Published in final edited form as:
J Am Chem Soc. 2011 August 10; 133(31): 12285–12292. doi:10.1021/ja204856a.

Inverse Electron Demand Diels–Alder Reactions of 1,2,3-Triazines: Pronounced Substituent Effects on Reactivity and Cycloaddition Scope

Erin D. Anderson and **Dale L. Boger***
Department of Chemistry and The Skaggs Institute for Chemical Biology, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, California 92037

Abstract

A systematic study of the inverse electron demand Diels–Alder reactions of 1,2,3-triazines is disclosed, including an examination of the impact of a C5 substituent. Such substituents were found to exhibit a remarkable impact on the cycloaddition reactivity of the 1,2,3-triazine without altering, and perhaps even enhancing, the intrinsic cycloaddition regioselectivity. The study revealed that not only may the reactivity be predictably modulated by a C5 substituent (R = CO_2Me > Ph > H), but that the impact is of a magnitude to convert 1,2,3-triazine (**1**) and its modest cycloaddition scope into a heterocyclic azadiene system with a reaction scope that portends extensive synthetic utility, expanding the range of participating dienophiles. Significantly, the studies define a now powerful additional heterocyclic azadiene, complementary to the isomeric 1,2,4-triazines and 1,3,5-triazines, capable of dependable participation in inverse electron demand Diels–Alder reactions, extending the number of complementary heterocyclic ring systems accessible with implementation of the methodology.

Introduction

We have used the inverse electron demand Diels–Alder reactions of electron-deficient heterocyclic azadienes as powerful cycloaddition reactions central to a series of natural products total syntheses whose structures possess highly functionalized heterocyclic ring systems not easily accessed by conventional means.[1] Such reactions have also found widespread use in the synthesis of highly substituted heterocycles not accessible by other means,[2] in the divergent synthesis of screening libraries,[3] and recently in bioconjugation reactions.[4] To date, our own studies have focused largely on the fundamental cycloaddition reactions of 1,2,4,5-tetrazines,[5] 1,2,4-triazines,[6] 1,3,5-triazines,[7] 1,3,4-oxadiazoles,[8] and occasionally 1,2-diazines,[9] often followed by subsequent key transformations that now constitute general synthetic strategies for the preparation of five-membered[10] as well as six-membered heterocyclic ring systems. In a continuation of our efforts to explore heterocyclic and acyclic[11] azadiene Diels–Alder reactions and their applications, we recently examined the inverse electron demand Diels–Alder reactions of the parent 1,2,3-triazine (**1**), disclosing the first report of its unique capabilities for participating in previously unexplored [4 + 2] cycloaddition reactions with heterodienophiles.[12] Several prior key studies have demonstrated the ability of a limited number of 1,2,3-triazines to participate in inverse electron demand Diels–Alder reactions, typically with enamine[13] and ynamine[14] dienophiles. These prior studies have been reported largely in the pioneering efforts of

boger@scripps.edu.

Supporting Information Available. Full experimental details and compound characterizations are provided. This material is available free of charge via the internet at http://pubs.acs.org.

Okatani (Sugita)[13] or Igeta and Ohsawa[14] often times suggesting modest utility, and have not yet defined the role substituents may play in modulating the reactivity or regioselectivity of the cycloaddition reactions. Herein, we report a systematic study of the cycloaddition reactions of 1,2,3-triazines, focusing on the impact of 1,2,3-triazine C5 substituents. Such substituents were found to not only exhibit a remarkable impact on the now useful range of relative cycloaddition reactivities that may be predictably modulated by the substituents expanding the resulting range of participating dienophiles, but the studies also highlight the complementary nature of the heterocyclic ring systems generated by use of 1,2,3-triazines (Figure 1).

Results and Discussion

Synthesis of 1,2,3-triazines

The key 1,2,3-triazines chosen to examine the inverse electron demand cycloaddition reactivity and regioselectivity impact of a C5 substituent were 5-phenyl-1,2,3-triazine (**2**) and 5-carbomethoxy-1,2,3-triazine (**3**), bearing a C5 phenyl and carbomethoxy group. This was complemented by the comparative examination of the parent 1,2,3-triazine **1** itself as well as 5-bromo-1,2,3-triazine (**4**) because of its availability as a result of the approaches examined for the preparation of **2** and **3**. Since the unsubstituted 1,2,3-triazine **1** reacts with cycloaddition exclusively across N1/C4 in the studies disclosed to date, the C5 substitution was anticipated to further enhance this intrinsic regioselectivity while improving its modest reactivity. 1,2,3-Triazines are most directly accessed by N-amination of a symmetrical pyrazole followed by oxidative ring expansion and this approach could be used to prepare each of the four 1,2,3-triazines. The synthesis of 1,2,3-triazine (**1**) and 5-bromo-1,2,3-triazine (**4**) began with amination of the commercially available pyrazole (**5**) and 4-bromopyrazole (**7**), respectively, using hydroxylamine-*O*-sulfonic acid (3 equiv, aqueous 3.7 M NaOH, 30 min) and was followed by subsequent oxidative ring expansion of the N-aminopyrazoles **6** and **8** effected by treatment with $NaIO_4$ (2 equiv, CH_2Cl_2–H_2O, 12 h) at 0 °C to provide the desired 1,2,3-triazine **1**[13–15] as detailed[13e] (25%, 2 steps) and **4**[16] (89%, 2 steps), Scheme 1. Notably, the $NaIO_4$ oxidative ring expansion introduced by Okatani[13] for the synthesis of 1,2,3-triazines provides **1** in better conversions than alternative methods[15] and proved much more effective for the preparation of **4** than earlier reported methods.[16] Compounds **1** and **4** were isolated as tan solids and are stable for extended periods if kept free of moisture and stored at or below 0 °C.

5-Phenyl-1,2,3-triazine (**2**) was also prepared from commercially available 4-bromopyrazole (**7**), Scheme 1. Trityl protection of **7** (85%), Suzuki coupling of **9** with phenylboronic acid (94%), trityl deprotection of **10** and N-amination of **11** with hydroxylamine-*O*-sulfonic acid (3 equiv, aq NaOH, 30 min) followed by subsequent oxidative ring expansion of **12** also effected by treatment with $NaIO_4$ (2 equiv, CH_2Cl_2–H_2O, 12 h) at 0 °C provided 5-phenyl-1,2,3-triazine[17] (**2**, 80–85%, 3 steps) as small off-white crystals that proved stable to storage at room temperature.

5-Carbomethoxy-1,2,3-triazine (**3**)[15a] was accessed by lithium–halogen exchange of N-trityl-4-bromopyrazole (**9**) and subsequent reaction of the 4-lithiopyrazole with methyl chloroformate to provide **13** (60%), Scheme 2. Trityl deprotection (HCl–MeOH, CH_2Cl_2, 70%) provided **14**, which provided low and inconsistent conversions to the N-aminopyrazole **15** when treated with hydroxylamine-*O*-sulfonic acid under the required aqueous basic conditions (aq NaOH), even following reesterification ($TMSCHN_2$) of the unavoidable in situ hydrolyzed methyl ester. In efforts to find a more reliable route to **3**, the use of monochloroamine was examined, which has been reported for the N-amination of pyrroles and indoles.[18] Deprotonation of **14** with NaH (DMF) followed by addition of monochloroamine ($ClNH_2$ in ether, 30 min, 23 °C) provided the N-aminopyrazole **15** in

superb conversions (88–93%) that was oxidized with $NaIO_4$ (2 equiv, CH_2Cl_2–H_2O, 2 h) at room temperature to provide **3** (81%). Although this synthesis was used to prepare most of **3** employed in our studies, we have more recently found that the N-amination of **14** to provide **15** may be accomplished even more conveniently with *O*-(4-nitrobenzoyl)hydroxylamine[19] (1.1 equiv of $KOBu^t$, NMP, 20 min, 22 °C; 1.15 equiv of *O*-(4-nitrobenzoyl)hydroxylamine, NMP, 22 °C, 2 h, 75%). 5-Carbomethoxy-1,2,3-triazine proved to be especially reactive and was found to be sensitive to water. Consequently, **3** was handled typically in flame-dried glassware under an Ar atmosphere and flash chromatography was performed using oven-dried SiO_2. Although not extensively investigated, alternative routes to **3**, including Pd-catalyzed carbonylation in the presence of MeOH or lithium–halogen exchange of **4** followed by reaction with methyl chloroformate, proved unsuccessful likely due to the competitive reactions of **3** and/or **4** under the reaction conditions. In addition to their instability toward water, all four 1,2,3-triazines are unstable to protic solvents including MeOH with **3** and **4** reacting quickly even at −40 °C. 5-Bromo-1,2,3-triazine (**4**) was found to violently decompose at 112 °C while attempting to measure its melting point, whereas the 1,2,3-triazines **1**–**3** were all found to be stable at temperatures < 140 °C, the limit of our examination, as well as during our melting point determinations.

