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Dirhodium(II)-catalysed C–H insertion on α-diazo-α-phosphono-acetamides in an ionic liquid

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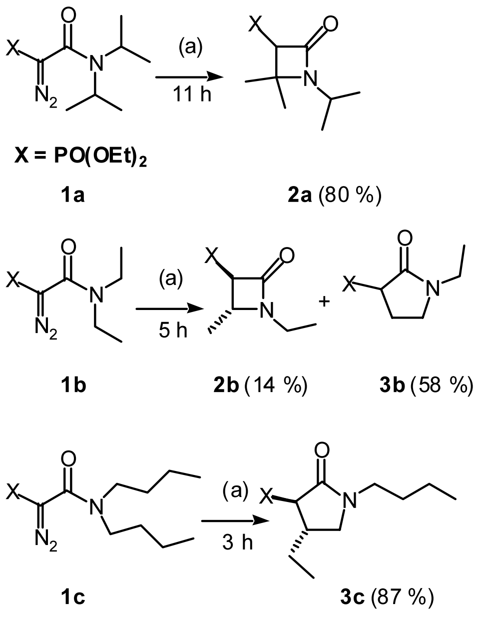
Abstract—α-Phosphono-lactams were obtained, with high regio and stereoselectivities via $Rh_2(OAc)_4$-catalysed intramolecular C–H insertion in an ionic liquid. This system proved to be highly efficient over 5–6 cycles.

The use of dirhodium(II) acetate and related carboxylates as catalysts in the formation of metal carbenes starting from diazo carbonyl compounds is one of the most useful carbon–carbon bond-forming procedures.[1] This methodology affords an entry into a broad spectrum of chemical transformations among which the intramolecular carbon–hydrogen (C–H) insertion reaction which is widely used in the carbocylic and heterocyclic ring syntheses.[2] High regioselectivity, stereocontrol and in some cases high enantioselectivity are some of the most important features of this reaction which has attracted the interest of many research groups.[3]

The development of efficient and reusable dirhodium(II) catalysts for the carbenoid C–H insertion reaction is still an open issue. Doyle et al. developed a procedure based on polyethylene dirhodium(II) 2-pyrrolidinone-5(*S*)-carboxylates which allowed catalyst recovery and reuse seven times.[4] Davis et al. reported the heterogenisation of $Rh_2(S\text{-DOSP})_4$ with a resin; this system proved to be highly efficient over 10 cycles.[5] More recently, although used in a different reaction, immobilisation of dirhodium(II) perfluorocarboxylate was achieved using a solid silica surface functionalised with long perfluoroalkyl chains.[6]

Room temperature ionic liquids (RTILs) have been recognised as an alternative to environmentally unattractive organic solvents, notably chlorinated hydrocarbons, mainly due to their negligible vapour pressure and insolubility in supercritical CO_2. Furthermore, the ability of dissolving a wide range of organic and inorganic compounds and their immiscibility with some organic solvents and *sc*CO_2 made them attractive media for recyclable chemical processes, in which the catalyst can be reused after product extraction.[7] Thus, the use of ionic liquids can be considered as an immobilisation method without ligand modification, as was shown when the cyclopropanation of styrene was



Scheme 1. *Reagents and conditions*: (a) $Rh_2(OAc)_4$ (1 mol%), [bmim][PF_6], 83°C.

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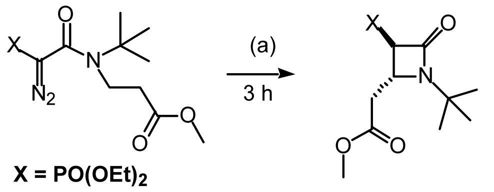
achieved via carbene formation, with immobilised bis(oxazoline)-copper.[8]

In the course of our studies[9] on the $Rh_2(OAc)_4$ intramolecular C–H insertion on α-diazo-α-phosphonoacetamides[10] and in the use of RTIL,[11] we found that the ionic liquid 3-*n*-butyl-1-methyl-imidazolium [bmim][PF_6] is an excellent medium for the immobilisation of $Rh_2(OAc)_4$ as shown in Scheme 1.[12]

Considering these results, the reaction proceeds with remarkable preference for the formation of five-member rings with exceptional stereocontrol for the *trans* diastereomer. These observations are similar to the results obtained in chlorinated solvents which are consistent with the proposed structure for the transition-state in which the substituents are preferentially in the more stable pseudoequatorial positions.[13]

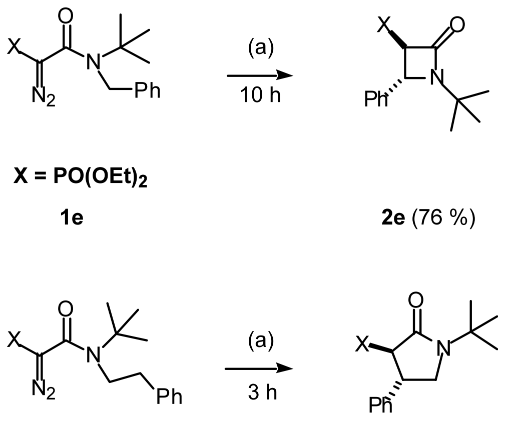
In order to observe the influence of the substituent near the insertion centre, the following reaction was performed (Scheme 2).

