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) have been used to discover novel bioactive molecules. With the most challenging facet of DOS being to efficiently access distinct molecular scaffolds, a number of approaches have been reported. 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, via 1,3-diene intermediates, into complex and distinct polycyclic scaffolds. 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). Although domino metathesis reactions of oxa- and aza-norbornene-ene scaffolds and unstrained cycloalkene-ynes have been investigated, few examples of this transformation using norbornene substrates have been reported. 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. Although these reactions have been exploited in the synthesis of natural products and related compounds, 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. Combined with the complication of two possible sites for reaction initiation, the domino metathesis of the test substrate A0 (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 B0 (the desired product); the endo isomer C0; the ring-opened enyne D0; the tetra-ene E0; and, the cross-metathesized norbornene F0. 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 A0 to F0.

In the presence of 1, the norbornene A1 was converted to the exo ring isomer B1 (Scheme 3). As the endo ring isomer C1 was not observed, this suggested that the RCEYM reaction to form B0 proceeded via an ene-then-yne mechanism. Further insight into the reaction mechanism came from the isolation of a small amount of the ring opened enyne D1. This suggested that ROM of the norbornene A1 occurred prior to RCEYM i.e. Path 1 with n = 1. Using the alternative substrate A2, the situation is somewhat different. Interestingly, catalyst 1 facilitates ROM to give D2 but the subsequent RCEYM does not occur and the exo ring isomer B2 was not formed. The sequential use of Grubbs’ more active catalyst 2 did, however, facilitate the formation of B2 from the enyne D2. Again an ene-then-yne mechanism was proposed. The stepwise use of catalysts 1 and 2 has previously been reported. As a side product of the metathesis reaction of D2, the tetra-ene E2 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 B2, is slower.

In an effort to increase reaction efficiency, the metathesis reactions of A1 and A2 were performed using catalyst 2 (Scheme 4). As a result of the competing ring opening metathesis polymerization (ROMP) process, reaction yields were low. Furthermore, mixtures of products resulted. In addition to both the exo B0 and the endo C0 ring isomers being produced, the tetra-ene compound E0 was also isolated. In both cases, the ring-opened enyne D0 was not observed. More significant was the formation of the cross-metathesized norbornene F0. These results suggest that different reaction pathways were in operation in the presence of catalyst 1 compared to 2.

The reaction of A0 with 1 appears to initiate with the primary ROM of the norbornene to give either MC1a or...
MC-1b (i.e. Path 1, Scheme 2). The subsequent steps and final products, i.e. the exo isomer B_{(n)} or the ring-opened enyne D_{(n)}), are dictated by the value of n in the starting material (see Scheme 3). Tentatively we propose that in the reaction of 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 Lee15a and Diver15b 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 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 A_{(1)}, 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
alternative substrate, with endo- and 16 also investigated. Although step was reduced; both catalysts react with the dienophile to give 12.

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.

In conclusion, we have developed an efficient process to convert decorated norbornenes into complex polyocyclic 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 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.

Notes and references


12. Full details including reaction yields and spectral data can be found in the ESI.


15. (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.

Scheme 7  Optimized Diels–Alder conditions.

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