Heterocycles

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Unveiling Latent α-Iminocarbene Reactivity for Intermolecular Cascade Reactions through Alkyne Oxidative Amination**

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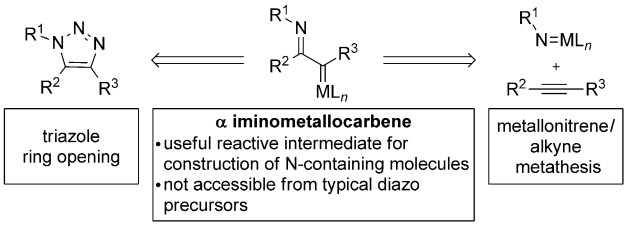
The chemistry of reactive (electrophilic) metallocarbenes, primarily obtained by metal-catalyzed decomposition of α-diazocarbonyl compounds, has been extensively developed and offers significant opportunity for strategic C–C, C–O, and C–N bond formation through a variety of well-defined reaction mechanisms.[1] Given the prevalence of nitrogen atoms in biologically and pharmaceutically relevant molecules and the intrinsic electronic similarities between carbonyl and imine functional groups, the development of analogous metallocarbene chemistry with an α imine providing the necessary electrophilic activation represents both an obvious and synthetically important extension of this chemistry. However, the requisite α-diazoimine precursors readily isomerize to 1,2,3-triazoles, and these heterocycles were long believed to represent a thermodynamic sink, thus significantly delaying the development of metallocarbene chemistry associated with such systems.[2] Nonetheless, the perception that reliable methods to access α-iminocarbene chemistry would offer the potential to build structurally complex nitrogen-containing molecules in a remarkably efficient manner has recently resulted in the development of several complementary solutions to the α-diazoimine isomerization problem (Scheme 1).



Scheme 1. Alternative routes for α-iminometallocarbene synthons.

Specifically, Park and co-workers showed that β oximinoesters can be diazotized with minimal rearrangement to the isomeric triazoles, thus providing an entry into α-oximino acceptor–acceptor carbenoid chemistry.[3] More generally, Fokin and co-workers demonstrated that 1,2,3-triazoles can themselves act as precursors to α-iminometallocarbene intermediates, participating predictably in a range of traditional metallocarbene reactions to generate α-functionalized imine products.[4] Implicit in this strategy is the recognition that alkynes can serve as precursors to both α-oxy- and α-iminocarbenes and that oxidation of an alkyne under appropriate reaction conditions could serve to reveal the desired reactive intermediate.[5] The approach of Raushel and Fokin separates the alkyne oxidation, which is achieved through copper-catalyzed azide–alkyne cycloaddition,[6] from the rhodium-catalyzed metallocarbene generation.

Studies in our laboratory have focused on the direct unveiling of an intermediate with an α-iminometallocarbene reactivity profile by a metallonitrene-initiated oxidative cascade process. In intramolecular settings we have demonstrated the feasibility of this direct approach, terminating the cascade in an array of predictable carbene reactions (oxygen-ylide formation/[2,3] Wittig rearrangement,[7] electrophilic aromatic substitution, and cyclopropanation).[8] Despite the inherent attractiveness of this single-step approach, reaction conditions that facilitate efficient intermolecular cascade termination are required for broad applicability and synthetic utility. Herein we describe the development of a metallonitrene-initiated alkyne oxidation cascade with intermolecular trapping of the reactive intermediate by a variety of allyl ethers to provide α-oxyimine products in which new C=N, C–O, and C–C bonds have all been generated.

The challenge associated with the development of an intermolecular reaction cascade is one of chemoselectivity. Under the conditions that were previously developed for intramolecular metallonitrene/alkyne cascades (treatment of the substrate with 2 mol% $[Rh_2(esp)_2]$ and 1.1 equivalents of $PhI(OAc)_2$), we recognized the possibility of a multitude of side reactions, including C–H amination,[9] aziridination,[5a] cyclopropanation, and carboxylate trapping (Scheme 2).[8] Indeed, when a mixture of sulfamate ester **1** and methyl allyl ether (**2**) were subjected to these established conditions for intramolecular reactions, a complex mixture of products was observed, and only a minor amount (< 5%) of the desired cascade product **3** was isolated.

