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Cycloruthenated compounds as efficient catalyst for asymmetric hydride transfer reaction*

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Abstract: Cycloruthenated complexes obtained by direct C–H activation of enantiopure aromatic primary and secondary amines are efficient catalysts in asymmetric hydride transfer reaction. Reduction of acetophenone has been achieved rapidly with enantiomeric excesses (ee's) ranging from 38 to 89 %. The importance of Ru–C bond in the catalytic efficiency is highlighted.

Keywords: cyclometallation; chirality; enantioselectivity; ketones; high-throughput experiments; reduction; catalysis; amines; ruthenium.

Transition-metal complexes built up with neutral bidentate chelates have been widely investigated as catalysts in the past three decades. Within this family of organometallic compounds, those containing metallacycles have recently emerged as a very efficient class of catalyst precursors [1–3], especially when the metal is palladium. We recently developed a new family of such metallacyclic compounds based on Ru(II) and chiral benzylic amines as catalysts precursors [4], which show an interesting potential in asymmetric catalysis. In the past few years, some examples of related ruthenacycles have been reported to be active catalysts in hydrogen transfer reactions [5–7], but only a few examples were known to display an asymmetric activity with rather poor enantioselectivity [5]. We report herein some results obtained in the field of asymmetric transfer hydrogenation of acetophenone with a library of cycloruthenated compounds, as well as some evidence showing the involvement of the metallacycle unit in the catalytic process.

A first attempt was performed with complex **1** (Fig. 1), derived from (*R*)-*N*,*N*-dimethyl-1-phenylethylamine [8]. We investigated the reduction of acetophenone using isopropanol as hydrogen donor. At room temperature, after 15 h, the conversion was 75 % and the enantioselectivity 12 %. As complex **1** was only fairly active, we investigated other amines as ligands in order to improve the efficiency of this compound. To check whether the presence of NH groups [9–11] would enhance both the activity and the selectivity of the reaction, we have synthesized complex **2**, analogous to **1**, but that was derived from the primary amine (*R*)-1-phenylethylamine [4]. The cycloruthenation of the latter ligand

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was thus performed in good yields (>70 %) in CH_3CN, at room temperature, in the presence of KPF_6 and NaOH. Complex **3** was also obtained in good yield (60 %) following the reaction conditions described in Fig. 2.

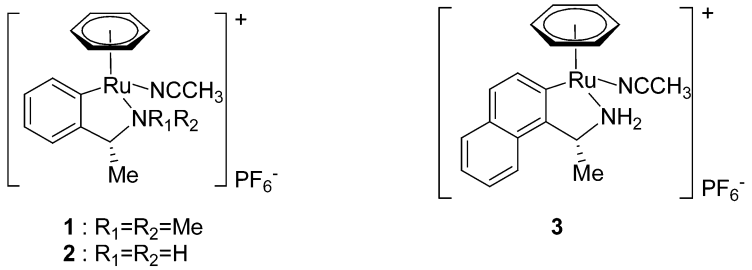

Fig. 1 Ruthenacycles used as hydrogen transfer catalysts.

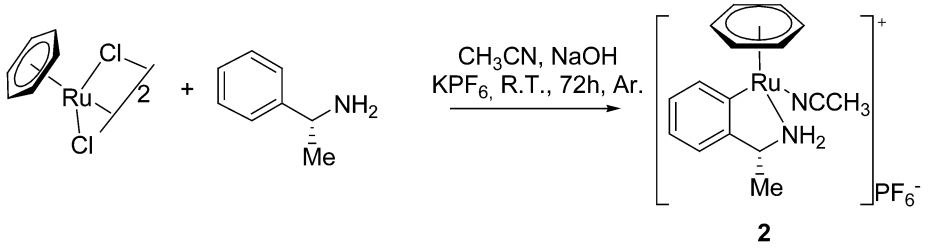

Fig. 2 Cycloruthenation reaction of a primary amine.

The cycloruthenated compounds **2** and **3** were characterized via combustion analysis (C,H,N), crystal structure determinations [4,13], and ^1H and ^{13}C NMR spectroscopy. The disappearance of one aromatic proton of the amine, the chemical shift of the proton ortho to the ruthenium atom and that of the η^6-benzene unit are particularly diagnostic of the existence of a cycloruthenated unit [8]. For example, in compound **3** the signals of the proton *ortho* to the Ru–C bond and that of the benzene ligand were shifted to higher frequencies by ca 0.5 ppm as compared to the corresponding protons in compound **4** (see below) in which the 1-naphthylethylamine was coordinated to the ruthenium atom via the nitrogen atom only.

