# Progress towards the Stereoselective Synthesis of 3,6-Disubstituted 1,2-Diamino-4-cyclohexenes by Ring Closing Metathesis Reaction

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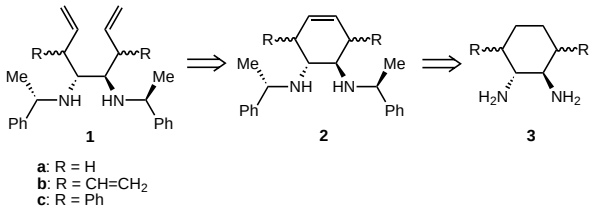
Received: July 31, 2002; Accepted: September 24, 2002

**Abstract:** The ring closing metathesis of 4(*R*),5(*R*)-bis[1(*S*)-phenylethylamino]-3,6-diethenyl-1,7-octadiene required the preliminary formation of the cyclic formaldehyde aminal, then the use of the Grubbs' ruthenium benzylidene complex (10 mol %) in refluxing toluene in the presence of 2 equivalents of trifluoroacetic acid. The cyclic aminal was cleaved *in situ* after the cyclisation step, so that the final product was the 1,2-diamino-3,6-diethenylcyclohex-4-ene derivative. The predominant $C_1$-symmetric diastereomer was isolated with 48% yield.

**Keywords:** diamine; diene; ring closing metathesis; ruthenium




**Scheme 1.** Synthetic route to 3,6-disubstituted 1,2-diaminocyclohexanes.

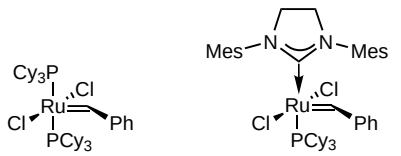



**Figure 1.** Ruthenium carbene complexes used for RCM reactions.

We have recently envisioned that the 1,2-diaminocyclohexane backbone can be constructed by applying transition metal-mediated or -catalysed cyclisation procedures to 4,5-diamino-1,7-octadiene derivatives, which are in turn available by the diastereoselective double addition of allylic organometallic reagents to the enantiopure 1,2-diimine derived from glyoxal and (*S*)- or (*R*)-1-phenylethylamine.[1] We have recently described reductive cyclozirconation reactions of the diamine **1a**,[1a] leading to different diastereomers of 4,5-dimethyl-1(*R*),2(*R*)-diaminocyclohexanes.[2] We have also exploited the ring closing metathesis (RCM)[3] reaction to convert the bis(hydrochloride) of the diamine **1a** to the diaminocyclohexene **2a** (Table 1, entry 1) using the ruthenium carbene complex **4** as the catalyst (Figure 1), then the saturated primary diamine **3a** was prepared by hydrogenation-hydrogenolysis (Scheme 1).[4] These cyclisation reactions opened new routes to ring-substituted 1,2-diaminocyclohexanes. In our opinion, it is worth studying the influence that substituents/stereocentres at the C-3 and C-6 positions of the 1,2-diaminocyclohexane skeleton can have in asymmetric reactions where *N*-derivatives of (*R*,*R*)- and (*S*,*S*)-1,2-diaminocyclohexane **3a** have acted as effective catalysts.[5]

Here we describe the results of the RCM reactions we have carried out on the 3,6-disubstituted 4(*R*),5(*R*)-bis[1(S)-phenylethylamino]-1,7-octadienes **1b**[1b] and **1c**[1c] (Scheme 1) using as catalysts ruthenium carbene complexes, i.e., the Grubbs' catalyst **4** and the more recently described catalyst **5**, which bears a *N*-heterocyclic carbene ligand[3n–q,6] (Figure 1). The results obtained on **1b** and its derivative **6** (Scheme 2) are reported in Table 1. These compounds feature the presence of diastereotopic vinyl groups, which should be discriminated by the ruthenium catalyst owing to the presence of the stereogenic centres at C-4 and C-5, so that two new stereocentres and possibly three diastereomers are formed in the cyclic product.[7] The protocol applied to **1b** was the same as that which previously worked successfully with **1a**[4] and involved the preliminary formation of the diamine bis(hydrochloride). In fact, the usual protection of the amino function as an amide or carbamate, which is generally adopted to perform RCM reactions of aminodienes, could be accomplished for only one of the two amino functions of compounds **1a–c**, even using an excess of the most

