JOC Article

Rh(II)-Catalyzed Intramolecular C−H Insertion of Diazo Substrates in Water: Scope and Limitations

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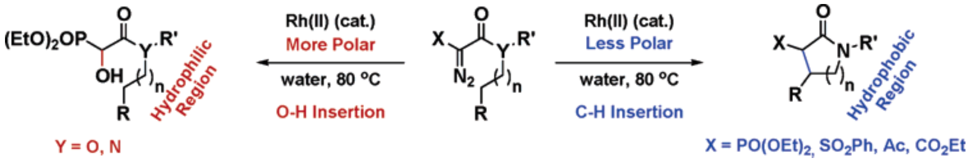

Preferential Rh(II) carbenoid intramolecular C−H versus O−H insertion derived from α-diazo-acetamides can be achieved in water by using an appropriate combination of the catalyst and amide groups, which creates a larger hydrophobic environment around the reactive carbenoid center.

Introduction

Dirhodium(II) carbenoids generated from diazo compounds are powerful reactive intermediates in nonasymmetric and asymmetric C−C and C−H insertions (intramolecular and intermolecular), being widely used in the synthesis of a diverse range of valuable substrates.[1] The intramolecular C−H insertion of Rh(II) carbenoids derived from α-diazo-ketones, esters, and amides occurs preferentially on the carbon atom in the γ- and δ-positions to the carbenoid carbon center, yielding the corresponding four- and five-membered ring compounds.[1−3] The regio, stereo, and asymmetric selectivities are strongly dependent on a combination of factors such as the Rh catalyst, the substrate structure, the C−H bond nature, and the functional group in the α-position.[3a,4a,b]

α-Phosphono-β- and γ-lactams are molecules of considerable interest, not only because the phosphoryl group mimics the carboxyl group, but also because it allows a simple additional functionalization in the α-position by a reaction with aldehydes (Horner−Wadsworth−Emmons reaction).[5] In the past few years, we observed that α-phosphono-α-diazo-acetamides are feasible candidates for the synthesis of a considerable range of β- and γ-lactams via $Rh_2(OAc)_4$-catalyzed C−H insertion.[4] The observed regio and stereoselectivity using $Rh_2(OAc)_4$ and the lower enantioselectivity for several types of Rh(II) chiral catalysts, demonstrated that the α-phosphoryl group originates a Rh(II) carbenoid with a reactivity profile quite different from the acetyl, sulfonyl, or carboxyl groups.[1a,4] During those studies, we observed that the C−H insertion was not affected by the use of nonanhydrous 1,2-dichloroethane or wet ionic liquids.[4c] Hence, these observations prompted us to test the transformation in water.[4d]

Water is certainly the cheapest and most environmentally friendly solvent available.[6,7] Apart from this, water has also been

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10.1021/jo060397a CCC: $33.50

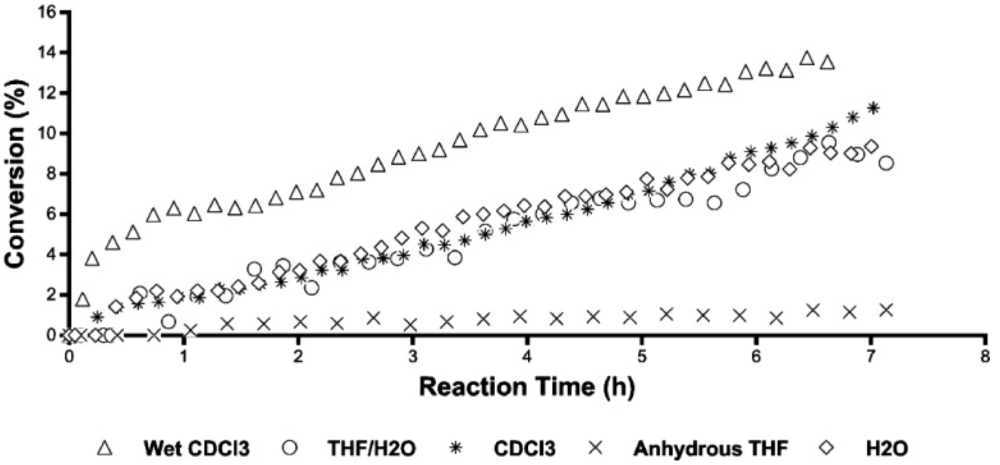
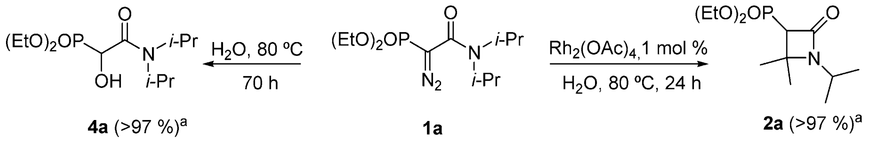


FIGURE 1. Solvent dependence of the observed conversion of diazo substrate **1a** to β-lactam **2a**: **1a** (0.075 mmol), $Rh_2(OAc)_4$ (1.0 mol %), solvent (0.5 mL; $CDCl_3$, wet $CDCl_3$, THF, THF/water (1:1), and water); conversion determined by ^{31}P NMR (δ 1**a** = 14.70 ppm; δ **2a** = 19.34 ppm).

SCHEME 1[a]



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

reported as a very useful solvent for highly polar catalyst reuse under homogeneous conditions by simple product recovery, using nonpolar solvent extraction or membrane technology.[7e,8] Despite the nucleophilic character of the oxygen atom, the reactivity of the O−H bond, and the high polarity, water can still be used as solvent in a specific number of synthetic transformations.[6,7] The preferential intramolecular cyclopropanation on styrene and the C−H insertion on triptophan residues of myoglobin by α-diazo-acetates catalyzed by Rh(II) in aqueous media have been recently reported.[9] These observations are in clear contrast to the well-assumed reactivity of Rh(II) carbenoides, where preferential X−H insertion occurs for labile bonds such as water, alcohols, amines, or thiols.[10] This preferential reactivity has also been efficiently applied for several synthetic transformations.[11] As a result of the present ongoing interest to enhance the portfolio of synthetic transformations in water and following our preliminary studies,[4d] we performed a systematic study to extend the scope of Rh(II)-catalyzed C−H insertion of diazo substrates in net water, essentially by studying the selectivity of C−H and C−H versus O−H insertions.

Discussion

When the substrate model **1a** was heated in water at 80 °C for a long period of time (70 h), only the corresponding alcohol **4a** was detected by ^{31}P NMR.[4d] This product may be the result of O−H insertion of the formed carbene or the result of a stepwise mechanism.[12] On the contrary, in the presence of $Rh_2(OAc)_4$ at the same temperature (80 °C) for 24 h, complete conversion to β-lactam **2a** was observed. This was due to the exclusive reaction of the Rh(II) carbenoid via a C−H insertion pathway instead of the expected O−H insertion (Scheme 1).[4d]

Monitoring the conversion of diazo substrate **1a** to β-lactam **2a** at room temperature by ^{31}P NMR under different solvent conditions ($CDCl_3$, wet $CDCl_3$, THF, THF/water (1:1), and water), we observed that water had a remarkable effect on the reaction rate (Figure 1). The catalyst and the substrate **1a** were incompletely solubilized at room temperature in $CDCl_3$ and water, respectively; this fact may eventually limit the reaction rate. In the absence of water, almost no reaction occurs in THF. In contrast, for THF/water, $CDCl_3$, or water, the reaction presents similar behavior. Interestingly, the fastest reaction occurs for wet $CDCl_3$.

Assuming that the rate determining step is the Rh(II) carbenoid formation[13] and according to the proposed mechanism,[3] the first step should involve the removal of the labile axial ligand (if present)[14] on the $Rh_2(OAc)_4$ catalyst and nucleophilic attack of the diazo group, followed by N_2 extrusion. The very limited reaction in anhydrous THF is probably due to

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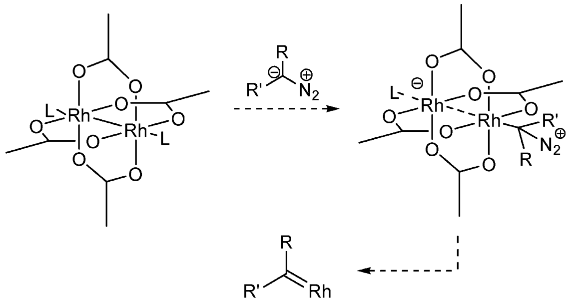
SCHEME 2



Di-rhodium (II) carbenoid

the formation of a more stable $Rh_2(OAc)_4$ complex as a result of THF complexation in the axial positions. In water and in other wet solvents tested, water molecules probably occupy those positions,[14a] and the catalyst becomes more reactive due either to a more labile Rh-ligand bond or to the increased stabilization of the intermediate that results from the diazo attack on one of the Rh catalyst atoms (Scheme 2).

