

Intramolecular Diels–Alder/1,3-Dipolar Cycloaddition Cascade of 1,3,4-Oxadiazoles

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Abstract: Full details of a systematic exploration of the intramolecular [4 + 2]/[3 + 2] cycloaddition cascade of 1,3,4-oxadiazoles are disclosed in which the scope and utility of the reaction are defined.

Introduction

In the development of a synthetic approach to the vinca alkaloids based on the cycloaddition reactions of electron-deficient heterocyclic azadienes,^{1–3} we reported the first intramolecular examples of a tandem Diels–Alder/1,3-dipolar cycloaddition reaction of 1,3,4-oxadiazoles.^{4–6} Prior to these studies, Vasilev,⁷ Sauer,⁸ Seitz,⁹ and Warrenner¹⁰ each disclosed examples of the participation of electron-deficient and typically symmetrical 1,3,4-oxadiazoles in an intermolecular reaction cascade with electron-rich or strained olefins providing 2:1 cycloadducts (Figure 1). The reactions with such alkenes proceed by an initial inverse electron demand Diels–Alder reaction to provide a cycloadduct that loses N₂ to generate a carbonyl ylide

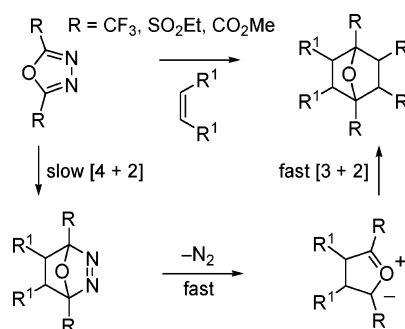


Figure 1. 1,3,4-Oxadiazole cycloaddition cascade.

that in turn further reacts with the alkene in a 1,3-dipolar cycloaddition (Figure 1). The initial 1:1 adducts were not observed, and the second 1,3-dipolar cycloaddition proved faster than the initiating Diels–Alder reaction limiting the synthetic potential of the process to the generation of symmetrical 2:1 cycloadducts. Herein we provide full details of the examination of the intramolecular cycloaddition cascade of 1,3,4-oxadiazoles highlighting the advances made since our initial disclosure⁴ that extend the range of alkenes and oxadiazoles that participate in the reaction, permit the use of unsymmetrical dienophiles and oxadiazoles, control the cycloaddition regioselectivity and diastereoselectivity, and define the scope and utility of the tandem [4 + 2]/[3 + 2] cycloaddition reactions of such heterocyclic azadienes.

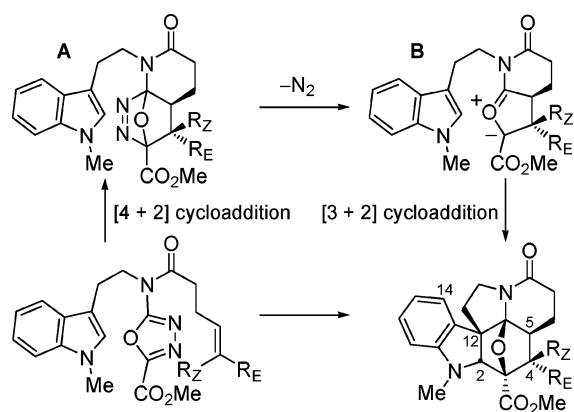
Results and Discussion

Initiating Dienophile. Given that our studies to date have been conducted concurrent with the development of a synthetic approach to vindoline,⁶ the initial substrates examined bear a tethered indole to serve as the dipolarophile trap of the in situ generated carbonyl ylide.¹¹ An unusually wide range of tethered dienophiles were found to be effective at initiating the reaction cascade (Scheme 1). In each case, a single diastereomer of the

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Scheme 1



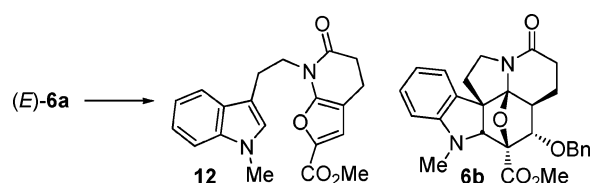
1a , R = H	<i>o</i> -Cl ₂ C ₆ H ₄ , 180 °C, 3 h	87% 1b
<i>(E)</i> - 2a , R = Me	<i>o</i> -Cl ₂ C ₆ H ₄ , 180 °C, 6 h	65% 2b
<i>(Z)</i> - 3a , R = Me	<i>o</i> -Cl ₂ C ₆ H ₄ , 180 °C, 6 h	65% 3b
<i>(E)</i> - 4a , R = CH ₂ OTBS	<i>o</i> -Cl ₂ C ₆ H ₄ , 180 °C, 24 h	86% 4b
<i>(E)</i> - 5a , R = Ph	<i>o</i> -Cl ₂ C ₆ H ₄ , 175 °C, 14 h	61% 5b
	or TIPB, 230 °C, 5 h	60%
<i>(E)</i> - 6a , R = OBn	TIPB, 230 °C, 6 h	94% 6b
<i>(Z)</i> - 7a , R = OBn	TIPB, 230 °C, 6 h	61% 7b
<i>(E)</i> - 8a , R = CO ₂ Me	TIPB, 230 °C, 46 h	71% 8b
<i>(Z)</i> - 9a , R = CO ₂ Me	TIPB, 230 °C, 60 h	62% 9b
<i>(E)</i> - 10a , R = CN	TIPB, 230 °C, 22 h	79% 10b
	<i>o</i> -Cl ₂ C ₆ H ₄ , 170 °C, 144 h	76%
<i>(Z)</i> - 11a , R = CN	TIPB, 230 °C, 22 h	74% 11b

