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# Synthesis of Small Molecules with High Scaffold Diversity: Exploitation of Metathesis Cascades in Combination with Inter- and Intramolecular Diels–Alder Reactions

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**Abstract:** Our knowledge of the biological relevance of regions of chemical space is shaped, in large part, by the synthetic accessibility of small molecules. Historically, however, chemists have explored chemical space in an exceptionally uneven and unsystematic way. We have previously demonstrated that metathesis cascade chemistry may be harnessed to yield small molecule collections with high scaffold diversity. Here, we describe the extent to which inter- and intramolecular Diels–Alder reactions, when used in conjunction with metathesis cascades, can extend the range of molecular scaffolds that are accessible. A range of metathesis substrates was prepared from combinations of two or three building blocks. Metathesis cascades were exploited to "reprogram" the molecular scaffolds. In many cases, the metathesis products were 1,3-dienes, which were potential substrates for either inter- or intramolecular Diels–Alder reactions. The synthesis and functionalisation of the products was often facilitated by fluorous tagging, for example by using a "safety-catch" linker that we have developed. It was demonstrated that, in certain cases, Diels–Alder reactions could extend the range of molecular scaffolds that may be prepared by using metathesis cascade reactions.

**Keywords:** cycloaddition · diversity-oriented synthesis · domino reactions · metathesis · molecular diversity

## Introduction

Our knowledge of the biological relevance of regions of chemical space is shaped, in large part, by the synthetic (and biosynthetic) accessibility of small molecules.[1] The field of biology-oriented synthesis,[2] for example, seeks to target bioactivity "islands"[3,4] by designing libraries around scaffolds[4b,5] that have been biologically validated. Historically, however, chemists have explored chemical space in an exceptionally uneven and unsystematic manner, with half of known compounds being based on just 0.25% of the known molecular scaffolds![6]

The development of synthetic methods that allow the systematic variation of molecular scaffolds has proved extremely challenging.[7] Synthetic strategies have been developed to allow the scaffolds of small molecules to be varied. In the "folding" pathway strategy,[8] the scaffolds of products are determined by structural features in starting materials (sometimes known as σ elements[8]). In contrast, in the "branching" pathway strategy,[9] complementary reaction conditions are used to convert starting materials into a range of skeletally diverse products. The scaffolds of small molecules may also be varied by using the "build-couple-pair" strategy in which building blocks are exploited judiciously in combination:[7c,10] here, building blocks are prepared (built), connected (coupled) and then reacted intramolecularly (paired), to yield alternative molecular scaffolds. Some examples of branching and folding pathways

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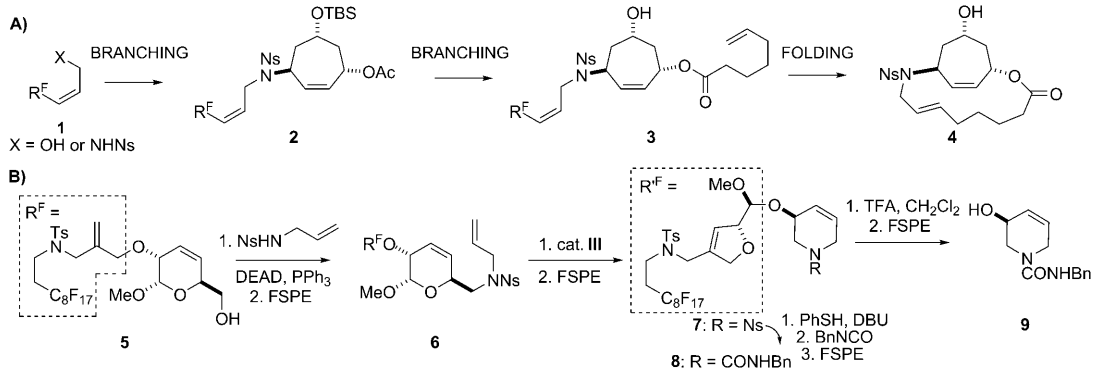


