Gold–Catalyzed Atom–Economical Cascade Reactions of Alkynes for Ring Formation

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Abstract: The development of cascade reactions is an area of considerable interest in modern organic chemistry. Recent advances in homogeneous gold catalysis have opened up further possibilities for atom–economical cascade reactions for efficient synthesis of complex target molecules. We have been involved in the development of cascade reactions based on the activation of carbon–carbon triple bonds by a gold catalyst to facilitate intra– and intermolecular nucleophilic attack. Quite recently, we succeeded in forming gold carbenoids, which are useful intermediates for further elaborations, from ynamides. This account describes our efforts towards the development of gold–catalyzed cascade reactions for atom–economical synthesis of fused carbazoles, naphthalenes, dihydropyrazoles/indazoles, and indoloquinolines.

1. Introduction

Cascade reactions, including domino reactions and “time and space integration” of reactions, have been the subject of intense research in recent years.1 Such reactions facilitate sequential formation of several new bonds in a single operation, rapidly increasing the molecular complexity, while also reducing time and labor requirements, and waste generated during the synthesis. Another advantage of these reactions is that they make possible the utilization of reactive intermediates that are not stable enough for isolation. Because many gold–mediated elementary transformations generate new reactive species in atom economical manner,2 gold catalysis is extremely useful for the design of efficient cascade reactions.3

Homogeneous gold catalysis has attracted much interest in modern organic chemistry.4 Gold efficiently activates carbon–carbon triple bonds promoting their reactions with various types of partners including alkene (Scheme 1, eq 1), gold acetylide (eq 2), arene/enol/enamine (eq 3), heteronucleophile (eq 4), and azide (eq 5) to provide reactive species such as gold carbenoids A,4 gold vinylidene B,6 oxoniums/iminiums C,6 enols/enamines D, and imine–conjugated gold carbenoids E,7 respectively. These are valuable intermediates for further elaboration(s) including cyclopropanation, ring–expansion, nucleophilic addition, C–H bond activation/insertion, electrophilic reaction, and cycloaddition to give complex target compounds with good atom economy.2

Recently we have been involved in investigating cascade reactions of the type shown in eq 4 using alkynylanilines.8 This chemistry was extended to intermolecular reactions of o–dialkynylbenzene derivatives to provide naphthalenes9 and dihydropyrazoles derivatives.10 Quite recently, we have developed (azido)ynamide cyclization to generate nitrogen–substituted gold carbene species E (R=NR3R3) as shown in eq 5.5 In this account, we wish to describe our efforts towards development of gold–catalyzed atom–economical cascade reactions for the synthesis of fused carbazoles, naphthalenes, dihydropyrazoles/indazoles, and indoloquinolines.

2. Consecutive Cyclization of Alkynylaniline Derivatives

Addition of heteronucleophiles to an alkynyl produces enol/enamine–type intermediates D (Scheme 1), which may undergo further cyclization. In 2000, the Hashmi group reported the propargyl ketone I bearing a homopropargyl

Scheme 1. Classification of gold–catalyzed cascade cyclization of alkynes.

[ tròcal]

alcohol moiety underwent tricyclization to give the spirocyclic product 2 (Scheme 2). This reaction can be rationalized by initial furan formation, hydroarylation from 3 at the furan 3-position to give 4, and hydroalkoxylation to form spirocycle 2. In contrast, cascade cyclization of alkynylaniline derivatives to form aryl-annulated carbazoles had not been reported.

Scheme 2. Cascade cyclization through furan formation, hydroarylation, and hydroalkoxylaion reported by Hashmi et al. in 2000.

2.1 Synthesis of Benzo[a]carbazoles and Related Compounds

Aryl- and heteroaryl-annulated[a]carbazoles are an important structural unit in a number of biologically active compounds. Most of the existing synthetic methods for them include stepwise introduction or construction of the pyrrole and benzene rings. To develop a more atom-economical and direct synthetic method to aryl-annulated[a]carbazoles 6, we designed a cyclosomerization cascade on the basis of gold-catalyzed 5-endo-dig hydroamination and subsequent 6-endo-dig hydroarylation of diynes 5 (Scheme 3). The advantage of this strategy would be that no waste products are formed in these two steps. Furthermore, the substrates can be easily prepared by Sonogashira coupling.

