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# Synthesis of Bridged Polycyclic Ring Systems via Carbene Cascades Terminating in C−H Bond Insertion

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Supporting Information

**ABSTRACT:** A carbene cascade reaction that constructs functionalized bridged bicyclic systems from alkynyl diazoesters is presented. The cascade proceeds through diazo decomposition, carbene/alkyne metathesis, and C−H bond insertion. The diazoesters are easily synthesized from cyclic ketones. Substrate ring size and substitution patterns control the connectivity and diastereomeric preference found in the products.

Functionalized bridged bicycles are common structural motifs in natural products, many of which have impressive bioactivities (Figure 1). Strategies devised for the construction of bridging rings include radical additions,[1] enolate additions,[2] cycloadditions,[3] and multistep reaction cascades.[4] Typically, a given strategy only produces a particular bridged bicyclic isomer. A strategy that predictably generates products varying in ring size and points of connectivity from common, easily accessed precursors is thus in demand. Herein is described a general strategy to form functionalized bridged polycyclic systems of varied size and structure via a cascade reaction[5] that is primed by the diazo functional group.[6] The reaction proceeds through initial rhodium-catalyzed diazo decomposition, formation of a rhodium carbene, carbene/alkyne metathesis, and C−H bond insertion to form multiple C−C bonds and a strained bridged bicycle in a single reaction.

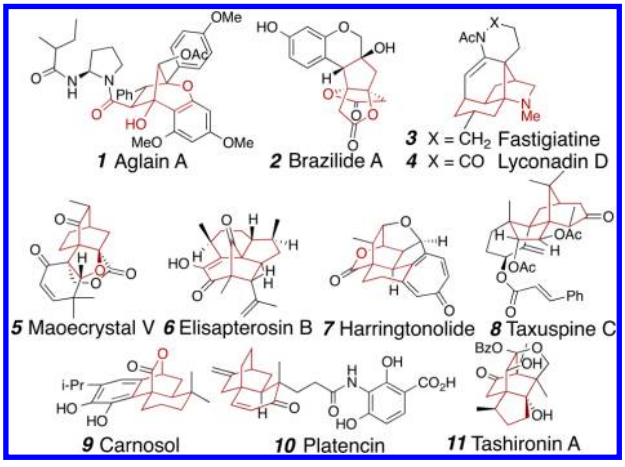
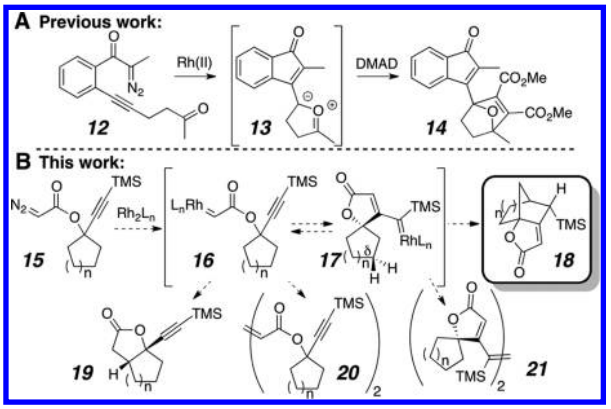



**Figure 1.** Examples of bridged polycyclic natural products.

Padwa designed a cascade reaction with a carbene/alkyne metathesis followed by a 1,3-dipole cycloaddition[7] to synthesize bridgehead-functionalized bicyclo[*n*.2.1]alkanes (Scheme 1A).[8] To access a greater variety of bridged polycycles, a cascade reaction was conceived that would commence from alkynyl diazoesters like **15** (Scheme 1B). These esters would be conveniently synthesized from the appropriate cyclic ketone in two steps. Upon exposure to the catalyst, a metal carbene **16** would be formed with concomitant loss of dinitrogen. The adjacent alkyne can then insert into the carbene to generate a butenolide ring and a new carbene **17**. This carbene would then insert into the δ-C−H bond to form bridged bicycle **18**.

**Scheme 1. Carbene Cascade Reactions for Functionalized Bridged Bicyclics**




Few studies have been reported for C−H bond insertions in the context of bridged bicycles,[9] though many reports exist on the selectivity for C−H bond insertion to form single or fused rings.[10] The increased steric demands and ring strain in the formation of bridged bicyclic products can be expected to show altered selectivity patterns relative to acyclic.[11,12] While several carbene[8] and nitrene[13] initiated cascades with alkynes have been explored, few examples have been reported incorporating C−H bond insertion as the final step. Thus, this application also explores new territory in carbene/alkyne metathesis cascades.