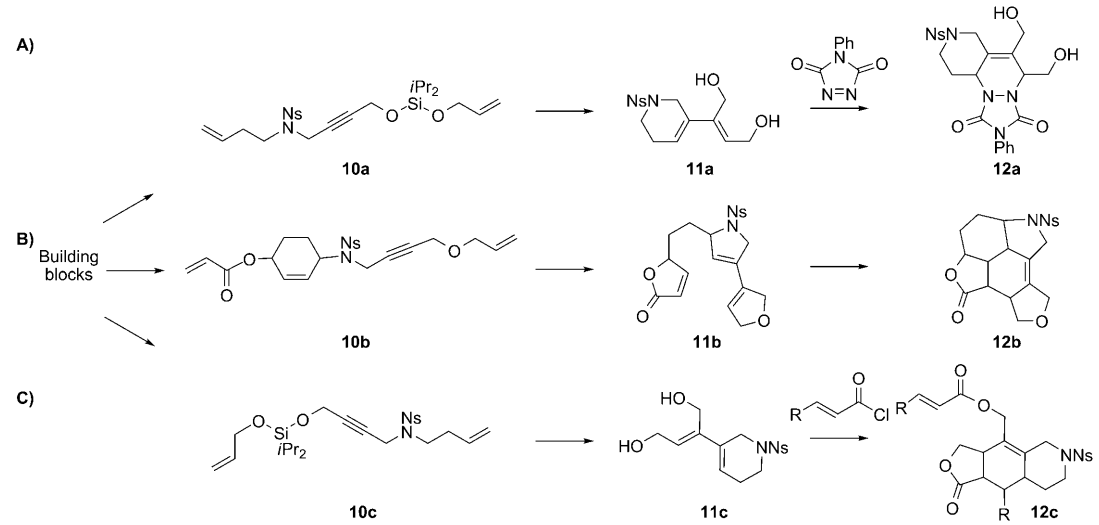

Scheme 1. Application of fluorous-tagged linkers in the synthesis of skeletally diverse small molecules. A) An approach to the combinatorial variation of the scaffolds of natural product-like small molecules. Building blocks were iteratively attached to a fluorous-tagged linker **1** to yield metathesis substrates, such as **3**. Metathesis cascades were used to reprogram the molecular scaffolds (e.g., **3**→**4**) to yield final products, such as **4** with over 80 distinct scaffolds. The substituent $R^F$ was fluorous-tagged. B) A fluorous-tagged safety-catch linker for preparing functionalised heterocycles. The fluorous tag facilitates purification of each of the synthetic intermediates by fluorous solid-phase extraction (FSPE). Crucially, only the products of successful metathesis cascades are ultimately released from the fluorous tag (**8**→**9**). Bn = benzyl, TBS = *tert*-butyldimethylsilyl, Ts = tosyl.

can also be considered to exemplify the build-couple-pair strategy.[7c]

Recently, we reported a general approach to the combinatorial variation of molecular scaffolds (Scheme 1A).[11] The approach adopted the build-couple-pair strategy and, essentially, combined the virtues of both branching and folding pathways. Building blocks were prepared (built) and then, in a branching pathway, attached iteratively onto a fluorous-tagged linker (coupled) (e.g., **1**→**2**→**3**). Subsequently, metathesis cascades (e.g., **3**→**4**) were used to fold the substrates (pair), and to release the products of successful cascades from a fluorous tag. The approach yielded a library of unprecedented scaffold diversity (>80 scaffolds, around two-thirds of which were previously unknown).[3,11,12]

More recently, we described a fluorous-tagged "safety-catch" linker that facilitated the functionalisation of metathesis products (Scheme 1B).[13] After attachment of building blocks to the linker (**5**→**6**), metathesis cascades were exploited to define the scaffolds of the final products (e.g., → **7**). Crucially, however, the metathesis products (e.g., **7**) were still fluorous-tagged, facilitating purification of the products after derivatisation (e.g., →**8**). Finally, acid-catalysed cleavage (e.g., →**9**) released only the products of successful metathesis cascades from the fluorous-tagged linker.

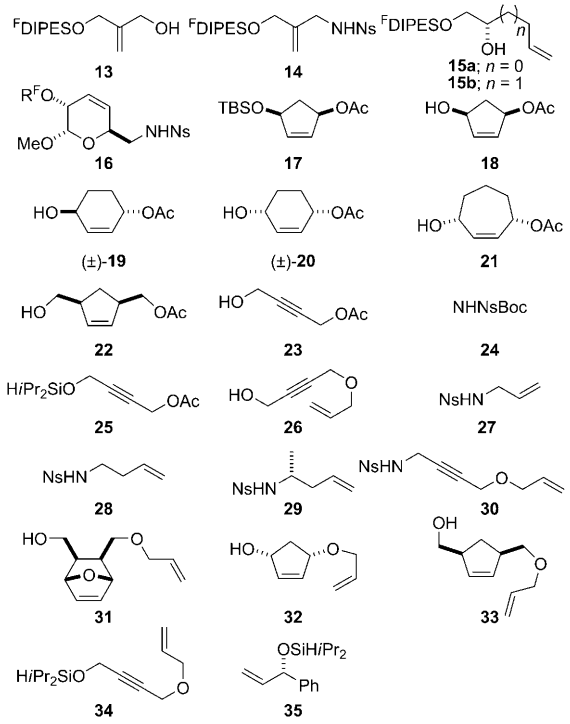
In this paper, we demonstrate that the scope of our diversity-oriented approach may be extended by using metathesis cascades to prepare substrates for both inter- and intramolecular Diels–Alder reactions (Scheme 2). We envisaged




