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Catalytic Metallonitrene/Alkyne Metathesis: A Powerful Cascade Process for the Synthesis of Nitrogen-Containing Molecules

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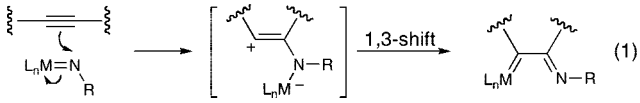
The direct incorporation of nitrogen-containing functionality into simple organic hydrocarbons represents an attractive strategy for the synthesis of biologically important natural products, pharmaceutical agents, and novel materials. Transition metal catalysts capable of supporting reactive metallonitrenes have been developed for both C–H amination[1,2] and olefin aziridination reactions.[3] In this context, considerable effort has been invested exploring many different metal catalysts. Rh,[4] Cu,[5] Ru,[6] Mn,[7] and Ag,[8] supported by a diverse range of ligands, are all commonly utilized. Despite this catalyst diversity, the chemistry of reactive metallonitrenes remains limited to two general classes of reaction (C–H amination, olefin aziridination). The rich chemistry of analogous metallocarbene species[9] stands in stark contrast to the paucity of metallonitrene chemistry, and has inspired us to investigate catalysts that utilize metallonitrenes for conceptually novel C–N bond forming reactions.

In this Communication, we report the development of a new metallonitrene/alkyne metathesis reaction (eq 1). We envisaged a process in which a metallonitrene species would react with an alkyne, leading to a zwitterionic intermediate. A [1,3] metal shift would complete the metathesis, generating a new imine and a reactive metallocarbene to cascade into further C–C, C–O, or C–N bond-forming reactions.



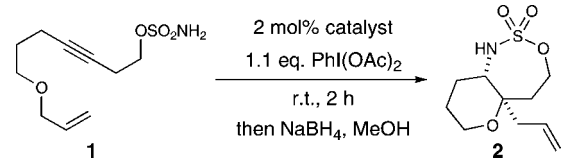
(1)

Dirhodium(II) tetracarboxylate salts were identified as promising catalysts for this metathesis reaction, as they are known to support both reactive metallonitrene and metallocarbene ligands. Equally importantly, they have also been shown to catalyze metallocarbene/alkyne metathesis cascades analogous to the new reaction outlined in eq 1.[10]

We initiated our study by examining the oxidative cyclization of sulfamate ester **1** using a variety of dirhodium(II) tetracarboxylate salts as catalysts (Table 1). To our delight, treatment of **1** with stoichiometric bisacetoxyiodobenzene and catalytic $Rh_2(OAc)_4$ gave, after reductive workup, oxathiazepane **2** (72% conversion, entry 1). This cascade process results in the formation of a new C–N bond, a C–O bond, and a C–C bond, and generates a sterically congested bicyclic system from a remarkably simple starting material, demonstrating the power of this new metallonitrene reaction. The reaction is efficiently catalyzed by a range of dirhodium(II) tetracarboxylate salts (entries 1–3) in a variety of common solvents (entries 3–7). The electron deficient $Rh_2(TFA)_4$ failed to give the desired metathesis product. Du Bois' $Rh_2(esp)_2$ catalyst is particularly effective for all the substrates we have investigated to date (Table 2).[2e]

Mechanistically, cyclization of the sulfamate ester onto the distal alkyne carbon precludes a [2 + 2] metathesis mechanism. We propose that that the alkyne attacks the electrophilic rhodium

Table 1. Optimization of Reaction Parameters for the Metallonitrene/Alkyne Metathesis Reaction

