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Ring closing metathesis of phenyl-substituted dienes

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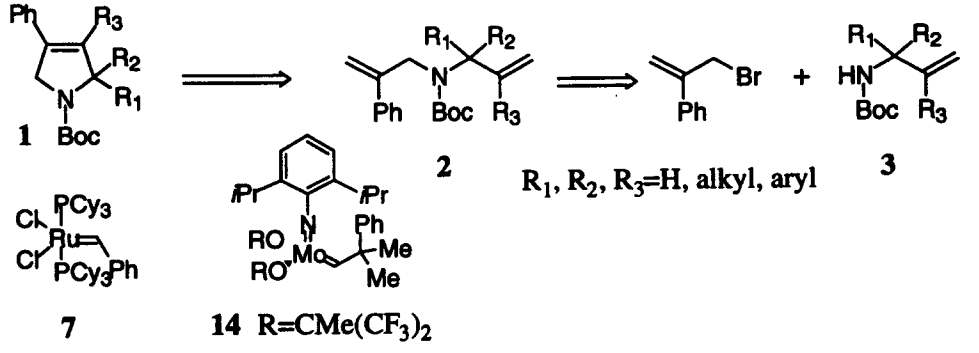
Abstract

A series of phenyl-substituted heterodienes **2a–f** and **6** was prepared and subjected to ring closing metathesis (RCM) to give differently phenyl-substituted dihydropyrroles and dihydrofuran.

Keywords: metathesis; dihydropyrroles; dihydrofuran; phenyl-substituted dienes.

Ring closing metathesis (RCM) is a powerful method for the construction of functionalised carbocycles and heterocycles.[1] The discovery of the well-defined ruthenium alkylidene **7**[2] and molybdenum alkylidene **14**[3] catalysts has greatly expanded the scope and utility of this reaction. As part of a study of new transition state analogues, we became interested in the synthesis of phenyl-substituted dihydropyrroles **1** which should be readily prepared by RCM of the corresponding phenyl-substituted dienes **2**. These dienes should be accessible by the alkylation of allylamines **3** with 2-phenylallylbromide (Scheme 1). To our knowledge, only two examples of RCM on phenyl-substituted dienes have been reported in the literature, one as part of a study by Grubbs et al. on the effects of olefin substitution on



Scheme 1.

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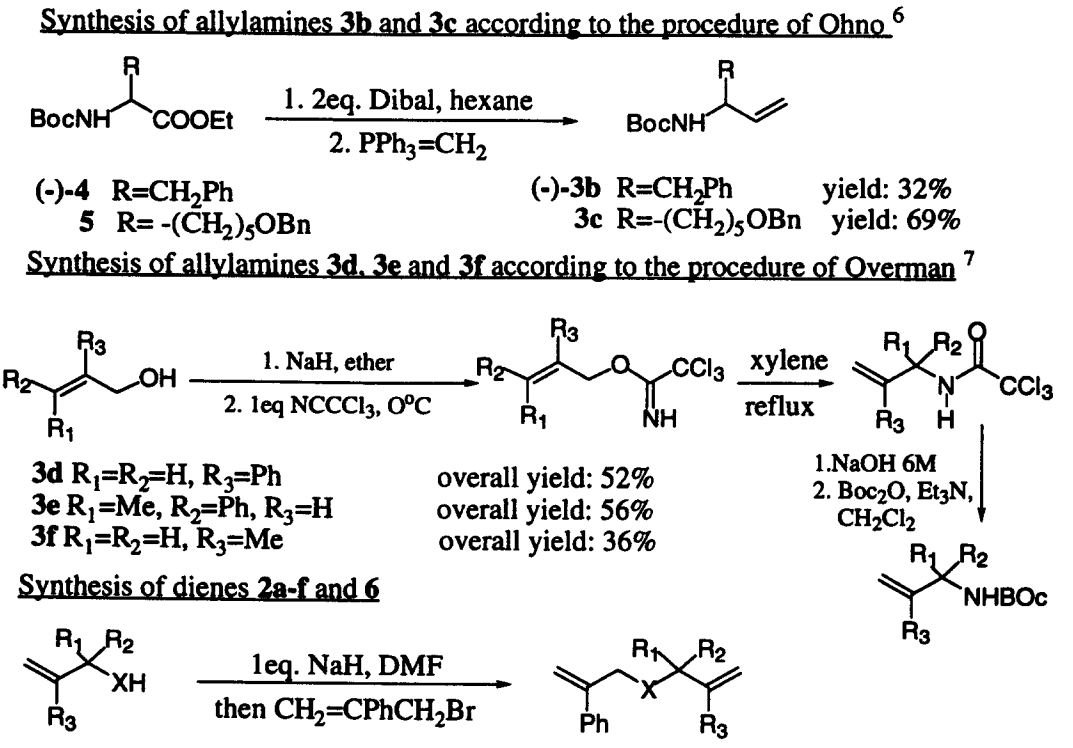
the ring closing metathesis of dienes,[4] the other on a phosphinate template.[5] Herein, the synthesis and the reactivity of a variety of phenyl-substituted substrates is presented.

