

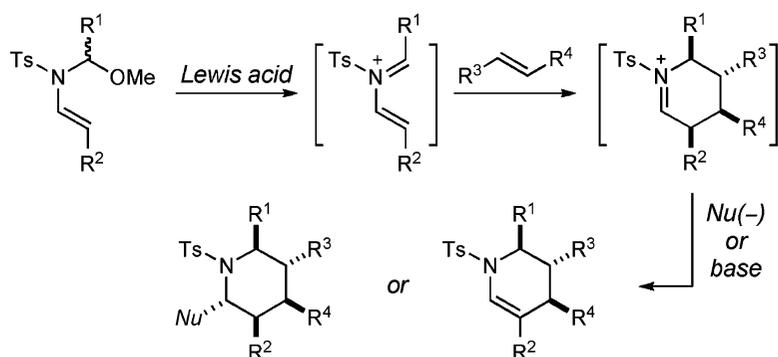
Communication

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[4 + 2] Cycloadditions of *N*-Alkenyl Iminium Ions: Structurally Complex Heterocycles from a Three-Component Diels–Alder Reaction Sequence

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Nitrogen-containing heterocycles are ubiquitous substructures in a myriad of biologically active natural products and small-molecule pharmaceuticals.¹ Accordingly, a wide range of target-directed and diversity-oriented synthesis activities are devoted to heterocycle synthesis. As a strategy for expanding existing hetero-Diels–Alder-based approaches to heterocycle synthesis, we were attracted to cationic 2-azadienes **1** as conduits to three-component [4 + 2] cycloaddition reactions accessing structurally and stereochemically diverse piperidine derivatives (Figure 1).² The putative *N*-alkenyl iminium ion–alkene [4 + 2] cycloadditions would generate tetrahydropyridinium ion cycloadducts **2**, allowing further functionalization through nucleophilic addition to the transposed iminium ion **2**. Herein, we describe *N*-alkenyl iminium ions **1** as enabling tools for three-component [4 + 2] cycloaddition–iminium ion addition reactions that afford an efficient and versatile synthesis of highly substituted piperidines.

Despite the prominence of 2-azadienes in the Diels–Alder lexicon,^{3,4} reaction designs offering in situ functionalization of incipient cycloadducts as a conduit to expanded functionality or structural diversity are relatively rare.⁵ This analysis inspired our interest in developing a general method for accessing cationic 2-azadienes under conditions conducive to realizing the putative intermolecular cycloaddition–iminium ion functionalization reaction sequence (Figure 1). Literature precedent

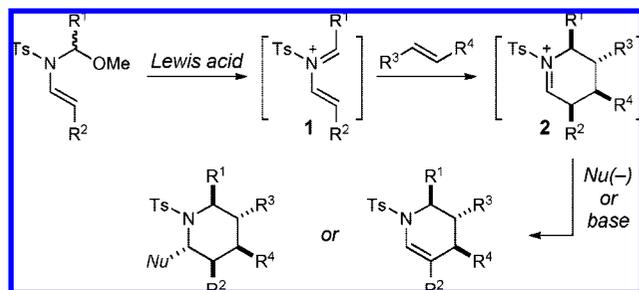
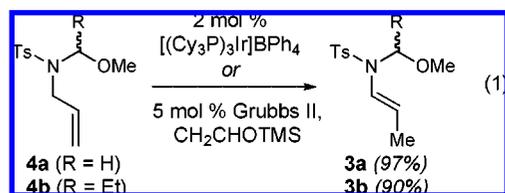
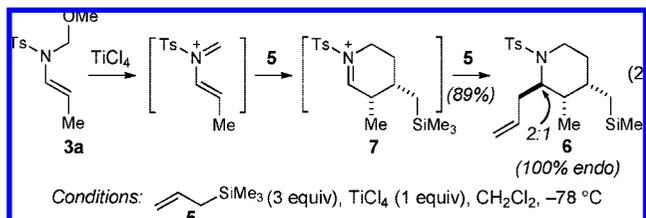


Figure 1. [4 + 2]Cycloadditions of *N*-alkenyl iminium ion dienes.