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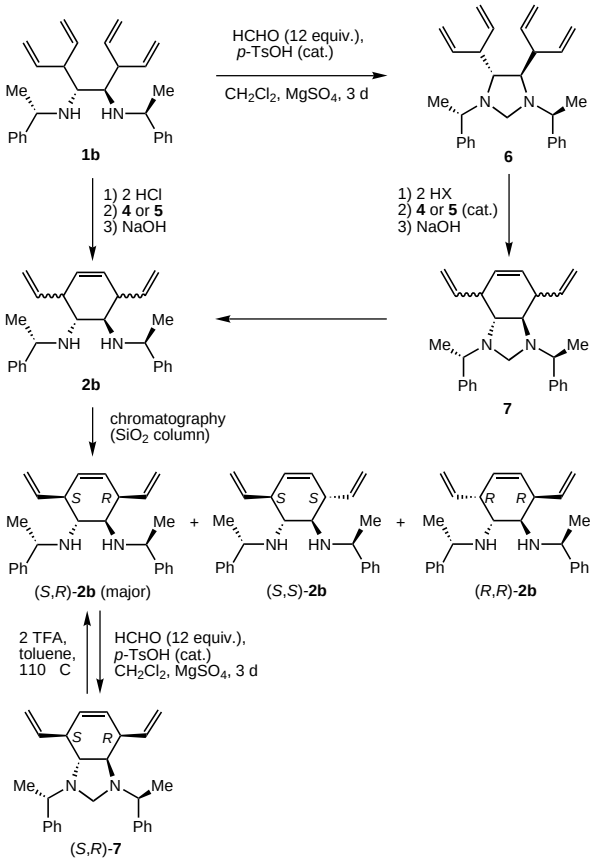



**Scheme 2.** Diastereoselective RCM reactions of diaminotetraene derivatives.

reactive acyl and sulphonyl halides. This is probably due to steric hindrance in the second protection step. Unfortunately, working on **1b**-2 HCl and using 10 mol % of the Grubbs' catalyst **4** in $CH_2Cl_2$ at room temperature, complete recovery of the starting compound **1b** was observed after 12 h, at which time the mixture was made basic and the organic material was extracted with $CH_2Cl_2$ and analysed (GC-MS and $^1$H NMR). The failure of the cyclisation was attributed to steric factors, owing to the double allylic substitution of the 1,7-octadiene chain. Therefore, more forcing reaction conditions were applied, but only *ca.* 3% conversion of **1b** to **2b** after 24 h in refluxing benzene was determined by GC-MS analysis (entry 2). We then turned our attention to the catalyst **5** and first checked its activity in the acidic conditions required by the substrate: the RCM reaction of **1a**-2 HCl in $CH_2Cl_2$ at 40 °C with a 10% loading of **5** gave an almost quantitative conversion to **2a** after 1 h (entry 3). Then the cyclisation of **1b**-2 HCl was attempted in refluxing toluene (110 °C), but after repeated additions of the catalyst for an overall amount of 30 mol % during 24 h, **2b** was formed in 30% yield as a mixture of two diastereomers (dr 82:18), most of the substrate **1b** being recovered (entry 4).

We reasoned that the moderate efficiency of the RCM reactions was in part due to the difficulty to attain the required conformation where the terminal alkene moiety is close to the initially formed ruthenacyclobutane complex.[8] Aiming to overcome this obstacle, we decided to reduce the rotational freedom of the carbonic chain by reversible formation of the imidazolidine ring, as in **6**. This compound was slowly but quantitatively obtained by the acid-catalysed reaction of **1b** with paraformaldehyde (Scheme 2). However, no reaction occurred when **6** was treated with 10 mol % of catalyst **4** in benzene solution, even at reflux, avoiding the preliminary acidification step. With this regard, it should be observed that a few examples of successful RCM reactions of 1,n-dienes in the presence of tertiary amine functions have been described.[9]

Successively, working on **6**-2 HCl with **4** in refluxing toluene no reaction was observed after 3 h (entry 5). Instead, substitution of trifluoroacetic acid (TFA) for hydrochloric acid allowed us to obtain the bicyclic product **7** with 54% yield using the catalyst **4** (10 mol %)