A few potential complications are worth noting. The initial metal carbene in **16** could ignore the nearby alkyne and directly insert into the ring, forming a fused bicycle **19**.[14] Either of the carbene intermediates **16** and **17** could react intermolecularly to generate olefinic dimers (**20** and **21**). These side reactions could be exacerbated by the increased ring strain in the transition state to form bridged product **18** relative to **19**−**21**.[11]

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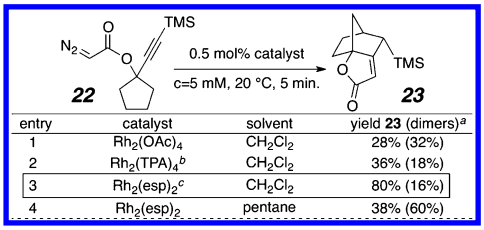
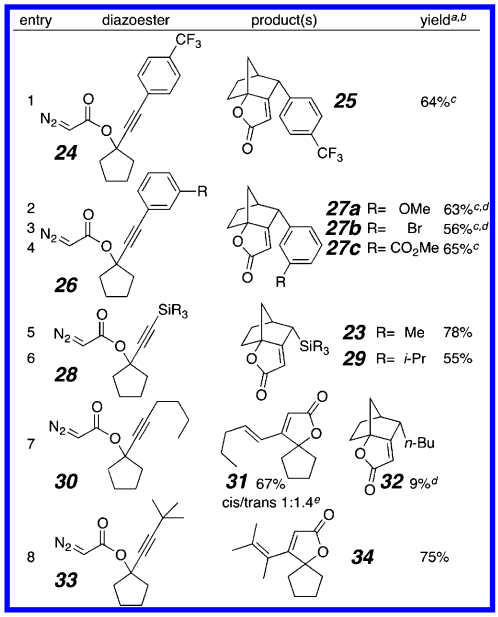
**Table 1. Reaction Optimization**




| entry | catalyst | solvent | yield **23** (dimers)[a] |
|---|---|---|---|
| 1 | $Rh_2(OAc)_4$ | $CH_2Cl_2$ | 28% (32%) |
| 2 | $Rh_2(TPA)_4$[b] | $CH_2Cl_2$ | 36% (18%) |
| 3 | $Rh_2(esp)_2$[c] | $CH_2Cl_2$ | 80% (16%) |
| 4 | $Rh_2(esp)_2$ | pentane | 38% (60%) |

[a]Yields are from a single run of experiments run in parallel. [b]TPA = triphenylacetate. [c]$Rh_2(esp)_2$ = $Rh_2$(*R,R,R′,R′*-tetramethyl-1,3-benzenedipropionate).

