Asymmetric ruthenium-catalyzed 1,4-additions of aryl thiols to enones†‡

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Well defined, stable, one-point binding ruthenium complexes **1** and **2** selectively bind and activate α,β-unsaturated carbonyl compounds for cycloaddition reactions. These mild Lewis acids catalyze asymmetric 1,4-addition reactions of aryl thiols to enones with product selectivities up to 87% ee. ^{31}P NMR experiments provide an insight into the intricate equilibria governing the reaction mechanism. The absolute configuration of the major products indicates enones to react in the *syn-s-trans* orientation. Models based on X-ray structures of the Ru complexes can be used to rationalize selectivity.

Introduction

Life itself is the uncontested, ever-present proof of the importance of sulfur-containing and sulfur-based compounds. Many biochemical processes in nature involve sulfur, be it in organic or inorganic form.[1] From a purely synthetic point of view, the words variety and richness describe best the chemistry of sulfur.[2] Enzyme mimics, natural product synthesis, semi-labile ligands or building blocks for asymmetric synthesis are but a few of the applications that sulfur-containing compounds find nowadays.[3]

Among the various methods for the generation of carbon–sulfur bonds,[4] the Michael addition (or 1,4-addition) reaction is a straightforward route. This transformation takes advantage of the mild nucleophilicity of sulfur nucleophiles in general and of the thiophenolate anion in particular. Its propensity to react with activated double bonds provides thioethers as products.[5] Diversity of the reaction partners, flexibility of the Michael adduct (that can be used as such or easily cleaved, reduced or oxidized) and the potential for asymmetric conjugate addition reactions are the driving forces of interest in this field.

Sulfa-Michael additions have been shown to be promoted by a number of compounds, including organic and inorganic bases, Lewis acids, water or even the absence of solvent.[6] First asymmetric versions described were organocatalytic.[7] Since, the field has significantly evolved and rationally designed organocatalysts now provide access to unprecedented levels of activity and selectivity for this transformation.[8] By far the most efficient metal-based catalysts belong to the family of heterobimetallic complexes developed independently by Sundararajan,[9] Shibasaki,[10a] and later by Narasimhan.[11] The work of Shibasaki *et al.* is all the more remarkable since the sulfa-Michael addition, asymmetric protonation, and kinetic resolution[10b] developed were further applied in natural product synthesis.[10c] The innovative use of a C_2-symmetrical enantiopure *N*-oxide/CdI_2 system by Nakajima *et al.* is also a fine achievement.[12] While mechanistic details are not yet established, this procedure allowed for the extension of the Michael acceptors to enals. Processes involving a Ca-BINOL complex,[13] chiral 2-amino alkoxides[14] and ethers,[15] or bidentate proline-derived Michael acceptors[16] were also successfully employed for the asymmetric catalytic sulfa-Michael addition.[17]

We have prepared iron- and ruthenium Lewis acid catalysts based on structurally well-defined monocationic half-sandwich complexes bearing chiral electron-poor diphosphinite ligands (Fig. 1).[18] The ligand's perfluorinated aryl rings contribute to the Lewis acidity of these complexes and, together with the aromatic roofs and the ligand's backbone, generate a chiral binding site that is ideal for the activation of α,β-unsaturated carbonyl compounds.

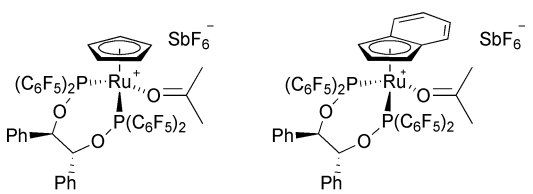

Fig. 1 Chiral Ru Lewis acid precatalysts.

These mild chiral Lewis acids proved to be excellent catalysts for the Diels–Alder reactions of dienes with enals[18,19] and 1,3-dipolar cycloadditions with nitrones[20] and nitrile oxides.[21] In both cases enal over dipole coordination was preferred and the expected products were obtained with good yields and selectivity.

More recently, this was extended to Diels–Alder reactions of acyclic enones.[22] Not only are these less reactive dienophiles, but due to the similarity of the two modes of coordination to the metal (*syn* or *anti*), stereocontrol with a single site catalyst is much more challenging.[23]

In the present article we probe the potential of the ruthenium catalysts in conjugate addition reactions. Specifically, we detail our study on the use of [Ru(acetone)(*R*,*R*-BIPHOP–F)Cp][SbF_6] (**1**) as catalyst for the Michael addition of thiols to enones.

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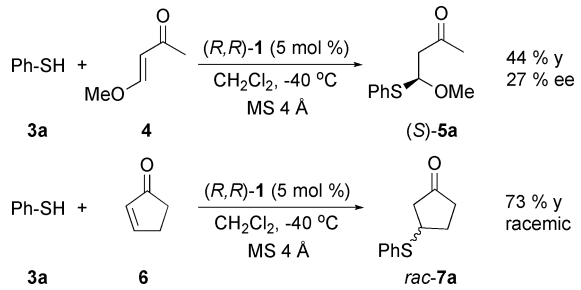
† Electronic supplementary information (ESI) available: General experimental information, a complete table of solvent and temperature optimization, full experimental procedures and characterization data for all compounds, and a discussion on the X-ray structure of **22**. CCDC reference numbers 747701 and 750039. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b918877k

‡ Dedicated to the memory of Christophe M. Saudan

Results and discussion

Benchmark Michael additions usually involve enones since the stable products are readily analysed.[17] We initially selected *trans*-4-(OMe)-3-buten-2-one (**4**), 2-cyclopenten-1-one (**6**) and 2-cyclohexen-1-one (**8**) as Michael acceptors and thiophenol (**3a**) as the nucleophile. Racemic reference samples were obtained from the reaction catalyzed either by diazabicyclo[5.4.0]undec-7-ene (DBU) or 1,8-bis(dimethylamino) naphthalene ("proton sponge").

