Cyclization Reactions

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Divergent C–H Insertion–Cyclization Cascades of *N*-Allyl Ynamides

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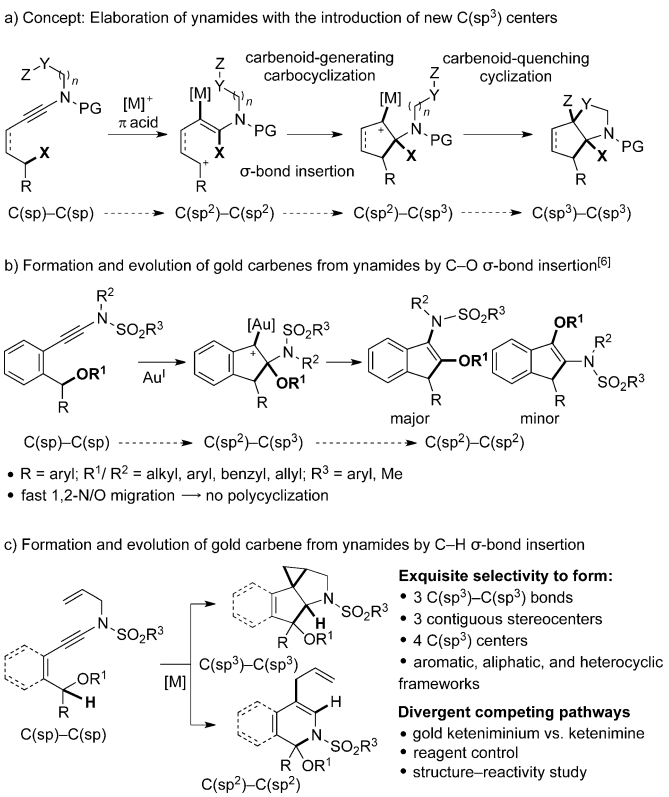
Abstract: *Gold carbene reactivity patterns were accessed by ynamide insertion into a C(sp^3)–H bond. A substantial increase in molecular complexity occurred through the cascade polycyclization of N-allyl ynamides to form fused nitrogen-heterocycle scaffolds. Exquisite selectivity was observed despite several competing pathways in an efficient gold-catalyzed synthesis of densely functionalized C(sp^3)-rich polycycles and a copper-catalyzed synthesis of fused pyridine derivatives. The respective gold–keteniminium and ketenimine activation pathways have been explored through a structure–reactivity study, and isotopic labeling identified turnover-limiting C–H bond-cleavage in both processes.*

Access to molecules with stereogenic centers and a higher fraction of C(sp^3) is increasingly desirable in pharmaceutical fragment design and lead discovery, as it is associated with improving chances of clinical success.[1] The use of π-acid catalysis to generate metal–carbene character directly from triple bonds offers a rapid route to molecular complexity.[2] Ynamides are attracting increasing attention in this regard, as the polarized π-system allows for regioselective carbenoid formation in the presence of other π-systems, oxidants, or nitrenoids.[3–5] Potent transformations based on this approach enable the elaboration of a C(sp)–C(sp) unit into C(sp^2)–C(sp^2) or C(sp^3)–C(sp^2) units. We envisioned that the challenging C(sp^3)–C(sp^3) system might be directly accessed from ynamides if a carbenoid could be generated by σ-bond insertion and then quenched by cyclization onto the nitrogen substituent (Scheme 1a).

With reference to this strategy, a gold carbene was formed previously by the formal insertion of an ynamide into a C–O σ-bond (Scheme 1b).[6,7] However, further cyclization was not observed. Instead, 1,2-migration dominated to give indenyl amides, regardless of the substituents present. Herein we show that carbenoid-based polycyclization can be induced by the C(sp^3)–H insertion of ynamides (Scheme 1c).[8–10] Notably, exquisite selectivity was established over several divergent pathways in the preparation of heteroaromatic compounds or N-heterocycles with three new C(sp^3)–C(sp^3) bonds, three new fused rings, and up to four contiguous stereocenters.