Cycloaddition reactions with ynamines

Consistent with prior reports, the Diels–Alder reaction of the unsubstituted 1,2,3-triazine (**1**) with ynamines[14] proceeded well, but required warming the reaction mixtures at 60 °C ($CHCl_3$, 3–12 h) for complete reaction indicative of a modest reactivity. The reactions proceeded with clean regioselectivity with cycloaddition across N1/C4 of the 1,2,3-triazine (Figure 2). The C5 substituted 1,2,3-triazines **2** and **3**, bearing a conjugated phenyl substituent and a more strongly electron-withdrawing methoxycarbonyl substituent, respectively, exhibited a progressively enhanced reactivity (R = CO_2Me > Ph > H) and the same characteristic exclusive N1/C4 cycloaddition regioselectivity, benefiting from the complementary azadiene substitution. Remarkably, the modest reactivity of the parent 1,2,3-triazine (**1**, 60 °C, 3–12 h) is transformed into a reaction that proceeds in minutes at room temperature, providing improved conversions to the corresponding pyridines, with the introduction of the C5 methoxycarbonyl group (**3**, 5–15 min, 72–83%). Although the comparisons based on the reaction with ynamines are limited, the results also suggest that 4-bromo-1,2,3-triazine (**4**) exhibits a reactivity intermediate that of **2** and **3** (R = CO_2Me > Br > Ph > H).

Cycloaddition reactions with additional acetylenic dienophiles

Representative of potential cycloaddition reactions with less electron-rich or even conjugated acetylenic dienophiles, the reactions of the 1,2,3-triazines with ethoxyacetylene (**25**) and phenylacetylene (**26**) were examined. Whereas both 1,2,3-triazine (**1**) and 5-phenyl-1,2,3-triazine (**2**) failed to exhibit a detectable reactivity toward either ethoxyacetylene or phenylacetylene in dioxane at 100 °C, the more electron-deficient 5-methoxycarbonyl-1,2,3-triazine (**3**) displayed a measurable reactivity, Figure 3. This was optimized by conducting the reactions at higher temperatures (xylenes, 140 °C), requiring a shorter reaction time for completion (< 24 h), and provided the Diels–Alder products **27** (62%) and **28** (59%), respectively, in good conversions and as single regioisomers. 1,2,3-Triazines **1** and **2** were examined at even higher reaction temperatures (200 °C) under concentrated conditions and failed to provide evidence of cycloaddition. Clearly and especially because of the regiospecific reaction with phenylacetylene that one would not ordinarily expect with an electron-deficient heterocyclic azadiene, the scope of cycloadditions of **3** with acetylenic dienophiles is broad and portends extensive usage.

Cycloaddition reactions with enamines

Consistent with Okatani's prior reports[13] and as detailed in our recent study,[12] we found that the reaction of the parent 1,2,3-triazine **1** with enamines ($CHCl_3$, 60 °C) proved more limited than the analogous reactions of 1,2,4- or 1,3,5-triazines,[6,7] providing modest yields of the expected pyridine products and a disappointing scope, Figure 4. In contrast, the C5 substituted 1,2,3-triazines **2** and **3**, bearing a conjugated phenyl substituent and a more strongly electron-withdrawing methoxycarbonyl substituent, respectively, exhibited a progressively enhanced reactivity (R = CO_2Me > Ph > H), providing good yields of the corresponding pyridine products and a generalized scope accommodating enamines typically problematic (**29b**). Products derived from liberated pyrrolidine addition to the starting 1,2,3-triazine were detected with **1** (in the reaction with both **29a** and **29b**) and occasionally with **2** (in the reaction with **29b**) that reflect a slow [4 + 2] cycloaddition reaction relative to aromatization and that may account in part for their more modest conversions. By contrast, no evidence of liberated pyrrolidine addition was observed with **3** or **4**, presumably reflecting their more rapid [4 + 2] cycloaddition that leads to complete consumption of the 1,2,3-triazine prior to liberation of any pyrrolidine. Consistent with this behavior, the reaction of 1,2,3-triazines **3** and **4** with enamines leads to an instantaneous color change and evolution of N_2 even at −20 °C, but provides poor conversions to product at these low temperatures (**3** + **29b**: 22 °C, 2 h, 0%; 22 °C for 1 min and 45 °C, 30 min, 54%; 22 °C for 1 min and 60 °C, 12 h, 90%). Because of this, the inclusion of 4 Å molecular sieves (4 Å MS) in the reaction mixture first utilized with 1,2,4-triazines[6] was found to aid the aromatization step and improve the overall conversions, especially with the dienophile **29b**. Using this modification, the reactions summarized in Figure 4 were initiated at 22 °C (for **3**) and 0 °C (for **4**) and only after the exothermic evolution of N_2 was complete were the reaction mixtures warmed to promote aromatization and completion of the reaction. In each case, the 1,2,3-triazines exhibited the now characteristic exclusive N1/C4 cycloaddition regioselectivity with the nucleophilic carbon of the electron-rich dienophile attached to C4, benefiting from the additional complementary azadiene substitution in the case of **2**–**4**. Importantly, the reactivity of **2**–**4** imparted by the C5 substituents provide substantially improved cycloaddition reactions with enamine dienophiles realizing a synthetic scope and efficiency first envisioned by Okatani.[13]

Diels–Alder reactions with additional electron-rich olefinic dienophiles

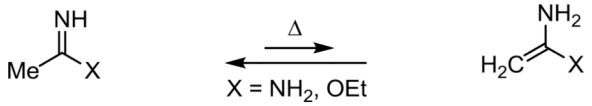
In our recent survey of the cycloaddition reactions of the parent 1,2,3-triazine (**1**),[12] a key series of additional potential electron-rich dienophiles were examined, including ketene acetals ($(EtO)_2C{=}CH_2$), and enol ethers ($Ph(OMe)C{=}CH_2$ and $Ph(OTMS)C{=}CH_2$), that failed to react with **1** under the conditions examined. As a result, the reactivity of **2**–**4** with such dienophiles was of special interest potentially expanding the synthetic scope of the 1,2,3-triazine cycloaddition reactions, Figure 5.

Consistent with the relative reactivity of the dienophiles and the anticipated impact of the 1,2,3-triazine C5 substituents examined (R = CO_2Me > Ph > H), 5-carbomethoxy-1.2.3-triazine (**3**) was found to react with both the ketene acetal **38** and the enol ether dienophiles **39** and **40** under conditions that reflect the relative reactivities of the electron-rich olefins (ketene acetals > enol ethers), whereas 5-phenyl-1,2,3-triazine (**2**) was found to only react with the ketene acetal **38** and not with the less reactive enol ethers **39** and **40** under the conditions examined. Thus, the reaction of **2** with the ketene acetal **38** proceeds slowly in dioxane at 100 °C (24 h, 88%; 98% based on recovered starting material) and proceeds to completion when run in xylenes at 140 °C (24 h, 94%), whereas the reaction of **3** with **38** is complete in dioxane at 60 °C within 30 min. In fact, the initial Diels–Alder reaction of **3** with **38** (5 equiv) occurs at temperatures as low as −10 °C where N_2 evolution and a distinct color change is observed, but initially provided only low conversions to the expected

pyridine product **27** (18%). Instead, the lactam **43**,[20] the product of a subsequent nucleophilic addition of the ketene acetal **38** to the intermediate cycloaddition product prior to aromatization, was isolated as the major product (80%), Scheme 3. Beautifully, reducing the amount of dienophile (1.0 equiv) and the addition of Hunig's base (*i*-Pr_2NEt, 0.8 equiv) to the reaction mixture combined with its heating (60 °C, dioxane) led to rapid aromatization to provide **27** in superb yield (99%) with complete suppression of the formation of lactam **43**. Significantly, this series of dienophiles clearly differentiates the reactivity of the three 1,2,3-triazines **1**–**3**, indicating that the incorporation of an appropriate C5 substituent can convert substrates incapable of reaction with **1** even at temperatures of 200 °C, to those that exhibit remarkably effective cycloaddition rates without altering the intrinsic cycloaddition regioselectivity. This is especially evident with 1,2,3-triazine **3** that initially reacts with the ketene acetal **38** (1,1-diethoxyethylene) at temperatures as low as −10 °C.

