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In situ catalytic activities of 1,3-dialkyltetrahydropyrimidinium salts/$[RuCl_2(p\text{-cymene})]_2$ system for transfer hydrogenation reactions

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Hydrogen-transfer reduction processes are attracting increasing interest from synthetic chemists in view of their operational simplicity. In the present study novel ruthenium carbene complexes were generated in situ and tested for their transfer hydrogenation reactions. The in situ prepared 3 component 1,3-dialkyltetrahydropyrimidinium salts (LHX)/$[RuCl_2(p\text{-cymene})]_2$ and KOH catalyzed quantitatively the transfer hydrogenation of ketones under mild reaction conditions in 2-propanol.

Key Words: Ruthenium, tetrahydropyrimidin-2-ylidene, *N*-heterocyclic carbene, transfer hydrogenation, ketone

Introduction

The reduction of ketones or aldehydes is an important reaction in organic synthesis. One of the most commonly used methods is transfer hydrogenation (Scheme 1); it is a valuable, atom-efficient reaction, and compared with conventional hydrogenation, using molecular hydrogen, transfer hydrogenation offers a safer, more cost

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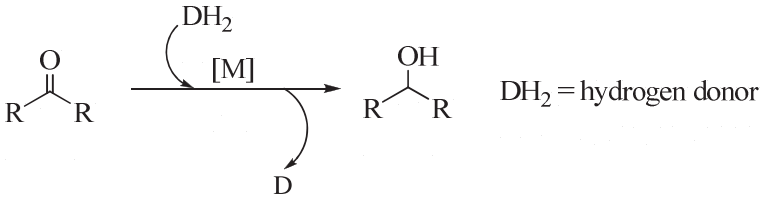
effective, and simpler experimental procedure. A large number of alcohols and other reagents are available as a source of hydrogen, and mild reaction conditions are used.[1] Transfer hydrogenation of ketones by 2-propanol is convenient in large-scale synthesis since there is no need to employ a high hydrogen pressure or to use hazardous reducing agents.[2]



