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Cycloruthenated Primary and Secondary Amines as Efficient Catalyst Precursors for Asymmetric Transfer Hydrogenation

Jean-Baptiste Sortais,[†] Vincent Ritleng,[†] Adeline Voelklin,[†] Alexandre Holuigue,[†] Hakima Smail,[†] Laurent Barloy,[†] Claude Sirlin,[†] Gerard K. M. Verzijl,[‡] Jeroen A. F. Boogers,[‡] André H. M. de Vries,[‡] Johannes G. de Vries,*[,‡] and Michel Pfeffer*[,†]

CNRS, UMR 7513, Laboratoire de Synthèses Métallo-Induites, Université Louis Pasteur, 4 rue Blaise Pascal, 67000 Strasbourg, France, and DSM Pharma Chemicals, Advanced Synthesis, Catalysis and Development, P.O. Box 18, 6160 MD Geleen, The Netherlands

hans-jg.vries-de@dsm.com; pfeffer@chimie.u-strasbourg.fr

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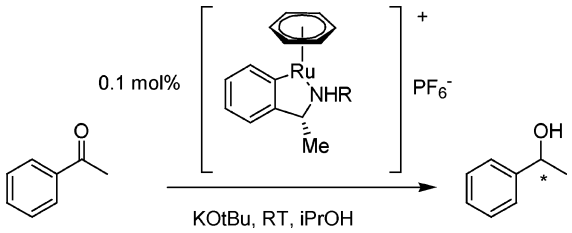
ABSTRACT



Ruthenacycles obtained by cyclometalation of enantiopure aromatic primary or secondary amines with [(η^6-benzene)$RuCl_2$]$_2$ or with [(η^6-p-cymene)$RuCl_2$]$_2$ are efficient catalysts for asymmetric transfer hydrogenation (TOF up to 190 h^{-1} at room temperature). Enantioselectivities in the transfer hydrogenation of acetophenone ranged from 38% to 89%. It is possible to prepare the catalysts in situ, which allows the use of high throughput experimentation.

Among the very large palette of polydentate ligands that have proven to be useful in homogeneous catalysis, the so-called cyclometalated ligands, i.e., those ligands that are bound to the metal via a carbon−metal σ bond, stabilized by one or two intramolecular dative heteroatom to metal bonds, are currently the subject of intensive investigation.[1] Indeed, almost a decade ago it was shown that cyclopalladated phosphorus-, nitrogen-, or sulfur-containing ligands were interesting catalyst precursors for the formation of a whole range of C−C as well as C−H or C−X bonds.[2] The apparent efficiency (activity: TOF, TON) of these Pd(II) complexes was very frequently found to be several orders of magnitude higher than that of the known classical Pd(0) catalysts stabilized by mono- or polydentate phosphine ligands.[1,2] It is now generally accepted that these cyclopalladated compounds are in fact interesting reservoirs of ligand-free Pd(0) species that form the genuine active catalysts.[3] In contrast to their palladium counterparts, cyclometalated complexes

[†] Université Louis Pasteur.
[‡] DSM Pharma Chemicals.

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based on ruthenium have been much less studied. Recently, a few groups have reported the catalytic properties of NCN, PCP, and CP cycloruthenated terdentate and bidentate ligands, and interesting activities for the transfer hydrogenation of ketones were found.[4] Some of us have recently published a general way to attain the cycloruthenation of aromatic tertiary amine derivatives,[5] and we wondered whether these cycloruthenated compounds might display catalytic activities. In this communication we disclose our first results showing not only that cycloruthenated compounds are efficient catalyst precursors for the asymmetric transfer hydrogenation of prochiral ketones[6] but also that their synthesis may be performed in situ, thus avoiding an unnecessary time-consuming workup for their purification procedures.