Reactions were carried out in the presence of a catalytic amount of the [Ru(acetone)(*R*,*R*-BIPHOP–F)Cp][SbF_6] complex (**1**). *Trans*-4-(OMe)-3-buten-2-one (**4**) afforded addition product (*S*)-**5a** in moderate yields (18 h) and low enantiomeric excess (Scheme 1). Switching to more reactive 2-cyclopenten-1-one (**6**) only led to racemic product **7a**.



Scheme 1 Non-optimized 1,4-addition reactions.

2-Cyclohexen-1-one (**8**) was chosen as the Michael acceptor for the optimization of the reaction conditions. In the same conditions as above (Scheme 1), product (*R*)-**9a** was obtained in fair yield but low selectivity (Table 1, entry 1). Raising the temperature had a negative effect on the results (entry 2).

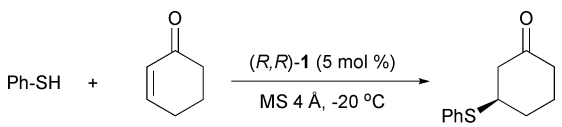
Different media were probed next and as already documented in the literature,[17] THF was found to be more suitable for this reaction than CH_2Cl_2 (entries 2, 3, and 5).[24] THF–toluene mixtures or more polar solvents (MeOH, EtOH) failed to improve the results.

With THF as the solvent of choice, temperature effects were studied next.[24] Enantioselectivity slowly increased with decreasing temperature with the best result obtained at –20 °C. Further lowering the temperature led to a sluggish reaction without improvement in selectivity (entries 4 to 6).

Despite numerous attempts to optimize the conditions, the isolated product yields were limited to about 60%. Addition of a base to the reaction mixture, along with the Ru catalyst, generally led to racemic products. At the end of the reaction the ruthenium thiophenol complex was isolated; catalyst poisoning by the Michael donor is likely to occur as this complex proved to be inactive. Slow addition of excess thiophenol (over a period of 12 h) allowed us to overcome this problem and yields were now good (entry 7 *vs.* entry 5).

The best set of conditions (entry 7) was then applied in the screening of Michael donors (Table 2). Reactions were stopped after 48 h for ease of comparison. As before, the racemic adducts were obtained by mixing equimolar amounts of Michael donor (**3a–k**) and 2-cyclohexen-1-one (**8**) for 24 h in THF in the presence of catalytic amounts of an organic base (5 mol% DBU).

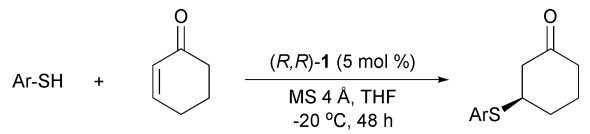
Table 1 Optimization for the Ru-catalyzed 1,4-addition of thiophenol (**3a**) to 2-cyclohexen-1-one (**8**)[a]



Entry	Solvent	T/°C	Time/h	Yield[b] (ee[c]) (%)
1	CH_2Cl_2	–40	72	64 (33)
2	CH_2Cl_2	–20	48	50 (11)
3	CH_2Cl_2–THF (1 : 1)	–20	48	40 (45)
4	THF	0	24	54 (45)
5	THF	–20	48	60 (68)
6	THF	–40	64	48 (60)
7[d]	THF	–20	48	82 (63)

[a] All reactions were carried out under N_2, using **3a** (0.38 mmol) and **8** (0.25 mmol), with 50 mg of powdered, activated MS 4 Å, in 1 mL of dry solvent. [b] Isolated yield. [c] Determined by HPLC analysis. [d] Slow addition of **3a** over 12 h.

Table 2 Aryl thiol screening for the Ru-catalyzed 1,4-addition to 2-cyclohexen-1-one (**8**)[a]



Entry	RSH	Yield (%)[b]	ee (%)[c]
1	PhSH (**3a**)	82	63[d]
2	BnSH (**3b**)	21	47[d]
3	2-NapSH (**3c**)	74	33[d]
4	4-Cl-C_6H_4-SH (**3d**)	86	52[d]
5	4-Me-C_6H_4-SH (**3e**)	57	51[d]
6	4-*t*-Bu-C_6H_4-SH (**3f**)	73	57[d]
7	4-OMe-C_6H_4-SH (**3g**)	58	53[d]
8	2-OMe-C_6H_4-SH (**3h**)	32	41[d]
9	2-CO_2Me-C_6H_4-SH (**3i**)	39	53
10	2,6-Cl-C_6H_3-SH (**3j**)	89	0
11	2,6-Me-C_6H_3-SH (**3k**)	94	82

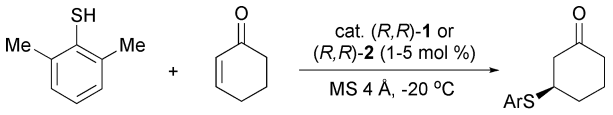
[a] All reactions were carried out under N_2, using **3a–k** (0.38 mmol) and **8** (0.25 mmol), with 50 mg of powdered, activated MS 4 Å, in 1 mL of dry THF, with slow addition of the aryl thiol over 12 h. [b] Isolated yield. [c] Determined by HPLC analysis. [d] Absolute configuration based on known literature data (sign of optical rotation).[12,26b]

Less reactive benzyl thiol (**3b**) provided adduct **9b** in poor yield and selectivity (Table 2, entry 2). 2-Naphthylthiol (**3c**) gave the expected thiol ether **9c** also in poor enantioselectivity, albeit in good yield (entry 3).

Next, a series of *para*-substituted aryl thiols were screened. Electronic effects seem to have small, if any, influence on the outcome of the reaction; the expected Michael adducts were obtained in moderate to good yields and, with a few exceptions, with ees in the range of 50–60% (entries 4 to 7).