The catalytic properties of **2**, under the same conditions as those used for **1**, were significantly improved since within less than an hour, the conversion was complete and the selectivity (ee) rose to 38 %. The search for the design of the best catalysts has been achieved by screening commercially available chiral benzylic amines with the help of a high-throughput experiment (HTE) [12]. Having established that cycloruthenation is an easy reaction to perform, we were able to find experimental conditions suitable for a one-pot synthesis and a reactivity study of these new catalyst precursors. A selection of a set of amines is represented in Fig. 3, and the results obtained in the hydrogen transfer reaction are presented in Fig. 4.

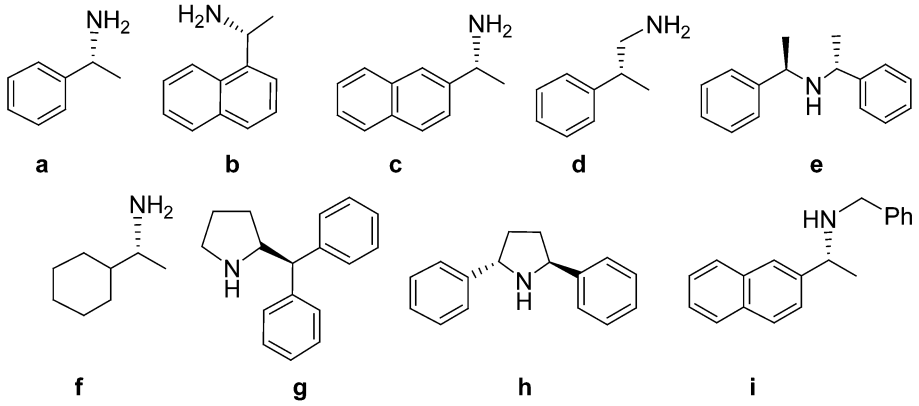

Fig. 3 The ligand library.

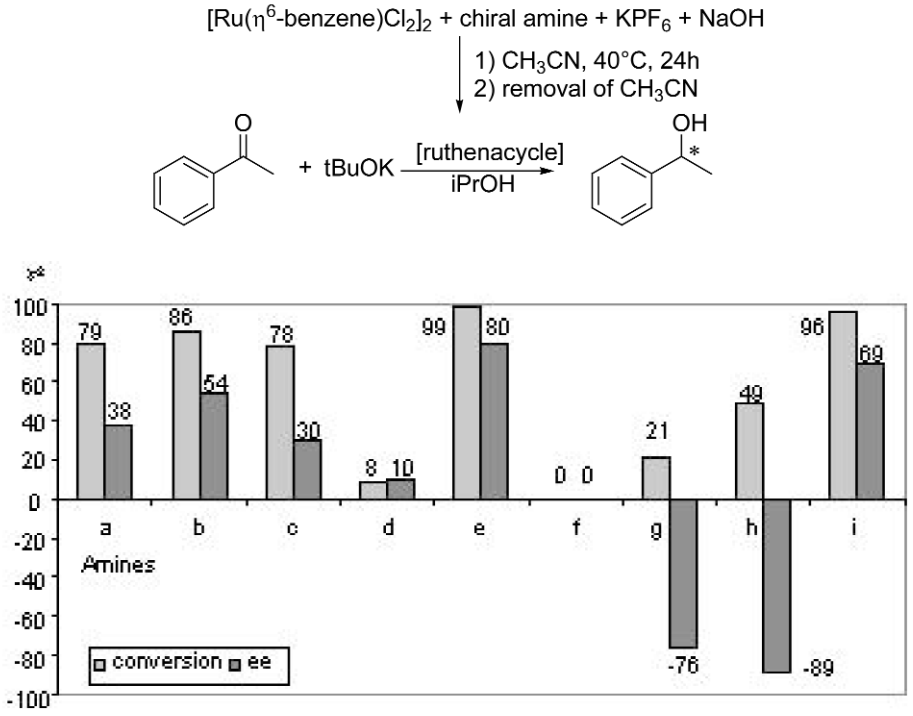

Fig. 4 HTE screening of chiral amines in Ru-catalyzed asymmetric transfer hydrogenation of acetophenone. Positive ee's correspond to the *R* configuration of 1-phenylethanol.

