Exploiting domino enyne metathesis mechanisms for skeletal diversity generation†‡

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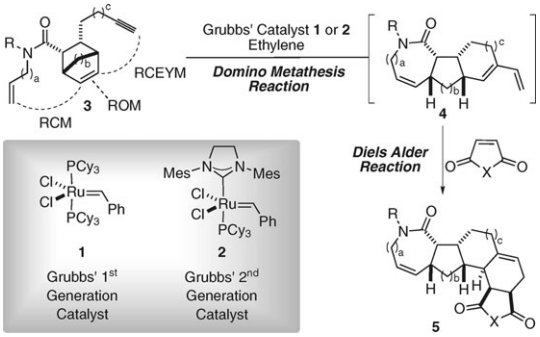
In the context of diversity-oriented synthesis, the exploration and optimization of the domino metathesis of decorated norbornenes allowed complex polycyclic architectures to be generated in a highly efficient and atom-economical process.

Structurally complex and skeletally diverse small molecule collections synthesized using diversity-oriented synthesis (DOS)[1] have been used to discover novel bioactive molecules.[2] With the most challenging facet of DOS being to efficiently access distinct molecular scaffolds, a number of approaches have been reported.[3] To this end we envisaged a strategy whereby, in the presence of Grubbs' catalyst **1** or **2**, a 'tandem' metathesis–Diels–Alder sequence reaction would convert decorated norbornenes **3**, *via* 1,3-diene intermediates **4**, into complex and distinct polycyclic scaffolds **5**. The key step (*i.e.* **3** to **4**) requires a 'domino' ring closing metathesis (RCM)–ring opening metathesis (ROM)–ring closing enyne metathesis (RCEYM) reaction sequence to occur (Scheme 1).[4] Although domino metathesis reactions of oxa- and aza-norbornene-enyne scaffolds[5] and unstrained cylcoalkene-enynes[6] have been investigated, few examples of this transformation using norbornene substrates have been reported.[7] In these systems reaction initiation can occur with either norbornene ring opening or enyne metathesis (Scheme 2); herein this mechanistic distinction was found to be controlled by the choice of catalyst *i.e.* Grubbs' first (**1**) or second (**2**) generation catalyst.

The RCEYM reaction can be used to efficiently produce 1,3-diene containing ring systems.[8] Although these reactions have been exploited in the synthesis of natural products and related compounds,[9] selectivity issues may arise. The product distribution can be highly dependent on the nature of the substrate and the catalyst used and, as a result, both *exo* and *endo* ring isomers are sometimes produced.[10] Combined with the complication of two possible sites for reaction initiation, the domino metathesis of the test substrate $\mathbf{A}_{(n)}$ (n = 1 or 2) was investigated initially.

From these studies, designed to probe the product distribution and reaction mechanism, five products were identified: the *exo* isomer $\mathbf{B}_{(n)}$ (the desired product); the *endo* isomer $\mathbf{C}_{(n)}$; the ring-opened enyne $\mathbf{D}_{(n)}$; the tetra-ene $\mathbf{E}_{(n)}$; and, the cross-metathesized norbornene $\mathbf{F}_{(n)}$. Two major pathways were proposed (Scheme 2); these initiated with either ROM of the norbornene (Path 1) or ruthenium carbene insertion into the alkyne (Path 2). A series of metathesis reactions could then give the products $\mathbf{A}_{(n)}$ to $\mathbf{F}_{(n)}$.



Scheme 1 Tandem reaction overview. RCM = ring closing metathesis; ROM = ring opening metathesis; RCEYM = ring closing enyne metathesis.

In the presence of **1**, the norbornene $\mathbf{A}_{(1)}$ was converted to the *exo* ring isomer $\mathbf{B}_{(1)}$ (Scheme 3). As the *endo* ring isomer $\mathbf{C}_{(1)}$ was not observed, this suggested that the RCEYM reaction to form $\mathbf{B}_{(n)}$ proceeded *via* an ene-then-yne mechanism.[11] A further insight into the reaction mechanism came from the isolation of a small amount of the ring opened enyne $\mathbf{D}_{(1)}$. This suggested that ROM of the norbornene $\mathbf{A}_{(1)}$ occurred prior to RCEYM (*i.e.* Path 1 with n = 1). Using the alternative substrate $\mathbf{A}_{(2)}$, the situation is somewhat different. Interestingly, catalyst **1** facilitates ROM to give $\mathbf{D}_{(2)}$ but the subsequent RCEYM does not occur and the *exo* ring isomer $\mathbf{B}_{(2)}$ was not formed. The sequential use of Grubbs' more active catalyst **2** did, however, facilitate the formation of $\mathbf{B}_{(2)}$ from the enyne $\mathbf{D}_{(2)}$. Again an ene-then-yne mechanism was proposed. The stepwise use of catalysts **1** and **2** has previously been reported.[7a] As a side product of the metathesis reaction of $\mathbf{D}_{(2)}$, the tetra-ene $\mathbf{E}_{(2)}$ was also formed as a result of CM of the alkyne moiety with ethylene. This CM process is competitive since the RCEYM reaction, which yields the *exo* ring isomer $\mathbf{B}_{(2)}$, is slower.