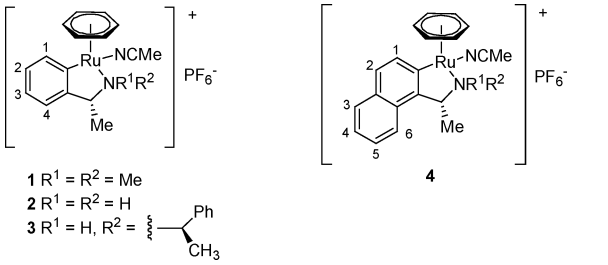
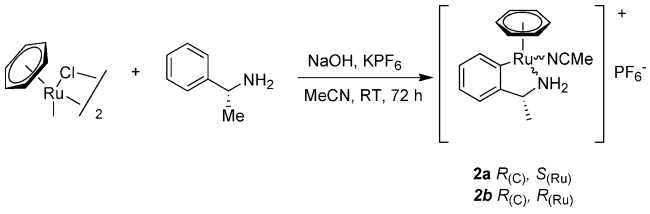


Figure 1. Ruthenacycles.

We found that the enantiopure compound **1**, which was synthesized earlier,[5] exhibited a poor activity when used as a catalyst for the asymmetric transfer hydrogenation of acetophenone with 2-propanol. Indeed, performing the reaction at room temperature with 1 mol % of catalyst afforded 48% conversion after 2 h and 75% conversion after 15 h and the enantioselectivity was very low (ee = 10%). Looking for ways to improve the catalytic activity as well as the enantioselectivity, we decided to investigate the importance of the substituents on nitrogen. Although the cyclometalation of primary or secondary arylalkylamines by palladium(II) has been well studied, nothing is known about this reaction with ruthenium.[7] We have applied our cycloruthenation procedure to (*R*)-1-phenylethylamine with the hope of achieving the cyclometalation reaction (Scheme 1).[5] Optimizing the reaction conditions by performing the reaction at room temperature instead of 45 °C and allowing the reaction to proceed for a longer period (72 h) afforded the expected compound **2** with a good yield (ca. 70%). Combustion analysis, as well as ^{1}H and ^{13}C NMR data were in accord with the structure of **2**.[8] The complex consisted of a mixture of the two diastereomers **2a** and **2b** that differ in the configuration of the metal. An X-ray diffraction study on a single crystal of **2a** has been performed and its ORTEP is depicted in Figure 2.

Scheme 1. Synthesis of Ruthenacycle 2



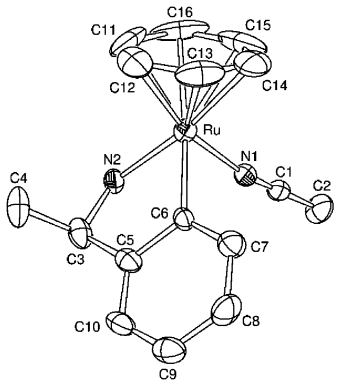
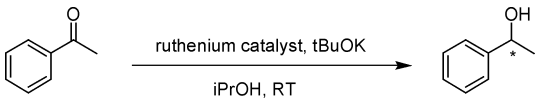


Figure 2. X-ray structure of **2**.

We found that the new compound **2** was a much more efficient catalyst for the asymmetric transfer hydrogenation of acetophenone by 2-propanol than compound **1**, as under similar conditions the reaction was complete within 1 h at room temperature (97%) and the enantioselectivity of the reaction was significantly improved (ee = 38%, see Table 1, entry 2). No mechanistic studies have been performed so

Table 1. Ruthenacycle-Catalyzed Asymmetric Transfer Hydrogenation of Acetophenone[a]



entry	catalyst	[S] (mol L^{-1})[b]	[S]/[C][c]	time (min)	yield[d] (%)	ee[d] (%)
1	**1**	0.1	100	120	48	10 (S)
2	**2**	0.1	100	60	97	38 (S)
3[e]	**2**	0.1	200	270	80	38 (S)
4	**3**	0.1	100	30	96	76 (S)
5[f]	**3**	0.1	100	120	95	**85** (S)
6	**4**	0.1	100	10	90	57 (S)
				60	100	47 (S)
7	**4**	0.01	100	20	79	62 (S)
				60	100	61 (S)
8	**4**	0.01	1000	240	76	61 (S)

[a] Conditions: ketone (1 mmol) in 10 mL of *i*PrOH; S:C:*t*BuOK = 100:1:5, room temperature, unless noted otherwise. [b] Initial substrate concentration. [c] [substrate]/[catalyst] ratio. [d] Determined by GC. The absolute configuration of the major enantiomer is given in parentheses. [e] Reaction performed with catalyst prepared in situ. For details see Table 2. [f] At 0 °C.