Scheme 2. An overview of the synthetic approaches described in this paper. Building blocks may be combined to yield metathesis substrates **10**, which may be folded to yield metathesis products **11**; the products **11** may be further functionalised by deprotection and derivatisation. Three approaches that exploit Diels–Alder chemistry may be envisaged to extend the range of scaffolds that may be prepared. A) Culmination with an intermolecular Diels–Alder reaction to yield scaffolds, such as **12a**. B) Formation of a dienophile and a diene (**11b**) in a metathesis cascade, followed by intramolecular Diels–Alder reaction to yield scaffolds, such as **12b**. C) Attachment of a dienophile to the diene, **11c**, and intramolecular Diels–Alder reaction to yield scaffolds, such as **12c**. Note that substituents, fluorous tags and stereochemistry are omitted for clarity.

that metathesis substrates, for example **10a–10c**, could be easily assembled from combinations of the building blocks shown in Scheme 3. To allow for purification of the synthetic intermediates by fluorous solid-phase extraction (FSPE),[14]




Scheme 3. Structures of the building blocks.

one of the first building blocks may be fluorous-tagged. For example, the building blocks **13–15** contain a fluorous-tagged version ($^{F}$DIPES) of the diisopropylethylsilyl (DIPES) protecting group, and the safety-catch linker, **16**, that we have previously described,[13] is also fluorous-tagged. A metathesis cascade may then be used to determine the scaffolds of the final products (e.g., **11a–11c**). At this stage, removal of the *o*-nitrosulfonyl (Ns) protecting groups would be possible to allow the functionalisation of the scaffolds.

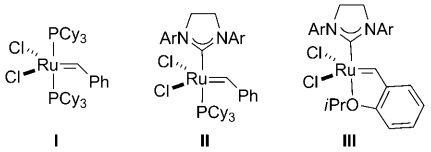
For metathesis products with an embedded 1,3-diene (e.g., **11a–11c**), however, we envisage three distinct approaches that would extend the range of scaffolds that may be prepared (Scheme 2). The approach shown in Scheme 2A would involve an intermolecular Diels–Alder reaction to yield polycyclic products (e.g., **11a**→**12a**). In the approach shown in Scheme 2B, the metathesis cascade would have revealed both a diene and a dienophile allowing the possibility of an intramolecular Diels–Alder reaction[15] (e.g., **11b**→**12b**). Finally, the approach shown in Scheme 2C would involve the tethering of a dienophile to the metathesis product (e.g., **11c**), followed by subsequent intramolecular Diels–Alder reaction (e.g. →**12c**). In this paper, we describe the scope and limitations of each of these complementary approaches, and their application in the synthesis of a library of skeletally and substitutionally diverse small molecules.

## Results and Discussion

A wide range of metathesis substrates was prepared from combinations of two or three building blocks (see Table 1 and Table 2). The allylic acetate **17** was reacted with the propargylic alcohol **26** in a Pd-catalysed allylic etherification reaction (Table 1, entry 1).[16] Similarly, the hydroxy acetates **19–22** were reacted with the propargylic sulfonamide **30** by using a Fukuyama–Mitsunobu[17] reaction to yield, after deprotection, compounds **37–40** (Table 1, entries 2–5). The fluorous-tagged safety-catch linker[13] **16** was treated with the hydroxy acetates **23**, **18** and **21** to yield, after FSPE and deacetylation, compounds **41–43** (Table 1, entries 6–8); the alcohol **41** was subsequently converted into the corresponding sulfonamide **44** (Table 1, entry 9). Finally, the building block **25** was attached to the fluorous-tagged building block **15a** to yield the silaketal **45**.

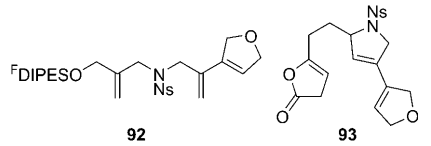
The synthesis of 23 metathesis substrates (**46–68**) was completed by the attachment of a "capping" building block (Table 2) by using three different reactions: the Fukuyama–Mitsunobu reaction,[17] unsymmetrical silaketal formation[18] and esterification. In general, fluorous-tagged metathesis substrates were purified by FSPE alone, with purities determined by 500 MHz $^{1}$H NMR spectroscopy.

The metathesis substrates **46–68** were each treated with a catalyst (Scheme 4) in refluxing dichloromethane (Table 2).



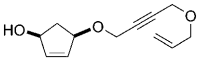
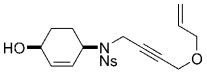
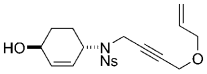
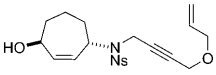
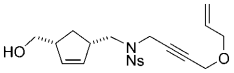
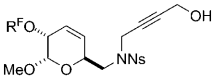
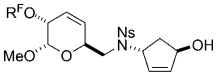
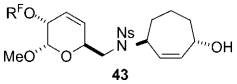
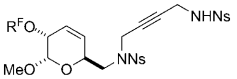
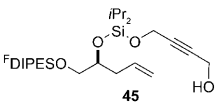

Scheme 4. Structures of metathesis catalysts. Ar = 2,4,6-trimethylphenyl; Cy = cyclohexyl.