The analysis of the results collected in this HTE revealed that ruthenacycles are good to very good catalyst precursors for the hydrogen transfer reaction. The enantioselectivities ranged from 10 to 89 %. With the amine **a**, we found that the in situ formed catalyst and the isolated catalyst (vide supra) led to identical enantioselectivity. The best ee's were obtained with the hindered secondary amines **e** and **h**. The amine **f** led to no activity at all. This latter result is very likely due to the lack of aromatic protons on this amine, this preventing obviously the cyclometallation taking place. With **d**, both yield and selectivity were low: The formation of metallacycles containing a 6-membered ring is usually disfavored compared to 5-membered rings, therefore, we may connect the poor catalytic activity with a low cyclo-

metallation yield. This was likely to be the case also for the amine **g**, which led to low yields of alcohol. However, in this case, the selectivity was much improved as compared to the previous amine, this being probably due to the presence of a cyclic secondary amine analogous to that present in compound **h**, which proved to be the best choice of amine so far. These results finally hint that only ruthenacycle-containing compounds are the likely catalytic precursors for the hydrogen transfer reaction.

To confirm this hypothesis, we synthesized the complex **4** in which the amine **b** is only bound to Ru via the N atom [14]. Compound **4** was synthesized in quantitative yield by mixing 1 equiv of $[Ru(\eta^6\text{-benzene})Cl_2]_2$ and 2 equiv of amine in CH_2Cl_2 (Fig. 5). The coordination of the amine **b** onto the Ru in CH_3CN, in the presence of KPF_6, but without base, led to a mixture of **4** and most probably the cationic mono-chloro, mono-acetonitrile *N*-coordinated complex, **5**. The ^1H NMR spectra (CD_3CN) of both compounds displayed the signals of 7 aromatic protons for the naphthyl units. Moreover, **5** was found to be a 1:1 mixture of two diastereoisomers as evidenced by the signals of the η^6-benzene ligand (5.68 and 5.69 ppm), whereas two signals only were found for the diastereotopic NH_2 unit (4.41 and 3.81 ppm). Compound **4** crystallized upon slow evaporation of CH_3CN from this mixture, however, **5** could not be isolated in a pure form as it was contaminated by **4**. The X-ray crystal structure of **4** was obtained, and the ORTEP plot of **4** is shown in Fig. 6.

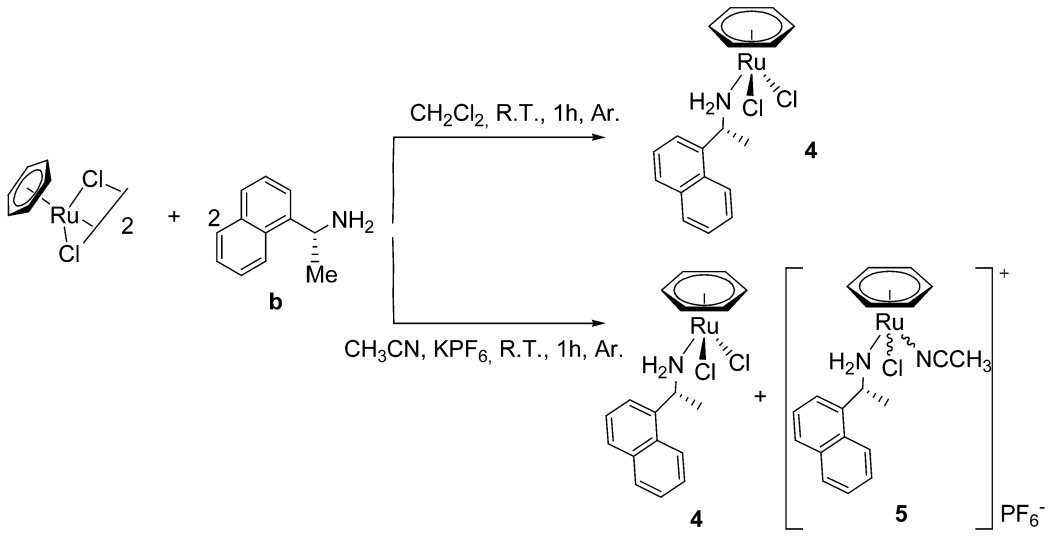

Fig. 5 Synthesis of compound **4**.