Scheme 1. Generation of gold carbenes from ynamides by carbocyclization. PG = protecting group.

An ynamide polycyclization cascade was pursued by the use of an *N*-allyl substituent as a viable carbenoid-quenching unit.[5h,i,n,11] Although several Au^I species/solvent combinations afforded only indenyl amides **2a/b** at room temperature, a breakthrough occurred when **1a** was heated with [Au(picolinate)Cl_2][12] in toluene (Table 1, entries 1 and 2; see also the Supporting Information). New diastereomeric products **3a** arose from insertion into the benzylic C–H σ-bond rather than the C–O σ-bond. The relative configuration across the fused ring junction is fixed. The methoxy group in **3a** is *anti* to the cyclopropyl methylene unit in the major diastereomer (see the Supporting Information).[13] The product distribution depended on the temperature, solvent, and catalyst.[14] Indenes **2a/b** were favored at lower temperatures and in more polar solvents (Table 1, entries 3–6; see also the Supporting Information). At higher temperatures, the use of $AuCl_3$ or $AuBr_3$ gave **3a** in lower yield and a 1,4-disubstituted isoquinoline **4** (Table 1, entries 7–10; see also the Supporting Information), which was also the main product with Au^I species. Degradation of **1a** was seen with $BF_3{\cdot}OEt_2$, whereas

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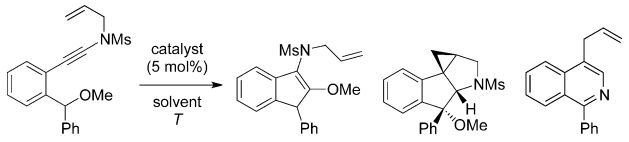
Table 1: Effect of reaction conditions on product distribution.[a]



1a **2a/b** (regioisomers) **3a** (X-ray) **4**

Entry	Catalyst	Solvent	*T* [°C]	Yield [%][b] **1a**/**2a**/**2b**/**3a**(d.r.)/**4**
1[6]	[(*p*-$CF_3C_6H_4$)$_3$PAuCl]/$AgNTf_2$	CH_2Cl_2	RT	–:74:9:–:–
2	[Au(picolinate)Cl_2]	toluene	80	–:21:7:61(3.4:1):–
3	[Au(picolinate)Cl_2]	toluene	RT	–:54:32:9:–
4	[Au(picolinate)Cl_2]	$MeNO_2$	80	–:45:19:9:–
5	[Au(picolinate)Cl_2]	toluene	100	–:11:6:66(2.9:1):–
6	[Au(picolinate)Cl_2]	*p*-xylene	120	–:7:5:75(2.3:1)[c]:–
7	$AuBr_3$	*p*-xylene	120	–:8:4:48(2.4:1):<5
8	$AuCl_3$	*p*-xylene	120	–:7:3:32(1.7:1):22
9	[Ph_3PAuCl]/$AgNTf_2$	*p*-xylene	120[d]	–:–:–:–:41
10	[(JohnPhos)Au(NCMe)]·SbF_6	*p*-xylene	120[d]	–:–:–:<5:27
11	BF_3·OEt_2	toluene	80	–:–:–:–:–
12	none	*p*-xylene	120[e]	23:–:–:–:16
13	CuI	toluene	100[f]	–:–:–:–:68[g]

[a] General reaction conditions: **1a** (0.1 mmol, 1.0 equiv), catalyst (5 mol%), solvent (0.1 M); the reaction mixture was stirred for 6 h unless otherwise stated. [b] Yields were determined by ^{1}H NMR spectroscopy. The diastereomeric ratio of **3a** is given in parenthesis. [c] The major diastereomer is shown (isolated in 49% yield). [d] Reaction time: 3 h. [e] Reaction time: 24 h. [f] Reaction time: 8 h. [g] Product **4** was isolated in 65% yield. Ms = methanesulfonyl, JohnPhos = 2-(di-*tert*-butylphosphanyl)biphenyl, Tf = trifluoromethanesulfonyl.