Cycloaddition reactions with heterodienophiles

Especially interesting was the reactivity of the 1,2,3-triazines toward heterodienophiles. Amidines, imidates and related reagents have been found to react with many heteroaromatic dienes by a reaction course that is dependent on the nature of the reactants and reaction conditions. Such reagents have been shown to react as either C=N or isomeric N,N- or N,O-ketene acetal dienophiles depending on the heterocyclic azadiene and reaction conditions examined (equation 1), and typically are characterized as cleanly proceeding through a single pathway.



(1)

Given the modest reactivity of **1** and like the behavior of 1,3,5-triazines,[7d] one might have anticipated that **1**–**4** would be a superb candidates for reaction with such reagents through their more reactive, in situ generated N,N- or N,O-ketene acetals. Remarkably and like 1,2,4,5-tetrazines,[5a] the aliphatic acetamidine (**44a**) and ethoxy acetimidate (**44b**) both underwent clean, rapid [4 + 2] cycloaddition with **1**–**4** as C=N dienophiles to provide the corresponding pyrimidines **45**–**48** in superb conversions with no evidence of reaction through their in situ generated and more reactive 1,1-diaminoethylene or 1-amino-1-ethoxyethylene tautomers, Figure 6. The reaction of even **1**, the least reactive of the 1,2,3-triazines, with the aliphatic amidine **44a** (CH_3CN, 25 °C, 5 min, 93%) was extraordinarily fast, proceeding in minutes at room temperature, whereas the reaction with the less reactive aliphatic imidate **44b** required higher temperatures and longer times for reaction with **1** (CH_3CN, 60 °C, 24 h, 64%, 99% based on recovered starting material). Even here, only the product derived from a regiospecific cycloaddition of the C=N dienophile across C4/N1 was detected independent of the reaction conditions examined (temperature, solvent polarity, free base vs HCl salt). Although complete conversion to the pyrimidine product required higher reaction temperatures, most remarkable of the initial observations was that even **1** reacts with the aliphatic amidine **44a** at −30 °C in minutes with an instantaneous evolution of N_2 and distinct color change indicative of a remarkably facile [4 + 2] cycloaddition. Similarly, the aryl amidines **44c** and **44e** provided the corresponding pyrimidines **49**–**56** in good to superb conversions in reactions where the disappearance of **1**–**4** precedes completion of the reaction, indicating that aromatization with loss of ammonia versus [4 + 2] cycloaddition is the slow step in the overall reaction sequence.

The reactions were completely regioselective with regard to both the amidine/imidate, providing only pyrimidine product with no trace of the corresponding pyridazine (1,2-diazine), as well as the 1,2,3-triazine, providing no trace of 1,2,4-triazine product consistent with cycloaddition only across C4/N1 versus C5/N2. In all cases and in contrast to our observations made with 1,3,5-triazines,[7] it was important to use the amidine or imidate free base rather than their HCl salts, which provided less reproducible and substantially lower yields. Perhaps the clearest depiction of the relative rates of reaction among the 1,2,3-triazines toward the C=N dienophiles emerged from the examination of the aliphatic and aryl imidates **44b** and **44d** (R = CO_2Me > Ph > H), the more electron-rich amidines were expectedly and considerably much more reactive than the corresponding imidates (**44a** vs **44b**, and **44c** vs **44d**), and the aliphatic amidine or imidate were more reactive than the corresponding conjugated aryl amidine or imidate (**44a** vs **44c** and **44b** vs **44d**). The reactions of the amidines with the more electron-deficient 1,2,3-triazines **3** and **4** are highly exothermic and are accompanied by the rapid N_2 evolution upon mixing. Often times, these reactions benefited from their mixing at low temperature to contain the exotherm followed by exposure to higher reaction temperatures to effect the slower aromatization (e,g., **4** + **44c**). Additionally, the most effective substrate examined was the 2-pyridylamidine **44e** (98–99% for **1**–**4**) in which the 2-pyridyl substituent presumably participates in the final, typically slow, aromatization step via an internal deprotonation to facilitate the elimination of ammonia.

Since the cycloaddition reaction of 1,2,3-triazine (**1**) itself with amidines had not been examined or reported prior to our studies,[12] its generality was further established with the amidines **44f**–**44m**, providing the corresponding pyrimidines **57**–**64** in superb conversions (90–99%), Figure 7. Given that **1** is the least reactive of the four 1,2,3-triazines examined, its broad scope portends extensive usage across the entire series.

Computational studies

Semiempirical computational studies (MNDO, AM1) of the parent ring systems as well as the substituted 1,2,3-triazines were carried out in efforts to shed insight into the relative behavior of the heterocyclic azadienes, Figure 8. Consistent with intuitive expectations, a comparison of the computed heats of formation (H_f) indicate that 1,2,3-triazine with three vicinal nitrogen atoms and their adjacent repulsive lone pairs is predicted to be more unstable (more reactive) than 1,2,4-triazine with two vicinal nitrogens that in turn is more unstable than 1,3,5-triazine. Potentially predictive of the relative reactivity in LUMO-controlled cycloaddition reactions, the computed LUMO energies followed this same trend. It was not possible to find a single class of dienophiles that have been reported to participate in Diels–Alder reactions with each of the isomeric parent triazines, rendering a direct experimental comparison difficult. The closest comparison that could be made was in their reactions with enamines, where both 1,2,4-triazine[6] and 1,3,5-triazine[7] perform much better and more dependably than 1,2,3-triazine. However, here it is not clear whether this is due to their intrinsic reactivity or whether the ensuing slow aromatization step complicates the comparison. What is clear from the computational studies is that 1,2,3-triazine would be expected to participate in effective inverse electron demand Diels–Alder reactions. This was observed most effectively with the C5 substituted 1,2,3-triazines **2** and **3** bearing the conjugating phenyl group and electron-withdrawing methoxycarbonyl group, respectively. Here, the computational studies accurately predict the relative reactivity of the 1,2,3-triazines examined (R = CO_2Me > Ph = Br > H), and define substantial differences in the LUMO energies that are of a magnitude that reflect the experimental observations.

Interestingly and whereas the LUMO coefficients accurately predict the cycloaddition regioselectivity of both 1,2,4-triazine and 1,3,5-triazine, they predict cycloaddition across C5/N2 (vs C4/N1) for 1,2,3-triazine. Additionally, all computational measures of electron

density (net atomic charge, Mulliken charge, electrostatic potential charge) indicate C4 is more electron deficient than C5, suggesting it would be the preferential site of nucleophilic attack consistent with qualitative predictions based on preferential subsequent charge delocalization onto nitrogen(s) following addition. As a result, the simple computational studies would suggest that the cycloaddition regioslectivity observed with 1,2,3-triazines is more consistent with stepwise addition-cyclization reactions than concerted cycloaddition reactions. To date, however, we have not isolated reaction byproducts to support this possibility.

Conclusions

Herein, a systematic study of the inverse electron demand Diels–Alder reactions of 1,2,3-triazines is disclosed, including an examination of the impact of 1,2,3-triazine C5 substituents. Such substituents were found to exhibit a remarkable impact on the relative cycloaddition reactivity of the 1,2,3-triazine without altering, and perhaps even enhancing, the intrinsic cycloaddition regioselectivity. The study revealed that not only may the reactivity be predictably modulated by the C5 substituent (R = CO_2Me > Ph > H), but that the impact is sufficient to convert 1,2,3-triazine (**1**) itself and its modest cycloaddition scope into a heterocyclic azadiene system with a reaction scope that portends extensive synthetic utility, substantially expanding the range of participating dienophiles. Significantly, the studies provide a now powerful additional heterocyclic azadiene, complementary to the isomeric 1,2,4- and 1,3,5-triazines, capable of predicable and useful participation in inverse electron demand Diels–Alder reactions, extending the range of complementary heterocyclic ring systems accessible with implementation of the methodology. Such applications in the total synthesis of natural products, complementing our past efforts,[21–24] are in progress and will be reported in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We gratefully acknowledge the financial support of the National Institutes of Health (CA042056) and the Skaggs Institute for Chemical Biology. E.D.A. is a Skaggs Fellow and recipient of a Novartis Graduate fellowship (2010–2011).

