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# Preparation and Diels−Alder Chemistry of 4-Vinylimidazoles

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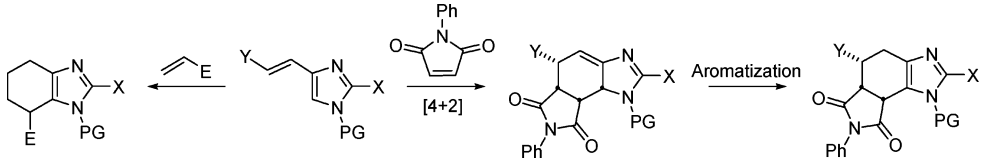


Various 4-vinylimidazole derivatives have been prepared from the corresponding 4-iodoimidazoles or from urocanic acid. Several methods for the elaboration of these vinylimidazoles and their Diels−Alder reactions are reported. All of the vinylimidazoles prepared in the course of this study react with *N*-phenylmaleimide quite readily with mild thermal activation providing a single cycloadduct, in most cases the initial, nonaromatic adduct. With more electron rich substrates, there is a tendency for these initial cycloadducts to undergo aromatization, ene reaction, and oxidation although this can be circumvented to a large extent by the choice of reaction conditions. Limited reactions were observed with other dienophiles, providing the expected cycloadducts in most cases, although an abnormal adduct was obtained in one case with dimethyl acetylene dicarboxylate. These substrates also participate in regioselective Diels−Alder reactions with monoactivated dienophiles, but require fairly forcing conditions, thus only providing the aromatized cycloadducts in modest yields. An investigation of substituent effects at the 2-position of the imidazole moiety was undertaken, in which electron-donating and weakly electron-withdrawing substituents are tolerated. In addition, several substrates with terminally substituted vinyl moieties have been investigated.

## Introduction

The Diels−Alder (DA) reaction continues to play a central role in many natural product total syntheses and in the construction of a large number of molecules of biological interest.[1,2] This reaction has been extensively investigated since its discovery and a large number of variants are known,[1] ranging from the all-carbon version to a number of heteroatom-based examples.[3] Many common heterocycles participate in this reaction, but unlike furan[4] and pyrrole[5] which react with various dienophiles to provide the expected adducts, there are limited examples of imidazoles participating in DA chemistry. Snyder and co-workers have demonstrated that electron-rich 2-aminoimidazoles can function as 2$\pi$-components in inverse electron demand DA reactions (both inter- and intramolecular variants are known), providing expedient approaches to imidazopyridine derivatives.[6,7] It has been reported by Yamazaki that imidazoles can react with electron-deficient acetylenes in DA reactions leading to the formation of pyrroles.[8] In a rare example, Wuonala and co-workers have reported one example of an intramolecular DA reaction of an imidazole in which it acts as a 4$\pi$-component, although ultimately the imidazole moiety does not remain intact in the product.[9] More recently, Romo and co-workers have reported several examples of DA reactions of vinylimidazol-

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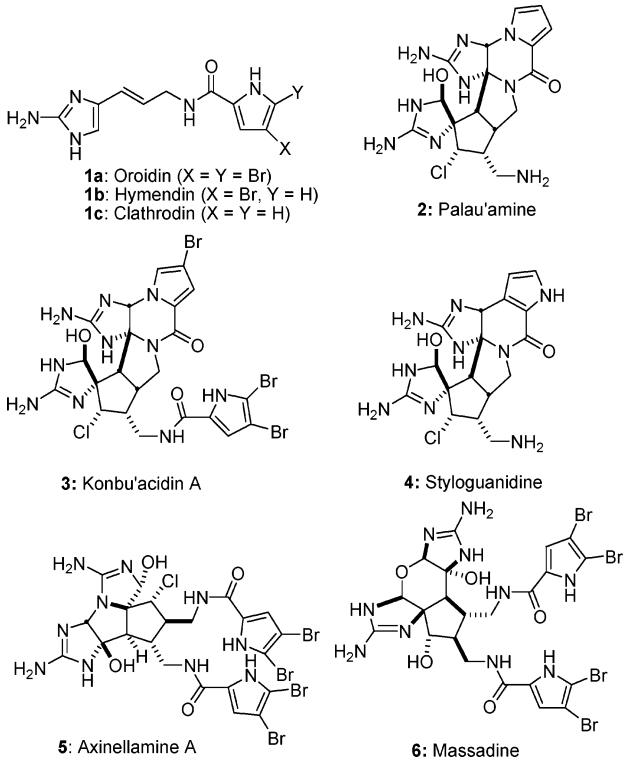


**FIGURE 1.** Oroidin and biogenetically derived alkaloids.

2-ones in their studies toward several oroidin-derived alkaloids.[10] On the basis of this general paucity of examples of imidazoles participating in DA chemistry, the significance of the imidazolyl moiety in medicinal chemistry[11] and its presence in several classes of natural products (e.g., Figure 1),[12] there appeared to be a significant opportunity to develop this area of synthetic chemistry.

Our own interest in the DA chemistry of imidazoles was stimulated by a report on the isolation of the oroidin-derived marine alkaloid (**1a**−**c**),[13] palau'amine (**2**) by Scheuer and Kinnel, in which they propose a biosynthesis of the natural product involving a DA reaction of a vinylimidazole derivative (Figure 2, **7** + **8** → **10**).[14−16] Quite recently, Romo and co-workers have suggested that the DA substrate may in fact be iminium ion **9** resulting from scission of the N9−C10 bond,

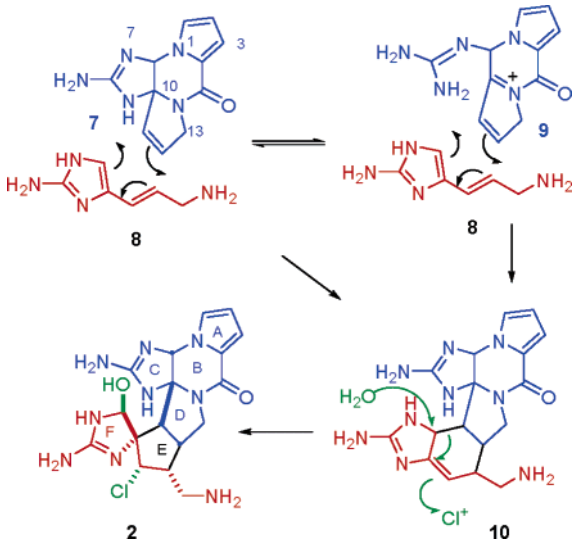


**FIGURE 2.** Proposed biosynthesis of Scheuer and Kinnel (**7** + **8** → **10**) and Romo's modification (**7** → **9** + **8** → **10**).

