SHORT COMMUNICATION

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Templated Carbene Metathesis Reactions from the Modular Assembly of Enol-diazo Compounds and Propargyl Acetates

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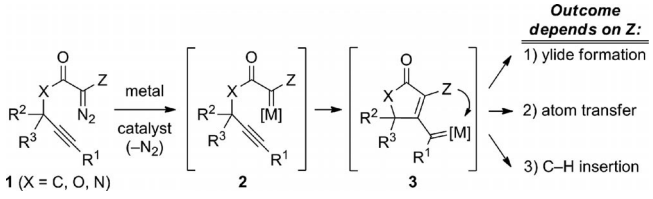
A Lewis acid mediated coupling reaction of enol-diazo nucleophiles and propargyl acetates has provided rapid and diverse access to complex alkynyl-tethered diazocarbonyl compounds. The ability of the coupling reaction to vary critical functionality flanking the diazo group was explored as a way to direct the outcome of a series of metal-catalyzed carbene metathesis cascade reactions. These cascade reactions provided diverse, biologically interesting carbocyclic and heterocyclic compounds in only a few steps from readily available materials.

Introduction

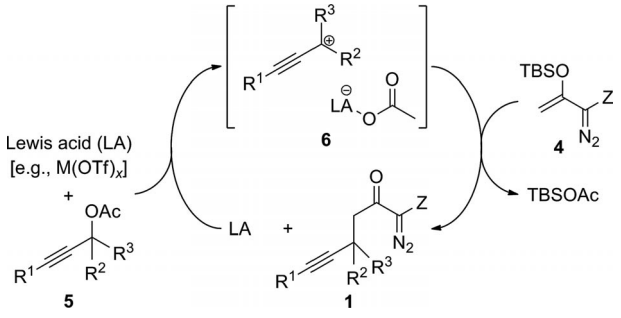
The diazocarbonyl functional group is one of the more versatile structural units in organic synthesis owing to the highly selective dual reactivity offered by the intermediate metal carbenes derived from catalytic dinitrogen extrusion reactions.[1] Furthermore, the ability to tune the reactivity and stability of the diazocarbonyl unit by placement of proximal functionality by using a variety of synthetic techniques offers a remarkable number of accessible reactivity and stability profiles. Some of the most impressive transformations of complex diazo compounds are the carbene-initiated cascade reactions that have been applied directly to the highly efficient synthesis of biologically active natural products.[2]

Early examples of carbene-initiated cascade reactions in the seminal work of Padwa[3] and Hoye[4] illustrated that alkynyl-tethered diazocarbonyl compounds such as **1** can undergo rhodium-catalyzed transformations to provide complex products in a single operation (Scheme 1). These reactions proceeded through net carbene metathesis of first-formed metal carbene **2** to give secondary vinyl carbene **3** that formed highly functionalized cyclopentenone (X = C),[5] butenolide (X = O), and pyrrolidinone (X = N) ring systems,[6] but they have been limited to simple diazo ketones and diazo esters.[3c] Although prior art related to this intriguing metathesis reaction demonstrated the potential utility of such cascades, their broad applicability has been impeded by the limited availability of complex alkynyl-tethered diazo compounds **1** that have a diversity of diazo substituents Z, particularly those bearing an all-carbon backbone (e.g., **1**, X = C). To overcome this limitation, we have developed a more efficient and general method to prepare **1** with the capability to vary the R^1–R^3 and Z substituents easily, and we demonstrate its general applicability in cascade processes for a broad diversity of templated reactions of secondary vinyl carbene **3** with the Z group (Scheme 1).



Scheme 1. Templated metal carbene metathesis cascade reactions.

Prior investigations have illustrated the high potential of coupling reactions of enol-diazoacetates **4** to provide complex organodiazo frameworks (Scheme 2) with a variety of different electrophilic partners in Lewis acid catalyzed aldol,[7a–7c] Michael,[7d–7f] and Mannich[7g] reactions, in which



Scheme 2. Enol-diazoacetate/propargyl acetate coupling process. TBS = *tert*-butyldimethylsilyl, Tf = trifluoromethylsulfonyl.