The report from Guthikonda and Du Bois indicating $[Rh_2(tfacam)_4]$ (tfacam = trifluoroacetamide) promoted metallonitrene interactions with π systems in preference to C–H bonds led us to explore its activity as a catalyst in the intermolecular cascade reaction.[5a] As anticipated, in all the experiments we conducted, $[Rh_2(tfacam)_4]$ proved to be the most effective catalyst for this cascade sequence, offering both an improvement in yield and reduction in the formation of side products.[10]

$PhI(O_2CtBu)_2$ was found to be a more efficient oxidant than $PhI(OAc)_2$,[11] and, after examining solvents, we estab-

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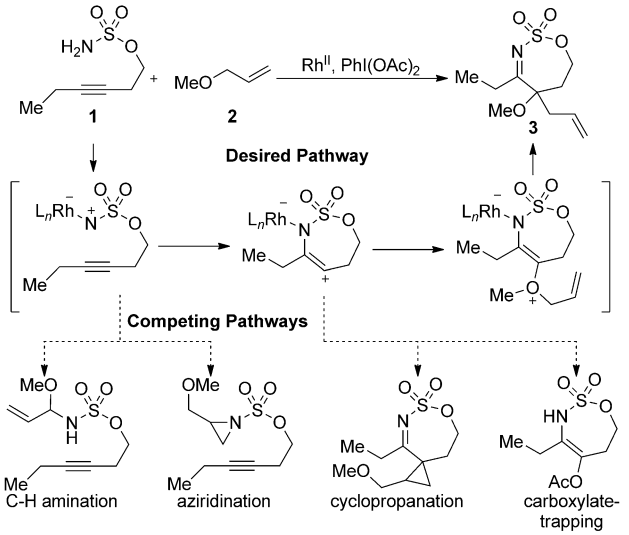


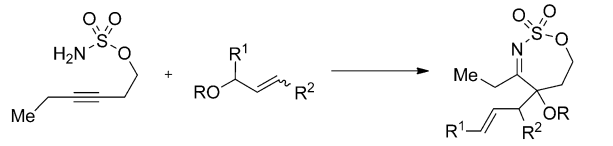
Scheme 2. Proposed intermolecular cascade mechanism with potential undesired side products.

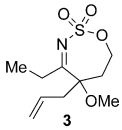
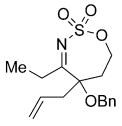
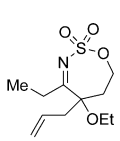
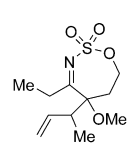
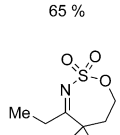
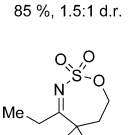
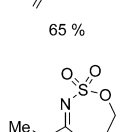
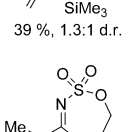
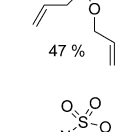
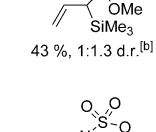
lished that the best conditions were 5 mol% $[Rh_2(tfacam)_4]$ in trifluorotoluene with 1.6 equivalents of $PhI(O_2CtBu)_2$. Under these reaction conditions, the product of the alkyne amination/intermolecular ylide formation/[2,3] Wittig rearrangement cascade (imine **3**) was isolated in 75% yield (Table 1, entry 1). This novel intermolecular cascade reaction is generalizable to a variety of simple allyl ethers, providing the corresponding products in good yields (entries 2–6). Although the yield for cascade termination with cylohexyl allyl ether (entry 5) was somewhat attenuated (46%), we note that the product of this reaction contains a tertiary-secondary dialkyl ether which would be particularly difficult to access by other methods. Benzyl allyl ether showed almost total selectivity for [2,3] Wittig migration of the allyl group (entry 6), providing the product with a benzyl-protected alcohol suitable for further manipulation, if required. *E*-Crotyl methyl ether was efficiently incorporated, predictably undergoing [2,3] Wittig rearrangement to provide the corresponding imine (entry 7) in excellent yield (85%). However, only limited diastereoselectivity was observed in this process, and a 1.5:1 mixture of diastereomeric products was isolated.[12]

Although both *E* and *Z* vinylsilanes could also participate in the reaction (Table 1, entries 8 and 9), providing useful allylsilane products, the yields were reduced in both cases (39% and 43%, respectively), and poor diastereoselectivity was observed. A secondary allyl ether underwent the cascade reaction to provide the disubstituted olefin product in 47% yield with a 3.5:1 *E*/*Z* ratio (entry 10).