**Table 1.** RCM reactions of substituted 1,7-octadienes.

| Entry | Substrate | Catalyst, [mol %] | Solvent | Temp. [°C] | Time [h] | Products, yield [%] (GC) | dr of **2b**[a] |
|---|---|---|---|---|---|---|---|
| 1 | **1a**-2 HCl | **4**, 3 | $CH_2Cl_2$ | 25 | 6 | **2a**, 73[b] | |
| 2 | **1b**-2 HCl | **4**, 10 | benzene | 80 | 24 | **2b**, 3 | |
| 3 | **1a**-2 HCl | **5**, 10 | $CH_2Cl_2$ | 40 | 1 | **2a**, 99 | |
| 4 | **1b**-2 HCl | **5**, 30[c] | toluene | 110 | 20 | **2b**, 30 | 0:88:12 |
| 5 | **6**-2 HCl | **4**, 10 | toluene | 110 | 3 | – | |
| 6 | **6**-2 TFA | **4**, 10 | Benzene | 80 | 5 | **7**, 54[d] | |
| 7 | **6**-2 TFA | **5**, 10 | toluene | 110 | 7 | **7**, 12;[e] **2b**, 88 | 5:60:35 |
| 8 | **6**-2 TFA | **4**, 10 | toluene | 110 | 3 | **2b**, 100 | 0:83:17 |

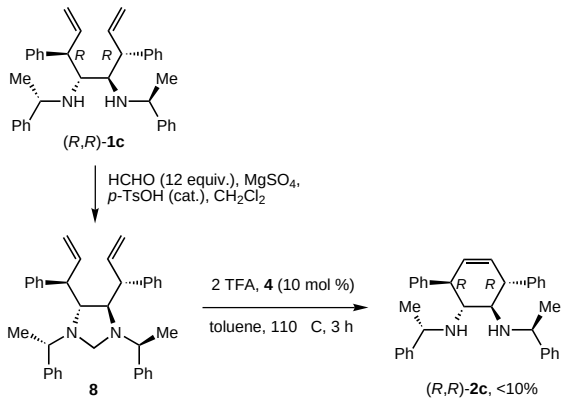
[a] According to the order of elution.
[b] Isolated yield.
[c] The catalyst was added in 3 portions every 6 h.
[d] dr 4:83:13; no reaction occurred in the absence of TFA.
[e] dr 70:30.

in refluxing benzene after 5 h (entry 6); in this case, the three diastereomers of **7** were formed with dr 4:83:13, according to the order of elution in the GC-MS analysis. Hence, the use of trifluoroacetic acid instead of HCl was determinant for preserving the activity of the carbene catalyst even at the high temperature, so allowing us to increase the yield of the metathesis product. Then, aiming to increase the reaction rate, we used the catalyst **5** (10 mol %) in refluxing toluene and were gratified to observe the quantitative cyclisation of **6**·2 TFA after 7 h (entry 7), but, unexpectedly, the reaction mixture was composed of the secondary diamine **2b** (88% by GC-MS analysis) and the bicyclic aminal **7** (12% yield), both compounds being mixtures of diastereomers with comparable ratios. Finally, the best result was achieved when **6**·2 TFA was heated in refluxing toluene in the presence of the Grubbs' catalyst **4** (10 mol %): after only 3 h, the complete conversion to **2b** with high diastereoselectivity (dr 83:17) was obtained (entry 8). The two diastereomers of **2b** obtained in entry 8 were separated by column chromatography: the major one (48%) had $C_1$ symmetry ($^1$H NMR analysis), hence we safely assigned to it the configuration of (*S*,*R*)-**2b**, referring only to the newly created stereocentres (Scheme 2). On the other hand, the minor diastereomer (8%) had $C_2$-symmetry and presumably is (*S*,*S*)-**2b**; in fact, the *trans*,*trans*,*trans* disposition of the ring substituents was suggested by the coupling constants ($J = 6.2$ Hz) of the ring methyne protons NCHCHN and comparison with the subsequently prepared compound (*R*,*R*)-**2c** (Scheme 3).