The reactions were monitored, and additional catalyst was added as needed. The phosphine, $P(CH_2OH)_3$,[19] and, for fluorous-tagged products, FSPE, were used to remove the catalyst. The metathesis products were generally purified by column chromatography. All reactions yielded the expected cascade products, although, for **47** (Table 2), cyclisation to the tetrasubstituted alkene **70** was slow,[20] and the by-product **92** was also observed (Scheme 5). With the first-generation Grubbs' catalyst (**I**), compound (±)-**76** (Table 2) underwent partial isomerisation to the unconjugated product **93** (Scheme 5). Finally, trifluoroacetic acid (TFA) released the metathesis products **81–91** (R = H; Table 2), but not any remaining substrate, from the fluorous-tagged safety-catch




Scheme 5. Structures of by-products of metathesis cascades.

Table 1. Building-block couplings.

| | Building blocks[a] | Method[b] | Product | Yield [%] |
|---|---|---|---|---|
| 1 | **17**, **26** | A, B1 |  **36** | 58 [90][c] |
| 2 | (±)-**19**, **30** | C, D1 |  **37** | 71[d] |
| 3 | (±)-**20**, **30** | C, D1 |  (±)-**38** | [e] |
| 4 | **21**, **30** | C, D1 |  **39** | [e] |
| 5 | **22**, **30** | C, D1 |  **40** | 77[d] |
| 6 | **16**, **23** | C, D2 |  **41** | >96[f] (86)[g] [83][c] |
| 7 | **16**, **18** | C, D2 |  **42** | >98[f] (>95)[g] [93][c] |
| 8 | **16**, **21** | C, D2 |  **43** | 97 [96][c] |
| 9 | **41**, **24** | C, E |  **44** | 86 [86][c] |
| 10 | **15a**, **25** | F, D2 |  **45** | 78 [35][c] |

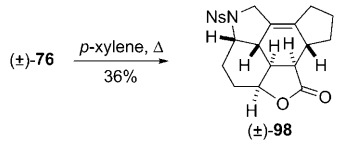
[a] The first building block specified was the limiting reagent. [b] Methods: A: building blocks (1 equiv), $Et_2Zn$, $Pd(OAc)_2$ (5 mol%), 2-$PhC_6H_4PtBu_2$ (7.5 mol%), $NH_4OAc$ (7.5 mol%), THF; B1: tetrabutylammonium fluoride (TBAF), THF; C: building block in excess (4 equiv), diethyl azodicarboxylate (DEAD) (4 equiv), $PPh_3$ (4 equiv), THF, 0°C, 1 h; D1: NaOMe, MeOH; D2: $NH_3$ in MeOH (sat.); E: DMSO, Δ; F: silyl ether (5.5 equiv); *N*-bromosuccinimide (NBS) (5 equiv); $CH_2Cl_2$, 0°C→RT. [c] Yield for the second step. [d] Yield over 2 steps. [e] Isolated as the corresponding acrylate (see Table 2). [f] Purified by FSPE. [g] Purity determined by 500 MHz $^1$H NMR spectroscopy.

linker.[13] Unfortunately, the 2,4-pentadien-1-ols **81**, **82**, **90** and **91** (Table 2) were prone to epimerisation under these reaction conditions.

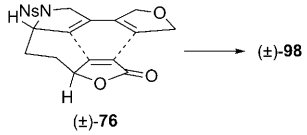
For the 1,3-diene metathesis products, we investigated the potential of the complementary approaches outlined in Scheme 2 to expand the range of accessible small molecule scaffolds. For the approach shown in Scheme 2A, we studied the Diels–Alder reactions of the 1,3-dienes **70**, (±)-**76**, **81** (R=R′$^F$) and **82** (R=R′$^F$) with the reactive dienophile 4-phenyl-[1,2,4]-triazole-3,5-dione (Table 3). The design of our safety-catch linker[13] meant that the metathesis products **81**–**82** (R=R′$^F$; Table 3) were still fluorous-tagged, allowing easy purification (by FSPE) of the corresponding Diels–Alder adducts **96**–**97** (R=R′$^F$; Table 3); TFA-catalysed acetal hydrolysis, followed by FSPE, gave the final products **96** (R=H) and **97** (R=H) (Table 3).

We next investigated the intramolecular Diels–Alder reactions of the metathesis products **74**–**78** (Table 2) (Scheme 2B); for each of these compounds, the 1,3-diene is tethered to a potential butenolide dienophile. Previously, a similar intramolecular Diels–Alder reaction involving a butenolide dienophile was exploited in a total synthesis of Forskolin.[21] After 3 days in refluxing *p*-xylene, the butenolide (±)-**76** gave the pentacyclic adduct (±)-**98** (Scheme 6) the relative configuration of which was determined through the observation of diagnostic NOE correlations; in addition, 35% of the starting material was recovered. The stereochemical outcome of the reaction is rationalised in Scheme 7. The tether between the dihydropyrrole and the butenolide rings determines which face of the diene and the dienophile reacts: thus, with the relative configuration of (±)-**76**, the reaction proceeds through an *exo* transition state to yield the product (±)-**98**.

