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Transition Metal-Free Decarboxylative Propargylic Substitution/ Cascade Cyclization with Azolium Enolates or Acyl Anions

Shenci Lu[+], Jun-Yang Ong[+], Si Bei Poh, Terence Tsang, and Yu Zhao*

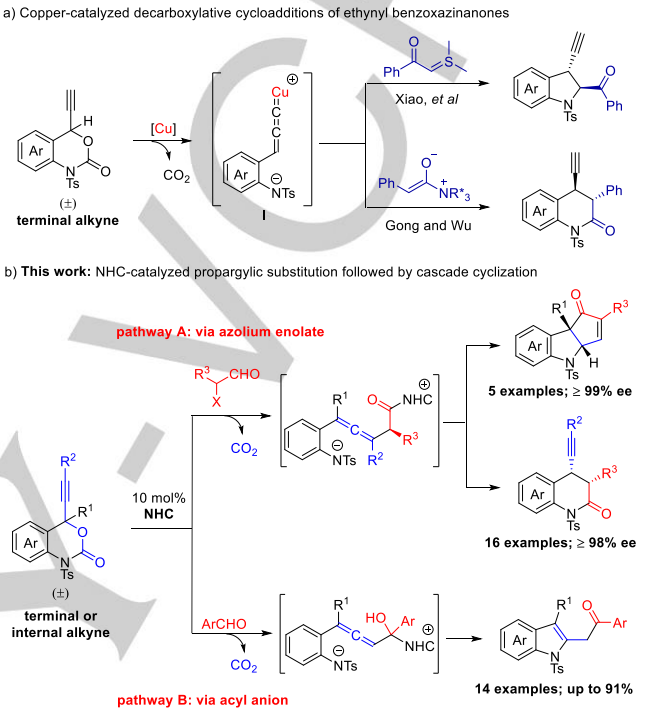
Abstract: We present herein unprecedented transition metal-free propargylic substitution reactions with azolium enolates or acyl anions that are generated from aldehydes under NHC catalysis. This new catalytic activation operates on readily available cyclic propargylic carbamates with decarboxylation, and generates reactive allene intermediates that can undergo divergent cyclization pathways to deliver skeletally diverse polycyclic compounds with high level of efficiency and excellent enantioselectivity.

Propargylic substitution represents an important and versatile carbon-carbon bond forming reaction in organic synthesis.[1] Notably, all the known catalytic stereoselective variants of this process rely exclusively on transition metal activation of the propargylic electrophile to deliver allene[2] or alkyne products.[3] An intriguing strategy involves the conversion of terminal alkynes to an allenylidene intermediate (such as **I**, Scheme 1a) that undergoes subsequent reaction. In particular, by the use of cyclic propargylic carbamate as the substrate, highly enantioselective Cu-catalyzed formal [4 + 1] and [4 + 2] cycloadditions have been achieved by the Xiao group, the Gong group and the Wu group.[4] The introduction of orthogonal catalytic activation modes to propargylic substitution will surely open up new opportunities in stereoselective synthesis.

N-heterocyclic carbene (NHC) catalysis has emerged as a powerful tool in stereoselective synthesis.[5] The generation of acyl anion intermediate has enabled the classical Benzoin/ Stetter reactions[6] as well as coupling with different alkyl/aryl electrophiles[7] and hydroacylation of alkenes/alkynes.[8] In contrast, the *in situ* access to azolium enolate intermediate from functionalized aldehydes has allowed the development of stereoselective annulation,[9] protonation,[10] aldol,[11] Mannich[12] as well as α-halogenation reactions.[13] However, the utilization of either acyl anion or azolium enolate for propargylic substitution, to the best of our knowledge, remains elusive in the literature.

