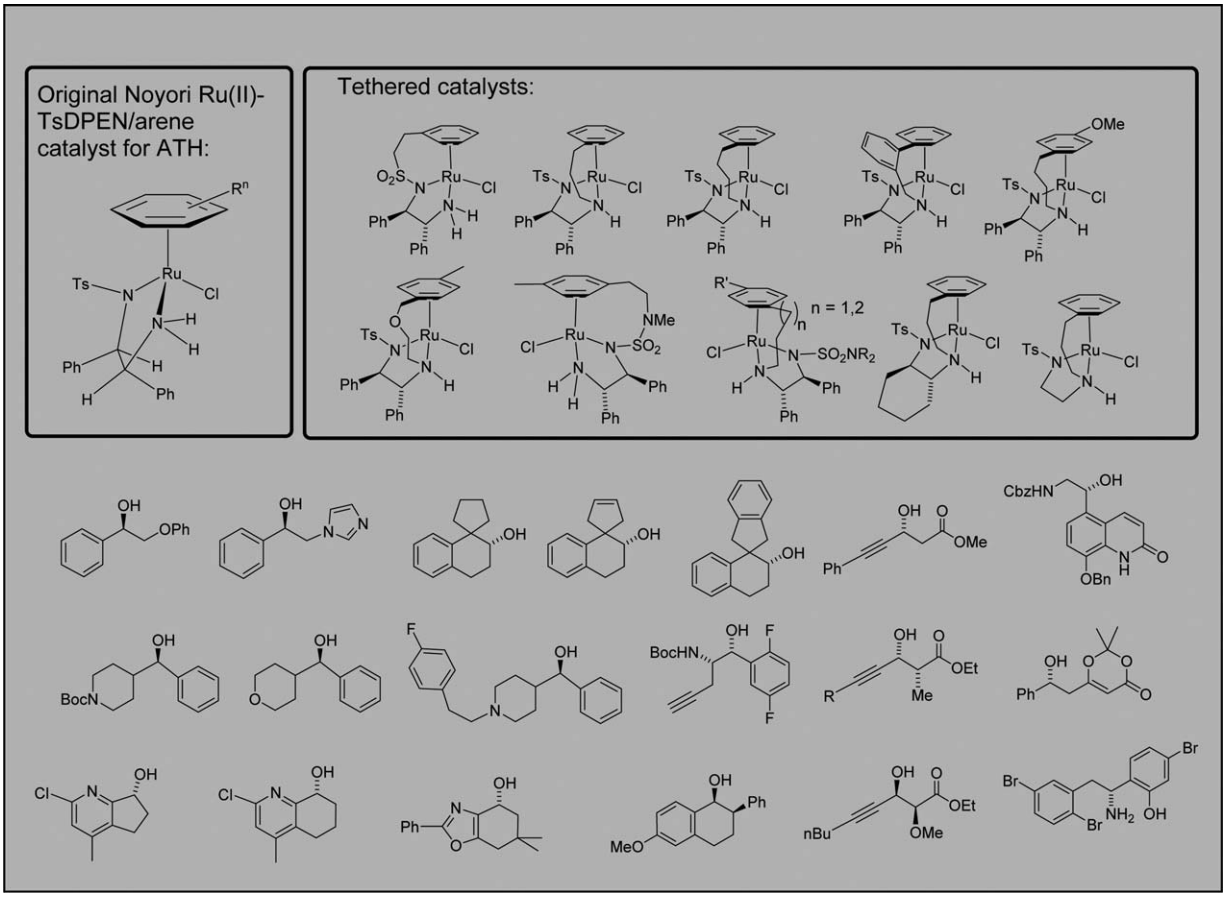

ABSTRACT: In this account, we describe the design, synthesis and applications of tethered versions of the Ru(II)/*N*-tosyl-1,2-diphenylethylene-1,2-diamine (TsDPEN) class of catalyst that are commonly used for asymmetric transfer hydrogenation and asymmetric hydrogenation of ketones and imines. The review covers key aspects of the reaction mechanisms and examples of applications, including industrial applications to pharmaceutically important target molecules. In addition, closely related catalysts based on Rh(III) and Ir(III) are also described.

Keywords: asymmetric catalysis, hydrogenation, reaction mechanisms, supported catalysts, tethered catalyst, transition metals

1. Introduction to Asymmetric Transfer Hydrogenation

The asymmetric reduction of ketones and imines is a pivotal method for the synthesis of chiral alcohols and amines, respectively. Typically, such transformations are carried out using either hydrogen gas, in the case of asymmetric hydrogenation (AH),[1] or an alternative hydrogen source, such as secondary alcohols or formates, in the case of asymmetric transfer hydrogenation (ATH).[2,3] The majority of the earliest examples of catalysts for AH reactions were based on precious-metal catalysts (usually Ru, Rh or Ir) containing enantiomerically pure phosphine ligands, with many excellent examples being reported through the 1970s and '80s. In contrast, the development of ATH catalysis evolved much more slowly at this time, with enantiomeric excesses (*ee* values) remaining low and the scope limited. However, in 1995, Noyori et al. published the first of a series of papers describing complexes of Ru(II) that were to prove transformative to the field of ATH of ketones and imines.[3b,4–7]

The innovative catalyst design by Noyori et al. required the incorporation of a bidentate ligand containing at least one NH function, as present in general structures **1** or **2** (Figure 1). The presence of the NH function critically modified the mechanism of the hydrogen-transfer reaction.[1] Recent reviews[2] give many examples that demonstrate that non-phosphine-based catalysts with no bidentate ligand containing at least one NH bond are active transfer hydrogenation catalysts.

The catalysts of general structures **1** or **2** are formed by in situ combination of either an aminoalcohol or monotosylated diamine, respectively, with the dimeric Ru(II) complex $[RuCl_2(\eta^6\text{-arene})]_2$ and base. In many cases, but not always, the complexes could be isolated and many are commercially available. The η^6-arene ring is typically benzene, *p*-cymene, 1,3,5-trimethylbenzene or hexamethylbenzene. However, it is catalyst **2**, derived from *N*-tosyl-1,2-diphenylethylene-1,2-diamine (TsDPEN) and where the arene is *p*-cymene,[8] that is the most widely applied example.[9] These complexes are commonly referred to as Noyori catalysts in the context of ATH. The complex in which the arene is 1,3,5-trimethylbenzene instead of *p*-cymene repeatedly gives slightly higher enantioselectivity in ATH and is also commercially available.

The mechanism of ketone reduction is closely related to that of some hydrogenation complexes.[1] Upon activation (usually in situ in a reaction), unsaturated complex **3** is formed by elimination of HCl.[7] This complex then abstracts two hydrogen atoms from the donor, typically isopropanol, formic acid/triethylamine (FA/TEA) mixture or sodium formate, to form hydride **4** (Figure 1). The isolation and characterisation of the 16-electron complex **3** and the hydride derivative **4**,[7] coupled to mechanistic studies[10–12] and several computational investigations,[8,13] have now provided an insight into the process of asymmetric induction. Importantly, complex **4** is formed predominantly as one diastereoisomer, rendering the Ru atom chiral and of one configuration. An outer-sphere mechanism subsequently operates, in which both hydrogen atoms are transferred to the ketone substrate by a concerted mechanism (Figure 2). In addition, a stabilising edge/face (or CH/π) electrostatic interaction favours the positioning of the substrate aryl group adjacent to the η^6-arene ring of the catalyst in the transition state. This ensures that a predictable major enantiomer of product is formed.[8,13] However, it should be noted that a minor hydride is often observed during in situ studies of the reduction reactions.[14] This may be due to the formation of a less reactive minor diastereoisomer of the hydride.

Ketones containing a combination of aromatic and aliphatic groups (which herein are termed acetophenone

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Dedicated to Professor Ryoji Noyori

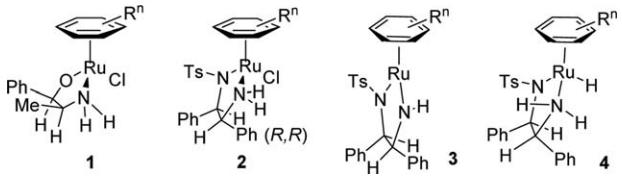


Fig. 1. Non-tethered Ru(II) complexes for ATH reactions.

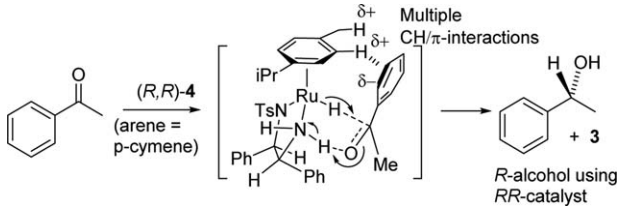


Fig. 2. Mechanism of hydride transfer from Ru/TsDPEN complex to a ketone.

derivatives) are usually reduced in high enantioselectivity, and many examples have been reported. Ketones flanked by two different aliphatic groups, on the other hand, are generally reduced in low *ee* due to a lack of purely steric-based discrimination, although some examples are described later. As a result of the unusually high dependence on electronic control, an interesting beneficial effect is the reduction, in moderate, but surprisingly good, *ee*, of a ketone containing two different aromatic rings; the more electron-rich one interacts with the η^6-arene of the catalyst (Figure 3).[3b,5]

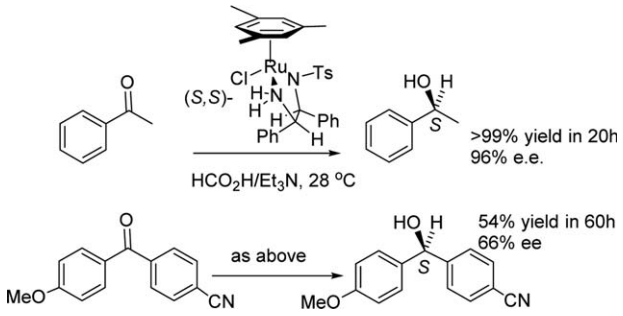


Fig. 3. Stereoelectronic effects control the sense of asymmetric reduction.

Although electrostatic interactions appear to be critical, results from molecular modelling have revealed that dispersion forces, solvent effects and steric effects also contribute to the enantioselectivity.[13e] The concerted nature of hydrogen transfer has also been the subject of closer investigation in recent years; more detailed recent modelling studies have also indicated that the hydrogen-transfer step is not fully concerted.[13g] Furthermore, the same mechanism cannot be applied to C=N reductions, which appear to operate through an open transition state.[11,12,15]

The Noyori catalysts (**2**) for ATH have now been extensively applied to synthetic applications,[9] and research efforts are ongoing, even 20 years after their initial introduction. In addition, the isoelectronic Rh(III) and Ir(III) derivatives, containing a cyclopentadiene ligand in place of the benzene ring

Hans Günter Nedden completed his PhD (Dr. rer. nat.) in chemistry at the University in Tübingen (Germany) under the supervision of Prof. U. Nagel in 1997, working on the synthesis of chiral PN ligands and use in Ni-catalysed asymmetric cross couplings. After postdoctoral studies with Prof. I. E. Markó in Belgium, working on catalysts for ethylene and propylene polymerisation, he joined ICI Synetix in 2001, later to become part of Johnson Matthey. His core interest is in catalytic research and in the synthetic development of ligands and metal compounds with catalytic activity. He supervises a team in Cambridge (UK) dedicated to bringing to market new homogenous catalysts for hydrogenation and transfer hydrogenation.