Scheme 3. Our concept: hydroamination and hydroarylation.

Initially, screening of gold catalysts for the cascade reaction was carried out using the aniline 5a (Table 1). Whereas Ph3PAuCl was ineffective (entry 1), reaction using AuCl or AuCl3 as a phosphine ligand free catalyst gave the desired carbazole in low yields (entries 2 and 3). To our delight, cationic gold complexes using a silver salt generally gave better results (data not shown, 70–80%). Among several silver(I) salts, AgOTf was the most effective affording the carbazole 6a in 80% yield (entry 5). As the reaction solvent, MeCN, EtOH, and 1,2-dichloroethane (DCE) can be used (entries 5–7).

Unfortunately, preliminary investigations of the substrate scope have revealed that the reaction of tolyl or anisyl derivatives 5b and 5e under the conditions shown in entry 5 gave the carbazoles in relatively low yields (42 and 29% respectively, entries 8 and 9). The lower reactivity of these substrates can be attributed to predominant coordination of the electron-rich aryl substituted alkyn to the gold complex, which might hinder the first cyclization step. We then further optimized the reaction conditions for the diyne 5b bearing a tolyl group. Several gold–phosphine complexes were tested in the expectation that the bulky diarylphosphine ligands such as L1–L3 (Figure 1) might effectively promote dissociation of the catalyst from the substrate, which would improve the chance of activation of the appropriate alkyn for hydroamination. Pleasingly, the reactions with 5 mol% of the catalysts bearing a bulky phosphine ligand exhibited significantly increased reaction to give the corresponding carbazoles 6b and 6e in good yields (entries 10–13, 71–83%).

Using the newly optimized conditions, the cascade cyclization was extended to other types of substituted anilines. In

Table 1. Optimization of the reaction conditions.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Diyne</th>
<th>R</th>
<th>Au catalyst (mol %)</th>
<th>Solvent</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5a</td>
<td>Ph</td>
<td>Ph3PAuCl</td>
<td>MeCN</td>
<td>NR</td>
</tr>
<tr>
<td>2</td>
<td>5a</td>
<td>Ph</td>
<td>AuCl (20)</td>
<td>MeCN</td>
<td>33</td>
</tr>
<tr>
<td>3</td>
<td>5a</td>
<td>Ph</td>
<td>AuCl3 (20)</td>
<td>MeCN</td>
<td>42</td>
</tr>
<tr>
<td>4</td>
<td>5a</td>
<td>Ph</td>
<td>NaAuCl2H2O (20)</td>
<td>MeCN</td>
<td>64</td>
</tr>
<tr>
<td>5</td>
<td>5a</td>
<td>Ph</td>
<td>Ph3PAuCl/AgOTf (5)</td>
<td>MeCN</td>
<td>80</td>
</tr>
<tr>
<td>6</td>
<td>5a</td>
<td>Ph</td>
<td>Ph3PAuCl/AgOTf (5)</td>
<td>EtOH</td>
<td>71</td>
</tr>
<tr>
<td>7</td>
<td>5a</td>
<td>Ph</td>
<td>Ph3PAuCl/AgOTf (5)</td>
<td>DCE</td>
<td>73</td>
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<tr>
<td>8</td>
<td>5b</td>
<td>4-Tol</td>
<td>Ph3PAuCl/AgOTf (5)</td>
<td>MeCN</td>
<td>42</td>
</tr>
<tr>
<td>9</td>
<td>5c</td>
<td>4-An</td>
<td>Ph3PAuCl/AgOTf (5)</td>
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<tr>
<td>10</td>
<td>5b</td>
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<tr>
<td>12</td>
<td>5b</td>
<td>4-Tol</td>
<td>L3AuCl2AgOTf (5)</td>
<td>MeCN</td>
<td>83</td>
</tr>
<tr>
<td>13</td>
<td>5c</td>
<td>4-An</td>
<td>L3AuCl2AgOTf (5)</td>
<td>MeCN</td>
<td>83</td>
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</table>

* The structures of L1–L3 are shown in Figure 1. † DCE = 1,2-dichloroethane. ‡ An = anisyl.