TIPB = 1,3,5-triisopropylbenzene

cycloadduct was produced in which the relative stereochemistry is set by a combination of the dienophile and dipolarophile geometry (C4/C5 and C2/C12 stereochemistry) and indole endo [3 + 2] cycloaddition sterically directed to the face opposite the newly formed lactam¹¹ (C5 vs C2/C12 stereochemistry). This latter exclusive endo indole diastereoselection is unique to the intramolecular 1,3-dipolar cycloaddition, and comparable intermolecular reactions proceed with indole exo cycloaddition directed to the analogous sterically less hindered face.¹² The indole endo addition observed with the substrates examined to date most simply may be attributed to a conformational (strain) preference for the 1,3-dipolar cycloaddition transition state that is dictated by the dipolarophile tether since it mirrors the relative strain energy of the four possible products (For **1a** (MM2): α -face endo < β -face endo ($\Delta E = 10.4$ kcal/mol) < α -face exo ($\Delta E = 16.6$ kcal/mol) < β -face exo ($\Delta E = 43.8$ kcal/mol)) and is of a magnitude that it is unaffected by the dienophile substitution.⁴ The stereochemical assignments for the cycloadducts were easily made with observation of diagnostic ¹H NMR NOEs (N¹-R/C4 α -substituent, C4/C5 α -substituents, C14-H/C5 α -substituent) and, in many instances, confirmed with X-ray structures. The relative ease of the tandem [4 + 2]/[3 + 2] cycloaddition reaction with **1–11a** is consistent with the cascade being initiated by an inverse electron demand Diels–Alder reaction, but even unactivated and electron-deficient dienophiles participate effectively, and each is followed by the loss of N₂ and a subsequent 1,3-dipolar cycloaddition of the tethered indole.

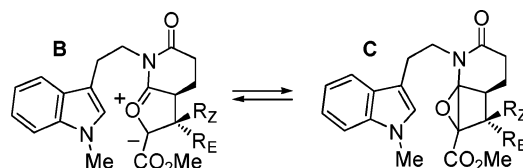
In most instances, the [3 + 2] cycloaddition is sufficiently fast under the reaction conditions that products derived from the quenched 1,3-dipole are not observed even if the reaction

Scheme 2



5 mM, <i>o</i> -Cl ₂ C ₆ H ₄ , 180 °C, 6 h	72%	0%
0.1 mM TIPB, 230 °C, 6 h	0%	94%

- Starting material disappearance need not coincide with product generation
- More, not less vigorous conditions drive reaction to successful completion
- The 1,3-dipole is remarkably stable or a cyclobutene epoxide serves as reversible source



is stopped prior to consumption of the starting material. However, there are notable instances where the initiating [4 + 2] cycloaddition is faster than the subsequent [3 + 2] cycloaddition⁶ and/or that the latter reaction is sufficiently slow that significant amounts of the intermediate carbonyl ylide or its corresponding cyclobutene epoxide^{6,10,13} buildup and a premature workup leads to products derived from their quench. In such instances, extending the reaction time, increasing the reaction temperature, and enlisting diluted reaction concentrations (≤ 5 mM, presumably to preclude competitive intermolecular cycloadditions) were found to enhance the conversions. Notably, the observation of such products can be mistakenly interpreted to represent an instability of the intermediate 1,3-dipole under the reaction conditions, and the behavior of substrates *(E)*-**6a** and *(Z)*-**7a** are representative of such cases. Both provide the respective cycloaddition cascade products **6b** and **7b** in good conversions when taken to completion, but both provide the furan **12** if the reactions are prematurely stopped (Scheme 2). Furan **12**, which is derived from water addition to the 1,3-dipole followed by aromatization (elimination of water and benzyloxy alcohol) upon workup, is not an intermediate enroute to **6b** or **7b**, nor is it present in the thermal reaction mixtures (¹H NMR). Analogous observations are described in detail in ref 6 and may arise as a consequence of dienophile substitutions that accelerate the [4 + 2] cycloaddition and that sterically (*E*-substituent) or electronically (*Z*-substituent) slow the typically fast [3 + 2] cycloaddition (Figure 2). Moreover, the subtleties of these effects are beautifully manifested in the comparisons of *(E)*-**6a** and *(Z)*-**7a**. The benzyloxy substituent of *(E)*-**6a** accelerates the initiating inverse electron demand Diels–Alder reaction and may *sterically* slow the ensuing [3 + 2] cycloaddition such that the [4 + 2] cycloaddition reaction is a relatively faster step of the tandem cascade. If this reaction is not run under relatively dilute reaction conditions, the yields of **6b** are more modest (30–50% at 5 mM, 74% at 1 mM, 82% at 0.5 mM, and 94% at 0.1 mM)

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(13) Such cyclobutene epoxides have been utilized as sources of the corresponding carbonyl ylides (1,3-dipoles); see ref 10.