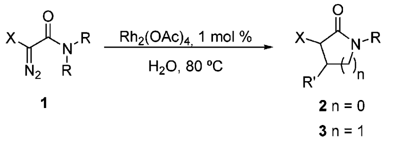
These observations prompted us to test the transformation for a range of substrates in net water. Apart from the phosphoryl group, the scope of the reaction was studied for different substituents in the α-position of **1**, such as sulfonyl, acetyl, and ethoxycarbonyl (Table 1, entries 1−4). For all of these substrates **1b**−**d**[4d,15] and **1e**,[15b] only C−H insertion was observed, yielding the corresponding β-lactams **2b**−**e** in high yields. The cyclization of α-diazo-α-phosphoryl-acetamides **1f**−**h** originated the expected β- and γ-lactams with similar regioselectivities for the C−H insertion as the ones previously reported in 1,2-dichloroethane.[4a−c]

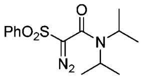
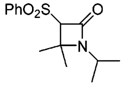
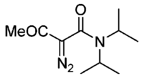
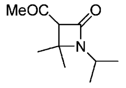
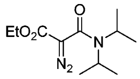
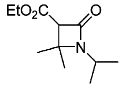
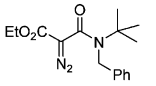
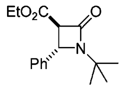
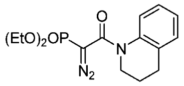
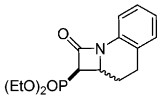
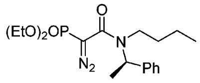
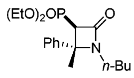
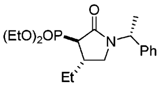
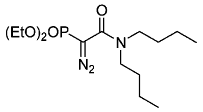
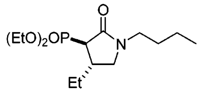
Despite the success achieved in the cyclization of α-diazo-α-phosphoryl-acetamides, the decomposition of α-diazo-α-phosphoryl-acetates in water yielded exclusively the corresponding alcohol **4i** instead of the lactone, a product that would have resulted from a more favorable intramolecular C−H insertion (Scheme 3).

To explore the solvent influence on the insertion chemioselectivity, a series of reactions were carried out. The cyclization of **1j** in different reaction media achieved a higher selectivity toward the γ-lactam formation when water was used as the solvent. This effect was even more pronounced when a saturated solution of water/NaCl was used (Table 2, entries 1−5).

Taking into consideration the reported findings, we presume that water stabilizes the intermediate that leads to the γ-lactam formation via aromatic substitution, which occurs without competitive O−H insertion (Table 2). The aromatic substitution is thought to proceed via an electrophilic attack of the metalo-carbenoid carbon atom on the aromatic ring followed by a 1,2-hydride shift with a concomitant dissociation of the catalyst and subsequent aromatization, rather than via a direct C−H insertion.[16] This explanation is corroborated by the exclusive formation of the γ-lactam when the α-diazo-acetamide **1j** reacted with $Rh_2(pfb)_4$, this catalyst has more electron-withdrawing ligands than their counterparts $Rh_2(OAc)_4$ and $Rh_2(Ooct)_4$ and, for this reason, generates a more electrophilic metalo-carbenoid more prone to undergo aromatic substitution either in $C_2H_4Cl_2$ or in water (Table 2, entries 7 and 8).[17]

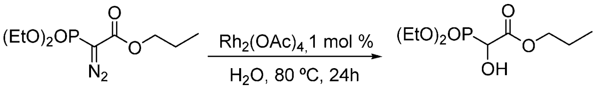
TABLE 1. $Rh_2(OAc)_4$-Catalyzed Insertion of α-Diazo-acetamides 1b−h in Water



Entry	Substrate	Time (h)	Product(s) Yield[a]
1	 **1b**	21	 **2b** – 73 %
2	 **1c**	24	 **2c** – 77 % (>97 %)
3	 **1d**	24	 **2d** – 76 %
4	 **1e**	24	 **2e** – 79 % (>97 %)[b]
5	 **1f**	24	 **2f** – 40 %[c] (50 %)
6	 **1g**	18	 +  **2g** **3g** 97 %[d] (>97 %)
7	 **1h**	29	 **3h** – 59 % (63 %)

[a] Isolated yields after purification by flash chromatography; in parentheses is presented the observed conversion of the crude reaction mixture (by ^1H NMR). [b] The crude reaction mixture contains the trans and cis isomers (1.3:1). [c] Isolated as a mixture of trans and cis isomers (6:1). [d] Isolated as a mixture of **2g**/**3g** (1:10).

SCHEME 3[a]



1i **4i** - 78 % (90 %)[a]

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

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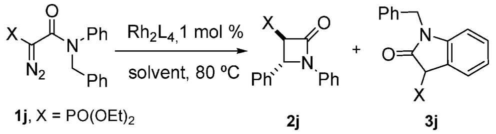
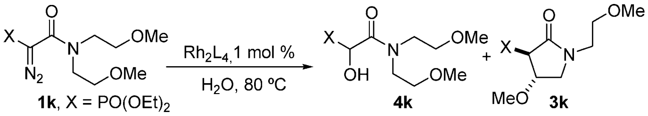
TABLE 2. Regioselectivity Dependence of α−Diazo-acetamide 1j with Rh(II) Catalyst and Solvent



entry	solvent	time (h)	catalyst	yield[a] (%)	**2j/3j**[b]
1	$C_2H_4Cl_2$	24	$Rh_2(OAc)_4$	50	1:4.8
2	C_6H_6	24	$Rh_2(OAc)_4$	88	1:5.7
3	perfluorodecalin	24	$Rh_2(OAc)_4$	79	1:7.2
4	water	26	$Rh_2(OAc)_4$	97	1:10
5	water, NaCl (20% w/w)	24	$Rh_2(OAc)_4$	87	1:24
6	water	48	$Rh_2(Ooct)_4$	92	1:6.3
7	$C_2H_4Cl_2$	6	$Rh_2(pfb)_4$	97	only **3j**
8	water	48	$Rh_2(pfb)_4$	97	only **3j**

[a] Isolated yield as a mixture of **2j** and **3j** after purification by flash chromatography. [b] Observed conversion of the crude reaction mixture (by ^{31}P NMR).

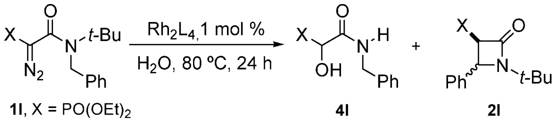
TABLE 3. Catalyst Effect on the Insertion of 1k in Water



entry	time (h)	catalyst	yield[a] (%)	**4k/3k**[b]
1	48	$Rh_2(OAc)_4$	71	only **4k**
2	24	$Rh_2(pfb)_4$	73	1:0.85
3	24	$Rh_2(Ooct)_4$	62	1:0.46

[a] Isolated yield as a mixture of **4k** and **3k** after purification by flash chromatography. [b] Observed selectivity of the crude reaction mixture (by ^{31}P NMR).

TABLE 4. Catalyst Effect on the Insertion of 1l in Water



entry	catalyst	yield[a] (%) of **4l**	yield (%) of **2l** (trans/cis)[a]
1	$Rh_2(OAc)_4$	25 (26)[b]	57 (4.5:1)
2	$Rh_2(pfb)_4$	*c*	84 (0.6:1)
3	$Rh_2(Ooct)_4$	*c*	97 (1.3:1)

[a] See footnote (a) in Table 1. [b] Reaction less clean; other minor unidentified peaks (14%) were observed by ^{31}P NMR. [c] None of the alcohol **4l** was detected by ^{31}P NMR of the crude reaction mixture.

Therefore, the increasing selectivity toward the γ-lactam formation obtained using solvents with higher polarities may be a result of solvent stabilization of the zwitterionic intermediate on the aromatic substitution (Table 2, entries 1−5).

During this study, the observation was made that substrates with higher solubility in water, namely the α-diazo-α-phosphoryl-acetates (Scheme 3), yielded considerably more alcohol than those substrates that formed droplets of bulk diazo in the aqueous phase, typically the diazo-acetamides tested (Table 1). Exploring this hydrophobic effect,[18,19] we anticipated that more hydrophilic *N*-substituents would increase the intermediate interaction with water and, therefore, would lead to a higher yield of alcohol. As expected, when α-diazo-acetamide **1k** was submitted to $Rh_2(OAc)_4$-catalyzed cyclization, the corresponding alcohol **4k** was preferentially obtained (Table 3, entry 1).

Apart from the substrate hydrophobic nature, the catalyst may also influence dramatically the intermediate reactivity. When more hydrophobic catalysts such as the rhodium(II) heptafluorobutyrate dimer ($Rh_2(pfb)_4$) and the rhodium(II) octanoate dimer ($Rh_2(Ooct)_4$) were used in the cyclization of **1k**, an increase was observed in the intermediate hydrophobic nature, and for this reason, the formation of the γ-lactam was accomplished in 34 and 29% conversion, respectively (Table 3, entries 2 and 3). The same effect was observed in the cyclization of substrate **1j** (Table 2, entry 6). The catalyst influence was further explored in the cyclization of substrates, which yielded mixtures of alcohols and lactams in the standard cyclization with $Rh_2(OAc)_4$. In line with the observations for the cyclization of substrate **1k**, we envisioned that an increment on the hydrophobic nature of the reactive carbene by the catalyst would prevent the presence of water nearby the reactive metalocarbenoid, avoiding in this way the alcohol formation. In fact, a dramatic change in the reaction selectivity was observed when more hydrophobic catalysts were tested, particularly the $Rh_2(Ooct)_4$, which completely suppressed the alcohol formation, yielding 97% of the β-lactam **2l** (Table 4, entry 3). In this particular substrate in which the *N*-substituent is the bulky *tert*-butyl group, the deprotection of the nitrogen moiety was observed. This occurred during the reaction and not as a consequence of the purification procedure.

As in the previous case, the reaction of α-diazo-acetamide **1m** yielded a mixture of alcohol **4m** and γ-lactam **3m** when the reaction was carried out in the presence of $Rh_2(OAc)_4$. In the same way, a remarkable selectivity was achieved when $Rh_2(Ooct)_4$ was used, yielding the desired γ-lactam **3m** in a 76% yield (Table 5). Despite the catalyst used, the reaction occurred in water with high regioselectivity. Only the γ-lactam **3m** was detected in all the crude mixtures, without β-lactam formation.

Similiar to the formation of **4l**, the alcohol **4m** lost the *tert*-butyl group during the reaction.

Interestingly, when the diazo acetamide **1m** was submitted to prolonged heating in the absence of catalyst, the expected alcohol was not formed. The stability of this diazo compound contrasts with the reported reaction of diazo **1a** in similar conditions, which yielded exclusively the alcohol **4a** (Scheme 1).