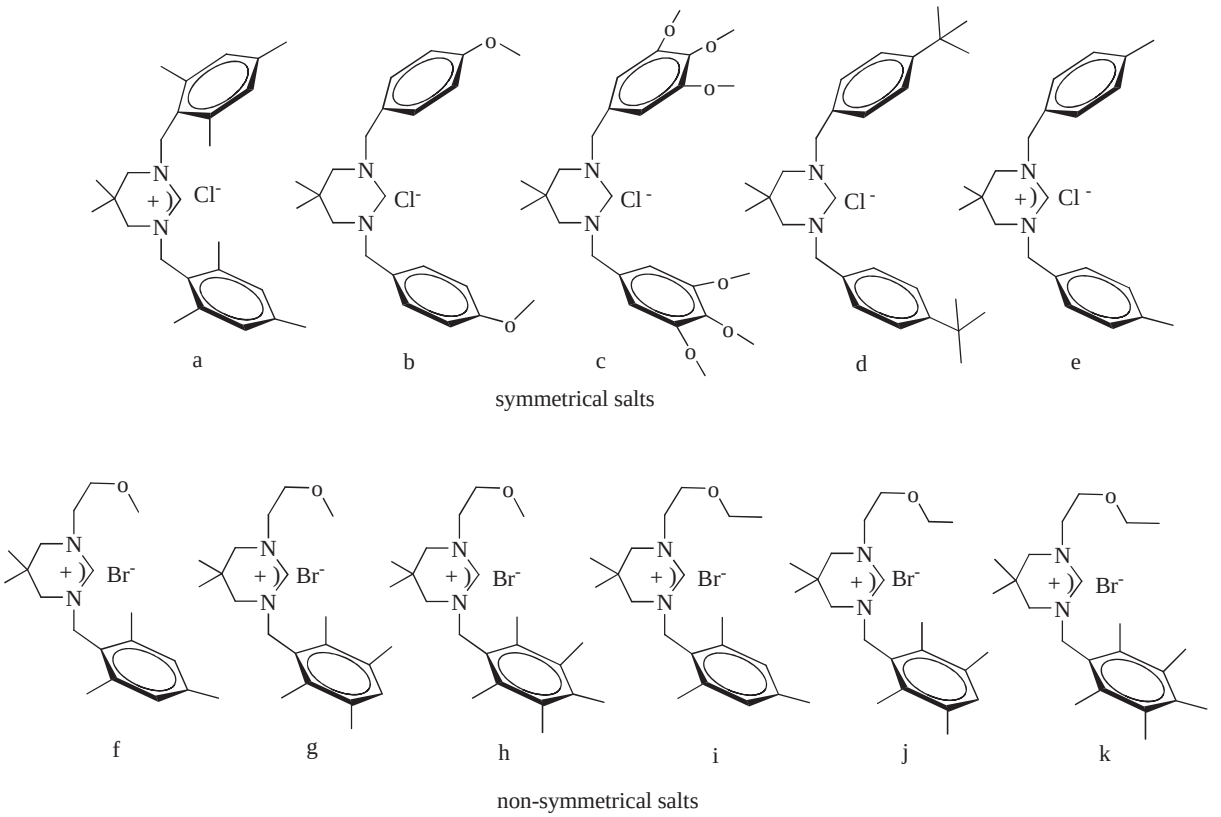
Scheme 1

A large number of ruthenium complexes have been reported as catalyst precursors for transfer hydrogenation of ketones and have shown high activity.[3–6] Several recent examples of ruthenium complexes bearing phosphane,[7–9] *N*-heterocyclic carbene,[10–12] diamin,[13,14] diaminodiphosphane or aminodiphosphane,[15–17] amine-bis(phenolate),[18] chiral phosphanes,[19–22] nitrogen containing chiral ligands,[23] and nitrogen containing heterocyclic ligands[24–28] have become the most prominent members for the reduction of ketones in high yields.

The use of *N*-heterocyclic carbene ligands (NHCs) for the preparation of homogeneous catalysts has now become one of the most productive fields in organometallic chemistry. Since 1995, when Herrmann reported the first use of a NHC ligand in the preparation of a homogeneous catalyst,[29] there have been enormous developments in NHC chemistry, which has been triggered by the search for enhanced or even new catalytic processes.[30–34] Probably one of the main benefits of NHCs is that their preparation is simple and that the coordination methodologies that are now available allow the preparation of NHC complexes of almost any transition metal in a variety of oxidation states, affording a wide set of potential catalytic applications. The nucleophilic *N*-heterocyclic carbenes (NHCs),[35] with stronger σ-donor properties than bulky tertiary phosphines,[36] have emerged as a new family of ligands. In contrast to metal phosphine complexes, the metal-NHC complexes appear to be extraordinarily stable towards heat, air, and moisture due to the high dissociation energies of the metal-carbon bond.[37]

Recently, research has also been devoted to the synthesis of functionalized ligands containing NHC moieties, in order to modify the ligand properties and catalytic activities.[38–41] The first application of NHC complexes for the transfer hydrogenation reaction was reported by Nolan in 2001.[42] With regard to transfer hydrogenations different carbene or carbene-phosphane systems containing Rh,[43,44] Ir,[45–47] Ru,[48–50] and Ni[51] have been reported.

Due to the economical benefit of Ru metal compared to Rh or Ir and the advantages of phosphine-free systems, it is an important goal to search for more active ruthenium carbene catalysts. Herein, we report the use of the in situ generated catalytic system composed of $[RuCl_2(p\text{-cymene})]_2$ as ruthenium source, 1,3-dialkyl-3,4,5,6- tetrahydropyrimidinium halide,[52] **1a-k**, (Scheme 2) as carbene precursors and KOH as a base for transfer hydrogenation of aryl ketones in 2-propanol.



Scheme 2. 1,3-Dialkyl-tetrahydropyrimidinium salts.