The influence of the electron withdrawing group directed the reaction towards the exclusive β-lactam formation. After purification using basic alumina, only the *trans* **2d** isomer was obtained.



1d **2d** (89 %)

Scheme 2. *Reagents and conditions*: (a) $Rh_2(OAc)_4$ (1 mol%), [bmim][PF_6], 83°C.



1e **2e** (76 %)

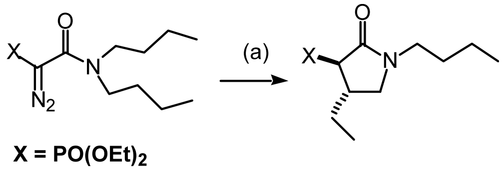
1f **3f** (78 %)

Scheme 3. *Reagents and conditions*: (a) $Rh_2(OAc)_4$ (1 mol%), [bmim][PF_6], 83°C.

When the aromatic group was introduced in the molecule, the expected C–H insertion products **2e** and **3f** were obtained (Scheme 3)[11] although the reaction was not as clean as when only alkyl groups were present, as shown previously in Scheme 1.

To evaluate the immobilisation efficiency of this system, the reaction was performed with the substrate *N*,*N*-dibutyl-α-diazo-α-phosphonoacetamide **1c** using hexane and *ter*-butyl-methyl-ether (TBME) as extracting solvents (Scheme 4).

When using hexane, more extractions were needed to extract the γ-lactam **3c** due to the solvent being more hydrophobic. On the other hand, no further purification by flash chromatography was required. Under these conditions were achieved six cycles and high yield of **3c** (71–93%) and high turnover number of catalyst (TON = 493). When *ter*-butyl-methyl-ether (TBME) was used as extracting solvent, three extractions were enough but after the fifth cycle the yield of lactam **3c** decreased by 23% (from 73 to 50%). This observation is probably due to the higher polarity of TBME (in comparison with hexane) that allow it to extract some catalyst from the reaction medium. In fact, when more catalyst was added to both systems (7 cycle), as expected the reactions proceeded again normally and high yield was observed for both systems. The high yield obtained in the seventh cycle with hexane as the extracting solvent, can be explained by the incomplete extraction of diazo substrate **1c** from the previous cycle, in which the reaction was not completed.



1c **3c**

Cycle	Hexane[b] (%)	TBME[c] (%)
1	77	80
2	75	83
3	93	98
4	89	99
5	88	73
6	71	50[d]
7[e]	100	94

Scheme 4. *Reagents and conditions*: (a) **1c** (0.3 mmol), [bmim][PF_6] (0.5 mL), $Rh_2(OAc)_4$ (1 mol%), 4 h at 83°C; after extraction with hexane or TBME more substrate **1c** (0.3 mmol) was added to the next cycle. (b) Isolated yield after extractions (15 min each) with hexane (13×5 mL); the yields presented for cycles 1 to 6 corresponds to the average values of two independent experiments. (c) Isolated yield after extractions (15 min each) with TBME (3×5 mL) and purification by flash chromatography (basic alumina). (d) Observed conversion of the crude reaction mixture by ^{31}P NMR. (e) $Rh_2(OAc)_4$ (1 mol%) was added to the reaction mixture.

Although highly reactive species are involved in this reaction, it was confirmed by NMR spectroscopy of the ionic liquid after the 7 cycles mentioned above, that there was no reaction between the metallocarbene and the ionic liquid.

In summary, the ionic liquid [bmim][PF_6] proved to be an efficient medium for the immobilisation of dirhodium-(II) tetraacetate catalyst. This procedure allowed the formation of β- and γ-lactams in high yields and with high regio and stereocontrol. Six cycles of $Rh_2(OAc)_4$ catalysed C–H insertion of α-diazo-α-phosphonoacetamides were readily achieved in high yield.

Acknowledgements

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12. Typical procedure for the catalysed decomposition of substrates **1a**–**f**: 0.30 mmol of diazo compound **1a**–**f** were added to 0.50 mL of [bmim][PF_6] with 1 mol% of $Rh_2(OAc)_4$. The mixture was vigorous stirred at 83°C until nitrogen formation ceased. Extractions with Et_2O and purification by flash chromatography (basic alumina) yield the desired compounds. All new compounds were characterised by IR, ^{1}H, ^{13}C, ^{31}P and HRMS.[9]
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