In an effort to increase reaction efficiency, the metathesis reactions of $\mathbf{A}_{(1)}$ and $\mathbf{A}_{(2)}$ were performed using catalyst **2** (Scheme 4). As a result of the competing ring opening metathesis polymerization (ROMP) process,[12] reaction yields were low. Furthermore, mixtures of products resulted.[13] In addition to both the *exo* $\mathbf{B}_{(n)}$ and the *endo* $\mathbf{C}_{(n)}$ ring isomers being produced, the tetra-ene compound $\mathbf{E}_{(n)}$ was also isolated. In both cases, the ring-opened enyne $\mathbf{D}_{(n)}$ was not observed. More significant was the formation of the cross-metathesized norbornene $\mathbf{F}_{(n)}$. These results suggest that different reaction pathways were in operation in the presence of catalyst **1** compared to **2**.[14]

The reaction of $\mathbf{A}_{(n)}$ with **1** appears to initiate with the primary ROM of the norbornene to give either ***MC-1a*** or

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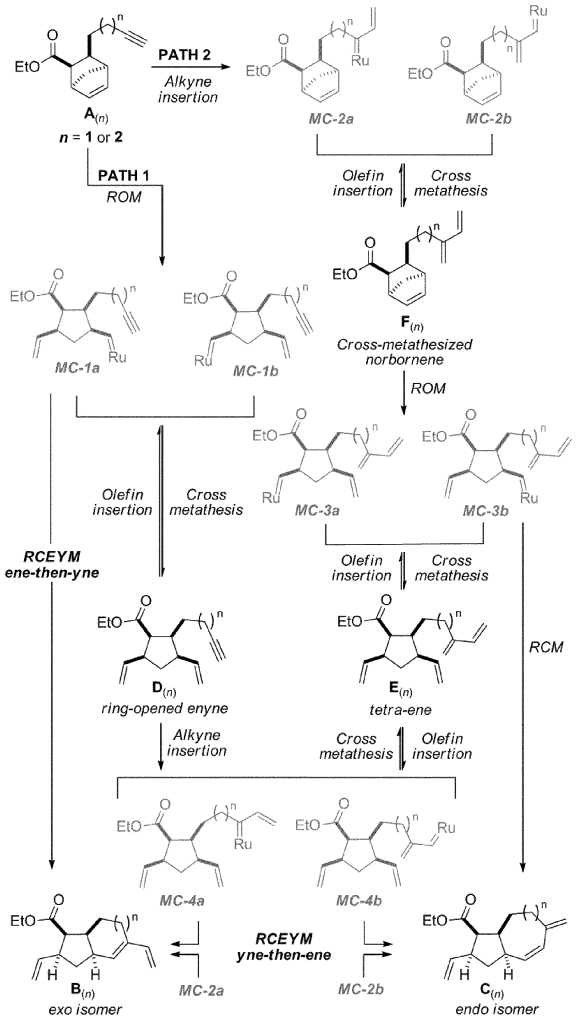
† Dedicated to Professor Sir Jack Baldwin in celebration of his 70th birthday.
‡ Electronic supplementary information (ESI) available: Full experimental details and spectra. See DOI: 10.1039/b807278g