far, but we can speculate that the increased activity is due to a mechanism involving the NH proton as in the Noyori transfer hydrogenation mechanism.[9]

At this stage we investigated whether we could modify the reaction conditions in order to be able to perform it in a high-throughput experimentation (HTE) procedure.[10] Thus, we first checked in a single Schlenk tube that the yield and the selectivity of the catalytic reaction were comparable to those reported above when **2** was prepared in situ, i.e., in the conditions depicted. The ruthenacyclic compound **2** was therefore not isolated, and the reaction mixture was used as such after removal of the solvent (MeCN) in vacuo. A good agreement was observed between the catalytic results obtained with pure **2** and those obtained in the in situ process (compare entries 2 and 3, Table 1). For the HTE experiments, we then assembled a focused library of chiral primary and secondary amines (**a**-**i**) that were treated in situ either with $[(\eta^6\text{-benzene})RuCl_2]_2$ or with $[(\eta^6\text{-p-cymene})RuCl_2]_2$ under the cycloruthenation conditions (Figure 3).[5]

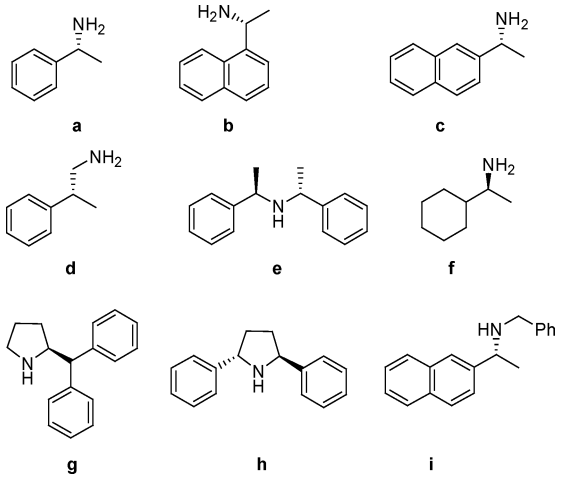
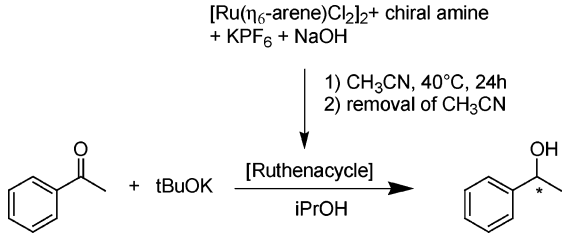


Figure 3. Ligand library.

The analysis of the results obtained after performing the catalytic asymmetric reduction of acetophenone in 2-propanol

Table 2. High-Throughput Screening of Chiral Amines in Ruthenium-Catalyzed Asymmetric Transfer Hydrogenation of Acetophenone[a]



entry	amine	arene	yield[b] (%)	ee[b] (%)
1	**a**	benzene	79	38 (S)
2	**a**	*p*-cymene	10	37 (S)
3	**b**	benzene	86	54 (S)
4	**b**	*p*-cymene	5	56 (S)
5	**c**	benzene	78	30 (S)
6	**c**	*p*-cymene	38	25 (S)
7	**d**	benzene	8	10 (S)
8	**d**	*p*-cymene	35	24 (S)
9	**e**	benzene	99	**80** (S)
10	**e**	*p*-cymene	79	44 (S)
11	**f**	benzene	0	
12	**f**	*p*-cymene	4	9 (S)
13	**g**	benzene	21[c]	76 (R)
14	**h**	benzene	49[c]	**89** (R)
15	**i**	benzene	96[c]	69 (S)
16	**i**	benzene	20[c,d]	**86** (S)

[a] Conditions: [substrate] = 93 mM; [substrate]/[base]/[catalyst] = 56/1.5/1; t = 4.5 h unless stated otherwise. [b] Determined by GC. The absolute configuration of the major enantiomer is given in parentheses. [c] After 1 h. [d] At 0 °C.

