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Carbene cascades for the formation of bridged polycyclic rings

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ABSTRACT

A general strategy to synthesize bridged polycyclic molecules is presented. The synthesis is accomplished via a cascade reaction initiated by rhodium carbene formation. Subsequent intramolecular reaction with an alkyne is then followed by a transannular C–H bond insertion. A rationale for prediction of the major structural isomer that is formed is described and applied to a wide variety of substrates. This rationale is based on conformational and stereoelectronic considerations for the ring system in the substrate.

1. Introduction and background

Examples abound of polycyclic natural products where a bridged bicyclic core is fused with additional rings (Fig. 1). These compounds routinely possess important biological activities that are applicable to the study of biochemical pathways and the development of new disease treatments. Many of these natural products are isolable in only scarce quantities from natural sources. Thus, a practical synthetic approach is needed to furnish the material to investigate the properties of these compounds. There has been a significant effort to develop methods for the synthesis of bridged bicycles. The variety of strategies developed to synthesize different bridged rings includes ring formation via radical intermediates,[1] enolate additions,[2] pericyclic cycloadditions,[3] and Michael reaction cascades.[4] However, each of these methods typically targets only one unique size and connectivity for the bridged ring system. For example, the bicyclo[2.2.2]octane cores of tashironin A (**1**) and maoecrystal V have been targeted with an intramolecular Diels–Alder reaction.[5] However, adenanthin (**5**) would require a completely different strategy. A rapid, generalized approach to generate different bridged polycycles from common starting points would increase synthetic utility, flexibility, and efficiency.

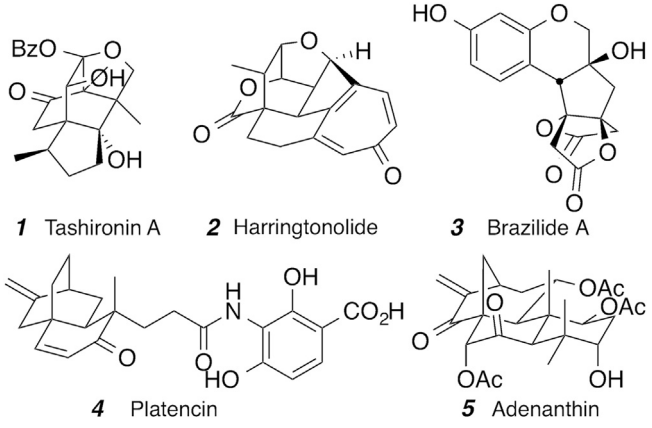

Fig. 1. Bridged polycyclic natural products.

We recently disclosed a generalized strategy to synthesize bridged polycycles like **9** (Scheme 1).[6] By altering the ring in **6**, a variety of bridged ring sizes may be formed with differing points of connection. This cascade reaction approach to bridged polycycles is initiated through catalytic diazo decomposition[7] of an α-diazo carbonyl[8] like **6** and terminates in a C–H bond insertion.[9] Importantly, the C–H bond insertion allows for new C–C bond formation without prefunctionalization of the carbocycle, allowing for greater synthetic efficiency.[10] The carbene cascade reaction proposed herein forms multiple C–C bonds in a single reaction to further increase efficiency. While bridged ring systems contain 17–23 kcal/mol of ring strain relative to cyclohexane,[11] the high reactivity of the carbene intermediates allow the reaction to proceed.

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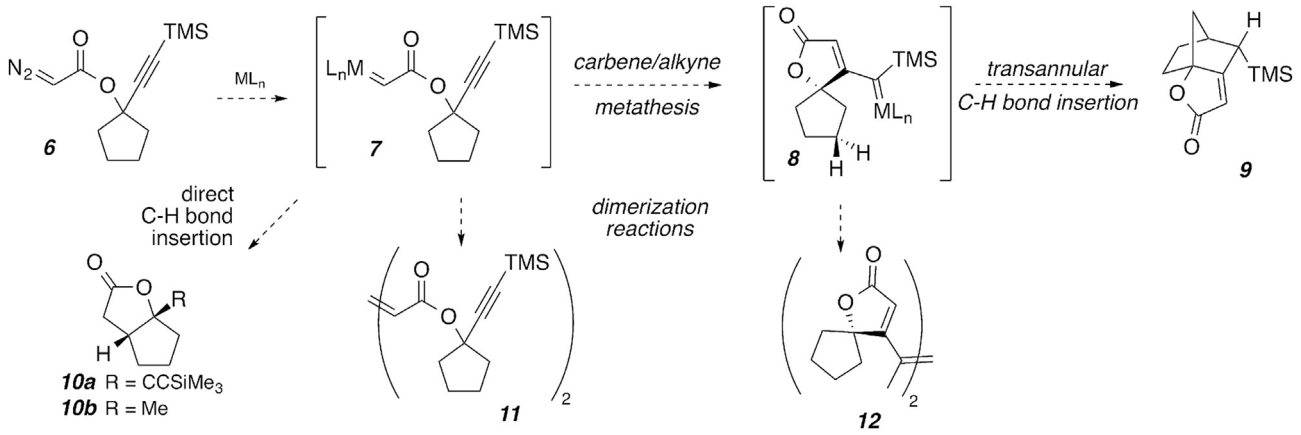
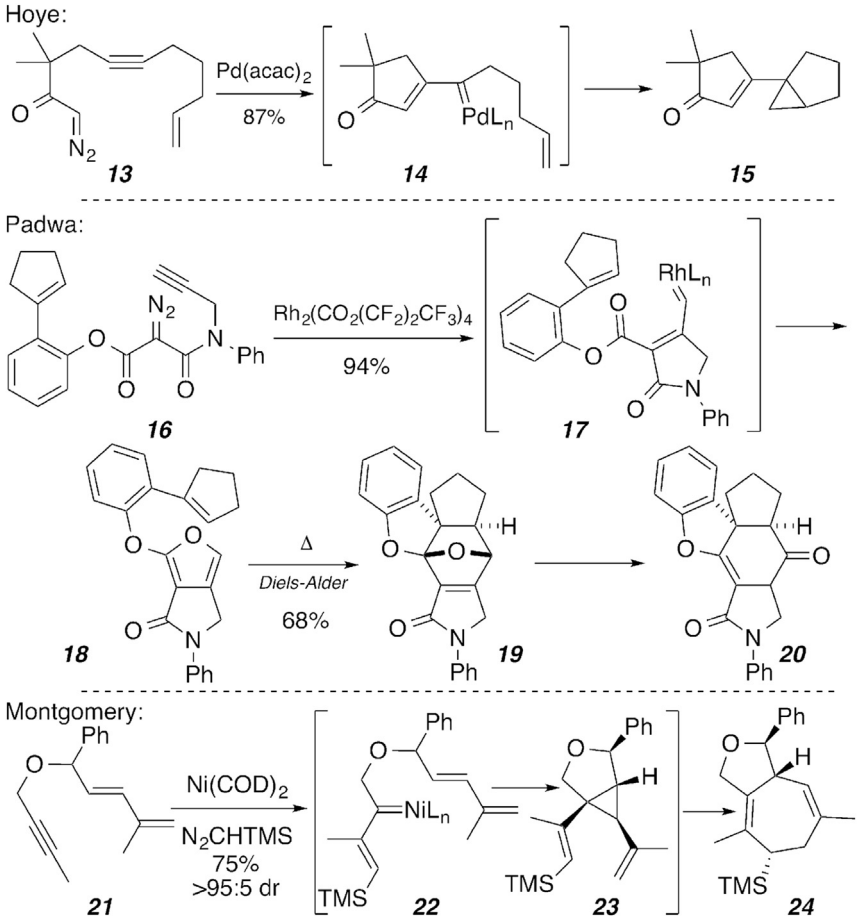


Scheme 1. The carbene cascade and potential side reactions.

Also central to the cascade strategy is the intramolecular insertion of a nearby alkyne to form a putative spirocyclic intermediate like **8**. Such a process has precedent in work by Padwa,[12] Hoye,[13] and others[14] (Scheme 2). In those examples, a carbene is generated from a diazocompound, usually in the presence of a transition metal catalyst that controls the carbene reactivity. This initial carbene rapidly reacts with a nearby alkynyl group intramolecularly to form a new carbene intermediate such as **14** or **17**. This new carbene can then proceed through additional reactions. An intermolecular example has even been shown by Montgomery with a Ni complex. However, little work had been reported on a cascade reaction that terminates in C–H bond insertion to form bridged polycycles.

The allylic metal carbenes **14** and **17**, which would result from a 'carbene alkyne metathesis'[12e] from the initially formed carbene, are useful hypothetical intermediates to consider and understand these reactions. However, the actual mechanistic intermediates are likely more complex. Hoye demonstrated this complexity with an elegant study that compared diazoketone **25** and diazo enone **26** (Scheme 3).[15] If the cascade sequence from **25** proceeded purely through a metathesis reaction to form intermediate **29**, both **25** and **26** would be expected to give the same product distribution. As can



Scheme 2. A few examples of carbene/alkyne cascade sequences.