Antonio Zanotti Gerosa obtained his degree (Laurea, 1991) and PhD (Dottorato, 1994) at the University of Milano (Italy) under the supervision of Prof. S. Maiorana working on Fisher-type carbene–metal complexes. He later worked in Lausanne (Switzerland) with Prof. C. Floriani (1994–97). In 1997, he joined Chirotech (Cambridge, UK), where he became involved in the development of industrial applications of homogenous asymmetric catalysis, which included, in 1998, a secondment to the laboratory of Prof. R. Noyori in Nagoya University (Japan). In 2003, he joined Johnson Matthey, where he currently leads the Catalysis and Chiral Technologies research team in Cambridge (UK).

Martin Wills completed a BSc in 1985 at Imperial College London and a DPhil in 1988 from Oxford University, under the supervision of Prof. S. G. Davies. Following postdoctoral studies with Prof. W. Oppolzer (Geneva), he took up a lectureship at Bath University. In 1995 he moved to Warwick University. His research interests lie in asymmetric catalysis and the development of novel synthetic methodology.

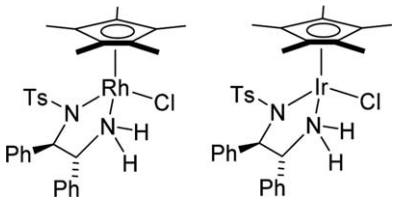


Fig. 4. Rh(III) and Ir(III) Cp* complexes of TsDPEN used in ATH.

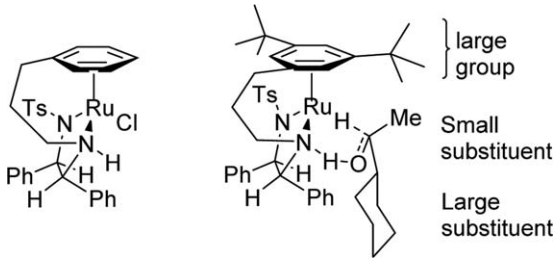


Fig. 5. Tethered catalyst design and concept for switching to steric control of reduction.

on the metal, have been introduced and widely studied (Figure 4).[16]

2. The Rationale behind the Tethered Catalyst Design

In the early 2000s, Wills et al. sought to modify the [Ru(II)(TsDPEN)(η^6-arene)] design by introducing a structural modification in the form of a tether between the η^6-arene and the diamine(or aminoalcohol) ligand. By preventing the inevitable rotation of the η^6-arene, it could be decorated with functional groups that would modify its catalytic properties. For example, the introduction of large groups selectively at positions 3 and 5 might be able to switch the selectivity from electronic to steric control by forcing the larger substrate group away from the η^6-arene (Figure 5). Another speculation was the possibility of the inclusion of directing groups, which could create hydrogen bonds to substrates, and hence, direct their selective reduction.

In 2004–2005, Wills et al. introduced a series of new catalysts, **5**–**8**, each containing the required tethering moiety (Figure 6). The Rh(III)/Cp* complex **5** was derived from an amino alcohol,[17] as was the Ru(II) complex **6**,[18] whereas **7** and **8** were prepared from DPEN.[19–21] The aminoalcohol derivatives **5** and **6** proved to be effective as catalysts, but were not very stable, whereas the diamine-derived catalysts worked more effectively. Linking through the SO_2 group (in **7**) was initially tested, since it was felt, at the time, that it was essential

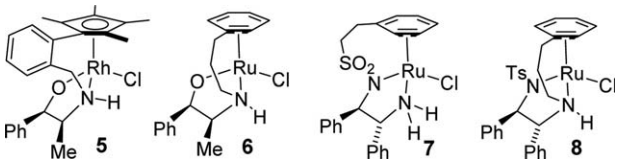


Fig. 6. Examples of early tethered catalysts.

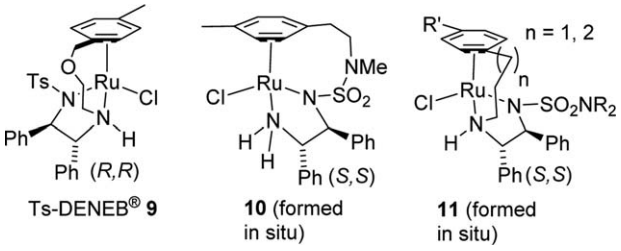


Fig. 7. Later tethered catalysts.

to have a primary amine for optimal activity,[5] and in this respect compound **7** worked effectively, but was no more active than the untethered complex. More success, and through a shorter and more efficient synthesis, was however achieved by linking the η^6-arene to the diamine through the basic N group to create catalyst **8**.[20,21] On a small scale, early samples of this complex, and related derivatives, can be purified by chromatography on silica gel, and are robust in reductions, with no exceptional requirements for oxygen exclusion. Tethered complex **8** proved to be highly active in reduction reactions under transfer hydrogenation conditions. For example, acetophenone ([S]=2M, FA/TEA) reduction using 0.5 mol% of **8** at 40 °C went to completion within 3 h (without significant erosion of *ee*), whereas the same reaction with an untethered catalyst required 24 h.[21] This allowed the catalyst loading of **8** to be reduced to 0.01 mol%, giving a product in 98% conversion in 84 h and 96% *ee*; notably, a very low background reverse reaction is observed, and hence, long reaction times do not result in reduced *ee* values. In 2006, a mg sample of catalyst **8** was supplied to Johnson Matthey. The catalysts, tested against complex poly-functionalised targets, were quickly found to outperform first-generation Noyori catalysts in terms of activity and resilience to deactivation (unpublished results).

Due to the modular nature of the synthetic approach, it is possible to change the sulfonyl group and the length and type of tether. Through these modifications, there is potential for the rapid optimization of the catalysts towards specific target molecules. Several of the modified tethered catalysts, described both by ourselves and by others, are described in more detail in the next section. The success of the tethered catalyst design led to the subsequent development of a number of other catalysts, including Ts-DENEB® **9** and the Mohar catalysts **10** and **11** (several structural variants; Figure 7).

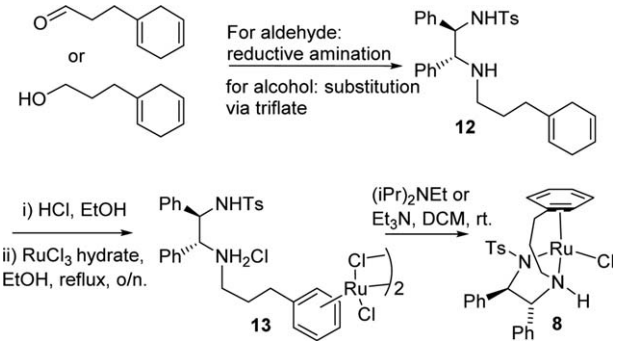


Fig. 8. Synthetic approaches to tethered Ru(II) catalysts.

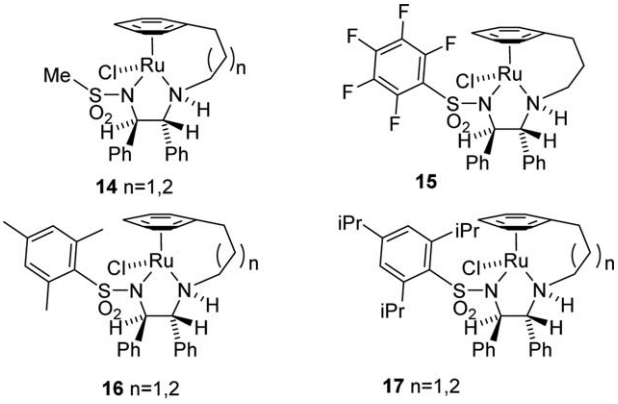


Fig. 9. New tethered Ru(II) catalysts for ATH.

3. Synthetic Approaches to Tethered Catalysts

Synthetic approaches to the tethered catalysts differ in the way the precursor containing the cyclohexadienyl linked to TsDPEN (**12**) is produced. Compound **12** is reacted as a hydrochloride salt with $RuCl_3$ to form the $[RuCl_2(arene)]_2$ dimer **13**. The treatment of dimer **13** with a mild base removes HCl from the TsDPEN moiety, allowing coordination of the diamine followed by removal of a further mole of HCl to form **7** (Figure 8).[20,21] Precursor **12** was initially synthesized using reductive amination between cyclohexadienyl–alkylcarbaldehyde and TsDPEN. Unfortunately, the formation of an aminal impurity required chromatographic purification of **12**. As the synthesis of **12** was developed at Johnson Matthey, monoalkylation of the TsDPEN moiety by an sulfonate activated cyclohexadienyl-alkanol was demonstrated to give better yields of **12** with a purity that could be used in downstream chemistry.[22] As a further modification to the initial synthesis using Birch reduction to yield the cyclohexadienylalkanols, a Diels–Alder reaction can be used to create the precursor, notably for *para*-substituted η^6-arenes.[23,24]

The route through alkylation of monosulfonated diamines to yield ligands of type **12** has been applied to several

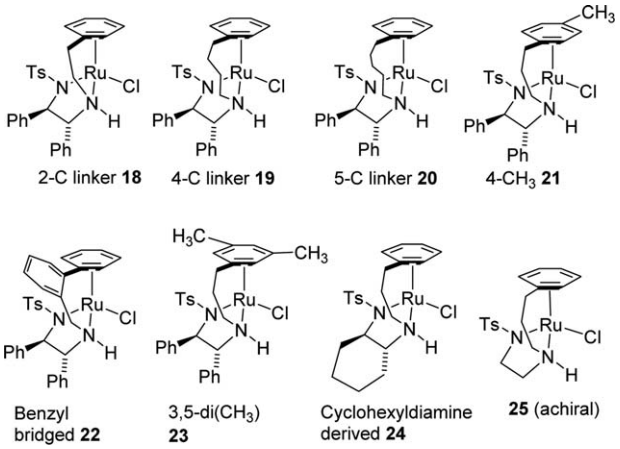


Fig. 10. Tethered catalysts formed using the approach outlined in Figure 8.

target structures, demonstrating the scope of this improvement.[25] Firstly, Johnson Matthey have used this approach for the commercial synthesis of kg quantities of **8** and derivatives. We have investigated the synthesis of a range of complexes **14**–**17** with smaller (methanesulfonyl (Ms)), larger (2,4,6-trimethylphenylsulfonyl (Mts) and 2,4,6-triisopropylphenylsulfonyl (Tris)) and electron-poor (pentafluorophenyl)sulfonyl groups (Figure 9).[25] The synthetic approach based on alkylation of the sulfonylated diamine ligands with a cyclohexadienyl moiety has found broad application (see subsequent sections on ether- and amine-tethered catalysts).

We have also described alkylene-tethered catalysts containing tethers of different lengths and with methyl groups on the η^6-arene ring: **18**–**25** (Figure 10).[26–28] Achiral versions of the tethered catalysts (e.g., **25**) have also been prepared and used in synthetic applications.[22] Other complexes, which have been prepared through the 1,4-cyclohexadiene route, include the 1,2-cyclohexyldiamine-based complex **24** and benzyl-bridged **22**;[27] both are competent catalysts.