which might be expected to be a better dienophile than **7**.[10c] Subsequent rearrangement of the DA adduct **10**, presumably triggered by a chloroperoxidase, leads to ring contraction and formation of the spiro fusion of the imidazole and the cyclopentane ring, and assembly of the stereochemically and functional group rich cyclopentyl E-ring. Although there was no experimental basis for this biosynthetic proposal, it suggested a strategically appealing cycloaddition−rearrangement approach to the congested cyclopentane ring found in **4** and other related marine natural products, konbu'acidin (**3**),[17] styloguanidine (**4**),[14,18] axinellamine A (**5**),[19,20] and massadine (**6**) depicted in Figure 1.[21] However, if this general approach were to be viable, it required establishing whether vinylimidazoles would participate in DA chemistry in a general sense, and further, it necessitated the development of reliable synthetic procedures for the assembly and functionalization of vinylimidazoles. When we initiated this research program only two reports,[22,23] containing a total of three examples, existed in the literature describing the DA chemistry of vinylimidazoles as 4$\pi$-components. These reports were of very limited scope and did not provide any indication of stereochemical or regiochemical outcome of this type of reaction. Furthermore, in the most closely related work to that envisioned, Walters and Lee describe the reaction of two 5-vinylimidazoles with *N*-phenylmaleimide (NPM).[22] Although both reactions proceeded, they were moderately efficient (~40%) and provide only the aromatized adduct, rather than the initial adduct, which was required as a substrate for investigation of "biomimetic" rearrangement (**10** → **2**, Figure 2). A more recent report indicated that the primary adduct could be obtained, but this example employed the highly reactive *N*-phenyl-1,3,4-triazoline-2,5-dione (PTAD) as dienophile.[23] It

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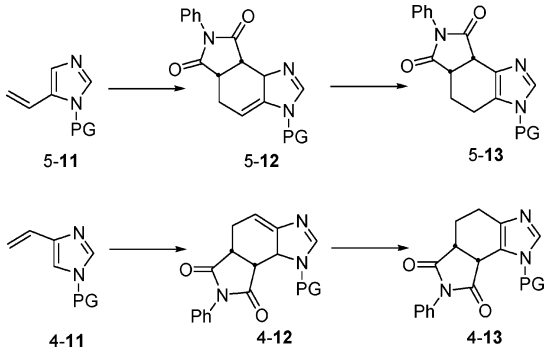


**FIGURE 3.** Comparison of 4- and 5-vinylimidazoles.

has also been reported that 4-vinylimidazoles can function as dienophiles in the DA reaction, although this was a very limited study.[24,25] After our initial reports, Ohta described the dimerization reactions of several 5-vinylimidazoles, which were moderately efficient and were employed in an approach to ageliferin-type molecules.[26] Quite recently, Lindel and coworkers have reported some intermolecular reactions of oroidin derivatives with NPM.[25] Herein, we describe in full our investigation of the synthesis and intermolecular DA chemistry of 4-vinylimidazoles.[27]

Although the literature reports with 5-vinylimidazoles 5-**11** provided encouraging precedent for the proposed first step in an approach to palau'amine (**2**), the inability to obtain the initial cycloadduct (enamine, 5-**12**) even with the reactive all-carbon dienophile NPM was of some concern (Figure 3).[22,23] However, on the basis of our analysis of the products from the Diels−Alder reaction, it appeared that the isomeric 4-vinylimidazole 4-**11** might provide a more realistic opportunity to access the initial adducts 4-**12**. The justification for this relatively simple modification lay in the observation that the diene was cross-conjugated and thus the initial cycloadducts 4-**12** would be conjugated and therefore might be expected to be more stable, potentially less likely to rearomatize, and possibly react under milder reaction conditions thereby preventing aromatization.

To establish the general viability of the DA chemistry with 4-vinylimidazoles, the known 1-trityl-4-vinylimidazole (**16**) was prepared, although not via the reported Wittig route.[28] Imidazole was polyiodinated by treatment with a solution of iodine in aqueous KI under basic conditions, and the resulting mixture of di- and triiodoimidazole **14** was treated with an aqueous ethanolic solution of $Na_2SO_3$ to provide 4(5)-iodoimidazole.[29] Reaction with trityl chloride provides the corresponding protected 4-iodoimidazole **15**,[30] which was subjected to a Stille cross-coupling reaction with tributylvinylstannane, producing

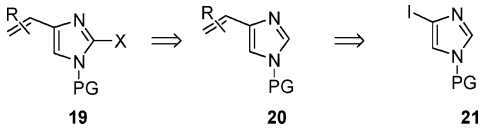


**FIGURE 4.** Synthetic approach to 4-vinylimidazoles.

the known 4-vinylimidazole **16** in good yield.[28] We were delighted to find that when this substrate was reacted with NPM in benzene at reflux two cycloadducts were formed and could be isolated by column chromatography in 63% and 8% yield, respectively. Analysis of the $^1$H NMR data indicated that the products were the required initial adduct **17** (major), as a single diastereomer, and the corresponding aromatic (minor) derivative **18**. A survey of various solvents indicated that the initial adduct was favored in lower boiling solvents, and indeed was the only isolated product in dichloromethane and chloroform. Notably, in the higher boiling solvents significant or complete decomposition occurred; presumably this is due to loss of the trityl group. Although encouraged by these preliminary experiments, the *N*-trityl protecting group was not viewed as being optimal for our long-term goals in total synthesis; therefore we evaluated other *N*-substituents on the efficiency of the DA reaction.

To address the influence of the *N*-protecting group, an efficient approach to 4-vinylimidazoles needed to be identified that ultimately would permit the greatest amount of flexibility in terms of incorporating a number of different substituents on nitrogen (protecting groups), at C2 (particularly for the introduction of an amine or amino surrogate), and on the vinyl moiety. On the basis of this set of prerequisites, the general approach outlined in Figure 4 evolved in which the fully substituted derivative **19** would be prepared from the parent substrate **20** by C2-functionalization.[31] Vinylimidazole **20** would be assembled via an appropriate cross-coupling reaction from the corresponding 4-haloimidazole,[32] which in turn would be derived from the halogenation and protection of imidazole.

