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COMMUNICATIONS

Published on Web 06/25/2008

[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 functionaliztion reaction sequence (Figure 1). Literature precedent

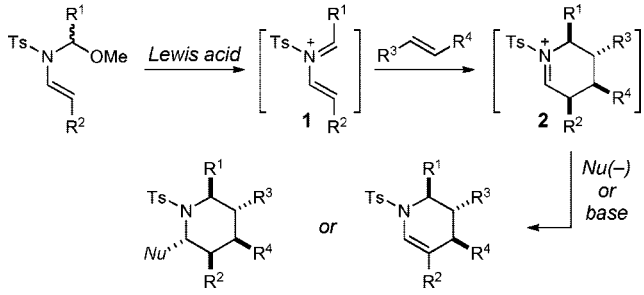
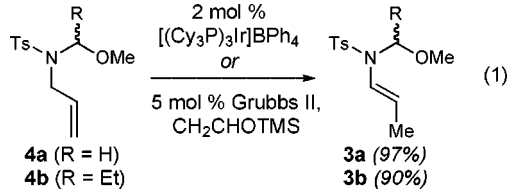


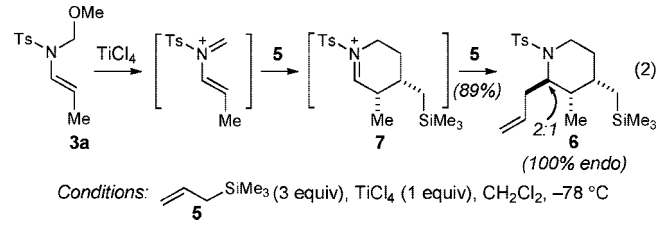
Figure 1. [4 + 2]Cycloadditions of *N*-alkenyl iminium ion dienes.

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]



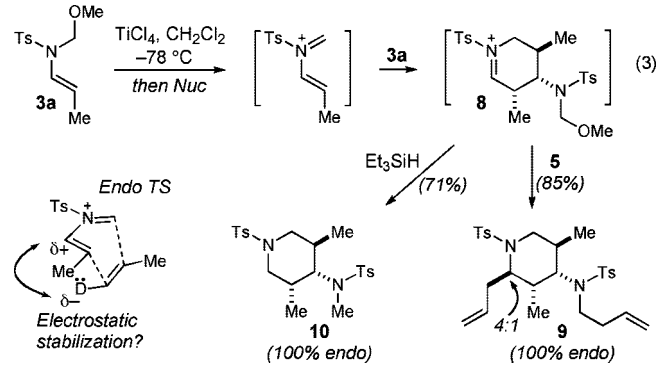
(1)

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 $TiCl_4$ (1 equiv, CH_2Cl_2, −78 °C) delivered the C_1-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 C_1 epimers.[11]



(2)

Rapid cycloaddition with electron-rich olefins is a defining feature of the *N*-alkenyl iminium ion dienes. For example, reacting **3a** with $TiCl_4$, 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 C_1 allylation in addition to ionization/allylation of the pendant *N*,*O*-acetal to afford the tetrasubstituted piperidine **9** as a 4:1 mixture of C_1 epimers (85%).[12] Alternatively, hydride-mediated reduction of **8** generated the 3,4,5-trisubstituted piperidine **10** as a single endo-diastereomer. 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.

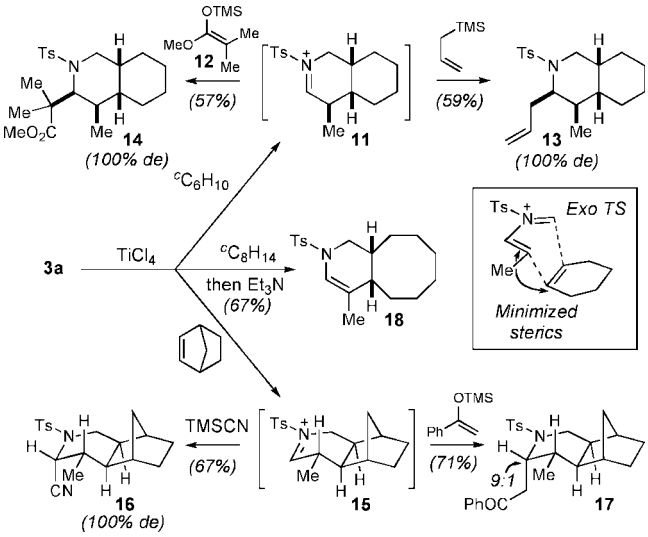


(3)

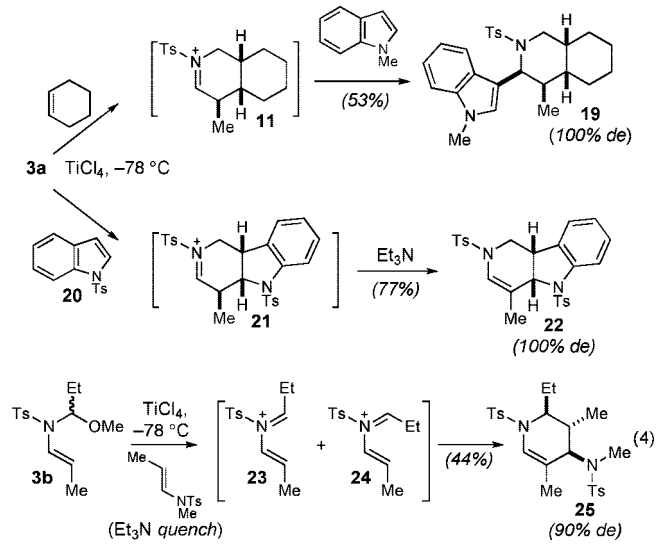
The *N*-alkenyl iminium ions express sufficient reactivity to engage electronically unactivated olefins as dienophiles in [4 + 2] cycloadditions. Activating **3a** with $TiCl_4$ (1 equiv) in the presence of

10.1021/ja8028153 CCC: $40.75

Scheme 1



Scheme 2



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 trimethylsilylcyanide 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 altenative 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 C_1-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.

Acknowledgment. Support from the National Institutes of Health (R01 GM63151 and P50 GM067082 supporting the UPCMLD) and the Merck Research Laboratories is gratefully acknowledged.

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

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JA8028153