Electrocyclization

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Single-Step Modular Synthesis of Unsaturated Morpholine *N*-Oxides and Their Cycloaddition Reactions

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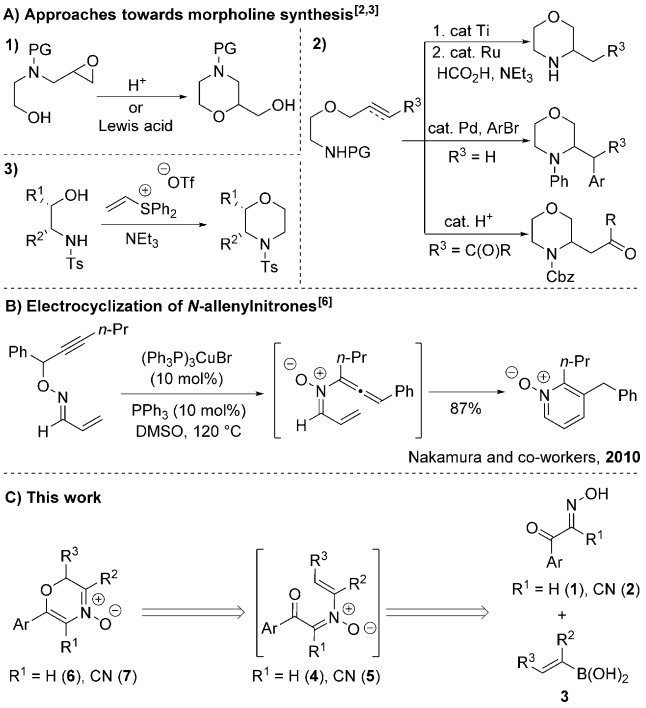
Abstract: *A single-flask procedure for the generation of α-keto-N-alkenylnitrones through a Chan–Lam coupling and subsequent spontaneous 6π electrocyclization of these intermediates for the synthesis of 2H-1,4-oxazine N-oxides has been developed for a variety of α-ketooximes and alkenylboronic acids. This transformation provides a new approach to C-substituted unsaturated morpholine derivatives that are poised to undergo further functionalization for the preparation of a diverse array of novel heterocyclic structures. The scope of the new method for the synthesis of 2H-1,4-oxazine N-oxides is discussed, in addition to initial studies describing the cycloaddition reactivity of these new heterocyclic intermediates.*

The prevalence of N-heterocyclic scaffolds in molecules that exhibit important biological and electronic activity has spurred the development of methods that provide access to novel N-heterocyclic architectures.[1] In particular, substituted morpholines are common motifs in biologically active molecules and are often prepared by displacement or addition reactions involving 1,2-amino alcohols (Scheme 1 A).[2,3] While a variety of elegant and efficient synthetic routes to substituted morpholines have been implemented using these strategies, these approaches are usually limited to the installation of functional groups and stereochemical information prior to or during oxazine ring formation.[4] We wondered if the electrocyclization of α-keto-*N*-alkenylnitrones might provide a new route to novel dehydrogenated morpholines, which could be easily functionalized for divergent synthetic applications.

Recently, our group has shown that *N*-alkenylnitrones can be accessed by Chan–Lam couplings of oximes and alkenylboronic acids and that these compounds undergo a variety of novel rearrangements, as well as addition and rearrangement reactions.[5] In related studies, Nakamura and co-workers have investigated the electrocyclization of *N*-allenylnitrones, accessed through a 2,3-rearrangement from *O*-propargyloximes, to give substituted pyridines (Scheme 1 B).[6] The inherent stability of pyridines makes them resistant to further functionalization; however, we anticipated that if a related electrocyclization could be triggered with α-keto-*N*-alkenylnitrones **4** and **5**—generated in situ through the coupling of oxime **1** or **2** with alkenylboronic acid **3**—the unsaturation pattern embedded in the resulting novel heterocyclic scaffolds **6** and **7** could be exploited to access a broad and diverse range of substituted morpholines (Scheme 1 C). While many new methods focus on finding better routes to known heterocycles, we have discovered that 2*H*-1,4-oxazine *N*-oxides **6** and **7** can be prepared by this approach. To the best of our knowledge, these types of unsaturated morpholine *N*-oxides have not been previously reported and are poised to undergo further synthetic manipulation.[7] Herein, we report the scope of this transformation for the synthesis of 2*H*-1,4-oxazine *N*-oxides **6** and **7**, as well as the facile conversion of these densely functionalized motifs into more complicated heterocyclic structures.