Finally, the substrate **1n** was designed to contain diverse *N*-substituents in their hydrophobic nature. The rationale behind the choice of this molecule was the observed preference for the formation of products that resulted from the insertion in the

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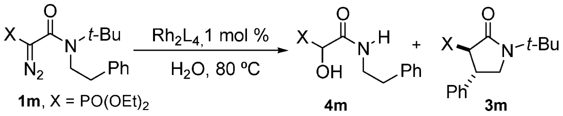
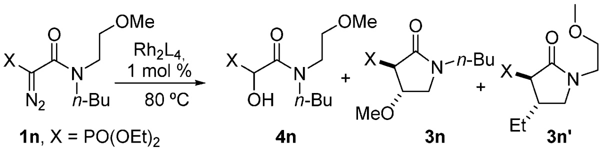
TABLE 5. Catalyst Effect on the Insertion of 1m in Water



entry	time (h)	catalyst	yield[a] (%)	**4m/3m**[b]
1	48	no catalyst	c	
2	48	$Rh_2(OAc)_4$	86	2.4:1
3	24	$Rh_2(pfb)_4$	64	0.1:1
4	24	$Rh_2(Ooct)_4$	76[d]	only **3m**[d]

[a] Isolated yield as a mixture of **4m** and **3m** after purification by flash chromatography. [b] Observed selectivity of the crude reaction mixture (by ^{31}P NMR). [c] No decomposition of **1m** was observed from the crude reaction (by ^{31}P NMR). [d] None of **4m** was detected by ^{31}P NMR of the crude reaction mixture.

TABLE 6. Catalyst Effect on the Insertion of 1n in Water

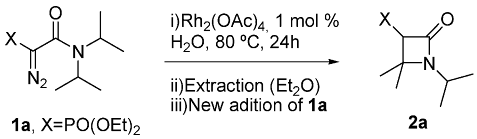


entry	solvent	catalyst	time (h)	yield[a] (%)	**4n/3n/3n′**[b]
1	$C_2H_2Cl_2$	$Rh_2(OAc)_4$	3	88	0:1.1:1
2	water	$Rh_2(OAc)_4$	24	85	0.6:0.15:1
3	water	$Rh_2(pfb)_4$	24	68[c]	0.5:0.5:1[c]
4	water	$Rh_2(Ooct)_4$	24	52[c]	0.3:0.86:1[c]

[a] Isolated yield as a mixture of **3n**, **3n′** and **4n** (except for entry 1) after purification by flash chromatography. [b] Observed selectivities of the crude reaction mixture (by ^{31}P NMR). [c] Reaction less clean; other minor unidentified peaks (17−23%) were observed by ^{31}P NMR.

N-substituents in closer proximity to the reactive metalocarbenoid. With the diazo compound **1n**, we expected that in water the formation of the hydrophobic region would be accomplished with the more hydrophobic *n*-butyl group and, therefore, the insertion would take place preferentially in this substituent. Interestingly, an increased selectivity in favor of the γ-lactam **3n′** was achieved in water when compared with that of the cyclization in $C_2H_4Cl_2$, where a 1:1 ratio of **3n**/**3n′** was obtained (Table 6).

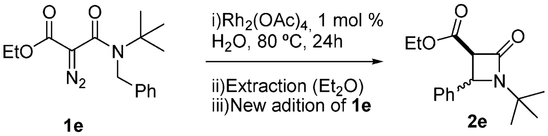
TABLE 7. Reuse of the $Rh_2(OAc)_4$ Catalyst Using the Substrate Model 1a[a]



run	yield (%)	Rh in Et_2O (%)
1−9	88[b]	1.6[c]
10	90	1.1
11	(63)[d]	0.2

[a] For detailed results, see ref 4d. [b] Average value of isolated yields of **2a**. [c] Average value of percentages of rhodium relative to the initial amount detected by ICP in the organic phase. [d] Observed conversion by ^{31}P NMR.

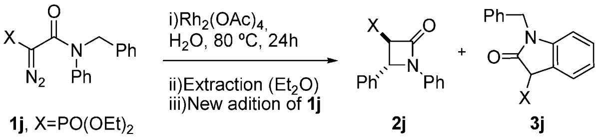
TABLE 8. Reuse of the $Rh_2(OAc)_4$ Catalyst Using the Substrate 1e[a]



run[a]	1	2	3	4	5
yield[b] (%)	93	105	98	87	(20)[c]

[a] All reactions were carried out using **1e** (0.15 mmol), $Rh_2(OAc)_4$ (1.0 mol %), and water (1.5 mL) at 80 °C for 24 h, followed by extraction with Et_2O and then reloaded with **1e**. [b] Isolated yield of **2e** after solvent evaporation (pure by ^1H NMR and TLC). [c] Observed conversion by ^1H NMR (**1e**, 80%; **2e**, 20%).

TABLE 9. Reuse of the Dirhodium(II) Catalyst Using 1 and 0.1 Mol % of Catalyst and the Substrate 1j



1 mol % catalyst			0.1 mol % catalyst		
run	conversion after 26 h[a] (%)	**2j/3j**	run	conversion after 48 h[a] (%)	**2j/3j**
1	99	1:11	1	63	1:13
2	87	1:11	2	39	1:41
3	89	1:16	3	29	1:34

[a] Observed conversion by ^{31}P NMR.

As already mentioned, water is a desirable solvent for chemical reactions for reasons of cost, safety, and environmental concerns; furthermore, the use of water as the solvent in this particular transformation allows a simple, efficient, and robust system for the $Rh_2(OAc)_4$ catalyst reuse. In fact, after the cyclization of the model substrate **1a**, the aqueous solution containing the $Rh_2(OAc)_4$ catalyst and some traces of the 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 11 times, after which an erosion in the conversion was observed (Table 7).[4d] 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 coupled plasma atomic spectroscopy (ICP). As can be seen, the rhodium catalyst is retained in the recycled aqueous phase, because only 0.4−2.3% is lost to the organic phase (Table 7). Surprisingly, when the cyclization of the substrate **1e** and the catalyst recycle were performed, only four efficient cycles were achieved (Table 8). The efficiency of the catalyst reuse is strongly dependent on the initial amount of the catalyst used. A comparative study of the C−H insertion of substrate **1j** was performed in the presence of 1 mol % and 0.1 mol % of $Rh_2(OAc)_4$ (Table 9). Like expected, in the first run the conversion decreases to 63% after 48 h in the presence of 0.1 mol % versus the quantitative yield achieved in 26 h when the 1 mol % of catalyst was used.

To exclude the hypothesis of a species formed by the reaction of the rhodium dimer with water to be the catalyst of the reaction, which possibly would not be extracted with ethyl ether, dirhodium(II) tetraacetate was heated at 80 °C in water for 24 h, and after recrystallization in this solvent, a green solid similar to the initial one was analyzed by microanalysis and was determined to be $Rh_2(OAc)_4{\cdot}2H_2O$. This recrystallized sample was further used in the cyclization of substrate **1j**, and after 26 h at 80 °C, a mixture of **2j** and **3j** (1:12) was obtained by extraction with ethyl ether in 71% yield. The presence of $Rh_2(OAc)_4{\cdot}2H_2O$ goes in account with what was said above about the complexation of the solvent with the axial positions of the catalyst (Scheme 2).

In summary, the present study shows that Rh(II) carbenoids derived from α-diazo-acetamides can originate *β*- and *γ*-lactams via intramolecular C−H insertion in water. In more detail, this study showed that the selectivity of the C−H insertion depends on the structure of the catalyst and the hydrophobic nature of the amide substituents. An appropriate balance between these factors leads to a more hydrophobic environment around the carbenoid center that reduces the competitive attack by the water. The use of water as a solvent allows a simple, efficient, and robust system for $\mathrm{Rh_2(OAc)_4}$ catalyst reuse and opens further applications on the use of Rh(II) carbenoid chemistry for the synthesis of more complex molecules under conditions potentially more environmentally friendly.

Experimental Section

Preparation of α-Diazo Compounds. The preparation of the substrates not described was already described elsewhere (compounds **1a**, **2a**, **1g**−**i**, **2g**, **3g**−**h**, **1k**−**m**, **3k**, **2l**, and **3m**, described in ref 4a; **1f** and **2f** in ref 4b; **1b** and **2b** in ref 15a; **1d**, **2d**, **1e**, and **2e** in ref 15b; and compounds **1c** and **2c** in ref 4d). The *p*-toluenesulfonyl azide used was prepared from *p*-toluenesulfonyl chloride and sodium azide, following a reported procedure.[20] The structural assignment of all new compounds was made by bidimensional NMR techniques (COSY and HMQC).

Preparation of *N*-(Benzyl)-α-(diethoxyphosphoryl)-*N*-(phenyl)acetamide. α-Bromoacetyl bromide (18.9 mmol) was slowly added at 0 °C to a solution of *N*-benzylphenylamine (16.4 mmol) and anhydrous triethylamine (19.6 mmol) in anhydrous dicloromethane (25 mL) under an argon atmosphere. The mixture was briefly stirred at 0 °C and then at room temperature for 2 h. The reaction mixture was washed with 3 M HCl (20 mL), and the aqueous layer was extracted with dichloromethane (3 × 4 mL). The combined organic layers were washed with saturated $\mathrm{NaHCO_3}$ solution and then dried with $\mathrm{Na_2SO_4}$. The residue was concentrated under reduced pressure and used for the next reaction without further purification.