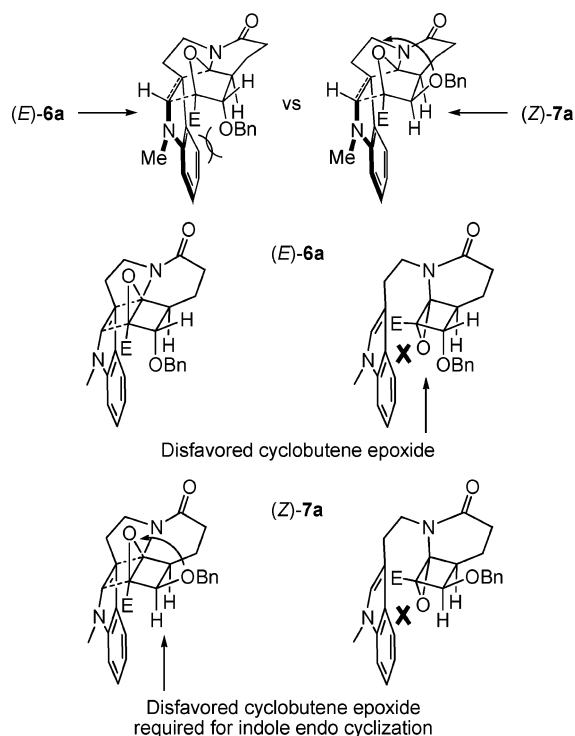


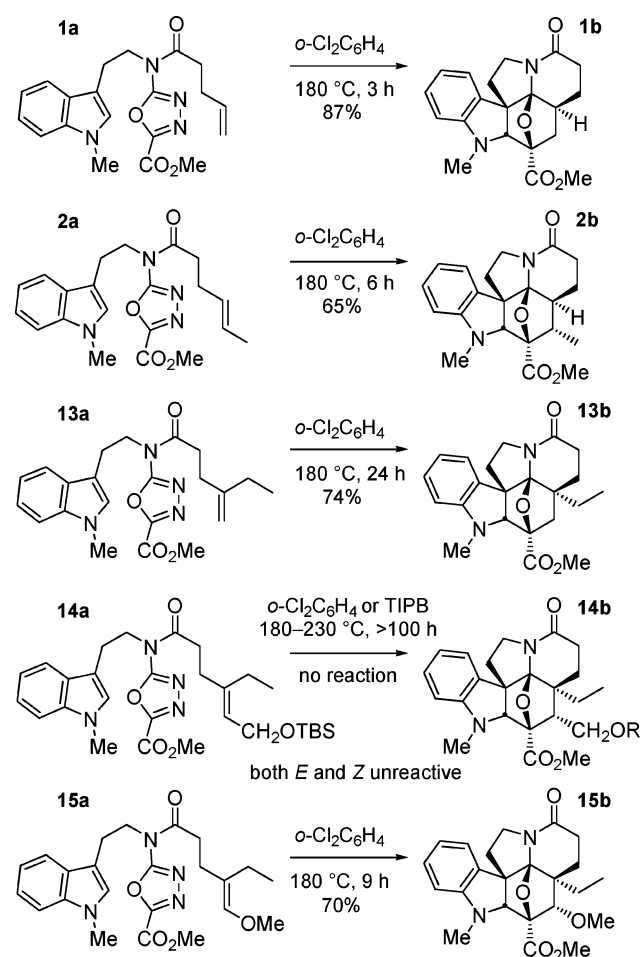
Figure 2. [3+2] Cycloaddition transition state and potential cyclobutene epoxide intermediates.

suggesting that competitive intermolecular reactions of the intermediate 1,3-dipole may compete. Similarly, the benzyloxy substituent of (*Z*)-**7a** accelerates the initiating Diels–Alder reaction and *electronically* slows the subsequent [3 + 2] cycloaddition. This latter effect is unique to an electronegative substituent (e.g., OBn vs Me, compare (*Z*)-**3a** vs (*Z*)-**7a**), its magnitude is surprisingly large, and the observations may reflect the intermediacy of the cyclobutene epoxides. A full discussion of these effects is provided in ref 6, where their delineation proved crucial to the total synthesis of vindoline and vindorosine. However, the important feature of these studies that is intuitively difficult to appreciate is that the starting material disappearance need not coincide with cascade product formation and that more vigorous (not milder) reaction conditions at dilute concentrations often drive the reactions to successful completion.

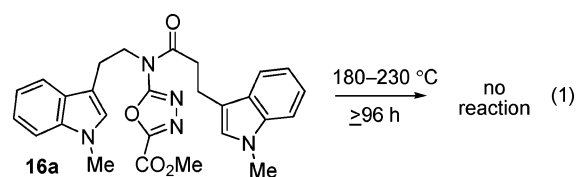
The addition of substituents to the tethered dienophile has a significant impact on the ease of cycloaddition. Even the addition of activating substituents at the alkene terminus slows the reaction relative to the unsubstituted terminal alkene (**1a**, Scheme 1). As additional unactivating substituents are added to the dienophile, the reaction slows (**1a** > (*E*)-**2a** or **13a** >> **14a**), and this appears to be relatively independent of the site of substitution ((*E*)-**2a** ≥ **13a**, Scheme 3). The exceptions to these generalizations include the trisubstituted enol ethers such as **15a**, and those disclosed in ref 6, that remain suitably reactive to initiate the cycloaddition cascade via an inverse electron demand Diels–Alder reaction. Impressively, the cycloadditions remain diastereoselective providing a single detectable product.