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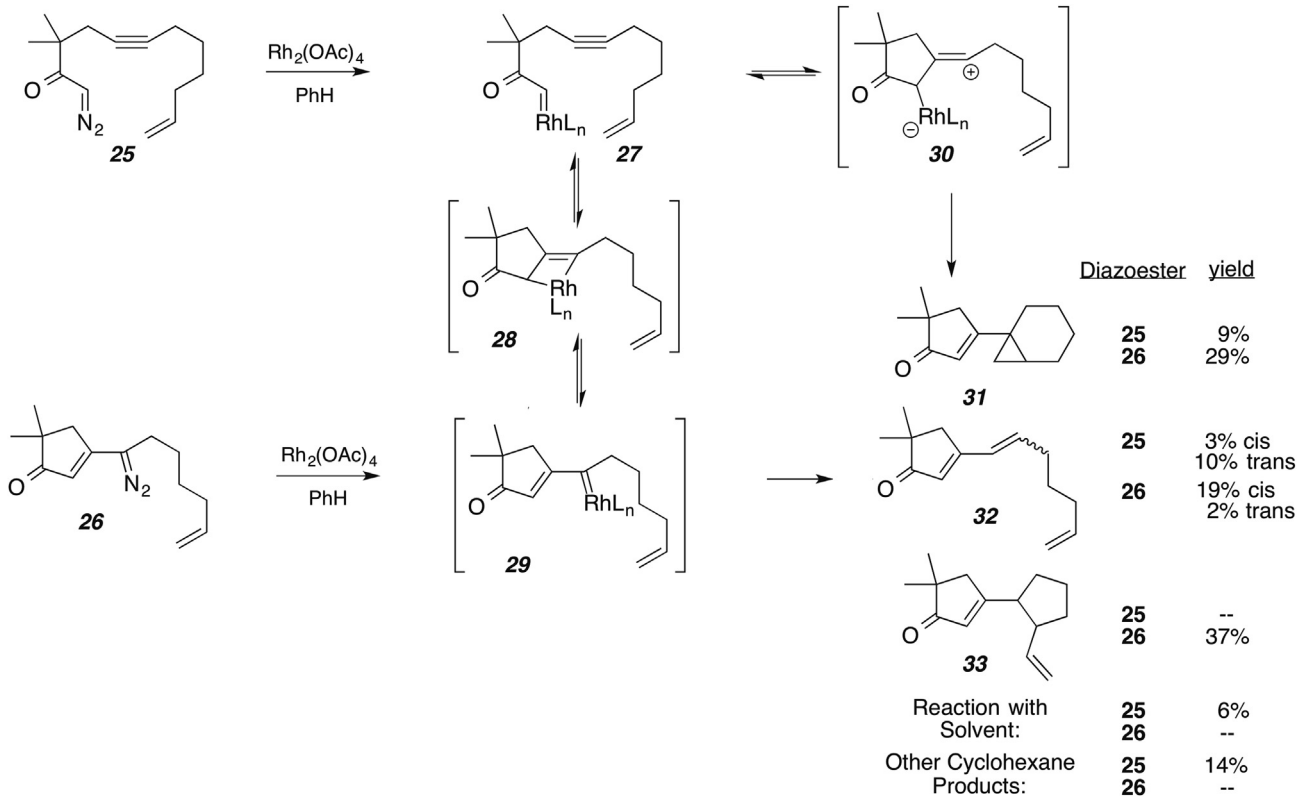

Scheme 3. Hoye's mechanistic study.

be seen in Scheme 3, however, quite different product distributions were observed, implying that the intermediates are not accessed identically from each diazoketone. One alternate pathway was proposed to proceed through vinyl cation **30**,[15] which would explain the greater production of the trans isomer of olefin **32**. 1,2-Hydride migrations for metal carbenes like **29** generally have a higher propensity to form *cis* olefins.[16] Given the uncertainty of the precise mechanistic intermediate in these alkynyl cascades, we will use the term 'carbenoid' herein to denote the developing carbene character at the alkynyl carbon, even though there may not be a fully formed carbene at that carbon. It should also be noted that the expected cyclopropane, 1,2-hydride migration, and C–H bond insertion products in Hoye's study (**31**, **32**, and **33**, respectively) are more pronounced when **29**, the 'carbene/alkyne metathesis product,' is the likely intermediate as generated from **26**. None of the C–H bond insertion product is obtained from diazoketone **25**, further supporting that the intermediates from **25** lack the strong enone carbene character that would be exhibited by **29**. To obtain the desired C–H bond insertion for the cascade sequence in Scheme 1, the reactivity that would be manifested by intermediate **8** (and not a vinyl cation like **30**) is needed. Otherwise the bridged bicyclic products could fail to form.

Doyle,[17] Taber,[18] Hashimoto,[19] and others[20] have reported a number of experiments that describe the selectivity of C–H bond insertion in intramolecular reactions to generate monocycles and fused polycycles. In brief, the following trends are observed: (A) five-membered ring formation is favored over other ring sizes. (B) The rate of insertion is generally $R_3CH > R_2CH_2 \gg RCH_3$. (C) C–H bonds on an oxygenated or nitrogenated carbon are the most reactive to insertion if proper orbital alignment with the heteroatom lone pair is possible. (D) Allylic and benzylic C–H bonds are preferred to unactivated hydrocarbons, and (E) C–H bonds close to electron withdrawing groups are deactivated for insertion. Davies has noted and taken advantage of the properties of acceptor/donor carbenes, which show greater insertion selectivity.[21]

The few applications to synthesize functionalized bridged bicyclics using C–H bond insertions reported to date are diazoketone studies by Wolff[20a] and Adams[20b–d] to form bicyclo[3.2.1]octanes **35** from cyclohexyl and pyranyl diazoketones **34** in the context of determining C–H bond insertion preferences (Scheme 4). Sonawane,[22] Srikrishna,[23] and Lee[24] have provided examples of intramolecular C–H bond insertion to functionalize preformed bridged bicyclics. Lee demonstrated how the inductive electron withdrawing and hyperconjugative donating abilities of oxygen can be independently observed in rigid polycyclic systems like **40**. In the same vein, the application of the sequence in Scheme 1 to the synthesis of caged and bridged bicycles can be expected to show altered selectivity patterns relative to established acyclic examples because of the increased steric demands, ring strain, and rigidity in the products. As shall be described herein, ring conformations in particular must be assessed to enable predictions of reactivity.

A few potential complications of the proposed cascade in Scheme 1 were worth contemplating at the outset of our endeavor. The initial metal carbene in **7** could bypass the nearby alkyne and directly insert into the ring, forming the fused bicycle **10a** with an angular alkynyl group (R=$CCSiMe_3$). Doyle observed this product with a methyl in place of the alkyne (**10b**, R=Me).[25] Either of the carbenoid intermediates **7** or **8** could react with a diazoester or a second carbene intermolecularly to generate olefinic dimer products like **11** or **12**. Rearrangements of carbene intermediates could also occur.[26] These side reactions could be exacerbated by the increased ring strain in the transition state to form bridged products **9** relative to monocyclic or fused bicyclics. On the other hand, one side reaction that is unlikely to happen is insertion at a C–H bond immediately adjacent to the point of attachment for the spirocyclic rings in **8**. Doing so would generate a highly strained 5-4-5 fused ring system with a very distorted olefin. Consequently,

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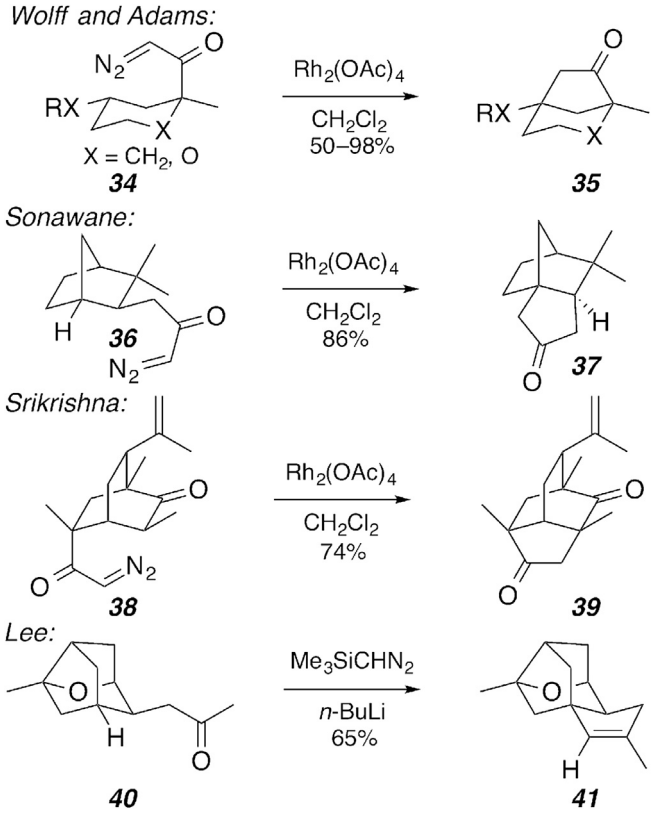
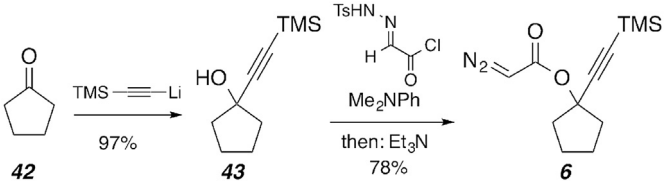


Scheme 4. C–H insertion with bridged rings.

a transannular insertion to generate a bridged ring would be the only available option for intramolecular C–H bond insertion from **8**.