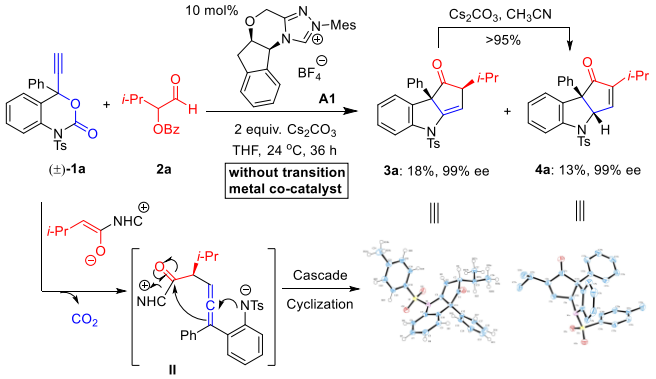
We report herein our discovery and development of highly enantioselective transition metal-free formal decarboxylative cycloaddition[14] of cyclic propargylic carbamates with aldehydes under NHC catalysis to deliver a few families of valuable heterocycles (Scheme 1b). By the use of α-functionalized aldehydes (Pathway A), the reaction proceeds through an unprecedented propargylic substitution of azolium enolates followed by cascade cyclization of the allene intermediate, and delivers 4-alkynyl dihydroquinolinones with high efficiency and uniformly excellent enantioselectivity. In contrast, the use of aromatic aldehydes under NHC catalysis resulted in the preparation of 2,3-difunctionalized indoles (Pathway B), in which an intermolecular propargylic substitution with the acyl anion intermediate takes place followed by cyclization.

Our group has been exploring stereoselective heterocycle synthesis through an intermolecular cycloaddition approach, with a particular interest in medium-sized (7-10 membered) heterocycles.[15] With lessons learnt from these studies and inspired by the reports shown in Scheme 1a,[4] we proposed that



Scheme 1. Approaches of Propargylic Substitution

effective cycloaddition between **1a** and functionalized aldehydes such as **2a** could be realized under cooperative catalysis with NHC and transition metal (Scheme 2).[16] The use of tertiary propargyl carbamate as in **1a**, in particular, was hypothesized to favor reaction at the alkyne terminal position to induce medium sized-ring formation.



Scheme 2. Discovery of Transition Metal-free Fused Indoline Synthesis

After much efforts along the proposed idea, however, no formation of the desired product could be detected at all. Instead, we made a highly intriguing discovery: *under transition metal-free conditions*, the reaction of **1a** and **2a** in the presence of NHC catalyst **A1** produced two unexpected fused indolines

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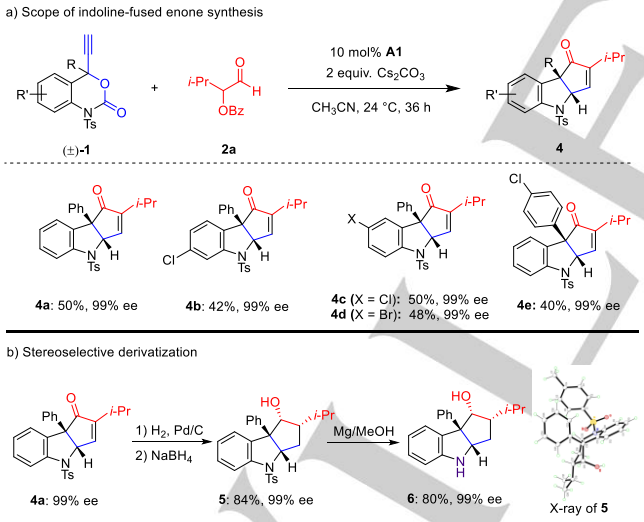
3a and **4a** as a single diastereomer with superb enantiopurity (99% ee), albeit in low yield. The structures of both compounds were unambiguously assigned by single crystal X-ray analysis, and conjugate enone **4a** was determined to be an isomerization product of **3a** under the catalytic conditions or simply under basic conditions (>95% conv. using Cs_2CO_3 in CH_3CN). These products are synthetically valuable fused indolines that are key structural units in bioactive entities.[17] In addition, this transformation represents an unprecedented reactivity for NHC catalysis: the azolium enolate generated *in situ* from **2a** is believed to attack **1a** in a decarboxylative propargylic substitution fashion to generate the allene intermediate **II** without the need for transition metal activation. Instead of yielding the originally hypothesized eight-membered allene-containing lactam that is likely highly strained, an alternative cascade cyclization of **II** proceeds to yield fused indoline **3a**.

With this attractive lead in hand, efforts were then focused on the optimization of the efficiency of this transformation (see Table S1 in SI for details). Under optimal conditions, the scope of this transformation was examined (Scheme 3a). Different halogen substituents on the backbone of **1** could be well-tolerated to produce **4a-4d** in moderate yield with uniformly 99% ee. Substrate bearing a substituted aryl ring at the propargylic position also participated the reaction smoothly to produce **4e** in 99% ee. All these compounds could be further derivatized through cross coupling at the halogen site.

