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Hydrazone-Initiated Carbene/Alkyne Cascades to Form Polycyclic Products: Ring-Fused Cyclopropenes as Mechanistic Intermediates

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Supporting Information

ABSTRACT: A hydrazone-based carbene/alkyne cascade produced a variety of bridged and fused polycyclic products. $NaOSiMe_3$ is a superior base for conversion of hydrazones to diazoalkanes. A key mechanistic intermediate, a ring-fused cyclopropene, has been isolated and characterized.

Oxygenated bridged polycyclic natural products exhibit varied and potent biological activities. For example, carnosol,[1] harringtonolide,[2] and tashironin A[3] (Figure 1) have

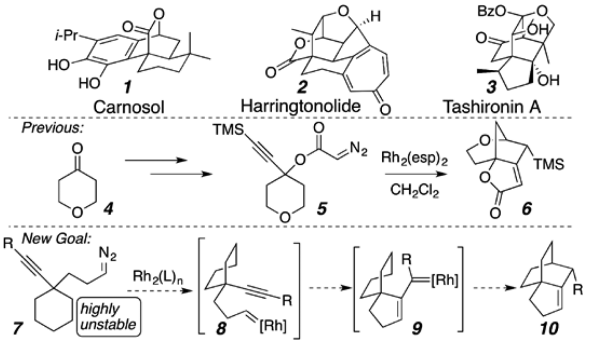

Figure 1. Natural products and strategies.

antimicrobial,[4] cytotoxic,[5] and neurotrophic[3,6] effects, respectively. Past efforts to synthesize these difficult targets have been made.[7] We designed a strategy that will allow the core structures of these targets to be synthesized from readily available components like ketone **4** through a diazoester-initiated carbene cascade reaction.[8] Through the power of a terminating C−H bond insertion, this strategy afforded products with the variety of ring sizes and connectivity often found in bridged polycyclic natural products.[9] However, all of the bicycles had ring-fused butenolides (e.g., **6**). As can be seen in Figure 1, many targets have carbocyclic rings fused to the bridged core, which would imply the use of a diazoalkane like **7**. However, diazoalkanes are difficult to synthesize and handle safely. Here, we demonstrate that hydrazone-initiated carbene cascades synthesize these important architectures and characterize a key mechanistic intermediate.

Carbene/alkyne cascades have a robust history, with Hoye[10] and Padwa[11] disclosing early reports. Other recent reports described transition-metal-catalyzed cascades ending in C−C bond formation.[12−14] The use of hydrazones to initiate these cascades has been rare,[15] though Bamford and Stevens made their seminal report with tosyl hydrazones in 1952.[16] Alkyl carbene reactivity could also be recapitulated from aziridinyl imines.[17] Aggarwaal,[18] Stoltz,[19] and others[20] demonstrated that hydrazone decomposition to diazocompounds was compatible with catalysis. While Stoltz showed that tandem reaction sequences could be initiated from aziridinyl imines,[19] coupling hydrazone-derived carbenes to a carbene/alkyne metathesis/C−H bond insertion cascade reaction would further advance this field.

At the outset of this endeavor several potential problems were anticipated (Figure 2). The most problematic would be a

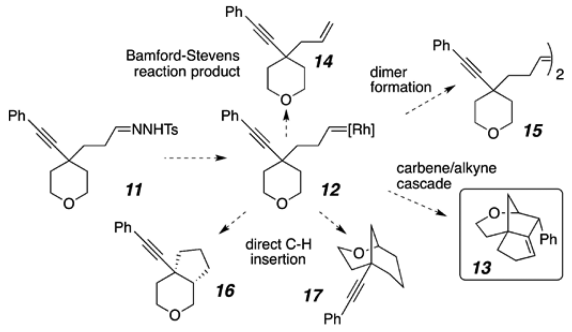

Figure 2. Potential side reactions.

competing Bamford−Stevens reaction to form the terminal olefin **14**. Alternatively, the alkyl carbene **12** could perform a C−H bond insertion before reacting with the alkyne to provide **16** or **17**. Olefinic dimers were also possible but were expected to be less prevalent than for the diazoesters since the concentration of diazoalkanes from hydrazones would be low. To avoid the potential side products **14**−**17**, the reaction of the carbene with the proximal alkyne in **12** would have to be rapid.

