

Letter

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Highly Efficient Abnormal NHC Ruthenium Catalyst for Oppenauer-type Oxidation and Transfer Hydrogenation Reactions

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KEYWORDS N-heterocyclic carbenes • alcohols • carbonyl compounds • Ruthenium • Oppenauer-type oxidation • transfer hydrogenation • smart ligands.

ABSTRACT: The ruthenium complex $[Ru(OAc)(a-PC)_2]Br$ (3) containing two abnormal NHC ligands is obtained by reaction of $Ru(OAc)_2(PPh_3)_2$ (1) with 1-(2-diphenylphosphinoethyl)-3-mesitylimidazolium bromide in the presence of NaOAc. Complex 3 catalyzes the Oppenauer-type oxidation of a number of alcohols at unrivalled reaction rates reaching TOFs up to 550 000 h⁻¹, at low catalyst loadings (down to 0.01 mol%) and using acetone in stoichiometric amounts. Complex 3 is also highly active in the reverse transfer hydrogenation of several ketones with 2-propanol, displaying TOFs up to 600 000 h⁻¹.

Alcohol oxidation to carbonyl compounds is a fundamental reaction in organic synthesis and several protocols have been developed to achieve high selectivity and functional group tolerance.¹⁻² The Oppenauer oxidation, which is in principle a reversion of the classical Meerwein-Ponndorf-Verley reduction, has been widely employed as efficient synthetic route for the preparation of aldehydes and ketones and entails the use of acetone with Al isopropoxide.³⁻⁵ Acetone, which is a non-hazardous and environmentally friendly oxidant, has usually been used as solvent to shift the equilibrium toward the formation of carbonyl compounds, according to the redox potential of the carbonyl-alcohol couple (eq 1).⁶

$$\begin{array}{c} OH \\ R \\ R \\ R' \end{array} + \begin{array}{c} O \\ R \\ R' \end{array} + \begin{array}{c} O \\ R \\ R' \\ R' \end{array} + \begin{array}{c} OH \\ R \\ R' \end{array} + \begin{array}{c} OH \\ R' \\ R' \end{array}$$
 (1)

In order to apply this reaction for the preparation of carbonyl (*via* oxidation) and alcohol (*via* reduction) compounds, catalytic versions have been developed, to overcome the problem of the use of stoichiometric amounts of Al or alkali metal reagents which entail tedious workup processes.^{7.8} For the Oppenauer-type reaction several transition metal complexes have been developed⁹⁻¹⁶ with particular attention to phosphine ruthenium derivatives (Figure 1).¹⁶⁻²⁷ Thus, RuCl₂(PPh₃)₃ has been applied in the Oppenauer-type oxidation of 3β-hydroxy steroids,²⁵ whereas chiral ruthenium oxazoline derivatives RuCl₂(PPh₃)(PN) are active in the oxidative kinetic resolution of alcohols.²⁸ It is worth mentioning that for the Oppenauer-type reaction, the substrate to catalyst (S/C) ratio is



Figure 1. Ruthenium phosphine catalysts for Oppenauer-type oxidation.

generally lower than 10³, which may limit possible applications. By contrast, the reverse transfer hydrogenation (TH) of carbonyl compounds has become a reliable reduction strategy,²⁹⁻³¹ the pincer amino-pyridine ruthenium complexes RuCl(CNN)(PP) displaying high rates and productivities with a wide substrate scope.³² Therefore, the design of more efficient catalytic systems for the Oppenauer reaction is crucial to achieve a broader application in the alcohol oxidation. In addition, no highly active system for both Oppenauer and TH reaction has been described. In the last decades, considerable efforts have been dedicated to complexes with robust and oxygen tolerating *N*-heterocyclic carbene (NHC) ligands in

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place of phosphines, 1,3-di-R-imidazoline-2-ylidenes being among the most frequently explored NHCs.³³ Interestingly, abnormal NHC (aNHC) ligands with the 1,3-di-R-imidazoline-4-ylidene structure, display a higher electron donation capability and altered steric properties compared to the normal 1,3-di-R-imidazoline-2-ylidene NHCs.³⁴⁻³⁵ Although NHC ruthenium complexes³⁶⁻³⁷ are widely employed in catalytic C-C³⁸⁻³⁹ and C-H⁴⁰⁻⁴¹ bond forming reactions, aNHC ruthenium catalysts have been sparingly reported.⁴²⁻⁴⁸ Herein we describe the isolation of the first example of a ruthenium complex with two aNHC ligands displaying outstanding catalytic activity in the Oppenauer-type oxidation of alcohols and in the reverse TH of ketones under mild reaction conditions and at low catalyst loading.