Although it is possible that an indole [4 + 2] cycloaddition initiates the reaction cascade especially in the instances where closure would provide an entropically favored fused five-membered ring, the substrate **16a** containing only an indole

Scheme 3



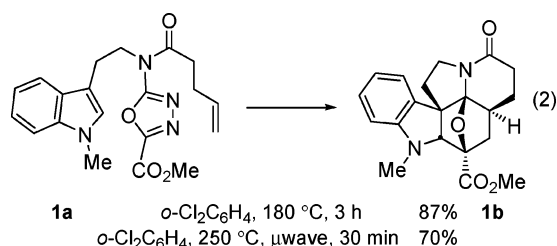
dienophile and dipolarophile failed to react even when exposed to forcing reaction conditions (eq 1). As such, the cascade



reactions exemplified herein can be confidently described as being initiated by [4 + 2] cycloaddition of the tethered alkene. To date, the only exceptions to this generalization represent the special cases where the *N*-acyl amide carbonyl is placed in the dipolarophile tether with a length of two atoms and the substrate contains a poor initiating alkene dienophile. In these instances which are detailed in ref 6, products arising only from the initial indole [4 + 2] cycloaddition are observed but not those arising from the cycloaddition cascade (no [3 + 2] cycloaddition).

Throughout the course of the studies, the most useful solvents to emerge from our surveys have been *o*-dichlorobenzene (*o*-Cl₂C₆H₄, 180 °C) and 1,3,5-triisopropylbenzene (TIPB, 230 °C).^{4–6} Reactions will oftentimes be slightly faster in the former solvent, but those requiring more extended reaction times are generally cleaner when conducted in TIPB. Typically, the reactions are conducted at concentrations of 5 mM although many may be conducted at higher concentrations without impacting the conversions. Some, which entail an unusually slow

[3 + 2] cycloaddition, benefit from the use of even lower reaction concentrations and appear to suffer competitive intermolecular reactions.⁶ Finally, a range of alternative reaction conditions have been examined for conducting the cycloaddition cascade including the use of high pressure (13 kbar), Lewis acid catalyzed reaction conditions, and microwave heating. Whereas the former two have not yet proven useful, the use of microwave heating often provides a useful alternative to the thermal conditions enlisted herein (eq 2). Interestingly, these

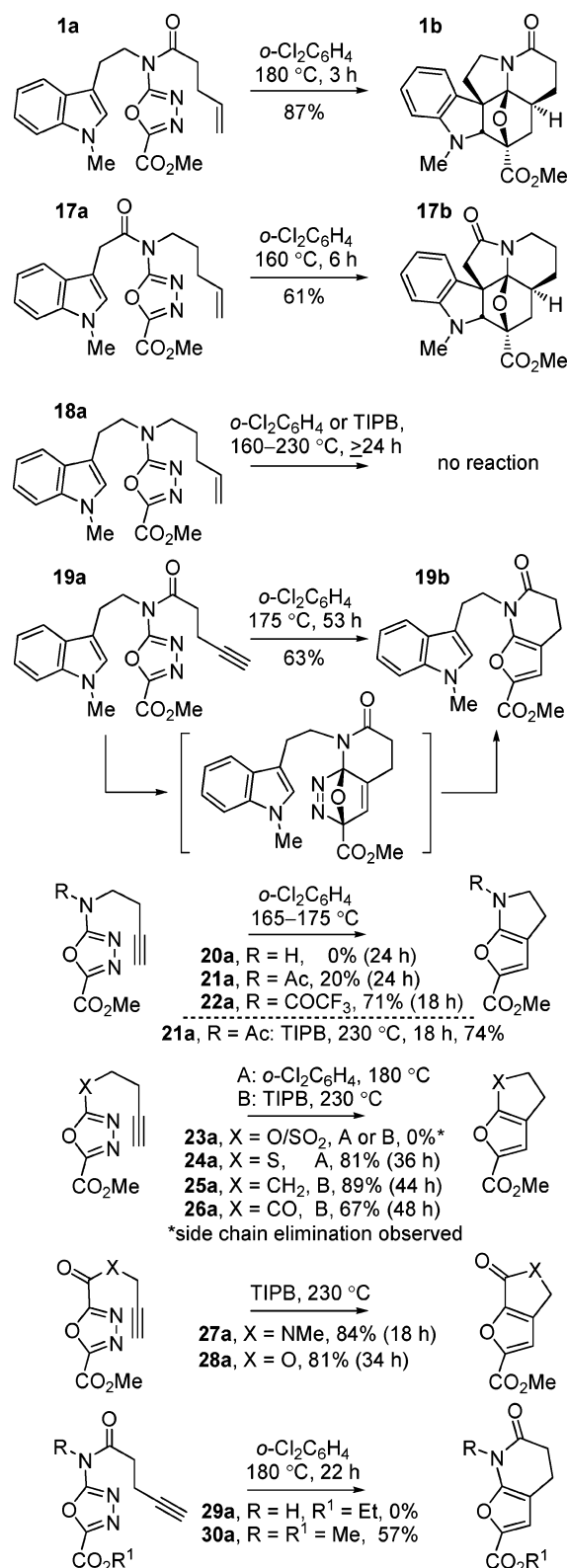


generally have not provided improved conversions largely because the thermal cycloaddition cascades are so clean with both the starting oxadiazoles and the cycloadducts being remarkably stable to the thermal conditions.

N-Acylation: Requirement, Substitution, and Location.

