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Catalytic activity of Ru/tetrahydropyrimidinium salts system for transfer hydrogenation reactions

Emine Özge Karaca[a], Nevin Gürbüz[a], Hakan Arslan[b], Don VanDerveer[c] and İsmail Özdemir[a]*

New 1,3-dialkyltetrahydropyrimidinium salts as NHC precursors have been synthesized and characterized. The *in situ* prepared three-component 1,3-dialkyltetrahydropyrimidinium salts/[$RuCl_2$(*p*-cymene)]$_2$ and KOH catalyzes quantitatively the transfer hydrogenation of ketones under mild reaction conditions in 2-propanol. Also, the molecular structure of 1,3-bis(2-methylbenzyl)-3,4,5,6-tetrahydropyrimidinium was determined using single-crystal X-ray diffraction. Ions of the title compound are linked by C–H…Cl and O–H…Cl hydrogen bonding interactions. The N–C–N bond angle (124.3(2)°) and C–N bond lengths (1.316(3) and 1.314(3) Å) confirm the existence of strong resonance in this part of the molecule. Copyright © 2015 John Wiley & Sons, Ltd.

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Keywords: ruthenium; tetrahydropyrimidin-2-ylidene; *N*-heterocyclic carbine; 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; it is a valuable, atom-efficient reaction, and compared with conventional hydrogenation, using molecular hydrogen, transfer hydrogenation offers a safer, more cost-effective and simpler experimental procedure. Transfer hydrogenation is the addition of hydrogen to an unsaturated molecule using a reagent other than H_2. Although the direct hydrogenation of ketones is more widely applied, transfer hydrogenation is an attractive alternative. This method is often more convenient and frequently less hazardous than direct hydrogenation with H_2 gas.[1,2] Transfer hydrogenation reactions require typically a hydrogen donor such as 2-propanol together with a strong base and transition metal catalyst, and are preferred for large-scale industrial use in the hope of developing a greener process by reducing waste production and energy use and lowering toxicity.[3] Catalytic transfer hydrogenation represents a viable alternative to the more classical reduction method using molecular hydrogen or metal hydrides.[4] Among various possible hydrogen sources, alcohols,[4,5] water,[6] formic acid[7] and alkylammonium formates[8] have found the broadest applications. So far, the transfer hydrogenation reaction has been extensively studied and continues to generate a high degree of interest, given the need to develop environmentally friendly and simple processes.[9]

The NHC ligand set has become well established in homogeneous transition metal catalysis of many transformations,[10,11] including direct and transfer hydrogenation. Of the many reactions that have been investigated using NHC-containing catalysts, hydrogenation and transfer hydrogenation have featured prominently, which is in part due to their wide-ranging use in synthetic chemistry and continued industrial importance. The first application of an NHC–Ru complex for the transfer hydrogenation reaction was reported by Grubbs and co-workers in 2001.[12] In NHC chemistry transfer hydrogenation has been described for ruthenium,[13–17] rhodium,[18–22] iridium,[18–20,23–26] osmium,[27] nickel[28] and palladium[29] pre-catalysts for the reduction of carbonyl, imine and nitro functionalities.

The nature of the NHC ligand has a tremendous influence on the rate of catalyzed reactions. Whilst modifications to the five-membered ring of the ligand aryl substituent have been described, relatively little attention has been paid to the effect of the ring size. Due to their six-membered ring geometry, tetrahydropyrimidin-2-ylidenes are stronger σ-donating ligands in comparison to their five-membered relatives.[30]

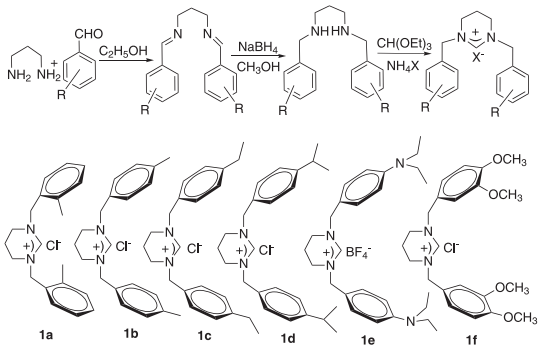
We have previously reported imidazolidine, benzimidazole-2-ylidene–ruthenium(II) complexes and an *in situ* formed tetrahydropyrimidine–ruthenium(II) system which exhibit high activity.[31–33] In order to find more efficient ruthenium catalysts we have prepared a series of new 1,3-dialkyl-3,4,5,6-tetrahydropyrimidinium salts, **1a–f** (Scheme 1), and we now report the use of the *in situ* generated catalytic system composed of [$RuCl_2$(*p*-cymene)]$_2$ as ruthenium source, **1a–f** as carbene precursors and KOH as a base for the transfer hydrogenation of aryl ketones in 2-propanol for 1 h. All synthesized compounds were characterized using ^{1}H NMR, ^{13}C NMR and IR spectroscopy and elemental analysis, the results of which support the proposed structures. The molecular and crystal structure of 1,3-bis(4-methylbenzyl)-3,4,5,6-tetrahydropyrimidinium chloride salt was determined using the single-crystal X-ray diffraction technique.