***N*-Protecting Group.** The first issue that required attention was the efficient preparation of the protected 4-iodoimidazole derivatives. While the introduction of the bulky trityl group could be achieved directly from the 4(5)-iodoimidazole (Scheme 1), this approach was not anticipated as being generally applicable for the preparation of other derivatives. While this was not true for the synthesis of the known tosyl derivative **21a** (Scheme 2), other derivatives provided mixtures of 4- and 5-iodoimidazoles. For example, 4(5)-iodoimidazole provided a 2:1 mixture, albeit separable, of the corresponding 4- and 5-iodoimidazoles, **21e** and **24e** (Scheme 2).[33] To circumvent this problem, two approaches to the selective syntheses of the 4-iodo derivatives were developed. The first involved the preparation of the *N*-substituted 4,5-diiodo derivatives **26b**−**f** from **25**,[34] which were then selectively deiodinated in the 5-position by treatment with EtMgBr, followed by protonation of the thus formed Grignard to afford the corresponding 4-iodoimidazoles **21b**−**f** (Scheme 3).[34,35] An alternative approach was developed later that involved isomerization of the

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**SCHEME 1**

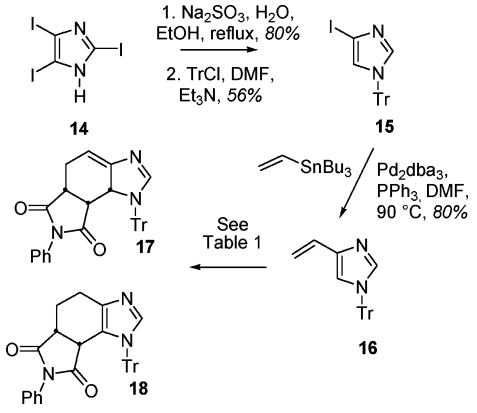



**TABLE 1. Solvent Dependence on Isolated Product Yield**

| entry | solvent (reaction time/h)[a] | enamine[c] **17**/% | imidazole[c] **18**/% |
|---|---|---|---|
| 1 | xylene (1) | 0 | 0 |
| 2 | toluene (3) | 52 | 8 |
| 3 | benzene (12) | 63 | 8 |
| 4 | benzene (30)[b] | 60 | 3 |
| 5 | chloroform (24) | 84 | 0 |
| 6 | dichloromethane | 52 | 0 |

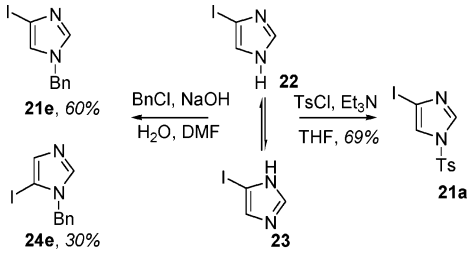
[a] A solution containing 1.0 equiv of **16** and 2.5 equiv of NPM in the indicated solvent (3 mL) was heated at reflux for the indicated time. [b] 1.3 equiv of NPM was employed. [c] These are isolated yields of chromatographically purified products.

initially formed mixture of 4- and 5-iodo derivatives,[36] although the approach described in Scheme 3 is more convenient for large-scale preparations. With the 4-iodoimidazoles in hand, it was found that they participate smoothly in the Stille cross-coupling reaction with vinyl(tributyl)stannane to provide the corresponding vinylimidazoles **27a**−**f** in moderate to excellent yield.[37] The Me- and MOM-derivatives, **27b** and **27f**, were somewhat water soluble, leading to loss of material during the aqueous workups employed.

These vinylimidazoles **27a**−**f** were subjected to the DA reaction with NPM in either $CH_2Cl_2$ or PhH, and in general terms, the outcomes can be divided into two groups. Substrates possessing an electron-withdrawing group on nitrogen **27a**−**d** provide a single cycloadduct, the initial adduct **29a**−**d**, in generally good isolated yield (Table 3, Scheme 4). As far as can be determined, a single stereoisomer is formed which, based on an X-ray crystal structure (Figure S1 in the Supporting Information) of the Ts-protected derivative **29a**, derives from an *endo* transition state (**28**, Scheme 4). NOESY experiments on the remaining derivatives, as well as the broadly similar $^1$H NMR spectra, suggested that the other cycloadducts shared a common stereochemical framework.

The more electron rich derivatives, the Bn- and Me-substrates **27e** and **27f**, provided a more diverse collection of adducts that depended to a large extent on the precise reaction conditions employed (Table 4). Initial experiments with the Bn-derivative provided relatively complex mixtures of products including the anticipated initial adduct **29e**, the aromatized derivative **30e**,

**SCHEME 2**




**SCHEME 3**

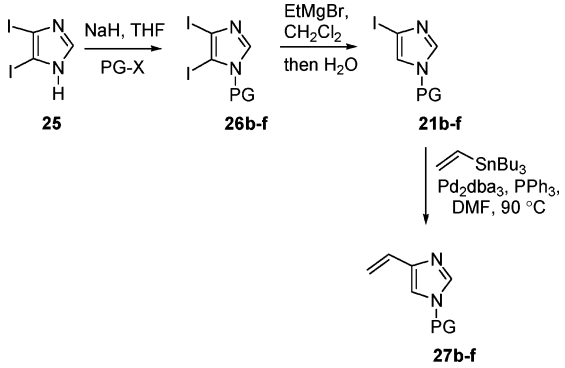



**TABLE 2. Yields in Protection and Deiodination**

| PG | | **26**/% | **21**/% | **27**/% |
|---|---|---|---|---|
| Ts | **a** | | | 92 |
| MOM | **b** | 89 | 90 | 52 |
| $SO_2NMe_2$ | **c** | 62 | 54 | 79 |
| SEM | **d** | 91 | 80 | 76 |
| Bn | **e** | 90 | 93 | 90 |
| Me | **f** | 93 | 87 | 30 |