The superior performance of the carbene complex **4** with respect to the second-generation complex **5** is surprising, but can be explained by considering that **5** bears a basic heterocyclic carbene ligand, which can undergo decomposition by the acid at high temperature.[10] It is also noteworthy that when the progress of the reaction (entry 8) was monitored over time by GC-MS analysis, the formation of the intermediate **7** and its progressive conversion to **2b** was demonstrated. It should be also underlined that the same result was obtained in different runs. The *in situ* conversion of the cyclic aminal **7** to the secondary diamine **2b** posed us the problem of determining the cause of the aminal cleavage, so we prepared the compound (*S*,*R*)-**7**, which we had not isolated previously, by treatment of the diamine (*S*,*R*)-**2b** with paraformaldehyde (Scheme 2). Treatment of (*S*,*R*)-**7** with the Grubbs' catalyst **4** in refluxing toluene left the substrate unchanged after 3 h, whereas the alternative reaction with TFA (2 equivalents) in refluxing toluene for 3 h caused its almost complete transformation to (*S*,*R*)-**2b**, presumably owing to the presence of water (Scheme 2). We could also demonstrate that the cleavage of the aminal function followed the RCM reaction since, in a separate experiment, the aminal **6** was completely recovered after treatment with 2 equivalents of TFA in refluxing toluene for 5 h.

The protocol which proved successful for the cyclisation of **1b** to **2b** was then applied to the diaminodiene (*R*,*R*)-**1c**[1c] carrying a phenyl substituent in both the allylic positions, despite the presumed difficulty to obtain good results, owing to the steric hindrance exerted by the Ph group in the alkene-Ru complexation steps. Thus, the aminal **8** was routinely prepared and submitted to the reactions conditions which were optimal for **6**: 2 equivalents of TFA, 10 mol % of **4**, toluene, 110 °C, 3 h (Scheme 3), but less than 10% conversion to the diamine (*R*,*R*)-**2c** was observed, and several unidentified by-products were formed; moreover, no progress of the RCM reaction was observed after further 3 h. It is noteworthy that the bicyclic aminal which should be formed as an intermediate in the first step was not detected in the reaction mixture. Unfortunately, (*R*,*R*)-**2c** was not obtained pure by column chromatography of the crude product, but its structure was confirmed by $^1$H NMR analysis of an enriched sample.

In conclusion, it should be observed that the Grubbs' catalyst has been rarely employed to catalyse RCM reactions at such a high temperature. To the best of our knowledge, there are only two reports describing that such reactions are possible in toluene at 100 or 110 °C,[11] although the alkene isomerisation is a competitive reaction under these conditions.[12,13] Further studies are needed to find the optimal reaction conditions for the RCM of diaminodienes carrying bulky allylic substituents, e.g., **1c**, for example, by using the molybdenum-based Schrock's catalyst,[5] which is less sensitive to steric hindrance with respect to the ruthenium-based catalysts, but is more expensive and less practical to be used.




**Scheme 3.** RCM reaction of the diaminodiene (*R*,*R*)-**1c**.

## Experimental Section

### General Information

Melting points are uncorrected. Solvents were distilled over the appropriate drying agent in $N_2$ atmosphere before use:

benzene and toluene (Na, then $LiAlH_4$), $CH_2Cl_2$ ($P_2O_5$). Optical rotations were measured on a digital polarimeter in a 1-dm cell and $[\alpha]_D$ values are given in $10^{-1}$ deg cm$^3$ g$^{-1}$. $^1$H NMR spectra were recorded on a Varian Gemini instrument at 300 or 200 MHz for samples in $CDCl_3$ which was stored over Mg: $^1$H chemical shifts are reported in ppm relative to $CHCl_3$ ($\delta_H = 7.27$) and $J$ values are given in Hz. Mass spectra were taken at an ionising voltage of 70 eV on a Hewlett-Packard 5970 or 5890 spectrometer with GLC injection. Chromatographic separations were performed on columns of $SiO_2$ (Merck, 230–400 mesh) at medium pressure. The catalysts **4** and **5** were purchased from Aldrich. All the organometallic reactions were performed in a flame-dried apparatus under a static atmosphere of dry $N_2$.