**Table 2. Alkyne Substituent Effects**



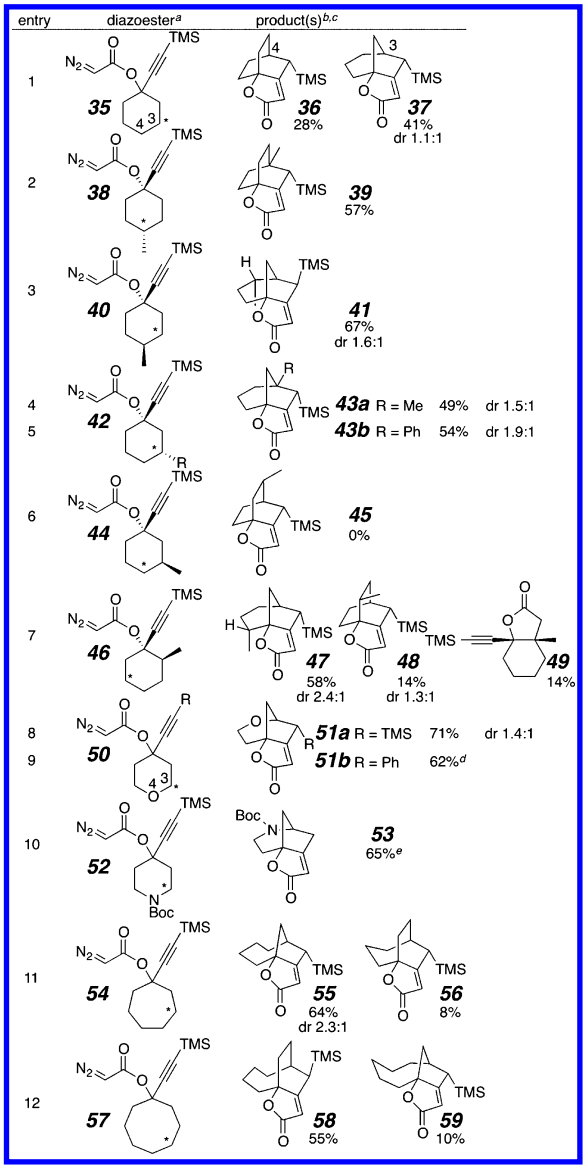

[a]$Rh_2(esp)_2$, $CH_2Cl_2$, 20 °C. [b]Yields are averages of multiple trials. [c]Reaction at reflux. [d]Yield based on NMR peak integration relative to an internal standard. [e]In pentane, **31** was obtained in 50% yield (cis/trans 2:1)

Rearrangements of carbene intermediates could also occur.[15] Finally, in larger rings (**15**, $n \geq 2$) multiple possible sites of insertion and conformational flexibility in the ring could lead to mixtures of products.

To avoid the last of these issues, our initial trials focused on alkynyldiazoester **22** (Table 1), which is derived from cyclopentanone.[16] Our initial trial in dichloromethane using $Rh_2(OAc)_4$ as a catalyst primarily produced carbene dimers, but 28% of the bicyclo[2.2.1]heptane **23** was also observed (entry 1). The relative stereochemistry of the product was determined from 1D NOE experiments.[16] This encouraging result led to an examination of individual reaction parameters. While metals other than rhodium did not efficiently provide **23**,[16] dirhodium(II) carboxylates generally produced the bridged bicycle in isolable amounts (entries 1−3). Changing the solvent from dichloromethane proved detrimental to product formation, as did increasing the concentration. $Rh_2(esp)_2$[17] uniquely provided the product in excellent yield with only a small amount of olefinic dimer formation (entry 3). This catalyst has proven its effectiveness in a variety of applications where other catalysts fared poorly.[18]

Next, the tolerance of various functional groups on the alkyne was examined (Table 2). Terminal alkynes are known to

**Table 3. Ring Variations**




[a]The asterisk denotes the point of C−H insertion for the major product. [b]$Rh_2(esp)_2$, $CH_2Cl_2$, 20 °C. [c]Yields are averages of multiple trials. [d]Yield based on NMR peak integration relative to an internal standard. [e]yield for two steps including desilylation.[16]

afford mixtures of products derived from both 5-exo and 6-endo alkyne insertion.[19] Aryl alkynes generally provided products cleanly. A *p*-$CF_3$-$C_6H_4$-modified alkyne **24** was a good substrate for bridged bicycle formation (entry 1). Aryl alkynes with *meta* groups gave uniformly good yields independent of the electronic nature of the substituent (entries 2−4). Silyl-substituted alkynes **28** provided bridged rings in useful yields (entries 5 and 6). This result was pleasing as silyl groups can subsequently be removed[20] or oxidized.[21] Aliphatic alkynes produced more varied results. The *n*-butyl acetylene **30** showed that 1,2-hydride migration outcompeted C−H insertion for bridged bicyclic formation (entry 7).[22] More of the cis isomer of alkene **31** was formed in pentane (50% yield, 2:1 cis/trans) than in dichloromethane (1:1.4 cis/trans), and **32** was not observed. For comparison, hydride migration was suppressed in pentane for intramolecular C−H bond insertion with an *acyclic* alkynyl substrate.[22,23] Thus, the observation of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hydride migration in pentane illustrates an increased barrier to C−H insertion that is likely due to the additional ring strain introduced during the formation of the product. Lastly, a *tert*-butyl-substituted alkyne **33** showed that a 1,2-methyl shift to form butenolide spirocycle **34** is faster than C−H bond insertion (entry 8).[24]

The variety of carbocycles and heterocycles that can be incorporated in the cascade sequence demonstrates the power of this strategy. The ring size and substituents of substrates have a profound impact on the bridged bicycle that is produced. While cyclopentane diazoester **22** produced bicyclo[2.2.1]-heptane **23** as a single diastereomer (Table 1), cyclohexyl diazoester **35** produced a mixture of bicyclo[2.2.2]octane **36** and both diastereomers of bicyclo[3.2.1]octane **37** (Table 3, entry 1). The mixture of products observed likely arises from the conformational flexibility of the cyclohexane.