The cationic aNHC complex **3** (85% yield) can be easily obtained by treatment of the ruthenium precursor $Ru(OAc)_2(PPh_3)_2(1)$ with 2 equiv of **PC-HBr**, containing a C₂ backbone between the P and N atoms, in the presence of NaOAc (10 equiv) in THF at 60 °C (Scheme 1).



Scheme 1. Syntheses of the aNHC ruthenium complex 3 from 1 and 2.

This compound is thermally stable in solution and can be kept under air for months in solid state. Alternatively, 3 can be prepared in 90% yield from the previously described neutral aNHC ruthenium complex 2^{46} by substitution of PPh₃ and bromide ligands with the PC ligand in THF (Scheme 1). The ${}^{31}P{}^{1}H$ NMR spectrum of 3 in CD₂Cl₂ shows one singlet at 56.6 ppm for the two phosphorus atoms. In the ¹H NMR spectrum, the three resonances at 2.31, 2.10 and 1.80 ppm (2:2:3 ratio) correspond to the six mesityl and the acetate methyl groups, consistent with a C2 symmetry complex. The doublet at 8.72 ppm (${}^{4}J_{HH} = 1.7 \text{ Hz}$) is assigned to the two imidazolium NCHN protons, shifted down-field with respect to the corresponding proton of **2** (7.89 ppm).⁴⁶ In the ${}^{13}C{}^{1}H$ NMR spectrum, the resonance for the two abnormal carbene carbons appears as a triplet at 165.3 ppm with a ${}^{2}J_{CPcis}$ of 12.4 Hz. Single crystals suitable for SC-XRD were obtained by layering a solution of 3 in CH₂Cl₂ with diethyl ether, the structure showing the two mesityl groups pointing away from the metal center (Figure 2). Although few ruthenium complexes containing one aNHC ligand have been described,^{42, 44,47, 49-51}, no examples for ruthenium complexes bearing two aNHC ligands have been reported so far. The Oppenauer-type oxidation of alcohols is usually carried out in acetone as solvent, which shifts the equilibrium to the product side and enhances the reaction rate, but dictates the use of weak bases (i.e. K₂CO₃) to prevent aldol condensation reactions with Me₂CO. Complex 3 catalyzes the clean and unprecedentedly fast oxidation of several secondary alcohols with stoichiometric amounts of acetone (2-6 equiv), in presence of KOtBu. Thus, α -tetralol **a** is quantitatively and selectively converted to α -tetralone using acetone (6 equiv) at 30 °C within 20 min with 3 (S/C = 2000) in tBuOH as solvent, affording a TOF of 12 000 h^{-1} (Table 1, entry 1). By increasing the



Figure 2. ORTEP-style molecular structure of **3**. Ellipsoids are shown at a 50% probability level. Hydrogen atoms, counter ion (bromide) and disorders are omitted for clarity. Phenyl and mesityl substituents are depicted wireframe style for clarity. Grey = carbon, blue = nitrogen, yellow = phosphorus, red = oxygen, turquoise = ruthenium. Selected bond lengths (Å) and angles (°): C1-Ru1 2.098(5), C6-Ru1 2.096(5), O1-Ru1 2.240(4), O2-Ru1 2.210(4), P1-Ru1 2.2185(14), P2-Ru1 2.2181(15); C1-Ru1-C6 170.4(2), C1-Ru1-P1 90.39(15), C6-Ru1-P2 91.02(17), P1-Ru1-P2 92.00(5), O1-Ru1-O2 59.00(14).