Although the stable, isolated monomeric complexes are normally used in catalytic applications, the chloride-bridged ruthenium dimer can also be used directly in reactions in FA/TEA because it is converted into the monomer in situ.[20]

3.1. Catalysts with an Ether Tether

The idea of replacing the alkylene tethering chain by one containing heteroatoms was independently put into practice by two groups, each including members from academia and industry (Figure 11). A group led by Ikariya and championed by Takasago, prepared what has now been commercialized by Takasago as Ts-DENEB®.[24] The approach by Ikariya et al. employed a Williamson ether synthesis between metal precursor **26** and *N*′-hydroxyethyl-functionalized TsDPEN **27** to make the final monomeric complexes. The alternative route by Wills et al., and championed by Dr. Reddys, UK, first

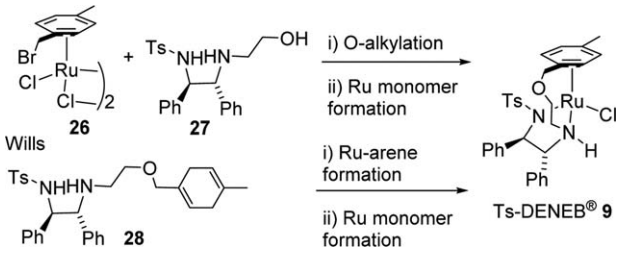


Fig. 11. Synthetic approaches to catalysts with an oxygen-containing tether.

assembled the TsDPEN ligand bearing the tethered cyclohexadienyl moiety **28**, followed by coordination to Ru and base-induced formation of the monomeric complex.[29] Although Wills et al. still used the reductive amination reaction for the ligand synthesis, synthesis of this ligand by direct alkylation has also been demonstrated.[24]

In common with the original tethered catalyst **8**, its close derivatives are stable crystalline solids.

3.2. Tethered Catalysts with Sulfamoylamino (NSO_2N) Groups

In very recent studies, Mohar et al. reported tethered Ru(II) catalysts **10** and **11**, containing a sulfamoylamino (NSO_2N) unit in place of the more widely used sulfonamide unit (Figure 12). In the case of **10**, the tether was attached through the NSO_2N group,[30,31] and in the later version **11** R_2NSO_2 replaced the tosyl group in **8**.[32] For the synthesis of **10**, firstly, the imidazole-containing starting material **29** was prepared. This was activated by N-methylation and then subsequent substitution with DPEN led to formation of ligand precursor **30**. Protonation and complexation with $RuCl_3$ gave dimer **31**, which could be readily isolated and used directly in reduction reactions in FA/TEA mixture (presumably via the formation of **10**). Attempts to isolate **10** were unsuccessful, however, and the monomeric active species was formed in situ during applications. Through this approach, several derivatives of **10** were prepared with varying tether lengths and arene substitution. However, attempts to form **10** through an arene-exchange strategy were also unsuccessful.[31]

For complexes **11**, a modification of the established protocol through alkylation of a triflate derivative was employed, using R_2NSO_2DPEN in the displacement step, followed by complexation with $RuCl_3$ to give dimer **32**. The dimer was again used directly in catalytic experiments, since monomer **11** could not be isolated. All ligands containing DPEN attached to a cyclohexadiene group, prepared by us and Mohar et al., readily formed the $[RuCl_2(arene)]_2$ dimer complexes;[25,32] however, the latter had to use the dimer as a pre-catalyst for catalytic experiments.

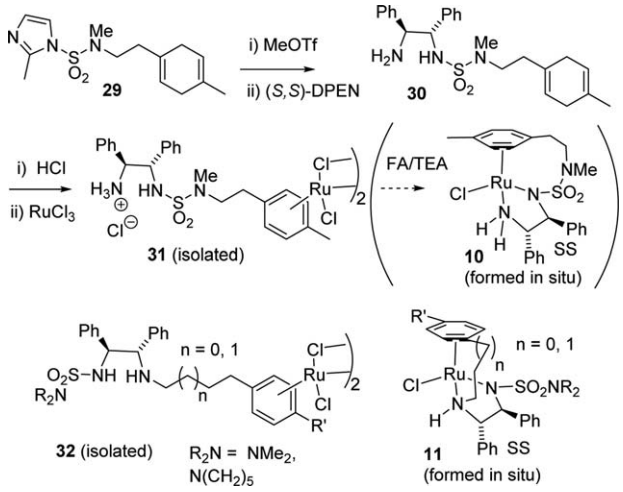


Fig. 12. Synthesis of tethered complexes **10** and **11**.

3.3. η^6-Arene Ligand Exchange Route

In the case of 1,4-cyclohexadiene precursors that are electron-rich or highly functionalised, attempts at complexation result in prior aromatisation of the diene before it has formed a complex. This was reflected in a paper by Bennett et al., in which it was reported that the Birch reduction of hexamethylbenzene could not be readily achieved.[33]

A potential solution to this problem, and attractive in its elegance, is the direct formation of a tethered complex through intramolecular η^6-arene exchange. Unfortunately, all of our attempts to achieve this reaction in an intramolecular manner from a preformed complex failed to give more than 15% conversion of highly impure material. Whilst there are many examples of cyclisations through arene substitution of Ru–P-type ligands,[34] there are only two precedents for cyclisations of Ru–N-type complexes, and both of very simple structures.[35,36] However, a solution to this problem was recently found by rapid heating of the reaction of a precursor ligand, such as **33**, in the absence of base, or in the presence of a mild base (Figure 13).[37] Through this route, complexes **34** and **35** were prepared and isolated. Both new catalysts, and a series of further derivatives, all proved to be competent catalysts in ATH reactions.

The electron-rich derivatives **34** and **35** are stable crystalline solids that can be purified by flash chromatography and even analysed by open TLC analysis.

4. Application to Reductions of Acetophenone Derivatives

One of the striking (and unexpected) features of the tethered catalyst **8**, and of many of its derivatives, is its high activity relative to the untethered (Figure 14).[20,21] Increased activities

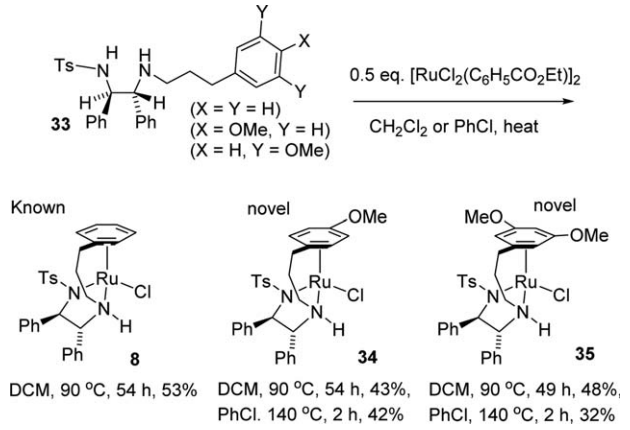


Fig. 13. Arene-exchange strategy to tethered complexes.

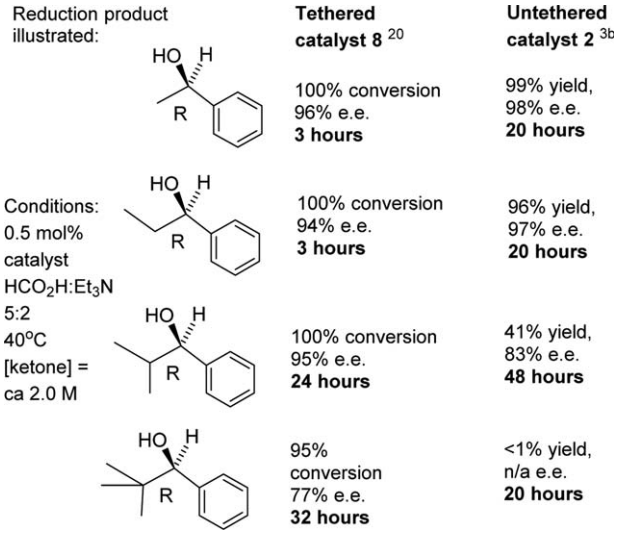


Fig. 14. Comparison of reaction times for increasingly hindered acetophenone derivatives.

have been observed across a range of substrates and in one striking result the very hindered substrate tBuCOPh was reduced in 95% conversion after 32 h and in 77% *ee* (0.5 mol% catalyst at 40 °C, FA/TEA).[20] In contrast, this substrate is reported to be resistant to reduction by the untethered catalysts (<1% reduction reported under the same conditions).[3b]

In further studies, it was found that additional quantities of ketone substrate and FA could be added to the reaction medium and each portion was sequentially reduced in good *ee*, indicating that the catalyst remained active and stable for extended periods.[20] The untethered catalyst is prone to degradation (with the speculation of nanoparticle formation),[38] and also to dissociation of the ligand under low-pH conditions;[39] however, the tethered catalyst appears to benefit from significantly improved stability, which may account for many of the improved results observed.[40]

A study of the substrate scope and reactivity of a small range of tethered catalyst derivatives indicated that those with three or four carbon atoms in the tether (notably, **8** and **19**) were the most effective, whereas the shorter or longer tether catalysts were not as active.[26,28] Tethered catalysts, including the original 3-C-tethered **8**, and the recently disclosed derivatives, have been applied to the ATH of a range of acetophenone derivatives. Such substrates are generally reduced in high enantioselectivity and some representative data, for the FA/TEA system at T=28–60 °C, are listed in Table 1. The absolute configurations of the products match those predicted using the general model for acetophenone reduction and depend on which catalyst enantiomer was used. The published data offer the opportunity to compare the performance of various tethered catalysts with the first-generation Noyori catalysts (some are reported in Table 1). Although the catalysts show broad acceptance of a variety of acetophenone derivatives, as is often the case in catalysis, no single catalyst excels on all transformations and an appropriate matching of the substrate with the catalysts must be sought. In addition, it should be kept in mind that, in case of a requirement for a preparative synthesis, most reactions can be further optimized by working on the choice of solvents, temperature and hydrogen donor. The ATH of more specialized substrates is described in later sections and the list in Table 1 is designed to be illustrative rather than exhaustive; further examples are given in the references. Although not included in Table 1, the 4-C-tethered catalyst **19** is marginally more active in ATH than 3-C **8**, but gives products in similar *ee*.[26] The electron-rich complex containing a 3,5-dimethoxy substitution pattern (i.e., **35**) is generally less enantioselective for aromatic ketones than the 4-methoxy catalyst **34**.

In an effort to further explore the structural and electronic space of these catalysts, variation of the sulfonamide group was investigated.[25] All of these catalysts, with tethered lengths of three and four carbon atoms, worked efficiently, although the advantages of varying sulfonyl group substitution and length of the tether becomes particularly evident on certain substrates (see the next section). As an example, the full reduction of α-hydroxyacetophenone was achieved in 5 h using just 0.01 mol% of the Tris catalyst **17** (n=1) in >95% *ee* (Figure 15).

On some substrates (e.g., acetophenone, tetralone), variation of the sulfonyl group and the length of the tether leads to modest changes in reactivity and enantioselectivity.[25] On the contrary, there are more difficult substrates, such as 3,5-bis(trifluoromethyl)acetophenone, for which a remarkable swing in enantioselectivity is observed from the Ts- and Ms-substituted catalysts (Figure 16 features additional examples not in Table 1), for example, (*R*,*R*)−3-C Ts **8** (56% *ee* (*R*)) to catalysts with larger MTs and Tris substituents, such as (*R*,*R*)−4-C-Tris **17** (n=2) (81% *ee* (*S*)).