and others including the ene product **31e**[38] and the bis DA adduct **33e** (see Figure S2 in the Supporting Information for an X-ray structure). Purification of these products by chromatography, particularly **29e**, was difficult due to aromatization to **30e**, even with pretreatment of silica gel with triethylamine (Table 4, entry 1). However, it was found that allowing the reaction to run for shorter periods limited the formation of these other adducts, and so **29e** could be readily purified by trituration of the crude reaction mixture (Table 4, entry 2). The aromatized product **30e** can be obtained as the only product by the addition of *p*-TsOH (Table 4, entry 3). If the reaction was conducted in toluene and allowed to proceed until all of **29e** was consumed then **30e** could be obtained (Table 4, entry 4), although it was accompanied by the formation of **31e** and **33e**. The ene adduct arises through addition of the excess NPM to the electron-rich enamine, and reaction via this manifold then permits rearomatization of the imidazole fragment. The bis DA adduct results from oxidation of **29e** to the cyclic vinylimidazole **32e**, which undergoes a second *endo* selective DA reaction with NPM. We were curious as to the identity of the oxidant in this reaction; our initial suspicion was that it was dissolved oxygen as addition of BHT (Table 4, entry 6) prevented the oxidation (as did degassing the solvent by bubbling nitrogen through the reaction mixture prior to heating), although some **31e** was still observed in this case. Further evidence in support of this hypothesis arose

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(38) The relative stereochemistry of this product is assumed by analogy to the two related adducts **31f** and **51** for which X-ray crystal structures were determined.

**SCHEME 4**

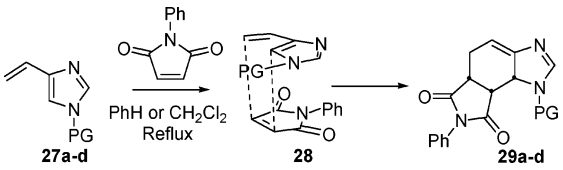



**TABLE 3. Yields for the Cycloaddition Reactions**[a]

| entry | R | **29** | solvent[a] | time/h | yield/% |
|---|---|---|---|---|---|
| 1 | Ts | **a** | PhH | 27 | 80 |
| | | | | 48 | 89 |
| 2 | MOM | **b** | PhH | 2.5 | 70 |
| | | | | 17 | 86 |
| 3 | $SO_2NMe_2$ | **c** | PhH | 9 | 93 |
| | | | | 48 | 94 |
| 4 | SEM | **d** | PhH | 5 | 85 |
| | | | | 6 | 78 |

[a] A solution containing 1.0 equiv of **27a**−**d** and 2.5 equiv of NPM in the indicated solvent (3 mL) was heated at reflux for the indicated time.

**TABLE 4. Yields and Product Distributions of DA Reactions of 27e and 27f with NPM**[a]

| entry | PG | | solvent | temp/°C | time/h | **29**/% | **30**/% | **31**/% | **33**/% |
|---|---|---|---|---|---|---|---|---|---|
| 1 | Bn | **27e** | $CH_2Cl_2$ | 50 | 14 | 80[b] | | 9 | |
| 2 | Bn | **27e** | $CH_2Cl_2$ | 50 | 10 | 88 | | | |
| 3 | Bn | **27e** | $CH_2Cl_2$ | 50 | 18[c] | | 80 | | |
| 4 | Bn | **27e** | PhH | 90 | 21[d] | | 18 | 18 | 28 |
| 5 | Bn | **27e** | PhH | 90 | 21[e] | | 75 | | |
| 6 | Bn | **27e** | PhH | 90 | 21[f] | | 74 | 19 | |
| 7 | Bn | **27e** | PhH | 90 | 21[g] | | 32 | | 19 |
| 8 | Me | **27f** | $CH_2Cl_2$ | 50 | 3.5 | | 39[h] | 21 | |
| 9 | Me | **27f** | $CH_2Cl_2$ | 50 | 24 | | 21 | 36 | |
| 10 | Me | **27f** | $CH_2Cl_2$ | 50 | 13 | | 76 | | |
| 11 | Me | **27f** | PhH | 90 | 6[d] | | 46 | 15 | |

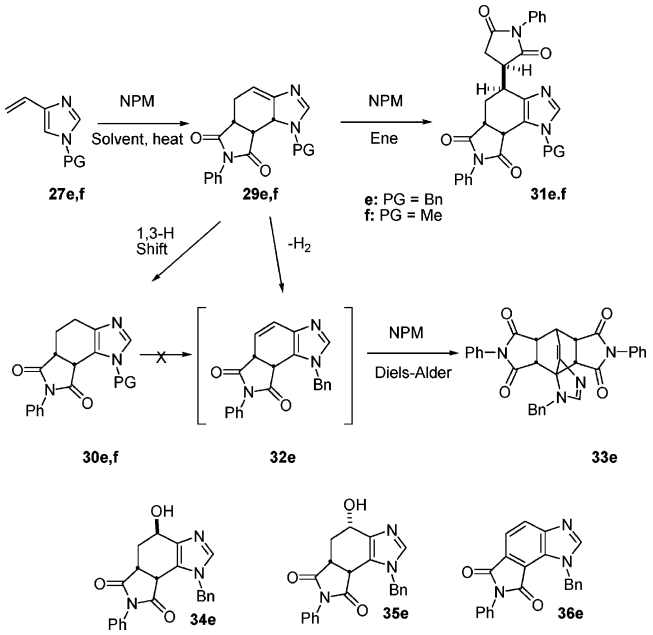
[a] A solution containing 1.0 equiv of **27a**−**d** and 2.5 equiv of NPM in the indicated solvent (3 mL) was heated at reflux for the indicated time. [b] Contaminated with a few percent of the aromatic product **30e**. [c] 30 mol % *p*-TsOH. [d] Reaction was allowed to run until all of **29e** or **29f** was consumed to assist in product isolation. [e] The reaction was run in the presence of catechol (30 mol %). [f] The reaction was run in the presence of BHT (30 mol %). [g] Oxygen was bubbled through the reaction prior to heating. [h] Overall yield from **27f** after treatment of the "purified" enamine with *p*-TsOH.

from an effort to increase the quantity of the bis adduct—air was bubbled through a mixture of **27e** and NPM prior to subjecting it to the DA reaction under otherwise analogous conditions (Table 4, entry 7).[39] Surprisingly (initially at least) in addition to the aromatized adduct **30e** and the bis DA product **33e**, the major byproduct from a fairly complex mixture of products was an ca. 1:1 mixture of epimeric 4-hydroxy derivatives **34e** and **35e** (28%).[40] In control reactions, both **29e** and **30e** were subjected independently to the DA reaction conditions in the presence of NPM. Only **29e** led to the formation of new products providing **30e** (56%), the bis adduct **33e** (16%), the ene product **31e** (9%), and an epimeric mixture of **34e** and **35e** (9%). Further, it was found that by heating a solution of **29e** in benzene until it was completely consumed several products were isolated including the fully aromatized adduct **36e** and the cyclic vinylimidazole **32e**, in addition to **34e**/**35e** and **30e**.