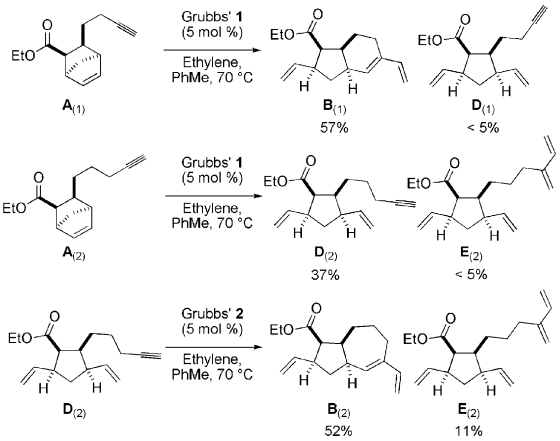


Scheme 2 An overview of the primary reaction pathways illustrating the products (black) and intermediates (grey). Norbornene ROM and alkyne insertion are shown as irreversible.[16a] Polymerization (not shown) is a possible alternative in many of the steps. Pathways 1 and 2 may occur concomitantly.[16b] RCM = ring closing metathesis; ROM = ring opening metathesis; RCEYM = ring closing enyne metathesis; MC = metallocarbene intermediate $n = 1$ or 2. For $\mathbf{X}_{(n)}$, where **X** is **A**–**F**, $\mathbf{X}_{(1)}$ = $n = 1$ and $\mathbf{X}_{(2)}$ = $n = 2$.

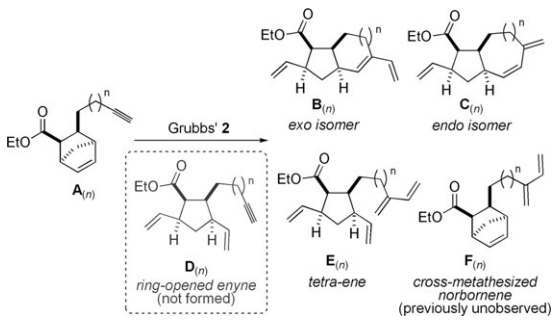
MC-1b (*i.e.* Path 1, Scheme 2). The subsequent steps and final products, *i.e.* the *exo* isomer $\mathbf{B}_{(n)}$ or the ring-opened enyne $\mathbf{D}_{(n)}$, are dictated by the value of *n* in the starting material (see Scheme 3). Tentatively we propose that in the reaction of $\mathbf{A}_{(n)}$ with **2**, initial alkyne insertion to give ***MC-2a*** or ***MC-2b*** (*i.e.* Path 2, Scheme 2) is prevalent.

After extensive optimization, and considering the above results, a novel metathesis protocol, which merged and modified the approaches of the North,[7a] Porco,[15c] Lee[15a] and Diver[15b] research groups was identified for the amide substrates **3** (Scheme 1). This protocol, which required the reaction to be performed in ethylene saturated solvent and with microwave irradiation, allowed the conversion of **6** to **7** and **8** to **9** and **10** (Scheme 5). To prevent product decomposition a polar isocyanate was used to quench the reaction mixture before work-up.[15b]

The diversity-oriented synthetic utility of the reaction of **8** to form two distinct scaffolds (**9** and **10**) was further demonstrated by the conversion of the tetra-ene **10** to both *exo*-**9** and



Scheme 3 Observed products with test substrates.

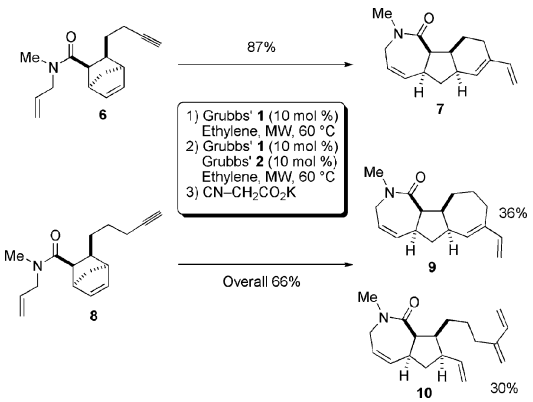


Scheme 4 Products identified using Grubbs' catalyst **2**.

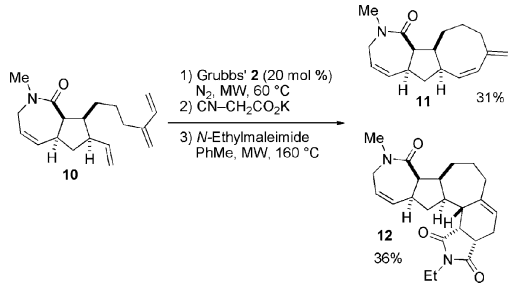
endo-**11** (an inseparable mixture). In addition to confirming the hypothesis that tetra-ene compounds can be converted to both ring isomers (Scheme 2), a Diels–Alder reaction could be used to further diversify the *exo* compound **9**, yielding **12**, and also to isolate the *endo* isomer **11** (Scheme 6).

The *exo*-1,3-diene compounds $\mathbf{A}_{(1)}$, $\mathbf{A}_{(2)}$, **7** and **9** were converted to the corresponding polycyclic adducts **12**–**15** in excellent yield under microwave irradiation (Scheme 7). Excellent facial selectivity was observed in all cases and the products proposed resulted exclusively from *endo*-/top face attack of *N*-ethylmaleimide on the 1,3-diene.