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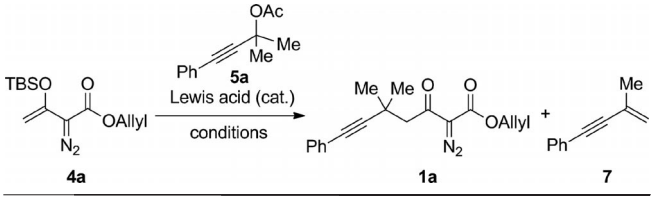
the diazo function is maintained. However, these reactions have been limited to the couplings of acetoacetate-derived enol-diazo compounds **4** (Z = COOR). In an effort to expand the scope of these coupling processes, especially those directed towards **1** with variable R^1–R^3 and Z substituents, we used Lewis acid catalyzed S_N1 reactions of enol-diazo compounds **4** to couple with propargyl acetates **5** via corresponding propargyl cation **6** (Scheme 2).[8] Given that both enol-diazo compounds **4** and propargyl acetates **5** are readily available, this approach represents a remarkably efficient tactic by which to synthesize **1**.

Results and Discussion

To optimize the propargyl acetate coupling reaction, enol-diazoacetate **4a** (Z = COOAllyl) and propargyl acetate **5a** (R^1 = Ph; R^2, R^3 = Me) were chosen as test substrates, and the activities of metal-based Lewis acid catalysts, including those of scandium, zinc, indium, and tin triflates as well as $AuCl_3$ and Cu(hfacac)$_2$ (hfacac = hexafluoroacetylacetonate), were assayed in CH_2Cl_2 at room temperature (Table 1, entries 1–7). Of these, Sc(OTf)$_3$ (5 mol-%) provided the highest reactivity in forming a mixture (62:38) of desired product **1a** and elimination byproduct **7**. The coupling reactions in MeCN and 1,2-dichloroethane (DCE) at room temperature, in contrast, exhibited reaction times of mere minutes, and the formation of elimination product **7** was less problematic. Other solvents, including PhMe, $CHCl_3$, and THF, led to significant increases in reaction time and higher amounts of elimination byproduct **7**. In MeCN, the reaction temperature could be lowered to 0 °C without a significant decrease in reaction rate, and the **1a**/**7** ratio was further increased to 85:15 (Table 1, entry 13). Finally, by raising the molar equivalents of **4a** to 1.5 relative to propargyl acetate **5a**, the **1a**/**7** ratio was improved to >95:5, thus affording **1a** in 90% isolated yield (Table 1, entry 14). Alternatively, with the use of a stoichiometric amount of TMSOTf in MeCN at –40 °C (Table 1, entry 15), **1a** was formed in 84% yield.

Table 1. Catalyst screening and optimization of the reaction conditions.[a]



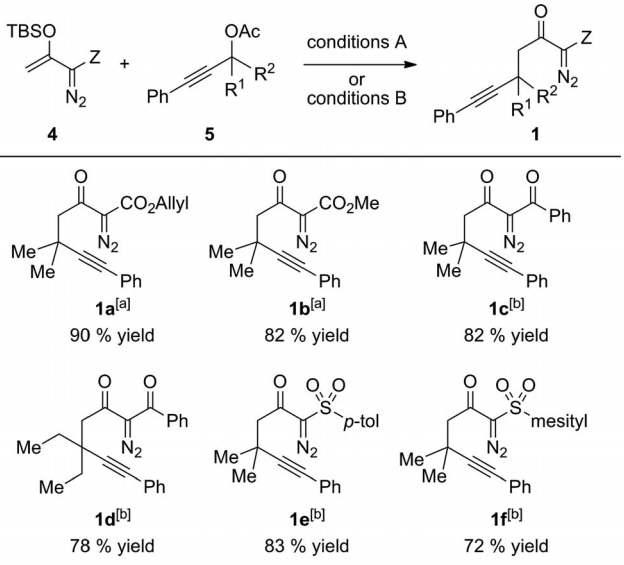
4a **1a** **7**

Entry	Lewis acid	Solvent	Time [h]	Conv. [%]	Ratio **1a**/**7**[b]
1	$Zn(OTf)_2$	CH_2Cl_2	12	85	53:47
2	$CuPF_6$	CH_2Cl_2	12	66	85:15
3	Cu(hfacac)$_2$	CH_2Cl_2	12	trace	–
4	$Sn(OTf)_2$	CH_2Cl_2	12	95	40:60
5	$Sc(OTf)_3$	CH_2Cl_2	12	>95	62:38
6	$In(OTf)_3$	CH_2Cl_2	12	>95	60:40
7	$AuCl_3$	CH_2Cl_2	12	30	95:5
8	$Sc(OTf)_3$	DCE	1	>95	71:29
9	$Sc(OTf)_3$	MeCN	1	>95	77:23
10	$Sc(OTf)_3$	PhMe	12	68	44:56
11	$Sc(OTf)_3$	$CHCl_3$	12	63	60:40
12	$Sc(OTf)_3$	THF	12	44	36:64
13[c]	$Sc(OTf)_3$	MeCN	1	>95	85:15
14[c,d]	$Sc(OTf)_3$	MeCN	1	>95 (90)[e]	>95:5
15[f]	TMSOTf	MeCN	1	>95 (84)[e]	90:10