* *Correspondence to: İsmail Özdemir, Inönü University, Catalysis Research and Application Center, 44280 Malatya, Turkey. E-mail: iozdemir@inonu.edu.tr*

a *Inönü University, Catalysis Research and Application Center, 44280 Malatya, Turkey*

b *Department of Chemistry, Faculty of Arts and Science, Mersin University, 33343 Mersin, Turkey*

c *Department of Chemistry, Clemson University, Clemson, SC, 29634 USA*



Scheme 1. Preparation 1,3-dialkyl-3,4,5,6-tetrahydropyrimidinium salts.

Experimental

Materials

All reactions for the preparation of **1** were carried out under argon in flame-dried glassware using standard Schlenk-type flasks. Chemicals and solvents were purchased from Sigma Aldrich Co. (Dorset, UK). The solvents used were purified by distillation over drying agents (Et_2O over Na/K alloy; C_2H_5OH over Mg) and were transferred under argon. Elemental analyses were performed by the İnönu University Scientific and Technology Center.

Melting Point Determination

Melting points were measured in open capillary tubes with an Electrothermal 9200 melting point apparatus and are uncorrected.

IR Spectroscopy

IR spectra were recorded as KBr pellets in the range 400–4000 cm^{-1} using an ATI UNICAM 1000 spectrometer.

NMR Spectroscopy

^1H NMR and ^{13}C NMR spectra were recorded using a Varian As 400 Merkur spectrometer operating at 400 MHz (^1H) or 100 MHz (^{13}C) in $CDCl_3$ with tetramethylsilane as an internal reference. The NMR studies were carried out using high-quality 5 mm NMR tubes. Signals are quoted in parts per million downfield from tetramethylsilane (0.00 ppm). Coupling constants (*J* values) are given in hertz. NMR multiplicities are abbreviated as follows: s, singlet; d, doublet; t, triplet; m, multiplet.

Gas Chromatography

All reactions were monitored using an Agilent 6890 N GC system with flame ionization detection with an HP-5 column of 30 m length, 0.32 mm diameter and 0.25 μm film thickness.

X-ray Diffraction

Single-crystal X-ray diffraction data were collected with a Rigaku AFC8S Mercury CCD diffractometer[34] using monochromated Mo Kα radiation. The structure was solved using direct and conventional Fourier methods.[35] Full-matrix least-squares refinement[35] was based on F^2. Apart from hydrogen, all atoms were refined anisotropically; hydrogen atom coordinates were calculated at idealized positions and refined using a riding model. Further details concerning data collection and refinement are given in Table 1. Molecular graphics were prepared with SHELXTL software.[36]

General Preparation of 1,3-Dialkyl-3,4,5,6-tetrahydropyrimidinium Salts (1)

Aromatic aldehyde (20 mmol) and 1,3-propanediamine (10 mmol) were stirred overnight in methanol. The diimine was collected as a white solid, filtered and recrystallized from an alcohol–ether mixture. The diimine (10 mmol) was subsequently reduced using $NaBH_4$ (30 mmol) in CH_3OH (30 ml). The solution was then treated with 1 N HCl, and the organic phase was extracted with CH_2Cl_2 (3 × 30 ml). After drying over $MgSO_4$ and evaporating, the diamine was isolated as a solid. The diamine was then treated in a large excess of triethyl orthoformate (50 ml) in the presence of 10 mmol of NH_4Cl or NH_4BF_4 at 110°C in a distillation apparatus until the removal of ethanol ceased. Upon cooling to room temperature, a colorless solid precipitated, which was collected by filtration and dried under vacuum. The crude product was recrystallized from absolute ethanol to give colorless needles and the solid was washed with diethyl ether (2 × 10 ml) and dried under vacuum.

1,3-Bis(2-methylbenzyl)-3,4,5,6-tetrahydropirimidinium Chloride (1a)

Yield 5.17 g (90%); m.p. 107–108°C. IR, $\nu_{(CN)}$: 1670 cm^{-1}. ^1H NMR (399.9 MHz, $CDCl_3$, δ, ppm): 2.02 (quin, $J = 6$ Hz, 2H, $NCH_2CH_2CH_2N$), 2.38 (s, 6H, $CH_2C_6H_4(CH_3)$-2), 3.24 (t, $J = 6$ Hz, 4H, $NCH_2CH_2CH_2N$), 4.98 (s, 4H, $CH_2C_6H_4(CH_3)$-2), 7.18–7.30 (m, 8H, $CH_2C_6H_4(CH_3)$-2), 10.08 (s, 1H, NC*H*N). $^{13}C\{H\}$NMR (100.5 MHz, $CDCl_3$, δ, ppm): 18.9 ($NCH_2CH_2CH_2N$), 19.5 ($CH_2C_6H_2(CH_3)$-2), 41.9 ($NCH_2CH_2CH_2N$), 56.6 ($CH_2C_6H_4(CH_3)$-4), 126.6, 129.1, 129.7, 131.0, 131.2, 137.2 ($CH_2C_6H_4$