Triethyl phosphite (19.0 mmol) was added to a solution of α-bromoacetamide (13.4 mmol) in anhydrous dichloromethane (13 mL) under an argon atmosphere. The mixture was heated at reflux for 4 h and at room temperature during the night. The solvent was removed under reduced pressure, and after flash chromatography purification on silica gel, *N*-(benzyl)-α-(diethoxyphosphoryl)-*N*-(phenyl)acetamide was obtained in 74% yield: orange oil, $R_f = 0.26$ (silica, AcOEt/hexane, 3:2). ^{1}H NMR ($\mathrm{CDCl_3}$, ppm): δ 1.26 (t, $J = 7.1$ Hz, 6H, $\mathrm{OCH_2C\mathit{H}_3}$), 2.79 (d, $J_{\mathrm{P-H}} = 21.7$ Hz, 2H, $\mathrm{CC\mathit{H}_2PO}$), 4.05−4.13 (m, 4H, $\mathrm{OC\mathit{H}_2CH_3}$), 4.87 (s, 2H, $\mathrm{NC\mathit{H}_2Ph}$), 7.04−7.31 (m, 10H, *Ph*). ^{13}C NMR ($\mathrm{CDCl_3}$, ppm): δ 16.1 ($\mathrm{OCH_2\mathit{C}H_3}$), 16.2 ($\mathrm{OCH_2\mathit{C}H_3}$), 33.3 (d, $J_{\mathrm{C-P}} = 137.4$ Hz, $\mathrm{OC\mathit{C}H_2PO}$), 53.1 ($\mathrm{N\mathit{C}H_2Ph}$), 62.2 ($\mathrm{O\mathit{C}H_2CH_3}$), 62.3 ($\mathrm{O\mathit{C}H_2CH_3}$), 127.2 (*Ph*), 128.2 (*Ph*), 128.4 (*Ph*), 128.5 (*Ph*), 129.5 (*Ph*), 136.8 (*Ph*), 141.9 (*Ph*), 164.7 (d, $J^2_{\mathrm{C-P}} = 4.6$ Hz, $\mathrm{OCCH_2\mathit{C}O}$). ^{31}P NMR ($\mathrm{CDCl_3}$, ppm): δ 21.8. IR (film): 3053, 2985, 1655, 1265, 1028 cm^{-1}. MS (FAB$^+$) *m*/*z* (%): 362, 182, 179. HRMS (FAB$^+$) calcd for $\mathrm{C_{19}H_{25}NO_4P}$, 362.1521 [M + H]$^+$; found, 362.1521 [M + H]$^+$.

1j. *p*-Toluenesulfonyl azide (6.6 mmol) was slowly added to a solution of *N*-(benzyl)-α-(diethoxyphosphoryl)-*N*-(phenyl)acetamide (5.5 mmol) and sodium hydride (6.6 mmol) in anhydrous THF (81 mL) at 0 °C. After the addition, the mixture was stirred at room temperature over a period of 2.5 h. Water (25 mL) and ethyl ether (25 mL) were added, and the aqueous phase was extracted with ethyl ether (5 × 25 mL). The organic layers were dried with $\mathrm{Na_2SO_4}$, filtered, and concentrated under reduced pressure. After flash chromatography on silica gel, the desired diazocompound was obtained as a yellow oil in 71% yield. $R_f = 0.48$ (silica, AcOEt/hexane, 9:1). ^{1}H NMR ($\mathrm{CDCl_3}$, ppm): δ 1.34 (t, $J = 7.0$ Hz, 6H, $\mathrm{OCH_2C\mathit{H}_3}$), 4.09−4.26 (m, 4H, $\mathrm{OC\mathit{H}_2CH_3}$), 4.90 (s, 2H, $\mathrm{NC\mathit{H}_2Ph}$), 7.06−7.33 (m, 10H, *Ph*). ^{13}C NMR ($\mathrm{CDCl_3}$, ppm): δ 16.1 ($\mathrm{OCH_2\mathit{C}H_3}$), 16.1 ($\mathrm{OCH_2\mathit{C}H_3}$), 54.0 ($\mathrm{N\mathit{C}H_2Ph}$), 63.5 ($\mathrm{O\mathit{C}H_2CH_3}$), 63.6 ($\mathrm{O\mathit{C}H_2CH_3}$), 127.5, 127.9, 128.3, 128.3, 128.8, 129.8, 136.8, 141.0 (*Ph*), 161.6 (d, $J^2_{\mathrm{C-P}} = 11.5$ Hz, $\mathrm{O\mathit{C}CN_2PO}$). ^{31}P NMR ($\mathrm{CDCl_3}$, ppm): δ 14.0. IR (film): 3055, 2986, 2106, 1630, 1265, 1027 cm^{-1}. MS (FAB$^+$) *m*/*z* (%): 388, 359, 181. HRMS (FAB$^+$) calcd for $\mathrm{C_{19}H_{23}N_3O_4P}$, 388.1426 [M + H]$^+$; found, 388.1424 [M + H]$^+$.

***N*-(*n*-Butyl)-*N*-(2-methoxyethyl)amine.** Butyraldehyde (55.9 mmol) was added at room temperature in an argon atmosphere to a mixture of 4 Å powder molecular sieves (20 g) and *N*-(2-methoxyethyl)amine (39.9 mmol) in anhydrous dichloromethane (100 mL) under vigorous stirring and allowed to react overnight. The mixture was then filtered over a Celite pad and washed with dichloromethane. After solvent removal under reduced pressure, the residue was dissolved in anhydrous ethyl ether (140 mL), and aluminum lithium hydride (80.0 mmol) was slowly added at 0 °C under an argon atmosphere, stirring at this temperature for a while and at room temperature during the night. Water was slowly added (8 mL) until a white precipitate was formed, and the salt was filtered and washed with ethyl ether. After solvent removal, the residue was distilled at 30 °C/0.2 mmHg, yielding in 50% the desired amine as a colorless liquid. ^{1}H NMR ($\mathrm{CDCl_3}$, ppm): δ 0.85 (t, $J = 7.3$ Hz, 3H, $\mathrm{NCH_2CH_2CH_2C\mathit{H}_3}$), 1.25−1.31 (m, 2H, $\mathrm{NCH_2CH_2C\mathit{H}_2CH_3}$), 1.38−1.44 (m, 2H, $\mathrm{NCH_2C\mathit{H}_2CH_2CH_3}$), 1.71 (s, 1H, $\mathrm{\mathit{H}N(CH_2CH_2CH_2CH_3)(CH_2CH_2OCH_3)}$), 2.55 (t, $J = 7.3$ Hz, 2H, $\mathrm{NC\mathit{H}_2CH_2CH_2CH_3}$), 2.72 (t, $J = 5.2$ Hz, 2H, $\mathrm{NC\mathit{H}_2CH_2OCH_3}$), 3.29 (s, 3H, $\mathrm{NCH_2CH_2OC\mathit{H}_3}$), 3.44 (t, $J = 5.2$ Hz, 2H, $\mathrm{NCH_2C\mathit{H}_2OCH_3}$). ^{13}C NMR ($\mathrm{CDCl_3}$, ppm): δ 13.9 ($\mathrm{NCH_2CH_2CH_2\mathit{C}H_3}$), 20.4 ($\mathrm{NCH_2CH_2\mathit{C}H_2CH_3}$), 32.1 ($\mathrm{NCH_2\mathit{C}H_2CH_2CH_3}$), 49.3 ($\mathrm{N\mathit{C}H_2CH_2CH_2CH_3}$), 49.6 ($\mathrm{N\mathit{C}H_2CH_2OCH_3}$), 58.7 ($\mathrm{NCH_2CH_2O\mathit{C}H_3}$), 71.9 ($\mathrm{NCH_2\mathit{C}H_2OCH_3}$). IR (film): 2958, 2929, 2873, 2825, 1460, 1113 cm^{-1}. MS (CI) *m*/*z*: 71, 69, 59, 57, 55.

***N*-(*n*-Butyl)-α-(diethoxyphosphoryl)-*N*-(2-methoxyethyl)acetamide.** A solution of dicyclohexyl carbodiimide (4.2 mmol) in anhydrous dichloromethane (10 mL) was slowly added at 0 °C under an argon atmosphere to a solution of the starting amine (3.8 mmol) and diethylphosphonoacetic acid (4.2 mmol) in dichloromethane (25 mL), with dicyclohexyl urea (DCU) formation being observed. After 4 h at room temperature, the mixture was filtered over a Celite pad and concentrated under reduced pressure, and the remaining DCU was precipitated in cold ethyl ether. After other filtration over a Celite pad and concentration of the residue, this was washed with saturated $\mathrm{NaHCO_3}$ solution, and the aqueous layer was extracted with diethyl ether (2 × 10 mL). The combined organic layers were dried with $\mathrm{Na_2SO_4}$, filtered, and concentrated under reduced pressure. After flash chromatography (acetone/hexane, 1:5), *N*-(*n*-butyl)-α-(diethoxyphosphoryl)-*N*-(2-methoxyethyl)acetamide was obtained as a colorless liquid in 75% yield. $R_f = 0.38$ (silica, acetone/hexane, 2:3). ^{1}H NMR ($\mathrm{CDCl_3}$, ppm): δ 0.83−0.90 (m, 3H, $\mathrm{NCH_2CH_2CH_2C\mathit{H}_3}$), 1.21−1.30 (m, 8H, $\mathrm{NCH_2CH_2C\mathit{H}_2CH_3}$ and $\mathrm{OCH_2C\mathit{H}_3}$, overlapped signals), 1.45−1.50 (m, 2H, $\mathrm{NCH_2C\mathit{H}_2CH_2CH_3}$), 2.98 (d, $J_{\mathrm{P-H}} = 22.0$ Hz, 2H, $\mathrm{(EtO)_2OPC\mathit{H}_2CO}$, conformer), 3.12 (d, $J_{\mathrm{P-H}} = 21.8$ Hz, 2H, $\mathrm{(CH_3CH_2O)_2OPC\mathit{H}_2CO}$, conformer), 3.27 (s, 3H, $\mathrm{NCH_2CH_2OC\mathit{H}_3}$, conformer), 3.30−3.46 (m, 4H, $\mathrm{NC\mathit{H}_2CH_2OCH_3}$ and $\mathrm{NC\mathit{H}_2CH_2CH_2CH_3}$, overlapped signals), 3.55 (t, $J = 5.15$ Hz, 2H, $\mathrm{NCH_2C\mathit{H}_2OCH_3}$), 4.06−4.16 (m, 4H, $\mathrm{OC\mathit{H}_2CH_3}$). ^{13}C NMR ($\mathrm{CDCl_3}$, ppm): δ 13.68, 13.72 ($\mathrm{NCH_2CH_2CH_2\mathit{C}H_3}$, conformers), 16.16, 16.22 ($\mathrm{OCH_2\mathit{C}H_3}$), 19.85, 19.90 ($\mathrm{NCH_2CH_2\mathit{C}H_2CH_3}$, conformers), 29.4, 30.8 ($\mathrm{NCH_2\mathit{C}H_2CH_2CH_3}$, conformers), 33.1 (d, $J_{\mathrm{P-C}} = 135.3$ Hz, $\mathrm{(CH_3CH_2O)_2OP\mathit{C}H_2CO}$, conformer), 33.5 (d, $J_{\mathrm{P-C}} = 133.1$ Hz, $\mathrm{(CH_3CH_2O)_2OP\mathit{C}H_2CO}$, conformer), 46.1 ($\mathrm{N\mathit{C}H_2CH_2OCH_3}$), 48.3, 49.9 ($\mathrm{N\mathit{C}H_2CH_2CH_2CH_3}$, conformers), 58.7, 59.0 ($\mathrm{NCH_2CH_2O\mathit{C}H_3}$, conformers), 62.3−62.5 (m, $\mathrm{O\mathit{C}H_2CH_3}$, conformers), 70.6 ($\mathrm{NCH_2\mathit{C}H_2OCH_3}$), 164.7, 165.0 ($\mathrm{CH_2\mathit{C}ON}$, conformers). ^{31}P NMR ($\mathrm{CDCl_3}$, ppm): δ 21.7, 22.2 (conformers). IR (film): 2960, 1643, 1456, 1250, 1117, 1053, 1026,