Experimental

All reactions for the preparation of **1** were carried out under Ar in flame-dried glassware using standard Schlenk-type flasks. The 1,3-dialkyl-tetrahydropyrimidinium salts (**1a-k**) were prepared according to known methods.[52] The solvents used were purified by distillation over the drying agents indicated and were transferred under Ar: Et_2O (Na/K alloy), C_2H_5OH (Mg). All reagents were purchased from Aldrich Chemical Co. ^{1}H-NMR and ^{13}C-NMR spectra were recorded using a Varian AS 400 Merkur spectrometer operating at 400 MHz (^{1}H) and 100 MHz (^{13}C) in $CDCl_3$ with tetramethylsilane as an internal reference. Column chromatography was performed using silica gel 60 (70-230 mesh). All reactions were monitored on an Agilent 6890N GC system by GC-FID with a HP-5 column of 30 m length, 0.32 mm diameter, and 0.25 μm film thickness.

Typical procedure for catalytic transfer hydrogenation of ketones

Under an inert atmosphere $[RuCl_2(p\text{-cymene})]_2$ (0.01 mmol), tetrahydropyrimidinium salts, **1a-1k**, (0.02 mmol), KOH (4 mmol), and 10 mL of *i*-PrOH were added to a small Schlenk tube and the mixture was stirred at room temperature for 0.5 h. Then ketone (1 mmol) was added to the mixture, which was heated at 80 °C for 1 h. The solvent was then removed under reduced pressure and product distribution was determined

by ^{1}H-NMR spectroscopy and GC. The yield calculations were based on the relative areas of signal peaks of chromatograms.

Results and discussion

The symmetric and non-symmetric tetrahydropyrimidinium salts **1** were prepared in a 3-step procedure starting from the 2,2-dimethyl-1,3-diaminopropane according to a known procedure.[52] The symmetrical salts were obtained via initial formation of diimine, which were reduced to diamine salts and then ring closing using triethylortoformate. The non-symmetrical salts were synthesized by monoalkylation, ring closure, and quaternization steps. The salts are air and moisture stable both in the solid state and in solution.

Catalytic reduction is preferred to stochiometric reduction for large-scale industrial uses of ketones hydrogenation.[53] Hydrogen gas presents considerable safety hazards especially for a large-scale reaction.[54] The use of solvent that can donate hydrogen overcomes these difficulties. 2-Propanol is a popular reactive solvent for the transfer hydrogenation since it is easy to handle (b.p. 82 °C) and is relatively non-toxic, environmentally benign, and inexpensive. The volatile acetone product can also be easily removed to shift an unfavorable equilibrium.[3] Owing to its efficiency in the transfer hydrogenation of acetophenone derivatives, in situ generated ruthenium complexes were further investigated by transfer hydrogenation of various methyl aryl ketones.

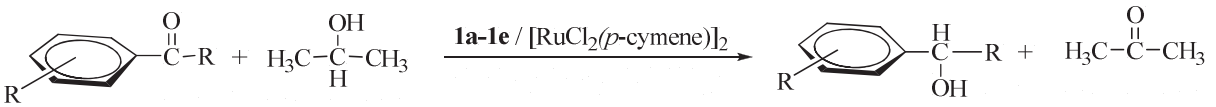
As the starting point, the performance of the catalysts in the transfer hydrogenation was screened by using acetophenone as a model substrate. In order to ensure complete formation of the active catalyst a 2-propanol solution of 1 mol% $[RuCl_2(p\text{-cymene})]_2$ and 2 mol% 1,3-bis(2,4,5-trimethylbeznyl)-5,5-dimethyl-3,4,5,6-tetrahydropyrimidine chloride (1a) was stirred in the presence of 4 mmol of KOH at room temperature for 0.5 h. Then acetophenone (1.00 mmol) was added and solution was produced at 80 °C over 1 h. The reactions were conducted at a substrate/catalyst/base (S/C/base) molar ratio of 1:0.01:4.