2. Results and discussion

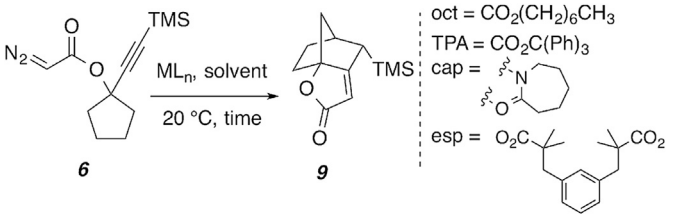
Carbocyclic alkynyl diazoesters like **6** were initially targeted to probe the proposed cascade sequence with the thought that they could be easily derived from cyclic ketones. Indeed, treatment of trimethylsilylacetylene with *n*-BuLi generates a lithium acetylide that adds to cyclopentanone in nearly quantitative yield (Scheme 5).[27] The resulting propargylic alcohol is then acetylated with the tosylhydrazone of glyoxylic acid chloride in the presence of dimethylaniline.[28] Subsequent treatment with triethylamine then converts the hydrazone to the requisite diazo group. Thus, nearly all of the substrates in this manuscript were synthesized in only two steps from cheap, commercially purchased ketones.



Scheme 5. Synthesizing alkynyl diazoesters.

Thermolyzing diazoester **6** resulted in nonspecific decomposition. A variety of transition metal catalysts that are commonly used in diazo-initiated carbene reactions were then examined. Silver(I) showed no reactivity (entry 1, Table 1), and Cu-based catalysts fared little better (entries 2 and 3). A more

Table 1
Analysis of reaction parameters



Entry	Catalyst (0.5 mol %)	Solvent	Rxn concn (M)	time	Yield **9**[a]	Yield dimers[a]
1	AgOTf	CH_2Cl_2	0.01		No reaction	—
2	$(CuOTf)_2 \cdot PhH$	CH_2Cl_2	0.005		Trace	Trace
3	$Cu(CH_3CN)_4PF_6$	CH_2Cl_2	0.005		Trace	Trace
4	$Rh_2(OAc)_4$	CH_2Cl_2	0.005	5 min	28%	32%
5	$Rh_2(oct)_4$	CH_2Cl_2	0.005	5 min	50%	24%
6	$Rh_2(TPA)_4$	CH_2Cl_2	0.005	5 min	36%	18%
7	$Rh_2(TFA)_4$	CH_2Cl_2	0.005	5 min	Trace	41%
8	$Rh_2(cap)_4$	CH_2Cl_2	0.005	5 min	—	Trace
9	$Rh_2(cap)_4$	CH_2Cl_2[e]	*0.005*	30 min	—	*Trace*
10	*$Rh_2(esp)_2$*	*CH_2Cl_2*	*0.005*	5 min	*77%*	*16%*
11	$Rh_2(esp)_2$	$ClCH_2CH_2Cl$	0.005	5 min	46%	5%
12	$Rh_2(esp)_2$	Pentane	0.005	5 min	38%	60%
13[b]	$Rh_2(esp)_2$	CH_2Cl_2	0.005	5 min	55%	23%
14	$Rh_2(esp)_2$	CH_2Cl_2	0.01	5 min	63%	27%
15[c]	$Rh_2(esp)_2$	CH_2Cl_2	0.005	2 h	70%	trace
16[d]	*$Rh_2(esp)_2$*	*CH_2Cl_2*	*0.005*	*30 min*	*85%*	—

[a] Isolated yields.
[b] Reaction run at 0 °C.
[c] Slow addition of **6** to $Rh_2(esp)_2$ in CH_2Cl_2 over 2 h.
[d] Slow addition of **6** to $Rh_2(esp)_2$ and activated 4 Å molecular sieves in CH_2Cl_2 over 30 min.
[e] Reaction at reflux.

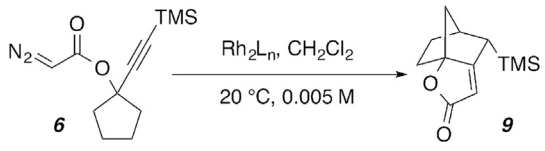
productive reaction was observed with rhodium(II) dimers used as catalysts. The simplest of these, $Rh_2(OAc)_4$ substantially improved product formation to 28%, but also increased the formation of olefinic dimers (entry 4). These dimers were a mixture of *cis* and *trans* olefins derived from the coupling of the acetate carbon. Rhodium complexes with a variety of steric and electronic differences were examined to find a combination that would favor the formation of the bridged bicycle **9**. The more lipophilic $Rh_2(oct)_4$ nearly doubled product formation (entry 5), but the sterically encumbered $Rh_2(TPA)_4$[29] behaved similarly to $Rh_2(OAc)_4$ (entry 6). A catalyst with electron withdrawing TFA ligands provided only dimers as products (entry 7). A caprolactam-bridged Rh dimer was catalytically ineffective in dichloromethane, even when refluxed (entries 8 and 9). A breakthrough occurred when a catalyst originally developed for nitrene chemistry, $Rh_2(esp)_2$,[30] allowed for the formation of the bridged product **9** while minimizing the dimerization observed (entry 10). The esp ligand has two substantial differences from the other carboxylate ligands screened. Firstly, a geminal dimethyl is found at the α-carbon of the carboxylate. Secondly, the ligand is bidentate, which is postulated to decrease ligand dissociation. Both of these factors could be serving to protect the carbenoid intermediate that is key to the cascade reaction.

Having identified a superior catalyst for bridged bicycle formation, we desired to know the impact other parameters of the reaction had on the outcome. Solvent is known to have a significant impact on carbene transformations,[31] though the range of compatible solvents is somewhat limited. The use of dichloroethane, which is similar in many ways to dichloromethane but has a higher boiling point, diminished the formation of both **9** and dimeric products (entry 11). A hydrocarbon solvent, which is also a common alternative, showed increased dimerization at the expense of the desired product (entry 12). When benzene was used, several compounds derived from reaction with benzene were observed in competition with **9**. Lowering the temperature at which the

reaction occurred in CH_2Cl_2 also served to increase the formation of dimers (entry 13). This result is not unexpected given the need for enough thermal energy to adopt a transition state to form the strained bridged bicycloheptane through C–H bond insertion. The concentration of the reaction also affected the ratio of products obtained. If the concentration was raised above 5 μM, dimer formation increased (entry 14). These observations suggested that for the desired alkyne insertion/C–H bond insertion cascade, a more facile dimerization pathway had to be avoided. An obvious technique to do this was to slowly add the diazocompound to a solution of the catalyst and thus maintain a very low concentration of reactive species. Indeed, slow addition of **6** to $Rh_2(esp)_2$ greatly decreased the formation of dimers (entry 15). However, the long introduction of **6** via syringe provided opportunity for exogenous water to enter the system and increase the OH insertion products observed to the detriment of the formation of **9**. The addition of activated molecular sieves suspended in the reaction resolved this problem and provided the product **9** in the highest yield (entry 16). Since these latter conditions are operationally more complex and provide a modest 8% higher yield than the simple, single-portion introduction of the starting material, all the subsequent experiments were performed with the conditions found in entry 8 of Table 1. We do note that as such, the reported yields below could be easily improved in a straightforward manner using slow addition.

An obvious next step in this reaction discovery was the use of enantioselective catalysts[32] to transform the *meso* starting material into enantioenriched product. We sampled several currently available catalysts with chiral carboxylate ligands seeking proficiency in the transformation. These initial trials were made using the reaction conditions found suitable for the use of $Rh_2(esp)_2$. The phthalimido adamantyl acetate ligand PTAD showed a greatly decreased formation of product relative to $Rh_2(esp)_2$ with only a 31% yield (Table 2, entry 1). However, it did provide the greatest enantioenrichment at 23% ee. The cyclopropane-based BTPCP[33] ligand and the proline-based DOSP ligand fared even worse (entries 2 and 3). Surprisingly, the DOSP relative 4-*t*-Bu-phenylsulfonyl proline ligand (*t*BuSP) demonstrated the greatest product yield, though the enantioinduction was noticeably less than the PTAD catalyst (entry 4). A bidentate proline-based ligand, biTISP, was hoped to be likely to replicate the efficacy of the esp ligand. Unfortunately, it provided the product **9** in the lowest yield of all of the catalysts. The product that did form, however, was obtained with 21% ee. Because significant ligand redesign will be needed to improve both the yield of product and the enantioinduction for this cascade reaction, we turned our attention to the substrate scope of the achiral catalyst $Rh_2(esp)_2$ before continuing with the asymmetric transformation.