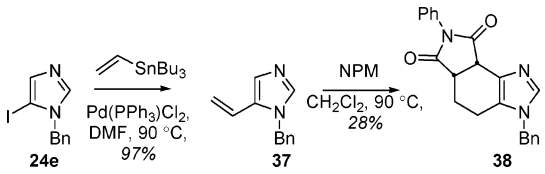
(39) (a) Noland, W. E.; Konkel, M. J.; Tempesta, M. S.; Cink, R. D.; Powers, D. M.; Schlemper, E. O.; Barnes, C. L. *J. Heterocycl. Chem.* **1993**, *38*, 183. (b) Pfeuffer, L.; Pindur, U. *Helv. Chem. Acta* **1987**, *70*, 1419.

(40) We have independently prepared both of these alcohols from **29e**, see ref 26c

**SCHEME 5**




**SCHEME 6**

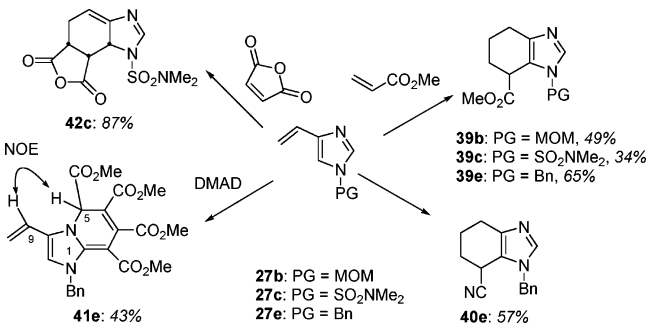



The Me-derivative behaved somewhat similarly to **27e** in that mixtures of products were obtained containing the primary adduct **29f**, the aromatized adduct **30f**, and the ene adduct **31f**. Unlike the Bn-derivative **29e**, the initial adduct **29f** was never obtained free of the aromatic adduct **30f**, and so typically the reaction was allowed to proceed until **29f** had been totally consumed. Under these conditions a mixture of the aromatized adduct and the ene adduct was obtained. The relative stereochemistry of the ene adduct was determined via X-ray crystallography (Figure S3 in the Supporting Information). Interestingly, none of the analogous bis DA adduct (cf., **33e**) was obtained with this substrate. Conceivably, the smaller methyl group renders rearomatization more facile than the benzyl-protected analogue due to reduced steric crowding with the pyrrolidine moiety derived from NPM and so conversion of **29f** to **30f** and **31f** occurs faster than oxidation to the corresponding cyclic vinylimidazole.

As noted above, our initial synthesis of vinylimidazole **27e** proceeded via a nonselective synthesis of the corresponding 4-iodoimidazole **21e** (Scheme 2). This approach provided significant quantities of the isomeric 5-iodoimidazole **24e**, which allowed the preparation of the corresponding 5-vinylimidazole **37** (Scheme 6). We found this to be a less effective diene, as on reaction with NPM in benzene for 24 h at 90 °C the aromatized cycloadduct was formed in 28% yield, with the material balance being largely unreacted starting materials. This result is in accord with the observations of Walters and Lee discussed above.[22]

It is notable that these cycloaddition reactions take place under exceedingly mild reaction conditions considering that the initial step involves dearomatization of the imidazole, albeit with a

**SCHEME 7**




reactive dienophile. For comparative purposes, styrene derivatives require substantially higher reaction temperatures and longer reaction times.[41] A second feature worth noting was the general ability to isolate the initial cycloadduct **29a**−**e** from reaction with NPM with all but the methyl derivative **27f**, which was not reported with the corresponding 5-isomer, either in published examples[22] or by us (e.g., with **37**). We suspect that several factors contribute to this observation. First, as alluded to in the introduction, the cycloadducts are conjugated, which presumably confers additional stability on these products compared to the 5-isomer. Second, on converting from the initial adduct to the aromatized isomer (**29a**−**e** → **30a**−**e**), there is an overall flattening out of the structure, which increases, presumably, the steric interaction between the imidazole *N*-substituent and pyrrolidine moiety, representing a barrier to isomerization. Third, in the cases of substrates with an electron-withdrawing *N*-substituent, the imidazole nitrogen lone pair (N1) is tied up (either through inductive or resonance effects), thereby preventing its ready incorporation in the aromatic sextet, and thus the driving force for aromatization is attenuated.

**Other Dienophiles.** One of the earliest variables that we investigated was the generality of the cycloaddition with respect to dienophiles other than NPM. To assess this, we evaluated three vinylimidazoles: the Bn-derivative **27e** (electron rich), MOM-derivative **27b** (moderately electron poor), and DMAS-derivative **27c** (highly electron poor). It was anticipated that this group of vinylimidazoles would offer a spectrum of reactivities, which in turn would provide a framework for the eventual use of this reaction in total synthesis endeavors vis à vis guiding the choice of protecting group.[42] Only the successful examples from these experiments are summarized in Scheme 7.[43] The most broadly reactive substrate was the Bn-protected derivative **27e** as it undergoes Diels−Alder reactions with several of these common dienophiles. With methyl acrylate and acrylonitrile, the anticipated adducts **39e** and **40e** were obtained, and each was isolated as a single regioisomer.[44] In the case of the acrylate derivative **39e**, the regiochemistry was confirmed through an X-ray analysis (Figure S4 in the Supporting Information). However, this is a very sluggish reaction, requiring a large excess of the dienophile (10 equiv total) and extended reaction times (10 days). **27e** also reacts with dimethyl acetylene dicarboxylate (DMAD), however, via a manifold other than the expected DA pathway. In this case, a bis addition adduct is obtained, which results from a net [2 + 2 + 2] cycloaddition similar to the reaction observed with simple alkyl imidazoles.[45] In addition a [1,5]-hydride shift occurs to then provide the observed adduct **41e**. A cross-peak observed in a NOESY experiment between the signals due to H5 and H9 is consistent with the formation of this constitutional isomer. The DMAS-protected derivative **27c** reacts quite nicely with maleic anhydride, providing the expected adduct **42c**. This derivative also reacts with methyl acrylate to afford **39c**, but less efficiently than the corresponding Bn-derivative **27e**, which is apparently due to thermal decomposition. Some reaction was observed with acrylonitrile; however, there was substantial decomposition and other side reactions that precluded complete purification and rigorous characterization. A similar result was obtained with the MOM-derivative **27b**, again leading to the formation of a single regioisomer **39b** with methyl acrylate.