Table 1. Crystal data, data collection and refinement values for 1,3-bis (2-methylbenzyl)-3,4,5,6-tetrahydropyrimidinium chloride monohydrate

Crystal data	
$C_{20}H_{25}N_2 \cdot H_2O \cdot Cl$	$V = 1883.4(6)$ Å^3
$M_r = 346.89$	$Z = 4$
Monoclinic, $P2_1/n$	Mo Kα radiation, $\lambda = 0.71073$ Å
$a = 11.631(2)$ Å	$\mu = 0.21$ mm^{-1}
$b = 7.6612(15)$ Å	$T = 272$ K
$c = 21.136(4)$ Å	$0.48 \times 0.48 \times 0.14$ mm
$\beta = 90.22(3)°$	
Data collection	
Rigaku AFC8S Mercury CCD diffractometer	3374 independent reflections
Absorption correction: multi-scan Jacobson, R. (1998)	2921 reflections with $I > 2\sigma(I)$
$T_{min} = 0.905$, $T_{max} = 0.971$	$R_{int} = 0.025$
14 246 measured reflections	
Refinement	
$R[F^2 > 2\sigma(F^2)] = 0.055$	3 restraints
$wR(F^2) = 0.154$	H atoms treated by a mixture of independent and constrained refinement
$S = 1.05$	$\Delta\rho_{max} = 0.84$ e Å^{-3}
3374 reflections	$\Delta\rho_{min} = -0.32$ e Å^{-3}
225 parameters	

(CH_3)-2), 154.7 (NCHN). Anal. Calcd for $C_{20}H_{25}N_2Cl$ (%): C, 73.04; H, 7.16; N, 8.52. Found (%): C, 72.93; H, 7.16; N, 8.58.

1,3-Bis(4-methylbenzyl)-3,4,5,6-tetrahydropyrimidinium Chloride (1b)

Yield 5.11 g (89%); m.p. 214–215°C. IR, $\nu_{(CN)}$: 1684 cm^{-1}. ^1H NMR (399.9 MHz, $CDCl_3$, δ, ppm): 1.91 (quin, $J = 6$ Hz, 2H, $NCH_2CH_2CH_2N$), 2.31 (s, 6H, $CH_2C_6H_4(CH_3)$-4), 3.18 (t, $J = 6$ Hz, 4H, $NCH_2CH_2CH_2N$), 4.83 (s, 4H, $CH_2C_6H_4(CH_3)$-4), 7.13 and 7.28 (d, $J = 7.8$ Hz, 8H, $CH_2C_6H_4(CH_3)$-4), 10.47 (s, 1H, NCHN). $^{13}C\{H\}$NMR (100.5 MHz, $CDCl_3$, δ, ppm): 18.9 ($NCH_2CH_2CH_2N$), 21.2 ($CH_2C_6H_2(CH_3)$-4), 41.7 ($NCH_2CH_2CH_2N$), 58.1 ($CH_2C_6H_4(CH_3)$-4), 128.8, 129.8, 130.1, 138.8 ($CH_2C_6H_4(CH_3)$-4), 154.2 (NCHN). Anal. Calcd for $C_{20}H_{25}N_2Cl$ (%): C, 73.04; H, 7.16; N, 8.52. Found (%): C, 72.98; H, 7.18; N, 8.49.

1,3-Bis(4-ethylbenzyl)-3,4,5,6-tetrahydropyrimidinium Chloride (1c)

Yield 4.70 g (88%); m.p. 195–196°C. IR, $\nu_{(CN)}$: 1692 cm^{-1}. ^1H NMR (399.9 MHz, $CDCl_3$, δ, ppm): 1.74 (t, $J = 7.5$ Hz, 6H, $CH_2C_6H_4(CH_2CH_3)$-4), 2.49 (quin, $J = 6$ Hz, 2H, $NCH_2CH_2CH_2N$), 3.15 (q, $J = 7.5$ Hz, 4H, $CH_2C_6H_4(CH_2CH_3)$-4), 3.74 (t, $J = 6$ Hz, 4H, $NCH_2CH_2CH_2N$), 4.19 (s, 4H, $CH_2C_6H_4(CH_2CH_3)$-4), 7.71 and 7.78 (d, $J = 8.1$ Hz, 8H, $CH_2C_6H_4(CH_2CH_3)$-4), 9.06 (s, 1H, NCHN). $^{13}C\{H\}$ NMR (100.5 MHz, $CDCl_3$, δ, ppm): 15.4 ($CH_2C_6H_2(CH_2CH_3)$-4), 18.8 ($NCH_2CH_2CH_2N$), 28.3 ($CH_2C_6H_2(CH_2CH_3)$-4), 41.9 ($NCH_2CH_2CH_2N$), 58.9 ($CH_2C_6H_4(CH_2CH_3)$-4), 128.7, 128.8, 130.0, 145.2 ($CH_2C_6H_4(CH_2CH_3)$-4), 153.0 (NCHN). Anal. Calcd for $C_{22}H_{29}N_2Cl$ (%): C, 74.03; H, 8.19; N, 7.85. Found (%): C, 74.09; H, 8.22; N, 7.81.