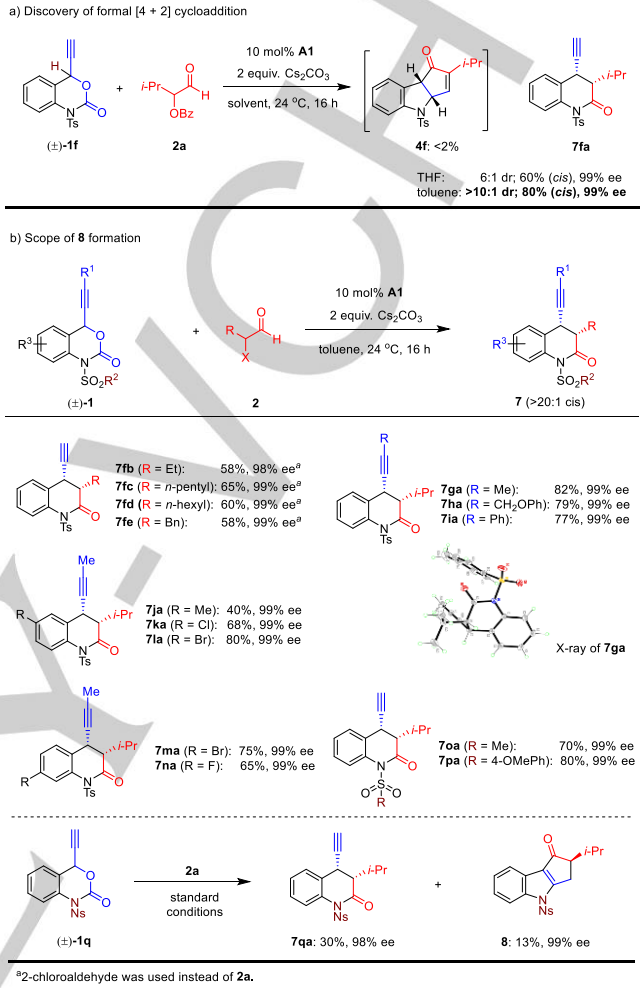
This class of indoline-fused cyclopentenones could serve as valuable building blocks in stereoselective synthesis. As shown in Scheme 3b, hydrogenation of **4a** under standard Pd/C conditions followed by $NaBH_4$ reduction of the ketone proceeded smoothly without optimization to yield the indoline fused-cyclopentanol **5** as a single stereoisomer in 84% yield. Both reductions took place exclusively from the convex face of enone **4a**. The tosyl protective group could be easily removed using Mg and MeOH, leading to the formation of free indoline fused-cyclopentanol **6** in an enantiomerically pure form.



Scheme 3. Indoline-fused Cyclopentenone Synthesis and Derivatization

In an effort to further expand the scope of indoline synthesis, we examined substrate **1f** bearing a secondary propargylic carbamate functionality (Scheme 4a). To our surprise, no formation of the expected indoline **4f** (or alternative isomerization product) was observed under the standard conditions at all. Instead, a skeletally different six-membered lactam **7fa** was formed with good diastereoselectivity (6:1 *cis*:*trans*) and excellent enantioselectivity of 99%. The major isomer was isolated in 60% yield. As such compounds also represent novel, potentially valuable targets,[18] we proceeded to optimize this formal [4 + 2] cycloaddition.

After much optimization, the pure *cis*-isomer **7fa** could be obtained in a high yield of 80% with 99% ee in toluene. It is noteworthy that a stereo-convergent process is operative to convert racemic **1f** to the diastereo- and enantioenriched product. At low conversion, however, low level of kinetic resolution of **1f** was observed (see SI for details).



[a]2-chloroaldehyde was used instead of **2a**.