Surprisingly, the diastereomeric substrate (±)-**75** (Table 2) gave a low yield (5%) of the same product (±)-**98** under these reaction conditions.




Scheme 6. Intramolecular Diels–Alder reaction of the metathesis product (±)-**98**.




Scheme 7. Rationalisation of the stereochemical outcome of the intramolecular Diels–Alder reaction of (±)-**76**

Table 2. Synthesis and cascade reactions of metathesis substrates; with starting materials (SM) **13**, **14**, **15b**, **15a**, **36**, (±)-**37**, (±)-**38** and **39**–**45** and capping building blocks (CBB) **27**–**35**.

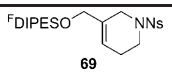
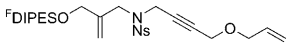
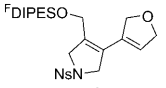
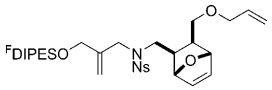
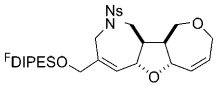
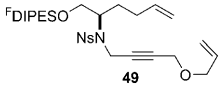
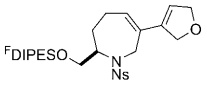
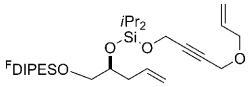
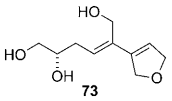
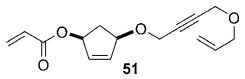
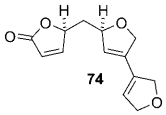
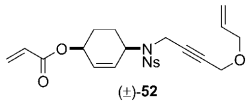
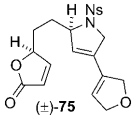
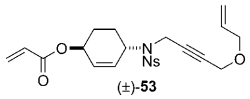
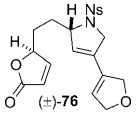
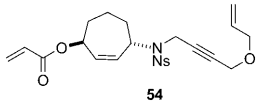
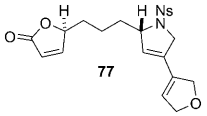
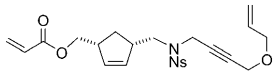
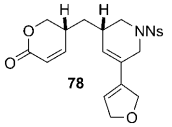
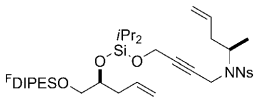
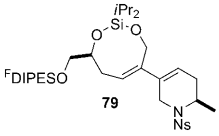
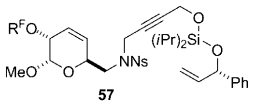
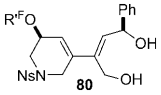
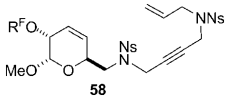
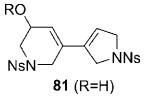
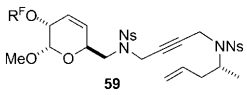
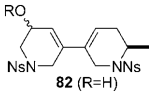
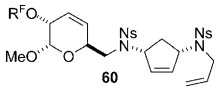
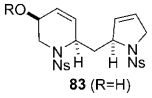
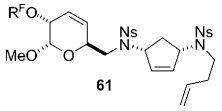
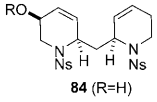
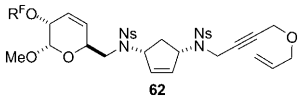
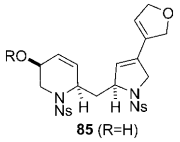
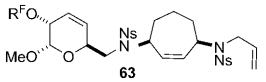
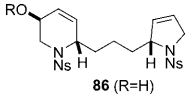
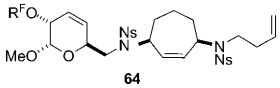
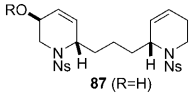
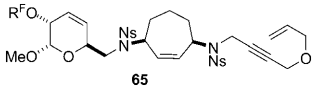
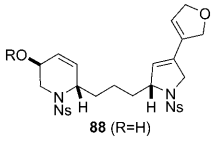
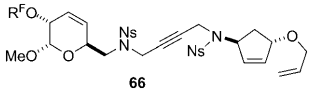
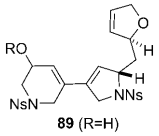
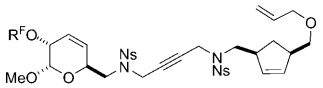
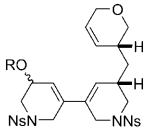
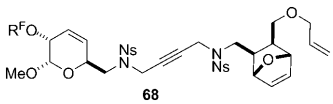
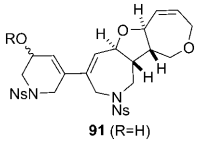
| | SM | CBB | Method[a] | Metathesis substrate[b] | Mass recovery[c] (purity[d]) [%] | Method (mol% cat.) | Product[b] | Yield [%] |
|---|---|---|---|---|---|---|---|---|
| 1 | **13** | **28** | C |  **46** | 95 (>85) | G1 (5) |  **69** | 95[c] (>90)[d] |
| 2 | **13** | **30** | C |  **47** | 96 (>85) | G2 (5) |  **70** | 57[e] |
| 3 | **14** | **31** | C |  **48** | 48[f] | G2 (5→10) |  **71** | 27 |
| 4 | **15b** | **30** | C |  **49** | 55[f] | G2 (5) |  **72** | 69 |
| 5 | **15a** | **34** | F |  **50** | 34 | G2 (5), B2 |  **73** | 51 [62][g] |
| 6 | **36** | – | H |  **51** | 87[f] | G2 (3) |  **74** | 46 |
| 7 | (±)-**37** | – | H |  (±)-**52** | 95[f] | G1 (5) |  (±)-**75** | 70 |
| 8 | (±)-**38** | – | H |  (±)-**53** | 62[h] | G1 (5) |  (±)-**76** | 72[i] |
| 9 | **39** | – | H |  **54** | 37[h] | G2 (3) |  **77** | 31 |
| 10 | **40** | – | H |  **55** | 78[f] | G2 (3) |  **78** | 56 |
| 11 | **45** | **29** | C |  **56** | 52[f] | G2 (2×5) |  **79** | 87 |
| 12 | **41** | **35** | F |  **57** | 67 (82) | G1 (4×5), B3 |  **80** | 16 |
| 13 | **41** | **27** | C |  **58** | 98 (85) | G2 (3×5), I |  **81** (R=H) | 61 [59][g] |
| 14 | **41** | **29** | C |  **59** | 68[f] | G2 (3×5), I |  **82** (R=H) | 74 [60][g,j] |
| 15 | **42** | **27** | C |  **60** | 80 (85) | G2 (5), I |  **83** (R=H) | 20[k] |