1,3-Bis(4-isopropylbenzyl)-3,4,5,6-tetrahydropyrimidinium Chloride (1d)

Yield 4.68 g (81%); m.p. 207–208°C. IR, $\nu_{(CN)}$: 1692 cm^{-1}. ^1H NMR (399.9 MHz, $CDCl_3$, δ, ppm): 1.20 (d, $J = 6.9$ Hz, 12H, $CH_2C_6H_4(CH(CH_3)_2)$-4), 1.95 (quin, $J = 6.3$ Hz, 2H, $NCH_2CH_2CH_2N$), 2.87 (sep, $J = 6.9$ Hz, 2H, $CH_2C_6H_4(CH(CH_3)_2)$-4), 3.21 (t, $J = 6.3$ Hz, 4H, $NCH_2CH_2CH_2N$), 4.97 (s, 4H, $CH_2C_6H_4(CH(CH_3)_2)$-4), 7.19 and 7.29 (d, $J = 7.8$ Hz, 8H, $CH_2C_6H_4(CH(CH_3)_2)$-4), 10.29 (s, 1H, NCHN). $^{13}C\{H\}$ NMR (100.5 MHz, $CDCl_3$, δ, ppm): 19.9 ($NCH_2CH_2CH_2N$), 23.9 ($CH_2C_6H_2(CH(CH_3)_2)$-4), 33.8 ($CH_2C_6H_2(CH(CH_3)_2)$-4), 41.3 ($NCH_2CH_2CH_2N$), 56.3 ($CH_2C_6H_4(CH(CH_3)_2)$-4), 127.2, 128.8, 130.5, 149.7 ($CH_2C_6H_4(CH_3)$-4), 154.2 (NCHN). Anal. Calcd for $C_{24}H_{33}N_2Cl$ (%): C, 74.87; H, 8.64; N, 7.28. Found (%): C, 74.79; H, 8.71; N, 7.33.

1,3-Bis(4-diethylaminobenzyl)-3,4,5,6-tetrahydropyrimidinium Tetrafluoroborate (1e)

Yield 6.29 g (81%); m.p. 157–158°C. IR, $\nu_{(CN)}$: 1691 cm^{-1}. ^1H NMR (399.9 MHz, $CDCl_3$, δ, ppm): 1.15 (t, $J = 6.9$ Hz, 12H, $CH_2C_6H_4N(CH_2CH_3)$-4)$_2$, 1.94 (quin, $J = 6$ Hz, 2H, $NCH_2CH_2CH_2N$), 3.22 (t, $J = 6$ Hz, 4H, $NCH_2CH_2CH_2N$), 3.22 (q, $J = 6.9$ Hz, 8H, $CH_2C_6H_4N(CH_2CH_3)_2$-4), 4.53 (s, 4H, $CH_2C_6H_4N(CH_2CH_3)_2$-4), 6.62 and 7.17 (d, $J = 8.7$ Hz, 8H, $CH_2C_6H_4N(CH_2CH_3)_2$-4), 8.35 (s, 1H, NCHN). $^{13}C\{H\}$ NMR (100.5 MHz, $CDCl_3$, δ, ppm): 12.5 ($CH_2C_6H_2N(CH_2CH_3)_2$-4), 18.8 ($NCH_2CH_2CH_2N$), 41.8 ($NCH_2CH_2CH_2N$), 44.3 ($CH_2C_6H_2N(CH_2CH_3)_2$-4), 58.7 ($CH_2C_6H_4N(CH_2CH_3)_2$-4), 111.7, 118.6, 130.3, 148.1 ($CH_2C_6H_4N(CH_2CH_3)_2$-4), 151.8 (NCHN). Anal. Calcd for $C_{26}H_{39}N_4BF_4$ (%): C, 63.16; H, 7.95; N, 11.33. Found (%): C, 63.05; H, 7.80; N, 11.39.

1,3-Bis(3,4-dimethoxybenzyl)-3,4,5,6-tetrahydropyrimidinium Chloride (1f)

Yield 4.99 g (79%); m.p. 213–214°C. IR, $\nu_{(CN)}$: 1684 cm^{-1}. ^1H NMR (399.9 MHz, $CDCl_3$, δ, ppm): 1.93 (quin, $J = 6$ Hz, 2H, $NCH_2CH_2CH_2N$), 3.20 (t, $J = 5.7$ Hz, 4H, $NCH_2CH_2CH_2N$), 3.83 (s, 6H, $CH_2C_6H_4(OCH_3)_2$-3), 3.90 (s, 6H, $CH_2C_6H_4(OCH_3)_2$-4), 4.81 (s, 4H, $CH_2C_6H_3(OCH_3)_2$-3,4), 6.78 (d, 1H, $J = 5.4$ Hz), 6.89 (d, 1H, $J = 5.4$ Hz), 7.18 (s, 1H, $CH_2C_6H_3(OCH_3)_2$-3,4), 10.52 (s, 1H, NCHN). $^{13}C\{H\}$NMR (100.5 MHz, $CDCl_3$, δ, ppm): 19.0 ($NCH_2CH_2CH_2N$), 42.2 ($NCH_2CH_2CH_2N$), 55.9 ($CH_2C_6H_2(OCH_3)_2$-3), 56.5 ($CH_2C_6H_2(OCH_3)_2$-4), 58.4 ($CH_2C_6H_4(OCH_3)_2$-3,4), 111.0, 112.3, 121.5, 125.6, 149.5, 149.6 ($CH_2C_6H_4(OCH_3)_2$-3,4), 154.2 (NCHN). Anal. Calcd for $C_{22}H_{29}N_2ClO_4$ (%): C,62.77; H, 6.94; N, 6.6. Found (%): C, 62.81; H, 6.97; N, 6.64.