(Table 2) revealed that these cycloruthenated primary and secondary amines are indeed excellent transfer hydrogenation catalysts and that both activity and enantioselectivity can be influenced by the choice of the chiral amine. No activity was observed in the vial containing the aliphatic amine **f**. This amine cannot be cycloruthenated because of the absence of an aromatic ring. This result confirms that a 1:1 combination of ruthenium precursor and a primary amine is not sufficient to elicit transfer hydrogenation activity. This corroborates our assumption that the activity in these HTE reactions is due to the formation of ruthenacycles. Activity of the catalyst based on ligand **d** was low. This may well be due to the less facile formation of the six-membered ruthenacycle (although Vicente was able to synthesize the

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analogous palladacycle).[7a] Good activities and good enantioselectivities were found for the catalysts formed in situ with the other aromatic amine ligands (see Table 2, entries 1−6, 9−10, and 13−16). Again, the results found with (*R*)-1-phenylethylamine (**a**) were almost identical to those obtained previously with the isolated catalyst **2**, this fact being a strong indication that cycloruthenated species have indeed been formed in the HTE. In general, a marked decreased efficiency on going from the benzene to the *p*-cymene derivatives was observed, this being also indicative of the presence of cycloruthenated units in the catalytically active species. Indeed cycloruthenation is typically an electrophilic substitution reaction like cyclopalladation,[11] and the use of a *p*-cymene ligand on the ruthenium center is usually detrimental to the cycloruthenation reaction, as this more electron releasing arene ligand markedly reduces the electrophilicity of the Ru center.[12] We found that the use of secondary amines led to high enantioselectivities. The secondary amine, bis[(*R*)-1-phenylethyl]amine **e**, induced high activity and good enantioselectivity (ee = 80%). Excellent results were also obtained with pyrrolidine-based ligands **g** and **h**, which induced the formation of (*R*)-1-phenylethanol in 76% and 89% ee, respectively. Ligand **i** led to formation of an extremely active ruthenacycle, which allowed us to test its activity at 0 °C. This resulted in an increase of the enantioselectivity of the alcohol of 69−86% albeit at a reduced rate.

To prove that cycloruthenated species were formed in these HTE experiments, we have analyzed the complexes **3** and **4** obtained after having treated the amines **e** and **b** respectively under the cycloruthenation procedures depicted above. We have isolated in both cases compounds containing a five-membered cyclometalated ring. We did not succeed in obtaining single crystals of any of these two species; however, the ^{1}H and ^{13}C NMR data and elemental analyses were informative enough to prove the success of the cyclometalation reaction.[8]

The catalytic activities of both pure cyclometalated compounds were also checked and found to be very similar to those of the catalysts generated in situ (compare the results in Table 1, entries 4 and 6 with those in Table 2, entries 9 and 3). Moreover we have also found it possible to improve the enantioselectivity of the reaction (i) by increasing the substrate dilution in 2-propanol 10-fold, which led to an increase in selectivity due to slowing down the reverse hydrogenation reaction at the cost of a minor loss in activity (Table 1, entry 7), and (ii) by performing the reaction at 0 °C, which led to an increase in the selectivity of ca. 10% for the best catalyst (85% ee, Table 1, entry 5). The catalysts were also rather robust as the substrate reduction could be repeated up to five times with the same catalytic mixture with loss in neither activity nor selectivity. A good activity was maintained after increasing the [substrate]/[catalyst] ratio to 1000, with no decrease of the enantioselectivity (Table 1, entry 8). The TOF of 190 h^{-1} obtained in this reaction is an order of magnitude higher than the rate obtained with the Noyori catalyst [Ru(TsDPEN)(C_6H_6)Cl] under similar conditions.[13]

In summary, we have shown that azaruthenacycles obtained in situ via cyclometalation of enantiopure aromatic amines following a very simple procedure are good catalysts for the asymmetric transfer hydrogenation of prochiral ketones. The HTE approach allows for their rapid testing on substrates of interest and the simplicity and associated low cost of the ligands will certainly ease their introduction in large-scale industrial production, thus increasing the arsenal of low-cost, easy-to-synthesize ligands.[14] It is clear that the commercially available enantiopure primary amines can easily be converted into a very large library of enantiopure secondary amines. Further work to explore the catalytic potential of these and related cycloruthenated species in other catalytic applications is under way.

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Supporting Information Available: Experimental details, spectral data, and crystallographic data in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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