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[20] Deyrup, J. A.; Moyer, C. L. *J. Org. Chem.* **1969**, *34*, 175−179.

970 cm^{-1}. MS (EI) *m*/*z*: 310, 179, 151, 130, 123, 98, 86. HRMS (EI − ESI) *m*/*z* calcd for $\mathrm{C_{13}H_{28}NNaO_5P}$, 332.160 $[\mathrm{M + Na}]^+$; found, 332.158 $[\mathrm{M + Na}]^+$.

1n. A solution of *N*-(*n*-butyl)-α-(diethoxyphosphoryl)-*N*-(2-methoxyethyl)acetamide (1.9 mmol) in anhydrous THF (3 mL) was slowly added at 0 °C in an argon atmosphere to a suspension of sodium hydride (2.3 mmol) and *p*-toluenesulfonyl azide (2.3 mmol) in THF (12 mL). The mixture was stirred at this temperature for 1 h and at room temperature overnight. Water (10 mL) and ethyl ether (10 mL) were added, and the aqueous phase was extracted with ethyl ether (4 × 10 mL). The combined organic layers were dried with $\mathrm{Na_2SO_4}$, filtered, and concentrated under reduced pressure. The desired compound **1n** was obtained as a yellow oil in 70% yield after flash chromatography (silica gel, AcOEt/hexane, 2:3). $R_f = 0.33$ (silica, AcOEt/hexane, 1:1). ^{1}H NMR ($\mathrm{CDCl_3}$, ppm): δ 0.90 (t, *J* = 7.3 Hz, 3H, $\mathrm{NCH_2CH_2CH_2C}\mathit{H}_3$), 1.23−1.35 (m, 8H, $\mathrm{NCH_2CH_2C}\mathit{H}_2\mathrm{CH_3}$ and $\mathrm{OCH_2C}\mathit{H}_3$, overlapped signals), 1.49−1.56 (m, 2H, $\mathrm{NCH_2C}\mathit{H}_2\mathrm{CH_2CH_3}$), 3.30 (s, 3H, $\mathrm{NCH_2CH_2OC}\mathit{H}_3$), 3.36 (t, *J* = 7.8 Hz, 2H, $\mathrm{NC}\mathit{H}_2\mathrm{CH_2CH_2CH_3}$), 3.51 (s, 4H, $\mathrm{NCH_2C}\mathit{H}_2\mathrm{OCH_3}$ and $\mathrm{NC}\mathit{H}_2\mathrm{CH_2OCH_3}$, overlapped signals), 4.13−4.23 (m, 4H, $\mathrm{OC}\mathit{H}_2\mathrm{CH_3}$). ^{13}C NMR ($\mathrm{CDCl_3}$, ppm): δ 13.7 ($\mathrm{NCH_2CH_2CH_2}\mathit{C}\mathrm{H_3}$), 16.02, 16.07 ($\mathrm{OCH_2}\mathit{C}\mathrm{H_3}$), 19.9 ($\mathrm{NCH_2CH_2}\mathit{C}\mathrm{H_2CH_3}$), 30.1 ($\mathrm{NCH_2}\mathit{C}\mathrm{H_2CH_2CH_3}$), 47.2 ($\mathrm{N}\mathit{C}\mathrm{H_2CH_2OCH_3}$), 48.5 ($\mathrm{N}\mathit{C}\mathrm{H_2CH_2CH_2CH_3}$), 58.8 ($\mathrm{NCH_2CH_2O}\mathit{C}\mathrm{H_3}$), 63.4, 63.5 ($\mathrm{O}\mathit{C}\mathrm{H_2CH_3}$), 70.6 ($\mathrm{NCH_2}\mathit{C}\mathrm{H_2OCH_3}$), 162.3 ($\mathrm{N_2C}\mathit{C}\mathrm{ON}$). ^{31}P NMR ($\mathrm{CDCl_3}$): δ 13.8 ppm. IR (film): 2960, 2933, 2100, 1624, 1419, 1259, 1119, 1018, 974 cm^{-1}. MS (CI) *m*/*z*: 336, 308, 280, 130. HRMS (EI − ESI) *m*/*z* calcd for $\mathrm{C_{13}H_{26}N_3NaO_5P}$, 358.150 $[\mathrm{M + Na}]^+$; found, 358.151 $[\mathrm{M + Na}]^+$.

General Procedure for the Cyclization of 1a, Followed by ^{31}P NMR. A solution of $\mathrm{Rh_2(OAc)_4}$ (1 mol %) dissolved in the reaction solvent (0.5 mL) was added, at room temperature without an argon atmosphere, to a NMR tube containing the diazocompound **1a** (75 μmol) and a capillary tube filled with deuterated chloroform. Right after the catalyst addition, the first spectrum was made and the consequents in 10, 15, or 20 min intervals over a period of approximately 8 h. Wet chloroform was prepared by adding 0.5 mL water to 1.0 mL chloroform, followed by organic layer removal.

Dirhodium-Catalyzed Decomposition of α-Diazo-α-(diethoxyphosphoryl)-acetamides in Organic Solvents. The general procedures for the transformations of dirhodium-catalyzed α-diazo-α-(diethoxyphosphoryl)-acetamides were followed according to the general procedure already described.[4a]