Scheme 1. Electrocyclization of *N*-alkenylnitrones for the synthesis of 2*H*-1,4-oxazine *N*-oxides. Cbz = benzyloxycarbonyl, PG = protecting group, Tf = trifluoromethanesulfonyl, Ts = *para*-toluenesulfonyl.

Our initial investigation of the synthesis of α-keto-*N*-alkenylnitrones **4** began by testing the reactivity of oxime **1a** and boronic acid **3a** under a variety of Chan–Lam coupling conditions. As shown in Table 1, entry 1, we were delighted to discover that when **1a** and **3a** were mixed in the presence of $Cu(OAc)_2$ in 1,2-dichloroethane (DCE) for 2 h, oxazine *N*-oxide **6a** was isolated in 79% yield. This preliminary result suggested that the 6π electrocyclization of *N*-alkenylnitrone (*E*)-**4a** can spontaneously occur after an initial C–N

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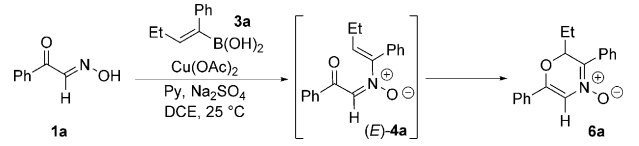
Table 1: Optimization of the synthesis of 2*H*-1,4-oxazine *N*-oxide **6a** from α-ketooxime **1a** and alkenylboronic acid **3a**.

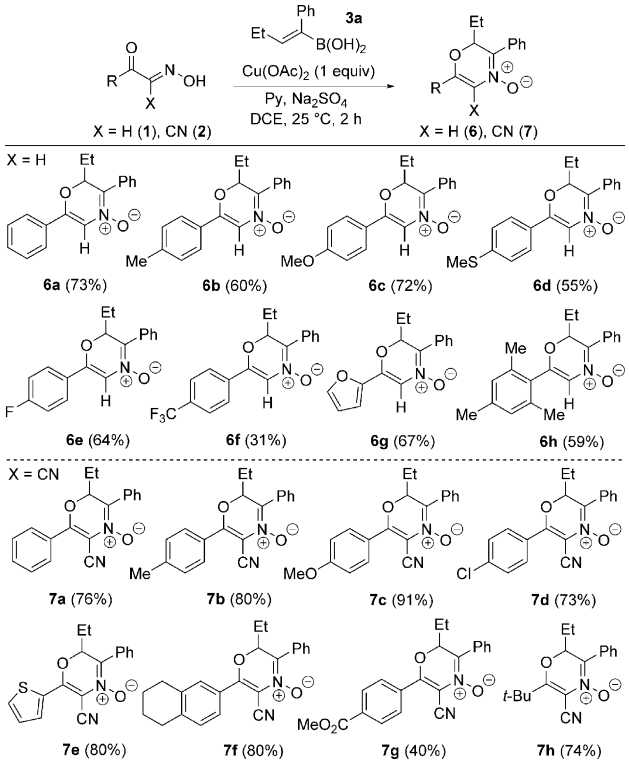


Entry	Catalyst	Base	Solvent	**6a** [%][a]
1	$Cu(OAc)_2$ (1 equiv)	Py	DCE	79
2	CuO (1 equiv)	Py	DCE	45
3	$CuBr_2$ (1 equiv)	Py	DCE	6
4	$Cu(OAc)_2$ (1 equiv)	NEt_3	DCE	26
5	$Cu(OAc)_2$ (1 equiv)	DABCO	DCE	46
6	$Cu(OAc)_2$ (1 equiv)	K_2CO_3	DCE	48
7	$Cu(OAc)_2$ (1 equiv)	Py	toluene	61
8	$Cu(OAc)_2$ (1 equiv)	Py	THF	51
9	$Cu(OAc)_2$ (1 equiv)	Py	EtOH	43
10	$Cu(OAc)_2$ (10 mol%)	Py	DCE	47

