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Insertion reactions of macrocyclic rhodium carbenoids: a novel method for the synthesis of cryptands

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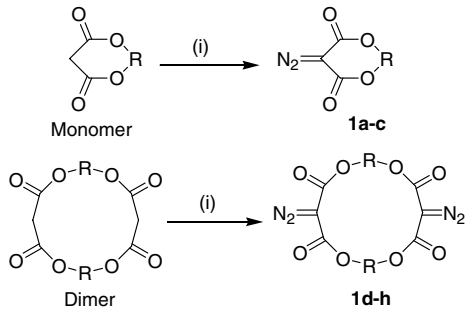
Abstract—Reaction of macrocyclic diazocarbonyl compounds and alcohols or diols in the presence of rhodium(II) acetate catalyst led to functionalized macrocyclic di- or tetralactones via O–H insertion. Interestingly, the double O–H insertion reaction with dihydroxy compounds gave cryptands of various ring sizes.

The formation of inter- and intramolecular ether linkages from diazo ketones and alcohols in the presence of rhodium(II) acetate is well studied.[1] The decomposition of α-diazocarbonyl compounds, predominantly with protic/aprotic and Lewis acids has also been well studied[2] and applied[3] to the synthesis of important natural products. Esterification of acids using diazomethane is very common, whereas the etherification reaction of alcohols using diazocarbonyl compounds is not widely used despite the fact that they often proceed in good yields via an O–H insertion reaction. Molecular recognition is a powerful technique that can be used to generate noncovalently bound host–guest complexes for a variety of purposes.[4] Macrocycles form a major class of molecules that encompass a wide range of structures and functional groups. They also perform a wide range of functions in areas as diverse as ion transport, gelation and catalysis. Chemists have been fascinated for many years by the inherent physical properties of macrocycles and by the synthetic challenge that these structures represent.[5] Contemporary chemistry, however, is increasingly directed towards the creation of molecules that are tailored to perform a well-defined function. The synthesis of macrocyclic diazocarbonyl compounds and their reactions have not been reported[6] so far. In continuation of our studies on diazocarbonyl compounds[7] and macrocycles,[8] we herein report a novel method for the synthesis of functionalized macrocyclic di- or tetralactones and cryptands via the O–H insertion reactions of macrocyclic rhodium(II) carbenoids.

With the aim to develop new ether linked macrocyclic tetralactones via O–H insertion reactions, we have synthesized a series of macrocyclic diazocarbonyl compounds[6] (Scheme 1). The macrocyclic diazocarbonyl compounds **1a**–**g** were synthesized by the reaction of malonylchloride with dihydroxy compounds to afford macrocyclic lactones. Subsequent diazotransfer reaction of the macrocyclic lactones afforded the corresponding macrocyclic diazocarbonyl compounds (Fig. 1).

Initially, the O–H insertion[9] reaction of macrocyclic diazocarbonyl compounds with alcohol was studied. Thus, the reaction of **1b** with DCM containing two drops of water at reflux in the presence of 2 mol % of rhodium acetate afforded O–H insertion product **2a** in



Scheme 1. Synthesis of macrocyclic diazocarbonyl compounds. Reagents: *p*-Acetamidobenzenesulfonyl azide, DBU, DCM.

Keywords: Carbenoids; Cryptands; Diazo ketones; Macrocyclic lactones; O–H insertion; Rhodium(II) acetate.
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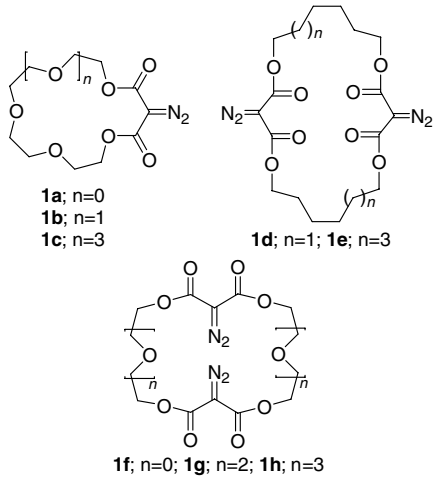
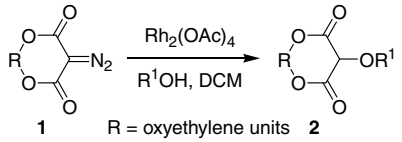


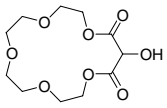
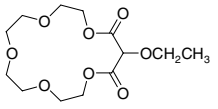
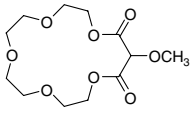
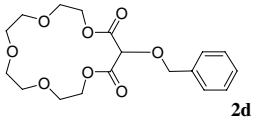
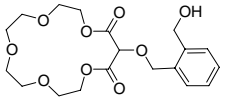
Figure 1. Synthesized macrocyclic diazocarbonyl compounds.