temperature to 40 and 50 °C with 2 equiv of acetone and without tBuOH quantitative formation of α -tetralone is achieved in 5 and 2 min, respectively. The TOFs are $100\,000$ and $550\,000$ h⁻¹, respectively, being the highest rates ever reported for Oppenauertype oxidation reactions (Table 1, entries 2 and 3). This protocol is highly interesting for synthetic applications as no solvent is used. Indeed, 0.98 g of α -tetralone (98%) can be easily obtained from 1.02 g of a and 1 mL of acetone (2 equiv) by employment of 3.5 mg of **3** (S/C = 2000) at 50 °C in 5 min. To broaden the scope of this procedure, the oxidation of several alcohols has been investigated in tBuOH to facilitate the handling and sampling. At 40 °C and with 3 (S/C = 2000), 1-hydroxyindane **b** is quantitatively oxidized in 5 min (TOF of 80 000 h^{-1} , Table 1, entry 4). With 9-hydroxyfluorene c the oxidation occurs at 60 °C within 60 min (95%, Table 1, entry 5). At a loading of S/C = 1000, 1-phenylethanol **d** is converted to acetophenone (92%) within 10 min, whereas 1-(4-biphenylyl)-1ethanol e gives the corresponding ketone (80%) within 15 min (Table 1, entries 6 and 7). The alkyl alcohol 4-heptanol **f** affords 4heptanone (87%) in 30 min (Table 1, entry 8). The sterically hindered alcohols isoborneol \mathbf{g} and borneol \mathbf{h} are completely oxidized to camphor at 40 and 60 °C within 20 and 10 min, respectively (Table 1, entries 9 and 10). Experiments carried out at 40 and 50 °C show significantly different reaction rates for the two stereoisomers, \mathbf{g} being more quickly reduced than \mathbf{h} using $\mathbf{3}$ (see Table S1 in SI). Cholest-5-en-ß-ol i is efficiently converted into

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Table 1. Catalytic Oppenauer-type oxidation of alcohols with acetone (6 equiv) with **3** $(S/C = 1000 - 10\ 000)$ and KOtBu (2 mol%) in tBuOH.

-						
	R	он о ↓ + ↓	3, Ku	OfBu O → ↓ OH) R	R' +	н
a	ОН	OH b	c	DH	OH d	e OH
OH f	\sim	g	н	н он h	i	B
Entry	S	S/C	T ∕°C	Conv.ª /%	t /min	$\mathrm{TOF}^{\mathrm{b}}/\mathrm{h}^{\mathrm{-1}}$
1	a	2000	30	97	20	12000
2^{c}	a	2000	40	98 ^d	5	100 000
3 ^c	a	10000	50	98	2	550 000
4	b	2000	40	99	5	80 000
5	c	2000	60	95	60	4000
6	d	1000	60	92	10	15000
7	e	2000	60	80	15	25 000
8	f	1000	60	87	30	10 000
9	g	2000	40	97	20	24 000
10	h	2000	60	99	10	60 000
11	i	1000	80	90	60	3400
12 ^e	a	2000	40	99	20	12000

^a The conversion was determined by GC and NMR analysis. ^b Turnover frequency (moles of alcohol converted to ketone per mole of catalyst per hour) at 50 % conversion. ^c reaction carried out without solvent, acetone/substrate = 2. ^d isolated yield after column chromatography. ^e with acetophenone in place of acetone.

cholest-4-en-3-one (90%) using **3** (S/C = 1000) in 60 min (Table 1, entry 11). Finally, **a** is efficiently oxidized to α -tetralone (99%) at 40 °C in 20 min (TOF of 12 000 h⁻¹) using acetophenone as hydrogen acceptor in place of acetone (Table 1, entry 12). Interestingly, complex **3** was also found highly active in the reverse Oppenauer-type oxidation reaction, namely the TH of ketones with 2-propanol (Table 2). At 80 °C acetophenone **j** (0.1 M) is quantitatively converted to **d** within 3 min using **3** (S/C = 10 000) in the presence of NaO*i*Pr (2 mol%; TOF of 300 000 h⁻¹) (Table 2, entry 1). At reflux the reduction of **j** occurs within 1 min, affording a TOF of 600 000 h⁻¹, which is among the highest TOFs reported,³² **3** being the most active carbene ruthenium catalyst for TH (Table 2, entry 2). The substrates 4-bromoacetophenone **k** and 4acetylbiphenyl **l** are quantitatively reduced in 5 min (TOF = 200 000 h⁻¹) (Table 2, entries 3 and 4),

Table 2. Catalytic TH of ketones with **3** (S/C = 10000) and NaO*i*Pr (2 mol%) in 2-propanol.

