Highly chemoselective α-diazo carbonyl insertion reactions into N–H and S–H bonds catalysed by [RuCl(η^5-C_5H_5)(PPh_3)$_2$]

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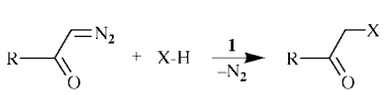
Complex [RuCl(η^5-C_5H_5)(PPh_3)$_2$], in chloroform at 60 °C, catalyses the chemoselective insertion of α-diazo carbonyl compounds into N–H and S–H bonds to afford α-keto-amines and α-keto-thioethers.

The α-diazo carbonyl insertion into N–H and S–H bonds of amines and thiols, respectively, represents a useful way of placing nitrogen- or sulfur-containing groups adjacent to the carbonyl function of ketones or esters.[1] The major improvement in this area has been done with the discovery of the high catalytic activity of rhodium(II) acetate and there are now several reports on both intra-[2] and inter-molecular[3] versions of the insertion reactions catalysed by $Rh_2(OAc)_4$ or related species. More recently, Simonneaux and co-workers reported that Ru(II)-porphyrin complexes catalyse the insertion reaction of ethyl diazoacetate (EDA) into N–H and S–H bonds under mild conditions and with reasonable to good yields.[4] In comparison, complex $RuCl_2(PPh_3)_3$, which had been previously tested, showed a lower catalytic activity for diazoketone insertions.[5]

We have now found that ruthenium(II) carbenoids, generated from the reaction of α-diazo carbonyl compounds with the half-sandwich complexes [RuCl(η^5-ligand)(PR_3)$_2$], undergo a wide range of synthetically useful transformations. Thus, recently we have established that the readily available [RuCl(η^5-C_5H_5)(PPh_3)$_2$] **1** is an excellent catalyst for the conversion of α-diazo carbonyl compounds into *cis*-enediones.[6,7] Detailed studies performed on the EDA–**1** system indicate that in the catalytic cycle a Ru–carbene intermediate is involved.[7] These results, together with our preliminary observations on the good activity of **1** in olefins cyclopropanation, prompted us to investigate the effectiveness of [RuCl(η^5-ligand)(PR_3)$_2$] complexes in other processes involving the formation of metal–carbenes, such as the insertion reaction of diazo compounds into polar X–H bonds (X = N, O, or S).

The first results of a study focused on the intermolecular α-carbonyl carbene insertion into N–H and S–H bonds catalysed by **1** are reported herein. As a matter of fact, α-keto-amines and α-keto-thioethers can be obtained in very good yields by reacting α-diazo carbonyl compounds with amines or thiols in 1 : 1 molar ratio in the presence of a catalytic amount (1 mol%) of **1** in chloroform at 60 °C (Scheme 1).†

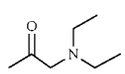
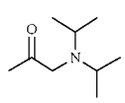
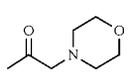
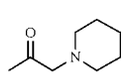
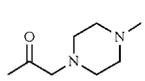
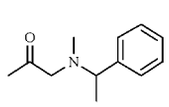
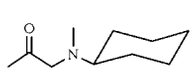
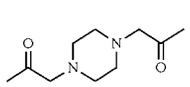
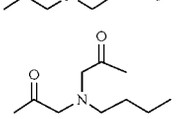
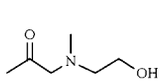
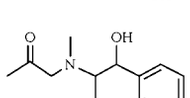


Scheme 1 Formation of α-keto-amines (X = R′R″N) and α-keto-thioethers (X = R′S) catalysed by **1**.

In order to test the effective catalytic potential of **1** in the insertion reactions, 1-diazopropan-2-one has been chosen as a model carbene precursor and reacted with different amines (Table 1) and thiols (Table 2). For the same purpose, different α-diazo carbonyl compounds have been tested in the reaction with morpholine and propane-2-thiol, suitably chosen as substrate models (Table 3).