Table 1. Comparison of reductions of a range of acetophenone derivatives using tethered catalysts with HCO_2H/Et_3N.[a]

Ketone	Cat. **2** (*p*-cymene)[3b,5]	Tethered cat. **8**[20,21,26]	Tethered *p*-OMe cat. **34**[37]	DENEB® **9**[b][24,29]	Sulfamoyl cat. **10**[c,d][30,31]	Sulfamoyl cat. **11**[c][32]	3-C Ms cat. **14** (n=1)[25]	3-C Tris cat. **17** (n=1)[25]	4-C Ts cat. **19**[25]
	>99% yield 98% *ee* (0.5% cat. 28°C, 20h)	100% conv. 96% *ee* (0.5% cat. 40°C 3h)	100conv. 96% *ee* (0.1% cat. 60°C 2h)	>99%yield 97% *ee* (0.1% cat. 60°C 3h)	>99%conv. 94% *ee* (0.5% cat. 60°C 2h)	100% conv. 96.2% *ee* (0.1% cat. 60°C 8.5h)	100% conv. 96% *ee* (0.2% cat. 40°C 5h)	85%conv. 96% *ee* (0.2% cat. 40°C 24h)	100% conv. 96% *ee* (0.2% cat. 40°C 5h)
	>99%yield 97% *ee* (0,5% cat. 28°C 60h)	100% conv. 94% *ee* (0.5% cat. 40°C 1.6h)	–	–	95%conv. 93% *ee* (1% cat. 40°C 20h)	–	100% conv. 95% *ee* (0.2% cat. 40°C 24h)	91%conv. 92% *ee* (0.2% cat. 60°C 24h)	96%conv. 95% *ee* (0.2% cat. 40°C 7h)
	>99%yield 98% *ee* (0.5% cat. 28°C 60h)	100% conv. 94% *ee* (0.02% cat. 40°C 20h)	–	–	100% conv. 98% *ee* (0.5% cat. 60°C 2h)	–			
	–	100% conv. 68% *ee* (0.5% cat. 40°C 3h)	100%conv. 96% *ee* (0.1% cat. 60°C 1.5h)	>99% yield 93% *ee* (0.1% cat. 60°C 24h)	100% conv. 93% *ee* (1% cat. 40°C 15h)	–	91%conv. 60% *ee* (0.2% cat. 40°C 24h)	94%conv. 22% *ee* (0.2% 40°C 24h)	96%conv. 95% *ee* (0.2% 40°C 5h)
	>99%yield 98% *ee* (0.5% cat. 28°C 36h)	100% conv. 98% *ee* (0.5% cat. 40°C 3h)	100%conv. 98% *ee* (0.1% cat. 60°C 2h)	>99%yield 98% *ee* (0.1% cat. 60°C 5h)	–	100% conv. 98.3% *ee* (0.1% cat. 40°C 15h)			
	–	100% conv. 97% *ee* (0.5% cat. 40°C 3h)	–	–	–	100%conv. 96.8% *ee* 0.1% cat. 40°C 15h			
	–	100% conv. 96% *ee* (0.5% cat. 40°C 3h)	>99% conv. 97% *ee* (0.1% cat. 60°C 1h)	>99%yield 97% *ee* (0.1% cat. 60°C 5h)	–	–	72%conv. >95% *ee* (0.2% cat. 40°C 3h)	100% conv. 93% *ee* (0.2% cat. 40°C 1h)	96%conv. 96% *ee* (0.2% cat. 40°C 1h)
	–	–	100% conv. 98% *ee* (0.1% cat. 60°C 2h)	98%yield 96% *ee* (0.1% cat. 60°C 5h)	–	–	100% conv. >95% *ee* (0.2% cat. 40°C 6h)	99%conv. 96% *ee* (0.2% cat. 40°C 5h)	100% conv. >95% *ee* (0.2% cat. 40°C 5h)
	–	–	100% conv. 98% *ee* (0.1% cat. 60°C 1h)	>99%yield 95% *ee* (0.1% cat. 60°C 5h)	100% conv. 96% *ee* (0.5% cat. 60°C 1h)	–			
	93%yield 83% *ee* (0.5% cat. 28°C	–	100% conv. 99% *ee* (0.1% cat. 60°C	94%yield 84% *ee* (0.1% 60°C	100%yield 99.9% *ee* (0.5% cat. 40°C,	–			

Table 1. (*Continued*)

Ketone	Cat. **2** (*p*-cymene)[3b,5]	Tethered cat. **8**[20,21,26]	Tethered *p*-OMe cat. **34**[37]	DENEB® **9**[b][24,29]	Sulfamoyl cat. **10**[c,d][30,31]	Sulfamoyl cat. **11**[c][32]	3-C Ms cat. **14** (n=1)[25]	3-C Tris cat. **17** (n=1)[25]	4-C Ts cat. **19**[25]
	36h) >99% yield 96% *ee* (0.5% cat. 28°C 22h)	–	3h) 100% conv. 94% *ee* (0.1% cat. 60°C 2h)	24h) [e] –	5h) [f] 100% conv. 96% *ee* (0.5% cat. 60°C 2h)	–			
		–	100% conv. 99% *ee* (0.1% cat. 60°C 3h)	>99%yield >99% *ee* (0.1% cat. 60°C 5h)	–	100%conv. 99.9% *ee* (0.1% cat. 60°C 3h)			
	>99% yield 99% *ee* (0.5% cat. 28°C 48h)	–	99%conv. 99% *ee* (0.1% cat. 60°C 5h)	85%yield 98% *ee* (0.1% cat. 60°C 24h) [g]	100% conv. 99.9% *ee* (0.5% cat. 40°C 20h)	100%conv. 99.4% *ee* (0.1% cat. 60°C 2h)	95%conv. 98% *ee* (0.2% cat. 40°C 24h)	82%conv. 99% *ee* (0.2% cat. 40°C 24h)	100% conv. 95% *ee* (0.2% cat. 40°C 5h)
	–	–	100% conv. 99% *ee* (0.1% cat. 60°C 3h)	–	100%conv. 97% *ee* (0.5% cat. 40°C 7h)	100conv. 94.5% *ee* (0.1% cat. 60°C 2h)			

[a] Typical conditions. unless otherwise listed: FA/TEA, 40°C, [S]=ca. 2M. [b] DENEB results from Ikariya et al. For results on similar substrates at 30°C and 0.5 mol% catalyst loading, see the paper by Wills et al. [c] Supplied to the reaction in the form of the dimer and presumed to be converted into monomer in situ. [d] Results are usually for the catalyst in which a 2C chain is present on the tether and a 4-methyl is on the η^6-arene ring, but in some cases are for the best-performing catalyst. [e] 97% *ee* with MsDENEB®. [f] 0.1% catalyst requires 22h. [g] On cycloheptyl analogue, using MsDENEB®

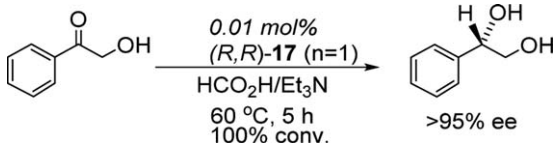


Fig. 15. ATH of α-hydroxyacetophenone using **17** (n=1).

Wills et al. found that Ts-DENEB® **9** was unable to reduce 2-acetylpyridine, whereas 3-C **8** gave a product with 94% *ee* (100% conv.) at 0.5 mol% loading (40 °C, 30 min) and 91% *ee* (100% conv.) at just 0.02 mol% loading (40 °C, 20 h).[29] Further tests revealed that 2-acetylpyridine inhibited Ts-DENEB® **9**, possibly due to a hydrogen-bond interaction of the protonated substrate with the catalyst.

The reduction of benzil (PhCOCOPh) to chiral (*S*,*S*)-hydrobenzoin is well established as an easy transformation.[41] This reduction was chosen to compare Ts-DENEB® with C4-tethered **19**. The reduction at 60 °C using just 0.001 mol% catalyst gave (*S*,*S*)-hydrobenzoin with >99% *ee* and a DL/*meso* ratio of 97.2:2.8. A difference in the rate of the reaction was observed without a report of the purity of the employed catalysts.

The *N*,*N*-dialkylsulfamoylamino-DPEN-derived class of catalysts introduced by Mohar et al., namely, **10** and **11**,[30,32] also perform very efficiently in ATH and appear to be particularly suited to the reduction of 1-naphthyl ketones.[30] Although not described in detail herein, a very comprehensive survey of the reductions of this class of substrate was carried out, with excellent results. One interesting result, however, was that 1′-acetonaphthone containing a 2′-OMe group was inert to reduction. Mohar et al. also commented on the observation of higher conversions using the tethered catalysts compared with the corresponding untethered sulfamoylamino-based ones, presumed to be a consequence of their significantly higher stability. These catalysts also worked well in the reduction of diketones to form diols (not illustrated), and the catalysts of class **11** gave some of the highest *ee* values recorded for reductions of benzo-fused ketone substrates (representative examples in Table 1).[32]

Notable within the examples in Table 1 are acetophenones containing a potentially sensitive α-chloro substituent, which provide access to valuable synthetic intermediates. In addition, several ketones containing α-substituents and heterocyclic groups have been demonstrated to be compatible with catalyst **8** (Figure 17).[26]

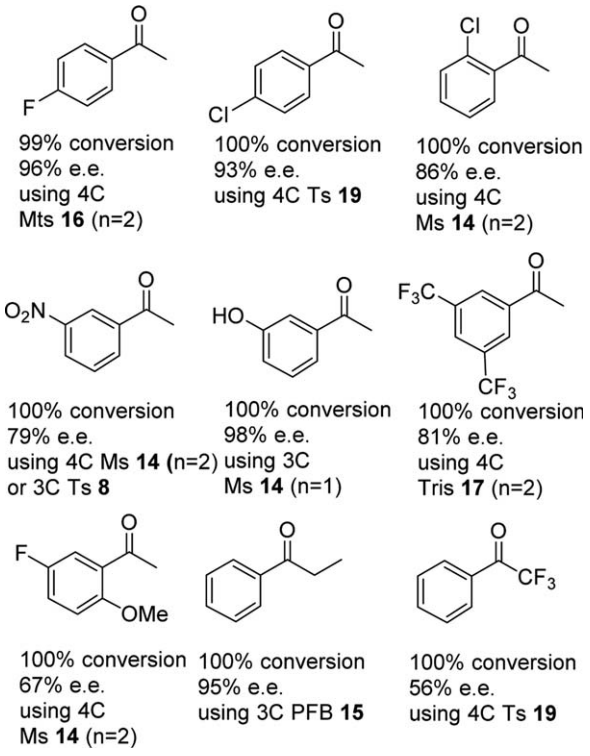


Fig. 16. Best catalyst for the reduction of specific ketones from the series with varied sulfonyl groups and tether lengths.[25]

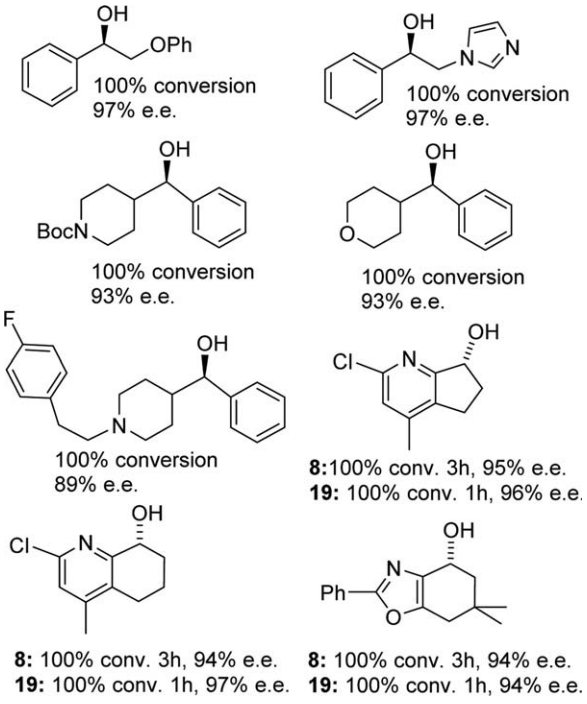


Fig. 17. ATH products from α-substituted acetophenones and heterocyclic ketones reduced by catalyst **8** and **19** (40°C, FA/TEA, 0.5 mol% catalyst).