[a] Reaction conditions: A mixture of enol-diazoacetate **4a** (1.2 equiv.), propargyl acetate **5a** (1.0 equiv.), and Sc(OTf)$_3$ (5 mol-%) in the specified solvent (0.5 M) was stirred at r.t. for the recorded time. [b] Determined by analysis of the reaction mixture by ^{1}H NMR spectroscopy. [c] Reaction was performed at 0 °C. [d] **4a** (1.5 equiv.). [e] Yield of the isolated product. [f] TMSOTf (1 equiv.) at –40 °C.

With this optimized reaction protocol, we strategically modified the substitution of enol-diazo compounds **4** and propargyl acetates **5** to accomplish our goal (cf. Scheme 1) to effect discrete changes in the outcome of the impending carbene metathesis cascade reactions. Thus, we expanded the scope of the coupling reaction to include a variety of enol-diazo compounds **4** bearing esters, ketones, and sulfones as Z substituents (Table 2). The synthesis of methyl diazoacetoacetate **1b** was also accomplished in 82% yield. Diazo ketone **1c**, however, was formed in only approximately 60% yield by using Sc(OTf)$_3$ as the catalyst, but the use of a stoichiometric amount of TMSOTf as the Lewis acid promoter gave an improved 82% yield of **1c**. The reaction of diethyl-substituted propargyl acetate **5** (R = Et) under stoichiometric TMSOTf conditions produced **1d** in a similar 78% yield. Finally, the synthesis of diazosulfones (Z = SO_2Ar) also occurred in higher yield by using TMSOTf-mediated conditions. In this way, diazosulfone **1e** bearing a *p*-tolylsulfonyl group as the Z substituent was produced in 83% yield, whereas the more sterically demanding mes-

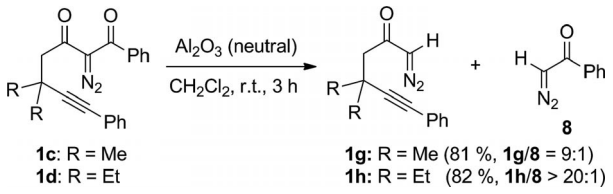
Table 2. Substrate scope of the coupling reaction.



[a] Conditions A: Enol-diazo **4** (1.5 equiv.), propargyl acetate **5** (1.0 equiv.), and Sc(OTf)$_3$ (5.0 mol-%) in MeCN (0.5 M) at r.t. [b] Conditions B: Enol-diazo **4** (1.5 equiv.), propargyl acetate **5** (1.0 equiv.), and TMSOTf (1.0 equiv.) in MeCN (0.5 M) at –40 °C.

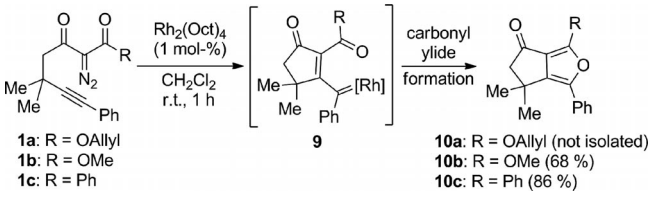
itylsulfonyl group as the Z substituent provided **1f** in a slightly diminished 72% yield.

To gain access to functionalized diazo ketones **1** in which Z = H (**1g**–**h**), benzoyl-substituted coupling products **1c** (Z = COPh; R^1, R^2 = Me) and **1d** (Z = COPh; R^1, R^2 = Et) were subjected to mild aluminum oxide diazo ketone cleavage conditions (Scheme 3).[9] Although the reaction of neutral alumina in CH_2Cl_2 with **1c** could have cleaved either the aryl or aliphatic ketone, reaction with **1c** favored addition to the carbonyl group of the aryl ketone with cleavage of the aryl ketone/diazo carbon bond to provide a mixture (9:1) of **1g**/**8**, which upon chromatographic purification provided **1g** in 81% yield. The same cleavage reaction with more sterically biased diazo ketone **1d** provided exclusively diazo ketone **1h** in 82% yield with no observable formation of **8**. More generally, this novel debenzoylation reaction could be paired with the myriad reactivity of enol-diazo nucleophiles **4** and electrophiles[7] to offer a unique and mild method to synthesize complex mono-diazo ketones that would be considerably more difficult to synthesize by traditional means.[10]