### Preparation of Formaldehyde Aminals

The mixture of the diamine **1b** (2.0 g, 5 mmol), paraformaldehyde (1.5 g, 0.06 mol), *p*-toluenesulphonic acid (10 mg) and anhydrous $MgSO_4$ (15 g) in $CH_2Cl_2$ (75 mL) was stirred at room temperature for 3 d, then was filtered through a Celite pad, and the organic phase was washed with $H_2O$ (25 mL), then dried again with $Na_2SO_4$, and concentrated to leave the aminal **6** as a yellow thick oil; yield: 2.01 g (97%). The aminals were used as obtained, avoiding any purification.

***N,N'*-Bis[1(*S*)-phenylethyl)]-4(*R*),5(*R*)-di(1-ethenyl-2-propenyl)imidazolidine (6):** $[\alpha]_D^{20}$: +2.3 (*c* 1.08, $CHCl_3$); $^1$H NMR (200 MHz, $CDCl_3$): $\delta = 7.35-7.10$ (m, 10H, Ph), 6.08–5.77 (m, 4H, C*H*=$CH_2$), 5.19–4.90 (m, 8H, CH=C$H_2$), 3.95 (q, $J$ = 7.0 Hz, 2H, C*H*Me), 3.36 (s, 2H, $NCH_2N$), 3.05 (m, 2H, NCHCHN), 2.80 (m, 2H, C*H*CH=$CH_2$), 1.68 (br, 2H, NH), 1.35 (d, $J$ = 7.0 Hz, 6H, CH*Me*); MS: *m*/*z* (relative intensity) = 105 (100), 173 (40), 278 (36), 69 (25), 79 (12), 106 (10), 345 (11).

**1,3-Bis[1(*S*)-phenylethyl)]-4(*R*),5(*R*),6(*S*),9(*R*)-6,9-diethenyl-2,3,4,5,6,9-hexahydro-1,3-diazaindene [(*S,R*)-7]:** thick yellow oil, yield: 95%; $[\alpha]_D^{20}$: −72.6 (*c* 0.42, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$): $\delta = 7.38-7.16$ (m, 10H, Ph), 5.87–4.97 (m, 8H, vinyl), 4.13 and 3.66 (2 q, $J$ = 7.0 Hz, 2H, C*H*Me), 3.90 and 3.32 (2 d, $J$ = 6.3 Hz, 2H, $NCH_2N$), 3.29 and 2.82 (2 m, 2H, C*H*CH=$CH_2$), 2.90 (dd, $J$ = 9.0 and 9.2 Hz, 1H, NC*H*CHN), 2.57 (dd, $J$ = 5.1 and 9.0 Hz, 1H, NC*H*CHN), 1.37–1.33 (2 d, $J$ = 7.0, 6 H, CH*Me*); MS: *m*/*z* (relative intensity) = 105 (100), 173 (23), 279 (21), 383 (19), 69 (16), 175 (16), 384 (13), 106 (12).

**1,3-Bis[1(*S*)-phenylethyl)]-4(*R*),5(*R*)-di[1(*S*)-phenyl-2-propenyl]imidazolidine (8):** thick yellow oil, yield: 98%; $^1$H NMR (300 MHz, $CDCl_3$): $\delta = 7.20$ (m, 16H, Ph), 6.98 (m, 4H, Ph), 5.99 (m, 2H, C*H*=$CH_2$), 5.05 and 4.86 (2 m, 4H, CH=C$H_2$), 3.54 (q, $J$ = 6.6 Hz, 2H, C*H*Me), 3.41 (s, 2H, $NCH_2N$), 3.35 (d, $J$ = 7.8 Hz, 2H, NCHCHN), 2.84 (m, 2H, C*H*Ph), 1.00 (d, $J$ = 6.6 Hz, CH*Me*).