In terms of steric effects, a methoxy (entry 8) or a carboxymethyl group (entry 9) *ortho* to the thiol only led to a decrease in both yield and selectivity. Important changes appear when bulk is added on both sides close to the thiol group (positions 2 and 6). Surprisingly, despite giving the product in good yield, 2,6-dichlorothiophenol (**3j**) led only to the formation of racemic adduct (entry 10). With

Table 3 Re-optimization of the conditions for the Ru-catalyzed 1,4-addition of 2,6-DMTP (**3k**) to 2-cyclohexen-1-one (**8**)[a]

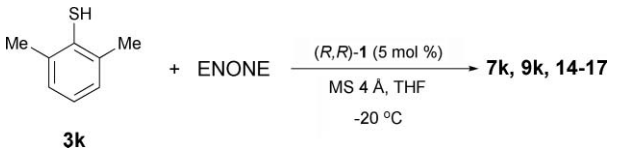


3k **8** (*R*)-**9k**

Entry	Solvent	Time/h	Yield (%)[b]	ee (%)[c]
1	THF[d]	24	94	82
2	THF	24	95	85
3	THF[e]	48	79[f]	71
4	Neat	> 72	—	—
5[g]	Water	24	41[f]	30
6[h]	THF	24	17[f]	79
7[i]	THF	24	95	–87
8[j]	THF	48	70	77
9[k]	THF	24	99	77
10[l]	THF	36	83	85
11[m]	THF	72	75	85
12[n]	THF	48	85	85

[a] All reactions were carried out under N_2, using **3k** (0.38 mmol) and **8** (0.25 mmol), with 5 mol% (*R*,*R*)-**1** and 50 mg of powdered, activated MS 4 Å, in 1 mL of dry solvent, unless mentioned otherwise. [b] Isolated yield. [c] Determined by HPLC analysis. [d] Slow addition of the aryl thiol over 12 h. [e] 5 mL of dry THF. [f] Full conversion not reached. [g] Run at 0 °C. [h] Without activated MS 4 Å. [i] 5 Mol% (*S*,*S*)-**1**. [j] 5 Mol% (*R*,*R*)-**2**. [k] 1 Mol% 2,6-lutidine as additive. [l] 2.5 Mol% (*R*,*R*)-**1**. [m] 1 Mol% (*R*,*R*)-**1**. [n] **3k** (2.2 mmol) and **8** (2 mmol), with 2 mol% (*R*,*R*)-**1** and 200 mg of activated MS 4 Å in 2 mL of dry THF.

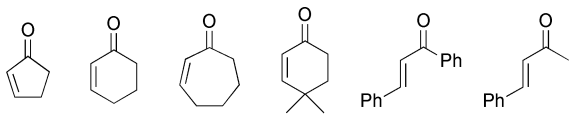
Table 4 Enone screening for the Ru-catalyzed 1,4-addition[a]



3k

Entry	Enone[b]	Product	Time/h	Yield (%)[c]	ee (%)[d]
1	**6**	**7k**	48	86	–16
2	**8**	**9k**	24	95	85
3	**10**	**14**	36	95	83
4	**11**	**15**	48	33[e]	52
5	**12**	**16**	16	35	–8
6	**13**	**17**	16	31	–4

[a] All reactions were carried out under N_2, using **3k** (0.38 mmol) and enone (0.25 mmol), with 50 mg of powdered, activated MS 4 Å, in 1 mL of dry THF. [b] Enones: 2-cyclopenten-1-one (**6**), 2-cyclohexen-1-one (**8**), 2-cyclohepten-1-one (**10**), 4,4-dimethyl-2-cyclohexen-1-one (**11**), *trans*-1,3-diphenyl-2-propen-1-one (**12**), *trans*-4-phenyl-3-buten-2-one (**13**). [c] Isolated yield. [d] Determined by HPLC analysis. [e] Full conversion not reached.



6 **8** **10** **11** **12** **13**

2,6-dimethylthiophenol (2,6-DMTP, **3k**), product **9k** was isolated in 94% yield and with 82% ee (entry 11). With respect to the observed selectivity, an increase in steric bulk is in agreement with the assumption of a non-orthogonal approach of the nucleophile (in contrast to the orthogonal approach in the cycloaddition reactions[19–22]). It should be noted that with bulky thiols **3j** and **3k**, a color change from yellow to orange was observed upon their addition to the reaction mixture; this was not observed with the other thiols. This suggests the appearance of charge-separated Ru-thiophenolate species that could be catalytically active.

A sterically demanding Michael donor should be beneficial not only for the selectivity, but also to the overall catalytic cycle, as the deactivation of the ruthenium catalyst (through Ru-thiol complexes) becomes less likely. Indeed, slow addition of the thiol **3k** is not required, thus simplifying the procedure (Table 3, entries 1 and 2).[24]

Running the reaction under more dilute conditions (x 5) had a negative effect on the results (entry 3). In the absence of solvent the reaction did not proceed at all, as indicated by TLC analysis (entry 4). Subsequent addition of 4 Å molecular sieves or solvent failed to start the reaction.

Water-catalyzed (racemic) Michael additions of thiols to enones are known.[6b] Interestingly, running the reaction in water led to substantial formation of the Michael adduct, albeit in low ee due to temperature limitations (entry 5). The Ru *aqua* complex was previously described and is known to act as an active precatalyst.[19e] Here, the product was formed despite the absence of "dry reaction conditions", whereas a reaction run in THF but in the absence of molecular sieves turned out to be very sluggish (entry 6). Using the enantiomeric complex (*S*,*S*)-**1** as precatalyst led, as expected, to the opposite product enantiomer (entry 7).

The indenyl analogue of the Ru precatalyst (**2**), designed to boost reactivity and selectivity for the Diels–Alder reactions,[19b] was also used for the standard reaction in the best conditions. However, it turns out that now the reaction was slower and the results were less impressive (entry 8).

2,6-Lutidine as additive in cycloaddition reactions with Fe and Ru Lewis acid catalysts is beneficial since Brønsted acid traces in the solvent are scavenged.[19,20] Running the standard reaction with 5 mol% of the [Ru(acetone)(*R*,*R*-BIPHOP–F)Cp][SbF_6] precatalyst (**1**) together with 1 mol% of 2,6-lutidine brought no increase in selectivity although the product was formed quantitatively (entry 9).