Decomposition of 1n by $\mathrm{Rh_2(OAc)_4}$ Catalyst in Dichloroethane. After consumption of all of the diazo compound (3 h, confirmed by TLC) and solvent removal, the reaction products were purified by flash chromatography (silica, AcOEt/hexane). A mixture of **3n′** and **3n** (1:1.3) was obtained in 88% yield. It was observed that decomposition of **3n** occurred in basic alumina and a partial decomposition occurred in silica. Further purification of one part resulted in the isolation of **3n′**, while **3n** was characterized as a mixture of both products. **3n′**: $R_f = 0.36$ (basic alumina, AcOEt/hexane, 7:3). ^{1}H NMR ($\mathrm{CDCl_3}$, ppm): δ 0.92 (3H, t, *J* = 7.3 Hz, $\mathrm{NCH_2CH(CH_2C}\mathit{H}_3\mathrm{)CH}$), 1.30−1.35 (6H, m, $\mathrm{OCH_2C}\mathit{H}_3$), 1.39−1.50 (1H, m, $\mathrm{NCH_2CH(C}\mathit{H}_2\mathrm{CH_3)CH}$), 1.60−1.64 (1H, m, $\mathrm{NCH_2CH(C}\mathit{H}_2\mathrm{CH_3)CH}$), 2.53−2.59 (1H, m, $\mathrm{NCH_2C}\mathit{H}\mathrm{(CH_2CH_3)CH}$), 3.12 (1H, d, $J_{\mathrm{H-P}}$ = 9.6 Hz, $\mathrm{OCC}\mathit{H}\mathrm{(CH)PO}$), 3.31 (3H, s, $\mathrm{OC}\mathit{H}_3$), 3.44−3.49 (5H, m, $\mathrm{NC}\mathit{H}_2\mathrm{C}\mathit{H}_2\mathrm{OCH_3}$ and $\mathrm{NC}\mathit{H}_2\mathrm{CH(CH_2CH_3)CH}$, overlapped signals), 3.72 (1H, t, *J* = 8.7 Hz, $\mathrm{NC}\mathit{H}_2\mathrm{CH(CH_2CH_3)CH}$), 4.12−4.23 (4H, m, $\mathrm{OC}\mathit{H}_2\mathrm{CH_3}$). ^{13}C NMR ($\mathrm{CDCl_3}$, ppm): δ 10.8 ($\mathrm{NCH_2CH(CH_2}\mathit{C}\mathrm{H_3)CH}$), 16.4 ($\mathrm{OCH_2}\mathit{C}\mathrm{H_3}$), 28.1, 29.6 ($\mathrm{NCH_2CH(}\mathit{C}\mathrm{H_2CH_3)CH}$), 35.1 ($\mathrm{NCH_2}\mathit{C}\mathrm{H(CH_2CH_3)CH}$), 42.8 ($\mathrm{N}\mathit{C}\mathrm{H_2CH_2OCH_3}$), 47.2 (d, $J_{\mathrm{C-P}}$ = 141.1 Hz, $\mathrm{OP}\mathit{C}\mathrm{H(CH)CO}$), 52.7 ($\mathrm{N}\mathit{C}\mathrm{H_2CH(CH_2CH_3)CH}$), 58.6 ($\mathrm{O}\mathit{C}\mathrm{H_3}$), 62.1, 63.0 ($\mathrm{O}\mathit{C}\mathrm{H_2CH_3}$), 70.7 ($\mathrm{NCH_2}\mathit{C}\mathrm{H_2OCH_3}$), 168.9 ($\mathit{C}\mathrm{{=}O}$). ^{31}P NMR ($\mathrm{CDCl_3}$): δ 24.3 ppm. IR (film): 2964, 2931, 1689, 1265, 1026, 972 cm^{-1}. MS (CI) *m*/*z*: 308. HRMS (EI − ESI) *m*/*z* calcd for $\mathrm{C_{13}H_{26}NNaO_5P}$, 330.144 $[\mathrm{M + Na}]^+$; found, 330.144 $[\mathrm{M + Na}]^+$. **3n**: $R_f = 0.5$ (basic alumina, AcOEt/hexane, 4:1). ^{1}H NMR ($\mathrm{CDCl_3}$, ppm): δ 0.84−0.92 (3H, m, $\mathrm{NCH_2CH_2CH_2C}\mathit{H}_3$, overlapped signals), 1.20−1.32 (8H, m, $\mathrm{OCH_2C}\mathit{H}_3$ and $\mathrm{NCH_2CH_2C}\mathit{H}_2\mathrm{CH_3}$, overlapped signals), 1.37−1.48 (2H, m, $\mathrm{NCH_2C}\mathit{H}_2\mathrm{CH_2CH_3}$, overlapped signals), 2.94 (1H, d, $J_{\mathrm{P-H}}$ = 23.9 Hz, $\mathrm{OPC}\mathit{H}\mathrm{(CH)CO}$), 3.18−3.34 (7H, m, $\mathrm{NC}\mathit{H}_2\mathrm{CH(OC}\mathit{H}_3\mathrm{)CH}$ and $\mathrm{NC}\mathit{H}_2\mathrm{CH_2CH_2CH_3}$, overlapped signals), 4.10−4.19 (5H, $\mathrm{NCH_2C}\mathit{H}\mathrm{(OCH_3)CH}$ and $\mathrm{OC}\mathit{H}_2\mathrm{CH_3}$, overlapped signals). ^{13}C NMR ($\mathrm{CDCl_3}$, ppm): δ 13.5 ($\mathrm{NCH_2CH_2CH_2}\mathit{C}\mathrm{H_3}$), 16.18, 16.24 ($\mathrm{OCH_2}\mathit{C}\mathrm{H_3}$ and $\mathrm{NCH_2CH_2}\mathit{C}\mathrm{H_2CH_3}$, overlapped signals), 19.6 ($\mathrm{NCH_2}\mathit{C}\mathrm{H_2CH_2CH_3}$), 42.7 ($\mathrm{N}\mathit{C}\mathrm{H_2CH(OCH_3)CH}$), 47.8 ($\mathrm{OP}\mathit{C}\mathrm{H(CH)CO}$), 52.6 ($\mathrm{N}\mathit{C}\mathrm{H_2CH_2CH_2CH_3}$, overlapped signals), 56.2 ($\mathrm{O}\mathit{C}\mathrm{H_3}$), 62.0−63.2 ($\mathrm{O}\mathit{C}\mathrm{H_2CH_3}$, overlapped signals), 75.0 ($\mathrm{OPCH(}\mathit{C}\mathrm{H)CO}$), 167.1 ($\mathit{C}\mathrm{{=}O}$). ^{31}P NMR ($\mathrm{CDCl_3}$): δ 21.0 ppm. IR (film): 2962, 2931, 1689, 1244, 1051, 1022, 970 cm^{-1}. MS (CI) *m*/*z*: 308, 276. HRMS (EI − ESI) *m*/*z* calcd for $\mathrm{C_{13}H_{26}NNaO_5P}$, 330.144 $[\mathrm{M + Na}]^+$; found, 330.144 $[\mathrm{M + Na}]^+$.

Decomposition of 1j by $\mathrm{Rh_2(OAc)_4}$ Catalyst in Dichloroethane. After the consumption of all of the diazo compound **1j** (24 h, confirmed by TLC) and solvent removal, the reaction products were purified by flash chromatography (basic alumina, AcOEt/hexane). Compounds **2j** and **3j** were obtained in 50% yield as a mixture of **2j**/**3j** (1:2). One part of the mixture was purified by flash chromatography on silica gel to achieve pure **3j** (decompose in alumina), and the other part was purified in basic alumina to achieve pure **2j** (decompose in silica gel). **3j**: $R_f = 0.38$ (silica, AcOEt/hexane, 7:3). ^{1}H NMR ($\mathrm{CDCl_3}$, ppm): δ 1.09 (t, *J* = 7.6 Hz, 3H, $\mathrm{OCH_2C}\mathit{H}_3$), 1.42 (t, *J* = 7.5, 3H, $\mathrm{OCH_2C}\mathit{H}_3$), 3.93−4.09 (m, 2H, $\mathrm{OC}\mathit{H}_2\mathrm{CH_3}$), 4.18 (d, $J_{\mathrm{P-H}}$ = 29.9 Hz, 1H, $\mathrm{C}\mathit{H}\mathrm{CO(PO)}$), 4.25−4.32 (m, 2H, $\mathrm{OC}\mathit{H}_2\mathrm{CH_3}$), 4.75 (d, *J* = 15.7 Hz, 1H, $\mathrm{NC}\mathit{H}_2\mathrm{Ph}$), 5.12 (d, *J* = 15.7 Hz, 1H, $\mathrm{NC}\mathit{H}_2\mathrm{Ph}$), 6.71 (d, *J* = 7.8 Hz, 1H, $\mathrm{NCC}\mathit{H}\mathrm{CH}$), 7.04 (t, *J* = 7.6 Hz, 1H, $\mathrm{NC(CH)_2C}\mathit{H}$), 7.18−7.31 (m, 6H, *Ph*, $\mathrm{NCCHC}\mathit{H}$), 7.55 (d, *J* = 7.3 Hz, 1H, $\mathrm{NCCC}\mathit{H}\mathrm{CH}$). ^{13}C NMR ($\mathrm{CDCl_3}$, ppm): δ 16.1 (d, $J^3_{\mathrm{C-P}}$ = 5.5 Hz, $\mathrm{OCH_2}\mathit{C}\mathrm{H_3}$), 16.3 (d, $J^3_{\mathrm{C-P}}$ = 6.0 Hz, $\mathrm{OCH_2}\mathit{C}\mathrm{H_3}$), 43.9 ($\mathrm{N}\mathit{C}\mathrm{H_2Ph}$), 46.3 (d, $J_{\mathrm{C-P}}$ = 135.9 Hz, $\mathit{C}\mathrm{HCO(PO)}$), 63.1 (d, $J^2_{\mathrm{C-P}}$ = 6.4 Hz, $\mathrm{O}\mathit{C}\mathrm{H_2CH_3}$), 63.8 (d, $J^2_{\mathrm{C-P}}$ = 6.2 Hz, $\mathrm{O}\mathit{C}\mathrm{H_2CH_3}$), 109.1 ($\mathrm{NC}\mathit{C}\mathrm{HCH}$), 122.7 ($\mathrm{NC(CH)_2}\mathit{C}\mathrm{H}$), 127.0 (*Ph*), 127.2 ($\mathrm{NCCH}\mathit{C}\mathrm{H}$), 128.7, 135.5 (*Ph*), 143.7 ($\mathrm{N}\mathit{C}\mathrm{CH}$), 170.3 ($\mathit{C}\mathrm{{=}O}$). ^{31}P NMR ($\mathrm{CDCl_3}$): δ 17.5 ppm. IR (film): 3055, 2986, 1712, 1611, 1265, 1023 cm^{-1}. MS (FAB$^+$) *m*/*z* (%): 360, 223, 136. HRMS (FAB$^+$) calcd for $\mathrm{C_{19}H_{22}NO_4P}$, 359.129 $[\mathrm{M}]^+$; found, 359.129 $[\mathrm{M}]^+$. **2j**: $R_f = 0.67$ (neutral alumina, AcOEt/hexane, 2:3). ^{1}H NMR ($\mathrm{CDCl_3}$, ppm): δ 1.34 (m, 6H, $\mathrm{OCH_2C}\mathit{H}_3$), 3.55 (dd, $J_{\mathrm{H-P}}$ = 15.6, $J_{\mathrm{H-H}}$ = 2.7 Hz, 1H, $\mathrm{NCOC}\mathit{H}\mathrm{CHPh}$), 4.14−4.32 (m, 4H, $\mathrm{OC}\mathit{H}_2\mathrm{CH_3}$), 5.22 (dd, $J^3_{\mathrm{P-H}}$ = 9.2 Hz, $J_{\mathrm{H-H}}$ = 2.7 Hz, 1H, $\mathrm{NCOCHC}\mathit{H}\mathrm{Ph}$), 7.06 (t, *J* = 6.9 Hz, 1H, *Ph*), 7.23−7.37 (m, 9H, *Ph*). ^{13}C NMR ($\mathrm{CDCl_3}$, ppm): δ 16.4 ($\mathrm{OCH_2}\mathit{C}\mathrm{H_3}$), 55.8 ($\mathrm{NCOCH}\mathit{C}\mathrm{HPh}$), 57.2 (d, $J_{\mathrm{C-P}}$ = 145.0 Hz, $\mathrm{NCO}\mathit{C}\mathrm{HCHPh}$), 62.8, 63.1 ($\mathrm{O}\mathit{C}\mathrm{H_2CH_3}$), 117.0, 124.3, 125.9, 128.9, 129.0, 129.3, 136.5 (*Ph*), 136.5 (quaternary *Ph*), 159.1 ($\mathit{C}\mathrm{{=}O}$). ^{31}P NMR ($\mathrm{CDCl_3}$): δ 18.3 ppm. IR (film): 3063, 2984, 2926, 1758, 1500, 1383, 1259, 1024 cm^{-1}. MS (FAB$^+$) *m*/*z* (%): 360, 331, 182. HRMS (FAB$^+$) calcd for $\mathrm{C_{19}H_{23}NO_4P}$, 360.136 $[\mathrm{M + H}]^+$; found, 360.137 $[\mathrm{M + H}]^+$.

