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π-Nucleophile Traps for Metallonitrene/Alkyne Cascade Reactions: A Versatile Process for the Synthesis of α-Aminocyclopropanes and β-Aminostyrenes

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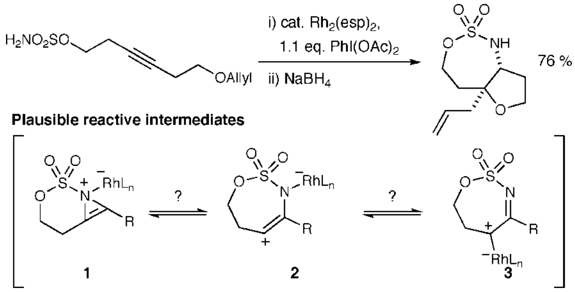
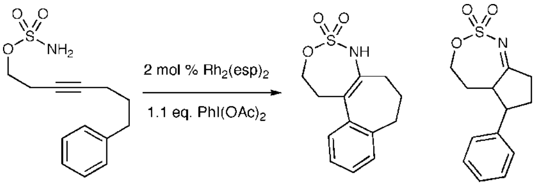
Inspired by the synthetic potential of a catalytic metallonitrene/alkyne metathesis process,[1] we recently disclosed a conceptually novel cascade reaction in which an electrophilic rhodium nitrenoid species was trapped by an alkyne, generating a new reactive intermediate that could react with tethered ethers in an ylide formation/migration sequence (Scheme 1).[2] The development of this reaction established the viability of the metallonitrene/alkyne metathesis concept, but the nature of the reactive intermediate(s) remained unclear.[3,4]

Scheme 1. Metallonitrene/Alkyne Cascade Reaction



Here, we establish the remarkable versatility of the reactive intermediate, demonstrating that the cascade can be terminated by a variety of π-nucleophiles leading to the formation of α-aminocyclopropanes and β-aminoaryl systems. Furthermore, we have established conditions for intermolecular cascade termination and probed the nature of the reactive intermediate. In all cases, these metallonitrene initiated cascade processes facilitate the rapid construction of complex heterocyclic architectures from readily available starting materials.

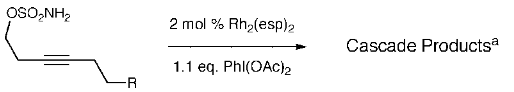
Following the discovery of the metallonitrene/alkyne/ylide formation cascade reaction, our immediate priority was to investigate the nature of the reactive intermediate generated upon reaction of the metallonitrene with an alkyne. Specifically, we set out to probe the potential equilibrium between an intermediate with "vinyl cation/metalloenamine" like character (e.g., **2**) and an isomeric α-iminometallocarbenoid species (e.g., **3**).

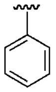
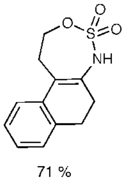
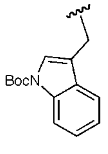
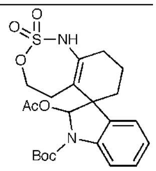
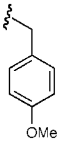
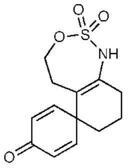
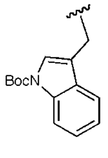
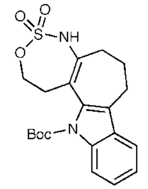
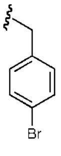
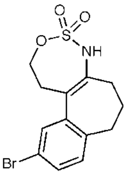
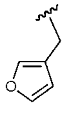
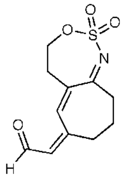


4 **5**, 72% yield **6**, not observed (1)

To this end, substrate **4** with an aryl ring tethered to the alkyne was synthesized. In the event that the reactive intermediate resembled an α-iminometallocarbenoid species, we would expect a facile benzylic C−H insertion reaction, to generate the bicyclic structure **6** (or an aryl cyclopropanation/ring expansion reaction).[5] However, when substrate **4** was treated with 2 mol % $Rh_2(esp)_2$ and 1.1 equiv of bisacetoxyiodobenzene, we observed the exclusive production of enamine **5** arising from an electrophilic aromatic substitution reaction. The C−H insertion product **6** was not observed, suggesting the reactive intermediate has substantial "vinyl-cation" like character.

Table 1. Friedel−Crafts Termination of the Metallonitrene/Alkyne Cascade Reaction



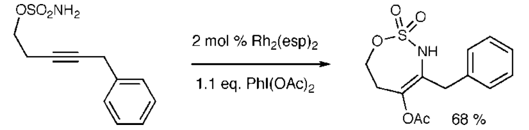
R	Product	R	Product
	 71 %	 **9**	 **10**, 80 %^{b}
	 70 %	 **9**	 **11**, 68 %^{c}
 **7**	 **8**, 28 %		 47 %

^{a} Standard reaction conditions: CH_2Cl_2, 40 °C. ^{b} 1 equiv of AcOH added to reaction mixture. ^{c} Reaction performed in toluene at 80 °C.