Typical Procedure for Catalytic Transfer Hydrogenation of Ketones

Under an inert atmosphere, $[RuCl_2(p\text{-cymene})]_2$ (0.01 mmol), tetrahydropyrimidinium salts **1a–1f** (0.02 mmol), KOH (2 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 mixture and was heated at 80°C for 1 h. At the conclusion of the reaction, the mixture was cooled, and the solvent was removed under reduced pressure and extracted with ethyl acetate–hexane (1:5), filtered through a pad of silica gel with copious washing, concentrated and purified by flash chromatography on silica gel. The product distribution was determined using ^1H NMR spectroscopy and GC. The yield calculations were based on the relative areas of signal peaks of chromatograms.

Results and Discussion

Synthesis of Tetrahydropyrimidinium Salts

The symmetric NHC precursors were prepared according to the general reaction pathway depicted in Scheme 1. The syntheses of the 1,3-diaryl-3,4,5,6-tetrahydropyrimidinium salts (**1**) were achieved according to Saba *et al.*[37] by reaction of *N,N*-dialkylpropane with triethyl orthoformate. Treatment of 1,3-propylenediamine with 2 equivalents of aromatic aldehyde in methanol at room temperature leads to the formation of the corresponding diimines. Their reduction with sodium borohydride in methanol, followed by treatment with triethyl orthoformate in the presence of ammonium chloride or ammonium tetrafluoroborate with continuous elimination of ethanol leads to the formation of the expected tetrahydropyrimidinium salts in excellent yields.

The tetrahydropyrimidinium salts were isolated as colorless solids in very good yields and fully characterized using ^1H NMR, ^{13}C NMR and IR spectroscopies and elemental analyses, and their melting points were determined (see Experimental section). The ^1H NMR spectra of the tetrahydropyrimidinium salts further support the assigned structures; the resonances for acidic C(2)–H are observed as a sharp singlet at 10.08, 10.47, 9.06, 10.29, 8.35 and 10.52 ppm, respectively, for **1a–f**. The position of the diethylamino groups on the phenyl rings also has a strong influence on the acidity of the proton as a chemical shift of 8.35 ppm is observed in the case of the 4-substitution in **1e**, whereas the 4-substituted dimethoxy pattern in **1f** leads to a signal at 10.52 ppm. ^{13}C NMR chemical shifts are consistent with

the proposed structures; the imino carbon appears as a typical singlet in the ^{1}H-decoupled mode at 154.7, 154.2, 153.0, 154.2, 151.8 and 154.2 ppm, respectively, for **1a–f**. The IR data for **1a–f** clearly indicate the presence of the –C=N– group with ν(C=N) vibrations at 1670, 1684, 1692, 1692, 1691 and 1684 cm^{-1}, respectively, for **1a–f**. The NMR values are similar to those reported for other tetrahydropyrimidinium salts.[38,39] The salts are air- and moisture-stable both in the solid state and in solution.

Structural Characterization

The structure of 1,3-bis(2-methylbenzyl)-3,4,5,6-tetrahydropyrimidinium chloride monohydrate was confirmed using crystallographic analyses. The molecular structure of 1,3-bis(2-methylbenzyl)-3,4,5,6-tetrahydropyrimidinium chloride monohydrate is depicted in Fig. 1, with selected bond lengths and angles provided in Table 2.

The structure consists of a 1,3-bis(2-methylbenzyl)-3,4,5,6-tetrahydropyrimidinium cation, a Cl$^-$ anion and 1 mol water molecule (Fig. 1). In the 1,3-bis(2-methylbenzyl)-3,4,5,6-tetrahydropyrimidinium cation (Fig. 1), the pyrimidine ring (C1/N6/C5/C4/C3/N2) is not planar, having total puckering amplitude $Q_T = 0.456(2)$ Å. The pyrimidine ring has an envelope conformation ($\phi = 238.7(4)°$ and $\theta = 49.7(3)°$) with atom C4 on the flap.[40,41] The deviation of atom C4 from the mean plane of the remaining five atoms C1/N6/C5/C3/N2 is 0.634(3) Å.