A slow addition of 1-diazopropan-2-one to a solution containing a secondary amine and **1** results in the nearly quantitative formation (92–98%) of α-keto-amines (Table 1, entries 1–7). Piperazine (entry 8) gives in high yield the bis(amino-ketone) by addition of two moles of 1-diazopropan-2-one per mol of substrate. It should be noted that the primary amine Bu^nNH_2 (entry 9) reacts with 1-diazopropan-2-one to give the product of double insertion $Bu^nN(CH_2COMe)_2$ even when reacted in 1 : 1 molar ratio. This clearly indicates that Bu^nNHCH_2COMe, initially formed, undergoes the insertion reaction faster than Bu^nNH_2. Contrarily, in the case of Ru(II)-

Table 1 Yields of α-keto-amines obtained from the reaction between 1-diazopropan-2-one and amines (1 : 1 molar ratio) in the presence of **1**

Entry	Substrate	Product	Yield (%)[a]
1	Diethylamine		98
2	Diisopropylamine		92
3	Morpholine		98
4	Piperidine		95
5	1-Methylpiperazine		97
6	*N*,α-Dimethylbenzylamine		94[b]
7	*N*-Methylcyclohexylamine		95
8	Piperazine[c]		92
9	Butylamine[c]		87
10	2-(Methylamino)ethanol		94
11	(1*R*,2*S*)-(−)-Ephedrine		92

[a] Determined by ^{1}H NMR analysis. [b] For both (*R*) and (*S*) isomers, respectively. [c] In 2 : 1 molar ratio.

porphyrin catalysts, EDA insertion into Pr^nNH_2 and Bu^tNH_2 affords the expected *N*-substituted glycine ethyl esters.[4] Furthermore, the low yields observed have been ascribed to a partial poisoning of the catalyst caused by amine coordination. However, we have spectroscopic evidence that **1** does not significantly coordinate amines (Bu^nNH_2 and morpholine) upon dissociation of PPh_3.

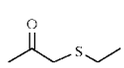
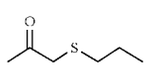
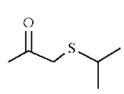
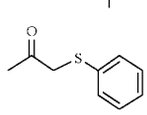
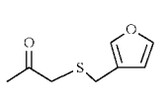
By means of the same procedure adopted for the preparation of α-keto-amines, thiols (Table 2) afford the corresponding α-keto-thioethers in excellent yield (92–97%). In the case of ethanethiol (entry 1), owing to its low boiling point (35 °C), the more labile complex $[RuCl(\eta^5\text{-}C_5H_5)\{PPh_2(2\text{-}MeC_6H_4)\}_2]$[7] has been employed, as this species is catalytically active at room temperature.

Importantly, the insertion reaction is regiospecific, since 2-(methylamino)ethanol and (1*R*,2*S*)-(−)-ephedrine (entries 10 and 11), where both N–H and O–H functions are present, give the corresponding α-keto-amines without formation of the ether moiety. Indeed, addition of 1-diazopropan-2-one to methanol or propan-2-ol resulted in the formation of very low amounts of compounds arising from insertion into the O–H bond, the major products being in both cases *cis*- and *trans*-hex-3-en-2,5-dione.

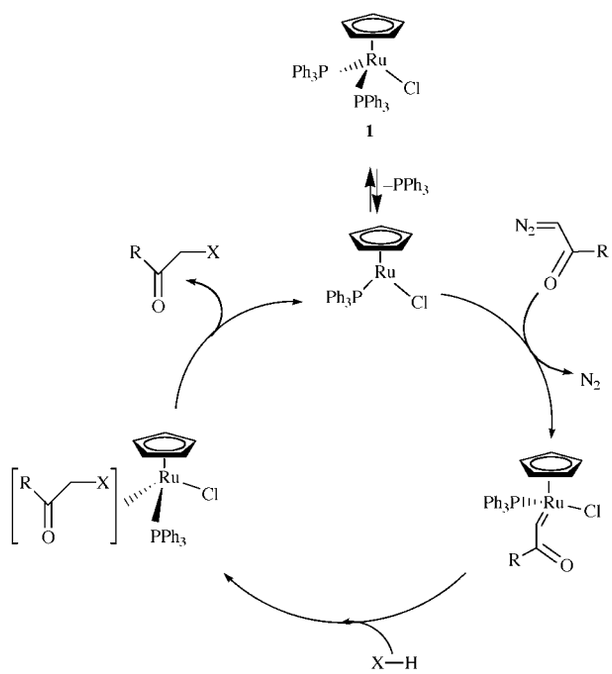
The data reported in Table 3 show that the insertion reactions catalysed by **1** can be extended to several other α-diazo carbonyl compounds. Thus, both morpholine and propane-2-thiol react with $RCOCHN_2$ compounds [R = Pr^n, Pr^i, $CH_3(CH_2)_n$ (n = 10 or 14) and Ph] to give products of insertion in yields always exceeding 90%. However, it should be noted that the use of EDA results in the formation of complicated mixtures containing low amounts of products of insertion.