A study on the impact of alkyne substitution pattern is presented in Table 2. Alkynes bearing extended alkyl chains capped with a primary tosylate (entry 1) and a silyl ether (entry 2) were well tolerated. Likewise, a sulfamate ester derived from a secondary homopropargylic alcohol was successfully cyclized under the standard reaction conditions, giving the *N*-sulfonyl imine in 55% yield (entry 3). However, the chiral center present in this substrate did not induce any

Table 1: Allyl ether scope for intermolecular cascade termination.[a]



Entry	Substrate	Product	Entry	Substrate	Product
1		 **3** 75%	6		 58%[b]
2		 65%	7		 85%, 1.5:1 d.r.
3		 65%	8		 39%, 1.3:1 d.r.
4		 47%	9		 43%, 1:1.3 d.r.[b]
5		 46%	10		 47%, 3.5:1 *E*/*Z*

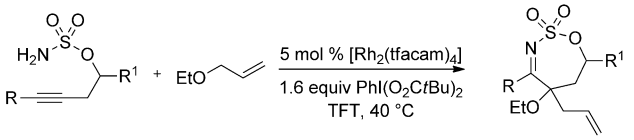
[a] Reaction conditions: 5 mol% $[Rh_2(tfacam)_4]$, 1.6 equiv $PhI(O_2CtBu)_2$, 6 equiv allyl ether, trifluorotoluene (TFT), 40°C. Yield is of isolated product. [b] 10 mol% $[Rh_2(tfacam)_4]$, 12 equiv allyl ether.

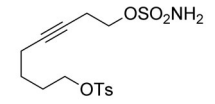
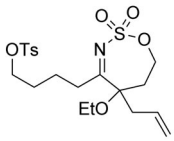
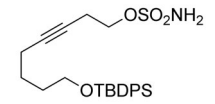
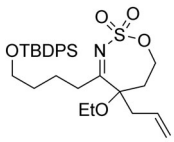
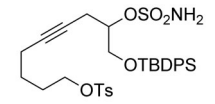
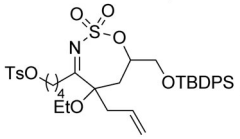
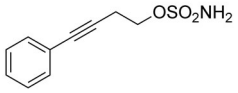
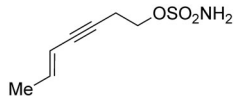
diastereoselectivity in the cascade process, thus resulting in a 1:1 mixture of diastereomeric products. Surprisingly, both phenyl and vinyl substitution of the alkyne suppressed the reaction under these conditions (entries 4 and 5). This phenomenon is exclusive to the intermolecular cascade and was not observed under the conditions previously established for intramolecular reactions.[7,8]

We note that it is possible to efficiently transfer stereochemical information from enantiomerically enriched allyl ethers to the cascade product.[13] Reaction of benzyl allyl ether (*R*)-**4** with alkyne **1** generated the quaternary-stereocenter-bearing imine **5** in good yield (67%) with excellent enantiocontrol [93%, Eq. (1)].

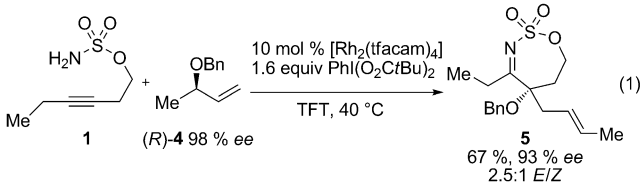
The rich functionality present in the cascade products is easily manipulated to provide an array of cyclic and acyclic building blocks. Stereoselective reduction of the oxathiazepine **6** (directed by the benzyl ether) with lithium aluminum

Table 2: Intermolecular metallonitrene/alkyne cascade sulfamate ester substrate scope.[a]



Entry	Substrate	Product	Yield [%]
1			50 %
2			60 %
3			55 % (1:1 d.r.)
4		no reaction	—
5		no reaction	—

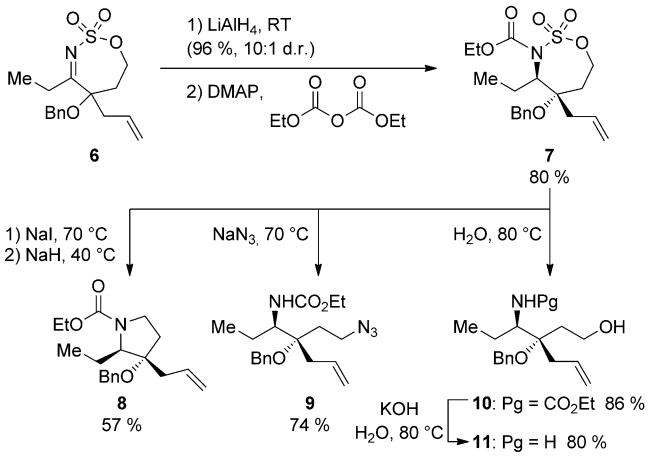
[a] Yield is of isolated product. TBDPS = *tert*-butyldiphenylsilyl.