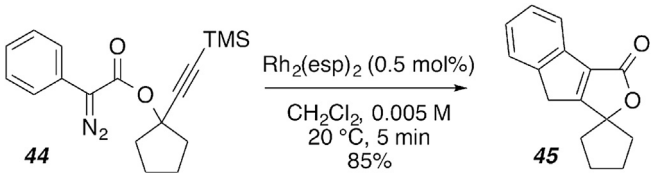
Table 2
Enantioselective catalysis



Entry	Catalyst	equiv	Time[a]	Yield[b]	ee[c]
1	Rh_2(*S*-PTAD)$_4$	0.3 mol %	1 h	31%	23%
2	Rh_2(*S*-BTPCP)$_4$	0.3 mol %	1 h	21%	6%
3	Rh_2(*S*-DOSP)$_4$	0.3 mol %	1 h	19%	12%
4	Rh_2(*S*-*t*BuSP)$_4$	0.6 mol %[d]	12 h	40%	16%
5	Rh_2(*S*-biTISP)$_2$	0.6 mol %[d]	12 h	10%	21%

[a] Reaction stopped when **6** was consumed.
[b] Isolated yields.
[c] Measured by HPLC with chiral stationary phase.
[d] Reaction started with 0.3 mol % and another 0.3 mol % added after 6 h.

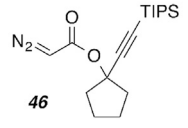
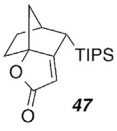
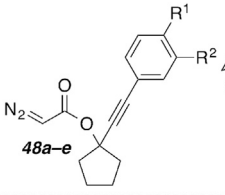
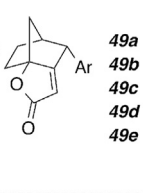
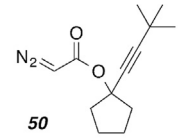
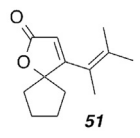
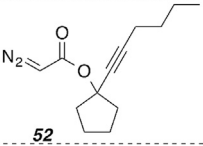
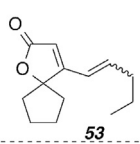
The reactivity of phenyl and vinyl diazoacetates in alkynyl cascade reactions was demonstrated by Padwa.[34] In that example the resulting carbenoid from carbene/alkyne metathesis reacted with the vinyl or aryl substituent in a 1,5-electrocyclization to form an indene. To confirm that the introduction of the carbocycle in our substrates did not alter this reactivity, we synthesized diazoester **44** (Scheme 6). Upon exposure to Rh(II), the alkyne insertion and 1,5-electrocyclization took place as expected to form indene **45**.



Scheme 6. The cascade with a phenyl diazoacetate.

The silyl group on the terminus of our initial substrate **6** proved to be important for the effective formation of the bridged bicyclic product **9**. If a terminal alkyne were instead used, a mixture of 5-*exo* and 6-*endo* alkyne cyclization products would be observed. Fortunately, the silyl group in **9** or any of the other silyl alkane products was easily removed through the use of Bu_4NF to provide the equivalent product to that derived from a terminal alkyne. If a more robust silyl group was needed, TIPS could be used in lieu of TMS (Table 3, entry 1). Aryl groups were also readily accommodated as alkynyl substituents, with the sole problem occurring with a strong resonance electron donor in the *para* position of the aromatic ring (**48c**, R^1=OMe, entry 2). The starting material was consumed in the reaction, but no well-defined product was observed. One hypothesis for this phenomenon may be that the donating group greatly stabilizes the intermediate carbenoid, rendering it insufficiently

Table 3
Alkynyl substituents

entry	diazoester	product(s)[a]	yield[b]
1			55%
2			**49a** R^1=CF_3, R^2=H, 64% **49b** R^1=H, R^2=CO_2Me, 65% **49c** R^1=OMe, R^2=H, 7%[c] **49d** R^1=H, R^2=OMe, 63% **49e** R^1=H, R^2=Br, 56%
3			75%
4			CH_2Cl_2: 67%, 1:1.4 cis/trans pentane: 50%, 2:1 cis/trans

[a] $Rh_2(esp)_2$ (0.5 mol%), CH_2Cl_2, 20 °C, 5 min.
[b] Isolated yields. [c] Yield based on integration of ^1H NMR spectrum compared to internal standard.

reactive to complete the reaction. A *para*-CF_3 group or any number of *meta* substituents were readily tolerated.

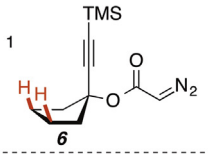
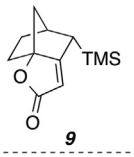
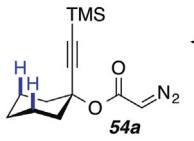
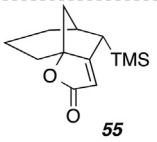
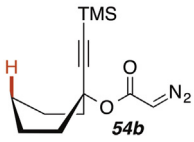
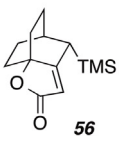
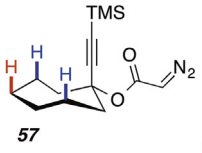
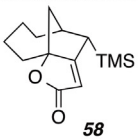
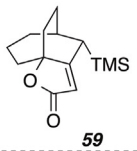
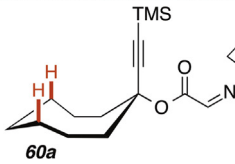
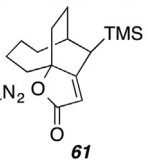
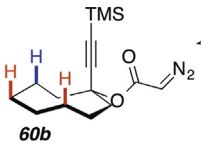
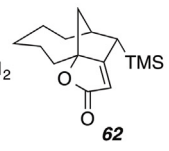
Alkyl substituents on the alkyne displayed differing reactivity. The *tert*-butyl group found in the alkynyl diazoester **50** provided opportunity for a 1,2-methyl migration to outcompete C–H bond insertion and form the trimethylvinyl butenolide **51**. Similarly, a 1,2-hydride shift in the *n*-butyl group of ester **52** generated the vinylbutenolide **53** as a mixture of cis and trans isomers. This occurred even in pentane as a solvent, which has previously been shown to discourage 1,2-migrations in carbene cascades.[12o,p] These migrations in alkyl alkynes find robust precedent in Padwa's work, where similar migrations occur after carbene/alkyne cascade reactions.[34] One note of interest is that the cis/trans ratios for **53** are intermediate between those seen for **32** in Hoye's study in Scheme 2. We may conclude that the early mechanistic steps in this cascade process are closely related to those seen in previous examples of the cascade.

Much of the most novel reactivity in this reaction was found in the variation of the ring found between the alkyne and the diazoester. Due to the ease of substrate synthesis, a number of permutations of the original structure were readily available. A study on the effects of ring sizes was performed early on to both establish the scope of the reaction and define the effects of ring conformations on product outcomes. Because of the conformational demands in the transition state for C–H bond insertion to form a bridged bicycloalkane, this analysis was deemed to be an important consideration. As can be seen in Scheme 1, the final step of the cascade sequence is a transannular C–H bond insertion from intermediate **8** (or its carbenoid mechanistic equivalent). The C–H bond that is geometrically available for this insertion will be the most likely site of C–C bond formation for the bridged bicycloalkane.

In the case of our study compound **6**, insertion into either of the C–H bonds highlighted in red in Table 4 provides bicyclo[2.2.1]heptane **9**, albeit as a racemic mixture (entry 1). However, in the case of the cyclohexyl derivative, insertion into the C–H bond at either of the 3-positions (see **54a**) would form the bicyclo[3.2.1]octane **55**, but insertion at the 4-position would instead form bicyclo[2.2.2]octane **56**. Given our goal to be able to access a broad selection of bridged ring sizes and connectivities, we need to be able to access either of those products at will. Fortunately, with no catalyst or substrate bias, the rates of insertion at those two positions occurred with a nearly statistical preference (entry 2). The similarity between insertion rates at those sites will allow for bias to be introduced either through substituents on the substrate or through the future synthesis of catalysts with more controlling ligands. We note that the silyl-bearing carbon in **55** was found as a mixture of α- and β-silyl diastereomers, but in all examples in which an aryl-substituted alkyne was used only one diastereomer was formed (see Table 6). The reason for the differences in diastereoselectivity are difficult to fully rationalize given the uncertain nature of the mechanistic intermediate formed from the metal carbene reacting with the alkyne. A rigid transition state for the formation of **47** and **49** where the transannular C–H bond insertion occurs from the midplane of the ring is likely responsible for the formation of only the *endo* diastereomer. Greater conformational flexibility in the cyclohexane ring would allow for attack of the C–H bond from either side, resulting in a mixture of diastereomers.