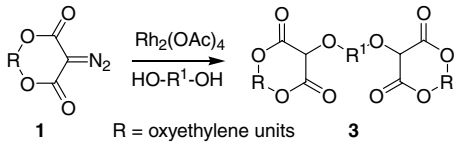
Scheme 2. Insertion reactions of macrocyclic carbenoids with alcohols.

90% yield (Scheme 2). Similarly, macrocyclic diazocarbonyl compound **1b** was treated with ethanol, methanol, benzyl alcohol and benzene-1,2-dimethanol to afford the corresponding ether functionalized macrocyclic dilactones **2b–e** in good yields (Table 1).

Table 1. Synthesis of macrocyclic lactones **2**

Entry	Diazo ketone	Macrocyclic lactone **2**	Yield (%) of **2**[a]
1	**1b**	 **2a**	99
2	**1b**	 **2b**	88
3	**1b**	 **2c**	78
4	**1b**	 **2d**	86
5	**1b**	 **2e**	82

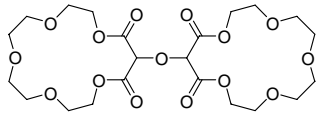
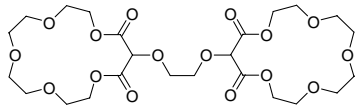
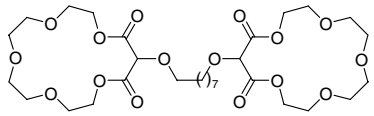
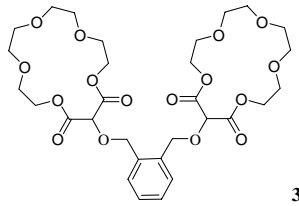
[a] Yields are unoptimized and refer to isolated yields.



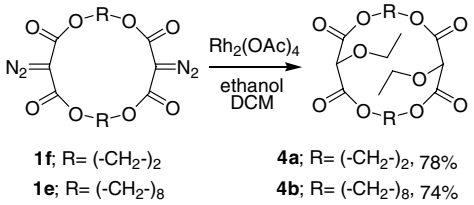
Scheme 3. Double carbenoid insertion with dihydroxy compounds.

Encouraged by this result, we envisaged the formation of two C–O bonds via double O–H insertion.[10] Thus, excess diazocarbonyl compound **1b** was refluxed with $Rh_2(OAc)_4$ in aqueous DCM to afford ether linked macrocycle **3a** in moderate yield (Scheme 3). Similar reactions of **1b** with ethylene glycol or 1,8-octanediol afforded the corresponding bis-crown compounds **3b**,**c** having an aliphatic linker (Table 2). The reaction of **1b** with 1,2-benzene dimethanol afforded the bis-crown compound **3d** having an aromatic linker. Next, the double O–H insertion reaction was investigated with bis-diazocarbonyl compounds. To this end, compounds **1e**,**f** were refluxed with ethanol to afford diethoxy-substituted tetralactones **4a**,**b** in good yields (Scheme 4).

Table 2. Synthesis of bis-crown ethers **3**

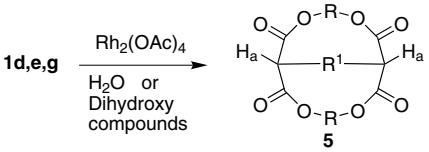
Entry	Diazo ketone	Product **3**	Yield (%) of **3**[a]
1	**1b**	 **3a**	52
2	**1b**	 **3b**	62
3	**1b**	 **3c**	58
4	**1b**	 **3d**	60

[a] Yields are unoptimized and refer to isolated yields.



Scheme 4. Reaction of bis-diazocarbonyl compounds with ethanol.

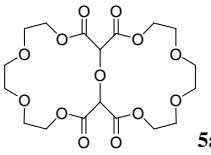
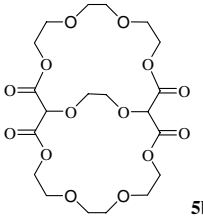
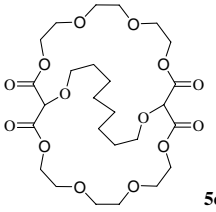
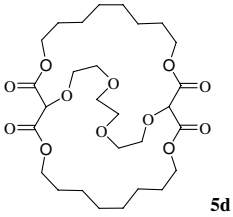
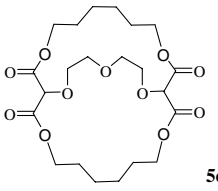
Finally, we investigated the synthesis of the cryptands based on the above successful double intermolecular O–H insertion[11] strategy. To this end, bis-diazocarbonyl compound **1g** was refluxed with $Rh_2(OAc)_4$ in DCM containing two drops of water to afford the oxygen linked bicyclic system **5a** in low yield (Table 3). Product