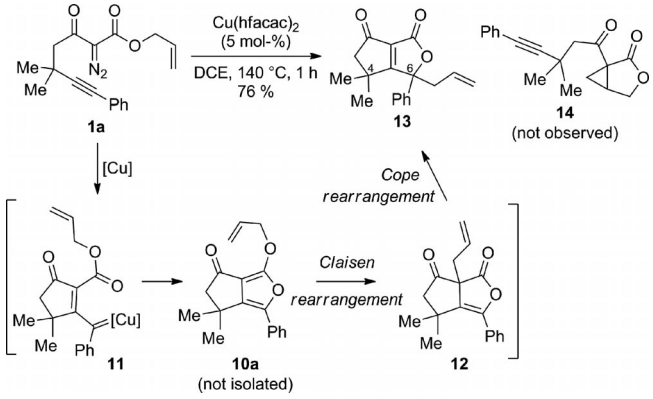
Scheme 3. Selective diazo ketone cleavage by debenzoylation.

The diversity of reactions of **1** that can be performed by using the carbene metathesis cascade is exemplified in five applications. With **1b** (Z = COOMe), reaction with a catalytic amount of $Rh_2(Oct)_4$ (1 mol-%, Oct = *n*-octanoate) initiated a cascade event that terminated in secondary carbene **9** forming a carbonyl ylide with the adjacent methyl ester (Scheme 4). This ylide spontaneously eliminated $Rh_2(Oct)_4$ to produce bicyclic furan **10b** in 68% yield. Alkoxyfurans such as this are known to be unstable; however, facile hydrolysis of these systems provides biologically important butenolides.[11] Moreover, 2-alkoxyfurans are reactive dienes in [4+2] cycloaddition reactions.[6a,12] If Z was a phenyl ketone (**1c**), the same cascade transformation occurred to provide diarylfuran **10c** in 86% yield.



Scheme 4. Carbene metathesis/carbonyl ylide formation reactions.

During the course of investigating the initial rhodium-catalyzed furan synthesis, we found that reactions of allyl ester substituted diazoacetoacetate **1a** (Z = COOAllyl) did not terminate at the alkoxyfuran as did the reactions of methyl ester analogue **1b** (cf. Scheme 4). In fact, the reaction provided mixtures of products that favored Claisen rearrangement product **12** (Scheme 5). However, Claisen product **12** was also found to undergo further rearrangement through a thermally induced Cope-type reaction to give butenolide **13**, the X-ray structure of which is shown in Figure 1. Upon optimization of this reaction (catalyst and conditions), we found that a catalytic amount of Cu(hfacac)$_2$ in superheated DCE provided fully rearranged butenolide product **13** in 76% yield.[13] As competitive intramolecular cyclopropanation to provide **14** was not observed in this reaction, carbene/alkyne metathesis occurs at a faster rate than cyclopropanation of diazoacetoacetate **1a**. This is especially striking considering that the alkyne was neopentyl, which makes metathesis more sterically demanding than the cyclopropanation pathway. This cascade process is synthetically notable in that highly substituted bicyclic butenolide **13** is formed in one step from readily available alkynyl diazoacetate **1a** bearing fully substituted centers at the remote C4 and C6 positions.



Scheme 5. Carbene metathesis/Claisen/Cope cascade reaction.