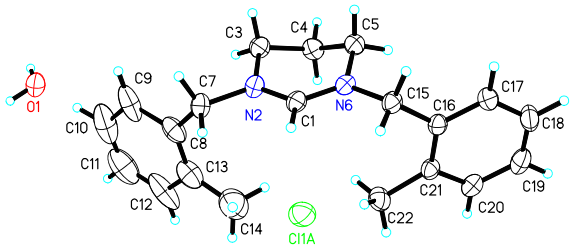
Atoms N1 and N6 are sp^2-hybridized, as evidenced by the sum of the valence angles around them, 359.68(18)° and 359.53(18)°, respectively. In addition, the C1–N2 and C1–N6 bonds are almost equivalent and both are shorter than the normal C–N single bond (1.48 Å). These results can be explained by the existence of resonance in this part of the molecule. All the other bond lengths are in normal ranges.[36]

The crystal structure is stabilized by C–H…Cl and O–H…Cl hydrogen bonding interactions (Fig. 1). In addition, intermolecular hydrogen bonds link the molecules, generating $R_4^2(8)$ (Fig. 1) ring motif,[42] to form a three-dimensional network.

Catalytic Transfer Hydrogenation of Ketones

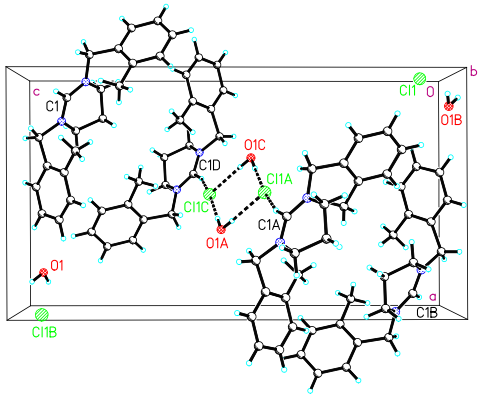
Catalytic reduction is preferred to stoichiometric reduction for large-scale industrial uses of ketones and hydrogenation is well known.[43] Hydrogen gas presents considerable safety hazards especially for large-scale reactions. The use of a solvent that can donate hydrogen overcomes these difficulties. 2-Propanol is a popular reactive solvent for transfer hydrogenation since it is easy to handle (b.p. 82°C), relatively non-toxic, environmentally benign and inexpensive. The volatile acetone product can also be easily removed to shift an unfavorable equilibrium.[1] Owing to their efficiency in the transfer hydrogenation of acetophenone derivatives, *in situ* generated ruthenium complexes were further investigated for the transfer hydrogenation of various methyl aryl ketones.

We examined the catalytic activity of *in situ* prepared tetrahydropyrimidinium salt/[RuCl$_2$(*p*-cymene)]$_2$ catalyst system in the transfer hydrogenation of aryl ketones with isopropanol to the corresponding alcohol. Isopropanol is the hydrogen source and KOH presumably enhances catalysis by promoting the formation of intermediates and deprotonation of salts. The reduction of acetophenone to 1-phenylethanol was initially used as a model reaction with *in situ* prepared Ru(II) systems with **1a–f** as catalysts in the transfer hydrogenation. In order to ensure complete formation of the active catalyst, a 2-propanol solution of 1 mol% [RuCl$_2$(*p*-cymene)]$_2$ and 2 mol% **1a** is stirred in the presence of 2 mmol of KOH at room temperature for 0.5 h. According to the literature during the formation of Ru–carbene complexes with [RuCl$_2$(*p*-cymene)]$_2$, one carbene molecule bonds to the Ru center.[17,31,32] Then acetophenone (1.00 mmol) is added and the reaction



(a)

(Symmetry code: Cl1A = -*x*, 1-*y*, 1-*z*). The anisotropic displacement parameters are displayed at a 50% probability level. Selected bond lengths (Å) and angles: C1- N2=1.316(3), C1-N6=1.314(3), N2-C3= 1.469(3), C5-N6=1.469(3), C3-C5=1.520(3), C4- C5=1.517(3), N6-C1-N2= 124.3(2), C1-N2-C3=121.06(18), C1-N2-C7=120.10(18), C1-N5-C5=121. 21(18), C1-N6-C15=120.11(18), C5-C4-C3= 110.57(18)



(b)

Hydrogen bonds are indicated as dashed lines [Symmetry codes: A = 0.5+*x*, 1.5-*y*, - 0.5+*z*; B = 1-*x*, 1-*y*, 1-*z*; D = 0.5-*x*, -0.5+*y*, 1.5-*z*].

Figure 1. (a) Molecular structure of 1,3-bis(2-methylbenzyl)-3,4,5,6-tetrahydropyrimidinium chloride monohydrate including atom labels. Symmetry code: Cl1A = $-x$, $1-y$, $1-z$. The anisotropic displacement parameters are displayed at a 50% probability level. Selected bond lengths (Å) and angles (°): C1–N2 = 1.316(3), C1–N6 = 1.314(3), N2–C3 = 1.469(3), C5–N6 = 1.469(3), C3–C5 = 1.520(3), C4–C5 = 1.517(3), N6–C1–N2 = 124.3(2), C1–N2–C3 = 121.06(18), C1–N2–C7 = 120.10(18), C1–N5–C5 = 121.21(18), C1–N6–C15 = 120.11(18), C5–C4–C3 = 110.57(18). (b) Packing diagram (unit cell shown) and hydrogen bonding of 1,3-bis(2-methylbenzyl)-3,4,5,6-tetrahydropyrimidinium chloride monohydrate including atom labels. Hydrogen bonds are indicated as dashed lines. Symmetry codes: A = 0.5 + x, 1.5 − y, −0.5 + z; B = 1 − x, 1 − y, 1 − z; D = 0.5 − x, −0.5 + y, 1.5 − z.

