Divergent C–H Insertion–Cyclization Cascades of N-Allyl Ynamides
Holly V. Adcock, Elli Chatzopoulou, and Paul W. Davies*

Abstract: Gold carbene reactivity patterns were accessed by ynamide insertion into a C(sp⁳)–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(sp³)-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(sp³) 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] Potent transformations based on this approach enable the elaboration of a C(sp)–C(sp) unit into C(sp³)–C(sp³) or C(sp³)–C(sp³) units. We envisioned that the challenging C(sp³)–C(sp³) 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 amides, regardless of the substituents present. Herein we observed. Instead, 1,2-migration dominated to give indenyl nitrenoids.[3–5] Potent transformations based on this approach enable the elaboration of a C(sp)–C(sp) unit into C(sp³)–C(sp³) or C(sp³)–C(sp³) units. We envisioned that the challenging C(sp³)–C(sp³) 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).

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An ynamide polycyclization cascade was pursued by the use of an N-allyl substituent as a viable carbenoid-quenching unit.[11] Although several Au¹ species/solvent combinations afforded only indenyl amides 2a/b at room temperature, a breakthrough occurred when 1a was heated with [Au(picolinate)Cl₃][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 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 AuCl₃ or AuBr₃ gave 3a in lower yield and a 1,4-disubstituted isquinoline 4 (Table 1, entries 7–10; see also the Supporting Information), which was also the main product with Au¹ species. Degradation of 1a was seen with BF₃·OEt₂, whereas bonds, three new fused rings, and up to four contiguous stereocenters.

Supporting information and ORCID(s) from the author(s) for this article are available on the WWW under http://dx.doi.org/10.1002/anie.201507167.

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

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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 1lp with large groups flanking the ynamide did not undergo the desired transformation. The less rigid dihydronaphthalene-substituted ynamide 1q reacted only slowly with the AuIII catalyst to give 3q, which was obtained in substantially improved yield with a linear AuCl 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(sp2)-rich polycycles 3r-x incorporating cycloalkyl, piperidinyl, 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.

Further mechanistic insight into the polycyclization was then sought. Complete deuteration 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 e-ne-ynamide cyclosomerization was observed, thus showing C–H insertion to be kinetically more productive than the attack of an alkene.[16,18] 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.

Isouquinoline formation from N-methanesulfonyl ynamides 1a/y could be interrupted by adding a base to afford alkyl 1,2-dihydoisoquinolines 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

### Table 1: Effect of reaction conditions on product distribution.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Solvent</th>
<th>T [°C]</th>
<th>Yield [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1[a]</td>
<td>([p-CF3C6H4]3PAuCl)AgNTf2</td>
<td>CH2Cl2</td>
<td>RT</td>
<td>–:74:9:–:–</td>
</tr>
<tr>
<td>2</td>
<td>[Au(picolinate)Cl]2</td>
<td>toluene</td>
<td>80</td>
<td>–:21:7:61(3.4:1):–</td>
</tr>
<tr>
<td>3</td>
<td>[Au(picolinate)Cl]2</td>
<td>toluene</td>
<td>80</td>
<td>–:54:32:9:–</td>
</tr>
<tr>
<td>4</td>
<td>[Au(picolinate)Cl]2</td>
<td>MeNO2</td>
<td>80</td>
<td>–:–:45:19:9</td>
</tr>
<tr>
<td>5</td>
<td>[Au(picolinate)Cl]2</td>
<td>toluene</td>
<td>100</td>
<td>–:–:11:6:66(2.9:1):–</td>
</tr>
<tr>
<td>6</td>
<td>[Au(picolinate)Cl]2</td>
<td>p-xylene</td>
<td>120</td>
<td>–:11:6:66(2.9:1):–</td>
</tr>
<tr>
<td>7</td>
<td>AuBr3</td>
<td>p-xylene</td>
<td>120</td>
<td>–:22:35:65(3.7:1):–</td>
</tr>
<tr>
<td>8</td>
<td>AuCl3</td>
<td>p-xylene</td>
<td>120</td>
<td>–:22:35:65(3.7:1):–</td>
</tr>
<tr>
<td>9</td>
<td>(Ph3PAuCl)/AgNTf2</td>
<td>p-xylene</td>
<td>120</td>
<td>–:–:–:–:6</td>
</tr>
<tr>
<td>10</td>
<td>([JohnPhos)Au(NCMe)2]SbF6</td>
<td>p-xylene</td>
<td>120</td>
<td>–:–:–:–:41</td>
</tr>
<tr>
<td>11</td>
<td>BF3·OEt2</td>
<td>toluene</td>
<td>80</td>
<td>–:–:–:–:–</td>
</tr>
<tr>
<td>12</td>
<td>none</td>
<td>p-xylene</td>
<td>120</td>
<td>–:–:–:–:6</td>
</tr>
<tr>
<td>13</td>
<td>CeI</td>
<td>toluene</td>
<td>100</td>
<td>–:–:–:–:68</td>
</tr>
</tbody>
</table>

[a] General reaction conditions: 1a (0.1 mmol, 1.0 equiv), catalyst (5 mol%), solvent (0.1 mL); the reaction mixture was stirred for 6 h unless otherwise stated. [b] Yields were determined by 1H 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, TFE = trifluoromethanesulfonyl. 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.[9] 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 dioxygen unit in the alkyne starting material instead of the benzylic 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 3j 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.
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 

Scheme 2. Structural effects on the ynamide C-H insertion-cyclop propane 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 NEt₃-deactivated silica. [d] The diastereomeric ratio before purification was 3.1:1. NR = no reaction, Ns = 4-nitrobenzenesulfonyl, Ts = π-toluenesulfonyl.
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intermediate A/\text{A}' and keteniminium \text{H} (Scheme 5). Deuterium labeling and the impact of (de)stabilizing substituents (see products 3k.n.o\textsuperscript{[20]} in Scheme 2) are consistent with the turnover-limiting formation of benzylic cation \text{B} by 1,5-hydride transfer from A/\text{A}' (path 1).\textsuperscript{[21]} The gold atom must be able to align in a plane with the carbon atom of the donor site (compare 11-\text{q}). Stepwise cyclization, to give gold carbene \text{C}, and cyclopropanation would give 3. An inverted order of bond formation, with cyclopropanation occurring before C–H insertion of a gold carbene,\textsuperscript{[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 \text{C} at adjacent heteroatom-substituted positions (compare the formation of 10 from 9) is surprising\textsuperscript{[22,23]} and could result from a more concerted polycyclization event (see \text{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\textsuperscript{[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 keteniminium \text{H} occurs in place of the 1,3-sulfonyl shift shown to be facile with aryl ynesulfonamides.\textsuperscript{[24]} A 6π electrocyclic ring closure would give the isolable heterocycles 11/14.\textsuperscript{[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\textsuperscript{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\textsuperscript{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 keteniminium activation in a copper-catalyzed rearrangement cascade. Investigations are ongoing to further elucidate the mechanism, stereocontrol factors, and wider synthetic potential of these reactions.

Acknowledgements

We thank the EPSRC and AstraZeneca plc (Studentship to H.V.A.) and the University of Birmingham (Studentship to E.C.) for funding, Dr. Louise Male (University of Birmingham) for X-ray crystallography, and Dr. Thomas Langer (AstraZeneca plc, Macclesfield, UK) for interesting discussions. Facilities used in this research were in part supported through Birmingham Science City AM2 by AWM and the ERDF.

Keywords: carbenes · cyclopropanation · gold · nitrogen heterocycles · ynamides

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