Decomposition of 1j by $\mathrm{Rh_2(pfb)_4}$ Catalyst in Dichloroethane. After the consumption of all of the diazo compound **1j** (6 h, confirmed by TLC) and solvent removal under reduced pressure, the reaction mixture dissolved in dichloromethane, filtered over a Celite pad, and evaporated to dryness giving **3j** in 97% yield.

Decomposition of 1j by $\mathrm{Rh_2(OAc)_4}$ Catalyst in Benzene. Compound **1j** (0.154 mmoL) was added to a solution of $\mathrm{Rh_2(OAc)_4}$ (1 mol %) in benzene (1.5 mL) under an argon atmosphere and heated at 80 °C over a period of 24 h. Water was added (2 mL), and the aqueous phase was extracted with ethyl ether (2 × 1.5 mL). After solvent evaporation under reduced pressure, a mixture of products (**2j**/**3j**, 1:11.6) was obtained in 88% yield.

Decomposition of 1j by $\mathrm{Rh_2(OAc)_4}$ Catalyst in Perfluorodecaline. Compound **1j** (0,154 mmoL) was added to a suspension of $\mathrm{Rh_2(OAc)_4}$ (1mol %) in perfluorodecaline (1.5 mL) under an argon atmosphere and heated at 80 °C over a period of 24 h. After solvent removal at 34 °C (1 mm Hg), water and ethyl ether were added. After extraction with ethyl ether (2 × 1.5 mL) and solvent removal, a mixture of products (**2j**/**3j**, 1:7) was obtained in 79% yield.

Decomposition of 1a in Water. A solution of **1a** (0.15 mmol) was heated at 80 °C over a period of 70 h in water (1.5 mL). After solvent removal, **4a** was obtained and fully characterized without further purification. $R_f = 0.38$ (silica, AcOEt/hexane, 7:3). ^{1}H NMR ($CDCl_3$, ppm): δ 1.12 (6H, d, $J = 6.5$ Hz, $NCH(CH_3)_2$), 1.25 (6H, d, $J = 5.6$ Hz, $NCH(CH_3)_2$), 1.31−1.39 (6H, m, OCH_2CH_3), 3.45−3.52 (1H, m, $NCH(CH_3)_2$), 3.92 (s, 1H, CHO*H*), 4.02−4.21 (5H, m, $NCH(CH_3)_2$ and OCH_2CH_3, overlapped signals), 4.65 (1H, d, $J_{H-P} = 7.6$ Hz, POC*H*OHCO). ^{13}C NMR ($CDCl_3$, ppm): δ 16.3 (OCH_2CH_3), 19.7, 19.9, 20.4, 20.7 ($NCH(CH_3)_2$), 46.8, 48.7 ($NCH(CH_3)_2$), 63.3, 63.5 (OCH_2CH_3), 67.0 (d, $J_{C-P} = 153.0$ Hz, POC*H*OHCO), 166.1 (*C*=O). ^{31}P NMR ($CDCl_3$): δ 16.9 ppm. IR (film): 3391, 3055, 1640, 1266, 1039 cm^{-1}. MS (FAB$^+$) *m/z* (%): 296, 278, 254, 158, 137. HRMS (FAB$^+$) calcd for $C_{12}H_{27}NO_5P$, 296.163 $[M + H]^+$; found, 296.162 $[M + H]^+$.

General Procedure for the Dirhodium(II)-Catalyzed Decomposition of α-Diazo Compounds in Water. To a solution of the dirhodium(II) catalyst (1.0 mol %) in water (1.5 mL) was added the appropriate diazo compound (0.154 mmol). The reaction mixture was heated at 80 °C until the disappearance of the substrate (determined by TLC). The mixture was concentrated under reduced pressure and the residue was purified by flash chromatography (basic/neutral alumina or silica with AcOEt/hexane), yielding the desired compounds.

Decomposition of 1f in Water in the Presence of $Rh_2(OAc)_4$. After consumption of all the diazo compound (24 h confirmed by TLC) and solvent removal, the reaction crude mixture was purified by PTLC (basic alumina, AcOEt/hexane, 3:2), and the product **2f** (described elsewhere[4b]) was obtained as a mixture of trans and cis isomers (6:1) in 40% yield.

Decomposition of 1g in Water in the Presence of $Rh_2(OAc)_4$. After consumption of all the diazo compound (18 h, confirmed by TLC) and solvent removal, the reaction crude mixture was purified by flash chromatography (basic alumina, AcOEt/hexane), and **2g** and **3g** (described elsewhere[4a]) were obtained as a mixture in a 1:10 ratio in 97% yield.

Decomposition of 1h in Water in the Presence of $Rh_2(OAc)_4$. After consumption of all the diazo compound (29 h, confirmed by TLC) and solvent removal, the reaction crude mixture was purified by flash chromatography (basic alumina, AcOEt/hexane), and the product **3h**[4a] was obtained in 59% yield.

Decomposition of 1l in Water in the Presence of $Rh_2(OAc)_4$. After consumption of all the diazo compound (24 h, confirmed by TLC) and solvent removal, the reaction products were isolated by flash chromatography (silica, AcOEt/hexane). **2l**[4a] was obtained in 57% yield and **4l** was obtained in 25% yield. **4l**: $R_f = 0.2$ (silica, AcOEt/hexane, 4:1), ^{1}H NMR ($CDCl_3$, ppm): δ 1.25−1.70 (6H, m, OCH_2CH_3), 4.07−4.34 (4H, m, OCH_2CH_3), 4.51−4.52 (3H, m, POC*H*OHCO and NCH_2Ph, overlapped signals), 7.26−7.36 (5H, m, *Ph*). ^{13}C NMR ($CDCl_3$, ppm): δ 16.3 (OCH_2CH_3), 43.9 (NCH_2-Ph), 64.1 (OCH_2CH_3), 68.0 (d, $J_{C-P} = 156.1$ Hz, POC*H*OHCO), 127.6, 127.7, 128.7 (*Ph*), 137.4 (quaternary *Ph*), 167.4 (*C*=O). ^{31}P NMR ($CDCl_3$): δ 18.2 ppm. IR (film): 3299, 2983, 2929, 1666, 1531, 1454, 1238, 1026, 976 cm^{-1}. MS (CI) *m/z*: 302, 286, 139, 91. HRMS (EI − ESI) *m/z* calcd for $C_{13}H_{20}NNaO_5P$, 324.144 $[M + Na]^+$; found, 324.097 $[M + Na]^+$.

Decomposition of 1l in Water in the Presence of $Rh_2(pfb)_4$ or $Rh_2(Ooct)_4$. After consumption of all the diazo compound (0.154 mmol, 24 h, confirmed by TLC) in the presence of rhodium catalyst and solvent evaporation under reduced pressure, the reaction mixture was purified by flash chromatography (basic alumina, AcOEt/hexane). When $Rh_2(pfb)_4$ was used, **2l** was obtained in 84% yield. In the case of cyclization catalyzed by $Rh_2(Ooct)_4$ and purification by flash chromatography (basic alumina, AcOEt/hexane), **2l** was obtained in 97% yield.

Decomposition of 1m in Water in the Presence of $Rh_2(OAc)_4$. After consumption of all the diazo compound (0.68 mmol, 48 h, confirmed by TLC) and solvent removal, the reaction products were purified by flash chromatography (basic alumina, AcOEt/hexane), yielding 86% of a mixture of products (**3m**/**4m**, 1:2.7). One part of the previous mixture was purified again on basic alumina (partial decomposition was observed) to obtain **4m** has a brown oil. **4m**: $R_f = 0.14$ (neutral alumina, AcOEt/MeOH, 3:2). ^{1}H NMR ($CDCl_3$, ppm): δ 1.21−1.29 (6H, m, OCH_2CH_3), 2.78 (2H, t, $J = 7.2$ Hz $HNCH_2CH_2$Ph), 3.50−3.55 (2H, m, NCH_2CH_2Ph), 3.95−4.18 (4H, m, OCH_2CH_3), 4.35 (1H, d, $J_{P-H} = 12.4$ Hz, OPC*H*OHCO), 6.99 (1H, s, $HNCH_2CH_2$Ph), 7.13−7.25 (5H, m, *Ph*). ^{13}C NMR ($CDCl_3$, ppm): δ 16.3, 16.4 (OCH_2CH_3), 35.5 (NCH_2CH_2Ph), 41.2 (NCH_2-CH_2Ph), 63.8, 63.9 (OCH_2CH_3), 67.9 (d, $J_{C-P} = 156.1$ Hz, POC*H*OHCO), 126.6, 128.6, 128.7 (*Ph*), 138.4 (quaternary *Ph*), 167.3 (*C*=O). ^{31}P NMR ($CDCl_3$): δ 18.2 ppm. IR (film): 3286, 2983, 2933, 1666, 1533, 1238, 1026, 976 cm^{-1}. MS (CI) *m/z*: 316, 178, 139, 104. HRMS (EI − ESI) *m/z* calcd for $C_{14}H_{22}NNaO_5P$, 338.113 $[M + Na]^+$; found, 338.113 $[M + Na]^+$.

