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An expeditious route to phosphorus heterocycles based on ring-closing metathesis

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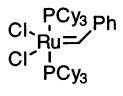
Abstract

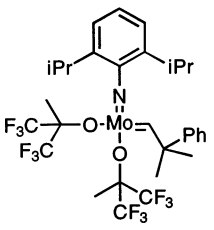
A convenient route for the synthesis of phosphorus diolefinic templates starting from the bifunctional reagent bis(diisopropylamino)vinylphosphine is presented. Ring closing olefin metathesis on this type of diene substrate revealed that the newly developed 4,5-dihydro-imidazol-2-ylidene ruthenium benzylidene complex **4** is in all aspects superior to the previously developed Grubbs' catalyst **1**.

Keywords: ring-closing metathesis; phosphitylation; phosphorus heterocycles.

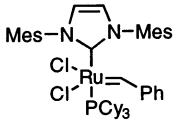
It is well established now that ring-closing olefin metathesis (RCM) is a powerful tool in the construction of complex organic molecules.[1] It also became clear that a successful outcome of a RCM reaction is not only restrained by the nature of the functional groups, but also by the number of atoms connecting the double bonds and the substitution pattern of the olefin moieties in the RCM template. Among the precatalysts developed thus far, only two are commercially available. One of them, Grubbs' ruthenium complex **1**,[2] has found the widest application. The other one, the oxygen and moisture sensitive molybdenum complex **2**,[3] proved to be more effective in the RCM of sterically congested olefins.



1

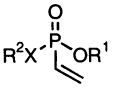


2



3 Mes = C_6H_2-2,4,6-$(CH_3)_3$

4



5 X = O
6 X = NR^2

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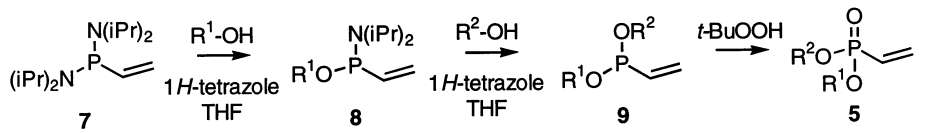
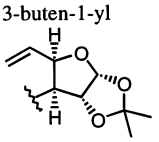
Recent studies[4] revealed that phosphorus containing heterocycles were accessible by RCM reaction on diolefinic phosphine oxides under the influence of Grubbs' catalyst (**1**). The results of these studies indicated that the outcome was not fully satisfactory in terms of yield and time duration. Additional advances in catalyst development resulted in the generation of the new imidazol-2-ylidene-substituted ruthenium-based catalysts **3**[5] and **4**.[6] Both catalysts display remarkable higher thermal stabilities and enhanced RCM activities.[5,7] Interestingly, catalyst loadings of as low as 0.05 mol% still proved to be effective in the case of the 4,5-dihydro-imidazol-2-ylidene Ru-based complex **4**. In addition, it was expected[8] that the presence of a saturated imidazol-2-ylidene ligand as in **4** would lead to higher catalyst activity than in its unsaturated counterpart **3**. Both aspects tipped the balance of using precatalyst **4** in RCM reactions on the vinylphosphonates **5a–e** and the vinylphosphonamides **6a,b**.

Herein we report that the dihydroimidazole carbene ruthenium complex **4** is in all aspects superior to Grubbs' catalyst **1** in RCM reactions on substrates **5a–e** and **6a,b**, which in turn were easily accessible from the bifunctional phosphitylating reagent bis(diisopropylamino)-vinylphosphine (**7**).

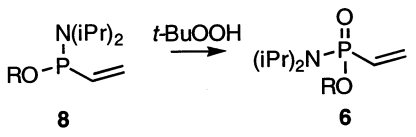
The preparation of the two types of diene substrates could be readily accomplished, as depicted below, starting from the known vinylphosphine **7**.[9] In the case of the symmetrical diene **5a**, vinylphospordiamidite **7** was treated with excess allyl alcohol in the presence of 1*H*-tetrazole (2 equiv.). In situ oxidation of the resulting intermediate **9** ($R^1 = R^2 =$ allyl; δ_P 165 ppm) with *t*-butyl-hydroperoxide gave, after workup and purification, homogeneous vinylphosphonate **5a**. The nonsymmetrical derivatives **5b–e** were prepared as follows. 1*H*-Tetrazole catalyzed the phosphitylation of benzyl alcohol (1 equiv.) with **7** and the condensation of purified **8** (R^1 = benzyl; δ_P 118 ppm) in the presence of 1*H*-tetrazole (1 equiv.) with a stoichiometric amount of the unsaturated alcohols R^2–OH (R^2 = allyl, butenyl or D-*gluco*-furanosyl[10]) led, after in situ oxidation, to the isolation of compounds **5b–e**. Similarly, condensation of **7** under the

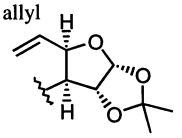
Preparation of phosphonates 5a-e



5a R^1 = allyl, R^2 = allyl	overall yield: quant.
5b R^1 = benzyl, R^2 = allyl	overall yield: 71%
5c R^1 = benzyl, R^2 = 3-buten-2-yl	overall yield: 74%
5d R^1 = benzyl, R^2 = 3-buten-1-yl	overall yield: 78%
5e R^1 = benzyl, R^2 = 	overall yield: 62%