Scheme 4. Scope of [4+2] Cycloadditions

With the optimal conditions in hand, we moved on to examine the scope of this NHC-catalyzed formal [4+2] cycloaddition. As shown in Scheme 4b, a wide range of α-functionalized aldehydes could be converted to **7fb-7fe** in uniformly high efficiency and selectivity. Substrates **1** bearing internal alkynes could also produce the desired products (**7ga-7ia**) with high yield and excellent ee. The absolute configuration of **7ga** was unambiguously assigned by single crystal X-ray diffraction analysis. Substituents on the aryl ring in **1** as well as different sulfonyl groups were well-tolerated to yield **7ja-7na** and **7oa-7pa** with high yield and excellent ee. When substrate bearing an electron-deficient Ns (4-nitrophenyl sulfonyl) group (**1q**) was examined, interestingly, a mixture of products **7qa** and indole-fused cyclopentanone **8** were obtained, which corresponded to the two reaction pathways shown in Schemes 3 and 4.

The formation of **7** from **1** seemed to differ from the previous formation of **4** as the alkyne moiety remained in the product structure. Instead of initiation at the alkyne terminal, the attack of the azolium enolate to the internal propargylic position could directly lead to the formation of **7**. To differentiate these two reaction pathways, various control reactions were carried out (Scheme 5). Firstly, allylic carbamate (**9**) or simple carbamate (**10**) failed to engage in the related substitution reactions

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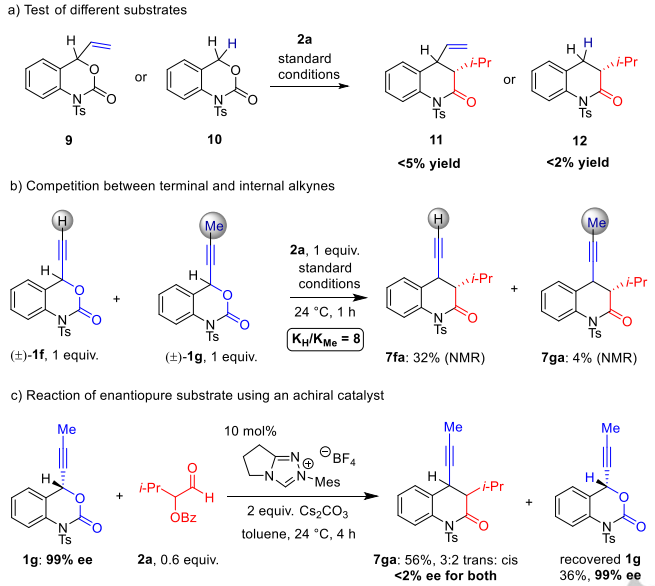
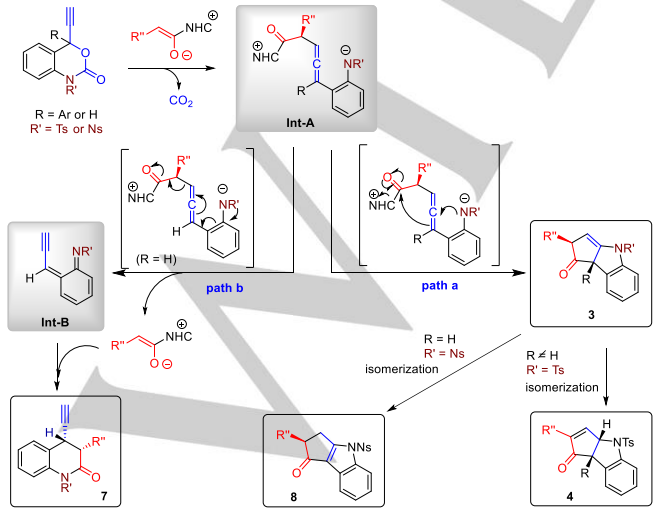
efficiently, underlying the importance of propargylic unit for this reaction (Scheme 5a). Secondly, competition experiment between a terminal alkyne substrate **1f** and an internal alkyne **1g** was carried out. When the reaction was stopped in one hour, the corresponding products **7fa** and **7ga** were obtained in a ratio of 8:1 as determined by ^{1}H NMR (Scheme 5b). The significant rate difference here suggested that the reaction likely initiates at the terminal position of the alkyne so that the steric difference between the substrates resulted in the different reaction rate.