Decomposition of 1m in Water in the Presence of $Rh_2(pfb)_4$. After consumption of all the diazo compound (0.154 mmol, 24 h, confirmed by TLC) and solvent removal, the reactions products were purified by flash chromatography (basic alumina, AcOEt/hexane), yielding 64% of a mixture of products **3m**/**4m** (12:1).

Decomposition of 1m in Water in the Presence of $Rh_2(Ooct)_4$. After consumption of all the diazo compound (0.154 mmol, 24 h, confirmed by TLC) and solvent removal, the mixture was purified by flash chromatography (basic alumina, AcOEt/hexane), yielding 76% of **3m**.

Decomposition of 1k in Water in the Presence of Dirhodium(II) Catalyst. After consumption of all the diazo compound (0.154 mmol, 48 h, confirmed by TLC) in the presence of $Rh_2(OAc)_4$, the reaction mixture was concentrated under reduced pressure and purified by flash chromatography (basic alumina, AcOEt/MeOH), yielding 71% of **4k** as a yellow oil.

When $Rh_2(pfb)_4$ or $Rh_2(Ooct)_4$ was used, after consumption of all the diazo substrate (24 h), the mixture of products was chromatographed (basic alumina or silica, AcOEt/MeOH), yielding the mixture of products in 73% (**3k**[4a]/**4k**, 1:1.1) and 62% yield (**3k**/**4k**, 1:4.2), respectively. **4k**: $R_f = 0.13$ (silica, AcOEt/hexane, 7:3). ^{1}H NMR ($CDCl_3$, ppm): δ 1.27−1.33 (m, 6H, $POCH_2CH_3$), 3.29 (s, 6H, OCH_3), 3.45−3.64 (m, 8H, NCH_2CH_2O), 4.15−4.23 (m, 4H, OCH_2CH_3), 4.53 (d, $J_{P-H} = 18.22$ Hz, 1H, COC*H*(OH)PO). ^{13}C NMR ($CDCl_3$, ppm): δ 15.3 ($POCH_2CH_3$), 47.2 (NCH_2CH_2O), 48.0 (NCH_2CH_2O), 58.8 (OCH_3), 63.1 ($POCH_2CH_3$), 63.6 ($POCH_2$-CH_3), 70.8 (NCH_2CH_2O), 74.0 (d, $J_{P-C} = 159$ Hz, CO*C*H(OH)-PO), 163.2 (N*C*OCH(OH)). ^{31}P NMR ($CDCl_3$): δ 16.7 ppm. IR (film): 3423, 3054, 2986, 1657, 1422, 1265, 1047 cm^{-1}. MS (FAB$^+$) *m/z* (%): 296, 268, 137. HRMS (FAB$^+$) calcd for $C_{12}H_{27}NO_7P$, 328.153 $[M]^+$; found, 328.152 $[M]^+$.

Decomposition of 1n in Water in the Presence of Dirhodium(II) Catalyst. After consumption of all the diazo compound (0.154 mmol, 24 h, confirmed by TLC) in the presence of dirhodium catalyst, the reaction mixture was concentrated under reduced pressure and chromatographed (silica, AcOEt/hexane). A different mixture of products was obtained depending on the used catalyst. **4n** was characterized from a mixture of **4n** and **3n′** in a 0.8:1 ratio. **4n**: $R_f = 0.13$ (basic alumina, AcOEt/hexane, 4:1). ^{1}H NMR ($CDCl_3$, ppm): δ 0.865 (t, $J = 7.3$ Hz, 3H, $NCH_2CH_2CH_2CH_3$, overlapped signals), 1.18−1.31 (m, 8H, OCH2C*H*$_3$ and NCH_2-$CH_2CH_2CH_3$, overlapped signals), 1.50 (t, $J = 7.6$ Hz, 2H, $NCH_2CH_2CH_2CH_3$, overlapped signals), 3.26−3.44 (m, 7H, OCH_3, $NCH_2CH_2OCH_3$, $NCH_2CH_2CH_2CH_3$, overlapped signals), 3.75−3.81 (m, 1H, $NCH_2CH_2OCH_3$), 4.07−4.25 (m, 5H, OCH_2CH_3 and $NCH_2CH_2OCH_3$, overlapped signals), 4.49 (d, $J_{JP-H} = 18.1$ Hz, 1H, OPC*H*(OH)CO). ^{13}C NMR ($CDCl_3$, ppm): δ 13.6 (NCH_2CH_2-CH_2CH_3), 16.3 ($POCH_2CH_3$), 19.8 ($NCH_2CH_2CH_2CH_3$), 28.8 ($NCH_2CH_2CH_2CH_3$), 42.7 ($NCH_2CH_2OCH_3$), 46.7 (NCH_2CH_2-CH_2CH_3), 58.5 (OCH_3), 62.86, 62.92, 63.08, 63.14 (OCH_2CH_3,

$NCH_2CH_2OCH_3$), 74.0 (d, J_{P-C} = 159.4 Hz, COCH(OH)PO), 162.8 (C=O). ^{31}P NMR ($CDCl_3$): δ 16.9 ppm. IR (film): 3458, 2962, 2933, 1654, 1242, 1024, 974 cm^{-1}. MS (CI) *m/z* 294.

Decomposition of 1j in Water in the Presence of $Rh_2(OAc)_4$. After consumption of all the diazo compound (0.154 mmol, 26 h, confirmed by TLC) in the presence of $Rh_2(OAc)_4$, the reaction mixture was extracted with ethyl ether (5 × 1.5 mL), and after solvent evaporation under reduced pressure, a mixture of products (**2j**/**3j**, 1:10) was obtained in 97% yield.

Decomposition of 1j in Water in the Presence of $Rh_2(pfb)_4$ or $Rh_2(Ooct)_4$. After consumption of all the diazo compound (0.154 mmol, 48 h, confirmed by TLC) in the presence of rhodium catalyst and solvent evaporation under reduced pressure, the reaction mixture was filtered over a Celite pad. When $Rh_2(pfb)_4$ was used, **3j** was obtained in quantitative yield. After cyclization, catalyzed by $Rh_2(Ooct)_4$, and filtration, a mixture of products (**2j**/**3j**, 1:6) was obtained in 92% yield.

Decomposition of 1j in Water in the Presence of $Rh_2(OAc)_4$ and Sodium Chloride. After dissolution of $Rh_2(OAc)_4$ (1 mol %) in an aqueous solution (1.5 mL) of sodium chloride (20 wt %), the diazo compound was added and heated at 80 °C over a period of 24 h. The reactions products were extracted with ethyl ether (5 × 1.5 mL), and after solvent evaporation, a mixture of **2j**/**3j** (1:21) was obtained in 87% yield.

Decomposition of 1i in Water in the Presence of $Rh_2(OAc)_4$. After consumption of all the diazo compound (0.154 mmol, 24 h, confirmed by TLC) in the presence of $Rh_2(OAc)_4$, the reaction mixture was concentrated under reduced pressure and purified by PTLC (silica, AcOEt/hexane, 95:5), yielding 78% of **4i** as a yellow oil. R_f = 0.35 (silica, AcOEt/hexane, 95:5). ^1H NMR ($CDCl_3$, ppm): δ 0.95 (t, *J* = 7.4 Hz, 3H, $OCH_2CH_2CH_3$), 1.32 (t, *J* = 7.1 Hz, 6H, $POCH_2CH_3$), 1.65−1.74 (m, 2H, $OCH_2CH_2CH_3$), 4.15−4.26 (m, 6H, $OCH_2CH_2CH_3$, $POCH_2CH_3$, overlapped signals), 4.53 (d, J_{P-H} = 15.8 Hz, 1H, COCH(OH)PO). ^{13}C NMR ($CDCl_3$, ppm): δ 10.1 ($OCH_2CH_2CH_3$), 16.26, 16.31 ($POCH_2CH_3$), 21.8 ($OCH_2CH_2CH_3$), 63.4−63.8 ($POCH_2CH_3$), 68.1 ($OCH_2CH_2CH_3$), 68.7 (d, J_{P-C} = 155.0 Hz, COCH(OH)PO), 169.5 (C=O). ^{31}P NMR ($CDCl_3$): δ 16.1 ppm. IR (film): 3427, 3056, 2984, 1740, 1266, 1089, 1025 cm^{-1}. MS (FAB^+) *m/z* (%): 255, 239, 167, 137. HRMS (FAB^+) calcd for $C_9H_{19}O_6P$, 225.100 $[M]^+$; found, 255.100 $[M]^+$.

Procedure for $Rh_2(OAc)_4$ Recycling. To a solution of dirhodium(II) tetraacetate (1.0 mol %) in water (1.5 mL) was added **1a** (0.154 mmol), **1e**, or **1j**. The reaction mixture was heated at 80 °C for 24 h, the product was extracted from the reaction medium with Et_2O (10 × 1.5 mL), and more substrate was added (0.154 mmol) to the system.

Procedure for Catalyst Stability Determination. Dirhodium(II) tetraacetate (0.0453 mmol) was heated in water (43 mL) at 80 °C for 24 h, and after concentration under vacuum, the product was recrystallized in water. The green solid obtained (9.6 mg) was identified by microanalysis as being $Rh_2(OAc)_4 \cdot 2H_2O$. Anal. Calcd for $C_8H_{16}O_{10}Rh_2$: C, 20.10; H, 3.37. Found: C, 20.31; H, 3.35.

This sample was used for cyclization of **1j**, according to the procedure described earlier. The diazo compound (0.154 mmol) was added to a solution of dirhodium(II) tetraacetate (1 mol %) in water (1.5 mL), and the mixture was heated at 80 °C, under stirring, for 26 h. The reaction products were extracted with Et_2O (3 × 1.5 mL), and a mixture of products (**2j**/**3j**, 1:12) was obtained in 71% yield.

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Supporting Information Available: Spectral data for all new compounds and crude spectral data for the reaction of **1j** in water for different catalysts. This material is available free of charge via the Internet at http://pubs.acs.org.

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