It is well known that transfer hydrogenation is sensitive to the nature of the base. For the choice of base, we surveyed K_2CO_3, KOH, NaOH, and *t*BuOK. Addition of bases like KOH or NaOH leads to similar final conversion, but the highest rate was observed when KOH was employed. In the absence of a base no transfer hydrogenation of the ketones was observed.

A variety of ketones were transformed to the corresponding secondary alcohols. Typical results are shown in Tables 1 and 2. Under those conditions *p*-methoxyacetophenone, 3,4,5-trimethoxyacetophenone, and *p*-floroacetophenone react very cleanly and in good yields with 2-propanol (Table 1, entries 8, 13, 28, and Table 2, entries 9, 14, 34).

Under the reaction conditions salt **1c** and **1h** proved to be most effective catalyst relative to other salts. The reduction of acetophenone with tetrahydropyrimidinium salts was completed within 1 h in high yields. It is evident that the NHC precursors that contain electron donating methoxyethyl, substituent (**1h**), are the most effective of the salts examined. Moreover, the best catalytic activity was observed with the salt bearing 3,4,5-trimethoxybenzyl substituent at the nitrogen atom.

Table 1. Transfer hydrogenation of ketones catalyzed by symmetrical tetrahydropyrimidium salts (**1a-1e**).[a]



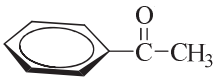
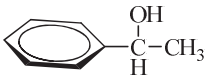
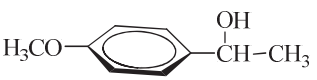
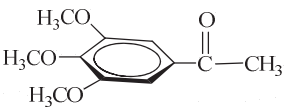
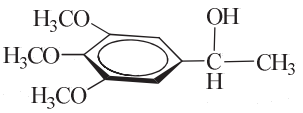
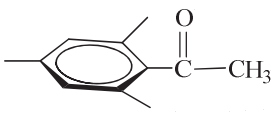
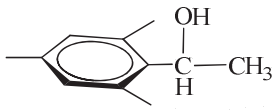
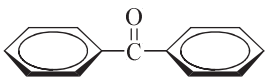
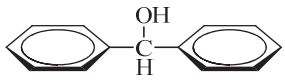
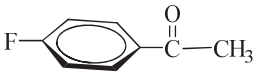
Entry	LHX	Substrate	Product	Yield(%)
1	**1a**			96
2	**1b**			91
3	**1c**			98
4	**1d**			98
5	**1e**			91
6	**1a**			95
7	**1b**			93
8	**1c**			98
9	**1d**			90
10	**1e**			89
11	**1a**			96
12	**1b**			95
13	**1c**			97
14	**1d**			98
15	**1e**			90
16	**1a**			67
17	**1b**			64

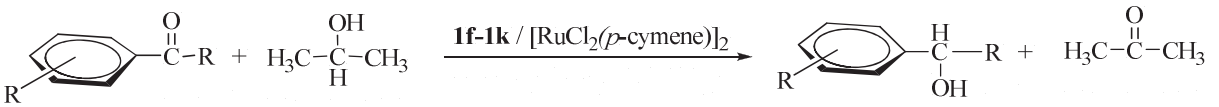
Table 1. Contunied.

Entry	LHX	Substrate	Product	Yield(%)
18	**1c**			72
19	**1d**			68
20	**1e**			62
21	**1a**			96
22	**1b**			96
23	**1c**			98
24	**1d**			97
25	**1e**			92
26	**1a**			90
27	**1b**			93
28	**1c**			99
29	**1d**			98
30	**1e**			90

[a] *Reaction conditions*: $[RuCl_2(p\text{-cymene})]_2$ (0.01 mmol), tetrahydropyrimidinium halide, **1a-1e**, (0.02 mmol), KOH (4 mmol), ^{i}PrOH (10 mL), substrate (1.0 mmol), 80 °C, 1 h. Purity of compounds is checked by GC and yields are based on ketones. The yield calculations were based on the relative areas of signal peaks of chromatograms.