The recently disclosed electron-rich complex **34** proved to be very effective in the reduction of ketones; it is noteworthy that due to their high stability, the reactions could be run at 60 °C using just 0.1 mol% of catalyst, but without any significant drop in *ee*. Substrates containing *ortho*-methoxy groups were exceptionally compatible, giving products of up to 96% *ee*, compared with about 68% *ee* observed using **7**. Figure 18 illustrates the reductions of a series of *ortho*-substituted ketones where the methoxy-substituted catalyst gives an improved outcome.[42]

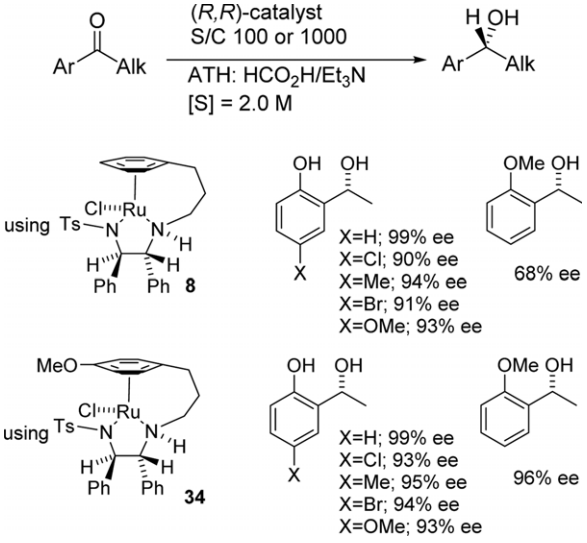


Fig. 18. Comparison between catalysts **8** and **34** in the reduction of *ortho*-methoxyacetophenone.

4.1. ATH in Water

Many examples have been published on the use of Ru(II)/TsDPEN catalysts under aqueous conditions (with sodium formate).[43] Tethered catalysts, likewise, are efficient under these conditions. Figure 19 summarises a series of reductions using the electron-rich catalyst.[42]

Electron-rich ketones, for example, containing alkoxy and amine substituents, are known to be challenging substrates for reduction.[44] However, in recent work, we were able to establish that tethered catalysts could reduce these efficiently under aqueous conditions (Figure 20).[42] The untethered catalyst is less active.

4.2. Alternative Hydrogen Donors

Williams et al, while examining the potential for use of an alternative hydride source in transfer hydrogenation, stressed

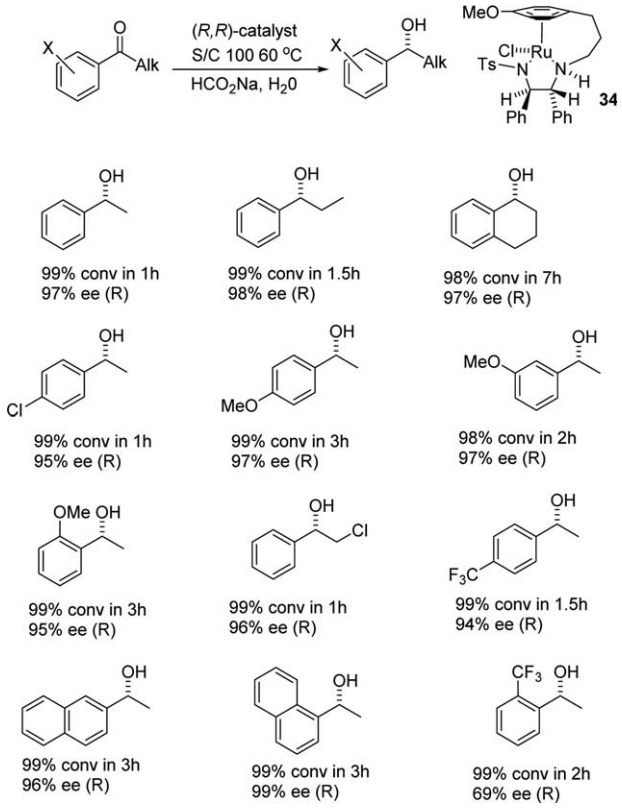


Fig. 19. Ketone reduction in water using catalyst **34**.

the superior activity of tethered catalyst **8** in the reduction of acetophenone derivatives in the presence of *cis*-1,4-butenediol (Figure 21).[45] The diol provides an efficient source of hydrogen through isomerisation first to 4-hydroxybutanal, lactol formation, and its subsequent irreversible oxidation to the lactone. In particular, the higher activity of the tethered catalyst permitted the reaction to be run at a lower temperature than would otherwise be required.

5. Application to Other Substrates: Beyond Acetophenone Derivatives

5.1. Reduction of Dissymmetric Alkyl Ketones

The striking lack of applications of Ru-TsDPEN/arene catalysts to the reduction of dissymmetric alkyl ketones indicates that they are poor catalysts for this class of substrate.[46] Tethered catalyst **8** does, however, reduce acetylcyclohexane in a valuable 69% *ee*.[26] We found that the addition of a 4-Me group to the η^6-arene had little effect on the selectivity or activity, whereas, in contrast, 3,5-dimethyl-substituted catalyst **23** gave much better selectivity with an *ee* of 89% for this substrate (Figure 22).[26] The fact that for this reduction the catalyst derived from the (*R*,*R*)-DPEN ligand gives the *S*-

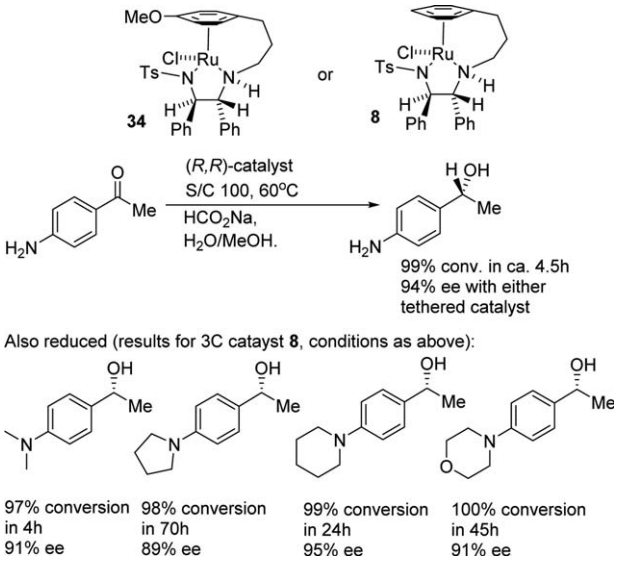


Fig. 20. ATH of electron-rich acetophenones with tethered catalysts.

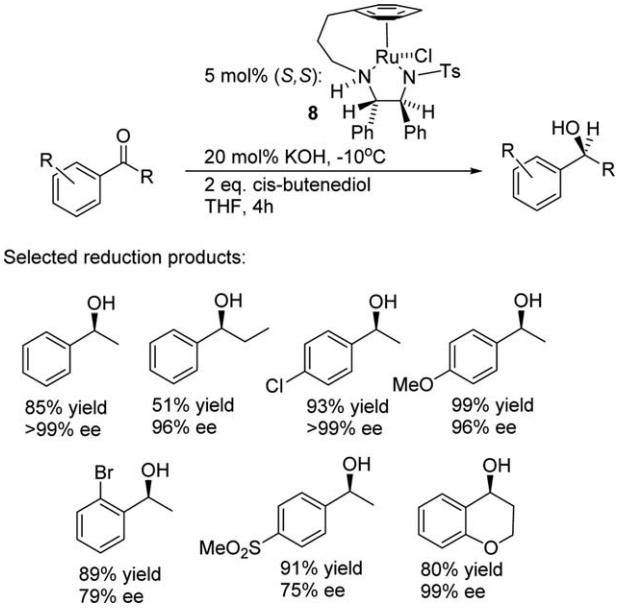


Fig. 21. ATH using catalyst **8** with *cis*−1,4-butenediol as a hydrogen source.

configuration product (vs. the *R*-configuration alcohol from acetophenone) indicates that the reduction is likely to be directed by steric effects rather than electronic ones, that is, the larger methyl groups force the larger group in the substrate into the more distal position (Figure 22). A similar trend is seen using the 4-OMe complex **34** (gives product in 37% *ee*) versus the 3,5-dimethoxy complex **35**, which gives the product in 73% *ee*.[37] Ts-DENEB® **9** gave essentially no asymmetric induction in the reduction of this acetylcyclohexane.[29]

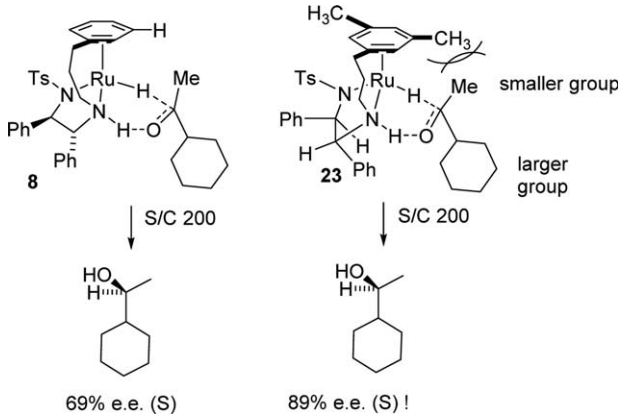


Fig. 22. ATH of acetylcyclohexane.

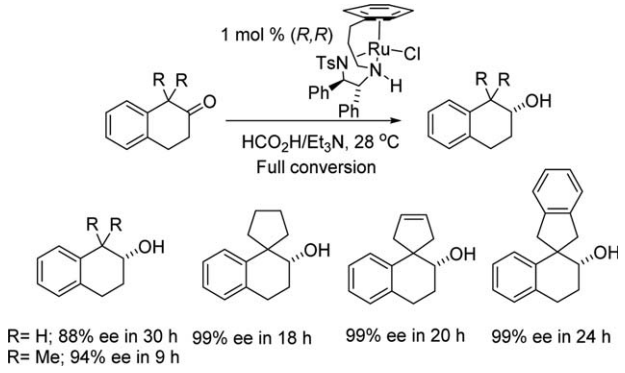


Fig. 23. ATH of hindered β-tetralone derivatives.