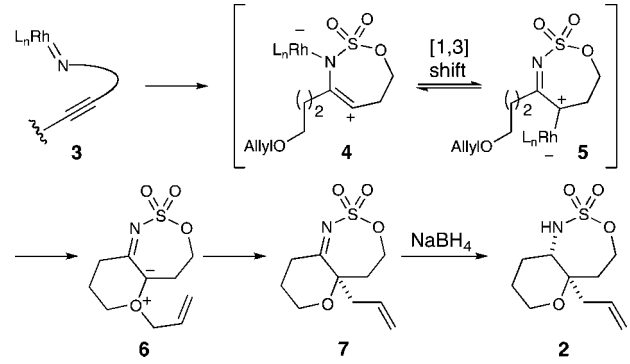


entry	catalyst	solvent	% yield[a]
1	$Rh_2(OAc)_4$	CH_2Cl_2	72
2	$Rh_2(TPA)_4$[b]	CH_2Cl_2	78
3	$Rh_2(esp)_2$[c]	CH_2Cl_2	85 (67)[d]
4	$Rh_2(esp)_2$	Toluene	85
5	$Rh_2(esp)_2$	IPAC[e]	73
6	$Rh_2(esp)_2$	Et_2O	81
7	$Rh_2(esp)_2$	*t*-BuOMe	84

[a] Determined by GC assay. [b] TPA = triphenylacetate. [c] $Rh_2(esp)_2$ = $Rh_2(\alpha,\alpha,\alpha',\alpha'$-tetramethyl-1,3-benzenedipropionate). [d] isolated yield. [e] IPAC = *i*-propylacetate.

nitrene intermediate **3** generating a transient vinyl cation **4** (Scheme 1). This vinyl cation can undergo a [1,3] rhodium shift, to give the anticipated intermediate metallocarbene **5**, or collapse directly to oxonium ylide **6**. Subsequent rearrangement produces *N*-sulfonyl imine **7** and stereoselective reduction gives the stable bicyclic product **2**.[11]

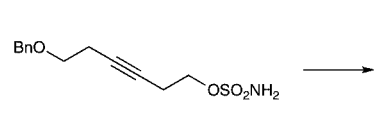
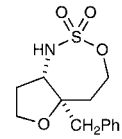
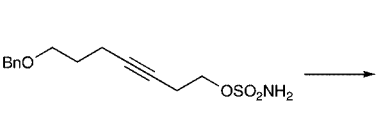
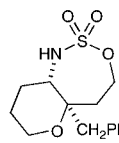
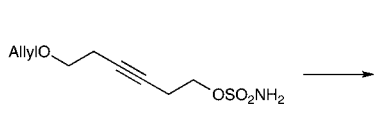
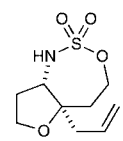
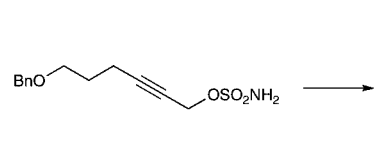
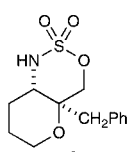
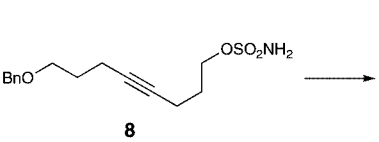
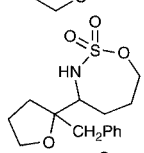
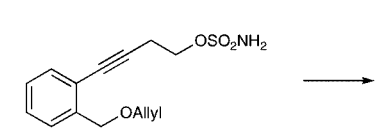
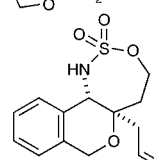
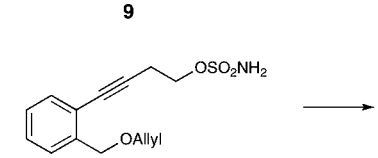
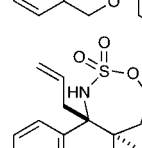
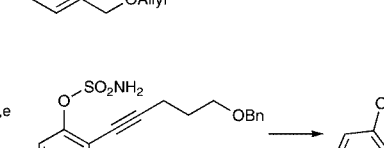
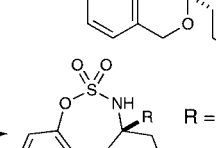
Scheme 1. Proposed Mechanism for the Rh(II)-Catalyzed Cascade Reaction



When substrate **1** is exposed to $Rh_2(esp)_2$ in the absence of an oxidant, no reaction is observed and starting material is cleanly recovered after 24 h. Similarly no reaction is observed when the sulfamate ester is replaced with a methyl ether, and the reaction is conducted in the presence of both $Rh_2(esp)_2$ and stoichiometric oxidant. These experiments indicate that the rhodium(II) catalyst does not promote the reaction by activating the alkyne for attack by the allyl ether (Scheme 2), and strongly suggest that the reaction is initiated by metallonitrene formation.

