Rh(II) catalysed intramolecular C–H insertion of diazo substrates in water: a simple and efficient approach to catalyst reuse†

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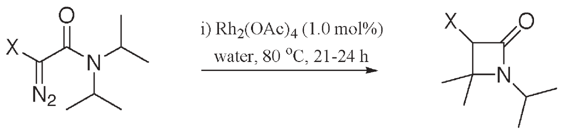
Water is an efficient solvent for the $Rh_2(OAc)_4$ catalysed intramolecular C–H insertion of a range of diazo substrates without competitive water insertion. Due to the high solubility and stability of the catalyst in water, the catalyst can be efficiently reused.

The intramolecular C–H insertion of dirhodium(II) carbenoids prepared from diazocompounds and catalysed mainly by $Rh_2(OAc)_4$ is a very powerful methodology for the synthesis of a diverse range of valuable compounds.[1] The possibility of reusing the expensive catalysts, including chiral ones, is an important issue. Several approaches have been developed, such as chemical immobilisation of the ligand by anchoring it in polyethylene,[2] coordination with pyridine functionalised polystyrene,[3] absortion on Rh_2(perfluorocarboylate)$_4$[4] on its fluorinated surface and by dissolution in ionic liquids.[5] This transformation is usually performed above room temperature using chlorinated solvents such as dichloromethane or 1,2-dichloroethane. If a protic solvent or reagent is used (*e.g.* amines, alcohols or thiols) it is generally assumed that a competitive X–H insertion of the carbenoid occurs.[6] More recently Charette and Wurz[7] demonstrated that the cyclopropanation of Rh carbenoids (also for Ru and Co) from diazoacetate can be efficiently performed in water if instead of $Rh_2(OAc)_4$ or $Rh_2(OCOCF_3)$, a more hydrophobic catalyst is used such as $Rh_2(C_7H_{15}CO_2)_4$ in combination with hydrophobic alkenes. According to the authors rationalisation, the effectiveness of this transformation is due to the formation of "small alkene/catalyst beads or micelles in water" in which the water soluble diazoacetate migrates to further the reaction inside the hydrophobic environment.

As a result of our ongoing studies on the C–H insertion of α-diazo-α-phosphono-acetamides, we observed that this transformation also occurs in wet organic solvent as well as in ionic liquids (ILs) containing considerable amounts of water or for ILs consisting of free hydroxyl groups.[5,8] These observations prompted us to test the transformation for a range of substrates in net water in which the catalyst $Rh_2(OAc)_4$ is completely soluble.† In Scheme 1 and Table 1 the substrates tested so far in water are presented. As can be seen, the intramolecular C–H insertion is the only reaction occurring in water for a range of α-diazo-acetamides including the ones containing the α-phosphono, α-sulfonyl or α-acetyl groups (Scheme 1 and Table 1, entries 1–4). These results are comparable to the ones reported in organic solvents.[8,9] Only the substrates with less hydrophobic groups such as the *n*-propoxycarbonyl or di-(2-methoxy-ethyl)aminocarbonyl gave exclusively the product as a result of O–H insertion (Table 1, entries 5 and 6). Interestingly, when the substrate **1a** was heated at 80 °C for 70 h in water without the $Rh_2(OAc)_4$ catalyst, complete conversion into the OH product **4a** (Scheme 2) was observed by ^{31}P NMR. Under identical conditions but in the presence of $Rh_2(OAc)_4$ a clean conversion into the β-lactam **2a** was observed (Scheme 1).

The unexpected high intramolecular C–H insertion reaction which is apparently dependent on the hydrophobic nature of the ester and the amide groups as well as of the presence of the catalyst, suggests that probably the formation of the hydrophobic carbenoid structure, in which the water does not acquire a position that can compete with the more favourable intramolecular C–H insertion, is crucial. Possibly, this organised hydrophobic aggregate around the rhodium reaction center is comparable to the one assumed for the efficient Diels–Alder reaction observed in water for hydrophobic substrates.[10] In this case, the catalyst which dissolves well in water needs to react with the diazo substrate and form a more hydrophobic rhodium(II) intermediate than the reagents.

The use of water as a solvent not only is advantageous due to it being the most 'green' solvent available[10] but also allows a simple, efficient and robust system for the reuse of the $Rh_2(OAc)_4$ catalyst. In fact, using the model substrate **1a** after the reaction, the aqueous solution containing the $Rh_2(OAc)_4$ catalyst and some traces of diazo **1a** was extracted with diethyl ether. To the remaining aqueous solution containing the $Rh_2(OAc)_4$ was added more substrate **1a** and the process was repeated eleven times (see



1 **2**

Substrate	Yield[a]	Conversion[b]
a, X = PO(OEt)$_2$	75 %	>97 %
b, X = SO$_2$Ph	73 %	
c, X = COMe	77 %	>97 %

[a] Isolated yields of lactams after purification by flash chromatography.[b] Observed conversion by ^{31}P (**a**) and ^1H (**c**) NMR of the crude reaction mixture.

Scheme 1 $Rh_2(OAc)_4$ catalysed insertion of α-diazo-*N*,*N*-diisopropyl-acetamides **1a–c** in water.