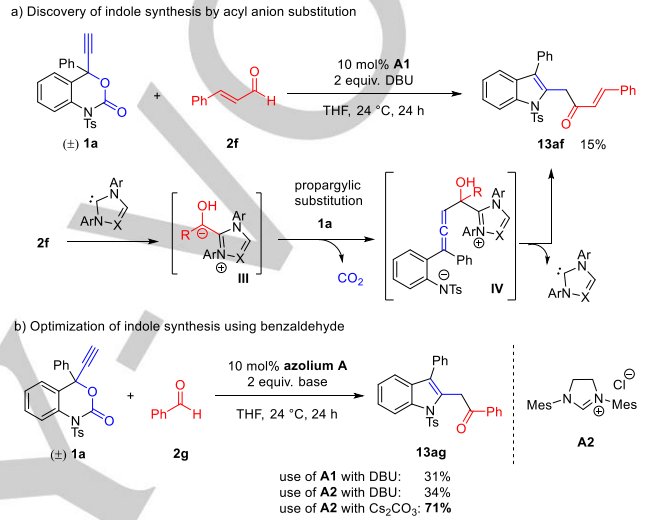
Scheme 5. Mechanism study.

As our reaction represents a stereoconvergent transformation, we were curious whether the substrate underwent racemization *in situ* or the reaction proceeded in a stereoablative fashion.[19] To probe this, we subjected enantiopure **1g** (from chiral HPLC) to the reaction catalyzed by an achiral NHC precursor (Scheme 5c). When the reaction was stopped at partial conversion, the product **7ga** was obtained as a mixture of *cis* and *trans*-isomers with both in a racemic form. In contrast, the recovered starting material **1g** remained enantiopure (99% ee). Clearly, no racemization of the racemic substrate took place under the NHC-catalyzed conditions, and the reaction likely proceeded through the formation of an achiral intermediate.



Scheme 6. Proposed mechanism.

On the basis of the above experimental and mechanistic studies, we propose the reaction pathways for the collective synthesis of 2,3-fused indolines **3/4/8** and 3,4-disubstituted dihydroquinolinones **7** (Scheme 6). We believe that all these reactions proceed through a common intermediate **Int-A** formed by decarboxylative propargylic substitution of substrates **1** with the azolium enolate. Depending on the substituent, **Int-A** can undergo different pathways leading to scaffold diversity. For substrates bearing an aryl substituent, attack of the amide to allene followed by C-acylation produces **3**, which undergoes isomerization to yield **4** or **8** (**path a**). For substrates bearing no substituent (R = H), we hypothesize that an achiral *aza-ortho*-quinone methide **Int-B**[20] may be formed via elimination of the azolium enolate, which then attacks back in a formal [4+2] cycloaddition fashion to yield the dihydroquinolinones **7** (**path b**).



Scheme 7. Discovery of Indole Synthesis.

Instead of the use of aldehydes bearing a α-leaving group, the reaction of enals such as **2f** under NHC catalysis may generate azolium enolate or homoenolate intermediates leading to further product diversity. To probe such possibilities, we examined the reaction of **1a** with **2f** under similar conditions as shown in Scheme 7a. Again, an unexpected 2,3-disubstituted indole **13af** was produced, albeit in low yield. This transformation is believed to proceed through decarboxylative propargylic substitution of **1a** with the acyl anion intermediate **III** to produce substituted allene **IV**, cyclization of which then generates the valuable ketone-containing indole product.

The reaction with cinnamaldehyde **2f** turned out to be difficult to optimize. We then turned our attention to the use of simple benzaldehyde **2g** as a more common acyl anion precursor (Scheme 7b). The related indole **13ag** could be obtained in 31% yield by the use of **A1**. As this transformation yields an achiral product, efforts were then directed to the use of commercial achiral NHC precursors to catalyze this reaction. From these studies, imidazolinium **A2** with Cs_2CO_3 was identified to be the optimal choice, which led to the formation of **13ag** in a good 71% isolated yield (see Table S3 in SI for details).

The scope of this catalytic system turned out to be broad (Scheme 8a). Various aromatic aldehydes bearing electron-withdrawing or electron-donating substituents underwent reaction with **1a** to yield **13ag-13ao** in high yield. Various tertiary propargyl carbamates bearing substituents on either aryl ring (**1b-1e**) also participated in the indole synthesis smoothly (**13bh-13eh**). In addition, secondary propargyl carbamate (**1f**) could also be converted to 2-substituted indole **13fh** in moderate yield.