Table 2. (Continued)

| | SM | CBB | Method[a] | Metathesis substrate[b] | Mass recovery[c] (purity[d]) [%] | Method (mol% cat.) | Product[b] | Yield [%] |
|---|---|---|---|---|---|---|---|---|
| 16 | **42** | **28** | C |  **61** | 53[f] | G2 (5), I |  **84** (R=H) | 98[c] (94)[d] [85][g] |
| 17 | **42** | **30** | C |  **62** | 98 (84) | G2 (2×5) |  **85** (R=H) | 48[c] (88)[d] [50][g] |
| 18 | **43** | **27** | C |  **63** | 74[f] | G2 (4×5), I |  **86** (R=H) | 12[k] |
| 19 | **43** | **28** | C |  **64** | | G2 (2×5), I |  **87** (R=H) | 66[k] |
| 20 | **43** | **30** | C |  **65** | 74[f] | G2 (2×5), I |  **88** (R=H) | 35 [58][g] |
| 21 | **44** | **32** | C |  **66** | 93 (84) | G2 (2×5), I |  **89** (R=H) | 50 [66][g,j] |
| 22 | **44** | **33** | C |  **67** | 93 (84) | G2 (2×5), I |  **90** (R=H) | 17[j,k] |
| 23 | **44** | **31** | C |  **68** | 43[f] | G2 (2×5), I |  **91** (R=H) | 10[j,k] |

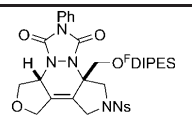
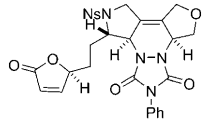
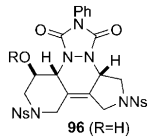
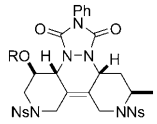
[a] Methods: B2: HF (50% aq) $CH_2Cl_2$–MeCN, 1 h, RT; B3: HF•pyridine, THF, RT then $Me_3SiOMe$; C: building block (4 equiv), DEAD (4 equiv), $PPh_3$ (4 equiv), THF, 0°C, 1 h; F: building block (5.5 equiv); NBS (5 equiv); $CH_2Cl_2$, 0°C→RT; G1: i) catalyst **I**, $CH_2Cl_2$, 45°C; ii) $Et_3N$, $P(CH_2OH)_3$ then silica then filter through Celite; G2: i) catalyst **III**, $CH_2Cl_2$, 45°C; ii) $Et_3N$, $P(CH_2OH)_3$ then silica then filter through Celite; H: acryloyl chloride, $iPr_2NEt$, $CH_2Cl_2$, 0°C; I: TFA (3%), $CH_2Cl_2$. [b] For the definitions of $R^F$ and $R'^F$, see Scheme 1B. [c] Purified by FSPE unless otherwise indicated. [d] Purity determined by 500 MHz $^1H$ NMR spectroscopy. [e] The triene **92** was also obtained in 6% yield. [f] Yield of the purified product after column chromatography. [g] Yield for the second step. [h] Yield over three steps from the corresponding hydroxy acetate ((±)-**20** or **21**). [i] The isomeric product **93** was also obtained in 13% yield. The yield of **76** was 34% and 36% with 5 mol% of the catalysts **III** and **II** respectively. [j] Obtained as diastereomeric mixture. [k] Yield over two steps.

