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N-Heterocyclic Carbene-Catalyzed (4 + 2) Cycloaddition/ Decarboxylation of Silyl Dienol Ethers with α,β-Unsaturated Acid Fluorides

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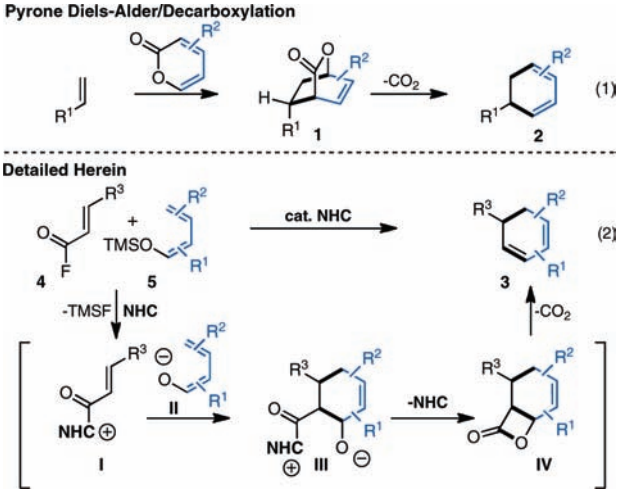
Supporting Information

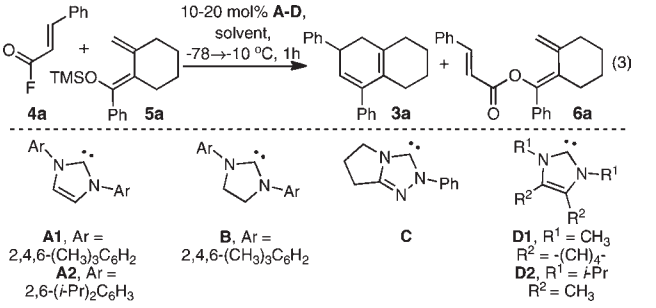
ABSTRACT: Herein we report the first all-carbon N-heterocyclic carbene-catalyzed (4 + 2) cycloaddition. The reaction proceeds with α,β-unsaturated acid fluorides and silyl dienol ethers and produces 1,3-cyclohexadienes with complete diastereocontrol (dr >20:1) while demonstrating a new type of reaction cascade exploiting α,β-unsaturated acyl azoliums.

Transformations that rapidly generate complexity are integral to the assembly of challenging molecular architectures.[1] In this regard, cycloadditions are peerless in advancing chemical synthesis.[2] This is exemplified by the (4 + 2) Diels−Alder cycloadditions of pyrones.[3] In addition to reacting with predictable stereo- and regioselectivity, the bicyclic products (i.e., **1**) undergo decarboxylation to produce 1,3-cyclohexadienes **2**, which are valuable for further elaboration (eq 1).[3] We postulated that olefins, when conjugated to acyl azoliums (i.e., **I**),[4] should possess the electronic and steric requirements appropriate to a dienophile in a (4 + 2) cycloaddition. This reaction, when followed by lactonization and decarboxylation,[5] would provide 1,3-cyclohexadienes[6] that are isomeric to those from pyrone Diels−Alder reactions . Herein we report the realization of this concept with the first all-carbon N-heterocyclic carbene (NHC)-catalyzed (4 + 2) cycloaddition (eq 2).[7]



In 2004, Bode[4a] and Rovis[4b] reported approaches to acyl azoliums via the reaction of NHCs[8] with redox-active aldehydes.

Table 1. Selected Optimization Studies



entry	cat. (mol %)[a]	base/solvent	3a:6a[b]	yield of 3a (%)[c]
1	**A1** (20)	KO^{t}Bu/Toluene	3:1	13
2	**A1** (10)	KO^{t}Bu/THF	>95:5	70
3	**A1** (10)[d]	THF	77:23	44
4	**A2** (10)	KO^{t}Bu/THF	3:1	48
5	**B** (10)	KHMDS/THF	–	10[e]
6	**C** (10)	KHMDS/THF	–	trace[e]
7	**D1** (10)	KHMDS/THF	–	–
8	**D2** (10)[f]	**THF**	**>95:5**	**76**

[a] All catalysts were generated using using equimolar base, except as noted. [b] Ratio determined by ^{1}H NMR analysis. [c] Isolated yield following flash column chromatography. [d] Generated from the imidazolium and isolated from KCl. [e] Conversion as judged by ^{1}H NMR analysis. [f] Generated by reduction of the corresponding thiourea.