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† Electronic supplementary information (ESI) available: Experimental procedures, crude spectral data, pictures of $Rh_2(OAc)_4$ in water before and after extraction. See http://www.rsc.org/suppdata/cc/b4/b414233k/

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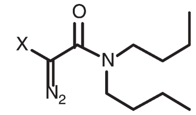
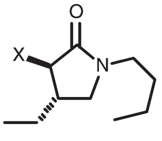
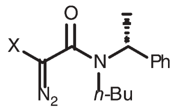
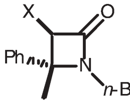
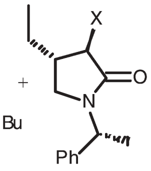
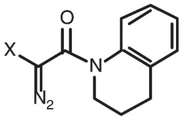
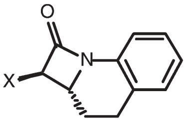
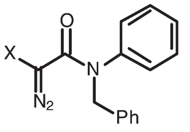
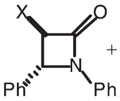
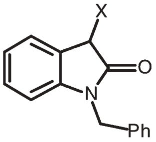
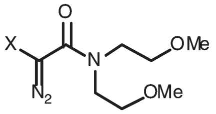
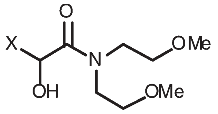
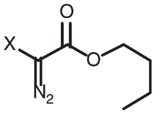
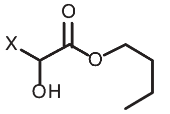
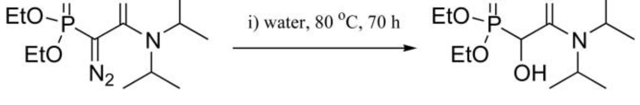
Table 1 $Rh_2(OAc)_4$ catalysed insertion of α-diazo-α-phosphono substrates in water[a]

Entry	Substrate (X = $PO(OEt)_2$)	Time/h	Product(s)[b]
1	 **1d**	29	 **3d**; 59% (63%)
2	 **1e**	18	 +  **2e** **3e** **2e**, **3e** 72%[c] (90%)
3	 **1f**	24	 **2f** 40%[d] (50%)
4	 **1g**	26	 +  **2g** **3g** **2g**, **3g** 97%[e] (>97%)
5	 **1h**	48	 **4h**; 71% (76%)
6	 **1j**	24	 **4j**; 78% (90%)

[a] Substrate (0.15 mmol), $Rh_2(OAc)_4$ (1.0 mol%), water (1.5 mL), 80 °C. [b] Isolated yields after purification by flash chromatography; in parentheses is presented the observed conversion of the crude reaction mixture as observed by ^{31}P NMR. [c] Isolated as a mixture of **2e**, **3e** (1 : 3). [d] Isolated as a mixture of *trans* and *cis* isomers (6 : 1). [e] Isolated as a mixture of **2g**, **3g** (1 : 10).



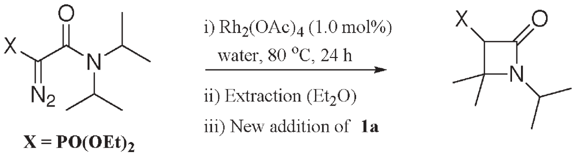
1a **4a**

(> 97%)[a]

[a] Observed conversion by ^{31}P NMR of the crude reaction mixture.

Scheme 2 Decomposition of α-diazo-α-phosphono-acetamide **1a** in water.

Table 2 Reuse of the $Rh_2(OAc)_4$ catalyst using the substrate model **1a**[a]



1a **2a**

Run	Yield (%)[b]	Rh in Et_2O (%)[c]	Run	Yield (%)[b]	Rh in Et_2O (%)[c]
1	75	2.3	7	96	1.1
2	72	1.8	8	94	0.9
3	113	4.4	9	70	0.4
4	90	1.2	10	90	1.1
5	86	1.4	11	(63)[d]	0.2
6	97	1.2			

[a] All reactions were carried out using **1a** (0.15 mmol), $Rh_2(OAc)_4$ (1.0 mol%), water (1.5 mL), 80 °C, 24 h followed by extraction with Et_2O and reloaded with **1a**. [b] Isolated yield of **2a** after solvent evaporation (pure by ^{31}P NMR and TLC). [c] Percentage of rhodium detected by ICP in the etheral phase relative to initial amount in the aqueous reaction media. [d] Observed conversion by ^{31}P NMR (**1a**, 37%; **2a**, 63%).

Table 2). As can be seen, only after eleven cycles was an erosion in the conversion observed.‡ For a total of 10 cycles a high TON number of 883 was obtained. The rhodium content in the organic phase of each cycle was also determined by Inductively Couple Plasma Atomic Spectroscopy (ICP). As can be seen, the rhodium catalyst is retained in the recycled aqueous phase because only 0.4% to 2.3% is lost to the organic phase.§

In conclusion, we have demonstrated that C–H insertion using dirhodium carbenoid can be efficiently performed in water for hydrophobic substrates. This true 'green' solvent opens up the opportunity of developing a simple, efficient and robust system for catalyst reuse due to the high partition of the $Rh_2(OAc)_4$ in the water phase. This method probably opens new opportunities for the use of this transformation in industrial processes by coupling with other efficient extraction procedures such as $sc$$CO_2$ or membrane technologies.

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Notes and references

‡ The observed increase of yields in some cases is due to an accumulation of product **2a** from previous cycles and/or incomplete removal of the organic phase. A smaller amount of catalyst (0.1 mol%) was tested for substrate **1g** giving lower conversion and higher erosion for the reuse experiments: First run 63% for 0.1 mol% and >97% for 1.0 mol%; second run 39% for 0.1 mol% and 87% for 1.0 mol%, third run 29% for 0.1 mol% and 89% for 1.0 mol%.

[§] The high value of observed rhodium content in the organic phase for cycle 3 is due to the undesired removal of traces of water during the separation of the organic phase (pipette method).

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