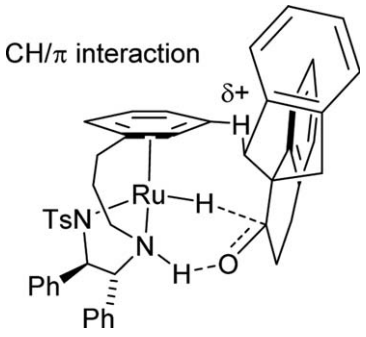


Fig. 24. Control of enantioselectivity in β-tetralone reduction.

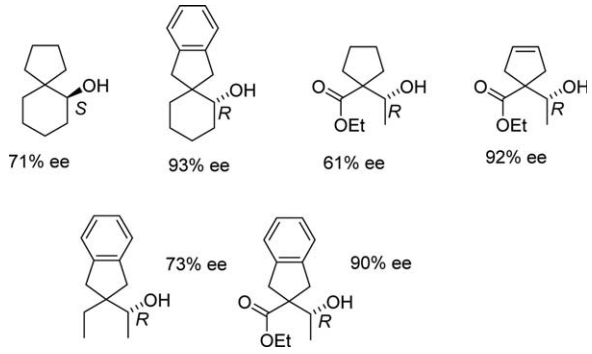


Fig. 25. Products of ATH of ketones adjacent to quaternary centres using catalyst **8**.

Due to the high reactivity of tethered catalysts, hindered ketones can be reduced in surprisingly high enantioselectivities, including several examples with adjacent quaternary centres, with the suggestion of a second directing effect operating.[47] This study arose from an unexpected observation that the 1,1-dimethyl derivative of β-tetralone was reduced in higher *ee* than the unsubstituted derivative; this was surprising because previous results suggested that the introduction of additional hindrance would reduce the selectivity.[20] The reduction of an extended series of β-tetralones revealed an increase in *ee* as the substituents became larger (Figure 23).

Our speculation for the control of this reaction was that an additional controlling interaction was operating (Figure 24) with further contributions from both electrostatic and dispersion forces contributing to the observed selectivity.

As evidence of this hypothesis, the new directing effect could be used by itself to direct further reactions. Examples are shown in Figure 25.

In all of the above examples, the presence of substituents α to the carbonyl group to be reduced appears to play a fundamental role in assuring good enantioselectivity. Shipman et al. used tethered catalyst **8** (as well as an untethered catalyst) in the synthesis of a functionalised tetrahydroxanthone related to kigamicin A (Figure 26),[48] but the product *ee* was modest, although superior to that obtained with the first-generation untethered catalyst.

5.2. Reduction of Alkynyl Ketones

In agreement with the observations made with non-tethered catalysts,[6q–u] acetylenic ketones are excellent substrates, and have been studied and employed extensively in many reported applications. The tethered catalysts have proved valuable and have been used in processes for the synthesis of propargylic alcohols in excellent *ee*.[49,50] They have also proven to be active without any need for pre-formation of the 16-electron species, which had been required in previous applications of first-generation catalysts.[6q–u] In our own work, we found that β-, γ- and δ-keto esters were excellent substrates, with the absolute stereochemical control appearing to follow the general rule that the triple bond occupies the position of the aromatic ring in reductions (Figure 27).

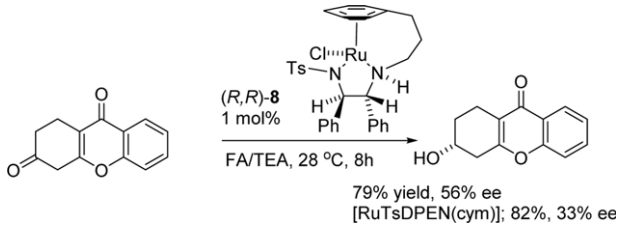


Fig. 26. A key ATH step in the synthesis of kigamycin A.

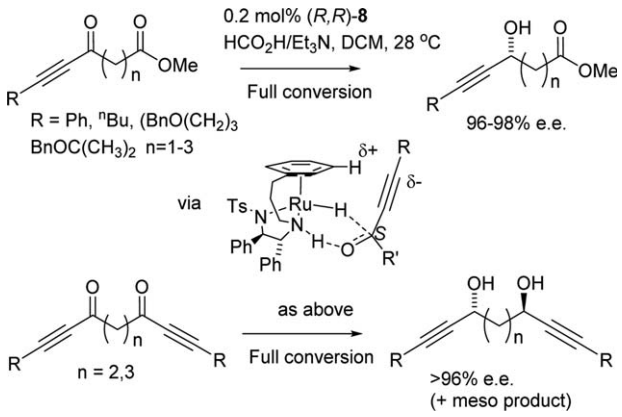


Fig. 27. ATH of acetylenic β-, γ- and δ-keto esters and diketones.

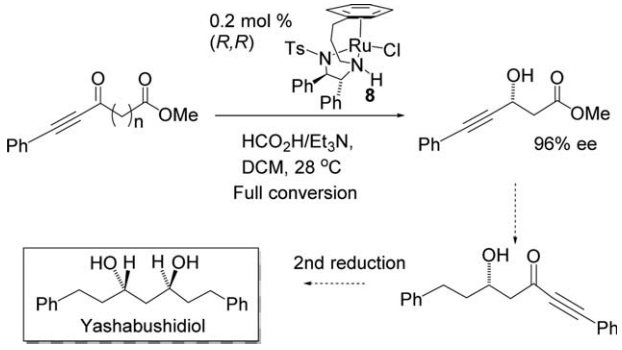
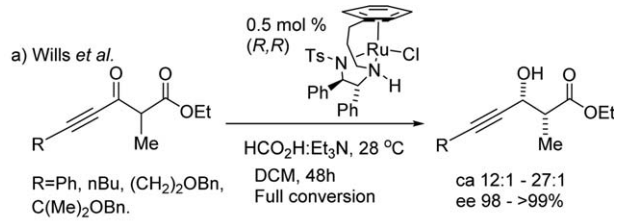


Fig. 28. Application of ATH to the synthesis of yashabushidiol.



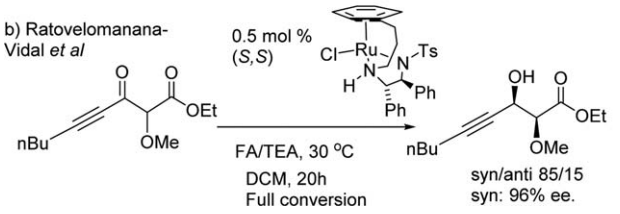


Fig. 29. ATH coupled to DKR.

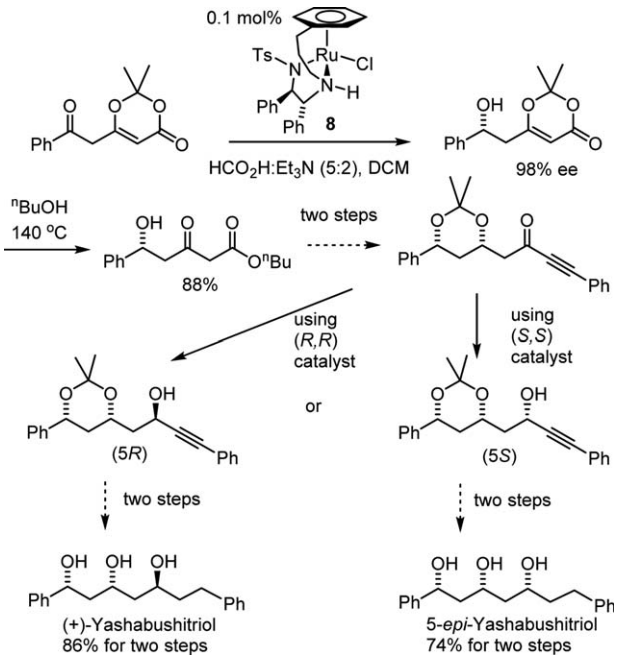


Fig. 30. ATH of 2,2-dimethyl-6-(2-oxoalkyl/oxoaryl)−1,3-dioxin-4-ones.

In one application, the alkyne directing effect could be used twice in a sequence to deliver a diol product, following alkyne reduction (Figure 28).[49a]

Dynamic kinetic resolution (DKR) with tethered catalysts was also achieved (Figure 29a).[49a] Ratovelomanana-Vidal et al. (with Roche) reported an analogous reduction of the α-methoxy series of substrates.[51] In several cases, it was essential to use the tethered catalysts because the non-tethered ones failed to give acceptable results (Figure 29b).

An interesting class of substrate for ATH are 2,2-dimethyl-6-(2-oxoalkyl/oxoaryl)−1,3-dioxin-4-ones because their asymmetric reduction provides the basis for the synthesis of 5-hydroxy-3-ketoesters.[49b] Asymmetric reduction leads to products with *ee* values of up to 98% and the subsequently deprotected ketone can be further reduced in a (known) diastereoselective process to either the *cis* or *anti* products. This sequence has been applied to the synthesis of (+)-yashabushitriol and one of its diastereoisomers; the final reduction selectivity is controlled by the catalyst and directed by the alkyne (Figure 30).

Dialkynyl ketones can also be reduced in high *ee*, although there is a requirement for the use of a large amount of catalyst

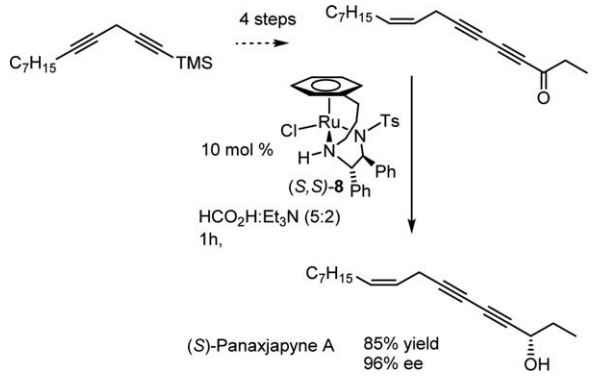


Fig. 31. ATH of dialkynyl ketones.

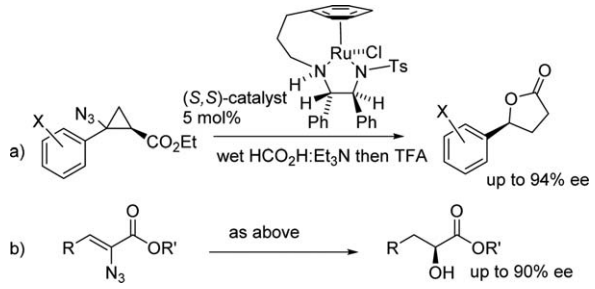


Fig. 32. Azide reduction coupled to ketone reduction.

to ensure rapid reduction before side reactions can take place (Figure 31).[50]

5.3. Other Transformations

A clever azide reduction/imine hydrolysis linked to ketone reduction by tethered catalyst **8** led to an asymmetric synthesis of a lactone through reduction and lactonisation (Figure 32a).[52] A closely related sequence on vinylic azides led to the asymmetric synthesis of α-hydroxy esters (Figure 32b).[53]

The reduction of trichloromethyl ketones was reported by Fox et al.[54] In many cases, the untethered catalysts gave good results; however, the tethered catalysts were very effective in several cases (Figure 33).