The 2-amino-1,3,4-oxadiazoles examined in Schemes 1–3 bear substituents that enhance a preferred [4 + 2] cycloaddition regioselectivity that is dictated by the dienophile tether and that subsequently stabilize the intermediate 1,3-dipole reinforcing a regioselectivity that is complementary to that of the tethered indole. However, such oxadiazoles are less electron-deficient than those previously examined^{7–10} (Figure 1, R = CO₂Me) resulting in a diminished reactivity toward the initiating [4 + 2] cycloaddition. Even here, *N*-acylation of the C2 amino group is required for observation of the initiating [4 + 2] cycloaddition (**1a** or **17a** > **18a**), and there is typically little distinction whether it is incorporated into the dienophile or dipolarophile tether for the tandem cascade reaction (**1a** vs **17a**, Scheme 4).¹⁴ Expectedly, the reaction rate increases as the electron-withdrawing properties of the activating amide increases (**22a** > **21a** > **20a**). Similarly, studies to date suggest that the conformational properties of a tertiary amide (vs secondary amide) facilitate the initiating Diels–Alder reaction by favoring the adoption of the compact *cis* amide conformation required for [4 + 2] cycloaddition (**30a** vs **29a** and **27a** vs **28a** and **26a**). Although the presence of such a tertiary amide is inherent in the approach utilized to access vindoline and related alkaloids, its use is more central to the success of the cycloaddition cascade than might be initially envisioned. These latter studies were best exemplified utilizing tethered alkyne dienophiles limiting the comparisons to the initiating [4 + 2] cycloadditions and result in the direct formation of furans derived from the loss of N₂ from the initial oxadiazole cycloadduct (e.g., **19b**). Utilizing such reactions, a series of substrates was additionally examined to define the importance of the dienophile linker and functionality connecting the tether to the oxadiazole. Aside from the secondary amine (**20a**, X = NH) which was unreactive under the conditions examined and the ether (**23a**, X = O) and sulfone (**23a**, X = SO₂) connections which suffered an elimination cleavage of the dienophile side chain, the remainder (**20**–**28a**) participated in

Scheme 4

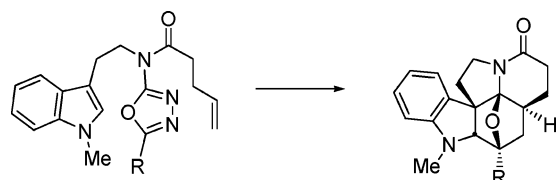


the oxadiazole [4 + 2] cycloaddition reaction effectively.¹⁵ Within this series, the thio connection (**24a**, X = S) was of intermediate reactivity relative to the two *N*-acylamines **21a** and **22a**; the methylene attachment (**25a**, X = CH₂) was just as

(15) At 180 °C in *o*-Cl₂C₆H₄, the reactions of **21a** (20% **21b** at 24 h), **25a** (10% **25b** at 60 h), **26a** (no reaction), and **28a** (32% **28b** at 70 h) failed to react to completion.

(14) An exception to this generalization is discussed in ref 6.

Scheme 5

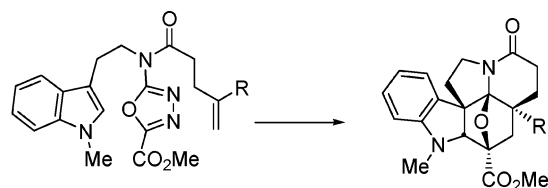


1a , R = CO ₂ Me	<i>o</i> -Cl ₂ C ₆ H ₄ , 180 °C, 3 h	87% 1b
31a , R = CONH ₂	<i>o</i> -Cl ₂ C ₆ H ₄ , 180 °C, 5 h	63% 31b
32a , R = CN	<i>o</i> -Cl ₂ C ₆ H ₄ , 180 °C, 3 h	75% 32b
33a , R = Ph	<i>o</i> -Cl ₂ C ₆ H ₄ , 180 °C, 24 h	42% 33b
	TIPB, 230 °C, 40 h	69% 33b
34a , R = Me	TIPB, 230 °C, 24 h	0%
35a , R = H	TIPB, 230 °C, 48 h	<5%
36a , R = STol	<i>o</i> -Cl ₂ C ₆ H ₄ , 180 °C, 12–36 h	0%
37a , R = S(O)Me	<i>o</i> -Cl ₂ C ₆ H ₄ , 180 °C, 12 h	0%
38a , R = SO ₂ Me	<i>o</i> -Cl ₂ C ₆ H ₄ , 180 °C, 14 h	0%
39a , R = OMe	<i>o</i> -Cl ₂ C ₆ H ₄ , 180 °C, 24 h	0%

