Diastereoselective Ring Closing Metathesis Reactions: Synthesis of Bicyclic Diallylic Alcohols and Ethers**

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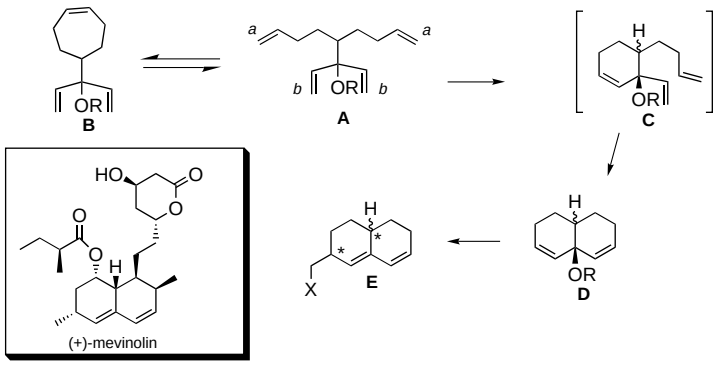
In recent years there has been a surge of interest in ring closing metathesis (RCM) reactions as a consequence of the development of well-defined metal alkylidene catalysts that display a wide range of functional group tolerance.[1] By far the two most widely employed catalysts are **1** (Cy = cyclohexyl) developed by Grubbs et al.[2] and **2** developed by Schrock et al.[3]

$[Cl_2(PCy_3)_2Ru{=}CHPh]$ **1**

$[PhMe_2CCH{=}Mo{=}N\{2,6\text{-}(i\text{Pr})_2C_6H_3\}\{OCMe(CF_3)_2\}_2]$ **2**

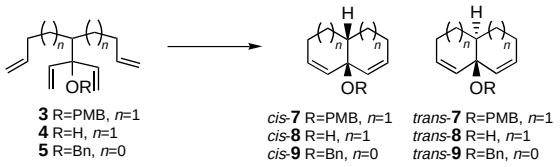
We now report a group-selective activation followed by a diastereoselective RCM (DSRCM) reaction to provide convenient access to a new class of bicyclic diallyl alcohols with a σ plane of symmetry that is not readily accessible by conventional approaches. When we began this investigation the diastereoselectivity of RCM reactions had not been explored. Very recently Blechert et al. reported a DSRCM reaction that gave five membered heterocycles in which they observed a reversal in the sense of the diastereoselectivity on switching from catalyst **1** to **2**, but noted complete loss of selectivity in their attempts to form six membered rings.[4] In addition to this report, there have been some examples of diastereomeric mixtures whose components cyclize at different rates.[5]

Our studies were conducted with tetraenes of general structure **A** (Scheme 1). Initial metal alkylidination at olefin *a* in preference to *b* would be expected upon treatment with **1** or **2** on the basis of literature reports, which suggests that the presence of substituents α to an olefin hinders its participation in the RCM reaction.[6] After the formation of a metal carbene at olefin *a*, the molecule can cyclize in one of two ways to give either triene **B** or **C**. In the event that **B** is initially formed it could eventually yield **C** by reacting with the catalyst to reform the alkylidine first generated by reaction of **A** with **1** or **2**. Triene **C** could then undergo a second RCM reaction to give bicyclo[4.4.0]decadiene **D**. We anticipated by analogy to the fully saturated decalin systems that *trans*-fused **D** would be thermodynamically preferred. If all the steps shown in Scheme 1 were reversible then a thermodynamic mixture of *cis* and *trans* decalins would be expected. Subsequent sigmatropic rearrangement of **D** to give **E** would provide an efficient entry into the tetrahydronaphthalene skeleton found in the HMG CoA reductase inhibitor (+)-mevinolin.



Scheme 1. Strategy for stereoselective preparation of bicyclodienes.

Our initial investigations (Scheme 2) have provided some surprising results, which are highlighted in Table 1. When tetraene **3** was treated with three mol% of **1** in CH_2Cl_2 at



Scheme 2. Formation of bicyclodienes from tetraenes. PMB = *p*-methoxybenzyl, Bn = benzyl. See Table 1 for the conditions.

Table 1. RCM reactions of tetraene substrates.

Entry	Starting material	Product	Conditions[a] [mol%, h]	*cis*:*trans*	Yield [%]
1	**3**	**7**	A[b] (12, 20)	8:1	80
2	**3**	**7**	B (12, 20)	8:1	82
3	**4**	**8**	A (10, 2.5)	1:2.8	84
4	**5**	**9**	A[b] (4, 20)	[c]	81
5	**5**	**9**	B (4, 2)	[c]	66

[a] Reaction conditions: A: 0.1M in CH_2Cl_2, cat. = **1**, 23 °C; B: 0.1M in C_6H_6, cat. = **2**, 23 °C; [b] Under an ethylene atmosphere. [c] Only the *cis* bicyclic product was observed, see text.