5a; R = $-CH_2(CH_2OCH_2)_2CH_2-$, R^1= -O-
5b; R = $-CH_2(CH_2OCH_2)_2CH_2-$, R^1= $-O(CH_2)_2O-$
5c; R = $-CH_2(CH_2OCH_2)_2CH_2-$, R^1= $-O(CH_2)_8O-$
5d; R = $-(CH_2)_8-$, R^1= $-OCH_2(CH_2OCH_2)_2CH_2O-$
5e; R = $-(CH_2)_6-$, R^1= $-OCH_2CH_2OCH_2CH_2O-$

Scheme 5. Synthesis of cryptands **5** via double carbenoid insertion.

Table 3. Synthesis of cryptands **5**

Entry	Diazo ketone	Cryptand **5**	Yield (%) of **5**[a]
1	**1g**	 **5a**	32
2	**1g**	 **5b**	60
3	**1g**	 **5c**	40
4	**1e**	 **5d**	42
5	**1d**	 **5e**	38

[a] Yields are unoptimized and refer to isolated yields.

5a showed[12] a characteristic singlet at 4.85 ppm for the H_a-proton and confirms the structure of the O–H insertion product. The formation of cryptand **5a** was also confirmed by the mass spectral data. The reaction of an equimolar amount of bis-diazocarbonyl compound **1g** and ethylene glycol afforded the corresponding cryptand **5b** in 60% yield containing an oxyethylene spacer (Scheme 5). Reaction of bis-diazo macrocyclic compound **1g** with 1,8-octane diol afforded cryptand **5c** having an alkoxy spacer.

The reaction of a bis-diazocarbonyl compound having an octane spacer **1e** with triethylene glycol afforded the corresponding cryptand **5d** in moderate yield. Similarly, the reaction of bis-diazocarbonyl compound **1d** with diethylene glycol afforded the corresponding cryptand **5e** in 38% yield. All of cryptands **5** (Table 3) obtained by this method were successfully characterized by spectral analysis. Reaction of bis-diazocarbonyl compound **1h** under similar conditions was not successful.

In conclusion, we have demonstrated the intermolecular O–H insertion reaction of macrocyclic diazocarbonyl compounds. The intermolecular O–H insertion reaction afforded several ether substituted macrocyclic dilactones. Intermolecular double O–H insertion reaction was also demonstrated with either bis-diazocarbonyl compounds or dihydroxy compounds. The advantage of the double O–H insertion methodology was demonstrated via the synthesis of cryptands possessing oxyethylene or octane spacers for the first time. Supramolecular studies on the synthesized macrocycles is under progress in our laboratory.