[a] Reaction conditions: **1a** (1 equiv), **3a** (5 equiv), base (3 equiv), Na_2SO_4 (6.6 equiv), 0.1 M in solvent, 25 °C. DABCO = 1,4-diazabicyclo-[2.2.2]octane, DCE = 1,2-dichloroethane, py = pyridine.

bond-forming event. Surprisingly, $Cu(OAc)_2$ was uniquely well-suited to this reaction. A variety of other Cu^I and Cu^{II} salts were tested but none exhibited significant conversion of **1a** into **6a** (entries 1–3), and none provided the proposed *N*-alkenylnitrone intermediate (*E*)-**4a**. The single-flask synthesis of **6a** from **1a** and **3a** was also dependent on the choice of base, and replacement of pyridine with NEt_3, DABCO, or K_2CO_3 led to attenuated yields (entries 4–6). The transformation was tolerant of a variety of different solvents but optimal results were achieved in DCE (entries 1 and 7–9). Decreasing the copper loading of the reaction mixture to 10 mol% also provided the desired product, albeit in moderate yield (entry 10). The data described in Table 1 indicated that the conditions in entry 1 were most appropriate to further explore the scope of the synthesis of **6** from **1** and **3** through this single-flask coupling and electrocyclization process.

The scope of the synthesis of unsaturated oxazine *N*-oxides **6** was initially investigated by varying the substituents on the oxime. As shown in Scheme 2, aldoximes with aryl ketone substituents with alkyl, ether, thioether, or halogen groups at the 4-position of the arene were well-tolerated and gave **6a**–**6e** in good yield. Oximes with electron-poor aryl ketone substituents gave products such as **6f** in attenuated yield. In addition to *para*-substituted aryl ketones, a furanyl ketone was also tolerated in this transformation to give **6g**, and a sterically hindered mesityl ketone was smoothly converted into **6h**. Aldoximes with alkyl ketone substituents were tested but a competing elimination reaction was favored over the formation of the corresponding oxazine.[8] In addition to α-ketoaldoximes, cyano-substituted oximes **2** were also treated with $Cu(OAc)_2$ and **3a** and shown to form oxazine *N*-oxides **7**. Cyano-substituted oximes with aryl ketone substituents generally gave higher yields than their aldoxime analogues for the synthesis of oxazine *N*-oxides such as **7a**–**7c**. The conversion of **2** into **7** also tolerated thiophenyl-substituted ketones to give **7e** and tetrahydro-

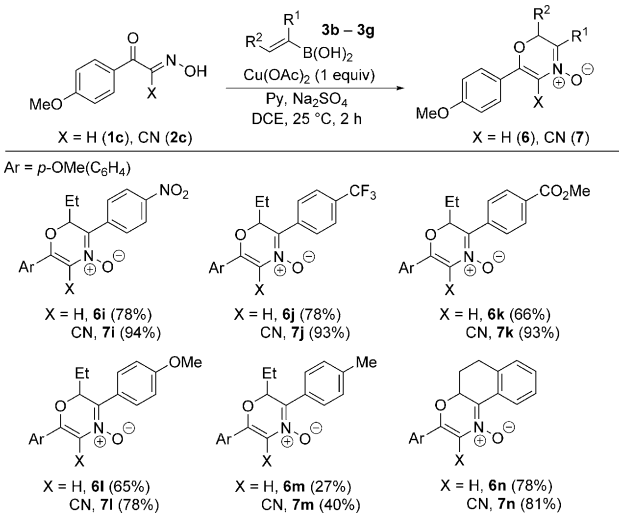


Scheme 2. Oxime scope of the oxazine *N*-oxide synthesis.