23 °C for three hours cycloheptene **6** (Figure 1) was isolated as the major product in 70% yield.[7] This suggests that the substituents α to olefin *b* are more influential than ring size in determining the type of cyclization that will occur first. However, treatment of **3** or **6** with 10–12 mol% of **1** at 23 °C for 20 h under an atmosphere of ethylene gave bicyclic product **7** in good yield as an 8:1 mixture of diastereoisomers (Table 1, entry 1). Furthermore, contrary to our initial expectations, the *cis* isomer was formed preferentially.[8] Treatment of **3** with **2** in C_6H_6 at 23 °C gave essentially the same result (entry 2). When the free alcohol **4** was treated with **1** (10 mol%) a 2.8:1 mixture of diastereomers was formed in good yield, with the *trans* isomer now pre-

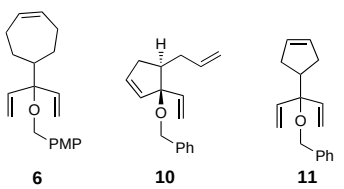


Figure 1. Intermediates and by-products of tetraene metathesis. PMP = *p*-methoxyphenyl.

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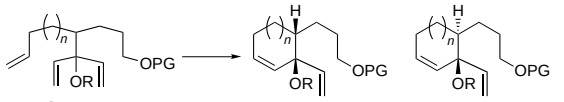
dominating (entry 3).[8] The use of ethylene presumably facilitates the formation of the more reactive methylidene catalyst.[2,9]

To evaluate the thermodynamic preference for *cis* versus *trans* decalins of this type, ab initio calculations on the two possible isomers were carried out. At the 3-21G* level the two isomers appear to have essentially the same ground-state energy, differing by less than 0.4 J mol^{-1}, which suggests that the formation of *cis*-decalin is a kinetic outcome and that at least one of the steps in the reaction sequence prior to the final bond formation is irreversible. The preparation of [3.3.0] bicyclic compounds was also examined. When tetraene **5** was treated with four mol % of **1** for 20 h the *cis* isomer of **9** was formed in 81 % yield, along with 12 % of the monocycle **10** (Figure 1), whose formation appears to be irreversible. This triene is unlikely to cyclize to give an extremely strained *trans* bicyclo[3.3.0]octadiene. Again, lower catalyst loadings and shorter reaction times gave a symmetrical triene **11** (Figure 1).

We also prepared trienes **12**–**15** (Scheme 3) to gain insight into the inherent diastereoselectivity in the first cyclization (Table 2).[7] A 2.8:1 mixture of diastereomers was obtained in



12 R=H, *n*=1
13 R=PMB, *n*=1
14 R=H, *n*=0
15 R=Bn, *n*=0

(*R**,*S**)-**16** R=H, *n*=1
(*R**,*S**)-**17** R=PMB, *n*=1
(*R**,*S**)-**18** R=H, *n*=0
(*R**,*S**)-**19** R=Bn, *n*=0

(*S**,*S**)-**16** R=H, *n*=1
(*S**,*S**)-**17** R=PMB, *n*=1
(*S**,*S**)-**18** R=H, *n*=0
(*S**,*S**)-**19** R=Bn, *n*=0

Scheme 3. Formation of vinyl cycloalkenes from trienes. See Table 2 for the conditions.

Table 2. RCM reactions of triene substrates.

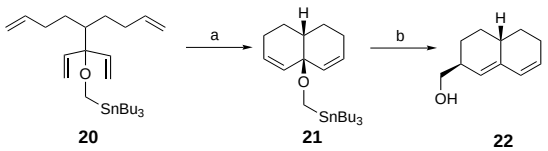
Entry	Starting material	Product	Conditions[a] [mol %, h]	*R**,*S**:*S**,*S**	Yield [%]
1	**12**[b]	**16**[b]	A (12,5)	1:2.8	80
2	**13**[b]	**17**[b]	A (3,3)	6.1:1	96
3	**13**[b]	**17**[b]	B (6, 1.5)	7.8:1	86
4	**14**[c]	**18**[c]	A (6, 1.5)	1:1	65
5	**15**[c]	**19**[c]	A (3, 1)	8.0:1	99
6	**15**[c]	**19**[c]	B (6, 0.5)	1.7:1	94

[a] Reaction conditions: A: 0.1 M in CH_2Cl_2, cat. = **1**, 23 °C; B: 0.1 M in C_6H_6, cat. = **2**, 23 °C. [b] PG = *t*BuPh$_2$Si. [c] PG = *t*BuMe$_2$Si.

good yield, with (*S**,*S**)-**16** favored (entry 1)[8] upon treatment of free alcohol **12** with catalyst **1**. When *p*-methoxybenzyl ether **13** was treated with **1** the formation of cyclohexene (*R**,*S**)-**17** was preferred by a ratio of 6.1:1 (entry 2). Treatment with **2** gave slightly higher levels of selectivity (7.8:1; entry 3).