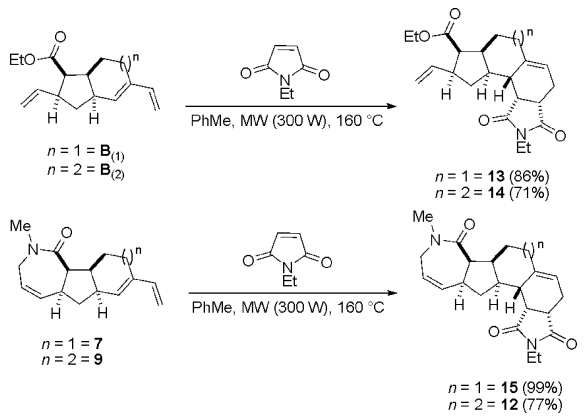
To realize our initial aim, and to more efficiently access the polycyclic scaffolds required, a more efficient protocol was developed whereby the *cis*-norbornene scaffold **6** could be



Scheme 5 Optimized domino metathesis conditions. MW = microwave heating.



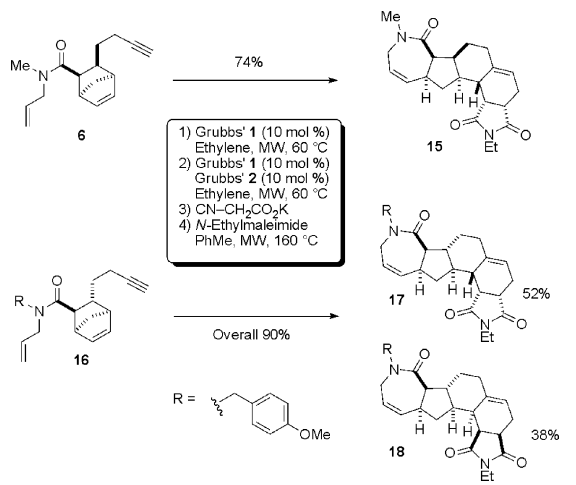
Scheme 6 Ring closing metathesis gave both *exo* and *endo* cyclized products (**9** and **11**, respectively), but only the *exo* isomer was able to react with the dienophile to give **12**.



Scheme 7 Optimized Diels–Alder conditions.

converted directly to the adduct **15** in 'one-pot' (Scheme 8). An alternative substrate, with *trans*-norbornene architecture, was also investigated. Although **16** performed well in the initial metathesis process, the selectivity in the Diels–Alder reaction step was reduced; both **17** and **18** (which resulted from *endo*-/top and *endo*-/bottom face attack, respectively) were formed.

In conclusion, we have developed an efficient process to convert decorated norbornenes into complex polycyclic systems. It is notable that the choice of Grubbs' metathesis catalyst affected the reaction pathway, the product distribution, and the yield. Optimum results were obtained when catalysts **1** and **2** were used in a stepwise fashion, to facilitate



Scheme 8 'One-pot', tandem domino metathesis–Diels–Alder reactions.

ROM of the norbornene before the RCM reactions (both olefin and enyne) occurred. The tandem domino metathesis–Diels–Alder strategy is currently being used in the preparation of skeletally diverse small molecule collections.