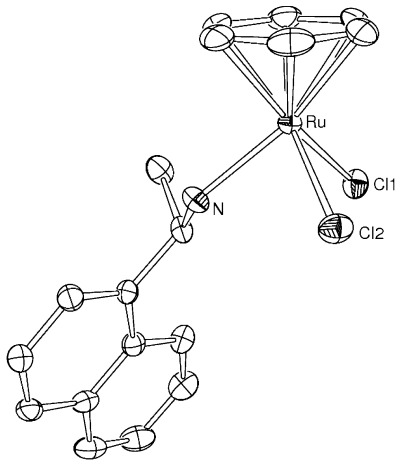

Fig. 6 ORTEP view of **4**.

We compared the activity of **3**, **4**, and the mixture (**4** + **5**) in transfer hydrogenation reactions (Fig. 7) [13]. The reduction with **3** was fast (95 %, 20 min), and the selectivity (60 %) was in agreement with that found with the HTE (see **b** in Fig. 4).

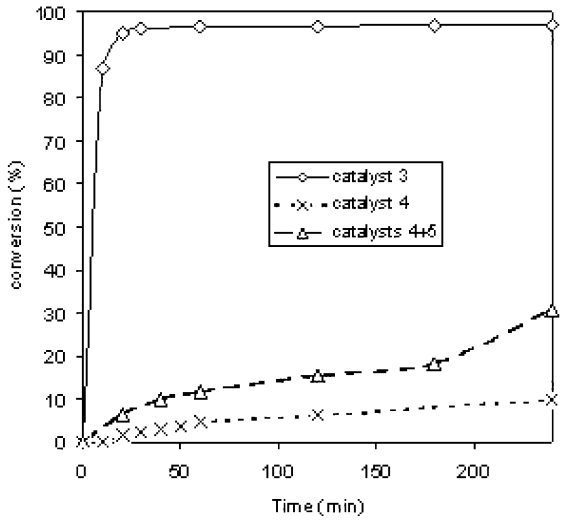

Fig. 7 Catalytic activities of **3**, **4**, and (**4** + **5**).

By comparison, for complex **4**, the reaction rate was very low: The conversion was about 1 % after 20 min, and it remained below 10 % after 4 h. Moreover, the selectivity measured was nil. The activity of the mixture containing additional amounts of **5** was remarkably different, as the conversion rate increased after 2 h and the enantioselectivity (55 %) was close to that observed with **3**.

These figures should be connected to the mechanism of the cycloruthenation reaction. It was postulated [8] that cationic species analogous to **5** are likely to be formed as intermediates prior to the cyclometallation reaction which occurred in the presence of a base. In the catalytic process, an excess of base (*t*BuOK) is indeed present, and hence the conditions necessary for the cycloruthenation to occur are fulfilled when **5** is present in the reaction mixture. In marked contrast, no cyclometallation should

take place when the neutral compound **4** only is used as a catalyst. Thus, the enantioselectivity measured in the catalytic reduction of the ketone in the presence of **5** must be due to the conversion of **5** into **3** during the process, this result highlights the fact that the presence of a cyclometallated ring is a prerequisite for both high activities and selectivities in this catalytic reaction.

Finally, we have found that using a higher [substrate]/[catalyst] ratio (10^4), the performance of the catalyst was markedly increased at 80 °C. Thus, with compound **3** as catalyst, TON and TOF values of 10^4 and 3.10^4 h^{-1}, respectively, were observed ([substrate] = 0.1 M). This result is a convincing argument showing the increased activity and robustness of cycloruthenated catalysts, a feature that was mentioned earlier for related compounds containing the P,C,P terdentate ligands [6,7].

CONCLUSION

We have shown that ruthenacyclic compounds obtained via the cyclometallation reaction of enantiopure primary and secondary amines are good catalyst precursors for the asymmetric transfer hydrogenation reaction of prochiral ketones. We have demonstrated the importance of the presence of the metallacyclic moiety in these compounds to achieve efficient reduction catalysis. This family of new original catalysts is easily extendable to a large scope of amines, especially with the use of HTE, and also to a larger scope of catalytic processes such as carbon–carbon and carbon–heteroatom bond syntheses [1]. The question of why these compounds that contain a C–Ru bond stabilized by intramolecular coordination of an amine function are that active in the hydrogen transfer reaction is not clearly understood yet. Further work is in progress to elucidate the mechanism of the reaction, with the hope that this will shed light on this phenomenon.

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