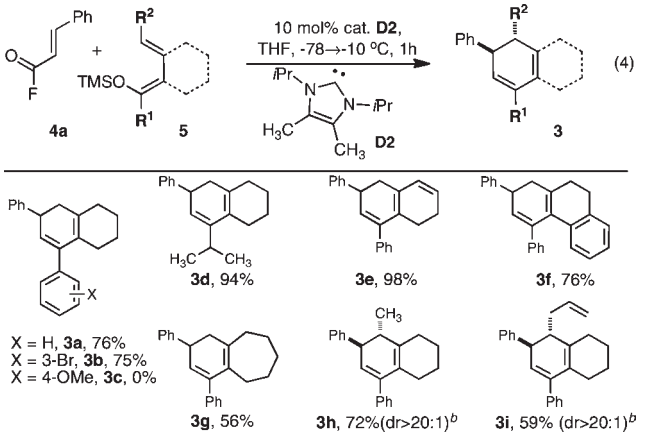
Subsequent to that work, these intermediates have been implicated in various transformations.[4] We recently developed a conceptually distinct strategy in which NHC-mediated substitution provides acyl azoliums, while concurrently liberating groups active in bond-forming cascades.[9] In the context of a (4 + 2) cycloaddition, this strategy would allow cascade activation of α,β-unsaturated acid **4** and TMS enol ether **5**, providing intermediates **I** and **II**, which could then form cycloadduct **III** (eq 2).

To test this hypothesis, IMes-substituted NHC **A1** (20 mol %) was exposed to substrates **4a** and **5a** (eq 3). Gratifyingly, these conditions resulted in the formation of cyclohexadiene **3a** in 13% yield along with α,β-unsaturated dienol ester **6a** (Table 1, entry 1).[10] Standard optimization showed that coordinating solvents and decreased catalyst loading provided **3a** in an improved yield of 70% with only a trace of ester **6a** (Table 1, entry 2).

Received: December 9, 2010
Published: March 10, 2011

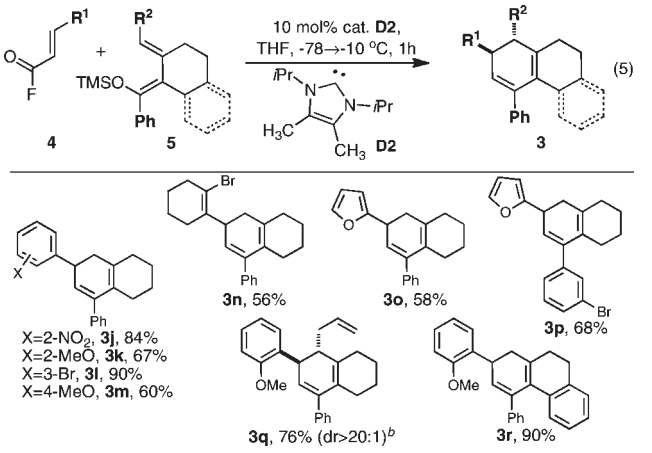
dx.doi.org/10.1021/ja111067j | J. Am. Chem. Soc. 2011, 133, 4694–4697

Table 2. Scope in Regard to Silyl Dienol Ether 5[a]



[a] Isolated yield following column chromatography. [b] dr determined by ^{1}H NMR analysis.