References and Notes

1. (a) Boger DL. Tetrahedron. 1983; 39:2869.(b) Boger DL. Chem. Rev. 1986; 86:781.(c) Boger, DL.; Weinreb, SM. Hetero Diels–Alder Methodology in Organic Synthesis. San Diego: Academic; 1987. (d) Boger DL. Chemtracts: Org. Chem. 1996; 9:149.
2. (a) Carboni RA, Lindsey RV. J. Am. Chem. Soc. 1959; 81:4342. For recent examples, see: (b) Raw SA, Taylor RJK. J. Am. Chem. Soc. 2004; 126:12260. [PubMed: 15453747] (c) Benson SC, Lee L, Yang L, Snyder JK. Tetrahedron. 2000; 56:1165. (d) Girardot M, Nomak R, Snyder JK. J. Org. Chem. 1998; 63:10063. (e) Klindert T, Stroetmann I, Seitz G, Hofner G, Wanner KT, Frenzen G, Eckhoff B. Arch. Pharm. 1997; 330:163.
3. (a) Panek JS, Zhu B. Tetrahedron Lett. 1996; 37:8151.(b) Moisan L, Odermatt S, Gombosuren N, Carella A, Rebek J Jr. Eur. J. Org. Chem. 2008:1673.(c) Volonterio A, Moisan L, Rebek J Jr. Org. Lett. 2007; 9:3733. [PubMed: 17711290] (d) Biros SM, Moisan L, Mann E, Carella A, Zhai D, Reed J, Rebek J Jr. Bioorg. Med. Chem. Lett. 2007; 17:4641. [PubMed: 17555961] (e) Lahue BR, Lo S-M, Wan Z-K, Woo GHC, Snyder JK. J. Org. Chem. 2004; 69:7171. [PubMed: 15471466]
4. (a) Blackman ML, Royzen M, Fox JM. J. Am. Chem. Soc. 2008; 130:13518. [PubMed: 18798613] (b) Han H, Devaraj NK, Lee J, Hilderbrand SA, Weissleder R, Bawendi MG. J. Am. Chem. Soc.

2010; 132:7838. [PubMed: 20481508] (c) Zibo L, Cai H, Hassink M, Blackman ML, Brown RCD, Conti PS, Fox JM. Chem. Commun. 2010; 46:8043.(d) Devaraj NK, Upadhyay R, Haun JB, Hilderbrand SA, Weissleder R. Angew. Chem., Int. Ed. 2009; 48:7013.(e) Devaraj NK, Weissleder, Hilderbrand SA. Bioconjugate Chem. 2008; 19:2297.(f) Schoch J, Weissler M, Jäschke A. J. Am. Chem. Soc. 2010; 132:8846. [PubMed: 20550120] (g) Pipkorn R, Waldemar W, Didinger B, Koch M, Mueller G, Wiessler M, Braun K. J. Pept. Sci. 2009; 15:235. [PubMed: 19177421] (h) Rossin R, Verkerk PR, van den Bosch SM, Vulders RCM, Verel I, Lub J, Robillard MS. Angew. Chem., Int. Ed. 2010; 49:3375.(i) Haun JB, Devaraj NK, Hilderbrand SA, Lee H, Weissleder R. Nat. Nanotech. 2010; 5:660.

5. (a) Boger DL, Panek JS. Tetrahedron Lett. 1983; 24:4511.(b) Boger DL, Panek JS, Coleman RS, Sauer J, Huber FX. J. Org. Chem. 1985; 50:5377.(c) Boger DL, Sakya SM. J. Org. Chem. 1988; 53:1415.(d) Boger DL, Panek JS, Patel M. Org. Synth. 1992; 70:79.(e) Sakya SM, Groskopf KK, Boger DL. Tetrahedron Lett. 1997; 38:3805.(f) Boger DL, Schaum RP, Garbaccio RM. J. Org. Chem. 1998; 63:6329. [PubMed: 11672266] (g) Soenen DR, Zimpleman JM, Boger DL. J. Org. Chem. 2003; 68:3593. [PubMed: 12713365] (h) Hamasaki A, Ducray R, Boger DL. J. Org. Chem. 2006; 71:185. [PubMed: 16388634]
6. (a) Boger DL, Panek JS. J. Org. Chem. 1981; 46:2179.(b) Boger DL, Panek JS, Meier MM. J. Org. Chem. 1982; 47:895.(c) Boger DL, Panek JS. J. Org. Chem. 1982; 47:3763.(d) Boger DL, Panek JS. Tetrahedron Lett. 1984; 25:3175.(e) Boger DL, Panek JS, Yasuda M. Org. Synth. 1987; 66:142.
7. (a) Boger DL, Schumacher J, Panek JS, Mullican MD, Patel M. J. Org. Chem. 1982; 47:2673.(b) Boger DL, Dang Q. Tetrahedron. 1988; 44:3379.(c) Boger DL, Dang Q. J. Org. Chem. 1992; 57:1631.(d) Boger DL, Kochanny MJ. J. Org. Chem. 1994; 59:4950.
8. (a) Wilkie GD, Elliott GI, Blagg BSJ, Wolkenberg SE, Soenen DR, Miller MM, Pollack S, Boger DL. J. Am. Chem. Soc. 2002; 124:11292. [PubMed: 12236743] (b) Elliott GI, Fuchs JR, Blagg BSJ, Ishikawa H, Tao H, Yuan Z-Q, Boger DL. J. Am. Chem. Soc. 2006; 128:10589. [PubMed: 16895427]
9. (a) Kessler SN, Wegner HA. Org. Lett. 2010; 12:4062. [PubMed: 20718452] (b) Boger DL, Coleman RS. J. Org. Chem. 1984; 49:2240.
10. Review: (a) Joshi U, Pipelier M, Naud S, Dubreuil D. Curr. Org. Chem. 2005; 9:261. Applications: (b) Bach NJ, Kornfeld EC, Jones ND, Chaney MO, Dorman DE, Paschal JW, Clemens JA, Smalstig EB. J. Med. Chem. 1980; 23:481. [PubMed: 7189782] (c) Boger DL, Coleman RS, Panek JS, Yohannes D. J. Org. Chem. 1984; 49:4405. (d) Boger DL, Baldino CM. J. Org. Chem. 1991; 56:6942. (e) Yeung BKS, Boger DL. J. Org. Chem. 2003; 68:5249. [PubMed: 12816485] (f) Daly K, Nomak R, Snyder JK. Tetrahedron Lett. 1997; 38:8611. (g) Joshi U, Josse S, Pipeleir M, Chevallier F, Pradere JP, Hazard R, Legoupy S, Huet F, Dubreuil D. Tetrahedron Lett. 2004; 45:1031. (h) Muller J, Troschutz R. Synthesis. 2006:1513. (i) Naud S, Pipelier M, Chaumette C, Viault G, Adjou A, Huet F, Legoupy S, Aubertin AM, Evain M, Dubreuil D. Eur. J. Org. Chem. 2007:3296. (j) Moisan L, Odermatt S, Gombosuren N, Carella A, Rebek J Jr. Eur. J. Org. Chem. 2008:1673. (k) Bakkali H, Marie C, Ly A, Thobie-Gautier C, Graton J, Pipelier M, Sengmany S, Leonel E, Medelec JV, Evain M, Dubreuil D. Eur. J. Org. Chem. 2008:2156.
11. (a) Boger DL, Kasper AM. J. Am. Chem. Soc. 1989; 111:1517.(b) Boger DL, Corbett WL, Wiggins JM. J. Org. Chem. 1990; 55:2999.(c) Boger DL, Curran TT. J. Org. Chem. 1990; 55:5439.(d) Boger DL, Corbett WL, Curran TT, Kasper AM. J. Am. Chem. Soc. 1991; 113:1713. (e) Boger DL, Nakahara S. J. Org. Chem. 1991; 56:880.(f) Boger DL, Zhang M. J. Org. Chem. 1992; 57:3974.(g) Boger DL, Corbett WL. J. Org. Chem. 1992; 57:4777.(h) Boger DL, Corbett WL. J. Org. Chem. 1993; 58:2068.(i) Clark RC, Pfeiffer SS, Boger DL. J. Am. Chem. Soc. 2006; 128:2587. [PubMed: 16492042]
12. Anderson ED, Boger DL. Org. Lett. 2011; 13:2492. [PubMed: 21488676]
13. (a) Sugita T, Koyama J, Tagahara K, Suzuta Y. Heterocycles. 1985; 23:2789. (b) Sugita T, Koyama J, Tagahara K, Suzuta Y. Heterocycles. 1986; 24:29. (c) Okatani T, Koyama J, Tagahara K, Suzuta Y. Heterocycles. 1987; 26:595. (d) Okatani T, Koyama J, Suzuta Y, Tagahara K. Heterocycles. 1988; 27:2213. (e) Okatani T, Koyama J, Tagahara K. Heterocycles. 1989; 29:1809. Lewis acid catalysis: (f) Koyama J, Ogura T, Tagahara K. Heterocycles. 1994; 38:1595. Microwave heating: (g) Diaz-Oritz A, de la Hoz A, Prieto P, Carrillo JR, Moreno A, Neunhoeffer H. Synlett. 2001; 2:236.