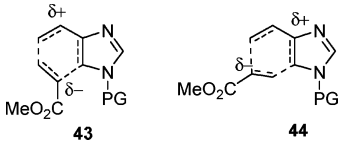



**FIGURE 5.** Possible regioisomeric cycloaddition transition states.

The regiochemistry observed in cycloadditions with nonsymmetric dienophiles is similar to that observed with other vinyl heterocycle derivatives in which the electron-withdrawing substituent ends up proximal to the heteroaromatic system.[46−48] This result can be understood in terms of a nonsynchronous transition state in which bonding is more developed with the vinyl moiety than the imidazole **43** (Figure 5), leading to the development of positive character at the benzylic position, which is stabilized by the electron-rich imidazole nucleus. Cycloaddition via the alternate regiochemistry would require loss of aromaticity, although the developing positive charge could be stabilized by N1 through resonance.

**C2-Substituents.** One of the long-term goals for this chemistry included its application in synthetic approaches to several of the oriodin family of alkaloids (Figure 1). A cursory glance at the members of this family reveals the presence of a 2-amino moiety in most examples (oxo in the remainder), and thus to have utility in this application, the DA reaction must be tolerant of a 2-amino group (or surrogate) on the substrates. Therefore, we set out to explore the influence of 2-substituents in general on the Diels−Alder reaction. While our manuscript was in preparation, Lindel and co-workers reported some examples of DA reactions with oroidin and some closely related congeners which possess a 2-amino substituent.[25] All of our initial experiments were carried out in the Bn-series as a result of the utility of this protecting group in the subsequent oxidative

(41) Wagner-Jauregg, T. *Synthesis* **1980**, 779.

(42) Although part of the motivation for this component of the study was to establish protecting group flexibility, we have subsequently discovered that in the oxidative rearrangement chemistry, strongly electron-withdrawing substituents are not tolerated, see ref 26c.

(43) Several common dienophiles, including methyl propriolate, dimethyl fumarate, and dimethyl maleate, were investigated and did not participate in a Diels−Alder reaction.

(44) We cannot unequivocally exclude the formation of the alternative regioisomer in this or related cases as these reactions occur under rather harsh reaction conditions, which leads to decomposition, and so it is conceivable that the other isomer is formed in small amounts and is not observed in the NMR spectra of the crude reaction mixtures, or isolated from them.

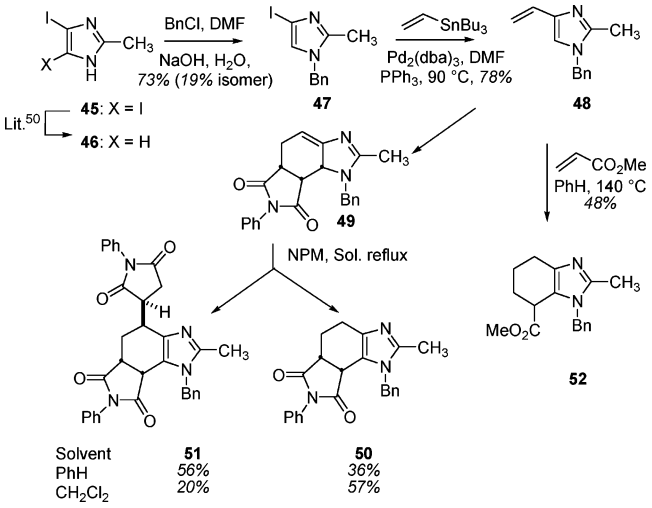
(45) Acheson, R. M.; Foxton, M. W.; Abbott, P. J.; Mills, K. R. *J. Chem. Soc. C* **1967**, 2218.

(46) Kusurkar, R. S.; Bhosale, D. K. *Synth. Commun.* **1990**, *20*, 101.

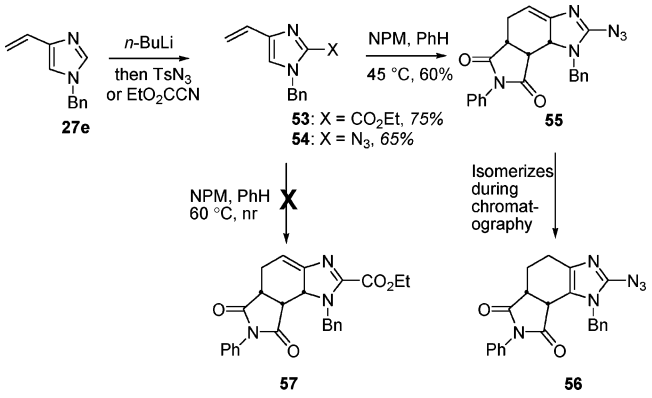
(47) Jones, R. A.; Marriot, M. T. P.; Rosenthal, W. P.; Arques, J. S. *J. Org. Chem.* **1980**, *45*, 4515.

(48) Abarca, B.; Ballesteros, R.; Enriquez, E.; Jones, G. *Tetrahedron* **1987**, *43*, 269.