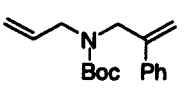
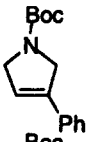
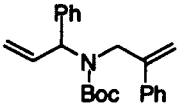
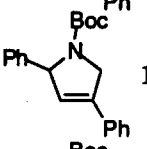
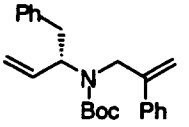
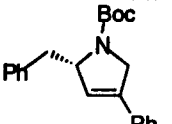
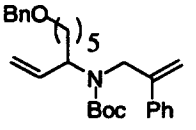
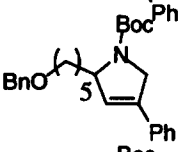
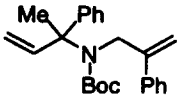
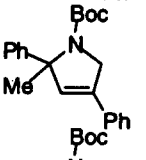
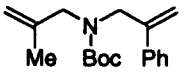
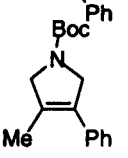
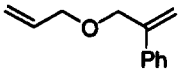
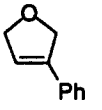
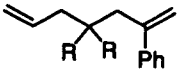
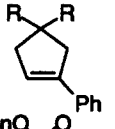
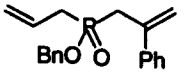
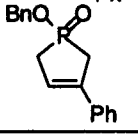
A series of allylamines **3a–f** was prepared according to two different procedures (Scheme 2). Allylamines **3b** and **3c** were synthesised from the corresponding protected aminoesters **4** and **5**.[6] The α-ester group of aminoesters **4** and **5** was first reduced with diisobutylaluminium hydride to an intermediate aluminoxy acetal that on reaction with the Wittig reagent afforded the allylamines **3b** and **3c** in 32 and 69% yield, respectively. Allylamines **3d**, **3e** and **3f** were prepared using the procedure of Overman et al.[7] The allylic alcohols were first condensed with trichloroacetonitrile to yield the corresponding allylic trichloroacetimidic esters. Thermolysis of these esters resulted in allylic rearrangement to afford the corresponding trichloroacetamides which are transformed into the free amines by treatment with 6 M NaOH. Protection of the amines was carried out in CH_2Cl_2 using Boc_2O and Et_3N. The dienes **2a–f** were all prepared in good yields (75–92%) by alkylation of the allylic amines **3a–f** with 2-phenylallylbromide. Diene **6** was prepared in a similar manner from allylic alcohol (Scheme 2).



Scheme 2.

The RCM of dienes **2a–f** and **6** in CH_2Cl_2 or benzene in the presence of 2–15% Ru-carbene **7** gave the corresponding cyclic products **1a–f** as detailed in Table 1. When diene **2a** was subjected to RCM conditions, 100% conversion to the cyclised product **1a** was observed. After purification by column chromatography, only 25% of **1a** was isolated along with the corresponding pyrrole resulting from the oxidation of **1a** (entry 1). Interestingly, the disubstituted dienes **2b**, **2c** and **2d** all cyclised in good isolated yields (entries 2, 3 and 4). However, when the trisubstituted diene **2e** was exposed to 10% of Ru-catalyst