Table 2. Hydrogen bond geometry

D–H···*A*	*D*–H (Å)	H···*A* (Å)	*D*···*A* (Å)	*D*–H···*A* (°)
O1–H1*A*···Cl1[a]	0.85(2)	2.32(2)	3.162(2)	170(3)
O1–H1*B*···Cl1[b]	0.85(2)	2.37(2)	3.213(2)	172(3)
C1–H(1)···Cl(1)[c]	0.96	2.53	3.453(2)	162

[a]Symmetry codes: $x+1$, y, $z+1$.
[b]Symmetry codes: $-x+1$, $-y$, $-z+1$.
[c]Symmetry codes: $-x$, $1-y$, $1-z$.

performed at 80°C for 1 h. When a lower catalyst molar ratio is used, conversion decreases (Table 3, entries 10 and 11). The reactions are conducted at a substrate/catalyst/base molar ratio of 1:0.01:2. When $[RuCl_2(p\text{-cymene})]_2$ is used as catalyst, phenylethanol is obtained in 55% yield.

Since the base facilitates the formation of a ruthenium alkoxide by abstracting a proton from isopropanol, various bases were used as promoters in the transfer hydrogenation of ketones. Acetophenone was kept as a test substrate and was allowed to react in isopropanol with $[RuCl_2(p\text{-cymene})]_2$/**1a** in the presence of various bases, namely NEt_3, Cs_2CO_3, K_2CO_3, NaOH, KOH, *t*-BuOK and NaOAc. With the organic base NEt_3 we observe only poor yields (Table 3, entry 1). Using inorganic bases the conversion shows a dependency upon the base strength. It is observed that NaOH and KOH show good conversions when compared to Cs_2CO_3, K_2CO_3, *t*-BuOK and NaOAc in the hydrogenation reactions. As in previous studies, the best results are obtained with KOH.[31–33] In the absence of a base no transfer hydrogenation of ketones is observed. Also, when the catalytic system is used in transfer hydrogenation of acetophenone at room temperature, formation of phenylethanol is not appreciable. When this catalytic system is used at 50°C, phenylethanol is observed in 10% yield (Table 3, entry 9). We tried this reaction for a duration of 30 min. However the yields are lower than those obtained for 1 h; for example, the reduction of acetophenone with **1a** is completed within 30 min with a yield of 69% (Table 3, entry 8).

Under the reaction conditions, the $[RuCl_2(p\text{-cymene})]_2$/**1b** system proves to be the most effective catalyst relative to **1a**, **1c**, **1d**, **1e** and **1 f**. The reduction of acetophenone with $[RuCl_2(p\text{-cymene})]_2$/**1b** is completed within 1 h with a yield of 98% (Table 4, entry 7).

We next extended our investigations to include transfer hydrogenation of substituted acetophenone derivatives. A variety of ketones are transformed to the corresponding secondary alcohols. Typical results are shown in Table 4. Under those conditions *p*-methoxyacetophenone, *p*-fluoroacetophenone and 3,4,5-trimethoxyacetophenone react very cleanly and in good yields with 2-propanol (Table 4, entries 8, 9, 10 and 15). The presence of an electron-withdrawing (F) or electron-donating (OCH_3) substituent on acetophenone (Table 4, entries 8 and 15) has a significant effect on the reduction of ketones to their corresponding alcohols. The maximum conversion of 4-fluoroacetophenone to corresponding alcohol is achieved over a period of 1 h (Table 4, entry 9). The conversion of ketones with a bulky substituent on the aromatic ring is not observed or is slightly decreased. For example, when 2,4,6-trimethylbenzylmethyl ketone is used conversion decreases

Table 3. Screening of transfer hydrogenation reaction conditions[a]

Entry	Catalyst	Catalyst amount (%)	Base	Yield (%)	TOF (h^{-1})[b]
1	$[RuCl_2(p\text{-cymene})]_2$/**1a**	1	NEt_3	9	9
2	$[RuCl_2(p\text{-cymene})]_2$/**1a**	1	Cs_2CO_3	65	65
3	$[RuCl_2(p\text{-cymene})]_2$/**1a**	1	K_2CO_3	51	51
4	$[RuCl_2(p\text{-cymene})]_2$/**1a**	1	NaOH	82	82
5	$[RuCl_2(p\text{-cymene})]_2$/**1a**	1	KOH	85	85
6	$[RuCl_2(p\text{-cymene})]_2$/**1a**	1	*t*-BuOK	74	74
7	$[RuCl_2(p\text{-cymene})]_2$/**1a**	1	NaOAc	39	39
8	$[RuCl_2(p\text{-cymene})]_2$/**1a**	1	KOH	69[c]	138
9	$[RuCl_2(p\text{-cymene})]_2$/**1a**	1	KOH	10[d]	10
10	$[RuCl_2(p\text{-cymene})]_2$/**1a**	0.5	KOH	65	130
11	$[RuCl_2(p\text{-cymene})]_2$/**1a**	0.25	KOH	42	168
12	$[RuCl_2(p\text{-cymene})]_2$	1	KOH	55	55
13	—	—	KOH	9	9