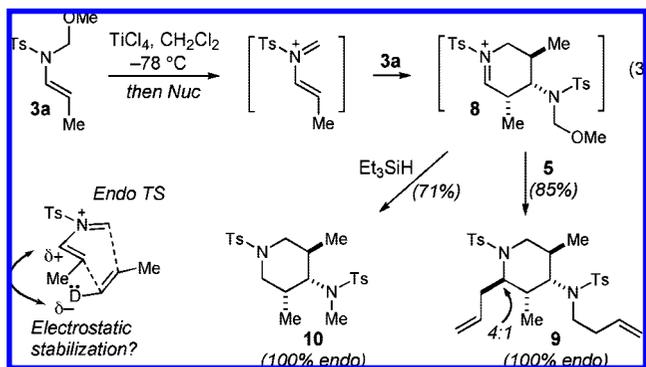
implicated *N*-alkoxymethyl enamines (e.g., **3**) as convenient precursors to the desired *N*-alkenyl iminium ion dienes via Lewis acid mediated *N,O*-acetal ionization (eq 1).^{4d,f,6} In the absence of a well-established method for preparing these *N*-alkoxymethyl enamines,⁷ we selected metal-catalyzed isomerization of allylic amine derivatives as a convenient route to the requisite diene precursors.⁸ Indeed, the easily obtained allylic sulfonamides **4a,b** participated in highly *E*-selective olefin isomerization using either Ir(I)- or Ru(II)-based catalysts to afford the putative diene precursors **3a,b** in high yield.^{9,10}



Preliminary assessment of the *N*-alkoxymethyl enamines as participants in the multicomponent Diels–Alder reaction sequence utilized **3a** as the diene precursor (eq 2). Allyltrimethylsilane (**5**) was selected as a representative electron-rich dienophile offering the ancillary advantage that excess reagent would directly alkylate the tetrahydropyridinium ion cycloadduct. Accordingly, adding enamine **4a** to a mixture of allyltrimethylsilane (3 equiv) and TiCl₄ (1 equiv, CH₂Cl₂, –78 °C) delivered the C₁-alkylated piperidine **6** (89%). Cycloaddition proved to be highly endo-selective with incomplete facial selectivity during nucleophilic addition to the iminium ion cycloadduct **7** providing **6** as a 2:1 mixture of C₁ epimers.¹¹

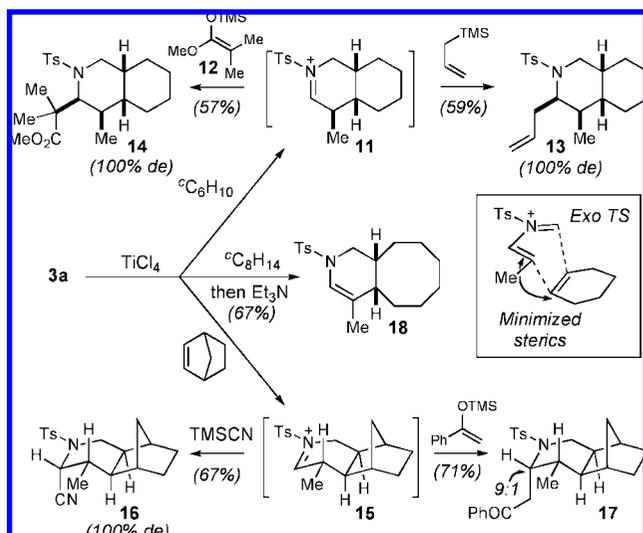


Rapid cycloaddition with electron-rich olefins is a defining feature of the *N*-alkenyl iminium ion dienes. For example, reacting **3a** with TiCl₄, without allyl silane present, affects [4 + 2] cycloaddition with un-ionized enamine **3a** to generate iminium ion **8** (eq 3); quenching cycloadduct **8** with allyl silane **5** promotes C₁ allylation in addition to ionization/allylation of the pendant *N,O*-acetal to afford the tetrasubstituted piperidine **9** as a 4:1 mixture of C₁ epimers (85%).¹² Alternatively, hydride-mediated reduction of **8** generated the 3,4,5-trisubstituted piperidine **10** as a single endo-dia stereoisomer. Consistent with the preceding allyl silane cycloadducts, the enamine cycloadditions were highly endo-selective.^{13,14} The four newly formed C–C σ -bonds in **9** exemplify the opportunities afforded by this reaction sequence for expanding structural diversity available from the traditional Diels–Alder manifold.