The use of seven- and eight-membered rings in the substrates showed that there is more conformational bias in those systems. Assuming that the carbenoid derived from the alkyne in cycloheptyl substrate **57** must be in a pseudoaxial position for transannular C–H bond insertion, a likely conformation is illustrated with the most likely points of C–H bond insertion highlighted in blue (entry 3). Indeed, the major product bicyclo[4.2.1]nonane **58** is derived from insertion at those axially-displayed C–H bonds. Similarly, the major product from the reaction of cyclooctyl

Table 4
Effects of ring size

entry	diazoester	product(s)[a]	yield[b]
1			77%
2			41% yield dr 1.1:1[c]
			28% yield
3			65% 2.3:1 dr[c]
			8% yield
4			55% yield
			10% yield

[a] $Rh_2(esp)_2$ (0.5 mol%), CH_2Cl_2, 20 °C, 5 min. [b] Isolated yields.
[c] Diastereomeric relationships were established via 1D nOe studies.

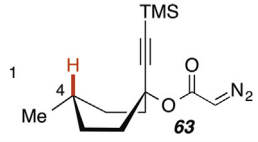
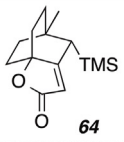
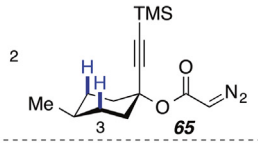
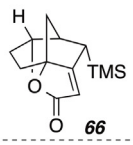
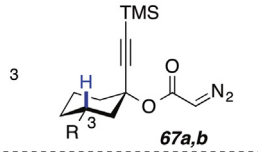
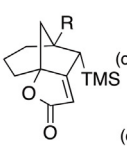
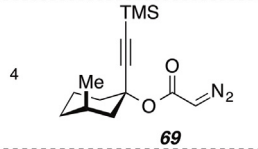
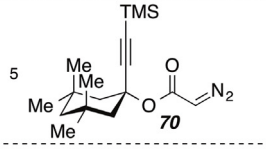
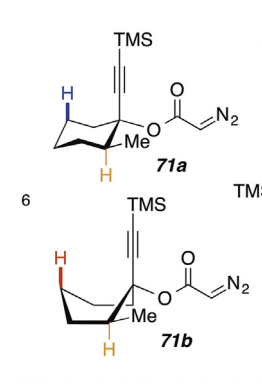
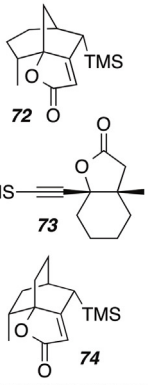
substrate **60** may be predicted. In this case, there are two somewhat equivalent conformations that put the alkyne pseudoaxial and have only 2 eclipsing interactions around the ring (entry 4). In the top case, only one possibility presents itself for C–H bond insertion, and in the lower case there are two non-equivalent C–H bonds that appear as targets for insertion. The product distribution reflects this with 5.5:1 preference for insertion into the red highlighted C–H bonds to provide bicyclo[4.2.2]decane **61** as the major product. Given the understanding of the conformations of variously sized rings with substitution,[11] this predictive ability is highly applicable to design a synthesis of a complex bridged polycycle using this strategy.

To further demonstrate the ability to predict reactivity based on stereoelectronic and conformational considerations, we turned our attention to cyclohexyl substrates with substituents at various positions around the ring and with differing diastereomeric relationships to the alkyne. Placing a methyl group in the ring's 4-position in a trans relationship to the alkyne as shown in **63**

(Table 5, entry 1) should activate the C4 C–H bond for insertion given the greater reactivity of methines versus methylenes toward Rh carbenes. Indeed, in contrast to the cyclohexyl substrate **54**, insertion occurred exclusively at the methine in the 4-position of the ring to form only bicyclo[2.2.2]octane **64**. On the other hand, the diastereomeric methine in **65** places the C–H bond on the opposite side of the ring to the developing carbenoid center (entry 2). Consequently, C–H bond insertion must occur at the methyl C–H or at the methylene at the 3-position. Since methyl C–H bond insertion is usually much slower than that for methylenes or methines, bicyclo[3.2.1]octane **66** is now the exclusive product formed. The *trans* 3-methylcyclohexyl or 3-phenylcyclohexyl substrates **67a** or **67b** mirror the reactivity of **63**, again producing the predicted major methine insertion product in each case (entry 3). However the diastereomeric **69** not only places the methine C–H bond out of reach for the carbenoid center, but also requires an axial orientation for the methyl in a transannular C–H bond insertion (entry 4). In this case and for tetramethylcyclohexane **70** (entry 5), no product is observed in the reaction. Surprisingly, a majority of the starting material is recovered for these examples even after refluxing in CH_2Cl_2 for several hours. Apparently, the catalyst is in some way inactivated or sequestered by these substrates, possibly by forming stable intermediates. With the methyl at the 2-position on the ring and cis to the alkyne, reactivity is restored and an interesting C–H bond insertion rate comparison is generated. The carbene initially generated from the diazoester has the option of either directly inserting into the C–H bond of the methine to form lactone **73** or reacting with the alkyne. As can be seen by the dominant formation of **72** and **74**, reaction with the alkyne is greatly favored over direct C–H bond insertion by the initial carbene, even though the final C–H bond insertion occurs at a methylene and not the methine. This ability to divert the reactivity of a carbene through an alkyne insertion pathway has significant implications to alter traditional orders of reactivity.

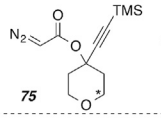
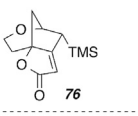
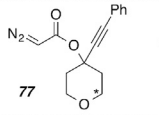
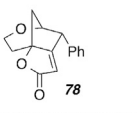
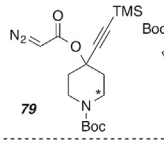
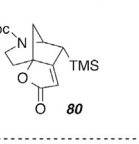
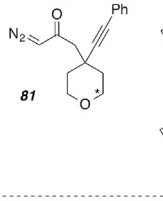
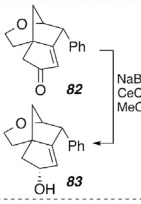
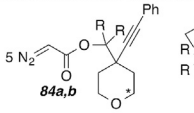
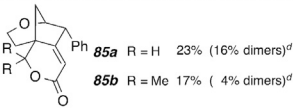
Heterocyclic rings displayed similar reactivity to the carbocycles. For example, the pyranone-derived diazoesters **75** and **77** produced the oxabicyclo[3.2.1]octanes **76** and **78**, where the final C–H bond insertion only occurred at the carbon adjacent to the oxygen (Table 6). Given oxygen's ability to activate C–H bonds for insertion if proper alignment is possible, these products were easily anticipated. Notably, the phenylalkyne substrate **77** produced a single product diasetereomer. Nitrogen-based heterocycles were also functional for the transformation, as the *N*-Boc-piperidinone-derived **79** provided the bridged azacycle **80**.

Table 5
Substituent effects on C–H bond insertion

entry	diazoester	product(s)[a]	yield[b]
1			56%
2			65% dr 1.4:1
3			**68a** R = Me 47% yield dr 1.6:1[c] (other bridged products: 13%) **68b** R = Ph 56% yield dr 2.3:1[c] (other bridged products: 8%)
4			No Reaction
5			No Reaction
6			58% yield dr 2.4:1[c] 14% yield 14% yield dr 1.3:1[c]

[a] $Rh_2(esp)_2$ (0.5 mol%), CH_2Cl_2, 20 °C, 5 min. [b] Isolated yields.
[c] Diastereomeric relationships were established via 1D nOe studies.

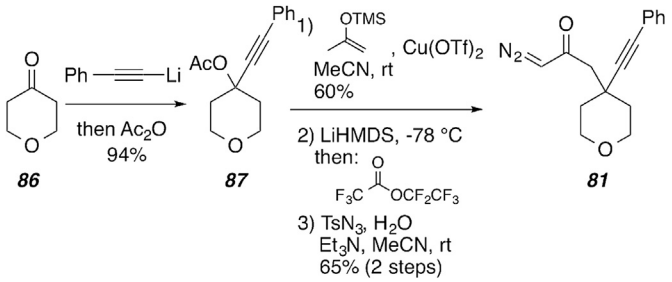
Table 6
Heterocyclic substrates

entry	diazo compound	product(s)[a]	yield[b]
1			71% 1.4:1 dr[c]
2			66%
3			62% 1.4:1 dr[c]
4			62% (2 steps)
5			**85a** R = H 23% (16% dimers)[d] **85b** R = Me 17% (4% dimers)[d]

[a] $Rh_2(esp)_2$ (0.5 mol%), CH_2Cl_2, 20 °C, 5 min. [b] Isolated yields.
[c] Diastereomeric relationships were established via 1D nOe studies.
[d] Yield based on integration of ^1H NMR spectrum compared to internal standard.