14. (a) Itoh T, Ohsawa A, Okada M, Kaihoh T, Igeta H. Chem. Pharm. Bull. 1985; 33:3050.(b) Itoh T, Okada M, Nagata K, Yamaguchi K, Ohsawa A. Chem. Pharm. Bull. 1990; 38:2108.

15. (a) Neunhoeffer H, Bopp R, Diehl W. Liebigs Ann. Chem. 1993:367.(b) Neunhoeffer H, Clausen M, Voetter H, Ohl H, Krueger C, Angermund K. Liebigs Ann. Chem. 1985:1732.(c) Ohsawa A, Heihachiro A, Itoh T, Kaihoh T, Okada M, Igeta H. J. Org. Chem. 1985; 50:5520.(d) Ohsawa A, Heihachiro A, Ohnishi H, Igeta H. J. Chem. Soc., Chem. Commun. 1981:1174.(e) Ohsawa A, Heihachiro A, Ohnishi H, Igeta H. J. Chem. Soc., Chem. Commun. 1980:1182.

16. Ohsawa A, Kaihoh T, Itoh T, Okada M, Kawabata C, Yamaguchi Y, Igeta H. Chem. Pharm. Bull. 1988; 36:3838.

17. (a) Itoh T, Nagata K, Kaihoh T, Okada M, Kawabata C, Arai H, Ohnishi H, Yamaguchi K, Igeta H, Ohsawa A, Iitaka Y. Heterocycles. 1992; 33:631.(b) Mättner M, Neunhoeffer H. Synthesis. 2003:413.

18. Hynes J, Doubleday WW, Dyckman AJ, Godfrey JD, Grosso JA, Kiau S, Leftheris K. J. Org. Chem. 2004; 69:1368. [PubMed: 14961694]

19. Parlanti L, Discordia RP, Hynes J Jr, Miller MM, O'Grady HR, Shi Z. Org. Lett. 2007; 9:3821. [PubMed: 17718497]

20. For **43**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.19 (s, 1H), 7.34 (s, 1H), 4.20 (q, *J* = 7.0 Hz, 2H), 3.73 (s, 3H), 3.36 (m, 1H), 2.71 (m, 1H), 2.63 (m, 1H), 2.50 (m, 1H), 2.40 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.6, 171.0, 166.6, 136.1, 110.6, 61.1, 52.1, 37.5, 35.5, 28.5, 14.6; IR ν_{max} 3276, 2952, 1693, 1645, 1440, 1367, 1303, 1254, 1195, 1099, 1032, 914, 765, 639 cm^{-1}; ESI-TOF HRMS *m/z* 242.1027 ($[M + H]^+$, $C_{11}H_{15}NO_5 + H^+$ requires 242.1023). Its immediate intermediate N,O,O-orthoester that hydrolyzes upon SiO_2 chromatography was also characterized: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.67 (s, 1H), 4.33 (q, *J* = 7.2 Hz, 2H), 4.14 (q, *J* = 6.8 Hz, 2H), 3.77 (s, 3H), 3.25 (m, 1H), 2.58–2.20 (m, 4H), 1.35 (t, *J* = 7.2 Hz, 3H), 1.27 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.8, 170.3, 167.5, 146.3, 116.2, 63.4, 61.0, 51.9, 36.2, 30.5, 27.5, 14.6, 14.5.

20. Streptonigrin: (a) Boger DL, Panek JS. J. Am. Chem. Soc. 1985; 107:5745. (b) Boger DL, Panek JS. J. Org. Chem. 1983; 48:621. Lavendamycin: (c) Boger DL, Panek JS, Duff SR, Yasuda M. J. Org. Chem. 1985; 50:5790. (d) Boger DL, Duff SR, Panek JS, Yasuda M. J. Org. Chem. 1985; 50:5782. PDE I and II: (e) Boger DL, Coleman RS. J. Am. Chem. Soc. 1987; 109:2717. (f) Boger DL, Coleman RS. J. Org. Chem. 1986; 51:3250. CC-1065: (g) Boger DL, Coleman RS. J. Am. Chem. Soc. 1987; 110:1321. (h) Boger DL, Coleman RS. J. Am. Chem. Soc. 1987; 110:4796. Trikentrin A: (i) Boger DL, Zhang M. J. Am. Chem. Soc. 1991; 113:4230. Pyrimidoblamic acid: Boger DL, Menezes RF, Honda T. Angew. Chem., Int. Ed. Engl. 1993; 32:273. P-3A: (k) Boger DL, Honda T, Menezes RF, Colletti SL, Dang Q, Yang W. J. Am. Chem. Soc. 1994; 116:82. Bleomycin A2: (l) Boger DL, Honda T. J. Am. Chem. Soc. 1994; 116:5647. (m) Boger DL, Colletti SL, Honda T, Menezes RF. J. Am. Chem. Soc. 1994; 116:5607. (n) Boger DL, Honda T, Dang Q. J. Am. Chem. Soc. 1994; 116:5619. (o) Boger DL, Honda T, Menezes RF, Colletti SL. J. Am. Chem. Soc. 1994; 116:5631. Phomazarin: (p) Boger DL, Hong J, Hikota M, Ishida M. J. Am. Chem. Soc. 1999; 121:2471. Anhydrolycorinone: (q) Boger DL, Wolkenberg SE. J. Org. Chem. 2000; 65:9120. [PubMed: 11149859] (r) Boger DL, Wolkenberg SE. J. Org. Chem. 2002; 67:7361. [PubMed: 12375965] Minovine: (s) Yuan Q, Ishikawa H, Boger DL. Org. Lett. 2005; 7:741. [PubMed: 15704939] Vindorosine: (t) Elliott GI, Velcicky J, Ishikawa H, Li Y, Boger DL. Angew. Chem., Int. Ed. 2006; 45:620. Vindoline: (u) Choi Y, Ishikawa H, Velcicky J, Elliott GI, Miller MM, Boger DL. Org. Lett. 2005; 7:4539. [PubMed: 16178578] (v) Ishikawa H, Elliott GI, Velcicky J, Choi Y, Boger DL. J. Am. Chem. Soc. 2006; 128:10596. [PubMed: 16895428] Vinblastine and vincristine: (w) Ishikawa H, Colby DA, Seto S, Va P, Tam A, Kakei H, Rayl TJ, Hwang I, Boger DL. J. Am. Chem. Soc. 2009; 131:4904. [PubMed: 19292450] (x) Ishikawa H, Colby DA, Boger DL. J. Am. Chem. Soc. 2008; 130:420. [PubMed: 18081297] Fendleridine and N-acetylaspidoalbidine: (y) Campbell EL, Zuhl AM, Liu CM, Boger DL. J. Am. Chem. Soc. 2010; 132:3009. [PubMed: 20148585] Vindoline and vindorosine: (z) Kato D, Sasaki Y, Boger DL. J. Am. Chem. Soc. 2010; 132:3685. [PubMed: 20187641] (aa) Sasaki Y, Kato D, Boger DL. J. Am. Chem. Soc. 2010; 132:13533. [PubMed: 20809620]

21. Prodigiosin: (a) Boger DL, Patel M. Tetrahedron Lett. 1987; 28:2499. (b) Boger DL, Patel M. J. Org. Chem. 1988; 53:1405. Isochrysohermidin: (c) Boger DL, Baldino CM. J. Am. Chem. Soc. 1993; 115:11418. Ningalin A, lamellarin O, lukianol A, and storniamide A: (d) Boger DL, Boyce

CW, Labroli MA, Sehon CA, Jin Q. J. Am. Chem. Soc. 1999; 121:54. Ningalin B: (e) Boger DL, Soenen DR, Boyce CW, Hedrick MP, Jin Q. J. Org. Chem. 2000; 65:2479. [PubMed: 10789460] Roseophilin: (f) Boger DL, Hong J. J. Am. Chem. Soc. 2001; 123:8515. [PubMed: 11525659] Ningalin D: (g) Hamasaki A, Zimpleman JM, Hwang I, Boger DL. J. Am. Chem. Soc. 2005; 127:10767. [PubMed: 16045367] Lycogarubin C and lycogalic acid: (h) Oakdale JS, Boger DL. Org. Lett. 2010; 12:1132. [PubMed: 20148525]