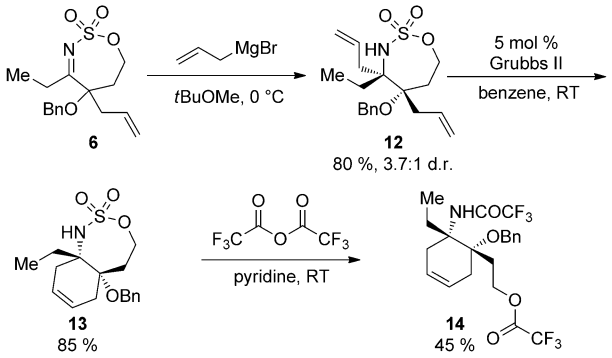
(1)

hydride at 25 °C provided the vicinal amino alcohol derivative in 96 % yield (10:1 d.r.; Scheme 3). To subsequently open the sulfamate ester with an external nucleophile, activation by N-acylation was necessary.[14] Acylation with CbzCl, the usual reagent of choice for such transformations,[15] was unsuccessful, likely a result of the hindered nature of the nitrogen nucleophile. However, N-acylation proceeded efficiently with $(EtOCO)_2O$, allowing reaction with NaI, followed by NaH, in a ring-opening/ring-closing reaction for pyrrolidine formation (**8**, 57 %).[7] This activated sulfamate ester **7** can be used for other transformations as well, such as opening with NaN_3 to provide azide **9** in 74 %, or with water to provide alcohol **10** in 86 %.[15a] The ethyl carbamate, although not commonly utilized as a protecting group, can be cleaved with aqueous potassium hydroxide, generating free amine **11** in 80 % yield.

Alternatively, addition of allylmagnesium bromide to cascade product **6** provided oxathiazepane **12** (80 %, 3.7:1 d.r.; Scheme 4), which contains vicinal tertiary amine/tertiary alcohol stereocenters. Ring-closing metathesis with the



Scheme 3. Strategies for oxathiazepane opening to provide synthetically useful building blocks. DMAP = 4-(dimethylamino)pyridine.

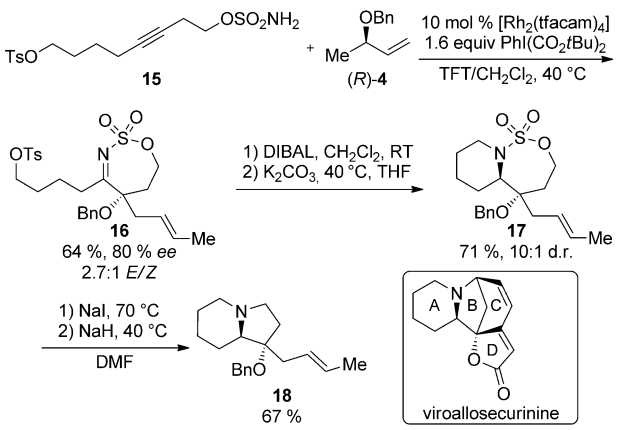


Scheme 4. Addition of Grignard reagent to cascade product and subsequent generation of disubstituted cyclohexene **14**.

Grubbs II catalyst formed bicyclic cyclohexene **13** in 85 % yield. In this particularly hindered system, we note that common acylation agents, including $(EtOCO)_2O$, could not be used to activate oxathiazepane **13** for nucleophilic SO_3 displacement.[16] However, a mixture of neat TFAA and pyridine allowed dual oxathiazepane activation and subsequent nucleophilic attack, thus forming the substituted cyclohexene **14** (45 %).

With an understanding of the parameters controlling this intermolecular cascade reaction, as well as the conditions required to manipulate the products, we highlight its synthetic potential with an efficient synthesis of the core AB ring system of the *Securinega* alkaloids, in which the cascade process generates the vicinal amino alcohol stereocenters central to this class of biologically active molecules (Scheme 5).[17,18] The cascade reaction of simple alkyne **15** and enantioenriched allyl ether (*R*)-**4** allowed access to protected tertiary alcohol **16**. After a diastereoselective reduction, S_N2 ring closure of the primary tosylate closed the A ring to provide piperidine **17**. Subsequent SO_3 extrusion with NaI/NaH generated octahydroindolizine **18** found at the core of viroallosecurinine.

In conclusion, we have developed reaction conditions for a metallonitrene/alkyne cascade with termination of the



Scheme 5. Synthesis of viroallosecurinine core using intermolecular metallonitrene/alkyne cascade. DIBAL = diisobutylaluminum hydride, DMF = *N*,*N*-dimethylaminopyridine, THF = tetrahydrofuran.

cascade process by intermolecular ylide formation/[2,3] Wittig rearrangement. A variety of substrates were explored, and enantioenriched products were generated by efficient transfer of stereochemical information from simple enantioenriched allyl ethers. The congested nature of the products required development of specialized conditions for their manipulation, and ultimately the utility of the cascade process was demonstrated through a streamlined synthesis of the bicyclic viroallosecurinine core.

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