Diazoketones also proved viable for the formation of cyclopentenone-fused bridged bicycloalkanes (entry 4). The diazoketone **81** was synthesized in four steps from pyranone **86** through acetylide addition, trapping as the acetate, Lewis acid-

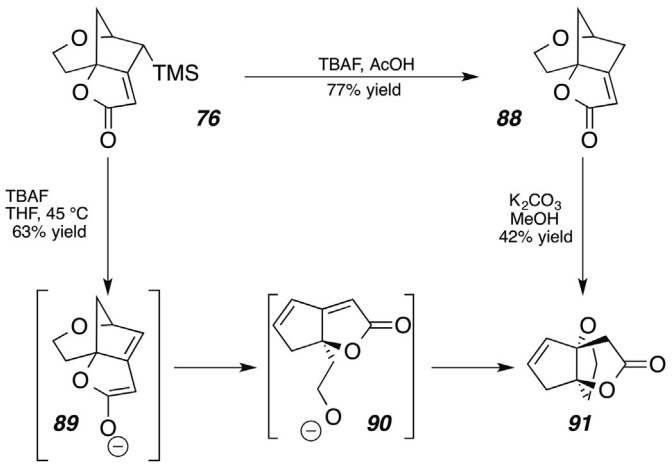
assisted displacement of the acetate by the appropriate silyl enol ether,[35] and diazotization[36] (Scheme 7). When exposed to $Rh_2(esp)_2$, ketone **81** rapidly formed enone **82**. Since this oxacycle was very prone to rearrangement (vide infra), a Luche reduction to allylic alcohol **83** was carried out to characterize the bridged product.



Scheme 7. Synthesis of diazoketone **81**.

Substrates that would provide larger rings fused to the bridged polycycle such as **84** were synthesized through propargylation of the corresponding aldehyde or ketone with 1-chloro-2-phenylacetylene.[37] When exposed to the standard reaction conditions, the anticipated bridged polycycle was indeed formed, though there remains room for improvement (Table 6, entry 5). While bridged rings **85** were the major products, numerous side products were also seen.

The products in Table 6 can undergo additional useful transformations. The proton located in the γ-position relative to the enone in **76** is fairly acidic (Scheme 8). It can be deprotonated in

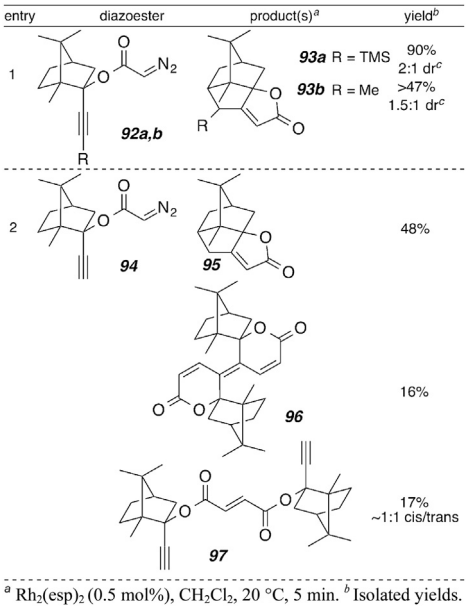


Scheme 8. Rearrangement of bridged oxacycles.

basic methanol or unbuffered Bu_4NF. Elimination of the δ-alkoxide may then occur, forming the fused bicycle **90**. The oxyanion can then add in an intramolecular Michael addition to the α,β-unsaturated carbonyl to form the propellane **91**. The ring strain inherent in the bridged bicycle acts as the driving force for the rearrangement. A phenyl group in place of the trimethylsilyl substituent (i.e., **78** or **82**) makes this process even more facile.

Beginning the cascade sequence with bridged bicyclic alkynyl diazoesters produced sterically congested caged polycycles. For example, the camphor-derived esters **92a** and **92b** cleanly generated the tetracycles **93a** and **93b** for silyl and methyl alkynes (Table 7). Again, if a terminal alkyne was used, mixtures of 5-*exo* and 6-*endo*

Table 7
Bridged bicyclic diazoesters



[a] $Rh_2(esp)_2$ (0.5 mol%), CH_2Cl_2, 20 °C, 5 min. [b] Isolated yields.

products were obtained that could be structurally characterized. Furthermore, this approach allows access to densely-functionalized caged systems from more easily accessed bridged bicycles.

3. Conclusion

This manuscript outlines a general approach for the synthesis of bridged polycyclic compounds. A carbene cascade reaction forms functionalized bridged bicyclics in only a few steps from cyclic ketones. Importantly, the bridge connectivity in the final product is predictable from conformational and stereoelectronic effects that are well known. This predictability allows the cascade to be applied the design of synthetic strategies for complex polycyclic targets.

4. Experimental

4.1. General procedure A (Table 1, entry 9)

A flame-dried round-bottom flask was charged with the diazoacetate (1.0 equiv) under an argon atmosphere. Anhydrous CH_2Cl_2 (to 0.005 M) was added. The reaction mixture was vigorously stirred at room temperature while adding $Rh_2(esp)_2$ (0.5 mol %) in one portion. After 5 min, the TLC analysis showed no starting material. The reaction mixture was concentrated under reduced pressure, and the residue was purified by flash column chromatography on silica gel.

4.2. General procedure B (Table 1, entry 15)

A round-bottom flask charged with 4 Å molecular sieves (~3 g/mmol) was flame-dried under high vacuum. The flask was allowed to cool to room temperature, and then it was purged with an argon atmosphere. $Rh_2(esp)_2$ (0.5 mol %) was added, followed by anhydrous CH_2Cl_2 (to 0.005 M). Diazoacetate (1.0 equiv) dissolved in anhydrous CH_2Cl_2 (0.1 M) was added dropwise slowly over 30 min via syringe pump. After the addition, the TLC analysis showed no starting material. The reaction mixture was concentrated under

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reduced pressure, and the residue was purified by flash column chromatography on silica gel.

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Supplementary data

Detailed experimental procedures, characterization data for all previously undisclosed compounds, and HPLC traces for enantioselective reactions are presented. Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2014.03.060.