We began with *t*-butoxide bases in 1,4-dioxane, which are typical conditions to transform a tosyl hydrazone to a diazoalkane.[17−20] $Rh_2(esp)_2$ was used as a catalyst since it proved to be most effective with the diazoester-initiated cascades. We immediately observed successful formation of bridged bicycle **13** (Table 1, entry 1). Li and K *t*-butoxide gave similar results to Na *t*-butoxide, but the latter produced the cleanest transformation.[21] 1,4-Dioxane was the best solvent (entries 1−4).[22] $NaOSiMe_3$ has not been reported for the conversion of tosyl hydrazones to diazo groups, but it proved to be a superb base (entry 5).[23] We anticipate that it will be applicable to a wide

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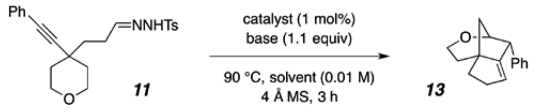
Table 1. Effects of Reaction Components



entry	catalyst	base	solvent	yield (%)
1	$Rh_2(esp)_2$	NaO*t*-Bu	1,4-dioxane	76[a]
2	$Rh_2(esp)_2$	NaO*t*-Bu	dichloroethane	23
3	$Rh_2(esp)_2$	NaO*t*-Bu	toluene	45
4	$Rh_2(esp)_2$	NaO*t*-Bu	acetonitrile	trace
5	$Rh_2(esp)_2$	$NaOSiMe_3$	1,4-dioxane	85[a]
6	$Rh_2(OAc)_4$	$NaOSiMe_3$	1,4-dioxane	52
7	$Rh_2(cap)_4$	$NaOSiMe_3$	1,4-dioxane	34
8	$Rh_2(TFA)_4$	$NaOSiMe_3$	1,4-dioxane	30
9	$Rh_2(piv)_4$	$NaOSiMe_3$	1,4-dioxane	88[a]

[a]Isolated yields (average of 2 runs).

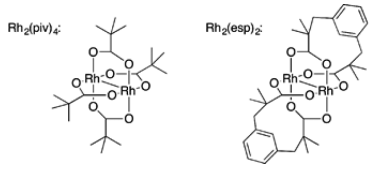
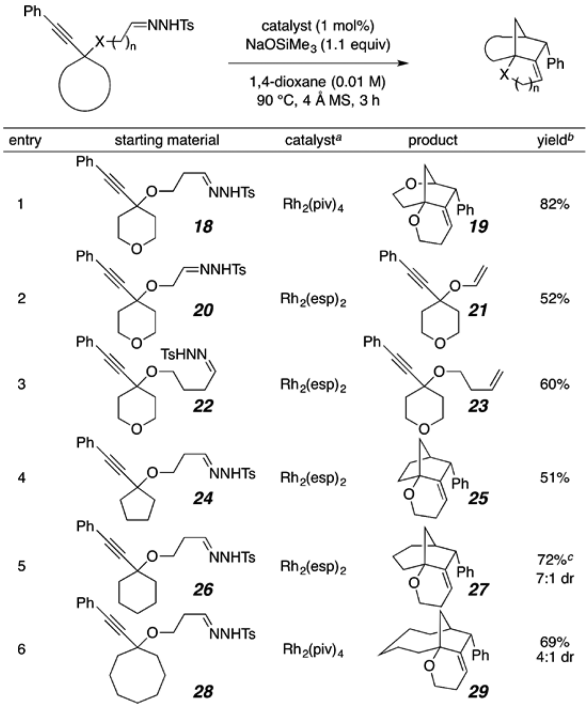


Table 2. Variation of Ring Sizes



[a]Chosen based on which catalyst gave the higher yield. [b]Isolated yields (average of 2 runs). [c]Reaction run at 140 °C in a sealed tube for 14 h.

range of hydrazone-initiated transformations. $Rh_2(piv)_4$ worked as well as $Rh_2(esp)_2$, though other rhodium catalysts were less effective for the cascade reaction (entries 6–9). Apparently, a carboxylate ligand with a quaternary carbon at the alpha-position is best for the cascade sequence. Surprisingly, if no catalyst were present, then nearly all of the starting material was recovered,[21] which supports the involvement of the rhodium in hydrazone decomposition as well as the cascade reaction.

We found that we could vary the size of the rings in the bridged bicycles, using ether linkages for ease of synthesis. Hydrazone **11** produced a cyclopentene-fused product via a 5-*exo*-dig-like cyclization with the alkyne (Table 1). The use of the hydrazone ether **18** sets up a potential 6-*exo*-dig cyclization by the alkyl carbene (Table 2, entry 1). An earlier attempt at a 6-*exo*-dig cyclization with a diazoester produced product in only 23% yield.[8] The hydrazone-initiated cascade proved more flexible and produced the dihydropyran-fused bridged bicycle **19** in 82% yield. A Bamford–Stevens hydride shift could be made dominant by ether activation (entry 2), though for almost all other 5-*exo*-dig and 6-*exo*-dig cyclizations terminal olefins like **21** were produced in only trace amounts.[19] A 7-*exo*-dig cyclization also proved to be too slow to compete with a Bamford–Stevens hydride shift (entry 3).[24] On the other hand, cyclopentane, cyclohexane, and cyclooctane substrates all produced products effectively (entries 4–6).