Table 3. Scope in Regard to Acyl Fluoride 4[a]

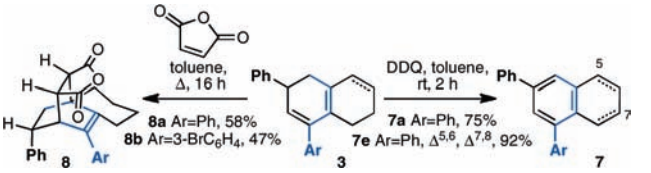


[a] Isolated yield following column chromatography. [b] dr determined by ^{1}H NMR analysis

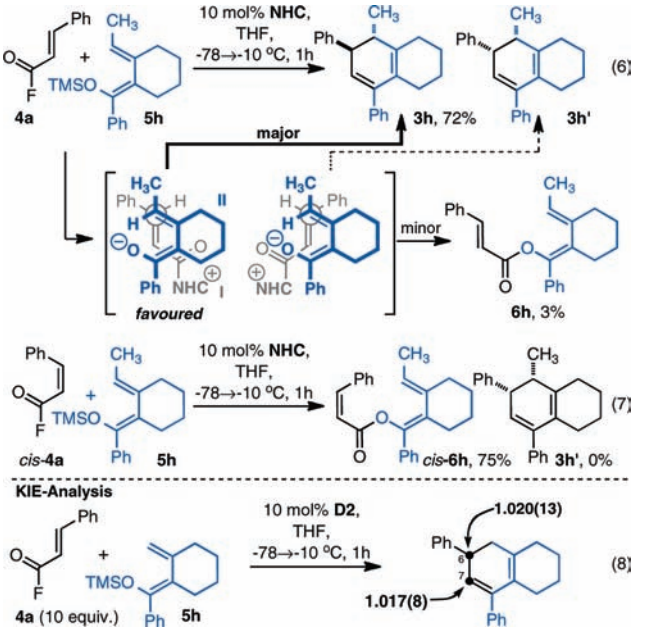
The transformation was highly sensitive to the nature of the catalyst. For example, use of NHC **A1** under salt-free conditions increased the amount of *O*-acylation, as did use of the more sterically demanding IDip-substituted NHC **A2** (Table 1, entries 3 and 4). Imidazolinium-derived NHC **B**, triazolium-derived **C**, and benzimidazole-derived **D1** all proved unsuitable for this reaction (Table 1, entries 5−7). These catalyst modifications suggested that dialkyl imidazolium-derived NHCs should display ideal nucleophilicity[11] and bulk. This proved to be the case, with an optimal yield obtained using NHC **D2** (Table 1, entry 8).

Exploration of the scope of the (4 + 2) cycloaddition/decarboxylation commenced with an examination of the functional group tolerance at R^1 (Table 2). Electron-poor aromatics gave 1,3-cyclohexadiene **3b** in good yield, while alkyl groups at R^1 were accommodated, with *i*-Pr-containing **3d** prepared in 94% yield. Unfortunately, electron-rich substrates (i.e., **5c**) were not suited to the conditions. Similarly, acyclic dienolates and aldehyde-derived substrates were incompatible, providing the *O*-acylated proucts.[12] The incorporation of additional degrees of unsaturation into the substrate gave triene **3e** in 98% yield, while polycyclic substrates and those containing larger rings reacted smoothly, providing dihydrophenanthrene **3f** and annulated cycloheptene **3g** in good yields. Alkyl groups at R^2 could be included, providing cyclohexadienes **3h** and **3i** in good yield with excellent diastereoselectivity (>20:1).[13]

Scheme 1. Derivatization of Cyclohexadienes 3a, 3b, and 3e



Scheme 2. Mechanistic Rationale



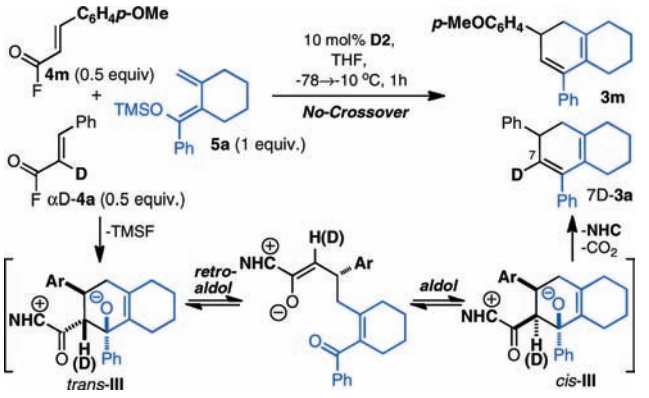
The nature of the α,β-unsaturated acid fluoride **4**[14] was investigated through the introduction of electron-releasing, electron-withdrawing, heteroaromatic, and olefinic groups (Table 3). Again, the reaction proved flexible, forming products **3j**−**r** in good yields with excellent sterocontrol.