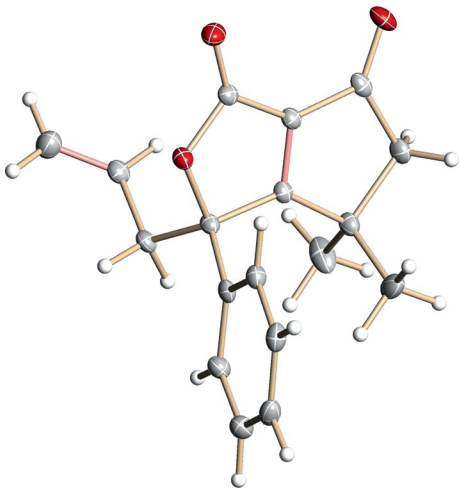
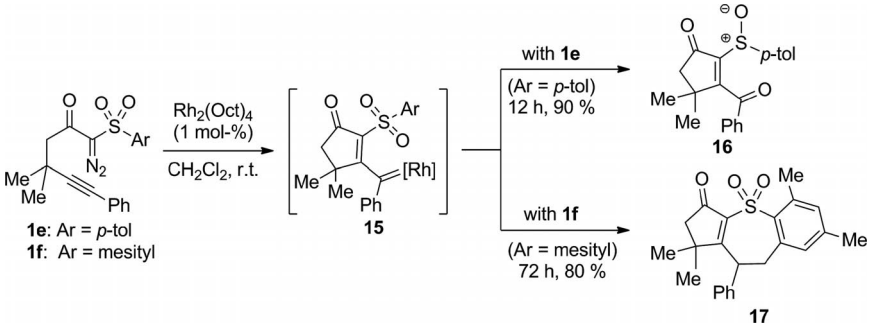


Figure 1. ORTEP view of **13**. Ellipsoids are shown at 30% probability.

The outcome of the cascade reaction with a sulfonyl Z substituent was remarkably different from that of the carb-

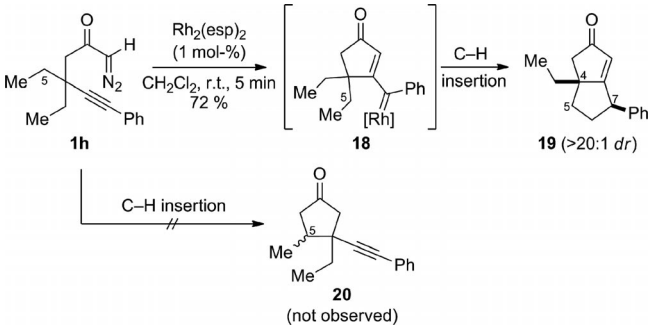


Scheme 6. Effect of aryl sulfone substitution cascade outcome.

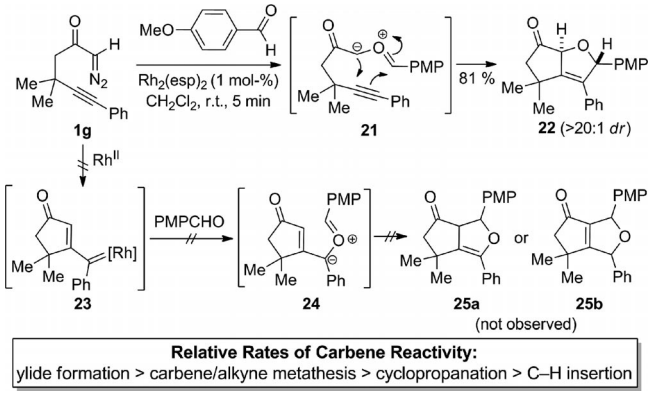
onyl series (Scheme 6). With substrate **1e** (Z = *p*-tolylsulfonyl), secondary carbene **15** reacted with the sulfone to provide an intermediate sulfoxonium ylide that underwent O-atom transfer to deliver racemic sulfoxide **16** in 90% yield. Surprisingly, if the arylsulfone was changed to mesityl-substituted system **1f**, the O-atom transfer process no longer occurred; instead, secondary carbene **15** underwent benzylic 1,7-C–H insertion to provide benzothiepine ring system **17** in 80% yield. Benzothiepine compounds have been shown to demonstrate a range of biologically activity,[14] and this approach represents a unique and potentially versatile way to access polyfunctionalized benzothiepines. Although ylide formation is believed to be kinetically favored over other carbene reactions (especially to form five-membered ylides), the preference for the cascade reaction of **1f** to selectively target the benzylic C–H bond is surprising and seems to indicate a conformational bias in the transition state brought about by the sterically encumbered mesityl group.

In the absence of a reactive functional group at the Z position, *gem*-diethyl diazo ketone **1h** provided a unique opportunity to direct the cascade reaction by terminating the cascade through intramolecular C–H insertion (Scheme 7). In this case, the reaction of **1h** with a catalytic amount of $Rh_2(esp)_2$ (esp = α,α,α′,α′-tetramethyl-1,3-benzenedipropionate) provided cyclopentenone product **19** in 72% yield as a single diastereomer. Interestingly, the reaction of the primary carbene of **1h** was selective toward carbene/alkyne metathesis to form secondary phenylvinyl carbene **18** in preference to intramolecular C–H insertion that would form **20**, which was not observed. Recently, May reported a similar catalyst-induced cascade of propargyl diazoacetates to provide bridged bicyclic butenolide products;[15] however, that approach does not provide access to the considerably more challenging all-carbon systems.