At an elevated temperature, ketone-based hydrazone **30** provided methylcyclopentene-fused **31** in good yield, despite the increased steric repulsion in a tetra-substituted olefin (Table 3, entry 1). A protected amine presented no problems for the transformation (entry 2), nor did the presence of a conformationally controlling *t*-butyl group on the cyclohexane (entries 3 and 4). With the alkyne *trans* to the *t*-butyl group, a single diastereomer of **35** was produced (entry 3). However, steric repulsion in the formation of the *endo*/*endo* product **37** caused the formation of a small amount of its *exo*-phenyl diastereomer (entry 4). These substrates also required the use of elevated temperature as discussed below. Cyclopropanation was found to be competitive with the cascade reaction in cyclohexene **38** (entry 5). Intriguingly, the bicyclo[3.2.1]octane seen in **40** is the result of insertion into a C–H bond not at the allylic position, which we believe is controlled by the ring conformation rather than electronics.[8b] Functional group tolerance is demonstrated by the reaction of epoxy-hydrazone **41**, which was transformed to **42** in exceptional yield (entry 6). We suspect that the epoxide predisposes a conformation where the carbene is close to the alkyne. The highly functionalized ring **43**, which has two activated benzylic positions, was next tested (entry 7). The caged product **44** was produced in good yield, with no competing reaction at the benzylic sites observed, suggesting that the alkyne reacted with the carbene rapidly and directed the C–H bond insertion to the unactivated position.

An electron-donating or -withdrawing group on the aryl ring did little to change the outcome (entries 8 and 9), though the former did require elevated temperature. An alkyl ether on the alkyne promoted a hydride shift to give spirocycle **50**, showing that the C–H bond insertion step is slower than an activated hydride migration.

Bridged bicyclics are not the only accessible products. Acyclic substrates like **51** and **53** produced fused rings (Scheme 1).[25] Only one diastereomer was seen in each case. While the allyl silane **54** was isolated in only 20% yield, this was due to its degradation during purification. Analysis of the crude NMR showed it to be produced effectively.

We next turned our attention to the reaction mechanism. Padwa had proposed a cyclopropenyl intermediate for the cascade.[26] Hoye produced experimental evidence suggesting that a discrete allylic carbene like **9** (Figure 1) is not formed in the cascade.[27] He proposed that a vinyl cation was operative, which could also explain Padwa's observations. Mykytka proposed a cyclopropene intermediate in tandem reactions initiated from alkynyl hydrazones.[28] However, no carbene/alkyne cascade process has been interrupted by the isolation of a mechanistically

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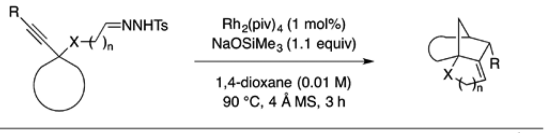
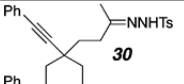
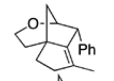
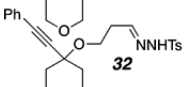
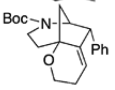
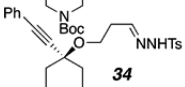
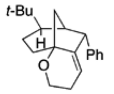
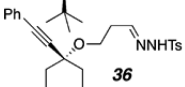
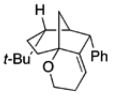
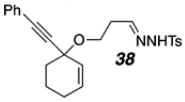
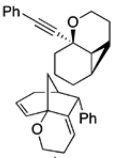
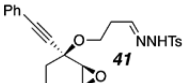
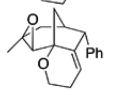
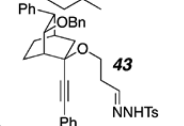
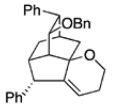
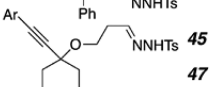
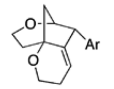
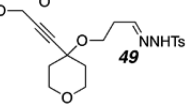
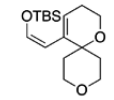
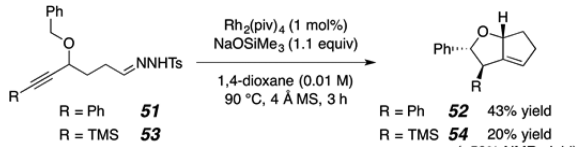
Table 3. Variation of Substitution



entry	starting material	catalyst[a]	product	yield[b]
1	 **30**	$Rh_2(esp)_2$	 **31**	52%[c]
2	 **32**	$Rh_2(piv)_4$	 **33**	82%
3	 **34**	$Rh_2(esp)_2$	 **35**	83%[c]
4	 **36**	$Rh_2(esp)_2$	 **37**	71%[c] 3:1 dr
5	 **38**	$Rh_2(esp)_2$	 **39** **40**	54% 24%
6	 **41**	$Rh_2(piv)_4$	 **42**	97%
7	 **43**	$Rh_2(piv)_4$	 **44**	54% 1.5:1 dr
8	 **45**	$Rh_2(esp)_2$	 **46**	Ar = 4-OMe-C_6H_4 68% yield[c]
9	**47**	$Rh_2(esp)_2$	**48**	Ar = 3-F-C_6H_4 85% yield
10	 **49**	$Rh_2(piv)_4$	 **50**	70% 2.6:1 *Z*/*E*

[a]Chosen based on which catalyst gave the higher yield. [b]Isolated yields (average of 2 runs). [c]Reaction run at 140 °C in a sealed tube for 14 h.