A decrease in catalyst loading was successfully accomplished without loss of selectivity, to 2.5 and then 1 mol% (entries 10 and 11), at the expense of reaction rate and a slight decrease in isolated yield. The reaction is robust and can be readily scaled-up (x 8) even with low catalyst loading (entry 12).

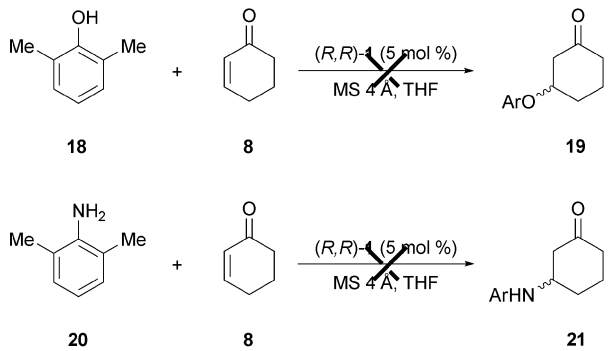
The optimized reaction conditions were next extended to a variety of Michael acceptors (Table 4). Thus, 2-cyclopenten-1-one (**6**) gives the opposite enantiomer in good yield but low ee (entry 1). 2-Cyclohepten-1-one (**10**) on the other hand gave the expected 7-membered adduct with results comparable to those for benchmark 2-cyclohexen-1-one (**8**) (entries 2 and 3). The bulkier 4,4-dimethyl-2-cyclohexen-1-one (**11**) not only showed poor reactivity but also afforded the product in lower selectivity, indicating possible unfavourable steric interactions between the activated enone and the Michael donor (entry 4).

Acyclic enones proved to be extremely poor Michael acceptors. Chalcone (**12**) and *trans*-4-phenyl-3-buten-2-one (**13**) afforded

addition products in low yield and enantiomeric excess (entries 5 and 6). Results with 3-alkyl enones were equally poor.

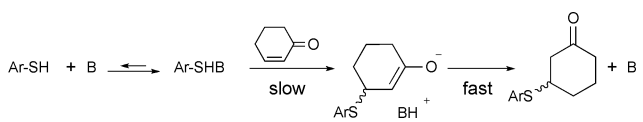
Another limitation of this transformation is encountered with cyclic 2- and/or 3-substituted enones. For the 3-substituted enones, no products could be isolated even upon addition of a base or temperature increase; these substrates are known for their low reactivity in 1,4-addition reactions. On the other hand, for 2-substituted enones we believe steric factors impede efficient coordination, and thus activation, at the metal center.

Extension to 2,6-dimethylphenol (**14**) and 2,6-dimethylaniline (**19**) as Michael donors was not met by success (Scheme 2). The deprotonation is expected to be more difficult (pK_a values in DMSO : thiophenol = 10.3, phenol = 18, aniline = 30.6), and, once formed, nucleophiles derived from phenols and anilines would have a greater propensity to irreversibly bind the Lewis acidic ruthenium center. For the reasons stated above, the asymmetric catalytic Michael additions with amine- and/or alcohol-based donors are scarce.[9d,25] Lowering the pK_a by using electron-poor aryl substituents or changing the reaction medium to water could make this transformation possible and it is worth further investigation.



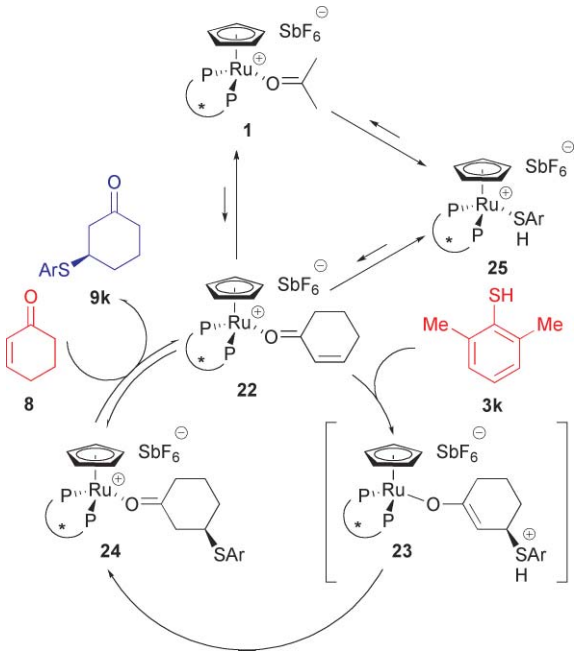
Scheme 2 Attempts to use phenols and anilines as Michael donors for the Ru-catalyzed 1,4-addition.

The general picture of the mechanism of the Michael addition is well known and supported by a wealth of theoretical and experimental data.[5] More specific, for the tertiary amine-catalyzed 1,4-addition of thiols to enones, early mechanistic studies suggested a rate-limiting transfer of the thiolate from of a 1 : 1 complex of thiol and base, to form an enolate intermediate which is rapidly protonated to give the product (Scheme 3). The reaction thus follows first order kinetics in each of the donor, acceptor, and base.[26]



Scheme 3 Mechanism of the amine catalyzed 1,4-addition of thiols to enones.

The absence of a base in our case suggests a more complex mechanism, in which several interconnected equilibria are playing a role on the reaction outcome and mechanism (Scheme 4).[27] We encountered a similar case when investigating asymmetric Lewis acid-catalyzed 1,3-dipolar cycloadditions with nitrones.[20a]



Scheme 4 Proposed catalytic cycle for the Ru-catalyzed 1,4-addition of thiols to enones. Complexes **1**, **22**, **24** and **25** were observed by ^{31}P NMR spectroscopy.

^{31}P NMR data showed competitive nitrone-enal coordination to the Ru-Lewis acid **1** with preferential binding of the enal and readily reversible binding of both enal and nitrone.