Trienes that lead to vinylcyclopentene derivatives were also examined. Treatment of free alcohol **14** with **1** yielded a 1:1 mixture of diastereomers (entry 4) in moderate yield and treatment of benzyl ether **15** with **1** gave cyclopentene **19** in excellent yield as an 8.0:1 mixture, with (*R**,*S**)-**19** favored (entry 5). In contrast to the formation of six membered rings, treatment of **15** with **2** resulted in a decrease in diastereoselectivity, although the *R**,*S** diastereomer was still favored by a ratio of 1.7:1 (entry 6).

In light of our interest in the conversion of diallylic ethers into conjugated dienes we carried out a study of the feasibility of the [2,3] Wittig rearrangement in this ring system (Scheme 4).[10] When the [4.4.0] system **21** was treated with *n*BuLi the Wittig rearrangement occurred to give the primary alcohol **22** in 67 % yield along with 17% of the product that arises from a [1,2] Wittig rearrangement.



20 **21** **22**

Scheme 4. Sigmatropic rearrangement of the bicyclo[4.4.0]decadiene **21**. a) **1** (12 mol %), CH_2Cl_2, reflux, 7 h, 86 %; b) *n*BuLi (1.2 equiv), HMPA (4.0 equiv), THF, −78 °C, 10 min, 67 %. HMPA = hexamethylphosphoramide.

In conclusion, we have developed a group and diastereoselective RCM approach to a novel class of bicyclic diallylic alcohols and ethers. While the cyclization of tetraenes initially gives symmetrical trienes of type **B**, longer reaction times lead selectively to the *cis* isomer of the bicyclodienes with a σ plane of symmetry. We have also demonstrated that it is possible to rearrange a bicyclo[4.4.0] product to give conjugated dienes. Our current efforts are directed toward the examination of enantioselective methods for the conversion of the diallylethers into chiral and enantiomerically enriched bicyclic dienes.

Experimental Section

Typical procedure for the stereoselective ring closing metathesis of a tetraene as exemplified by formation of *cis*-**9** (Table 1, entry 4): Compound **1** (12 mg, 0.015 mmol) was added to a solution of **5** (100 mg, 0.372 mmol) in CH_2Cl_2 (4 mL) at 23 °C. The resulting solution was stirred under an ethylene atmosphere for 20 h before PPh_3 (14 mg, 0.053 mmol) was added, and the mixture concentrated in vacuo. Purification by flash chromatography (2 % diethyl ether/hexane) on triethylamine-washed silica gel yielded 64 mg (81 %) of *cis*-**9** as a colorless oil. R_f = 0.11 (2 % diethyl ether/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.06–2.15 (m, 2H; allylic), 2.81–2.91 (m, 3H; allylic and C_3CH), 4.42 (s, 2H; benzylic), 5.83 (dt, ^3J(H,H) = 6, 2 Hz, 2H; olefinic), 5.92 (dt, ^3J(H,H) = 6, 2 Hz, 2H; olefinic), 7.21–7.26 (m, 1H; aromatic), 7.28–7.35 (m, 4H; aromatic); ^{13}C NMR: δ = 40.72, 43.03, 65.58, 105.70, 127.16, 127.55, 128.25, 132.54, 134.27, 139.56; IR (neat) $\tilde{\nu}$ = 3053, 2919, 2848, 1497, 1448, 1378, 1349, 1216, 1139, 1099, 1028, 991, 733, 697 cm^{-1}; HR-MS ($C_{15}H_{16}O$, M^+): calcd: 212.1201; found: 212.1196.

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[7] Tetraenes **3** – **5** and trienes **12** – **15** were prepared effeciently from dimethyl malonate by dialkylation and Krapcho decarboxylation followed by addition of two equivalents of vinylcerium and protection of the resulting tertiary diallylic alcohol. See supporting information for a detailed description of the starting material preparations.
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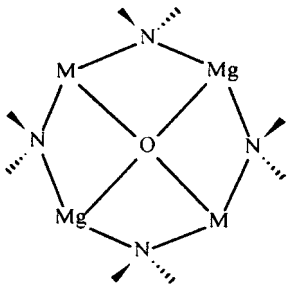
Mixed-Metal Sodium – Magnesium Macrocyclic Amide Chemistry: A Template Reaction for the Site Selective Dideprotonation of Arene Molecules