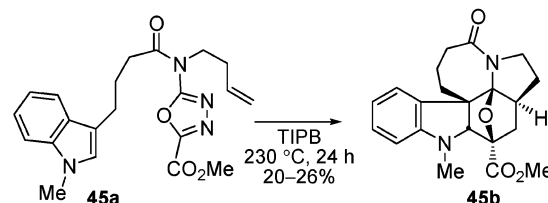
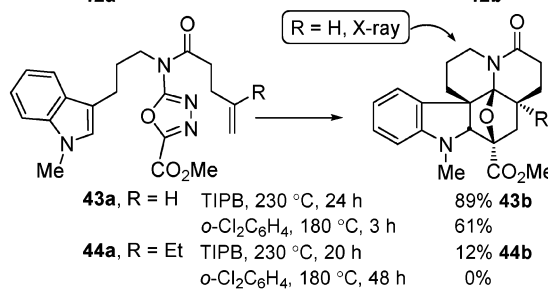
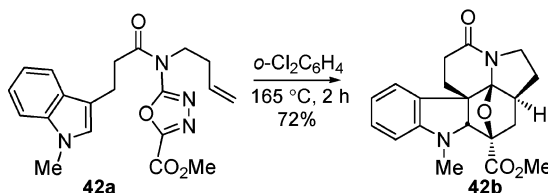
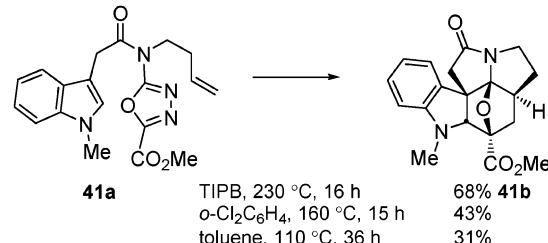
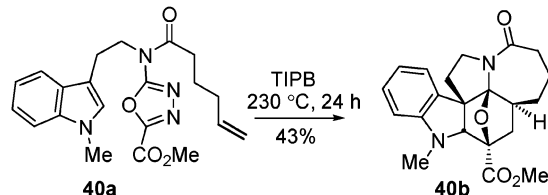
effective, but noticeably less reactive;¹⁵ and the ester (**28a**, X = CO₂) versus *N*-methylamide (**27a**, X = CONMe) exhibited a reactivity suggesting its preference for an extended conformation offsets its enhanced electronic activation.¹⁵ However, even the ketone **26a** (X = CO)¹⁵ was less reactive than **21a**, **22a**, or **24a** despite its enhanced electron-deficient character suggesting either that additional geometrical constraints facilitate their intramolecular reactions or that a complementary and weakly electron-donating oxadiazole substituent (X = *N*-acyl or S) enhances the oxadiazole Diels–Alder reaction with an unactivated dienophile.

1,3,4-Oxadiazole C5 Substituent. Beautifully, as detailed in ref 6, a C5 methyl ester on the 1,3,4-oxadiazole introduces the vindoline C3 methyl ester while reductive cleavage of the cycloadduct oxido bridge provides the C3 tertiary alcohol complete with control of the appropriate C3 stereochemistry. Consequently, the initial studies on the scope of the oxadiazole cycloaddition cascade were conducted with this C5 substituent. However, a study of its impact was conducted with a full range of C5 substituents. Electron-withdrawing substituents would be expected to enhance the electron-deficient character of the oxadiazole promoting the initiating inverse electron demand [4 + 2] cycloaddition reaction and subsequently stabilize the intermediate 1,3-dipole. Consistent with these expectations, electron-withdrawing (CO₂Me, CONH₂, CN) or conjugating (Ph) substituents provided oxadiazoles that participated effectively in the reaction cascade with the reactions of **31a** and **32a** being comparable with that of **1a**, whereas that of **33a** required more vigorous reaction conditions (Scheme 5). Unactivating (Me, H) or electron-donating substituents (OMe, STol) failed to support the tandem cycloaddition cascade even though the initiating [4 + 2] cycloaddition reaction was often observed providing a range of products derived from a carbene that arises from cleavage (O–C5 bond) of the unstabilized carbonyl ylide. Most surprising was the inability of a C5 sulfoxide or sulfone to support the tandem cycloaddition cascade. The latter oxadiazole simply proved unstable to the thermal conditions of the reaction undergoing a facile C–SO₂R homolytic cleavage, whereas the former intermediate 1,3-dipole preferentially rearranges (cleavage of O–C5 bond) to a carbene. Nonetheless, the clear definition of the oxadiazole C5 substituents that support the tandem cycloaddition cascade permit its implementation in studies beyond our own immediate interests.

Scheme 6

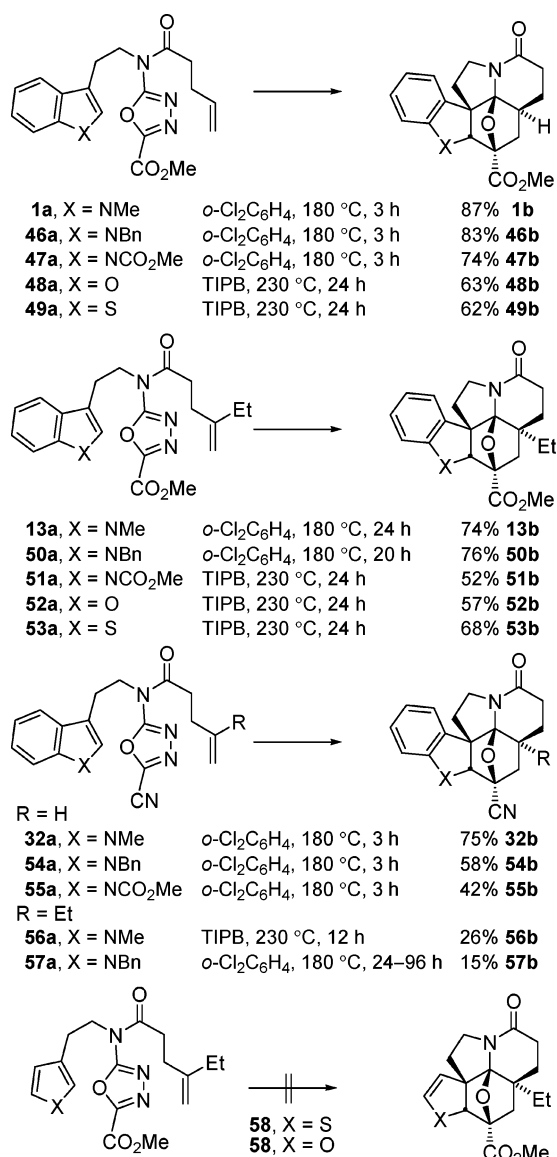


1a , R = H	<i>o</i> -Cl ₂ C ₆ H ₄ , 180 °C, 3 h	87% 1b
13a , R = Et	<i>o</i> -Cl ₂ C ₆ H ₄ , 180 °C, 24 h	74% 13b