Electron-donating and electron-withdrawing groups were well tolerated (products **3k** and **3m–o**), and a larger-scale reaction of **1o** proceeded smoothly with a reduced catalyst loading. In contrast, substrates **1l**,**p** with large groups flanking the ynamide did not undergo the desired transformation. The less rigid dihydronaphthalene-substituted ynamide **1q** reacted only slowly with the Au^{III} catalyst to give **3q**, which was obtained in substantially improved yield with a linear $Au^{I}Cl$ equivalent. This result is consistent with gold atom needing to be in plane with the hydrocarbon skeleton linking to the hydride-donor site.

The non-aromatic C(sp^3)-rich polycycles **3r–x** incorporating cycloalkyl, piperidine, and pyran motifs were assembled readily. The gold-catalyzed reactions proceeded smoothly, though products **3s–u** from benzylic ethers required careful handling and purification on deactivated silica. As illustrated with **3t**, although the catalysis is sufficiently mild to afford the product in high yield after 20 min at 55 °C, the polycyclization product undergoes elimination (to diene **5** in the case of **3t**) on further heating or on exposure to silica (yields and diastereomeric ratios determined by NMR spectroscopy and after purification by column chromatography on silica gel are shown in Scheme 2 for two different reaction temperatures.

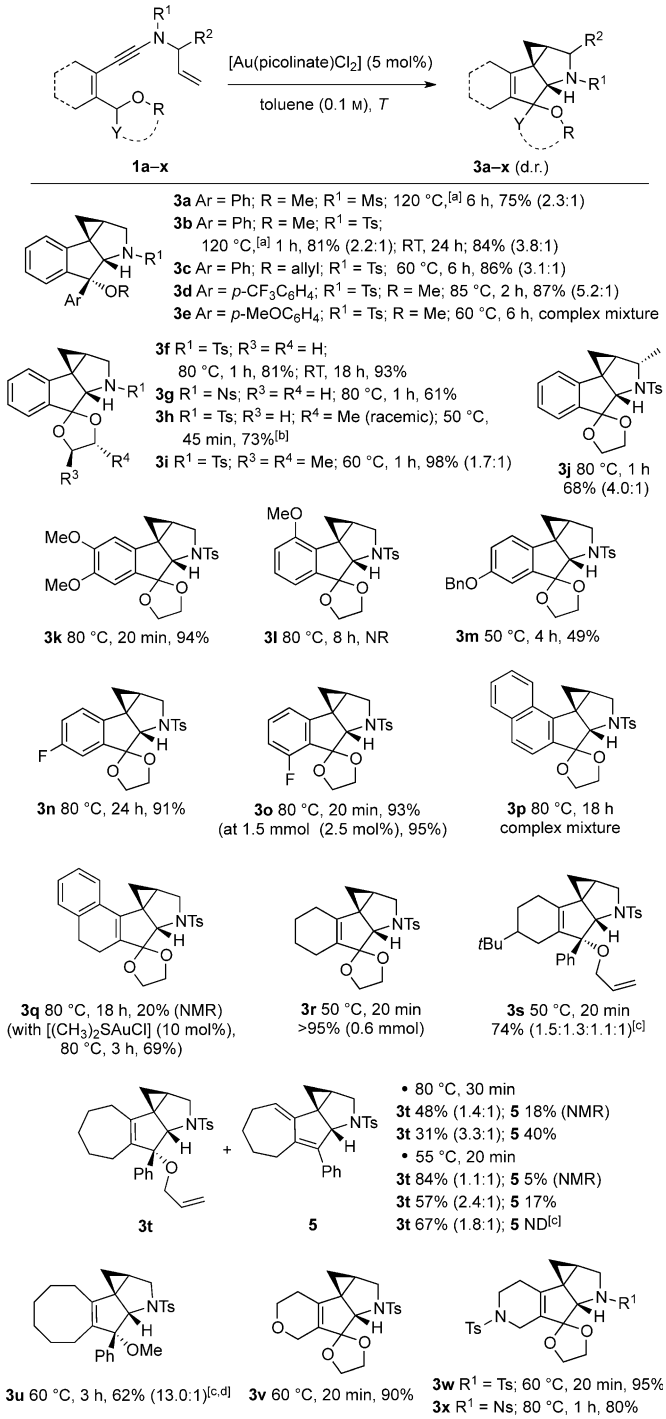
4 was formed in low yield on heating without an added catalyst (Table 1, entries 11 and 12). The use of CuI in toluene at 100 °C provided an effective balance between conversion into **4** and degradation (Table 1, entry 13; see also the Supporting Information).