David R. Armstrong, Alan R. Kennedy, Robert E. Mulvey,* and René B. Rowlings

In a new development in s block chemistry, we recently reported the first examples of mixed-metal (Group 1/Group 2) cationic ring systems with anionic oxo or peroxo cores.[1] Eight-membered macrocyclic amides, their basic motif, **1** (shown with an oxo core), consists of alternating nitrogen and metal atoms, two lithium or two sodium atoms combined with two magnesium atoms. The nitrogen atoms belong to sterically encumbered hexamethyldisilazide (HMDS) or 2,2,6,6-tetramethylpiperidide (TMP) ligands. This new class of compound can be regarded as antithetical "crown ether" complexes, where the host – guest (Lewis acid/Lewis base) positions have been reversed relative to those in conventional crown ether complexes: as such, they can be likened to the mercuracarborands pioneered by Hawthorne et al.[2] Here, in another link to crown ether chemistry, we reveal that a larger twelve-membered ($N_6Na_4Mg_2$) cationic ring system can be prepared. From the perspective of the number of metal centers in the ring, if the former macrocyclic amides prompt comparisons with [12]crown-4, then this new type can be compared to [18]crown-6. Most interestingly of all, the hexanuclear metallic ring acts as a host to the selectively dideprotonated arene molecules $[C_6H_3(CH_3)]^{2-}$ (from toluene) or $C_6H_4^{2-}$ (from benzene). The formation of these dianions suggests a template reaction is in operation.



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Complexes **2** and **3** can be prepared easily and reproducibly from a 1:1:3 molar ratio of *n*BuNa, Bu_2Mg, and TMPH in

$[(tmp)_6Na_4Mg_2\{C_6H_3(CH_3)\}]$ **2**

$[(tmp)_6Na_4Mg_2(C_6H_4)]$ **3**

hydrocarbon media, to which the appropriate arene is added in excess. Attempts to prepare them from a 2:1:3 molar ratio of reactants matching the stoichiometry in the crystalline products, are hampered by solubility problems at the amine addition step.

Disregarding the methyl substituent of the dimetalated toluene, the molecular structures of **2** and **3** are essentially equivalent.[3] Figure 1 shows **2** viewed from above the macrocycle, while Figure 2 shows an alternative side view of **3**. Notable features include: a) the severely puckered $N_6Na_4Mg_2$ ring possesses crystallographic inversion symmetry; b) the arene molecules lie almost orthogonal to the mean plane of this ring; c) the metalation sites of the toluene dianion (2,5-

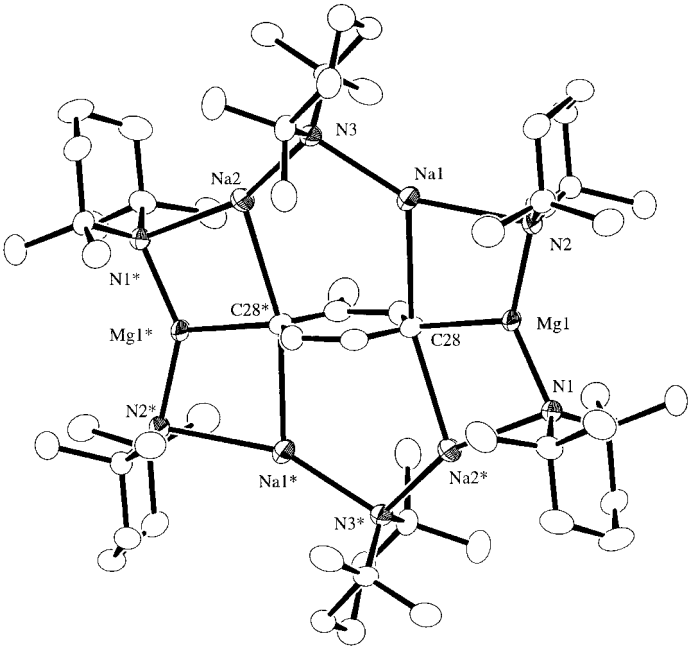

Figure 1. Molecular structure of **2** without hydrogen atoms and disorder component. Selected bond lengths [Å] and angles [°]: Na1 – N2 2.626(2), Na1 – N3 2.393(2), Na1 – C28 2.691(2), Na2 – N3 2.350(2), Na2 – N1* 2.596(2), Na2 – C28* 2.682(2), Mg1 – N1 2.048(2), Mg1 – N2 2.051(2), Mg1 – C28 2.200(2); N2-Na1-N3 156.25(6), N2-Na1-C28 80.18(6), N3-Na1-C28 123.31(7), N3-Na2-N1* 160.54(6), N3-Na2-C28* 116.54(7), N1*-Na2-C28* 82.36(6), N1-Mg1-N2 142.85(7), N1-Mg1-C28 109.75(7), N2-Mg1-C28 107.32(7), Na1-C28-Na2* 164.17(9), Na1-C28-Mg1 83.38(7), Na2*-C28-Mg1 80.93(7), C29-C28-C30* 113.3(2). * = 1 – *x*, 1 – *y*, 1 – *z*.

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