naphthalene substituents to give **7f**. Consistent with **6f**, cyano-substituted oximes with electron-deficient aryl ketone substituents gave attenuated yields for the preparation of oxazine *N*-oxides such as **7g**. In contrast to aldoximes **1**, pivaloyl-substituted **2h** was tested and smoothly converted into oxazine **7h**. The structures of **6c** and **7c** were confirmed by X-ray crystallography.[9] The synthesis of **6c** was also performed on 1 g scale, and purification by crystallization gave the desired product in 66% yield.[10] The results shown in Scheme 2 indicate that the Chan–Lam coupling and electrocyclization process to convert mixtures of oximes and alkenylboronic acids into 1,4-oxazine *N*-oxides is general for a variety of α-ketooximes and provides a reliable method to access unsaturated morpholines **6** and **7**.

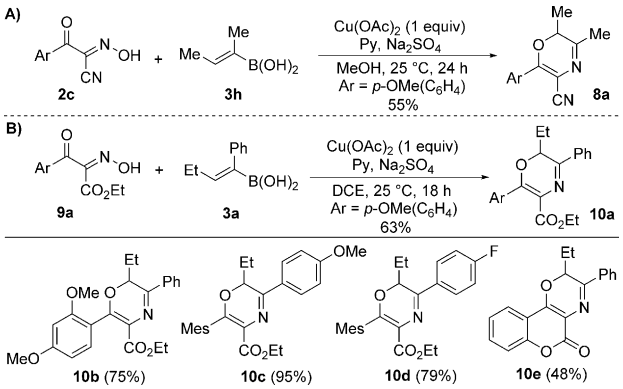
After investigating the tolerance of the unsaturated morpholine *N*-oxide synthesis with respect to the oxime, we decided to look at the scope of the alkenylboronic acid reaction partner. As shown in Scheme 3, a variety of electron-rich and electron-poor aryl groups were tolerated at the R^1 position of alkenylboronic acid **3** for the synthesis of **6** and **7**.[11] The alkyl group at the R^2 position could also be tethered to the R^1 position (see **6n** and **7n**). The same alkenylboronic acids were equally effective with both aldoxime **1c** and cyano-substituted oxime **2c**. Surprisingly, the C–N bond coupling and electrocyclization process seemed to require the combination of an aryl group at the R^1 position and an alkyl group at the R^2 position. Alterative reaction conditions were explored to expand the scope of **3** for the synthesis of oxazine *N*-oxides.

The scope of the oxime and alkenylboronic acid coupling and electrocyclization reaction can be expanded to include



Scheme 3. Alkenylboronic acid scope of the oxazine *N*-oxide synthesis.

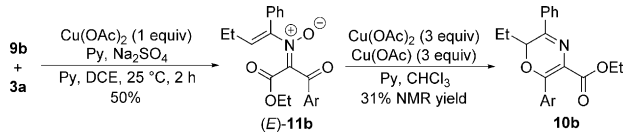
alkyl-substituted alkenylboronic acids such as **3h** by changing the reaction solvent. As shown in Scheme 4 A, when methanol was used as the reaction medium, 2-butenylboronic acid **3h** and oxime **2c** were converted into oxazine **8a**. This transformation occurs with a concomitant deoxygenation in contrast to formation of the predicted oxazine *N*-oxide.



Scheme 4. Oxazine synthesis through coupling, electrocyclization, and deoxygenation.

Further investigation of the scope of the oxime substrate showed that a similar Chan–Lam coupling, electrocyclization, and deoxygenation sequence was observed for ester-substituted oximes such as **9** (Scheme 4 B).[7] The use of copper catalysts and reagents for nitrone and pyridine *N*-oxide deoxygenation reactions has previously been reported.[12] Selective formation of oxazines **8** and **10** over oxazine *N*-oxides **6** and **7** appears to be a consequence of extended reaction times, and when cyano-substituted oxime **2g** was treated with **3a** for 4 h, the analogous oxazine product was isolated in contrast to the synthesis of **7g** described in Scheme 2.