**SCHEME 8**




**SCHEME 9**




rearrangement chemistry.[49] Two approaches to the construction of the requisite 4-substituted imidazoles were employed, depending on the nature of the 2-substituent. The 2-methyl derivative **48** was prepared from the known 4(5)-iodoimidazole **46**[50] by benzylation (3.8:1.0 mixture of separable 4- and 5-isomers) and Stille cross-coupling of the resulting 4-iodoimidazole **47** with vinylstannane (Scheme 8). The other derivatives were prepared from **27e** by metalation (*n*-BuLi) and electrophilic trapping with Mander's reagent ($EtO_2CCN$), or $TsN_3$,[51] providing the corresponding 2-ethyl ester (**53**) and 2-azide (**54**) in good yield (Scheme 9). At the outset, we were somewhat apprehensive about the viability of this direct metalation approach in these benzyl protected imidazole derivatives, as it had been previously shown that lateral lithiation occurs in *N*-benzyl benzimidazoles.[52] In the event, however, our concerns were unfounded with **27e** and the metalation proceeded uneventfully, and as best we could tell with high selectivity at the 2-position.

Each of these substrates was then subjected to a Diels−Alder reaction with NPM, initially in PhH at 90 °C. Under these conditions, the 2-Me-substituted derivative behaved similarly to the unsubstituted case (Scheme 8), providing the initial adduct **49**, the aromatized adduct **50**, and the ene adduct **51** (for X-ray, Figure S5 in the Supporting Information). Similarly to the parent case **27e**, the initial adduct could not be completely purified by column chromatography due to aromatization, and so to aid purification the reaction was allowed to proceed until all of this initial adduct had converted to **50** and **51**. The 2-methyl derivative also undergoes cycloaddition with methyl acrylate, providing **52** in reasonable yield (Scheme 8), although harsh reaction conditions are required, similar to the parent substrate **27e**. The carboxyethyl-containing derivative **53** did not participate in the DA reaction with NPM in any of the reactions attempted; however, the 2-azido derivative **54** did undergo cycloaddition, provided that the reaction temperature was moderated to 45 °C (Scheme 9), while at higher temperatures complex mixtures of products are formed. In the case of **54**, the $^1$H NMR spectrum of the crude reaction mixture indicated that the initial adduct **55** was the only product, but we were unable to fully purify this compound by column chromatography due to isomerization to the aromatic derivative **56**. It was found that the initial adduct **55** could be obtained in reasonable yield and purity by trituration of the crude reaction mixture. The cycloaddition reaction of the 2-azido derivative shows interesting chemoselectivity—at least at 45 °C, only reaction with the vinylimidazole and NPM is observed and apparently no [3 + 2] cycloaddition of the azide subunit was observed.

The 2-azido derivative **54** also served as a precursor for the preparation of several 2-amino derivatives which were obtained via $NaBH_4$ reduction providing the amine **58** (Scheme 10). The amine was then protected with $BOC_2O$ in the presence of TMEDA affording **59** or with a phthaloyl group on treatment with the modified Nefkens reagent affording **60** (Scheme 10).[53] This selective protection in the former case is worthy of note, and although the precise role of TMEDA is not clear, in its absence both acylation of the amino group and the imidazole N3 occurs.[54] Vinylimidazole **60** participated in the cycloaddition, but the reaction was extremely sluggish requiring heating at 120 °C, whereas both the BOC-protected **59** and the free amino derivative **58** engaged in the cycloaddition quite readily. The BOC-protected substrate **59** provided the initial adduct **61** in excellent yield on heating at 60 °C, whereas the phthaloyl substrate **58** provided the aromatic derivative **64** (plus a small quantity of the ene adduct **63**) at room temperature, provided only 1.0 equiv of NPM was employed. In contrast, when the reaction was conducted at room temperature, under standard conditions, 2.5 equiv of NPM, a cycloaddition occurred, but this was followed by an ene reaction with excess NPM, leading to the formation of **63** only. There is a fairly clear-cut correlation between the electron density of the vinylimidazole and the relative reactivity. The most electron rich derivative **58** reacts rapidly at room temperature, whereas the least electron rich derivative **60** requires heating at elevated temperature, which leads to rearomatization.

**Vinyl Substitution.** Three examples incorporating substitution on the terminus of the vinyl moiety were prepared and

(49) As part of general studies toward the oroidin family of natural products, we have found that reasonably electron rich tetrahydrobenzimidazoles can be converted into the corresponding spiro fused imidazolones through an oxidative rearrangement, therefore the reactivity of these benzyl-protected derivatives was investigated first.

(50) Cliff, M. D.; Pyne, S. G. *Synthesis* **1994**, 681.

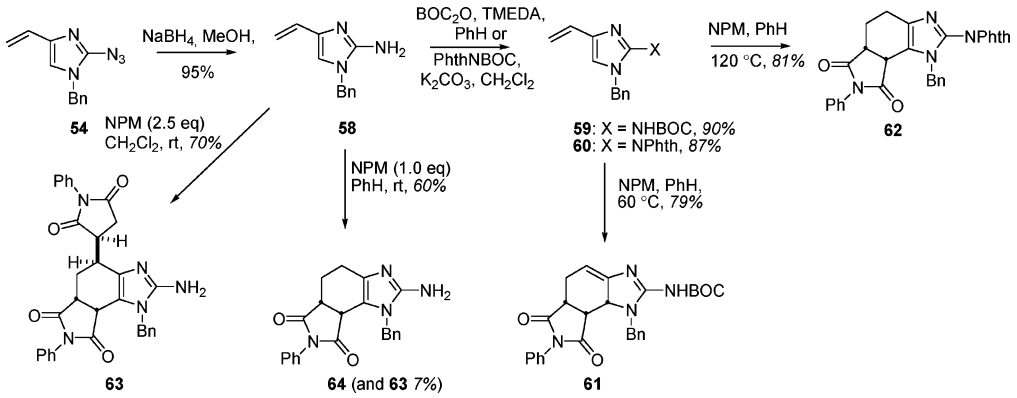
(51) Kawasaki, I.; Taguchi, Y.; Yamashita, M.; Ohta, S. *Heterocycles* **1996**, *43*, 1375.

(52) (a) Cuberes, M. R.; Moreno-Manas, M.; Trius, A. *Synthesis* **1985**, 302. (b) Moreno-Manas, M.; Bassa, J.; Llado, N.; Pleixats, R. *Heterocycles* **1990**, *27*, 673.