22. Streptonigrone: (a) Boger DL, Cassidy KC, Nakahara S. J. Am. Chem. Soc. 1993; 115:10733. Fredericamycin: (b) Boger DL, Hüter O, Mbiya K, Zhang M. J. Am. Chem. Soc. 1995; 117:11839. Nothapodytine B and mappicine: (c) Boger DL, Hong J. J. Am. Chem. Soc. 1998; 120:1218. Rubrolone: (d) Boger DL, Ichikawa S, Jiang H. J. Am. Chem. Soc. 2000; 122 Camptothecin: (e) Blagg BSJ, Boger DL. Tetrahedron. 2002; 58:6343. Piericidins: (f) Schnermann MJ, Boger DL. J. Am. Chem. Soc. 2005; 127:15704. [PubMed: 16277503] (g) Schnermann MJ, Romero FA, Hwang I, Nakamaru-Ogiso E, Yagi T, Boger DL. J. Am. Chem. Soc. 2006; 128:11799. [PubMed: 16953619]

Abbreviations

DME	1,2-dimethoxyethane
DMF	N,N-dimethylformamide
Py	pyridine
TMS	trimethylsilyl
Trt	trityl or triphenylmethyl

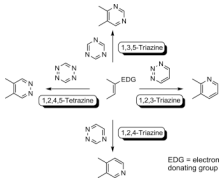
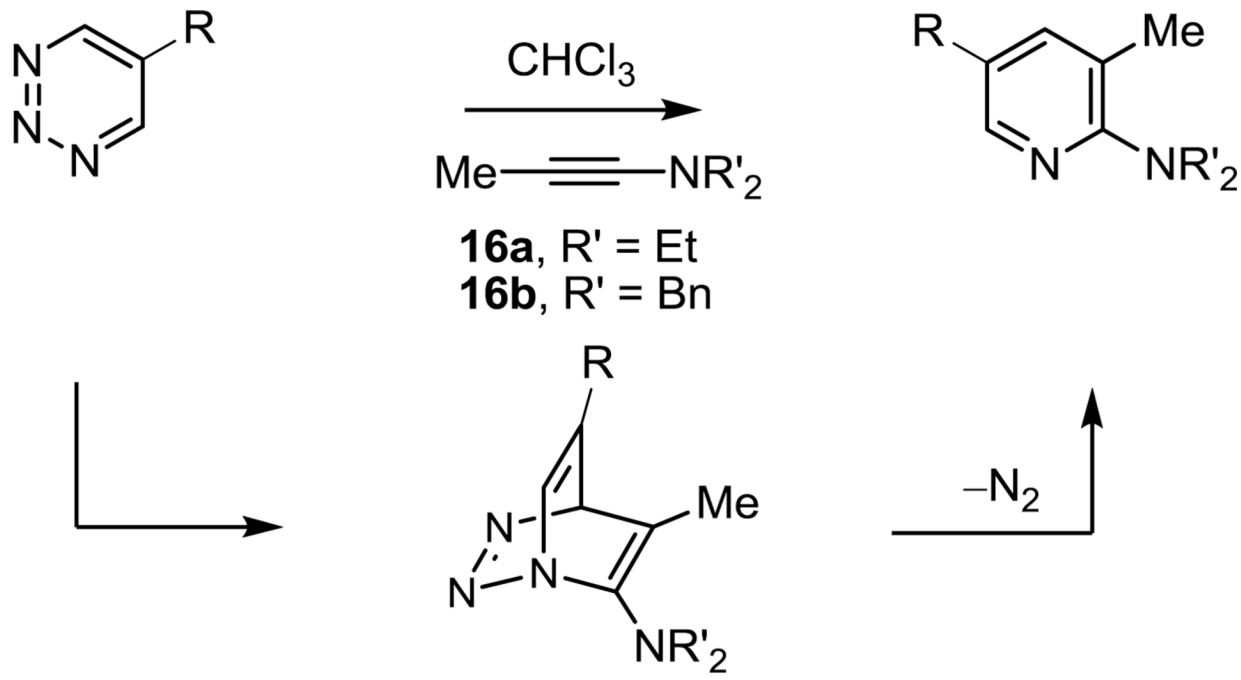
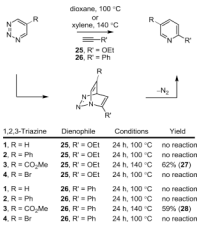


Figure 1.
Complementary cycloaddition reactions of key heterocyclic azadienes.



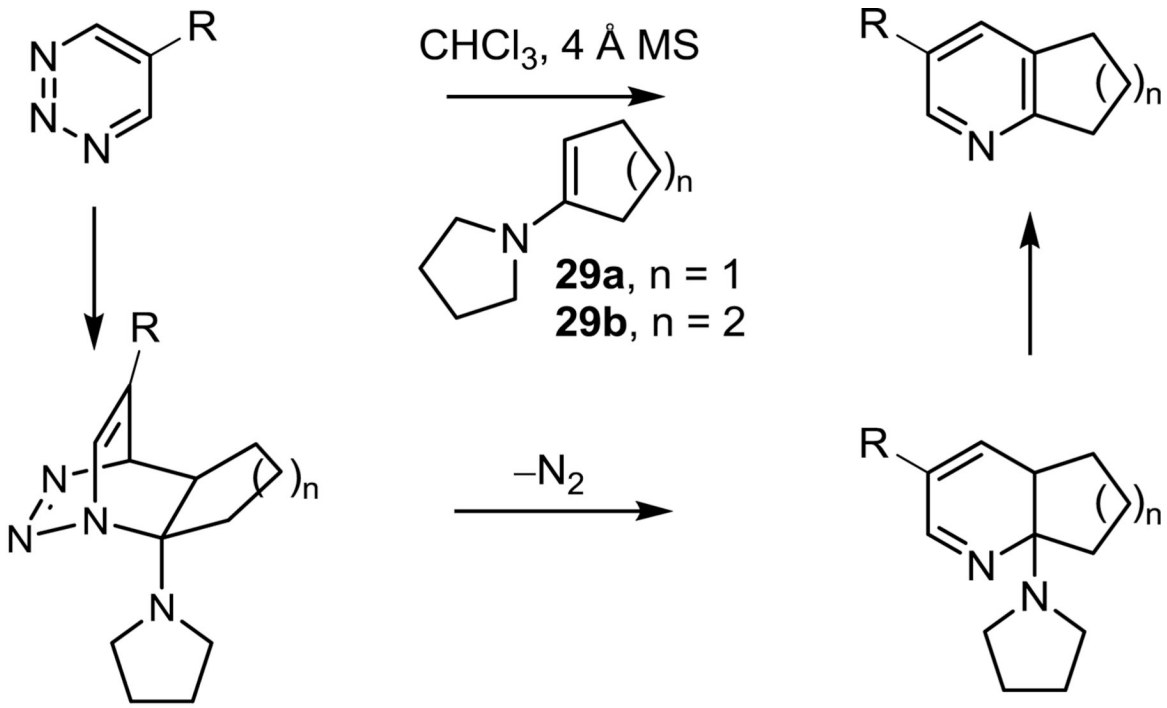
1,2,3-Triazine	Dienophile	Conditions	Yield
1, R = H	**16a**, R' = Et	3 h, 60 °C	64% (**17**)
2, R = Ph	**16a**, R' = Et	3 h, 22 °C	69% (**18**)
3, R = CO_2Me	**16a**, R' = Et	5 min, 22 °C	72% (**19**)
4, R = Br	**16a**, R' = Et	15 min, 22 °C	93% (**20**)
1, R = H	**16b**, R' = Bn	12 h, 60 °C	40% (**21**)
2, R = Ph	**16b**, R' = Bn	3 h, 60 °C	66% (**22**)
3, R = CO_2Me	**16b**, R' = Bn	15 min, 22 °C	83% (**23**)
4, R = Br	**16b**, R' = Bn	15 min, 22 °C	25% (**24**)

Figure 2.
Diels–Alder reactions of 1,2,3-triazines **1**–**4** with ynamines.