Reaction monitoring was used to detect the proposed *N*-alkenylnitrone intermediates prior to electrocyclization and oxazine formation. When β-ketoester oxime **9b** was treated with alkenylboronic acid **3a** under the optimized reaction conditions, alkenylnitrone **11b** was isolated after 2 h (Scheme 5). Surprisingly, **11b** was formed as the *E* isomer and

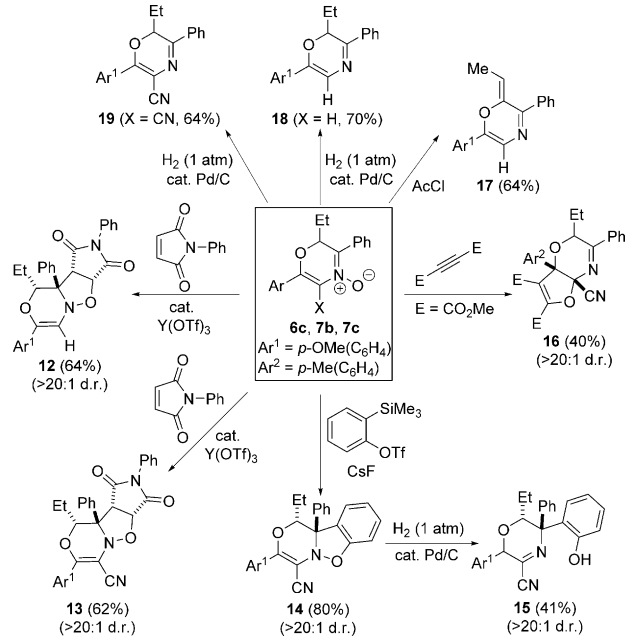


Scheme 5. Isolation of an *N*-alkenylnitrone.

resisted further conversion when resubjected to the reaction conditions. In contrast, when the reaction mixture used to form **11b** was stirred for 18 h, oxazine **10b** was isolated in 75 % yield (Scheme 4 B). Further screening showed that when **11b** was treated with an excess of Cu(OAc) and $Cu(OAc)_2$, **10b** was formed in 31 % yield.[13] These data provide support for the intermediacy of *N*-alkenylnitrones in the conversion of oximes **1**, **2**, and **9** into oxazine *N*-oxides **6** and **7** and oxazine **10**, respectively, but also suggest that rapid electrocyclization is needed to trap the active *N*-alkenylnitrone isomer prior to isomerization to the more stable isomer and that stabilization of the active isomer may require copper coordination to promote oxazine synthesis.[6,14]

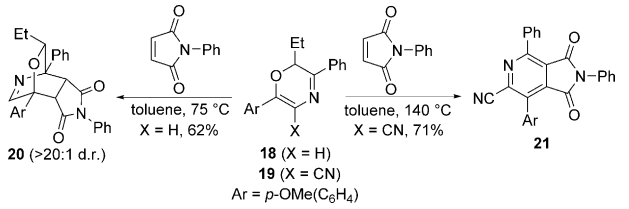
To the best of our knowledge, 2*H*-1,4-oxazine *N*-oxides **6** and **7** have not previously been reported, and discussions of oxazines similar to **10** are rare and limited to their use as latent azadienes.[7c,d] Due to the demand for new heterocycles for medicinal and material applications, we decided to explore the reactivity of **6** and **7** to determine how they might be applied in the preparation of new structurally diverse libraries. We decided to focus our study on the reactivity of **6** and **7** in [3+2] and [4+2] cycloaddition reactions (Scheme 6). When oxazines **6c** and **7c** were treated with *N*-phenylmaleimide in the presence of a Lewis acid catalyst, the dipolar cycloaddition products **12** and **13** were isolated in good yields with excellent diastereoselectivity. Similarly, **7c** underwent a [3+2] cycloaddition with a benzyne intermediate to form the fused oxazine-benzoxazolidine **14**. The N–O bond of **14** can be cleaved under hydrogenation conditions to give phenol-substituted morpholine **15**. Dimethylacetylene dicarboxylate also functioned as a dipolarophile when mixed with **7b**; however, the initial dipolar cycloaddition product rearranged to give furan-fused morpholine **16** under the reaction conditions. The structure of **16** was confirmed by X-ray crystallography.[9] Deoxygenation and elimination of **6c** was achieved by activation with AcCl to give **17**, and mild hydrogenation conditions allowed for the deoxygenation of **6c** and **7c** to give oxazines **18** and **19**, respectively. The transformations shown in Scheme 6 illustrate the versatility of **6** and **7** as precursors to novel heterocyclic compounds through both predictable and surprising pathways.