Scheme 1. Acyclic Substrates

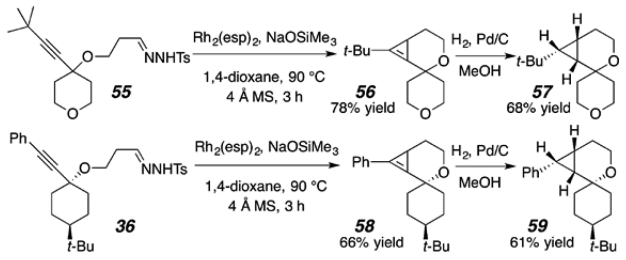


competent cyclopropene (or other intermediate) formed from the addition of a metal carbene to an alkyne.

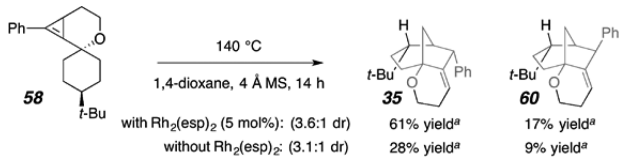
Notably, when the cascade reactions with **55** or **36** were performed at 90 °C, the ring-fused cyclopropenes **56** and **58**, respectively, were isolated (Scheme 2). In addition to spectroscopic analysis, their structures were confirmed by hydrogenation to the more easily handled cyclopropenes.[29]

These cyclopropenes were competent to produce the bridged bicyclic cascade products in a similar yield and diastereoselectivity to the hydrazones shown in Table 3 (Scheme 3). The use of a rhodium catalyst gave a higher yield of products but was not required. We hypothesize that rhodium may intercept a transient carbene formed from cyclopropene rearrangement and provide a more controlled reaction than occurs with the corresponding free carbene.

Scheme 2. Cyclopropene Formation



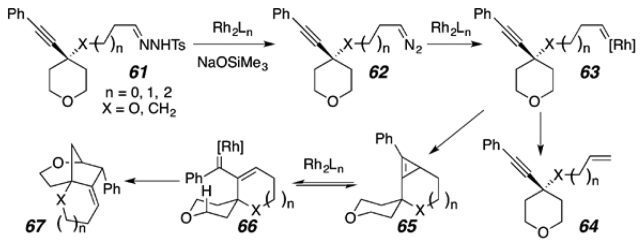
Scheme 3. Cyclopropene as an Intermediate



[a]Determined by integration of the ^{1}H NMR peaks relative to methyl 4-nitrobenzoate (average of 2 runs).

In light of the observations above, a mechanistic proposal is presented in Scheme 4. The rhodium catalyst aids the silanoate base in transforming hydrazone **61** to the diazoalkane **62**, which then affords the rhodium carbene **63**. This carbene slowly undergoes a hydride shift to give terminal alkene **64**. However, cyclopropenation to form the ring-fused cyclopropene **65** is faster for creating 5-atom (n = 0) or 6-atom (n = 1) rings. This strained intermediate can open to produce a new carbene **66**, which can be stabilized by rhodium when the catalyst is present in the reaction.[30] The cyclopropenes fused to a 5-atom ring (**65**, n = 0) would be too strained to observe. In fact, we have only been able to observe and characterize the cyclopropene intermediate for a few sterically hindered compounds. It is possible that for n = 0 an alternate mechanism is operative, but given the similarity in reactivity to when n = 1, we believe that the intermediates are similar. C−H bond insertion then forms the polycyclic product **67**.

Scheme 4. Mechanistic Proposal



In conclusion, we have shown that a cascade involving hydrazone decomposition, dediazotization, cyclopropenation, carbene generation, and C−H bond insertion can be initiated using $NaOSiMe_3$ and a rhodium catalyst. A large variety of bridged, caged, and fused polycyclic systems relevant to natural product synthesis have been presented, with variations in ring size and substitution. A ring-fused cyclopropene has been isolated for the first time in a carbene/alkyne cascade and shown to be a competent mechanistic intermediate.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b08157.

Control experiments, full experimental descriptions, and spectroscopic data (PDF)

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Notes

The authors declare no competing financial interest.

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