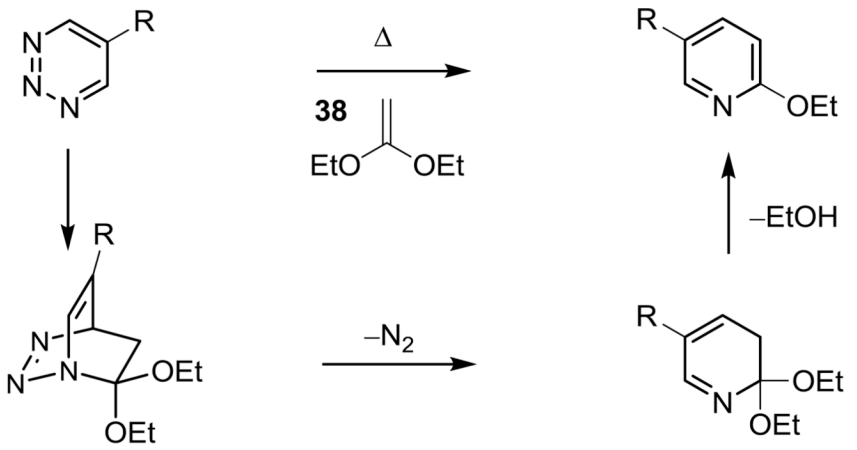
1,2,3-Triazine	Dienophile	Conditions	Yield
1, R = H	**25**, R' = OEt	24 h, 100 °C	no reaction
2, R = Ph	**25**, R' = OEt	24 h, 100 °C	no reaction
3, R = CO_2Me	**25**, R' = OEt	24 h, 140 °C	62% (**27**)
4, R = Br	**25**, R' = OEt	24 h, 100 °C	no reaction
1, R = H	**26**, R' = Ph	24 h, 100 °C	no reaction
2, R = Ph	**26**, R' = Ph	24 h, 100 °C	no reaction
3, R = CO_2Me	**26**, R' = Ph	24 h, 140 °C	59% (**28**)
4, R = Br	**26**, R' = Ph	24 h, 100 °C	no reaction

Figure 3.
Reaction with additional acetylenes.



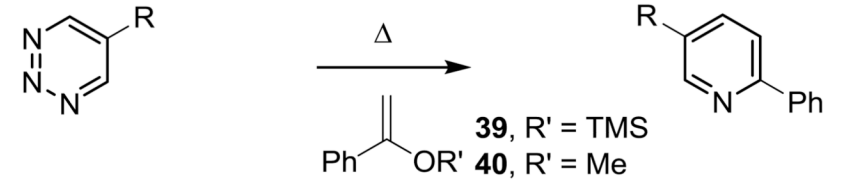
1,2,3-Triazine	Dienophile	Conditions	Yield
1, R = H	**29a**, n = 1	14 h, 60 °C	48% (**30**)
2, R = Ph	**29a**, n = 1	14 h, 60 °C	88% (**31**)
3, R = CO_2Me	**29a**, n = 1	30 min, 45 °C	84% (**32**)
4, R = Br	**29a**, n = 1	30 min, 45 °C	40% (**33**)
1, R = H	**29b**, n = 2	14 h, 60 °C	29% (**34**)
2, R = Ph	**29b**, n = 2	14 h, 60 °C	50% (**35**)
3, R = CO_2Me	**29b**, n = 2	14 h, 60 °C	90% (**36**)
4, R = Br	**29b**, n = 2	30 min, 45 °C	68% (**37**)

Figure 4.
Cycloaddition reactions of 1,2,3-triazines **1**–**4** with enamines.



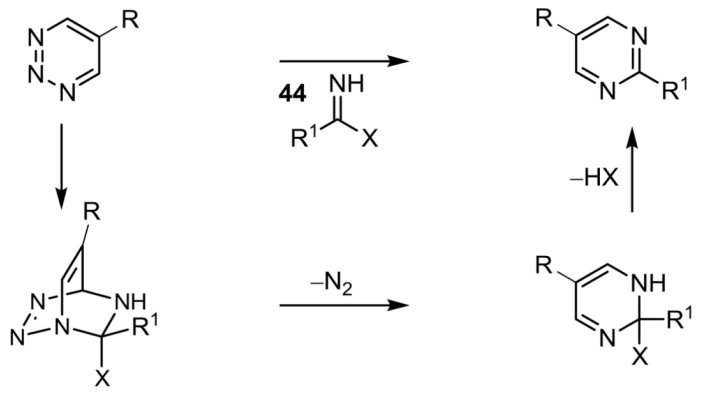
1,2,3-Triazine	Dienophile	Conditions	Yield
1, R = H	**38**	xylenes, 24 h, 140 °C	no reaction
2, R = Ph	**38**	xylenes, 24 h, 140 °C	94% (**41**)
3, R = CO_2Me	**38**	dioxane, 30 min, 60 °C[a]	99% (**27**)
4, R = Br	**38**	dioxane, 24 h, 100 °C	40% (**42**)

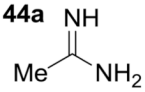
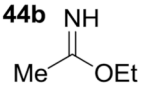
[a]Hunig's base (0.8 equiv)



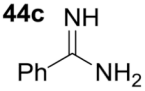
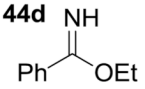
1,2,3-Triazine	Dienophile	Conditions	Yield
1, R = H	**39**	100–200 °C	no reaction
2, R = Ph	**39**	100–200 °C	no reaction
3, R = CO_2Me	**39**	xylenes, 24 h, 140 °C	48% (**28**)
1, R = H	**40**	100–200 °C	no reaction
2, R = Ph	**40**	100–200 °C	no reaction
3, R = CO_2Me	**40**	xylenes, 24 h, 140 °C	49% (**28**)

Figure 5.
Diels–Alder reactions of 1,2,3-triazines **1**–**4** with ketene acetals and enol ethers.



1,2,3-Triazine	Dienophile	Conditions	Yield
1, R = H	**44a** 	CH_3CN, 5 min, 22 °C	93% (**45**)
2, R = Ph		CH_3CN, 5 min, 45 °C	98% (**46**)
3, R = CO_2Me		CH_3CN, 10 min, 22 °C	62% (**47**)
4, R =Br		CH_3CN, 10 min, 22 °C	47% (**48**)
1, R = H	**44b** 	CH_3CN, 24 h, 80 °C	64% (**45**)[a]
2, R = Ph		CH_3CN, 24 h, 80 °C	94% (**46**)
3, R = CO_2Me		CH_3CN, 15 min, 22 °C	68% (**47**)

[a]99% based on recovered starting material

1,2,3-Triazine	Dienophile	Conditions	Yield
1, R = H	**44c** 	dioxane, 6 h, 22 °C	91% (**49**)
2, R = Ph		dioxane, 6 h, 22 °C	88% (**50**)
3, R = CO_2Me		dioxane, 5 min, 22 °C	99% (**51**)
4, R =Br		CH_3CN, 10 min, –20 °C	40% (**52**)
1, R = H	**44d** 	DMF, 24 h, 100 °C	16% (**49**)
2, R = Ph		DMF, 24 h, 100 °C	48% (**50**)
3, R = CO_2Me		DMF, 24 h, 100 °C	70% (**51**)

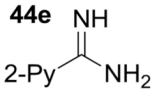
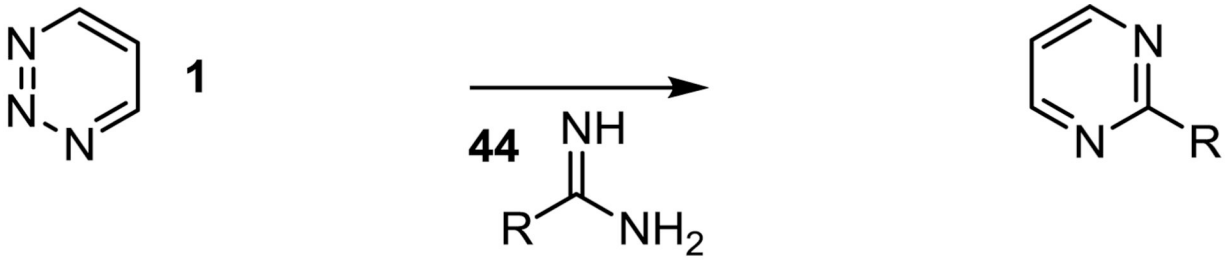
1,2,3-Triazine	Dienophile	Conditions	Yield
1, R = H	**44e** 	dioxane, 2 h, 60 °C	98% (**53**)
2, R = Ph		dioxane,15 min, 22 °C	99% (**54**)
3, R = CO_2Me		dioxane, 5 min, 22 °C	99% (**55**)
4, R =Br		dioxane, 5 min, 22 °C	99% (**56**)

Figure 6.
Reactions of 1,2,3-triazines **1**–**4** with amidines and imidates.