The *N*-alkenyl iminium ions express sufficient reactivity to engage electronically unactivated olefins as dienophiles in [4 + 2] cycloadditions. Activating **3a** with TiCl₄ (1 equiv) in the presence of

Scheme 1



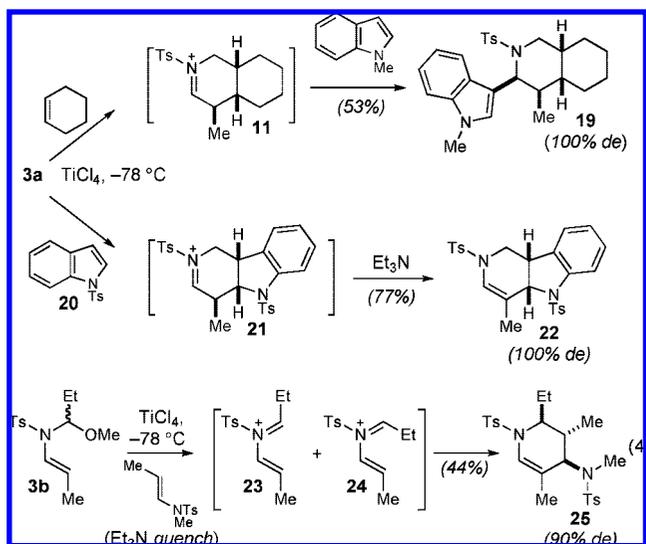
cyclohexene and quenching the intervening cycloadduct **11** with allyltrimethylsilane or ketene acetal **12** delivered the perhydroisoquinoline derivatives **13** (59%) and **14** (57%), respectively, as single diastereomers (Scheme 1). These cycloadditions are highly exo-selective, suggesting that minimized nonbonded interactions are the determining factor in transition state organization. Ensuing nucleophilic addition to the cycloaddition-derived iminium ion **11** proceeds from the convex face of the cis-fused octahydroisoquinoline ring system to deliver **13** (or **14**) with the fully stereocontrolled construction of three new C–C σ -bonds. Norbornene participates in similarly selective cycloadditions with trimethylsilyl cyanide or enol silane functionalization of the intervening cycloadduct **15**, affording cycloadducts **16** and **17**, respectively. Cyclooctene also reacts as the dienophile with **3a** to afford the [6.4.0] bicyclic heterocycle **18** (67%), wherein amine-mediated deprotonation was used as an alternative method for derivatizing the intervening iminium ion.

The utility of indole in the cycloaddition–alkylation sequence is illustrative of how similar reaction components can be alternated as dienophiles or nucleophiles to access dramatically different architectural types. *N*-Methyl indole functions as an effective nucleophile toward cycloadduct **11** to afford the perhydroisoquinoline **19** (53%) (Scheme 2). However, *N*-methyl indole is too Lewis basic to be compatible with the preceding Lewis acid mediated cycloaddition. *N*-Tosyl indole (**20**) possesses the correct electronics to participate in efficient [4 + 2] cycloaddition with **3a** but lacks sufficient nucleophilicity to add to the intervening cycloadduct **21**. As a result, ensuing iminium ion functionalization could be achieved independent of the preceding cycloaddition event; in this case, amine-mediated deprotonation of **21** delivered the tricyclic indole **22** in 77% yield.

The C₁-substituted *N*-alkoxymethyl enamine **3b** provides access to azadienes possessing substitution at both terminal carbons (eq 4). Lewis acid mediated ionization of racemic **3b** generates the anticipated mixture of (*Z,E*)- and (*E,E*)-dienes **23** and **24**, respectively. In situ cycloaddition of the more reactive (*Z,E*)-diene **23** affords the tetra-substituted piperidine **25** with high endo-selectivity (44%).

N-Alkenyl iminium ions enable multicomponent cycloaddition–iminium ion functionalization reactions, affording efficient access to structurally diverse and stereochemically rich piperidine derivatives. These attributes are expected to render this methodology generally useful in both target-directed and diversity-oriented synthesis activities.

Scheme 2



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Supporting Information Available: Experimental procedures and ¹H and ¹³C spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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