Acknowledgements

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9. *General procedure for the O–H insertion reaction*: *Method A for the synthesis of dilactones* **2**: A mixture of macrocyclic diazocarbonyl compound **1b** (0.5 mmol) and the appropriate alcohol (0.7 mmol) was taken in dry DCM (50 mL) under an argon atmosphere. To the above solution, 2 mol % of rhodium(II) acetate dimer catalyst was added and the mixture was stirred at reflux for 2 h. The progress of the reaction was monitored by TLC. The solvent was removed under reduced pressure and the resulting residue purified using 100–200 mesh silica gel column chromatography (hexane/EtOAc or EtOAc/MeOH) to afford the respective substituted macrocyclic dilactone **2**.
10. *Method B for the synthesis of dilactones* **3**: To an oven-dried flask, the appropriate alcohol (0.5 mmol) and 2 mol % of rhodium(II) acetate in dry benzene or DCM (100 mL) were added under an inert atmosphere and the mixture was heated at reflux. To the above refluxing mixture, macrocyclic diazocarbonyl compound **1b** (1.2 mmol) in dry benzene or DCM was added slowly over 1 h using a syringe pump and reflux for 6 h. The progress of the reaction was monitored by TLC. The solvent was removed under reduced pressure and the resulting residue purified using 100–200 mesh silica gel column chromatography (hexane/EtOAc) to afford the respective double O–H insertion products **3**. The macrocyclic tetralactones **4** were synthesized by the reaction of the bis-diazocarbonyl compounds **1d**–**h** (0.5 mmol) with an excess of the respective alcohol (1.5 mmol) in the presence of rhodium(II) acetate in dry benzene or DCM (100 mL) under reflux conditions.
11. *Method C for the synthesis of cryptands* **5**: A mixture of bis-macrocyclic diazocarbonyl compound **1d**,**e**,**g**,**h** (0.5 mmol) and the appropriate dihydroxy compound (0.5 mmol) was taken in dry DCM (50 mL) under an argon atmosphere. To the above solution, 2 mol % of rhodium(II) acetate dimer catalyst was added and the reaction stirred at reflux for 6 h. The progress of the reaction was monitored by TLC. The solvent was removed under reduced pressure and the resulting residue purified using 100–200 mesh silica gel column chromatography (hexane/EtOAc or EtOAc) to afford the respective cryptands **5**.
12. *Selected spectral data. Compound* **3d**: Colourless thick oil; IR (neat): 3002, 2946, 1740, 1448, 1355, 758 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) $\delta = 7.39$–7.31 (m, 4H, =C*H*), 4.70 (s, 2H, C*H*), 4.65 (d, 4H, OCH_2, $J = 4$ Hz), 4.48-4.17 (m, 8H, OCH_2), 3.74–3.64 (m, 8H, OCH_2), 3.63 (s, 16 H, OCH_2). ^{13}C NMR (50.3 MHz, $CDCl_3$): $\delta = 166.9$ (*C*=O), 142.1 (quat-*C*), 129.3 (=*C*H), 128.1 (=*C*H), 127.5 (=*C*H), 78.0 (O*C*H), 73.3 (OCH_2), 71.2 (OCH_2), 70.9 (OCH_2), 69.1 (OCH_2), 65.6 (OCH_2). HRMS (ESI^+) calcd for $C_{30}H_{42}O_{16}Na$ $(M+Na)^+$: 681.2371, found 681.2432. *Compound* **4a**: Colourless thick oil; IR (neat): 3010, 2952, 1744, 1452, 1310, 743 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) $\delta = 4.57$–4.46 (m, 10H, OCH_2 and O*CH*), 3.72–3.62 (q, 4H, OCH_2, $J = 7$ Hz), 1.33–1.26 (t, 6H, CH_3, $J = 7$ Hz). ^{13}C NMR (50.3 MHz, $CDCl_3$): $\delta = 166.6$ (*C*=O), 79.3 (O*C*H), 67.7 (OCH_2), 63.8 (OCH_2), 15.4 (OCH_2). HRMS (ESI^+) calcd for $C_{14}H_{20}O_{10}Na$ $(M+Na)^+$: 371.0954, found 371.0901. *Compound* **5a**: Colourless thick oil; IR (neat): 3020, 2958, 2873, 2403, 1744, 1539, 1452, 1356, 1305, 1216, 758 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) $\delta = 4.85$ (s, 2H, O*CH*), 4.57–4.49 (m, 4H, OCH_2), 4.33–4.26 (m, 4H, OCH_2), 3.77-3.71 (m, 8H, OCH_2), 3.64 (s, 8H, OCH_2). ^{13}C NMR (50.3 MHz, $CDCl_3$): $\delta = 165.1$ (*C*=O), 79.0 (O*C*H), 69.5 (OCH_2), 68.0 (OCH_2), 64.8 (OCH_2). HRMS (ESI^+) calcd for $C_{18}H_{26}O_{13}Na$ $(M+Na)^+$: 473.1271, found 473.1233. *Compound* **5b**: Colourless thick oil; IR (neat): 2952, 2875, 1754, 1597, 1384, 1320, 1270, 1087, 760 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): $\delta = 4.86$ (s, 2H, O*CH*), 4.59–4.18 (m, 8H, OCH_2), 3.94–3.72 (m, 12H, OCH_2), 3.67 (s, 8H, OCH_2). ^{13}C NMR (50.3 MHz, $CDCl_3$): $\delta = 166.5$ (*C*=O), 79.2 (O*C*H), 70.5 (OCH_2), 68.5 (OCH_2), 65.0 (OCH_2). HRMS (ESI^+) calcd for $C_{20}H_{30}O_{14}Na$ $(M+Na)^+$: 517.1533, found 517.1588. *Compound* **5d**: Colourless thick oil; IR (neat): 2934, 2862, 1743, 1645, 1458, 1351, 1270, 1118, 743 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): $\delta = 4.66$ (s, 2H, O*CH*), 4.22–4.19 (m, 4H, OCH_2), 3.74–3.60 (m, 16H, OCH_2), 1.66–1.52 (m, 8H, CH_2), 1.32 (s, 16H, CH_2). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 166.5 (*C*=O), 166.3 (*C*=O), 79.1 (O*C*H), 72.4 (OCH_2), 69.9 (OCH_2), 65.8 (OCH_2), 61.1 (OCH_2), 29.1 (CH_2), 28.8 (OCH_2), 28.3 (CH_2), 28.2 (CH_2), 25.6 (CH_2), 25.4 (CH_2). HRMS (ESI^+) calcd for $C_{28}H_{46}O_{12}Na$ $(M+Na)^+$: 597.2887, found 597.2861.