The ^{31}P NMR spectrum of the [Ru(acetone)(*R*,*R*-BIPHOP–F)Cp][SbF_6] complex (**1**) (18 mg, 0.025 mmol, 10 mol% based on enone) in THF-d_8 shows the expected peaks corresponding to the BIPHOP–F ligand bound to the monocationic CpRu fragment (doublets at 125 and 128 ppm, Fig. 2).[28]

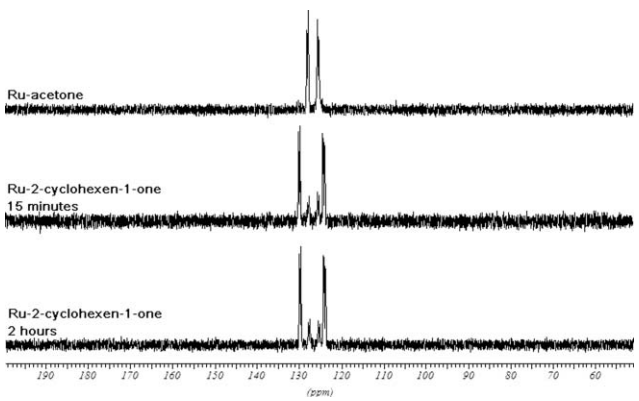


Fig. 2 ^{31}P NMR experiments showing the formation of [Ru(*R*,*R*-BIPHOP–F)Cp(2-cyclohexen-1-one)][SbF_6] (**22**) from the acetone complex **1**.[28]

Addition of 2-cyclohexen-1-one (**8**) (10 eq., 0.25 mmol) leads to an important decrease of the intensity of signals for the acetone complex **1**, along with the appearance of two new doublets (124 and 130 ppm, Fig. 2). These are assigned to the 2-cyclohexen-1-one complex **22**. The ratio of 4 : 1 in favour of **22** shows that in THF-d_8, at –20 °C, the ruthenium Lewis acid prefers coordinating acetone

over 2-cyclohexen-1-one (**8**) by a factor of 2.5 (10 : 1 reagent ratio acetone : 2-cyclohexen-1-one).

Addition of 2,6-DMTP (**3k**, 15 eq., 0.38 mmol) to the mixture above led to the appearance of two new sets of doublets (130 and 165 ppm, Fig. 3). The reaction was monitored by repeating a sequence of ^{1}H and ^{31}P analyses for 20 h at –20 °C. No change was observed in the spectra other than formation of the Michael adduct.

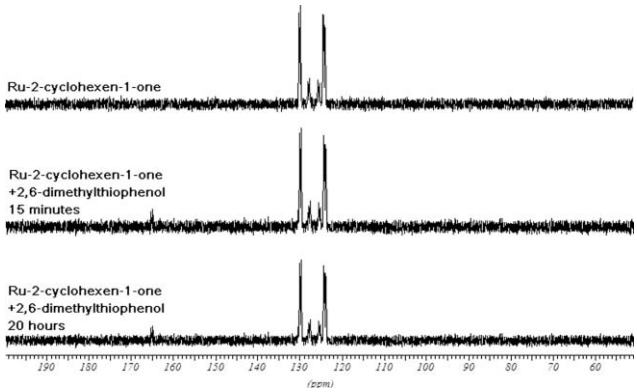


Fig. 3 ^{31}P NMR experiments showing the complexes **1**, **22**, **24** and **25** present during the Ru-catalyzed 1,4-addition of 2,6-DMTP (**3k**) to 2-cyclohexen-1-one (**8**).[28]

In order to determine the nature of the complexes formed during the reaction, 2,6-DMTP (**3k**) was added to a solution of the ruthenium acetone complex **1** in THF-d_8. This produced a color change from yellow to orange, suggesting appearance of charge-separated Ru-thiophenolate complex **26**, as in the case of usual catalytic reactions with thiol **3k**. However, the disappearance of peaks corresponding to the acetone complex **1** is accompanied by the formation of two pairs of doublets, the major complex at 130 and 165 ppm and the minor one at 126 and 163 ppm respectively (Fig. 4). The two complexes are in a ratio of approximately 5 to 1. While the minor complex cannot be assigned yet, the chemical shifts of the major complex confirm the formation of the Ru-2,6-DMTP complex (**25**) during the Michael addition.

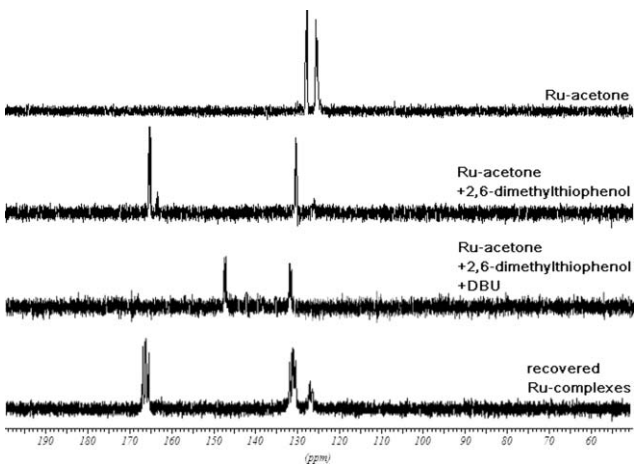


Fig. 4 ^{31}P NMR experiments showing the existence of Ru-2,6-dimethylthiophenol (**25**) and Ru-2,6-dimethylthiophenolate (**26**) complexes, possible intermediates in the catalytic cycle.[28]

Several attempts to isolate the Ru-thiophenolate complex **26** were carried out. Using NaH or NaOH in the presence of the ruthenium complex **1** led to decomposition. Deprotonation of 2,6-DMTP (**3k**) with DBU prior to adding the ruthenium acetone complex **1** gave quantitative formation of a single species, with clear doublets at 131 and 149 ppm, which were tentatively assigned to the [Ru(*R*,*R*-BIPHOP–F)Cp][2,6-dimethylthiophenolate] complex (**26**) (Fig. 4). To confirm this, isolated 2,6-DMTPNa salt was mixed with the Ru-acetone complex in THF-d_8. The ^{31}P NMR spectrum showed quantitative formation of **26**.