Subsequent investigations revealed that both electron-rich and -neutral aromatic moieties can engage the reactive intermediate in Friedel−Crafts cascade termination events, and in all cases the products are consistent with an electrophilic aromatic substitution mechanism (Table 1). However, the electron-poor bromobenzene substrate **7** was inefficient as a cascade terminator, and the product (**8**) was obtained in only modest yield. Tether lengths that result in either 6- or 7-membered ring formation allow for an efficient intramolecular cyclization to occur. If the tether length is shortened, geometric constraints prevent intramolecular Friedel−Crafts reaction, and the reactive intermediate is trapped in an intermolecular fashion by the acetate byproduct from the hypervalent iodine oxidant, resulting in efficient aminoacetoxylation of the alkyne (eq 2).

When indole substrate **9** was subjected to our standard reaction conditions a mixture of C3 (**10**) and C2 (**11**) alkylated products was

10.1021/ja809078d CCC: $40.75

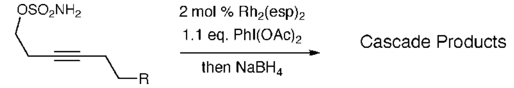


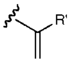
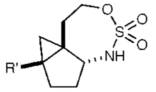
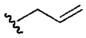
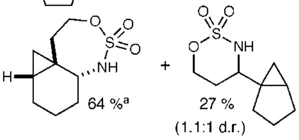
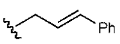
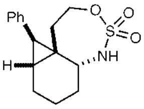
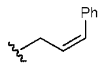
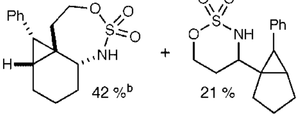
(2)

isolated (Table 1). Addition of 1 equiv of acetic acid promoted formation of the spirocyclic product **10**, or the C2 alkylated product **11** could be accessed by performing the reaction in toluene at 80 °C. Furan could also be used as an efficient π-nucleophile in the cascade reaction, resulting in the formation of a Z-α,β-unsaturated aldehyde. While consistent with a furan C2 attack on an electrophilic "vinyl-cation" reactive intermediate followed by furan fragmentation, this product is reminiscent of those obtained by established metal catalyzed furan cyclopropanation/rearrangement processes.[6]

Indeed, our investigations have revealed that the reactive intermediate formed in our metallonitrene/alkyne cascade process is capable of engaging tethered olefins in cyclopropanation reactions (Table 2).

Table 2. Cyclopropanation as a Metallonitrene/Alkyne Cascade Termination Event



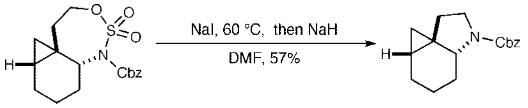
Entry	R	Product(s)
1 2		 R' = H, 67 %[a] R' = CH_3, 85 %[a]
3		 64 %[a] + 27 % (1.1:1 d.r.)
4		 70 %[b]
5		 42 %[b] + 21 %

[a] Relative stereochemistry established by NOE experiments. [b] Relative stereochemistry established by X-ray crystallography.

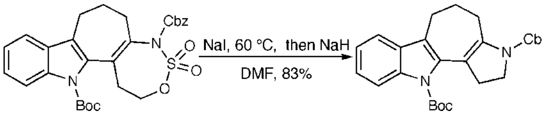
Terminal, 1,1- and 1,2-disubstituted olefins were all tolerated in the cyclopropanation reaction. Significantly, reaction of a *trans*-olefin gave rise to a *trans*-cyclopropane (entry 4), and reaction of a *cis*-olefin produced a *cis*-cyclopropane product (entry 5). We did not observe any evidence of isomerization during the cascade reaction, suggesting that the cyclopropanation is a concerted process.[7] Additionally, we observed that tether lengths resulting in 7,5,3-tricyclic products resulted in highly regioselective reactions (entries 1 and 2). However, extension of the tether between the alkyne and the olefin by a single carbon had a significant impact on the regioselectivity of the initial cyclization between the metallonitrene and the alkyne (entries 3 and 5). In these cases, cyclization of the sulfamate ester to the distal carbon of the alkyne (major) and to the proximal alkyne carbon (minor) is observed.

In light of these observations, we believe the intermediate formed in these reactions is best represented either as a zwitterionic species such as **2** (Scheme 1) or as a highly strained, electrophilic rhodium bound azirine (**1**, Scheme 1) with the sulfamate ester tether imparting a strong bias for nucleophile attack at the internal position of the azirine.[8] However, if the nucleophile is tethered to the azirine in a manner that prevents efficient orbital overlap for this internal attack, then competitive formation of the regioisomeric product is observed (Table 2, entries 3 and 5).

From a synthetic standpoint, sulfamate esters can be activated for nucleophilic displacement of sulfur trioxide by nitrogen acylation.[9] In the context of this metallonitrene/alkyne cascade reaction chemistry, and the observed selectivity for 7-membered oxathiazepane ring formation, we have developed a two-step protocol for sulfur trioxide extrusion to produce the corresponding pyrrolidine (eqs 3 and 4). After *N*-acylation with CbzCl, a one-pot reaction with NaI followed by NaH in DMF leads to a ring-opening/ring-closing cascade for pyrrolidine formation.



(3)



(4)

In conclusion, we have demonstrated that the reaction between a sulfamate ester derived rhodium nitrene and an alkyne leads to formation of a versatile intermediate capable of interacting with a variety of nucleophiles to produce a diverse array of heterocyclic products in a predictable manner. Further studies to address asymmetric catalysis of these metallonitrene/alkyne cascade reactions are underway in our laboratory.

Supporting Information Available: Experimental procedures, structural proofs, and analytical data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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