Table 1
Ring closing metathesis of dienes **2a–f**, **6**, **10** and **12** with the Ru- or Mo-catalysts **7** and **14**

Entry	Substrate		Product		Condition	yield [a] (%)
1		**2a**		**1a**	CH_2Cl_2, reflux 0.02M, 24h, 3% **7**	(100)[b] 25[c]
2		**2b**		**1b**	CH_2Cl_2, reflux 0.02M, 8h, 6% **7**	66
3		**2c**		**1c**	benzene, 50°C 0.02M, 6h, 2% **7**	83
4		**2d**		**1d**	benzene, 50°C 0.02M, 10h, 5% **7**	82
5		**2e**		**1e**	CH_2Cl_2, reflux 0.02M, 2days, 10% **7**	no RCM[d]
6		**2f**		**1f**	CH_2Cl_2, reflux 0.02M, 2days, 10% **7**	no RCM[d]
7		**6**		**8**	CH_2Cl_2, rt 0.02M, 3h, 3% **7**	85 0:100[e]
8					CH_2Cl_2, reflux 0.005M, 24h, 10% **7**	90 1:2[e]
9				**9**	CH_2Cl_2, reflux 0.001M, 24h, 15% **7**	(70) 3:1[e]
10		**10**		**11**	PhH, 65°C, 0.02M, 5% **7**	(25)[4]
11	R=COOEt				PhH, 65°C, 0.02M, 5% **14**	97[4]
12		**12**		**13**	CH_2Cl_2, reflux, 0.02M, 2days, 10% **7**	no RCM[5, d]

a:isolated yields, all products were characterised by ^1H, ^{13}C NMR, IR and mass spectrometry; b: conversion; c: the major product is the corresponding pyrrole; d:recovered starting material; e: ratio of products **8:9**

7 for 2 days, no reaction occurred. Similarly, alkylidene **7** showed no reaction with diene **2f** for the formation of the tetrasubstituted olefin in **1f**. These results could be rationalised in the following manner. For dienes **2a–d**, the monosubstituted olefin is the site of initiation. Once the alkylidene has initiated, the intramolecular reaction is favoured providing the cyclic product. In contrast, for diene **2e**, the presence of the methyl and the phenyl groups on the allylic position prevents the initial reaction of the alkylidene with the monosubstituted olefin of the substrate and the starting material was recovered. Similarly, diene **2f**, which does not include a monosubstituted olefin, is not reactive as initiation of the catalyst could not take place.

The RCM of diene **6** in CH_2Cl_2 in the presence of 3% of the catalyst **7** yielded only the dimeric product **9** (entry 7). At lower substrate concentration (0.005 M) in CH_2Cl_2 at reflux in the presence of 10% of **7** added portionwise, the dimer is still the major compound but some cyclised product **8** was observed as well (2:1) (entry 8). However, at a substrate concentration of 0.001 M, when the catalyst **7** (15%) was added all at once, 70% conversion was observed with the cyclised product **8** formed as the major product (3:1) (entry 9).

In comparison, Grubbs[4] has previously observed that the RCM of the phenyl-substituted carbodiene **10** afforded only 25% of the cyclic product **11** in the presence of 5% of the Ru-catalyst **7** (entry 10). However, in the presence of the more reactive Mo-catalyst **14**, 97% of cyclic product was isolated (entry 11). The failure of **10** to yield the desired product in higher yield when exposed to alkylidene **7** was postulated to be a combination of the steric effects of the substituent and the electron-withdrawing effects of the phenyl group. The higher reactivity of alkylidene **14** further underscores its generally higher activity. Also, we reported previously that the RCM of the phenyl-substituted phosphinate **12** was not possible using the Ru-catalyst **7** (entry 12).[5] The results described in this paper show that the Ru-catalyst **7** is effective for the RCM of dienes **2a–f** and **6**. One possible explanation is that these dienes adopt a conformation that is more favourable for cyclisation.

In summary, we have reported a new route to a series of phenyl-substituted dihydropyrroles **1a–f** and the dihydrotetrafuran **8** based on the RCM of the corresponding phenyl-substituted dienes. It was shown that the Ru-alkylidene **7** was an efficient catalyst for these reactions.

Acknowledgements

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