Preparation of phosphonamides 6a,b



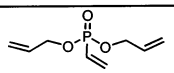
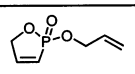
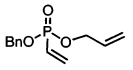
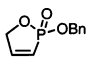
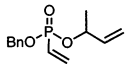
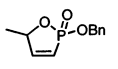
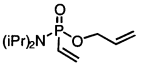
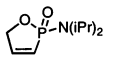
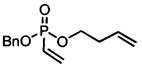
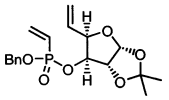
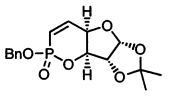
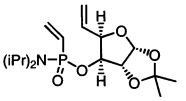
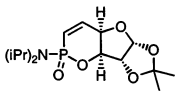
6a R = allyl  overall yield: 70%

6b R = overall yield: 90%

influence of a catalytic amount of 1*H*-tetrazole (0.1 equiv.), followed by in situ oxidation of the intermediate phosphoramidite **8** gave, after workup and purification, phosphonamides **6a**,**b**.

In order to explore in more detail the efficacy of catalyst **4**, two sets of RCM reactions were executed on the substrates **5a–e** and **6a**,**b** (0.02 M) utilizing 2 mol% of the initial precatalyst **1** or 1 mol% of the new Grubbs' precatalyst **4** in refluxing dichloromethane. The results of this study are recorded in Table 1.

Table 1
RCM on substrates **5a–e** and **6a**,**b** using precatalysts **1** and **4**

Substrate δ_P (ppm)		Product δ_P (ppm)		Yield (%) using **1**[a] (time)	Yield (%) using **4**[a] (time)
5a (18.65)		**10a** (43.15)		44 (ref. 4e) (6 h)	quant. (30 min)
5b (18.68)		**10b** (43.27)		25 (4 d)	quant. (15 min)
5c (17.72) (17.41)		**10c** (41.21) (40.70)		65 (2 d)	92 (30 min)
6a (21.33)		**10d** (45.80)		85 (1 d)	quant. (1 h)
5d (18.35)		**10e** (12.26)		85 (4 d)	quant. (20 min)
5e (18.68) (18.53)		**10f** (9.03) (8.49)		76 (4 d)	86 (30 min)
6b (21.99) (21.02)		**10g** (21.31) (8.55)		45 (4 d)	quant. (16 h)

[a]Isolated yields

In the first instance, it was established that vinylphosphonate **5a** was rapidly and quantitatively converted into the oxaphosphole **10a**[11] under the influence of the new catalyst **4**. This finding is in sharp contrast with the earlier reported[4e] formation of a mixture containing the 5- (44%) as well as the 7-membered (31%) P-heterocycles in the RCM of **5a** in refluxing CH_2Cl_2 (0.01 M) using 6 mol% Grubbs' catalyst **1**. The higher potency of precatalyst **4** over Grubbs' precatalyst **1** is also evident from the fast and high yielding conversion, as gauged by ^{31}P NMR, of the phosphonates **5b–c** into the respective 5-membered P-heterocycles **10b** and **10c**. Similarly, RCM reaction on the phosphonamide **6a** proceeded smoothly resulting in the formation of the 5-membered P-heterocycle **10d**. The outcome of the RCM reaction on substrate **5d** also reveals a substantial decrease in time duration of the expected formation of the 6-membered product **10e**. A similar tendency prevails in the transformation of the more sterically demanding substrates **5e** and **6b** into the *cis*-fused 5,6-bicyclic derivatives **10f** and **10g**.

The results presented in this paper clearly show that the new Grubbs' precatalyst **4** is highly effective in performing RCM reactions on vinylphosphonates as well as on vinylphosphonamides. In addition, the easily accessible bifunctional reagent bis(diisopropylamino)vinylphosphine (**7**) promises to be of great value in the preparation of highly functionalized and structurally diverse phosphorus containing diolefinic templates.

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11. All compounds were fully characterized by ^{1}H, ^{13}C and ^{31}P NMR and MS. Relevant example: 2-allyloxy-5*H*-[1,2]oxaphosphole 2-oxide (**10a**), ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.16 (ddt, 1H, *J* 46.29 Hz, *J* 8.53 Hz, *J* 1.69 Hz), 6.21 (ddt, 1H, *J* 34.11 Hz, *J* 8.54 Hz, *J* 2.42 Hz), 5.96 (ddt, 1H, *J* 17.12 Hz, *J* 10.42 Hz, *J* 5.53 Hz), 5.37 (m, 1H), 5.26 (m, 1H), 4.80 (m, 2H), 4.58 (m, 2H). ^{31}P NMR (243 MHz, $CDCl_3$): δ 43.23. ^{13}C NMR (50 MHz, $CDCl_3$): 148.3 (d, *J* 16.8 Hz), 132.8 (d, *J* 6.1 Hz), 118.1 (s), 116.9 (d, *J* 64.7 Hz), 70.6 (d, *J* 13.7 Hz), δ 67.4 (d, *J* 6.11 Hz). HRMS (FAB) calcd for $C_6H_9O_3P$ [M^+] 160.0289, found: 160.0280.