Having established reagent control of the competing pathways for the cyclization of **1a**, we undertook a structure–reactivity investigation. Intriguingly, the *N*-*p*-toluenesulfonyl ynamide **1b** underwent faster and cleaner polycyclization to give **3b** in excellent yield with no carboalkoxylation, even at room temperature (Scheme 2). Preorganization of the substituents may prevent adoption of the reactive geometry for carboalkoxylation.[6] Further studies with *N*-Ts ynamides showed that the C–H donor site could incorporate an allyloxy group (product **3c**) and an electron-deficient aryl substituent (product **3d**). The electron-rich aryl substituent in **1e** was not tolerated.[15]

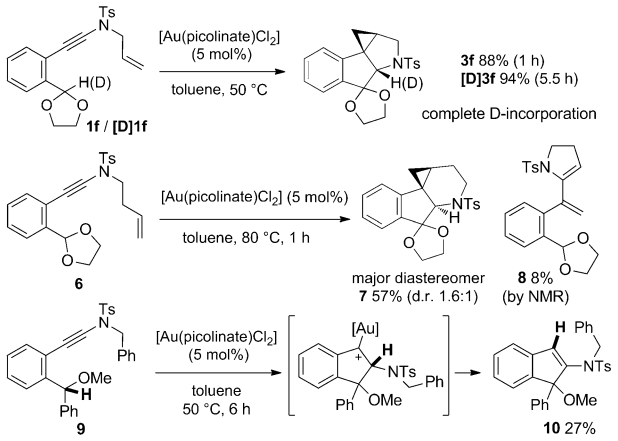
Polycycles bearing a protected ketone could be accessed as single diastereomers by incorporating a dioxolane unit in the alkyne starting material instead of the benzhydric moiety. Dimethylacetal and dioxane groups degraded under the reaction conditions; however, both **1f** and its *N*-nosylated analogue **1g** reacted smoothly, although **1g** required heating. Substituted dioxolanes were also reactive (products **3h**,**i**). The formation of **3i** as an unequal mixture of diastereomers from chiral-diol-derived **1i** provides promise for a future asymmetric synthesis of these complex N-heterocycles by a traceless-auxiliary approach. Interestingly, diastereoselectivity was also observed with an α-methyl-*N*-allyl group; thus, product **3j** was obtained with d.r. 4.0:1.

Further mechanistic insight into the polycyclization was then sought. Complete deuterium transfer from the benzylic site to the bridgehead position adjacent to the nitrogen atom was observed with [D]**1f** (Scheme 3). The quantitative analysis of initial reaction rates was hampered by an induction period (see the Supporting Information for an NMR study);[12] however, an approximately fivefold increase in reaction time was required over that for **1f**.[16,17] *N*-Homoallyl ynamide **6** was converted into the piperidine-fused polycycle **7** as the major product. Only a small amount of amidodiene **8** from ene–ynamide cycloisomerization was observed, thus showing C–H insertion to be kinetically more productive than the attack of an alkene.[5a,b] *N*-Benzyl ynamide **9** did not undergo polycyclization, but instead C–H insertion occurred to afford indenyl amide **10**.[18] Although further investigation is needed to explore the full scope of the polycyclization, the successful reaction with the more rotationally labile homoallyl group is promising.