6. ATH of Substrates of Industrial Interest

Both Ru tethered catalysts **8** and **9** (Ts-DENEB®) have generated significant industrial interest. Following initial reports on the tethered catalyst by the Wills group, Johnson Matthey developed a large-scale approach to carbon tethered catalysts. Early interest came from industrial research groups who had obtained promising results with research samples of C3-tethered catalyst **8** from the Wills group and Johnson Matthey.

AstraZeneca have used **8** to prepare anti-asthmatic bronchodilator drug structures; the reduction step was the

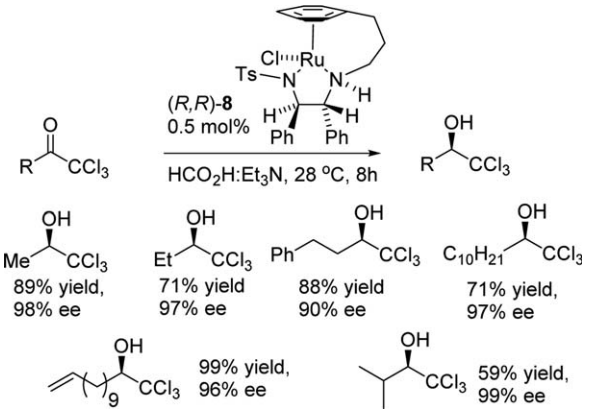


Fig. 33. ATH of trichloromethyl ketones.

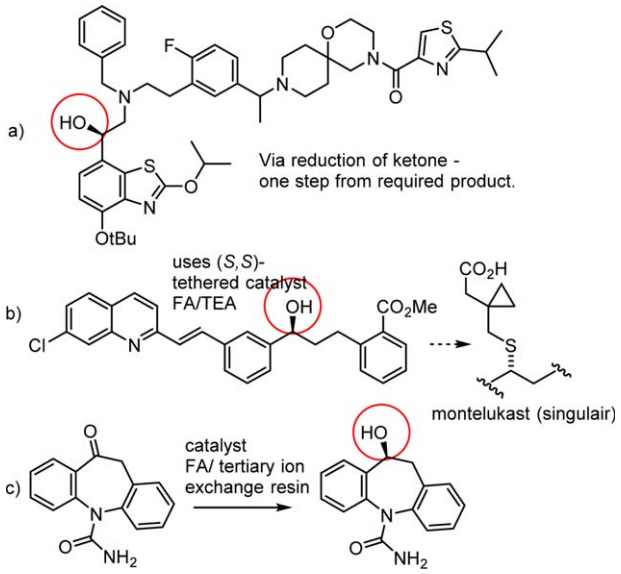


Fig. 34. Pharmaceutical applications of tethered catalyst **8**.

penultimate step in the synthesis and the reduction was not only enantioselective, but also chemoselective (Figure 34a).[55] Synthon BV described a synthesis of the established anti-asthmatic drug montelukast.[56] In this application, the tethered catalyst **8** was highlighted as giving excellent results in the transfer hydrogenation reaction (Figure 34b). Archimica GMBH reported the synthesis of the antiepileptic drug eslicarbazepine through reduction of a cyclic ketone (Figure 34c).[57]

The commercial availability of the Wills carbon tethered catalyst from Johnson Matthey and Ts-DENEB® from Takasago, and the availability of both from catalogue companies has been a significant step towards finding commercially viable applications.

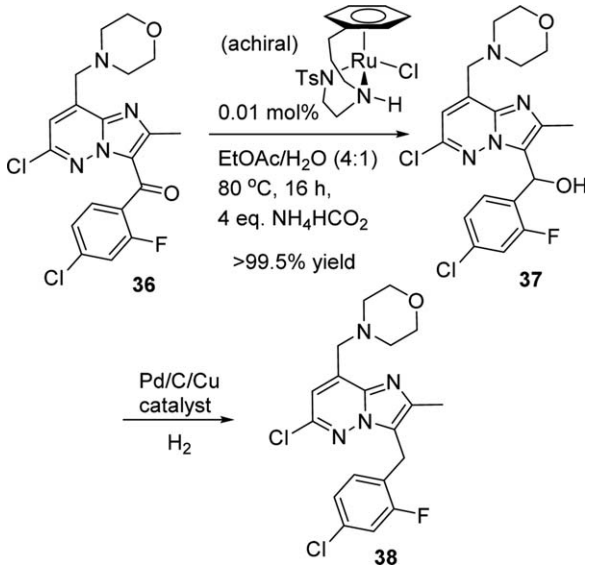


Fig. 35. Application of a non-chiral tethered catalyst.

From the perspective of industrial applications, it is important that the new classes of tethered catalysts (which are structurally more complex than first-generation catalysts and have a more involved synthesis) not only offer advantages, but also allow transformations that were previously impossible or gave unacceptable levels of conversion or selectivity.

The robustness of the tethered catalysts in the presence of poly-functionalized molecules is one of the features that make them particularly attractive for the reduction of functional groups in complex substrates of interest to the life sciences industry. The increased reactivity and stability provided by the tethered catalyst design can render it the reagent of choice, even when an asymmetric induction is not required. For example, the reduction of **36** to **38** proved to be very challenging and not compatible with most well-established catalytic and stoichiometric reagents. However, a successful route was developed by Eli Lilly in collaboration with Johnson Matthey using an achiral tethered catalyst derivative[22] in the first step to form intermediate alcohol **37**. This was followed by a carefully optimized hydrogenolysis in the second step (Figure 35).[58] As little as 0.01 mol% of the achiral catalyst was required in the first reduction; ammonium formate was conveniently used as the reducing agent.

Boehringer Ingelheim GmbH used tethered catalyst **7** to prepare an intermediate toward the synthesis of chemokine inhibitors (anti-inflammatory agent). Notably, 40 g of product **D** was formed using just 20 mg of the tethered catalyst (Figure 36), in sufficient purity to be used directly in the next step (w/w ratio of 2000/1).[59]

In 2015, Komiyama et al. reported the application of Ms-DENEB® **39** (the N-Ms derivative of Ts-DENEB®) to the

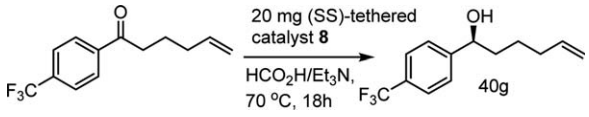


Fig. 36. Application of ATH by Boehringer Ingelheim GmbH.

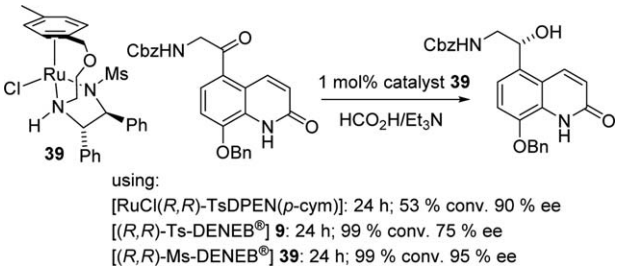


Fig. 37. ATH applied to the synthesis of an adrenergic receptor agonist.

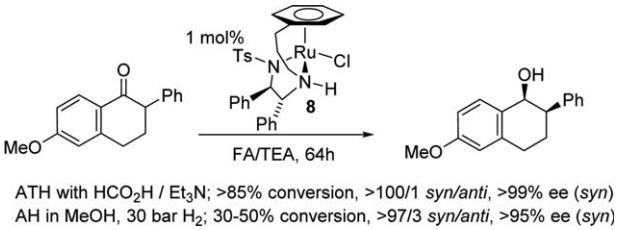


Fig. 38. DKR coupled to ATH.

synthesis of an adrenergic receptor agonist through ATH of an α-amino ketone precursor (Figure 37).[60] The Ms-DENEB® catalyst **39** outperformed Ts-DENEB® **9**, while the non-tethered [RuCl(*R,R*)-TsDPEN(*p*-cymene)] catalyst was even more enantioselective then the Ts-DENEB® catalyst.

The DKR of a cyclic ketone has been reported by Lek Pharmaceuticals (Sandoz).[61] In this process, 1 mol% of tethered catalyst **8** achieved full reduction to the *syn* isomer in >100:1 selectivity and 99% *ee* (Figure 38). Although a very similar transformation had been previously reported using the non-tethered catalyst,[62] the presence of an electron-rich substituent on the fused aromatic ring made the reduction more difficult and less than 20% conversion was achieved with the non-tethered catalyst. The tethered catalysts could also be used under hydrogenation conditions (see the following section), although with lower conversion.

Tethered catalysts with sulfamoylamino (NSO_2N) groups were demonstrated by the group of Mohar as effective catalysts for the ATH of α-CF_3(CO) indanones through DKR.[32b]

DKR has also been used by Ratovelomanana-Vidal et al. in the asymmetric reduction of α-amino-β-keto esters (Figure 39).[63] Several examples are featured, each containing aromatic substitution, which is important to control the reaction, and no conversion was reported using non-tethered catalysts.

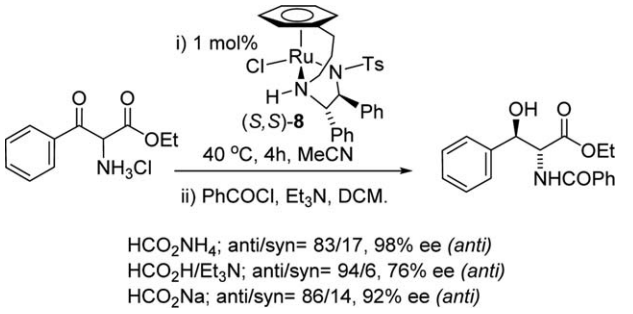


Fig. 39. ATH–DKR of α-amino-β-keto esters.

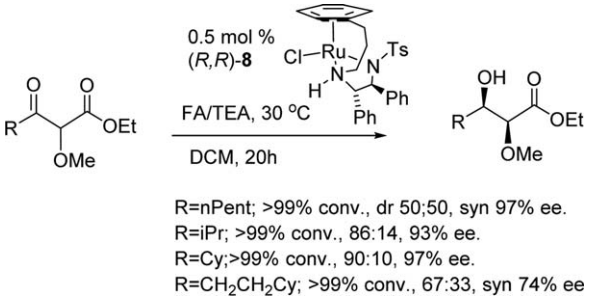


Fig. 40. ATH-DKR of α-methoxy-β-ketoesters.

The same group (in collaboration with Roche) also found that the use of 3-C-tethered catalyst **8** was essential for the conversion of a range of α-methoxy-β-ketoesters, notably, for substrates in which R was an alkyl group (Figure 40).[51] Less challenging substrates could be reduced effectively by the non-tethered catalysts.

In another DKR application, Ts-DENEB® **9** was employed in the synthesis of Omarigliptin, a type 2 diabetes drug (Figure 41)[64] Initially,[65] the best conditions were developed with the [RuCl($C_6F_5SO_2$DPEN)(*p*-cymene)] catalyst, which has been repeatedly demonstrated as one of the best catalysts in DKR applications.[66] Notably, FA is added to a mixture of DABCO (in place of TEA) and substrate with THF as a co-solvent to give optimal results in the DKR process. A further experimental study[64] using Ts-DENEB® **9**, and only slightly adapted reaction conditions, concluded that the performance of the tethered catalyst was superior in all aspects, despite the presence of an tosyl group instead of the $C_6F_5SO_2$ group.