The synthetic potential of the 1,3-cyclohexadienes was next investigated. As expected, they proved to be competent substrates for aromatization, providing highly substituted tetrahydronapthalene **7a** and naphthalene **7e**, and also acted as dienes in the Diels−Alder reaction, providing structurally rich tricyclic compounds **8a** and **8b** (Scheme 1).[15]

Mechanistically, we believe that the reaction commences with nucleophilic substitution of the acyl fluoride by the NHC followed by desilylation to generate **I** and **II**.[16] On the basis of the stereochemistry of compounds **3h**, **3i**, and **3q**, we propose that the annulation occurs via a concerted pathway with an endo orientation in the transition state (eq 6). When the reaction was performed using *cis*-cinnamoyl fluoride (*cis*-**4a**) and dienol silyl ether **5h**, unfavorable steric interactions in the endo transition state retarded the cycloaddition, and exclusive *O*-acylation occurred (eq 7). An alternate explanation for the annulation involves a stepwise vinylogous Michael/aldol sequence.[17] To explore the nature of the annulation, kinetic isotope effect (KIE)

dx.doi.org/10.1021/ja111067j |J. Am. Chem. Soc. 2011, 133, 4694–4697

Scheme 3. Crossover Studies



studies using natural abundance techniques[18] were undertaken. While the precision was modest (eq 8), positive KIEs at C6 and C7, implicates a concerted (4 + 2) cycloaddition as the turnover-limiting step (Scheme 2).[19] These data, together with the endo selectivity and the documented reactivity of related dienolates,[20] indicate that a concerted reaction is most likely.

A concerted endo-selective (4 + 2) cycloaddition results in a *trans* arrangement between the acyl azolium and the alkoxide (i.e., *trans*-**III**). However, lactonization and decarboxylation presumably occur via *cis*-**III**. Mechanistically, such an isomerization can occur by either an intermolecular proton transfer or a retro-aldol/aldol sequence.[21] To investigate these scenarios, a crossover experiment involving (α-D)-**4a** and **4m** was undertaken (Scheme 3). If proton transfer were required, then scrambling of the deuterium across the two cyclohexadiene products would have been expected. In the event, complete deuterium retention (formation of 7D-**3a** and no 7D-**3m**) indicated that the *trans*-**III** → *cis*-**III** isomerization likely occurs via a retro-aldol/aldol sequence.

To summarize, we have reported the first all-carbon NHC-catalyzed (4 + 2) cycloaddition. The reaction proceeds with a range of silyl dienol ethers and α,β-unsaturated acid fluorides, providing 1,3-cyclohexadienes in good yields with excellent diastereoselectivity. Mechanistic investigations suggest that the (4 + 2) cycloaddition proceeds in a concerted fashion with a preference for endo orientation of the coupling partners. The catalytic cycle is completed by isomerization via a retro-aldol/aldol sequence, lactonization, and then decarboxylation. These studies expound a new class of NHC-catalyzed transformation involving α,β-unsaturated acyl azoliums[22] and will contribute to further advances in nucleophilic organocatalysis. The application of this reaction in total synthesis and investigations into the mechanism using theoretical and experimental approaches are ongoing.

■ ASSOCIATED CONTENT

Supporting Information. Characterization data, NMR spectra, and detailed experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ ACKNOWLEDGMENT

We acknowledge financial support from the ARC (DP0881137) and Monash University (Research Accelerator Program), helpful discussions with Professor Tomislav Rovis (Colorado State University), and donation of catalysts (not discussed).

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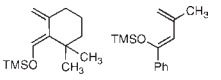

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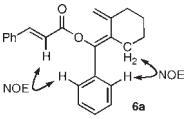

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