References and notes

1. (a) Chow, S.; Kreß, C.; Albæk, N.; Jessen, C.; Williams, C. M. *Org. Lett.* **2011**, *13*, 5286–5289; (b) Urabe, D.; Yamaguchi, H.; Inoue, M. *Org. Lett.* **2011**, *13*, 4778–4781; (c) Yoshimitsu, T.; Nojima, S.; Hashimoto, M.; Tanaka, T. *Org. Lett.* **2011**, *13*, 3698–3701.
2. (a) Boezio, A. A.; Jarvo, E. R.; Lawrence, B. M.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2005**, *44*, 6046–6050; (b) Li, P.; Payette, J. N.; Yamamoto, H. *J. Am. Chem. Soc.* **2007**, *129*, 9534–9535; (c) Li, P.; Yamamoto, H. *Chem. Commun.* **2009**, 5412–5414; (d) Movassaghi, M.; Tjandra, M.; Qi, J. *J. Am. Chem. Soc.* **2009**, *131*, 9648–9650; (e) Liau, B. B.; Shair, M. D. *J. Am. Chem. Soc.* **2010**, *132*, 9594–9595; (f) Zi, W.; Yu, S.; Ma, D. A. *Angew. Chem., Int. Ed.* **2010**, ; (g) Kanoh, N.; Sakanishi, K.; Iimori, E.; Nishimura, K.; Iwabuchi, Y. *Org. Lett.* **2011**, *13*, 2864–2867; (h) Oblak, E. Z.; Wright, D. L. *Org. Lett.* **2011**, *13*, 2263–2265; (i) Adams, G. L.; Carroll, P. J.; Smith Iii, A. B. *J. Am. Chem. Soc.* **2012**, *134*, 4037–4040; (j) Lebold, T. P.; Gallego, G. M.; Marth, C. J.; Sarpong, R. *Org. Lett.* **2012**, *14*, 2110–2113.
3. (a) Suzuki, T.; Sasaki, A.; Egashira, N.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2011**, *50*, 9177–9179; (b) Burns, N. Z.; Witten, M. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2011**, *133*, 14578–14581; (c) Chen, L.; Hua, Z.; Li, G.; Jin, Z. *Org. Lett.* **2011**, *13*, 3580–3583; (d) Mendoza, A.; Ishihara, Y.; Baran, P. S. *Nat. Chem.* **2011**, *4*, 21–25; (e) Peixoto, P. A.; Severin, R.; Tseng, C.-C.; Chen, D. Y. K. *Angew. Chem., Int. Ed.* **2011**, *50*, 3013–3016; (f) Bai, Y.; Tao, W.; Ren, J.; Wang, Z. *Angew. Chem., Int. Ed.* **2012**, *51*, 4112–4116; (g) Jones, A. C.; May, J. A.; Sarpong, R.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2014**, *53*, 2556–2591.
4. (a) Dekorver, K. A.; Wang, X.-N.; Walton, M. C.; Hsung, R. P. *Org. Lett.* **2012**, *14*, 1768–1771; (b) Green, J. C.; Pettus, T. R. R. *J. Am. Chem. Soc.* **2011**, *133*, 1603–1608; (c) Jadhav, A. M.; Bhunia, S.; Liao, H.-Y.; Liu, R.-S. *J. Am. Chem. Soc.* **2011**, *133*, 1769–1771.
5. (a) Cook, S. P.; Polara, A.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2006**, *128*, 16440–16441; (b) Peng, F.; Yu, M.; Danishefsky, S. J. *Tetrahedron Lett.* **2009**, *50*, 6586–6587; (c) Gong, J.; Lin, G.; Li, C.-C.; Yang, Z. *Org. Lett.* **2009**, *11*, 4770–4773; (d) Krawczuk, P. J.; Schöne, N.; Baran, P. S. *Org. Lett.* **2009**, *11*, 4774–4776; (e) Nicolaou, K. C.; Dong, L.; Deng, L.; Talbot, A. C.; Chen, D. Y. K. *Chem. Commun.* **2010**, 70–72; (f) Singh, V.; Bhalerao, P.; Mobin, S. M. *Tetrahedron Lett.* **2010**, *51*, 3337–3339; (g) Lazarski, K. E.; Hu, D. X.; Stern, C. L.; Thomson, R. J. *Org. Lett.* **2010**, *12*, 3010–3013; (h) Gong, J.; Lin, G.; Sun, W.; Li, C.-C.; Yang, Z. *J. Am. Chem. Soc.* **2010**, *132*, 16745–16746; (i) Baitinger, I.; Mayer, P.; Trauner, D. *Org. Lett.* **2010**, *12*, 5656–5659; (j) Gu, Z.; Zakarian, A. *Org. Lett.* **2011**, *13*, 1080–1082; (k) Dong, L.; Deng, L.; Lim, Y. H.; Leung, G. Y. C.; Chen, D. Y. K. *Chem.—Eur. J.* **2011**, *17*, 5778–5781; (l) Peng, F.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2012**, *134*, 18860–18867; (m) Lu, P.; Gu, Z.; Zakarian, A. *J. Am. Chem. Soc.* **2013**, *135*, 14552–14555.
6. Jansone-Popova, S.; May, J. A. *J. Am. Chem. Soc.* **2012**, *134*, 17877–17880.
7. (a) Dave, V.; Warnhoff, E. W. *The Reactions of Diazoacetic Esters with Alkenes, Alkynes, Heterocyclic and Aromatic Compounds*. Org. React. 2011, pp 217–401; (b) Marchand, A. P.; Brockway, N. M. *Chem. Rev.* **1974**, *74*, 431–469.
8. (a) Curtius, T. *Ber.* **1883**, *16*, 2230–2231; (b) Curtius, T. *J. Prakt. Chem.* **1888**, *38*, 396–440.
9. Moss, R. A.; Jones, M. Carbenes In*Moss, R. A., Jones, M., Eds.. Reactive Intermediates*; Wiley: New York, NY, 1985; Vol. 3, Chapter 3.
10. Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174–238.
11. Anslyn, E. V.; Dougherty, D. A. *Strain and Stability*. Modern Physical Organic Chemistry; University Science Books: Sausalito, CA, 2006; Chapter 2, pp 65–137.
12. (a) Padwa, A.; Krumpe, K. E.; Zhi, L. *Tetrahedron Lett.* **1989**, *30*, 2633–2636; (b) Kinder, F. R.; Padwa, A. *Tetrahedron Lett.* **1990**, *31*, 6835–6838; (c) Padwa, A.; Gareau, Y.; Xu, S. L. *Tetrahedron Lett.* **1991**, *32*, 983–986; (d) Padwa, A.; Austin, D. J.; Chiacchio, U.; Kassir, J. M.; Rescifina, A.; Xu, S. L. *Tetrahedron Lett.* **1991**, *32*, 5923–5926; (e) Padwa, A.; Krumpe, K. E.; Gareau, Y.; Chiacchio, U. *J. Org. Chem.* **1991**, *56*, 2523–2530; (f) Padwa, A.; Austin, D. J.; Xu, S. L. *Tetrahedron Lett.* **1991**, *32*, 4103–4106; (g) Padwa, A.; Krumpe, K. E. *Tetrahedron* **1992**, *48*, 5385–5453; (h) Padwa, A.; Austin, D. J.; Xu, S. L. *J. Org. Chem.* **1992**, *57*, 1330–1331; (i) Padwa, A.; Krumpe, K. E.; Kassir, J. M. *J. Org. Chem.* **1992**, *57*, 4940–4948; (j) Mueller, P. H.; Kassir, J. M.; Semones, M. A.; Weingarten, M. D.; Padwa, A. *Tetrahedron Lett.* **1993**, *34*, 4285–4288; (k) Padwa, A.; Chiacchio, U.; Fairfax, D. J.; Kassir, J. M.; Litrico, A.; Semones, M. A.; Xu, S. L. *J. Org. Chem.* **1993**, *58*, 6429–6437; (l) Padwa, A.; Austin, D. J.; Gareau, Y.; Kassir, J. M.; Xu, S. L. *J. Am. Chem. Soc.* **1993**, *115*, 2637–2647; (m) Padwa, A.; Kassir, J. M.; Semones, M. A.; Weingarten, M. D. *Tetrahedron Lett.* **1993**, *34*, 7853–7856; (n) Padwa, A.; Krumpe, K. E.; Weingarten, M. D. *J. Org. Chem.* **1995**, *60*, 5595–5603; (o) Padwa, A.; Weingarten, M. D. *Chem. Rev.* **1996**, *96*, 223–270; (p) Padwa, A. *Molecules* **2001**, *6*, 1–12; (q) Padwa, A. *Chem. Soc. Rev.* **2009**, *38*, 3072.
13. (a) Korkowski, P. F.; Hoye, T. R.; Rydberg, D. B. *J. Am. Chem. Soc.* **1988**, *110*, 2676–2678; (b) Hoye, T. R.; Dinsmore, C. J.; Johnson, D. S.; Korkowski, P. F. *J. Org. Chem.* **1990**, *55*, 4518–4520; (c) Hoye, T. R.; Dinsmore, C. J. *Tetrahedron Lett.* **1991**, *32*, 3755–3758; (d) Hoye, T. R.; Dinsmore, C. J. *Tetrahedron Lett.* **1992**, *33*, 169–172; (e) Hoye, T. R.; Vyvyan, J. R. *J. Org. Chem.* **1995**, *60*, 4184–4195.
14. (a) Cambeiro, F.; López, S.; Varela, J. A.; Saá, C. *Angew. Chem., Int. Ed.* **2012**, *51*, 723–727; (b) Thornton, A. R.; Blakey, S. B. *J. Am. Chem. Soc.* **2008**, *130*, 5020–5021; (c) Thornton, A. R.; Martin, V. I.; Blakey, S. B. *J. Am. Chem. Soc.* **2009**, *131*, 2434–2435.
15. Hoye, T. R.; Dinsmore, C. J. *J. Am. Chem. Soc.* **1991**, *113*, 4343–4345.
16. (a) Taber, D. F.; Herr, R. J.; Pack, S. K.; Geremia, J. M. *J. Org. Chem.* **1996**, *61*, 2908–2910; (b) Pirrung, M. C.; Hwu, J. R. *Tetrahedron Lett.* **1983**, *24*, 565–568; (c) Doyle, M. P.; High, K. G.; Su-Min, O.; Osborn, A. K. *Tetrahedron Lett.* **1989**, *30*, 3049–3052; (d) Sarkar, T. K.; Ghorai, B. K. *J. Chem. Soc., Chem. Commun.* **1992**, 1184–1186; (e) May, J. A.; Stoltz, B. M. *J. Am. Chem. Soc.* **2002**, *124*, 12426–12427.
17. (a) Doyle, M. P.; Bagheri, V.; Pearson, M. M.; Edwards, J. D. *Tetrahedron Lett.* **1989**, *30*, 7001–7004; (b) Doyle, M. P.; Pieters, R. J.; Taunton, J.; Pho, H. Q.; Padwa, A.; Hertzog, D. L.; Precedo, L. *J. Org. Chem.* **1991**, *56*, 820–829; (c) Doyle, M. P.; Protopopova, M. N.; Winchester, W. R.; Daniel, K. L. *Tetrahedron Lett.* **1992**, *33*, 7819–7822; (d) Padwa, A.; Austin, D. J.; Hornbuckle, S. F.; Semones, M. A.; Doyle, M. P.; Protopopova, M. N. *J. Am. Chem. Soc.* **1992**, *114*, 1874–1876; (e) Padwa, A.; Austin, D. J.; Price, A. T.; Semones, M. A.; Doyle, M. P.; Protopopova, M. N.; Winchester, W. R.; Tran, A. *J. Am. Chem. Soc.* **1993**, *115*, 8669–8680; (f) Doyle, M. P.; Westrum, L. J.; Wolthuis, W. N. E.; See, M. M.; Boone, W. P.; Bagheri, V.; Pearson, M. M. *J. Am. Chem. Soc.* **1993**, *115*, 958–964; (g) Bode, J. W.; Doyle, M. P.; Protopopova, M. N.; Zhou, Q. L. *J. Org. Chem.* **1996**, *61*, 9146–9155; (h) Doyle, M. P.; Kalinin, A. V.; Ene, D. G. *J. Am. Chem. Soc.* **1996**, *118*, 8837–8846; (i) Timmons, D. J.; Doyle, M. P. *J. Organomet. Chem.* **2001**, *617*, 98–104; (j) Doyle, M. P.; Hu, W.; Wee, A. G. H.; Wang, Z.; Duncan, S. C. *Org. Lett.* **2003**, *5*, 407–410; (k) Doyle, M. P.; Hu, W.; Wee, A. G. H.; Wang, Z.; Duncan, S. C. *Org. Lett.* **2003**, *5*, 407–410.
18. (a) Taber, D. F.; Petty, E. H. *J. Org. Chem.* **1982**, *47*, 4808–4809; (b) Taber, D. F. *Tetrahedron Lett.* **1985**, *26*, 3059–3062; (c) Taber, D. F.; Ruckle, R. E., Jr. *J. Am. Chem. Soc.* **1986**, *108*, 7686–7693; (d) Taber, D. F.; Hennessy, M. J.; Louey, J. P. *J. Org. Chem.* **1992**, *57*, 436–441; (e) Taber, D. F.; You, K. K. *J. Am. Chem. Soc.* **1995**, *117*, 5757–5762; (f) Taber, D. F.; Song, Y. *J. Org. Chem.* **1996**, *61*, 6706–6712; (g) Taber, D. F.; Kamfia, K.; Rheingold, A. L. *J. Am. Chem. Soc.* **1996**, *118*, 547–556; (h) Taber, D. F.; Christos, T. E. *Tetrahedron Lett.* **1997**, *38*, 4927–4930; (i) Taber, D. F.; Malcolm, S. C. *J. Org. Chem.* **1998**, *63*, 3717–3721.
19. (a) Hashimoto, S.-I.; Watanabe, N.; Ikegami, S. *J. Chem. Soc., Chem. Commun.* **1992**, 1508–1510; (b) Hashimoto, S.; Watanabe, N.; Ikegami, S. *Synlett* **1994**, 353–355; (c) Anada, M.; Sugimoto, T.; Watanabe, N.; Nakajima, M.; Hashimoto, S. *Heterocycles* **1999**, *50*, 969–980; (d) Kitagaki, S.; Anada, M.; Kataoka, O.; Matsuno, K.; Umeda, C.; Watanabe, N.; Hashimoto, S.-I. *J. Am. Chem. Soc.* **1999**, *121*, 1417–1418.
20. (a) Agosta, W. C.; Wolff, S. *J. Org. Chem.* **1975**, *40*, 1027–1030; (b) Adams, J.; Poupart, M.; Grenier, L.; Schaller, C.; Ouimet, N.; Frenette, R. *Tetrahedron Lett.* **1989**, *30*, 1749–1752; (c) Spero, D. M.; Adams, J. *Tetrahedron Lett.* **1992**, *33*, 1143–1146; (d) Wang, P.; Adams, J. *J. Am. Chem. Soc.* **1994**, *116*, 3296–3305; (e) Sulikowski, G. A.; Cha, K. L.; Sulikowski, M. M. *Tetrahedron: Asymmetry* **1998**, *9*, 3145–3169.
21. (a) Davies, H. M. L.; Saikali, E.; Jeffrey Clark, T.; Chee, E. H. *Tetrahedron Lett.* **1990**, *31*, 6299–6302; (b) Davies, H. M. L.; Smith, H. D.; Hu, B.; Klenzak, S. M.; Hegner, F. J. *J. Org. Chem.* **1992**, *57*, 6900–6903; (c) Davies, H. M. L.; Hu, B.; Saikali, E.; Bruzinski, P. R. *J. Org. Chem.* **1994**, *59*, 4535–4541; (d) Davies, H. M. L.; Matasi, J. J.; Ahmed, G. *J. Org. Chem.* **1996**, *61*, 2305–2313; (e) Davies, H. M. L.; Mark Hodges, L.; Matasi, J. J.; Hansen, T.; Stafford, D. G. *Tetrahedron Lett.* **1998**, *39*, 4417–4420; (f) Davies, H. M. L.; Hodges, L. M.; Thornley, C. T. *Tetrahedron Lett.* **1998**, *39*, 2707–2710; (g) Davies, H. M. L.; Hansen, T.; Hopper, D. W.; Panaro, S. A. *J. Am. Chem. Soc.* **1999**, *121*, 6509–6510; (h) Davies, H. M. L.; Ren, P. *Tetrahedron Lett.* **2001**, *42*, 3149–3151; (i) Davies, H. M. L.; Yang, J. *Adv. Synth. Catal.* **2003**, *345*, 1133–1138; (j) Davies, H. M. L.; Coleman, M. G.; Ventura, D. L. *Org. Lett.* **2007**, *9*, 4971–4974; (k) Hansen, J.; Autschbach, J.; Davies, H. M. L. *J. Org. Chem.* **2009**, *74*, 6555–6563.
22. Sonawane, H. R.; Bellur, N. S.; Ahuja, J. R.; Kulkarni, D. G. *J. Org. Chem.* **1991**, *56*, 1434–1439.
23. (a) Srikrishna, A.; Gharpure, S. J. *Chem. Commun.* **1998**, 1589–1590; (b) Srikrishna, A.; Gharpure, S. J. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3191–3193; (c) Srikrishna, A.; Ravi Kumar, P.; Gharpure, S. J. *Tetrahedron Lett.* **2001**, *42*, 3929–3931; (d) Srikrishna, A.; Gharpure, S. J. *J. Org. Chem.* **2001**, *66*, 4379–4385; (e) Srikrishna, A.; Satyanarayana, G. *Tetrahedron* **2005**, *61*, 8855–8859.
24. Yun, S. Y.; Zheng, J.-C.; Lee, D. *J. Am. Chem. Soc.* **2009**, *131*, 8413–8415.
25. Doyle, M. P.; Zhou, Q. L.; Conrad, E. R.; Roos, G. H. P. *Tetrahedron Lett.* **1995**, *36*, 4745–4748.
26. Doyle, M. P.; Dyatkin, A. B.; Autry, C. L. *J. Chem. Soc., Perkin Trans. 1* **1995**, 619–621.