In addition to examining the dipolar cycloaddition reactivity of **6** and **7**, we were also interested in investigating the [4+2] cycloaddition reactivity of 2*H*-1,4-oxazine *N*-oxides. Whereas **6** and **7** were resistant to [4+2] cycloadditions with both electron-rich and electron-poor dienophiles, oxazines **18**



Scheme 6. Functionalization of 2*H*-1,4-oxazine *N*-oxides.

and **19** were reactive towards *N*-phenylmaleimide. As shown in Scheme 7, when **18** was treated with *N*-phenylmaleimide, the bicyclic [4+2] cycloaddition product **20** was isolated in good yield and excellent diastereoselectivity. Oxazine **19** similarly underwent a [4+2] cycloaddition with the same dienophile but the initial cycloaddition product rearranged to the corresponding pyridine **21** under the reaction conditions.



Scheme 7. Cycloaddition of 2*H*-1,4-oxazines.

These transformations are in contrast to the reactivity reported for similar oxazines generated from 2*H*-azirines and diazoesters, which favor ring opening and rearrangement.[7c,d] The preparation of cycloaddition products **20** and **21** also further supports the unique utility of oxazines such as **6**–**8** and **10** for the diversity-oriented synthesis of new heterocyclic structures.

In summary, we have discovered that α-keto-*N*-alkenylnitrones can be generated from α-ketooximes through a Chan–Lam coupling and spontaneously undergo a 6π electrocyclization to give 2*H*-1,4-oxazine *N*-oxides **6** and **7** in a single step. The scope of this method has been shown to include a variety of aldoximes and cyano-substituted oximes in combination with alkenylboronic acids. Initial functionalization studies have shown that **6** and **7** can be used as intermediates for rapidly accessing complicated heterocyclic structures such as **12**–**21**. The development of a single-step modular synthesis of **6** and **7** has facilitated access to these unsaturated morpholine *N*-oxide intermediates, and further investigations of this method and the derivatization of these products are currently ongoing in our laboratory to address the demand for new heterocyclic structures for medicinal and material applications.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: Chan–Lam coupling · electrocyclization · morpholines · nitrones · oxazine *N*-oxides

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[10] See the Supporting Information for details.
[11] The attenuated yields for **6m** and **7m** are due to poor separation.
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[13] The remainder of the product mixture contained hydrolysis products; 4π electrocyclization products were not observed.
[14] See the Supporting Information for an independent synthesis of an analogous *N*-allenylnitrone and electrocyclization.

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Communications

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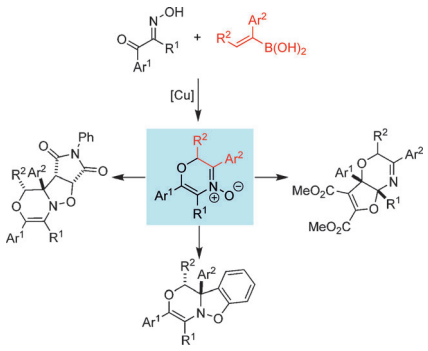

A new approach to substituted morpholines involves the preparation and functionalization of 2*H*-1,4-oxazine *N*-oxides. A Chan–Lam C—N bond coupling was used to generate α-keto-*N*-alkenylnitrones that spontaneously undergo a 6π electrocyclization to give unsaturated morpholine *N*-oxides, which can be further functionalized through a variety of cycloaddition reactions.