The in situ catalytic system also catalyzed the transfer hydrogenation of benzophenone very effectively (Table 1 entries 21-25 and Table 2 entries 25-30). The conversion of ketones with bulky substituent on the aromatic ring was not observed or slightly decreased. For example, when 2,4,6- trimethylbenzyl-methyl ketone was used conversion decreased (Table 1 entries 16-20 and Table 2, entries 19-24). The general trend can be summarized as follows: **1e** < **1b** < **1a** < **1d** ∼ g**c** in the symmetrical salts and **1j** < **1i** < **1g** < **1k** < **1f** ∼ g**h** in the non-symmetrical salts.

Table 2. Transfer hydrogenation of ketones catalyzed by non-symmetrical tetrahydropyrimidinium salts (**1f-1k**).[a]



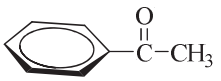
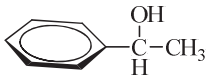
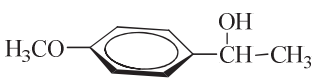
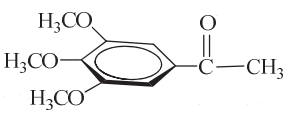
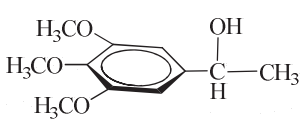
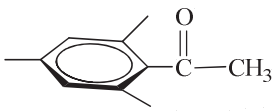
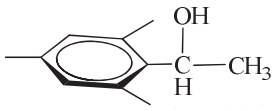
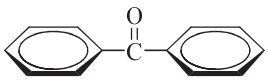
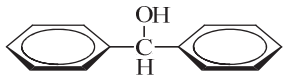
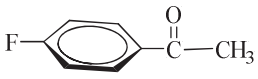
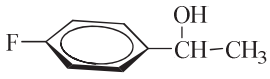
Entry	LHX	Substrate	Product	Yield(%)
1	**1f**			93
2	**1g**			92
3	**1h**			94
4	**1i**			92
5	**1j**			90
6	**1k**			93
7	**1f**			97
8	**1g**			96
9	**1h**			99
10	**1i**			90
11	**1j**			70
12	**1k**			90
13	**1f**			98
14	**1g**			95
15	**1h**			98
16	**1i**			96
17	**1j**			94
18	**1k**			97

Table 2. Contunied.

Entry	LHX	Substrate	Product	Yield(%)
19	**1f**			80
20	**1g**			68
21	**1h**			79
22	**1i**			67
23	**1j**			62
24	**1k**			69
25	**1f**			97
26	**1g**			91
27	**1h**			99
28	**1i**			84
29	**1j**			90
30	**1k**			98
31	**1f**			98
32	**1g**			96
33	**1h**			99
34	**1i**			97
35	**1j**			94
36	**1k**			99

[a] *Reaction conditions*: $[RuCl_2(p\text{-cymene})]_2$ (0.01 mmol), tetrahydropyrimidinium halide, **1f-1k**, (0.02 mmol), KOH (4 mmol), [i] PrOH (10 mL), substrate (1.0 mmol), 80 °C, 1 h. Purity of compounds is checked by GC and yields are based on ketones. The yield calculations were based on the relative areas of signal peaks of chromatograms.

Conclusions

We demonstrated the application of in situ prepared Ru catalysts containing carbene ligands. This concept for making catalysts in situ opens the way for the discovery of many new catalysts via the interaction of commercially available metal complexes and suitable electron releasing ligands. The 3,4,5,6tetrahydropyrimidin-2-ylidene ligand/$[RuCl_2(p\text{-cymene})]_2$ catalyst system disclosed herein represents an easy to handle, robust, and high yielding procedure for transfer hydrogenation reactions of ketones using 2-propanol in the presence of KOH. Furthermore, the procedure is simple and efficient towards various aryl ketones. Research in our lab is currently on-going to extend the coordination chemistry of functionalized NHCs to other transition metals such as Ru, Rh, Ag, and Au, and to explore their potential applications in catalysis.

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