Although the great majority of research work on ATH catalysts as tethered catalysts has focused on ketones, there have been some limited studies on C=N reduction.[67] However, this field is significantly less developed and the catalyst versatility is not as extensive, even with untethered catalysts, although there are some very impressive examples, particularly of cyclic imine reductions.[14,15,68–70] One very impressive recent

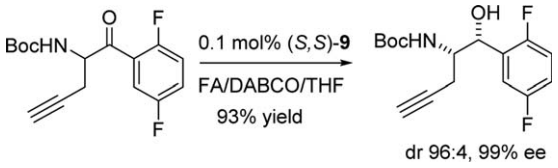


Fig. 41. DKR in the synthesis of Omarigliptin, using catalyst Ts-DENEB® **9**.

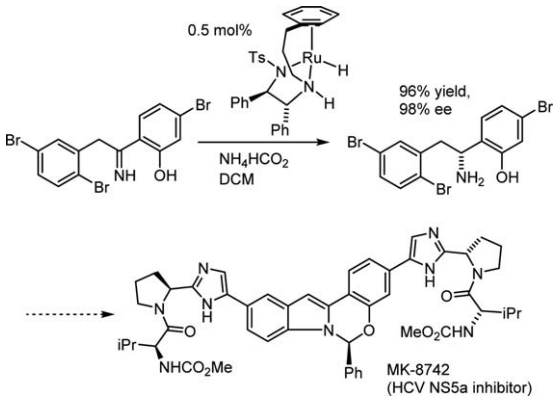


Fig. 42. Primary amine formation by ATH using catalyst **8**.

example of C=N reductions using a tethered catalyst was reported by scientists at Merck, who found that catalyst **8** was particularly beneficial, and indeed superior to other catalysts tested, in the reduction of an imine substrate to a primary amine during the synthesis of a target drug molecule (Figure 42).[71]

7. Hydrogenation

Noyori and Ohkuma et al. have demonstrated that non-tethered catalysts can be used in MeOH under hydrogenation conditions that is, using hydrogen as the reducing agent,[72,73] provided that they are converted into salts with weakly coordinating anions. On the contrary, tethered complexes work well in hydrogenation without such activation reactions, giving products in excellent yields and *ee* values in many cases (Figure 43).[22] The achiral catalyst **25** was also tested in this application and gave excellent results for the hydrogenation of aldehydes. The value of this application resides in the potential for the catalytic reduction of aldehydes when other functional groups are present (e.g., nitro, cyano, aromatic halides) that may be reduced by heterogeneous hydrogenation catalysts.

The methoxy-substituted catalyst **34** also promotes AH of ketones, in similar *ee* to the ATH reactions (Figure 44).[37]

Ts-DENEB® **9** was also reported to be active and effective for the reduction of aryl ketones under AH conditions (Figure 45) and has also been shown to be capable of hydrogenation of

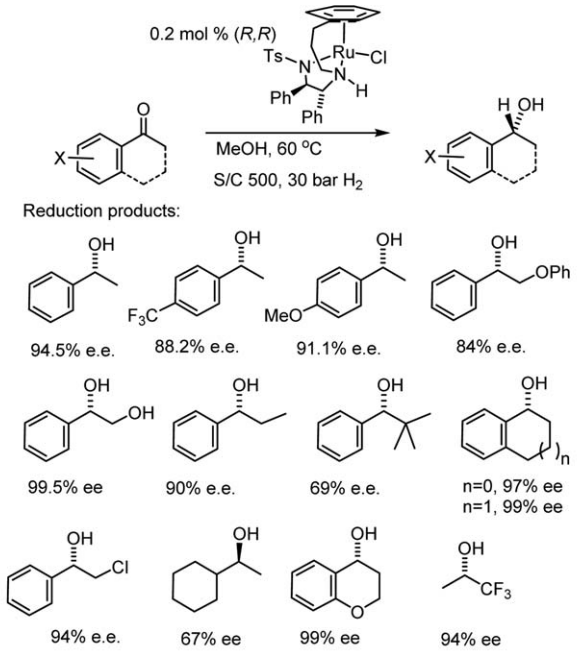


Fig. 43. AHs using the tethered catalyst **8**.

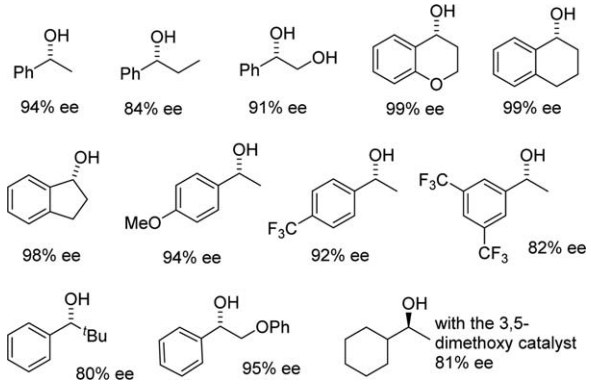


Fig. 44. AH products formed using catalyst **34**.

lactones.[24] Both the ruthenium chloride precatalyst and the unsaturated (16e$^-$) complexes were used in the reductions. Although the *ee* values were essentially the same, better conversions were achieved using the unsaturated complex (conditions: 3.0 MPa H_2, 60 °C, MeOH, 18–20h, 0.1 mol% catalyst).

Kačer et al. tabulated the activity of Ru tethered catalysts (**7** and Ts-DENEB® **9**) against a panel of cyclic imines, but under the following conditions: TFA, MeOH, 15 bar H_2, 40 °C.[74]

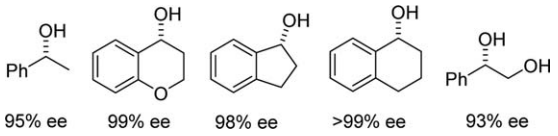


Fig. 45. AH products formed using Ts-DENEB® **9**.

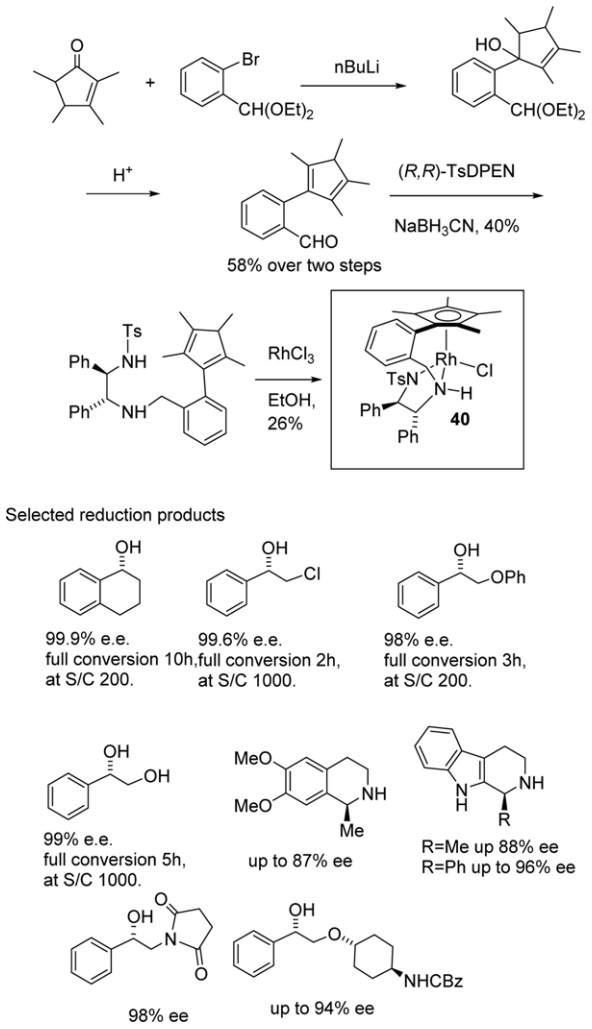


Fig. 46. Synthesis of Rh(III) tethered complexes and products of ketone ATH.

8. Tethered Rh(III) Derivatives

Alongside the development of Ru(II)/TsDPEN catalysts, several researchers reported isoelectronic complexes based on both Rh(III) and Ir(III) (Figure 4); the major difference is the use of a cyclopentadienyl ligand in place of the neutral arene to balance the charge and fulfil the 18-electron requirement.[16] This class of complex was developed as a commercial product under the trade name CATHy® catalysts by Avecia (now NPIL).

In 2005, Wills et al. reported the synthesis and applications of the tethered analogue of the Rh(III)/TsDPEN/cyclopentadienyl class of catalysts, **40**, which was prepared by the route shown in Figure 46, along with examples of results from reduction reactions.[75–77] Pivotal to the success of the route was the addition of a lithiated arene with a cyclopentadienone, followed by elimination of water. The structure of the complex was confirmed by X-ray crystallographic analysis, as was that of the cyclohexyl diamine derivative catalyst, which gave excellent results under aqueous conditions.[76]

As well as ketone reduction, tethered Rh(III) catalysts have been applied to imine reduction[77] and additionally to the ATH of quinolones, alongside the Ru(II) tethered catalysts. In this application, the Rh catalysts gave products with higher *ee*.[78] In 2010, Schomäcker et al reported a supported version of the Rh(III)/TsDPEN tethered catalyst, with linkage to a polymeric support. This proved to be robust, recoverable and reusable in a range of reactions.[79,80] A methoxy-substituted version of the Rh(III) tethered catalyst, similar to a derivative reported by Wills et al.,[77] was recently reported and proved to be active in a number of ATH applications.[51,81]

The synthesis of the Ir(III) version of the tethered catalyst has so far proved to be elusive and no purified catalyst has been isolated to date. However, attempts to form the catalyst in situ through the combination of the precursor ligand with $IrCl_3$ successfully resulted in the formation of a competent catalyst that was capable of reducing ketones in good enantioselectivity.[77]

9. Summary and Outlook

Tethered ruthenium and rhodium catalysts come from a rational improvement of the bifunctional design brilliantly introduced by Noyori. However, over the past 10 years, the tethered catalysts have proven to be successful beyond initial expectations, giving rise, in both academic and industrial laboratories, to a number of innovative applications that could not be achieved using first-generation catalysts. With the commercialization of this class of catalysts by Johnson Matthey and Takasago, the tethered catalysts have become indispensable tools for the catalytic homogeneous reduction of C=O and C=N functionalities, especially in the context of complex, multifunctionalised substrates. The main advantages of the tethered catalysts probably reside in their stability against deactivation and in their activity under a broad range of reaction conditions, even at low catalyst loading. More mechanistically related transformations are been developed, which suggests that the catalyst design will remain at the forefront of technology development for many years.

Acknowledgements

The application area of reduction of ketones and imines by Noyori complexes has benefited strongly from research visits to Noyori's laboratory by researchers in the early stages of their careers. Their gained experience has spread to a large number of authors of contributions to this area, as evidenced by the literature cited in this review. The further development of this synthetic methodology has made it a technology that is used worldwide for the sustainable production of active ingredients for pharmaceutical, animal health, agrochemical, and flavour and fragrances products. We acknowledge the financial support of the UK Technology Strategy Board (TSB) for a year of joint collaboration between Johnson Matthey and the University of Warwick. The many research councils, charities and industrial sponsors who generously supported the work are acknowledged in the cited references.

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