As regards the mechanism, we presume that the ruthenium–carbene complex $[RuCl(\eta^5\text{-}C_5H_5)(=CHCOR)(PPh_3)]$ is formed, as proposed for the synthesis of *cis*-enediones catalysed by **1**. This intermediate then most probably undergoes a nucleophilic attack by amine or thiol (X–H) to give the product $RCOCH_2X$ (Scheme 2). Heating to 60 °C is necessary to obtain, by PPh_3

Table 2 Yields of α-keto-thioethers obtained from the reaction between 1-diazopropan-2-one and thiols (in 1 : 1 molar ratio) in the presence of **1**

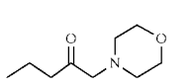
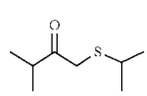
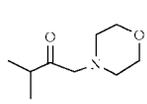
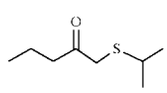
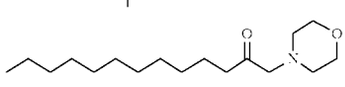
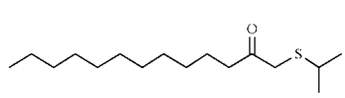
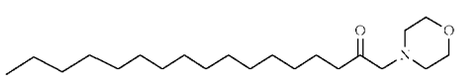
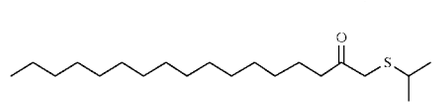
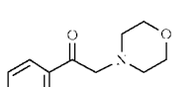
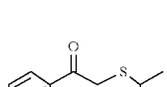
Entry	Substrate	Product	Yield (%)[a]
1	Ethanethiol[b]		95
2	Propane-1-thiol		92
3	Propane-2-thiol		95
4	Thiophenol		97
5	Furan-2-methanethiol		93

[a] Determined by ^{1}H NMR analysis. [b] $[RuCl(\eta^5\text{-}C_5H_5)\{PPh_2(2\text{-}MeC_6H_4)\}_2]$ has been used as catalyst.



Scheme 2 Mechanism and catalytic cycle proposed for the formation of α-keto-amines (X = R′R″N) and α-keto-thioethers (X = R′S).

Table 3 Yields of the reaction between morpholine or propane-2-thiol and α-diazo carbonyl compounds (RCOCHN$_2$) (in 1 : 1 molar ratio) in the presence of **1**. Yields[a] (%) are reported in parentheses

Entry	*R*	Product		Product	
1	Pr^n		(91)		(94)
2	Pr^i		(96)		(92)
3	$CH_3(CH_2)_{10}$		(91)		(97)
4	$CH_3(CH_2)_{14}$		(92)		(97)
5	Ph		(95)		(95)

[a] Determined by ^{1}H NMR analysis.

dissociation, the 16-electron unsaturated species [RuCl(η^5-C_5H_5)-(PPh_3)], which in turn gives the metal–carbene intermediate.

In conclusion, complex **1** has been proved to be an excellent catalyst for C–N and C–S bonds formation *via* carbene insertion into N–H and S–H bonds. These results, together with those obtained for C–C bond-forming reactions, suggest that **1** and related complexes constitute a new promising class of catalysts for chemo-, regio- and stereo-selective processes starting from diazo compounds.

Notes and references

† In a typical experiment for ^1H and ^{13}C NMR measurements, a 5 mm NMR tube is charged with 0.2 mmol of amine, 2 μmol of complex **1** and 0.25 ml of $CDCl_3$. The tube is heated to 60 °C in a bath and a solution of 0.2 mmol of α-diazo carbonyl compound in 0.25 ml of $CDCl_3$ is added dropwise within 10 min. The immediate evolution of nitrogen ensures a sufficient protection of the catalyst from atmospheric oxygen.

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