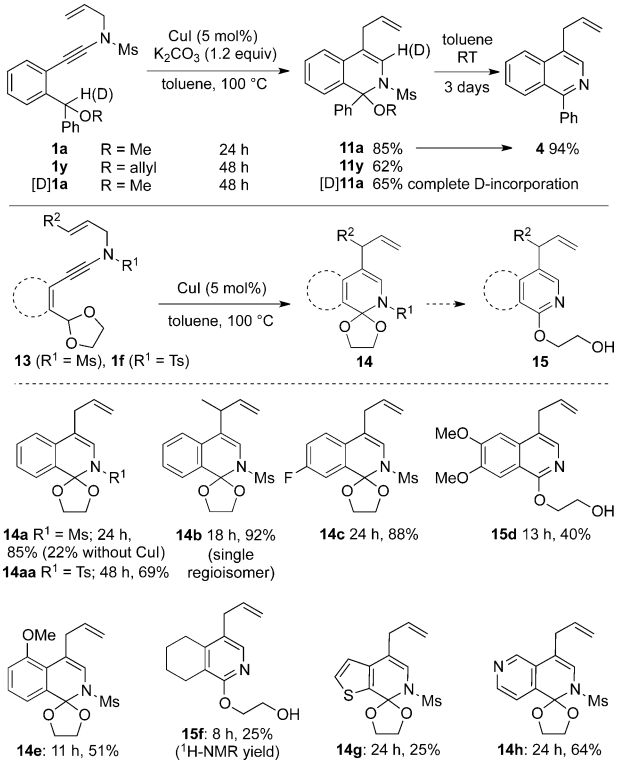
Isoquinoline formation from *N*-methanesulfonyl ynamides **1a**/**y** could be interrupted by adding a base to afford alkoxy 1,2-dihydroisoquinolines **11a**,**y**, which were readily converted into **4** (Scheme 4). The conversion of [D]**1a** took approximately twice as long as that of **1a** and led to full



Scheme 2. Structural effects on the ynamide C–H insertion–cyclopropanation cascade. Yields are for the isolated product after flash column chromatography. In each case, the major diastereomer is shown. [a] *o*-Xylene (0.1 M) was used as the solvent. [b] Product **3h** was isolated as a complex mixture of four diastereomers. [c] The product was purified on NEt_3-deactivated silica. [d] The diastereomeric ratio before purification was 3.1:1. NR = no reaction, Ns = 4-nitrobenzenesulfonyl, Ts = *p*-toluenesulfonyl.



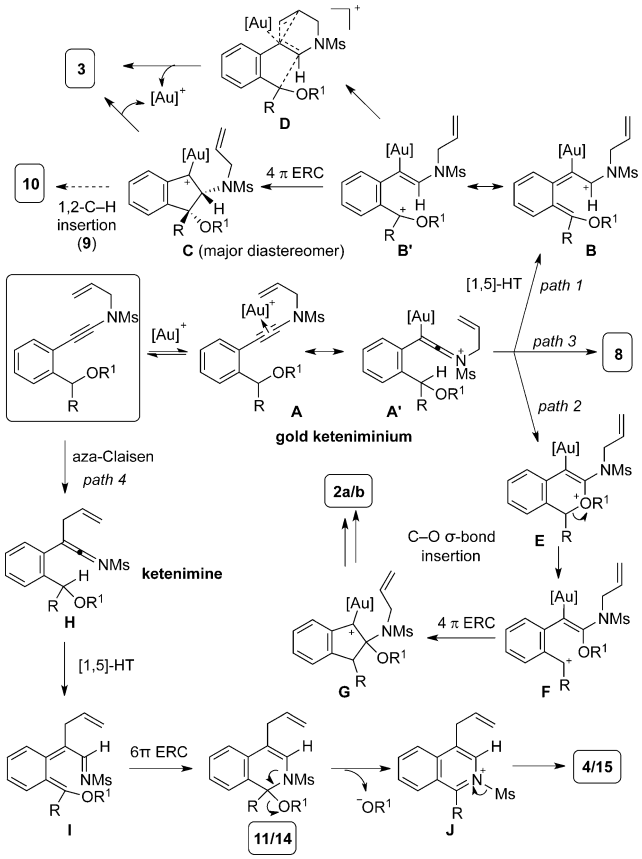
Scheme 3. Reactions to probe individual steps within the polycyclization cascade.