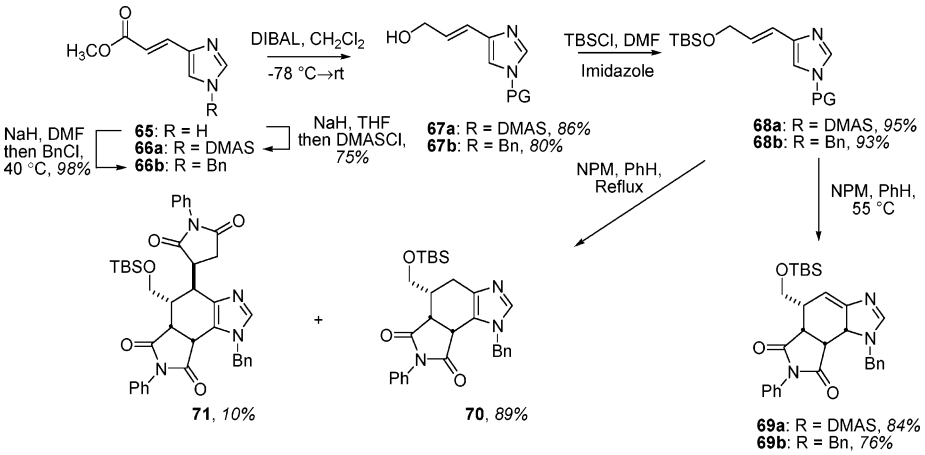
(53) Einhorn, C.; Einhorn, J.; Marcadal-Abbadi, C. *Synth. Commun.* **2001**, *31*, 741.

(54) (a) Koyanagi, K.; Tsucha, S. Preparation of (alkoxycarbonylamino)-heterocycles. Jpn Kokai Tokkyo Koho 93 164,438; *Chem. Abstr*. **1995**, *122*, 265365. (b) Koyanagi, K.; Tsucha, S. Method for Preparation of *N*-Heterocyclylurethane. Jpn Kokai Tokkyo Koho 93 164,378; *Chem. Abstr*. **1995**, *122*, 290878.

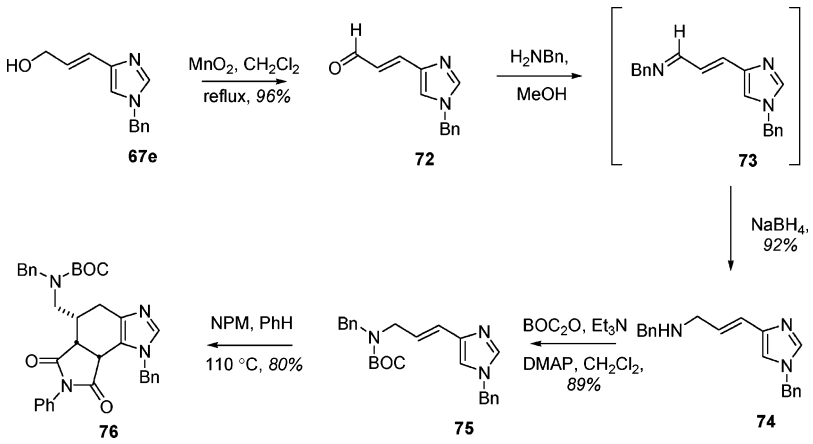
**SCHEME 10**




**SCHEME 11**




**SCHEME 12**




evaluated in the DA reaction. In this case urocanic acid, which is commercially available, or can be prepared in excellent yield from histidine, was utilized as the starting material. Conversion of the acid into the methyl ester[55] through standard Fischer esterification conditions and subsequent protection with either BnCl or DMASCl provided the corresponding derivatives **66a**[56] and **66b** in good yields and selectivities (Scheme 11). Reduction of the ester to the alcohol with DIBAL proceeded efficiently,[56] and then the resulting alcohol was protected as the silyl ether. Alternatively, allylic oxidation of **67a** with $MnO_2$, followed by treatment with benzylamine and then $NaBH_4$ provided the allylic amine, which can be protected with $BOC_2O$ to provide **75** (Scheme 12). Perhaps not unexpectedly, each of these substrates smoothly underwent cycloaddition with NPM to provide the enamines **69a** and **69b** with short reaction times, or the aromatized adducts **70** and **76** on extended reaction times. Formation of the ene adduct **71** also resulted when the reaction was conducted in benzene at reflux, but this could be readily separated. Each of these more elaborate adducts was obtained as a single stereoisomer, again derived from an *endo* transition state.

(55) Pirrung, M. C.; Pei, T. *J. Org. Chem.* **2000**, *65*, 2229.
(56) Greig, I. R.; Tozer, M. J.; Wright, P. T. *Org. Lett.* **2001**, *3*, 369.

In summary, we have developed synthetic approaches for the construction of a number of 4-vinylimidazoles with high levels of selectivity. 2-Substituted systems can be prepared either from the corresponding 2-substituted imidazoles or by lithiation of the 2-position and trapping with appropriate electrophiles. These vinylimidazoles smoothly participate in Diels−Alder reactions with NPM through the anticipated pathway under reasonably mild conditions; however, other doubly activated dienophiles generally do not react well (e.g., dimethyl fumarate, dimethyl maleate) or do not react via the Diels−Alder manifold (DMAD). All of these reactions with NPM are stereoselective, providing a single stereoisomer that appears to be derived from an *endo* transition state. Monoactivated dienophiles do react, but require considerably more forcing conditions, which leads to attenuated yields as a result of competitive substrate decomposition. Despite the lower reactivity, these reactions are regioselective, leading to the construction of 7-substituted tetrahydrobenzimidazole derivatives.

**Acknowledgment.** This research has been supported by the University of Texas at Arlington, the Texas Higher Education Coordinating Board-Advanced Research Program (ARP-003656-0004-1999), The Robert A. Welch Foundation (Y-1362 (C.J.L.) and Y-1289 (H.V.R.D.)), and the National Institutes of Health (GM065503). NMR spectrometers employed in this work were purchased in part with support from the NSF (CHE-0234811 and CHE-9601771).

**Supporting Information Available:** Experimental procedures and spectroscopic data for all new compounds, copies of $^{1}$H NMR and $^{13}$C NMR spectra for compounds (**17**, **18**, **21d**, **27b**,**d**,**e**, **29d**, **31e**, **30f**, **39b**,**c**, **40e**, **41e**, **52**−**56**, **58**−**64**, **68b**, **72**, **74**, **75**) lacking combustion analysis and CIF files for compounds **29a**, **31f**, **33e**, **39e**, and **51**. This material is available free of charge via the Internet at http://pubs.acs.org.

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