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Ruthenium catalysts for carbenoid intramolecular C–H insertion of 2-diazoacetoacetamides and diazomalonic ester amides

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Abstract—The intramolecular carbenoid C–H insertion of 2-diazoacetoacetamides, leading to γ- and/or β-lactams, is catalyzed effectively by dinuclear Ru(I,I) complexes of the type $[Ru_2(\mu\text{-}L^1)_2(CO)_4L^2_2]$, where L^1 is a bidentate bridging acetate, calix[4]arenedicarboxylate, saccharinate or 6-chloropyridin-2-olate ligand. By comparison with rhodium catalysts, namely dirhodium tetraacetate and dirhodium calix[4]arenedicarboxylate complexes, product yields are similarly high and the regioselectivity of the insertion reaction is the same. Surprisingly, even the ruthenium(0) cluster $Ru_3(CO)_{12}$ was found to be an effective catalyst for carbenoid C–H insertion of 2-diazoacetoacetamides and also of some diazoacetamides. In terms of diastereoselectivity, trans-isomers of β- and γ-lactams are obtained. However, the β-lactam obtained from diazomalonic ester amide **2** yields the cis-isomer stereoselectively, which slowly rearranges to the trans-isomer.

1. Introduction

Transition-metal catalyzed intramolecular carbenoid C–H insertion of appropriate α-diazocarbonyl compounds is a modern tool for the convenient construction of carbo- and heterocyclic compounds. The versatility of this approach has been documented in several reviews.[1–5] Dinuclear Rh(II,II) complexes such as $Rh_2(OAc)_4$, other dirhodium tetracarboxylates and structurally similar dirhodium tetraamidates are the current catalysts of choice for these transformations. A notable application of the rhodium-mediated carbenoid intramolecular C–H insertion strategy is the conversion of a variety of α-diazoacetamides, 2-diazoacetoacetamides, diazomalonic ester amides, α-diazo-α-(phenylsulfonyl)acetamides, and α-diazo-α-(dialkoxyphosphoryl)acetamides into β- and γ-lactams.[6] The influence of different factors, such as electronic properties of the catalyst, constitution of the diazo compound, and substitution pattern at the amide nitrogen atom, on the regio- and stereoselectivity of lactam formation has been reviewed.[7,8]

Recently, several types of ruthenium complexes are emerging as potential alternatives to the established rhodium catalysts for carbenoid transformations of diazo compounds. While most attention has been paid so far to ruthenium-catalyzed olefin cyclopropanation reactions,[9,10] some reports have indicated lately that certain ruthenium complexes effectively catalyze intramolecular carbenoid C–H insertion reactions as well. Thus, Che et al. have identified ruthenium porphyrins as effective catalysts for this reaction type, including the formation of β-lactams from the anion of 2-(tosylhydrazono)acetoacetamides.[11] Furthermore, they have reported that $[RuCl_2(p\text{-cymene})]_2$ effectively catalyzes the formation of lactams from diazomalonic ester amides and 2-diazo-3-oxocarboxamides.[12]

We have found that dinuclear Ru(I,I) complexes of the type $[Ru_2(\mu\text{-}L^1)_2(CO)_4L^2_2]$, where L^1 is a bidentate bridging carboxylate or amidate ligand and L^2 represents a weakly coordinating neutral axial ligand, catalyze effectively the conversion of α-diazoacetamides into γ- and/or β-lactams by carbenoid C–H insertion.[13] In particular, complexes with bridging 6-chloropyridin-2-olate or saccharinate ligands emerged as interesting alternatives to $Rh_2(OAc)_4$ and related rhodium catalysts. We have now turned our attention to ruthenium-catalyzed carbenoid reactions of 2-diazoacetoacetamides and diazomalonic ester amides. Due to the presence of a second electron-withdrawing substituent at the diazo function, the diazo carbon atom is less nucleophilic than in α-diazoacetamides, and we wondered whether our Ru(I,I) complexes, which appear to be somewhat less electrophilic than dirhodium tetraacetate, would be able to induce effectively the elimination of dinitrogen en route to the reactive ruthenium carbene intermediates. We report now that dinuclear Ru(I,I) carboxylate and amidate complexes catalyze very effectively the conversion of the mentioned 3-oxo-2-diazoacetamides into lactams; moreover, we show for the first time that the trinuclear ruthenium cluster $Ru_3(CO)_{12}$ catalyzes intramolecular carbenoid C–H

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insertion of diazoacetamides, 2-diazoacetoacetamides, and diazomalonic ester amides.

2. Results and discussion

2-Diazoacetoacetamides **1a–d** were prepared, with some modifications, along known procedures[14,15] by reaction of a *sec*-amine with diketene followed by a diazo transfer reaction using tosyl azide.[16] Diazomalonic ester amide **2** was also obtained by diazo group transfer (Fig. 1).

The catalysts used in this work are shown in Figure 2. We have reported before that dinuclear Ru(I,I) complexes **4** (existing as a coordination polymer in the solid state) and **6–8** are suitable catalysts for the conversion of α-diazoacetamides into lactams by intramolecular C–H insertion.[13] The Ru(II)-*p*-cymene complex **9** is less suited for this particular transformation, but was included here because it converts, e.g., the ethylester analog of **2** into a β-lactam in excellent yield.[12] The results obtained with the ruthenium catalysts were compared with those obtained with the benchmark catalyst $Rh_2(OAc)_4$ (**3**). In addition, dirhodium bis(calix[4]-arenedicarboxylate) **5** was included for comparison with the diruthenium calix[4]arenecarboxylate complex **6**; in both cases, it was interesting to learn whether the calixarene ligands would exert a steric influence on the regioselectivity of the intramolecular carbenoid C–H insertion.