The standard workup after a catalytic run involves addition of hexanes. The resulting suspension is filtered through a pad of Celite. The yellow–orange solution is then concentrated and purified to yield pure Michael adducts. The precipitate on the Celite contains a mixture of ruthenium complexes and can be eluted with acetone. The ^{31}P NMR spectrum shows the mixture to contain the Ru-2,6-DMTP complex (**25**, major, quartets at 131 and 166 ppm) along with an unidentified complex (minor, doublets at 127 and 131 ppm, Fig. 4).

Next, the possibility of the Michael adduct complexing the monocationic complex was considered. To a mixture of the ruthenium complexes **1** and **22** (ratio 4 : 1) in THF-d_8, excess Michael adduct (**9k**) was added (10 eq.). Only two doublets could be observed (124 and 127 ppm) that were attributed to the overlapping signals of the Ru-acetone **1** and Ru-adduct **24** complexes.

A Ru-enolate complex (**23**) was never observed; since protonation in the classical mechanism is the fastest step, such a complex is expected to rapidly lead to the Ru-adduct complex (**25**) (Scheme 4). While identification of all species involved in the catalytic cycle has not been realized, these NMR experiments provide insight to the complex nature of the equilibria present in the reaction mixture.

X-ray structures of Lewis acid substrate complexes help in for the rationalization of the observed selectivity in cycloaddition reactions.[19–23] Crystals suitable for X-ray analysis of the Ru-2-cyclohexen-1-one complex **22** were obtained from a dichloromethane–pentane solvent mixture (Fig. 5).[20] Complex **22** closely resembles the structure containing methylvinyl ketone described previously.[22] In both cases, the enone is coordinated in an *anti-s-trans* conformation and the Ru–O bond length (2.613 Å) and tilt angle of the bound enone are similar.[24]

Based on the X-ray structure of **22** the addition of the Michael donor would be expected to occur to the exposed alkene *Si* face of the enone, leading to the *S*-(–) adduct.

The assignment of absolute configuration for the Michael adducts **9a–g** was made by comparison of $[\alpha]_D$ values with literature data.[12] For the other products, the absolute configuration was assigned by analogy. To our surprise, measurements indicated Michael adduct **9k** to be *R*-(+). We came upon the same issue when assigning the absolute configuration for the Diels–Alder adducts of some enones and dienes.[22] We note here that enals react exclusively in the *anti-s-trans* orientation. In this case the ground state structure and the reacting conformation are identical. With enones, the two coordination modes *anti-s-trans* and *syn-s-trans* are sterically and electronically very similar. The results presented here for the 1,4-additions show that, as in some of the Diels–Alder reactions, the reactive coordination conformation of the Ru-enone is not the one adopted in the crystal structure but it

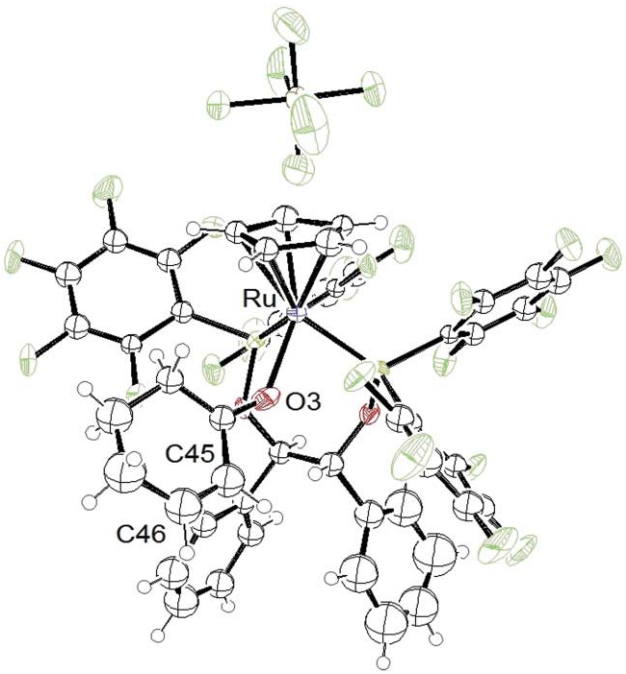


Fig. 5 X-Ray structure representation of [Ru(*R*,*R*-BIPHOP–F)-Cp(2-cyclohexen-1-one)][SbF_6] (**22**) showing the Ru-enone coordination to be *anti-s-trans*.[24]

is the *syn-s-trans* conformation. This being the case, the Michael donor approaches the more available alkene *Re* face of the enone, leading to the observed *R*-(+) product (see Fig. 6).

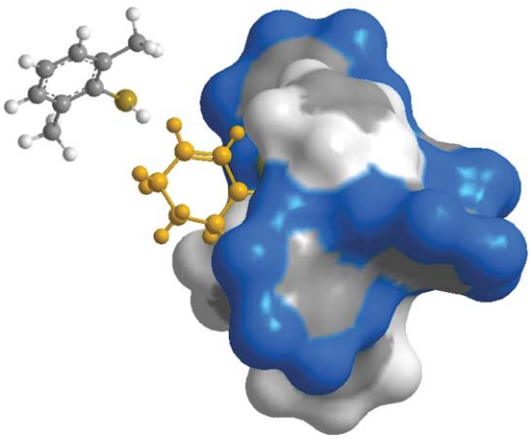


Fig. 6 Modelled approach of the thiol **3k** to the 2-cyclohexen-1-one (**8**) coordinated at the Ru center in a *syn-s-trans* conformation.[24]

Conclusions

The ruthenium half-sandwich Lewis-acidic complexes **1** and **2** can efficiently catalyze 1,4-additions of aryl thiols to enones. Whilst still somewhat limited in substrate scope, the ruthenium catalyzed asymmetric catalytic 1,4-addition of aryl thiols to enones shows the potential of such monocationic complexes for future applications. Remarkable levels of activity and selectivity are observed in spite of complex stereocontrol and potential catalyst inhibition.