Presumably, the *endo* transition state that is required for direct cycloaddition is disfavoured; instead, isomerisation to (±)-**76** via the unconjugated compound **93** was followed by intramolecular Diels–Alder reaction to give the pentacycle (±)-**98**. Intramolecular Diels–Alder reaction was not observed in refluxing *p*-xylene with either shorter (i.e., **74** or **78**) or longer (i.e., **77**) tethers between the diene and the dienophile.

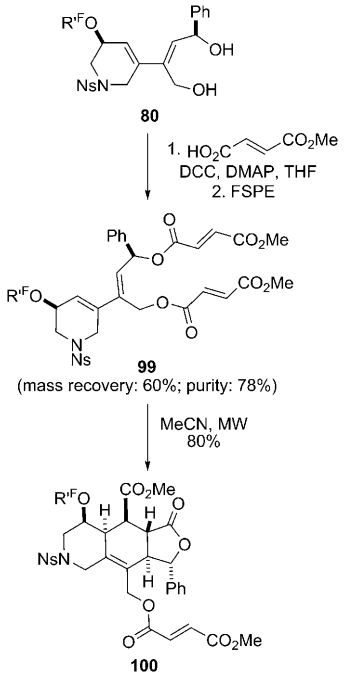
A dienophile was attached to both of the alcohols of **80** (Scheme 8); here, the fluorous-tagged safety-catch linker allowed the purification of the product **99** by FSPE alone. The intramolecular Diels–Alder reactions of fumarate esters of 2,4-pentadien-1-ols are well known.[22] Microwave irradiation[22c] of **99** (at 160°C) yielded the tricyclic fused product **100**. The stereochemical outcome of the reaction is rationalised in Scheme 9. The diastereoselectivity of intramolecular Diels–Alder reactions of achiral fumarate esters of 2,4-pentadien-1-ols has been studied previously and, with (*E*,*E*)-dienes, selectivity in favour of the *exo* (with respect to the tethering ester) product was observed. The reaction of **99** is more complicated because the substrate is chiral. The outcome of the reaction (→**100**) is consistent with reaction through an *exo* (with respect to the tethering ester) transition state in which 1,3-allylic strain is minimised.

Table 3. Intermolecular Diels–Alder reactions with 4-phenyl-[1,2,4]-triazole-3,5-dione.

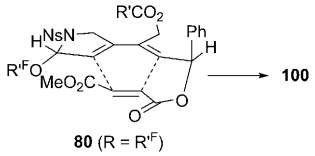
| | SM | Method[a] | Product | Yield [%] |
|---|---|---|---|---|
| 1 | **70** | J |  (±)-**94** | 84 |
| 2 | (±)-**76** | J |  (±)-**95** | 95 |
| 3 | **81**[b] | J, I |  **96** (R=H) | 88[c] (>95)[d] [58][e] |
| 4 | **82**[b] | J, I |  **97** (R=H) | 88[c] (90)[d] [75][e] |

[a] Methods: I: 3% TFA, $CH_2Cl_2$; J: 4-phenyl-[1,2,4]-triazole-3,5-dione, $CH_2Cl_2$. [b] R = R$^{rF}$; for the definition of R$^{rF}$, see Scheme 1B. [c] Determined by 500 MHz $^1$H NMR spectroscopy. [d] Yield of purified product after column chromatography. [e] Yield for the second step.




Scheme 8. Attachment of a pendant dienophile to the metathesis product **80** and intramolecular Diels–Alder reaction; DCC = *N,N*-dicyclohexylcarbodiimide, DMAP = 4-dimethylaminopyridine, MW = microwave.

Finally, a selection of fluorous-tagged products were derivatised to yield a range of amides, sulfonamides, ureas and thioureas (Table 4). The fluorous tag facilitated the purification by FSPE of the intermediates, both after removal of the Ns protecting group and after derivatisation of the resulting secondary amine. The final products **101**–**107** (Table 4) were obtained after removal of the fluorous tag either by desilylation (→**101**–**104** and **107**) or acetal hydrolysis (→**105** and **106**). In addition, treatment of the butenolide (±)-**76** with aqueous methylamine triggered conjugate addition and amide formation to yield the amino alcohol **108** (Table 4) as a single diastereomer.