Having successfully demonstrated that the outcomes of various carbene/alkyne metathesis reactions can be directly engineered by changes in the pivotal Z group and having developed a clearer picture of the rate of carbene/alkyne metathesis relative to other competitive carbene transformations, we queried whether the primary carbene (cf. **3**) could be trapped prior to the alkyne metathesis event. For this experiment, we treated protio-substituted diazo ketone **1g** with *p*-methoxybenzaldehyde (PMPCHO) in the presence of a catalytic amount of $Rh_2(esp)_2$ in an attempt to generate carbonyl ylide **21** (Scheme 8). Under these conditions, the reaction of **1g** with PMPCHO afforded dihydrofuran **22** in 81% yield as a single diastereomer, presumably through intramolecular 1,3-dipolar cycloaddition of ylide **21**. This result demonstrates that intermolecular carbonyl ylide formation proceeds at a faster rate than carbene/alkyne metathesis, as competing cycloaddition product **25** was not observed. This result also exemplifies that ylide formation/dipolar cycloaddition can be used as a method to utilize alkynyl-tethered diazo ketones **1** independent of the carbene/alkyne metathesis reaction, thus enhancing the value of the incipient enol-diazo coupling methodology.



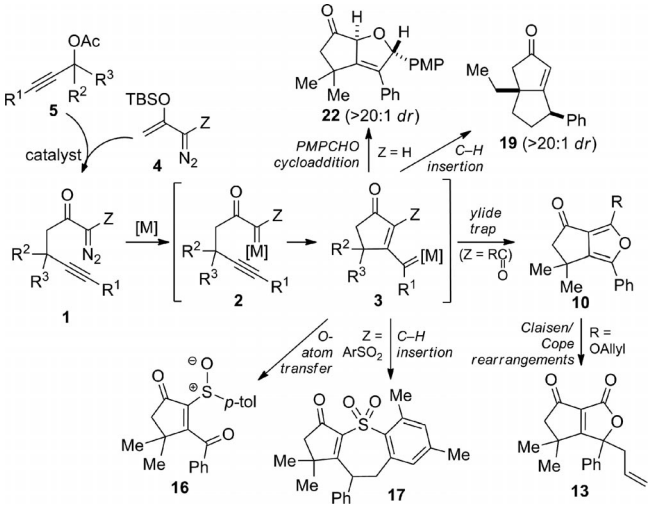
Scheme 7. Carbene metathesis/C–H insertion cascade reaction.



Scheme 8. Intramolecular ylide formation/dipolar cycloaddition.

Conclusions

In summary, we have developed an efficient protocol for the coupling of enol-diazo compounds **4** and propargyl acetates **5** to provide a diverse series of alkynyl-tethered diazo ketones **1** that undergo facile cascade transformations, the outcomes of which are controlled by the substituents of **1**. We have shown that the nucleophilic behavior of enol-diazo compounds **4** is not limited only to systems derived from acetoacetates (i.e., Z = ester) and that by varying the α′-substitution of these building blocks the outcome of carbene metathesis cascade reactions can be templated. In this way, the choice of enol-diazo nucleophile provides the embedded information required to direct the outcome of the carbene cascade to a number of diverse and discrete outcomes (exemplified, but not limited to, those in Scheme 9). As a result of these studies, the rate of carbene/alkyne metathesis relative to that of competitive processes (i.e., cyclopropanation, ylide formation, and C–H insertion) in complex environments has been clearly elucidated.[16] Furthermore, a number of novel processes have been made possible by the enol-diazo coupling that were previously unknown, namely, the benzylic C–H insertion of *o*,*o*-disubstituted arylsulfonyl systems and the tandem carbene cascade/Claisen/Cope rearrangements of allyl ester substituted systems. We are currently investigating additional applications and asymmetric variations of these cascade processes.



Scheme 9. Modular assembly of enol-diazo compounds and propargyl acetates for templated carbene metathesis reactions.

Supporting Information (see footnote on the first page of this article): Experimental procedures, characterization data, and ^{1}H NMR and ^{13}C NMR spectra for all new compounds.

Acknowledgments

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