As further demonstration of the utility of this method, the indole products bearing a 2-acylmethyl-3-aryl substituents could be converted to valuable benzo[*c*]carbazoles[21] such as **14** upon

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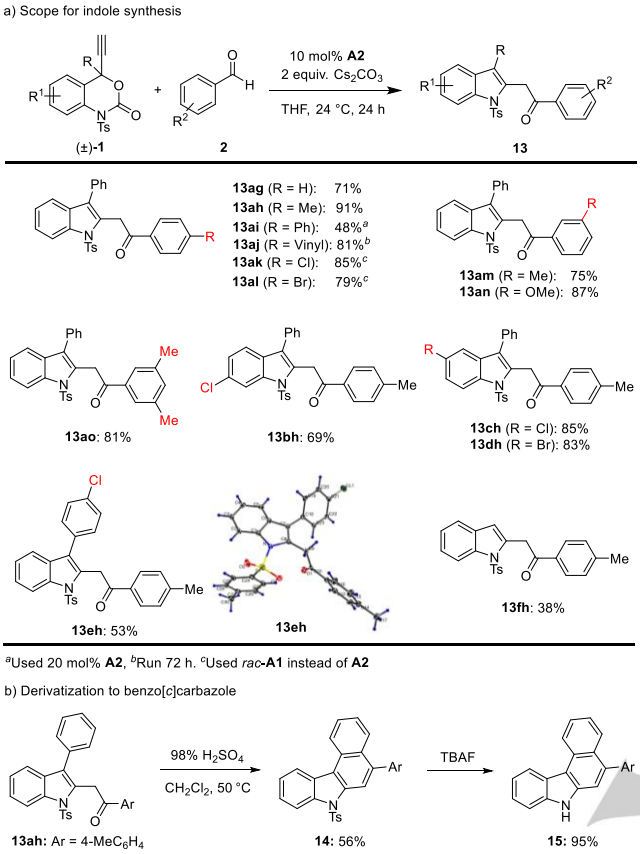
treatment of **13ah** with H_2SO_4 (Scheme 8b). The tosyl protecting group could be easily removed in the presence of TBAF, leading to the formation of free benzo[*c*]carbazole **15** in 95% yield.



Scheme 8. Scope of Substituted Indole Synthesis and Derivatization.

In conclusion, we have developed highly efficient and enantioselective propargylic substitution of azolium enolates and acyl anions that are generated from aldehydes under NHC catalysis without the need for transition metal activation. This new catalytic activation triggers novel cascade cyclizations to deliver skeletally diverse polycyclic compounds with good to high efficiency and uniformly excellent enantioselectivity. Current efforts in our laboratories are focused on the application of this new catalytic activation to the preparation of other important compounds in a stereoselective fashion.

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Keywords: decarboxylation • cycloaddition • propargylic substitution • heterocycle • enantioselectivity

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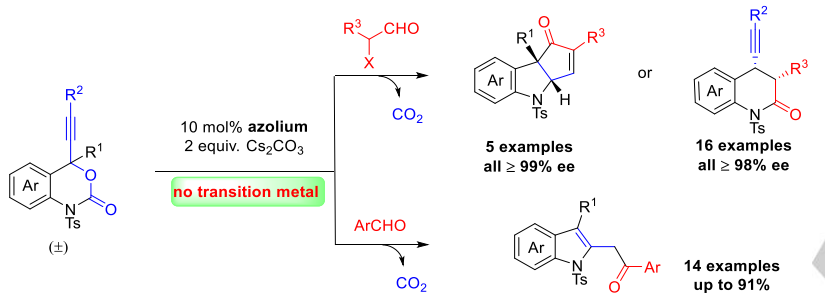

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Transition Metal-Free Decarboxylative Propargylic Substitution/ Cascade Cyclization with Azolium Enolates or Acyl Anions

We present herein unprecedented transition metal-free propargylic substitution reactions with azolium enolates or acyl anions that are generated from aldehydes under NHC catalysis. This new catalytic activation operates on readily available cyclic propargylic carbamates with decarboxylation, and generates reactive allene intermediates that can undergo divergent cyclization pathways to deliver skeletally diverse polycyclic compounds with high level of efficiency and excellent enantioselectivity.