Tether Lengths. A survey of the impact of the dienophile and dipolarophile tether lengths was also conducted (Scheme 6). The implementation of the cycloaddition cascade for the preparation of the vinca alkaloids enlists a dienophile tether that permits the preparation of the fused six-membered lactam and occurs with a facility that exceeds that typical of an unactivated alkene intramolecular Diels–Alder reaction. Further lengthening of this tether slows, but does not preclude, the cycloaddition cascade as illustrated with **40a** which provided the fused seven-membered lactam **40b** (43%) albeit requiring more vigorous reaction conditions (TIPB, 230 °C, 24 h). By contrast, shortening this dienophile tether length such that the Diels–Alder closure provides a five- versus six-membered ring leads to even more facile initiation of the cycloaddition cascade

Scheme 7



(**41a** and **42a**). Similarly, extending the dipolarophile tether length with **43a** to access the fused six- vs five-membered ring cycloadduct provided **43b** in superb conversions (89%) and with an unaltered diastereoselectivity affording a single product (X-ray)¹⁶ derived from endo indole [3 + 2] cycloaddition directed to the face of the 1,3-dipole opposite the fused lactam. In this latter instance and unlike **1a** versus **13a**, substitution of the dienophile (**44a**) resulted in a less effective tandem cycloaddition as did further extensions of the dipolarophile tether length (**45a**). Nonetheless, the scope of the cycloaddition cascade is such that deep-seated modifications in the core structure can be accommodated providing access to a remarkable range of ring systems.

Tethered Dipolarophile. The examination of variations in the tethered dipolarophile to date has been conducted largely to explore the requisite reactivity of the tethered indole or to probe deep-seated modifications that may be incorporated into the vindoline structure for accessing the corresponding vinblastine analogues (Scheme 7). Thus, a tethered *N*-benzylindole (**46a**

and **50a**) or the less nucleophilic *N*-carbomethoxyindole (**47a** and **51a**) participated in the reaction cascade in a manner and rate indistinguishable from those of **1a** or **13a**. In fact, reaction of an equimolar mixture of **1a** and **47a** provided 1:1 mixtures of their respective products **1b** and **47b** at all monitored stages of the reaction illustrating that the rate-limiting step of these reactions is the initiating [4 + 2] cycloaddition and that the modest differences in the dipolarophile reactivity have no apparent impact. Pertinent to our interests in accessing vindoline analogues in which the N¹ tertiary amine is replaced with nonbasic heteroatoms, both the tethered benzofurans **48a** and **52a** and the benzothiophenes **49a** and **53a**, but not the corresponding furan or thiophene (**58**, X = O or S), participated effectively in the cycloaddition cascade.¹¹

1,3,4-Oxadiazole versus 1,3,4-Thiadiazole and Oxazole.

Analogous to the results of prior studies indicating that 1,3,4-thiadiazoles and *N*¹-methyl-1,3,4-triazoles are progressively less reactive than 1,3,4-oxadiazoles,^{8–10} the thiadiazoles **59a** and **60a** did not undergo the cycloaddition cascade and failed to participate in the initiating Diels–Alder reaction (Scheme 8). Similarly, the potential that an oxazole may support an analogous tandem cycloaddition cascade, requiring the loss of a nitrile (vs N₂) from the initial [4 + 2] cycloadduct with cleavage of a C–C bond to generate the intermediate 1,3-dipole, was examined. Even with the addition of substituents that may facilitate this nitrile loss, the reaction was not found to be viable although a range of products were observed that were derived from the initial [4 + 2] cycloaddition reaction.

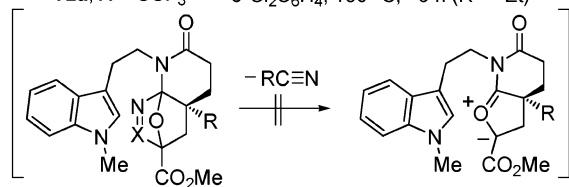
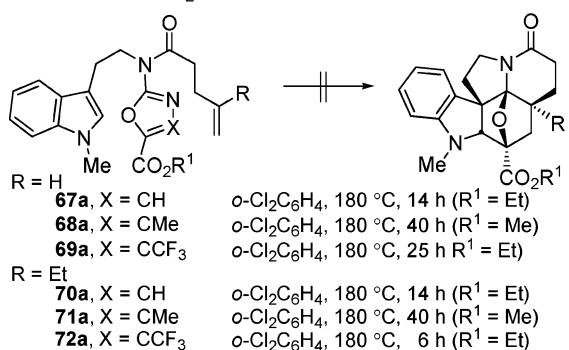
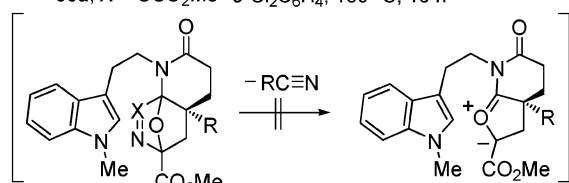
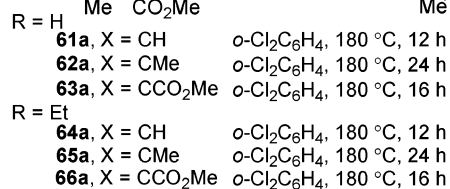
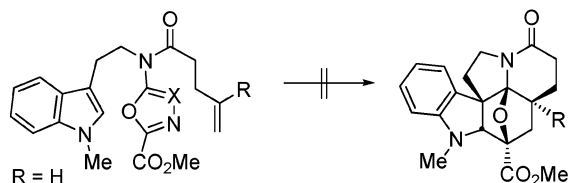
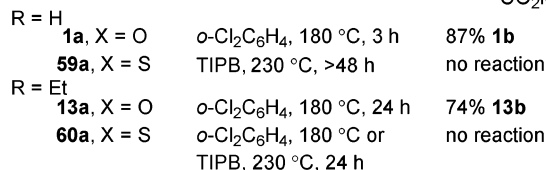
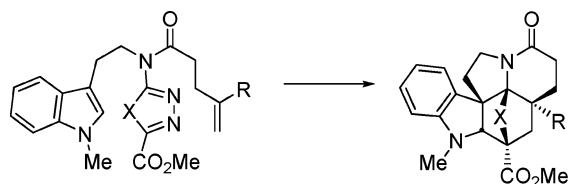
Alternative Tethering and Transannular Cycloadditions.