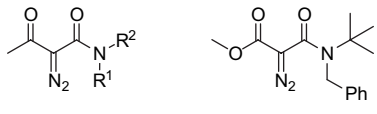


Figure 1.

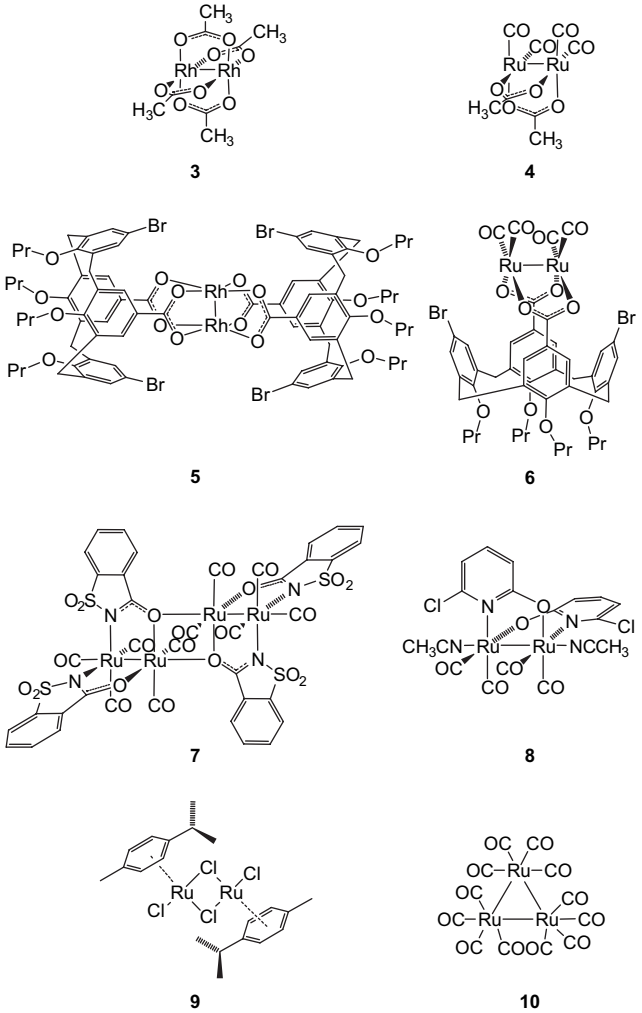
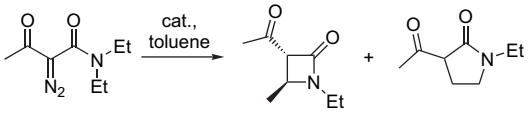


Figure 2. Catalysts used in this study.

The results of the catalytic decomposition of diazoamides **1a–d** and **2** are presented in Tables 1–5. In each case, the reaction with at least one of the catalysts was worked up, and the products were fully characterized. In all other cases, the yields were determined after complete conversion of the diazo compound by ^{1}H NMR analysis of the crude reaction mixture using naphthalene as an internal reference.

The following general observations were made: (a) the dinuclear Ru(I,I) carboxylate and amidate complexes **4** and **6–8** are excellent catalysts for the conversion of diazoacetoacetamides into γ- and/or β-lactams by carbenoid C–H insertion. In many cases, yields above 90% are achieved, which are practically the same as with the two rhodium catalysts **3** and **5**. Only in the case of diethylamide **1a**, the rhodium catalysts are the better choice, because they catalyze the carbenoid insertion into the non-activated methyl C–H bond, leading to γ-lactam **12a**, more effectively than the ruthenium catalysts. Nevertheless, it should be noted that the ruthenium catalysts convert **1a** into lactams **11a** and **12a** in a much higher combined yield (65–87%) than in the case of *N*,*N*-diethyl-2-diazoacetamide, where the γ-lactam was obtained in 5–28% yield and no β-lactam was formed.[13] (b) The reactions were fast and high-yielding under the chosen standard conditions (toluene, 70 °C, 3 mol % of catalyst). When the reactions with **1b** were run in dichloromethane at 40 °C,

Table 1. Catalytic decomposition of *N*,*N*-diethyl-2-diazoacetoacetamide (**1a**) in toluene at 70 °C



Catalyst[a]	Time [h]	Yield[b] [%]		Ratio of **12a/11a**	Total yield of lactams [%]
		11a	**12a**		
3	1	17 (11[c])	77 (68[c])	4.5	94 (79[c])
4	12	18	48	2.7	66
5	1	13	77	5.9	90
6	12	20	48	2.4	68
7	12	15	50	3.3	65
8	5	17	70	4.1	87
9	12	9	19	2.1	28

[a] Catalyst loading was 3 mol % (1 mol % for **11**).
[b] Yields were determined by ^{1}H NMR analysis of the reaction mixture.
[c] Isolated yield after purification by column chromatography over basic alumina.