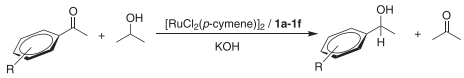
[a]Reaction conditions: KOH (2 mmol), ^{i}PrOH (10 ml), substrate (1.0 mmol), 80°C, 1 h. Purity of compounds checked using GC and yields are based on ketones.

[b]TOF = (mol product/mol catalyst) × h^{-1}.

[c]Reaction time is 30 min.

[d]50°C, 1 h.

Table 4. Transfer hydrogenation of ketones with catalyst system $[RuCl_2(p\text{-cymene})]_2$/(1a–f)[a]



Entry	Precursor	R	Yield (%)
1	**1a**	H	85
2		*p*-OMe	84
3		*p*-F	90
4		3,4,5-OMe	83
5		2,4,6-Me	69
6		*p*-C(O)Ph	66
7	**1b**	H	98
8		*p*-OMe	93
9		*p*-F	98
10		3,4,5-OMe	90
11		2,4,6-Me	62
12		*p*-C(O)Ph	86
13	**1c**	H	96
14		*p*-OMe	90
15		*p*-F	94
16		3,4,5-OMe	75
17		2,4,6-Me	50
18		*p*-C(O)Ph	80
19	**1d**	H	93
20		*p*-OMe	89
21		*p*-F	90
22		3,4,5-OMe	71
23		2,4,6-Me	60
24		*p*-C(O)Ph	78
25	**1e**	H	90
26		*p*-OMe	85
27		*p*-F	93
28		3,4,5-OMe	67
29		2,4,6-Me	50
30		*p*-C(O)Ph	70
31	**1f**	H	98
32		*p*-OMe	95
33		*p*-F	95
34		3,4,5-OMe	91
35		2,4,6-Me	40
36		*p*-C(O)Ph	82

[a]Reaction conditions: $[RuCl_2(p\text{-cymene})]_2$ (0.01 mmol), tetrahydropyrimidinium halide **1a–1e** (0.02 mmol), KOH (2 mmol), ^{i}PrOH (10 ml), substrate (1.0 mmol), 80°C, 1 h. Purity of compounds checked using GC and yields are based on ketones.

(Table 4, entries 25–30). The *in situ* catalytic system also catalyzes the transfer hydrogenation of benzophenone very effectively (Table 4, entries 6, 12, 18, 24, 30, 36).

Under the reaction conditions, salts **1f** and **1b** prove to be the most effective catalysts relative to the other salts. The reduction of acetophenone with tetrahydropyrimidinium salts is completed within 1 h in high yields. It is evident that the NHC precursors that contain electron-donating methoxy substituent (**1f**) and methyl substituent (**1b**) are the most effective of the salts examined.

Catalytic transfer hydrogenation by the use of inorganic salts is well established. It is noted that these reactions rely on long reaction times.[44,45] Beller and co-workers reported the application of *in situ* generated ruthenium carbene complexes in the reduction of various ketones. Acetophenone derivatives were reduced at 100°C for 12 h.[46] Bala and co-workers reported the use of ferrocenylimidazolium salts as catalysts for the transfer hydrogenation of ketones in propanol at 82°C for 24 h.[47] Compared with these results, the *in situ* prepared three-component 1,3-dialkyltetrahydropyrimidinium salts/$[RuCl_2(p\text{-cymene})]_2$ and KOH are active in the reduction of ketones under mild conditions with almost quantitative conversions and short reaction times.

Conclusions

We have synthesized new 3,4,5,6-tetrahydropyrimidinium salts as precursors of *N*-heterocyclic carbenes. All the compounds were characterized using ^{1}H NMR, ^{13}C NMR and IR spectroscopies and elemental analysis. One ligand was structurally characterized using single-crystal X-ray diffraction. They were associated with $[RuCl_2(p\text{-cymene})]_2$ to generate catalytic species. This concept for making catalysts *in situ* opens the way for the discovery of many new catalysts via the interaction of metal complexes and suitable ligands. The catalytic effects of this *in situ* prepared catalyst system have been investigated in the reduction of acetophenone and its derivatives using 2-propanol and KOH under mild reaction conditions. Also, the procedure is simple and efficient towards various aryl ketones. Detailed investigations focusing on new metal–NHC complexes and other applications are ongoing.

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Supporting Information

Additional supporting information may be found in the online version of this article at the publisher's web-site.

Crystallographic data for the structure reported in this paper has been deposited with the Cambridge Crystallographic Data Center: CCDC-1019867 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre, www.ccdc.cam.ac.uk/data request/cif.