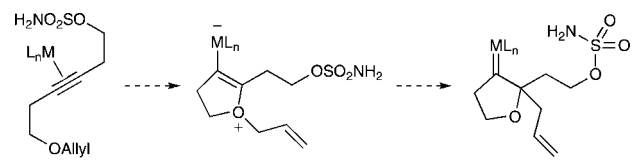
10.1021/ja7111788 CCC: $40.75

Table 2. Substrate Scope for the Intramolecular Metallonitrene/Alkyne Metathesis Cascade[a]

entry	substrate	product	yield
1[b]			71 %
2			56 %
3			76 %
4			--
5	 **8**		21 %
6	 **9**		98 %
7[c]			81 %
8[d,e]			R = H, 55 %
9[b,d,f]			R = Me, 48 %

[a] Reaction conditions: 2 mol % $Rh_2(esp)_2$, 1.1 equiv $PhI(OAc)_2$, CH_2Cl_2, room temp, 0.5 h then $NaBH_4$, MeOH. [b] Relative stereochemistry confirmed by X-ray crystallography (see Supporting Information). [c] Reaction quenched with allyl magnesium bromide at −78 °C in place of $NaBH_4$. [d] Reaction run at 40 °C for 1 h. [e] Reaction quenched with LAH at −78 °C in place of $NaBH_4$. [f] Reaction quenched with MeMgBr at −78 °C in place of $NaBH_4$.

Scheme 2. Control Experiments Rule out Alternative Mechanism



The intramolecular metallonitrene/alkyne metathesis reaction is effective for cyclizing sulfamate esters of homopropargylic alcohols, giving seven-membered ring products exclusively (Table 2, entries 1–3, 5–9). However, the geometric constraints of the sulfamate ester tether prevent cyclization of propargyl alcohol-based substrates (e.g., entry 4). Instead, products arising from intermolecular metallonitrene insertion into the activated benzylic C–H bonds of the substrate were observed.

When the tether length is extended (e.g., substrate **8**, entry 5), preference for seven-membered ring formation remains, and the product resulting from cyclization onto the proximal carbon of the alkyne is observed, albeit in reduced yield. In this case competitive metallonitrene insertion into the propargylic C–H bond is also observed.[11b] To date we have demonstrated that 7,6 and 7,5 bicyclic ring systems can be readily assembled using this methodology and that benzyl and allyl units are cleanly transferred in the cascade process.

Alkyl and aryl substituents are tolerated at either terminus of the alkyne, leading to a diverse array of products. The reaction of substrate **9** (entry 6) is particularly noteworthy, as the geometric preference for seven-membered ring formation remains dominant, despite the fact that formation of the regioisomeric six-membered ring product would proceed via a benzylic cation intermediate.

Although the sulfonyl imine generated in the cascade process can be isolated,[11] we have found it operationally convenient to reduce the imine in situ with sodium borohydride. Additionally, the imine can be trapped in situ with Grignard reagents, increasing the molecular complexity generated in the reaction (entries 7, 9).

The cyclic sulfamate ester is readily displaced under mild conditions, revealing both the amine and alcohol functionality, facilitating further elaboration of the products from this reaction.[2b]

In summary, we have developed a conceptually novel catalytic metallonitrene reaction for the construction of nitrogen containing compounds. The cascade process facilitates the assembly of complex bicyclic structures from readily assembled alkyne starting materials.

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

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(11) (a) The imine products can be isolated, but are sensitive to hydrolysis on purification. (b) See Supporting Information for details.

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