Experimental Section[24]

General experimental procedure

In a 50 mL oven-dried Schlenk tube equipped with a magnetic stirring bar, the catalyst (18 mg, 0.025 mmol, 5 mol%) was loaded along with powdered, activated MS 4 Å (50 mg) and the desired solvent (1 mL) was added. The mixture was stirred at the appropriate temperature and the enone (0.25 or 0.5 mmol, 1 eq.) was added. To the stirred solution, thiophenol (0.38 or 0.75 mmol, 1.5 eq.) was added dropwise by a syringe (or by means of a syringe pump, as a solution in THF, for the period indicated). The advancement of the reaction was followed by TLC (SiO_2, CH_2Cl_2). The reaction was stopped by precipitation of the [Ru(*R*,*R*-BIPHOP–F)Cp(PhSH)][SbF_6] complex with excess hexanes (8–10 mL), the mixture was filtered on a plug of Celite 545 (on frit) and then and volatiles were removed *in vacuo* to give the product as an oil. The crude product was further purified by FCC (SiO_2, pentanes/CH_2Cl_2 1/1, 0/1). Enantiomeric excess was determined by means of HPLC analysis (CHIRALPAK AD or CHIRACEL OD-H, ISO hexane–isopropanol 99.5 : 0.5). Units: $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}, *c* values are given in g 100 mL^{-1}, δ values are given in ppm, *J* values are given in Hz, t_R (retention times) are given in minutes.

(*S*)-3-(2,6-Dimethyl-phenylthio)-cyclopentanone (7k). Obtained in 86% yield (16% ee) according to the general procedure, after 36 h. $[\alpha]_D^{20}$ −1.5 (*c* 5 in $CHCl_3$, 16% ee, *S*); ν_{max}(film)/cm^{-1} (neat) 2959, 1744, 1460, 1403, 1376, 1242, 1156, 1056, 896, 774; ^{1}H NMR (500 MHz; $CDCl_3$) δ = 7.17–7.11 (m, 3H, CH_{ar}), 3.75–3.71 (m, 1H, CH), 2.66–2.55 (m, 2H, CH_2), 2.53 (s, 6H, CH_3), 2.58–2.44 (m, 2H, CH_2), 2.28–2.13 (m, 3H, CH_2), 2.00–1.95 (m, 1H, CH_2); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ = 217.3, 143.7, 132.2, 129.0, 128.6, 45.6, 43.8, 36.9, 29.7, 22.5; LR *m*/*z* (EI) 220 $(M)^+$, 149, 138, 105, 83, 55; HRMS *m*/*z* (EI+) calculated for $C_{13}H_{16}OS$ $(M+H)^+$ 220.0921, found $(M+H)^+$ 220.0922; HPLC (CHIRALPAK AD, ISO 99.5+0.5, 0.5 mL min^{-1}, 60 min, 254 nm) t_R 24.12 (42%, *R*), 28.35 (58%, *S*).

(*R*)-3-(Phenylthio)-cyclohexanone (9a). Obtained in 82% yield (63% ee) according to the general procedure, after 17 h. IR, ^{1}H NMR, ^{13}C NMR and MS matched literature data.[6b] $[\alpha]_D^{20}$ +65.5 (*c* 5 in $CHCl_3$, 63% ee, *R*); HPLC (CHIRALPAK AD, ISO 99.5+0.5, 0.3 mL min^{-1}, 120 min, 254 nm): t_R 71.31 (21%, *S*), 98.63 (84%, *R*).

(*R*)-3-(2,6-Dimethyl-phenylthio)-cyclohexanone (9k). Obtained in 95% yield (85% ee) according to the general procedure, after 48 h. IR, ^{1}H NMR, ^{13}C NMR and MS matched literature data.[30] $[\alpha]_D^{20}$ +84.0 (*c* 5 in $CHCl_3$, 85% ee, *R*); HPLC (CHIRALPAK AD, ISO 99.5+0.5, 0.3 mL min^{-1}, 120 min, 254 nm) t_R 31.46 (94%, *R*), 34.16 (6%, *S*).

(*R*)-3-(2,6-Dimethyl-phenylthio)-cycloheptanone (14). Obtained in 95% yield (83% ee) according to the general procedure, after 36 h. $[\alpha]_D^{20}$ +41.8 (*c* 5 in $CHCl_3$, 83% ee, *R*); ν_{max}(film)/cm^{-1} (neat) 2924, 1701, 1459, 899, 775; ^{1}H NMR (500 MHz; $CDCl_3$) δ = 7.15–7.10 (m, 3H, CH_{ar}), 3.20–2.14 (m, 1H, CH), 2.76–2.71 (m, 1H, CH_2), 2.66–2.53 (m, 2H, CH_2), 2.52 (s, 6H, CH_3), 2.51–2.43 (m, 1H, CH_2), 2.04–1.95 (m, 2H, CH_2), 1.86–1.81 (m, 1H, CH_2), 1.76–1.65 (m, 2H, CH_2), 1.46–1.42 (m, 1H, CH_2); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ = 212.0, 143.7, 132.5, 128.9, 128.6,

49.9, 44.8, 44.4, 37.4, 28.6, 24.2, 22.6; LR *m/z* (EI) 248 $(M)^+$, 138, 111, 83, 55; HRMS *m/z* (EI+) calculated for $C_{15}H_{20}OS$ $(M+H)^+$ 248.1235, found $(M+H)^+$ 248.1233; HPLC (CHIRALPAK AD, ISO 99.5+0.5, 0.5 mL min^{-1}, 60 min, 254 nm) t_R 18.79 (92%, *R*), 20.92 (9%, *S*).