Two final features of the cycloaddition cascade were briefly investigated that highlight several ways in which its scope may be extended. The first entails tethering the initiating dienophile through the oxadiazole C5 substituent rather than the C2 amino substituent. Thus, substrate **73a** was prepared and found to participate in an analogous tandem [4 + 2]/[3 + 2] cycloaddition cascade to provide **73b** (Scheme 9). Consistent with expectations based on ground-state modeling of the potential products (MM2 $\Delta E = 7.0$ kcal/mol for observed α - vs β -face endo and $\Delta E > 11.0$ kcal for α -endo vs α -face or β -face exo) and intuitive assessments of a stereochemical outcome (cis vs trans 5,5- and 5,6-fusions with the oxido bridged furans), a single diastereomer of **73b** is produced resulting from a defining and exclusive endo [3 + 2] cycloaddition of the tethered indole on the 1,3-dipole face opposite the newly formed lactam. Most significantly, this illustrates a second of many alternative ways in which the dienophile and dipolarophile may be tethered to the oxadiazole to produce alternative pentacyclic ring systems arising from a predictably diastereoselective cycloaddition cascade.

The second example illustrated in Scheme 9 constitutes a case in which the cycloaddition cascade is initiated by a transannular [4 + 2] cycloaddition reaction. Consistent with expectations, converting the initiating intramolecular [4 + 2] cycloaddition into a transannular Diels–Alder reaction substantially reduced the reaction temperature needed to initiate the reaction cascade where reaction was observed at temperatures as low as 80 °C (refluxing benzene). For the substrate **74a** bearing an unactivated cis olefin as the initiating dienophile, a single diastereomer of the cascade cycloaddition product was observed in which the cis C4/C5 stereochemistry is imbedded in the dienophile geometry and the remainder of the relative stereochemistry is

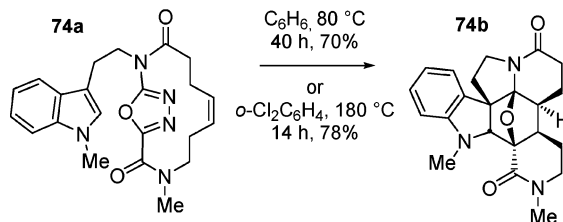
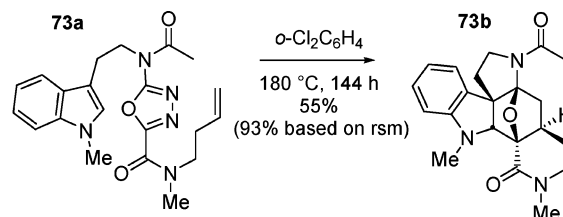
(16) The coordinates for the X-ray structure of **43b** (CCDC 297502) have been deposited with the Cambridge Crystallographic Data Centre.

Scheme 8



set in an endo indole [3 + 2] cycloaddition directed to the 1,3-dipole face opposite the newly formed fused lactams analogous to the reactions initiated by the intramolecular Diels–Alder reaction. Importantly, the ease of cycloaddition of **74a** illustrates

Scheme 9



a potentially powerful manner in which some of the more problematic cycloaddition cascades can be adapted to occur under mild conditions. These and related studies are the subject of our continuing investigations.

Conclusion

A systematic exploration of a tandem intramolecular [4 + 2]/[3 + 2] cycloaddition cascade of 1,3,4-oxadiazoles including a transannular variant was conducted in which the tethered initiating dienophile, the tethered dipolarophile, the 1,3,4-oxadiazole C2 and C5 substituents, the tether lengths and sites, and the central heterocycle were examined. Conducted largely with the concurrent development of a synthetic approach to vindoline⁶ and relative to the intermolecular reaction cascade,^{7–10} the studies extend the alkenes and oxadiazoles that participate in the reaction; permit the use of unsymmetrical dienophiles, dipolarophiles, and oxadiazoles; control the cycloaddition regioselectivity and diastereoselectivity; and define the scope and utility of the tandem Diels–Alder/1,3-dipolar cycloaddition reactions of such heterocyclic azadienes.

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Supporting Information Available: Full experimental details are provided. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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