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Notes and references

1. For recent reviews on DOS see: (*a*) T. E. Nielsen and S. L. Schreiber, *Angew. Chem., Int. Ed.*, 2008, **47**, 48–56; (*b*) D. S. Tan, *Nat. Chem. Biol.*, 2005, **1**, 74–84; (*c*) R. J. Spandl, D. R. Spring and A. Bender, *Org. Biomol. Chem.*, 2008, **6**, 1149–1158; (*d*) G. L. Thomas, E. E. Wyatt and D. R. Spring, *Curr. Opin. Drug Discovery Dev.*, 2006, **9**, 700–712 and references therein.
2. Selected recent examples: (*a*) S. K. Ko, H. J. Jang, E. Kim and S. B. Park, *Chem. Commun.*, 2006, 2962–2964; (*b*) E. E. Wyatt, S. Fergus, W. R. J. D. Galloway, A. Bender, D. J. Fox, A. T. Plowright, A. S. Jessiman, M. Welch and D. R. Spring, *Chem. Commun.*, 2006, 3296–3298; (*c*) G. L. Thomas, R. J. Spandl, F. G. Glansdorp, M. Welch, A. Bender, J. Cockfield, J. A. Lindsay, C. Bryant, D. F. J. Brown, O. Loiseleur, H. Rudyk, M. Ladlow and D. R. Spring, *Angew. Chem., Int. Ed.*, 2008, **47**, 2808–2812.
3. For a recent review see: R. J. Spandl, G. L. Thomas, M. Diaz-Gavilan, K. M. G. O'Connell and D. R. Spring, *Chem. Rec.*, 2008, DOI: 10.1002/tcr.20144, and references therein.
4. For recent reviews see: (*a*) S. G. Aitken and A. D. Abell, *Aust. J. Chem.*, 2005, **58**, 3–13; (*b*) S. J. Connon and S. Blechert, *Angew. Chem., Int. Ed.*, 2003, **42**, 1900–1923. For a recent example see: (*c*) C. K. Malik and S. Ghosh, *Org. Lett.*, 2007, **9**, 2537–2540.
5. (*a*) O. Arjona, A. G. Csaky, M. C. Murcia and J. Plumet, *Tetrahedron Lett.*, 2000, **41**, 9777–9779; (*b*) M. Mori, H. Wakamatsu, Y. Sato and R. Fujita, *J. Mol. Catal. A: Chem.*, 2006, **254**, 64–67.
6. (*a*) T. Kitamura, Y. Kuzuba, Y. Sato, H. Wakamatsu, R. Fujita and M. Mori, *Tetrahedron*, 2004, **60**, 7375–7389; (*b*) S. Randl, N. Lucas, S. J. Connon and S. Blechert, *Adv. Synth. Catal.*, 2002, **344**, 631–633.
7. For selected examples see: (*a*) D. Banti, E. Groaz and M. North, *Tetrahedron*, 2004, **60**, 8043–8052; (*b*) E. Groaz, D. Banti and M. North, *Eur. J. Org. Chem.*, 2007, 3727–3745 and references therein.
8. For recent reviews on enyne metathesis see: (*a*) H. Villar, M. Frings and C. Bolm, *Chem. Soc. Rev.*, 2007, **36**, 55–66; (*b*) S. T. Diver and A. J. Giessert, *Chem. Rev.*, 2004, **104**, 1317–1382.
9. M. Mori, *Adv. Synth. Catal.*, 2007, **349**, 121–135.
10. The selectivity problem in enyne metathesis has been reported/addressed previously: (*a*) T. Kitamura, Y. Sato and M. Mori, *Adv. Synth. Catal.*, 2002, **344**, 678–693; (*b*) E. C. Hansen and D. S. Lee, *Acc. Chem. Res.*, 2006, **39**, 509–519; (*c*) T. Kitamura, Y. Sato and M. Mori, *Chem. Commun.*, 2001, 1258–1259; (*d*) E. C. Hansen and D. S. Lee, *J. Am. Chem. Soc., 2004, 126, 15074-15080*, 2004, **126**, 15074–15080.
11. In the formation of 6- and 7-membered rings the ene-then-yne pathway yields the smaller *exo* ring isomer $\mathbf{B}_{(n)}$.[10a] This pathway is supported by: (*a*) G. C. Lloyd-Jones, R. G. Margue and J. G. de Vries, *Angew. Chem., Int. Ed.*, 2005, **44**, 7442–7447. For a recent review see: (*b*) S. T. Diver, *Coord. Chem. Rev.*, 2007, **251**, 671–701.
12. T. L. Choi and R. H. Grubbs, *Angew. Chem., Int. Ed.*, 2003, **42**, 1743–1746.
13. Full details including reaction yields and spectral data can be found in the ESI‡.
14. Observed previously: O. Arjona, A. G. Csaky, V. Leon, R. Medel and J. Plumet, *Tetrahedron Lett.*, 2004, **45**, 565–567.
15. (*a*) D. S. Lee, J. K. Sello and S. L. Schreiber, *Org. Lett.*, 2000, **2**, 709–712; (*b*) B. R. Galan, K. P. Kalbarczyk, S. Szczepankiewicz, J. B. Keister and S. T. Diver, *Org. Lett.*, 2007, **9**, 1203–1206; (*c*) E. Comer, E. Rohan, L. Deng and J. A. Porco, *E. Comer, E. Rohan, L. Deng, J. A. Porco, Org. Lett.*, 2007, **9**, 2123–2126.
16. (*a*) J. J. Lippstreu and B. F. Straub, *J. Am. Chem. Soc.*, 2005, **127**, 7444–7457; (*b*) a more detailed discussion can be found in section 3 of the ESI‡.