### Ring Closing Metathesis Reactions of Aminals 6 and 8

A solution of the aminal **6** (0.800 g, 1.94 mmol), trifluoroacetic acid (0.44 g, 3.90 mmol) and the Grubbs' catalyst **4** (0.160 g, 0.2 mmol) in dry toluene (20 mL) was de-aerated by blowing Ar for 5 min, then the reaction flask was placed in an oil bath, whose temperature was raised to 120 °C, and reflux was maintained for 3 h, then the mixture was allowed to cool in the air overnight. Gaseous HCl was blown through the solution for 2 min, 40% NaOH (10 mL) was carefully added to the cooled (0 °C) mixture, and the organic phase was extracted with $CH_2Cl_2$ (3 × 20 mL). The collected organic layers were dried ($Na_2SO_4$) and concentrated to leave a dark brown oil, which was chromatographed on an $SiO_2$ column eluting with cyclohexane-ethyl acetate, 20:1, to give the two diastereomers of **2b**.

***N,N'*-Bis[1(*S*)-phenylethyl)]-1(*R*),2(*R*)-diamino-3(*S*),6(*R*)-diethenylcyclohex-4-ene [(*S,R*)-2b]:** yellow oil, yield: 0.346 g (48%); $[\alpha]_D^{20}$: −116.3 (*c* 0.96, $CHCl_3$); $^1$H NMR (200 MHz, $CDCl_3$): $\delta = 7.35$ (m, 10H, Ph), 5.87–4.98 (m, 8 H, vinyl), 3.93 and 3.81 (2 q, $J$ = 6.8 Hz, 2H, C*H*Me), 3.08 and 2.65 (2 m, 2H, C*H*CH=$CH_2$), 2.40 (dd, $J$ = 5.2 and 11.0 Hz, 1H, NC*H*CHN), 2.26 (dd, $J$ = 8.4 and 11.0 Hz, 1H, NC*H*CHN), 1.36 and 1.23 (2 d, $J$ = 6.8 Hz, CH*Me*); $^{13}$C NMR (300 MHz): $\delta = 146.1$, 145.1, 142.0, 136.9, 130.1, 128.4, 128.1, 127.8, 127.0, 126.8, 126.7, 126.5, 117.6, 115.2, 57.0, 55.7, 55.3, 53.8, 51.2, 41.9, 25.5, 24.6.; MS: *m*/*z* (relative intensity) = 105 (100), 266 (18), 161 (18), 134 (17), 79 (14), 238 (6), 372 ($M^+$, 1); anal. calcd. for $C_{26}H_{32}N_2$: C 83.82, H 8.66, N 7.52%; found: C 83.84, H 8.67, N 7.49%.

***N,N'*-Bis[1(*S*)-phenylethyl)]-1(*R*),2(*R*)-diamino-3(*S*),6(*S*)-diethenylcyclohex-4-ene [(*S,S*)-2b]:** yield: 0.072 g (relatively impure due to the presence of tricyclohexylphosphine); $^1$H NMR (300 MHz, $CDCl_3$): $\delta = 7.38-7.20$ (m, 10H, Ph), 5.74 (m, 2H, C*H*=$CH_2$), 5.25 (s, 2H, CH=CH), 5.08 (m, 4H, CH=C$H_2$), 4.0 (q, $J$ = 6.6 Hz, 2H, C*H*Me), 2.64 (m, 2H, C*H*CH=$CH_2$), 2.23 (d, $J$ = 6.5 Hz, 2H, NCHCHN), 1.26 (br, 2H, NH), 1.21 (d, $J$ = 6.6 Hz, 6H, CH*Me*).

***N,N'*-Bis[1(*S*)-phenylethyl)]-1(*R*),2(*R*)-diamino-3(*R*),6(*R*)-diphenylcyclohex-4-ene [(*R,R*)-2c]:** yield: 0.055 g (*ca.* 75% pure by $^1$H NMR); $^1$H NMR (200 MHz, $CDCl_3$): $\delta = 7.58-7.0$ (m, 16H, Ph), 6.91 (m, 4H, Ph), 5.48 (s, 2H, CH=CH), 3.32 (m, 2H, NCHC*H*Ph), 2.89 (q, $J$ = 6.6 Hz, 2H, C*H*Me), 2.56 (d, $J$ = 6.2 Hz, 2H, NC*H*CHPh), 0.96 (d, $J$ = 6.6 Hz, 6H, CH*Me*).

## Acknowledgements

*Financial support from the Ministero dell'Universita` e della Ricerca Scientifica e Tecnologica, Roma, and The University of Bologna (National Project "Stereoselezione in Sintesi Organica. Metodologie e Applicazioni") is greatly acknowledged.*

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