(*R*)-3-(2,6-Dimethyl-phenylthio)-4,4-dimethyl-cyclohexanone (15). Obtained in 33% yield (52% ee) according to the general procedure, after 36 h. $[\alpha]_D^{20}$ +86.5 (*c* 5 in $CHCl_3$, 52% ee, *R*); ν_{max}(film)/cm^{-1} (neat) 2969, 1713, 1460, 1354, 1149, 1050, 772. ^1H NMR (500 MHz; $CDCl_3$) $\delta = 7.14–7.08$ (m, 3H, CH_{ar}), 3.08–3.02 (m, 1H, CH), 2.51 (s, 6H, CH_3), 2.49–2.38 (m, 2H, CH_2), 2.35–2.24 (m, 2H, CH_2), 1.95–1.90 (m, 1H, CH_2), 1.67–1.60 (m, 1H, CH_2), 1.32 (s, 6H, CH_3); ^{13}C NMR (125.8 MHz, $CDCl_3$) $\delta = 209.7$, 143.8, 131.9, 128.7, 56.1, 44.9, 39.0, 38.2, 35.1, 29.0, 22.6, 21.4; LR *m/z* (EI) 262 $(M)^+$, 138, 125, 83, 55; HRMS *m/z* (EI+) calculated for $C_{16}H_{22}OS$ $(M+H)^+$ 262.1391, found $(M+H)^+$ 262.1391; HPLC (CHIRALPAK AD, ISO 99.5+0.5, 0.5 mL min^{-1}, 60 min, 254 nm) t_R 25.59 (76%, *R*), 27.82 (24%, *S*).

(*S*)-3-(2,6-Dimethyl-phenylthio)-1,3-diphenyl-propan-1-one (16). Obtained in 35% yield (8% ee) according to the general procedure, after 6 h. $[\alpha]_D^{20}$ +1.51 (*c* 5 in $CHCl_3$, 8% ee, *S*); ν_{max}(film)/cm^{-1} (neat) 3059, 3030, 2924, 1686, 1598, 1449, 1334, 1223, 1002, 981, 772, 749, 690; ^1H NMR (500 MHz; $CDCl_3$) $\delta = 7.89–7.87$ (m, 2H, CH_{ar}), 7.59–7.51 (m, 1H, CH_{ar}), 7.46–7.43 (m, 2H, CH_{ar}), 7.24–7.17 (m, 5H, CH_{ar}), 7.12–7.02 (m, 3H, CH_{ar}), 4.65–4.62 (dd, 1H, *J* 4.6, CH), 3.72–3.55 (ddd, 2H, *J* 3.6, CH_2), 2.39 (s, 6H, CH_3); ^{13}C NMR (125.8 MHz, $CDCl_3$) $\delta = 196.4$, 143.2, 140.8, 136.2, 132.5, 131.4, 128.0, 128.0, 127.6, 127.4, 127.4, 126.8, 126.6, 47.3, 43.3, 21.2; LR *m/z* (EI) 346 $(M)^+$, 242, 209, 179, 137, 105, 77, 51; HRMS *m/z* (EI+) calculated for $C_{23}H_{22}OS$ $(M+H)^+$ 346.1391, found $(M+H)^+$ 346.1388; HPLC (CHIRALPAK AD, ISO 99.5+0.5, 0.5 mL min^{-1}, 60 min, 254 nm) t_R 27.61 (46%, *R*), 41.70 (54%, *S*).

(*S*)-4-(2,6-Dimethyl-phenylthio)-4-phenyl-butan-2-one (17). Obtained in 31% yield (4% ee) according to the general procedure, after 6 h. $[\alpha]_D^{20}$ +2.0 (*c* 5 in $CHCl_3$, 4% ee, *S*); ν_{max}(film)/cm^{-1} (neat) 3029, 2923, 1717, 1454, 1360, 1154, 1021, 774, 727, 697; ^1H NMR (500 MHz; $CDCl_3$) $\delta = 7.23–7.19$ (m, 3H, CH_{ar}), 7.14–7.09 (m, 3H, CH_{ar}), 7.06–7.02 (m, 2H, CH_{ar}), 4.45–4.42 (dd, 1H, *J* 4.4, CH), 3.15–2.99 (ddd, 2H, *J* 3.1, CH_2), 2.37 (s, 6H, CH_3), 2.07 (s, 3H, CH_3); ^{13}C NMR (125.8 MHz, $CDCl_3$) $\delta = 205.9$, 144.3, 141.6, 132.3, 129.0, 128.7, 128.4, 127.8, 127.7, 49.0, 47.9, 31.0, 22.2; LR *m/z* (EI) 284 $(M)^+$, 138, 121, 105, 77, 51; HRMS *m/z* (EI+) calculated for $C_{18}H_{20}OS$ $(M+H)^+$ 284.1235, found $(M+H)^+$ 284.1232; HPLC (CHIRALPAK AD, ISO 99.5+0.5, 0.5 mL min^{-1}, 60 min, 254 nm) t_R 20.02 (48%, *R*), 36.59 (52%, *S*).

Crystallographic data for 22. $Ru(C_{49}H_{25}F_{20}O_3P_2)\cdot(SbF_6)\cdot 2(C_6H_8O)$, Monoclinic *P*21, $a = 11.3765(3)$, $b = 20.5459(5)$, $c = 14.0307(3)$ Å, $\beta = 108.148\ (2)°$, $U = 3116.40(13)$ $Å^3$, $Z = 2$, $\mu = 0.854$ mm^{-1}, $d_x = 1.737$ g cm^{-3}, Mo-Kα radiation ($\lambda = 0.71073$ Å); 182349 independent reflections measured at 150 K, 17612 unique reflections ($R_{int} = 0.038$) of which 15610 with $|Fo| > 2\sigma(Fo)$. Full-matrix least-squares refinement based on F^2 gave final values $R = 0.0317$, w$R = 0.0652$, and $S = 0.8884$ for 959 variables and 17597 contributing reflections, using 259 restrains. The Flack parameter was determined to be $x = 0.013(9)$.

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28 NMR experiments were carried out in degassed, dry [D_8]THF, at –20 °C and under N_2, keeping the ratios between components as in the catalytic reactions. For practical reasons, no molecular sieves were used. Peaks of residual THF were used as internal standard in the ^{1}H NMR analyses that preceded all ^{31}P NMR spectra. Analyses were carried out on a Bruker Avance 500 spectrometer.