The diastereomeric alkynyldiazoesters **38**, **40**, **42**, **44**, and **46** demonstrate how ring substituents can dictate selectivity. When a methyl or phenyl group is *anti* relative to the alkyne (entries 2, 4, 5, and 6), the position with the substituent is more reactive since a methine is more susceptible to C−H bond insertion than a methylene.[10] Thus, bicyclo[2.2.2]octane **39** was formed as the major product from **38** and bicyclo[3.2.1]octane **43** was formed from **42**. With the alkyne *syn* to a 3- or 4-methyl group, the C−H bond insertion at the methine is blocked. Insertion could still occur at the 3-position of **40** in the presence of a 4-methyl substituent, as it is disposed equatorially (**60**, Figure 2).

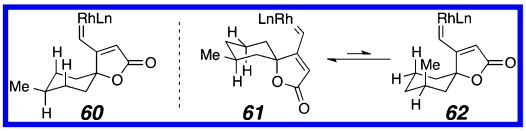
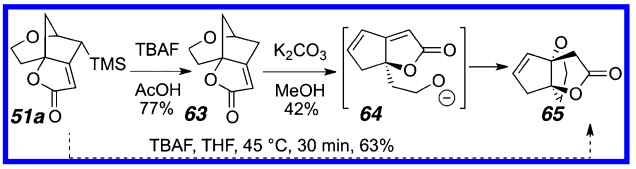



**Figure 2.** Insertion conformations.

Thus, the bicyclo[3.2.1]octane **41** was the only product from **40** (Table 3, entry 3). For the 3-substituted **44**, however, the conformation **62** for C−H bond insertion to form the bridged bicycle is higher in energy than **61** as it requires an axial methyl group. Moreover, this group blocks any methylene C−H bond insertion in **62**, and consequently no bridged bicyclic product was observed from **44**. **46** would again contain an equatorial methyl in the transition state, and insertion at the methylene furthest from the methyl in the ring gave the major product **47**.

If heteroatoms were present in the ring in the 4-position, only the butenolide-fused bicyclo[3.2.1]octanes **51** and **53** were produced (Table 3, entries 8−10). Not only is there no C−H bond at the ring's 4-position for insertion, but the 3-methylene is activated for insertion by the heteroatoms. As seen for **51b**, aryl alkynes generally provide *endo* products exclusively. The 2-oxabicyclo[3.2.1]octane **51a** models a synthetic approach to the synthesis of members of the aglain family of natural products (see **1**, Figure 1). The bridged heterocyclic product **51a** underwent further transformations to a key structural motif. Buffered TBAF desilylated the bicycle to give butenolide **63** (Scheme 2). If **63** was treated with base, $\gamma$-elimination of the alkoxide produced fused butenolide **64**, and 1,4-addition of the alkoxide then afforded propellane **65**. If **51a** was heated with TBAF, **65**, which is reminiscent of the core of brazilide A (**2**, Figure 1), could be accessed directly. In fact, the transformation of **50** to **65** was performed as a model system for the synthesis of brazilide A that is underway.

**Scheme 2. Post-cascade Modifications**




Both cycloheptanes and cyclooctanes showed noteworthy insertion selectivity (entries 11 and 12). Diazoester **54** primarily formed the bicyclo[4.2.1]nonane core **55** in 65% yield with moderate diastereoselectivity. Similarly, the cyclooctyl diazoester **57** generated the illustrated diastereomer of **58** in 56% yield, with another 11% of its constitutional isomer **59** isolated. Thus, the cyclooctyl ring showed the highest diastereoselectivity of all the ring sizes greater than 5 tested so far.

In conclusion, alkynyldiazoesters with cycloalkanes readily form bridged polycyclic systems through the use of $Rh_2(esp)_2$. Subsequent desilylation, hydrogenation, or rearrangement of the bridged products proceeds without difficutly.[16] The use of diazoketones in the cascade reaction and application of this strategy to the natural products in Figure 1 is underway.

## ■ ASSOCIATED CONTENT

### Ⓢ Supporting Information

Additional optimization data, experimental procedures, and characterization data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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### Notes

The authors declare no competing financial interest.

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