Scheme 4. Initial exploration of the ynamide cascade cyclization initiated by an aza-Claisen reaction.

deuterium incorporation at the 3-position. The products derived from dioxolane derivatives **13a–h** were generally isolated as dialkoxy 1,2-dihydroisoquinolines **14** unless elimination was aided by the substitution pattern (product **15d**) or aromatization (product **15f**). In stark contrast to the polycyclization, *N*-Ms ynamides gave faster and cleaner reactions than *N*-Ts ynamides (**14a** vs. **14aa**; **4** was formed in 20% yield from **1b**). The rearrangement cascade also tolerated increased substitution around the ynamide (product **14e**) and electronic variation (products **14c–e**). The reactions of thiophene- and pyridine-derived ynamides highlight the ability to access other desirable heteroaromatic motifs (products **14g,h**).[19]

According to our observations and previously reported studies, the reactions can be rationalized on the basis of competing activation of the substrate as a gold keteniminium



Scheme 5. Proposed mechanistic outline of competing pathways. For clarity, conformational changes are not shown. ERC = electrocyclic ring closure.

intermediate **A**/**A**′ and ketenimine **H** (Scheme 5). Deuterium labeling and the impact of (de)stabilizing substituents (see products **3k**,**n**,**o**[20] in Scheme 2) are consistent with the turnover-limiting formation of benzylic cation **B** by 1,5-hydride transfer from **A**′ (path 1).[21] The gold atom must be able to align in a plane with the carbon atom of the donor site (compare **1l**–**q**). Stepwise cyclization, to give gold carbene **C**, and cyclopropanation would give **3**. An inverted order of bond formation, with cyclopropanation occurring before C–H insertion of a gold carbene,[22] is unlikely on the basis of the results with **6** and **9**. The general lack of competition from 1,2-C–H insertion of **C** at adjacent heteroatom-substituted positions (compare the formation of **10** from **9**) is surprising[2,23] and could result from a more concerted polycyclization event (see **D**), which would also account for the diastereoinduction at the ring junction in the presence of a chiral N-substituent (formation of **3j**). This interaction is not, however, required for metal carbene formation by C–H insertion, as seen with **10**, in which case 1,2-insertion followed cyclization.

Attack of the ether oxygen atom or homoallyl group can lead to competing carbocyclizations of intermediate **A** (paths 2 and 3). Although carboalkoxylation is favored at lower temperatures, a thermal aza-Claisen pathway[24] can compete at higher temperatures and outperform π-activation pathways in the absence of a sufficiently electrophilic catalyst (path 4). A 1,5-hydride shift onto ketenimine **H** occurs in place of the 1,3-sulfonyl shift shown to be facile with aryl ynesulfonamides.[24] A 6π electrocyclic ring closure would give the isolable heterocycles **11**/**14**.[25,26] Neighboring-group-assisted elimination and desulfonylation would then afford **4**/**15**. A metal catalyst could potentially play a role during each stage of this thermally viable cascade.

In summary, the induction of gold carbene character by ynamide insertion into a C(sp^3)–H bond resulted in a novel polycyclization cascade of *N*-(homo)allyl ynamides. Superb selectivity was observed for an array of competing processes through the appropriate choice of reaction conditions and was reinforced by structural effects. Two protocols were developed to access substantial molecular complexity in a single step with simple catalysts and practically straightforward reaction conditions: Fused C(sp^3)-rich scaffolds resulted from a gold keteniminium pathway, in which C–H insertion outperformed carboalkoxylation and enyne cycloisomerization, and heteroaromatic pyridine-fused derivatives were prepared through ketenimine activation in a copper-catalyzed rearrangement cascade. Investigations are ongoing to further elucidate the mechanism, stereocontrol factors, and wider synthetic potential of these reactions.

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