R	O ↓ R'	• OH	3, NaO <i>i</i> Pr ◀	ОН R Р' +	o
o C	Br				o I
j		k	Ī		m
°		o U			0 L
n		ο	р		q
Entry	S	T ∕°C	Conv.ª /%	t /min	$\mathrm{TOF}^{\mathrm{b}}/\mathrm{h}^{\mathrm{-1}}$
1	j	80	99	3	300 000
2	j	reflux	99	1	600 000
3	k	80	99	5	200 000
4	1	80	97	5	200 000
5	m	80	80	10	100 000
6	n	80	99	3	300 000
7	0	80	98	20	120 000
8	р	80	98	10	120 000
9	q	80	91	20	70 000

 $^{\rm a}$ The conversion was determined by GC. $^{\rm b}$ Turnover frequency (moles of ketone converted to alcohol per mole of catalyst per hour) at 50% conversion.

whereas benzophenone **m** is converted to benzhydrol (80%) in10 min (TOF = 100 000 h⁻¹) (Table 2, entry 5). The cyclic ketones cyclopentanone **n** and cyclohexanone **o** are reduced to their respective alcohols within 3 min and 20 min (TOF = 300 000 and 120 000 h⁻¹), respectively (Table 2, entries 6 and 7), while the linear aliphatic ketones 2-pentanone **p** and 3-pentanone **q** are converted to the corresponding pentanols (98% and 91%), with TOF = 120 000 and 70 000 h⁻¹ (Table 2, entries 8 and 9). Catalytic tests on the TH of **j** show that **3** at 80 °C requires an induction time of about 1 min, (TOF_{max} = 470 000 h⁻¹), while at reflux conditions, no induction time is observed, leading to a TOF_{max} of 1 300 000 h⁻¹ (see Figure S9 of SI). At 80 °C and with a S/C of 20 000, **j** leads to 90 % conversion, affording a TON of 18 000 (see SI).

VT-NMR experiments reveal that by addition of NaOiPr (1 equiv) to **3** in 2-propanol-d₈ at RT, a rapid H/D exchange occurs at the NCHN protons of the two aNHC ligands (proton responsive ligand). At 50 °C, the *ortho*-protons of the phenyls are selectively deuterated, possibly through a γ -agostic interaction vs. orthometalation reaction involving a Ru-D species formed in basic alcohol media (see Figure S8 of SI).⁵²⁻⁵⁴ Reaction of **3** with NaOiPr (10 equiv) in 2-propanol at 80 °C for 2 h leads to the formation of the dihydride complex **4** bearing normal NHC ligands (Scheme 2).

Complex 4 can also be formed from 3 and H_2 (5 bar) in toluene with KOtBu (5 equiv) at 60 °C after 2 h (Scheme 2). Single crystals

NaO*i*Pr Иes + Br 80 °C. 2 h -Mes *i*PrOH H₂ (5 bar) KOtBu -Mes 60 °C, 2 h toluene



Scheme 2. Formation of 4 from 3 via alkoxide or H₂ cleavage.

suitable for SC XRD measurements have been obtained from a solution of 4 in *n*-hexane at -31 °C (Figure S7 of SI), but attempts to isolate 4 as pure complex failed due to the presence of decomposition products. In-situ addition of j to the preformed dihydride 4 shows poor conversion to 1-phenyl ethanol, indicating that **4** is inactive in catalytic TH. Thus, the formation of the hydride species 4 *via* alkoxide β -H-elimination and concomitant isomerization from abnormal to normal carbene can be regarded as a catalyst deactivation pathway. The abnormal coordination is therefore crucial to achieve high catalytic performances, on account of the lower steric hindrance of the mesityl groups (confirmed by buried volume calculations, see SI) and possibly through the deprotonation at the C2 carbene position (proton responsive ligand).

In summary, the isolation of an unprecedentedly active ruthenium catalyst 3 in the Oppenauer-type oxidation of alcohols using acetone in stoichiometric amounts is reported. Complex 3, which is the first complex bearing two abnormal NHC ligands, is also very active in the reverse TH of ketones with 2-propanol. The presence of the abnormal coordination mode is crucial for the high performances in both reactions. Current studies are in progress to elucidate the mechanism of the catalytic C-H activation reactions and to increase the number of highly efficient abnormal ruthenium catalysts.

ASSOCIATED CONTENT

Supporting Information. General materials and methods, synthetic procedures, catalysis procedures, characterization methods and spectra, crystallographic data, DFT calculational details.

This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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Graphical Abstract

Highly Efficient Abnormal NHC Ruthenium Catalyst for Oppenauer-type Oxidation and Transfer Hydrogenation Reactions

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A ruthenium complex with two abnormal NHC ligands catalyzes the unprecedently fast Oppenauer-type oxidation of alcohols with stoichiometric amounts of acetone and the reverse transfer hydrogenation of ketones with TOFs up to $600\ 000\ h^{-1}$.