Scheme 9. Rationalisation of the stereochemical outcome of the intramolecular Diels–Alder reaction of **80**.

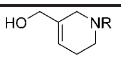
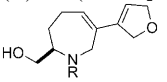
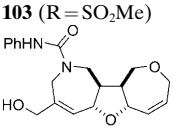
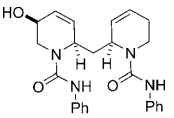
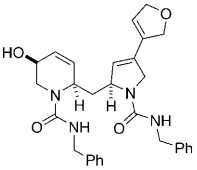
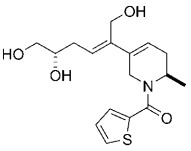
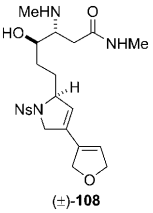
## Conclusion

Metathesis cascade chemistry is an exceptionally powerful reaction for the synthesis of skeletally diverse small molecules. Metathesis substrates were easily assembled from combinations of two or three building blocks; thereafter, metathesis cascades allowed the molecular scaffolds to be reprogrammed. The overall approach was facilitated by fluorous tagging of one of the building blocks, allowing easy purification (by FSPE) of synthetic intermediates and metathesis products. The presence of a fluorous tag also facilitated the subsequent functionalisation of the metathesis products. A fluorous-tagged safety-catch linker[13] was particularly useful since it facilitated purification at each stage of the synthesis, whilst only allowing the products of successful metathesis reactions to be released from the fluorous tag.

The use of Diels–Alder reactions extended the range of scaffolds that were synthetically accessible. The products of several metathesis cascades were 1,3-dienes that are potential substrates for inter- or intramolecular Diels–Alder reactions. A challenge posed by diversity-oriented synthesis is that structurally diverse products are likely to exhibit diverse reactivity. The scope of our approach is a testament to the remarkable generality of ring-closing metathesis.[23] The Diels–Alder reaction allowed more complex scaffolds to be prepared in certain cases: however, the scope of the intramolecular Diels–Alder reaction limited the range of additional scaffolds that were accessible. Synthetic approaches that yield skeletally diverse small molecules are rare: developing new diversity-oriented approaches, particularly those that do not rely on metathesis chemistry, remains a very significant challenge for synthetic chemists.

Table 4. Functionalisation of metathesis products.

| SM | Method[a] | Product | Yield [%] |
|---|---|---|---|
| **69** | K, L, B2 |  **101** (R=COPh) | 50 |
| **69** | K, L, B2 | **101** (R = 2-thiophenecarbonyl) | 77 |
| **69** | K, L, B2 | **101** (R = 5-isoxazolecarbonyl) | 70 |
| **69** | K, M, B2 | **101** (R = CONHPh) | 69 |
| **69** | K, M, B2 | **101** (R = CSNHBn) | 38 |
| **69** | K, L, B2 | **101** (R = $SO_2$Ph) | 84 |
| **69** | K, L, B2 | **101** (R = $SO_2$Me) | 61 |
| **94** | K, L, B2 |  (±)-**102** (R=2-thiophenecarbonyl) | 84 |
| **94** | K, L, B2 | (±)-**102** (R = 5-isoxazolecarbonyl) | 61 |
| **94** | K, M, B2 | (±)-**102** (R = CONHPh) | 37 |
| **94** | K, L, B2 | (±)-**102** (R = $SO_2$Ph) | 72 |
| **72** | K, L, B2 |  **103** (R=COPh) | 81 |
| **72** | K, L, B2 | **103** (R = 2-thiophenecarbonyl) | 94 |
| **72** | K, L, B2 | **103** (R = 5-isoxazolecarbonyl) | 56 |
| **72** | K, L, B2 | **103** (R = $SO_2$Ph) | 75 |
| **72** | K, L, B2 | **103** (R = $SO_2$Me) | 60 |
| **71** | K,[c] M, B2 |  **104** | 38 |
| **84**[b] | K, M, I |  **105** | 21 |
| **85**[b] | K, M, I |  **106** | 63 |
| **79** | K, L, B2 |  **107** | 43 |
| (±)-**76** | N |  (±)-**108** | 48 |

[a] Methods: B2: HF (50% aq) $CH_2Cl_2$–MeCN, 1 h, RT then $Me_3SiOMe$; I: TFA (3%), $CH_2Cl_2$; K: $K_2CO_3$ (4 equiv), PhSH (3 equiv), DMF, RT; L: acid chloride or sulfonyl chloride (4 equiv), DMAP, $CH_2Cl_2$; M: isocyanate or thioisocyanate (4 equiv), $CH_2Cl_2$, RT; N: $MeNH_2$ (aq). [b] R = $R^{rF}$; for the definition of $R^{rF}$, see Scheme 1B. [c] Performed in MeCN with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as base.

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