27. Iritani, K.; Yanagihara, N.; Utimoto, K. *J. Org. Chem.* **1986**, *51*, 5499–5501.
28. Corey, E. J.; Myers, A. G. *Tetrahedron Lett.* **1984**, *25*, 3559–3562.
29. Hashimoto, S.; Watanabe, N.; Ikegami, S. *Tetrahedron Lett.* **1992**, *33*, 2709–2712.
30. (a) Espino, C. G.; Fiori, K. W.; Kim, M.; Du Bois, J. *J. Am. Chem. Soc.* **2004**, *126*, 15378–15379; (b) Kim, M.; Mulcahy, J. V.; Espino, C. G.; Du Bois, J. *Org. Lett.* **2006**, *8*, 1073–1076; (c) Fiori, K. W.; Du Bois, du, J. *J. Am. Chem. Soc.* **2007**, *129*, 562–568; (d) Kurokawa, T.; Kim, M.; Du Bois, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 2777–2779; (e) Fiori, K. W.; Espino, C. G.; Brodsky, B. H.; Du Bois, J. *Tetrahedron* **2009**, *65*, 3042–3051; (f) Zalatan, D. N.; Bois, du, J. *J. Am. Chem. Soc.* **2009**, *131*, 7558–7559.
31. Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods Organic Synthesis with Diazo Compounds*, 1st ed.; John Wiley & Sons: New York, NY, 1998.
32. Doyle, M. P.; Liu, Y.; Ratnikov, M. *Catalytic, Asymmetric, Intramolecular Carbon–Hydrogen Insertion*. Org. React., 2013; pp 1–132.
33. Qin, C.; Boyarskikh, V.; Hansen, J. H.; Hardcastle, K. I.; Musaev, D. G.; Davies, H. M. L. *J. Am. Chem. Soc.* **2011**, *133*, 19198–19204.
34. Padwa, A.; Chiacchio, U.; Garreau, Y.; Kassir, J. M.; Krumpe, K. E.; Schoffstall, A. M. *J. Org. Chem.* **1990**, *55*, 414–416.
35. Zhan, Z.; Wang, S.; Cai, X.; Liu, H.; Yu, J.; Cui, Y. *Adv. Synth. Catal.* **2007**, *349*, 2097–2102.
36. Danheiser, R. L.; Miller, R. F.; Brisbois, R. G.; Park, S. *J. Org. Chem.* **1990**, *55*, 1959–1964.
37. Please see Supplementary data for the synthesis and structural characterization for all new compounds.

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