Dienophile	Conditions	Yield
44f, R = 4-$MeOC_6H_4$	dioxane, 2 h, 60 °C	93% (**57**)
44g, R = 4-BrC_6H_4	CH_3CN, 4 h, 60 °C	99% (**58**)
44h, R = 4-FC_6H_4	CH_3CN, 2 h, 60 °C	99% (**59**)
44i, R = 3-$NO_2C_6H_4$	CH_3CN, 5 h, 60 °C	99% (**60**)
44j, R = 2,6-$Cl_2C_6H_4CH_2$	CH_3CN, 2 h, 60 °C	90% (**61**)
44k, R = 2-pyrimidinyl	CH_3CN, 5 h, 60 °C	99% (**62**)
44l, R = 2-thienyl	CH_3CN, 2 h, 60 °C	95% (**63**)
44m, R = cyclopropyl	CH_3CN, 1 h, 60 °C	95% (**64**)

Figure 7.
Additional reactions of 1,2,3-triazine (**1**) with amidines.

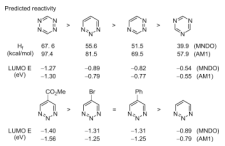
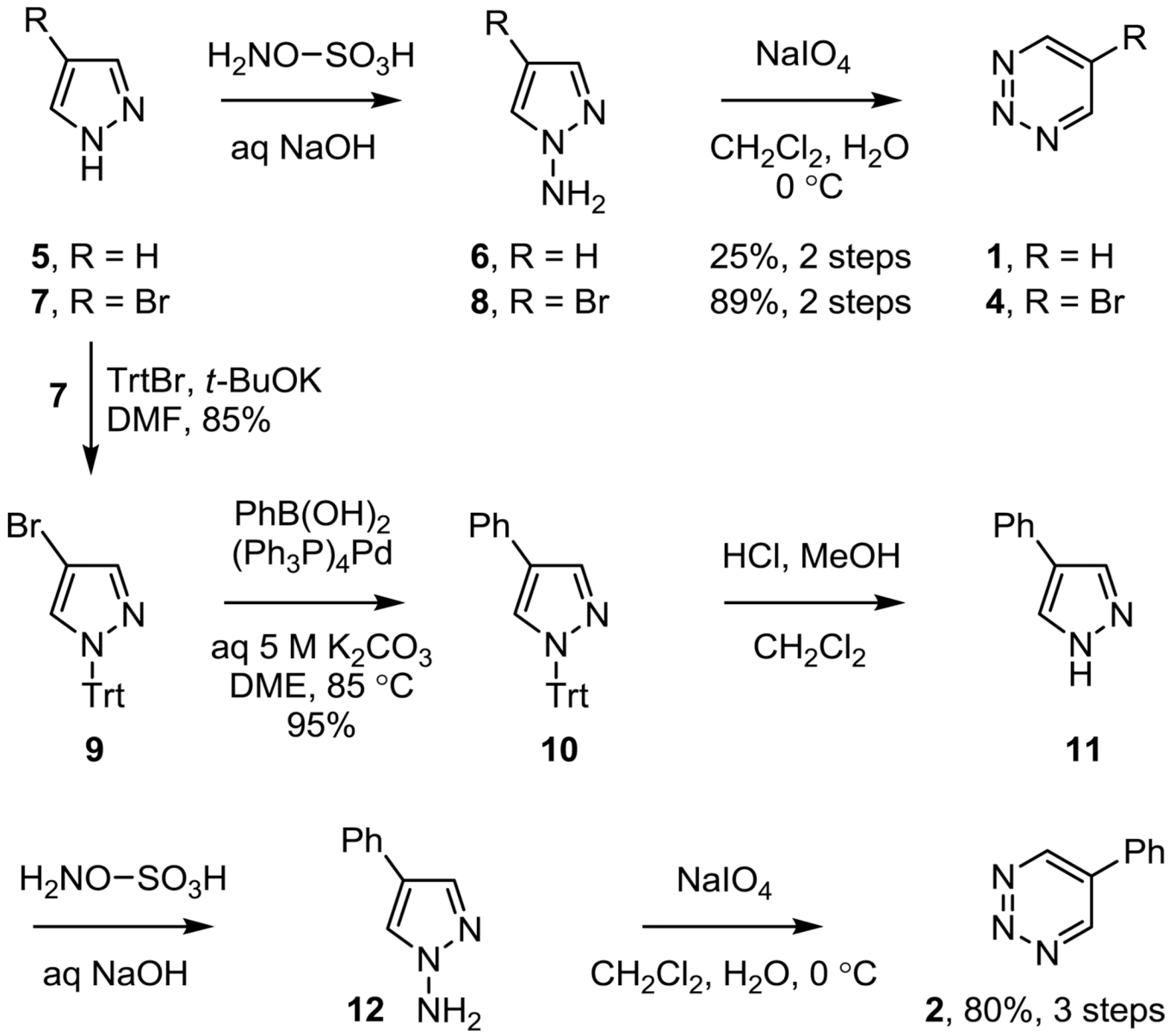
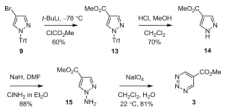


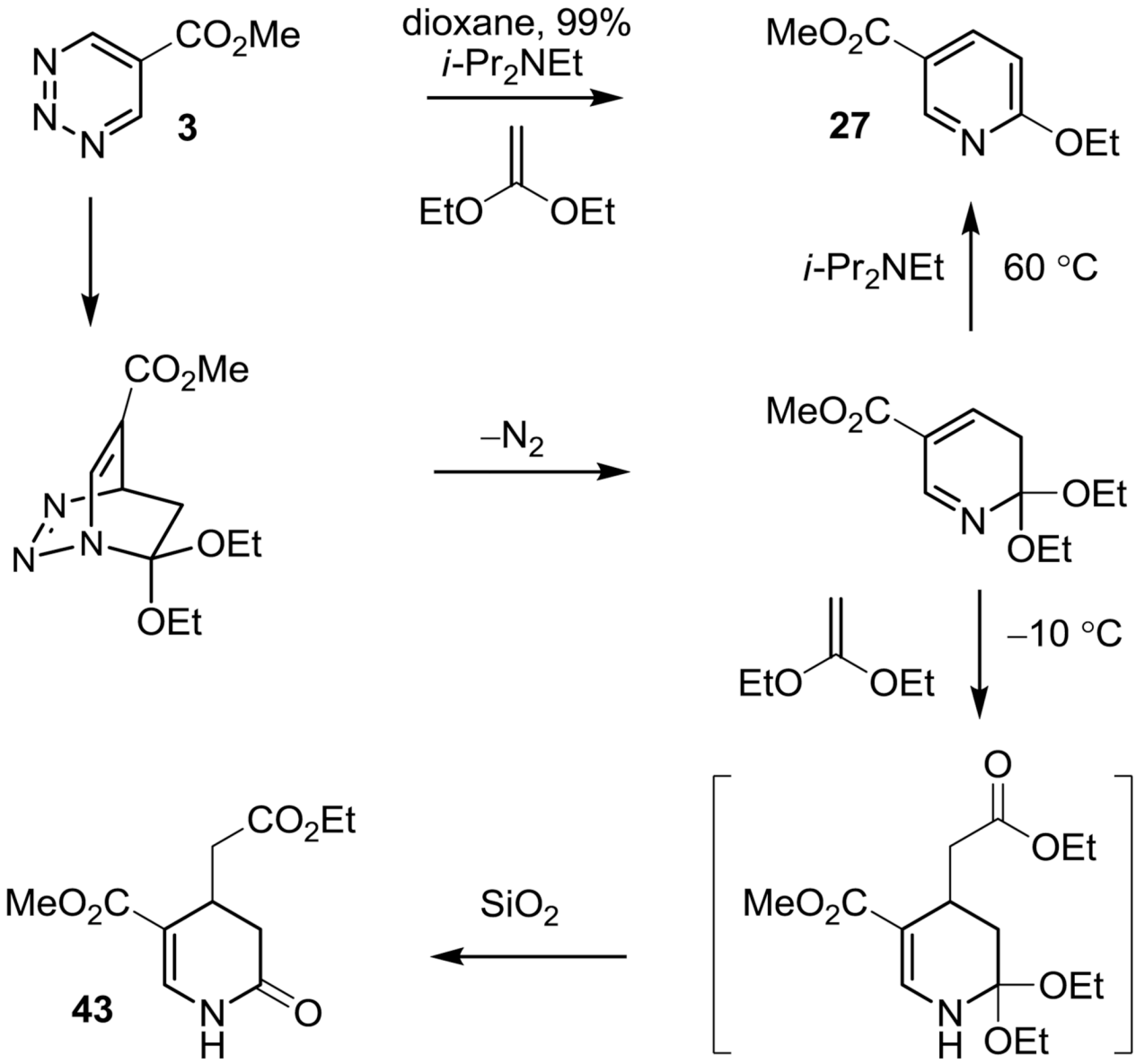
Figure 8.
Computational comparisons.



Scheme 1.



Scheme 2.



Scheme 3.