Figure 1. Structures of ligands (used throughout the manuscript).
most cases, the desired products were afforded in good to
excellent yields (Table 2, entries 1–4 and 6−12). It should
be noted that an o−cyano group at R1 (entry 5) significantly
decreased the yield, while the effect of the cyano group itself
was less important (entry 2). This is presumably because of a
coordination effect of the cyano group ortho to the alkynyl
group, which would promote an undesired interaction between
this triple bond and the catalyst before hydroamination. This
explanation is partly supported by the high yield when an o−
tolyl derivative was used (entry 4), showing that any steric hin-
drance due to the o−substituents is unimportant.

Table 2. Reaction of various aniline derivatives.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Diyne</th>
<th>R1</th>
<th>R2</th>
<th>R3</th>
<th>Time (min)</th>
<th>Yield (%)</th>
</tr>
</thead>
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<tr>
<td>1</td>
<td>C2H4(3-Me)</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>30</td>
<td>76</td>
</tr>
<tr>
<td>2</td>
<td>C2H4(3-CN)</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>30</td>
<td>79</td>
</tr>
<tr>
<td>3</td>
<td>C2H5(3-CN)</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>40</td>
<td>96</td>
</tr>
<tr>
<td>4</td>
<td>C2H5(2-Me)</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>40</td>
<td>82</td>
</tr>
<tr>
<td>5</td>
<td>C2H5(2-CN)</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>250</td>
<td>10</td>
</tr>
<tr>
<td>6</td>
<td>c-pentyl</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>40</td>
<td>90</td>
</tr>
<tr>
<td>7</td>
<td>3-thienyl</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>40</td>
<td>74</td>
</tr>
<tr>
<td>8</td>
<td>Ph</td>
<td>CO2Me</td>
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<td>H</td>
<td>120</td>
<td>68</td>
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<tr>
<td>9</td>
<td>Ph</td>
<td>Me</td>
<td>H</td>
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<td>Ph</td>
<td>Cl</td>
<td>H</td>
<td>H</td>
<td>40</td>
<td>92</td>
</tr>
<tr>
<td>11</td>
<td>o-hexyl</td>
<td>Cl</td>
<td>H</td>
<td>H</td>
<td>90</td>
<td>96</td>
</tr>
<tr>
<td>12</td>
<td>o-hexyl</td>
<td>CF3</td>
<td>H</td>
<td>H</td>
<td>90</td>
<td>87</td>
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</table>

We next investigated the reaction of other types of diynes (Figure 2). Aniline derivatives bearing a Boc or methyl group
on the nitrogen atom also produced the benzo−fused carbazoles 6p and 6q in good yields. Whereas anilines which have a
furanyl group tethering the alkyn moiety provided the desired carbazole 8a in good yields, the pyridine derivative
proved to be a poor substrate giving 8b in only 37% with an
increased catalyst loading (20 mol%). An aliphatic primary
amine−derived diyne, when protected by a Boc group, reacted
with the gold catalyst cleanly affording the dihydrobenzoazepine
derivative 9 in high yield (99%). Similarly, this cascade reaction was applicable to the synthesis of naphthalene−fused dihydro-
furan 10, and indole−fused seven−membered ring hetero−
carboycles 11a−c.

2.2 Synthesis of Benzo[a]naphtho[2,1−c]carbazoles and
Related Compounds

We next expected that introduction of another alkyn moiety
to the substrates might allow a second hydroarylation from the
intermediate 13 (Scheme 4), leading to benzo[a]naphtho[2,1−c]carbazoles 14 (n=1). If a third and further hydroarylations
successfully proceeded from 14, polycyclization products such as 15 would be obtained. In this strategy, the
challenging issue becomes selective activation of the appropriate
alkyne among several alkynes at each step. We prepared polyene−type anilines 12 (n=1−3) and examined the consecutive
6−endo−dig hydroarylation cascade.

We first tested the tricyclization (Table 3). Fortunately, the
reaction with 20 mol% Ph3P AuCl and AgOTf produced the
benzonaphtocarbazole 14a in 77% yield (entry 1). However,
decreasing the loading of the catalyst to 5 mol% was not suc-
cessful, producing the intermediate 13a (29%, entry 2) with
recovery of the starting material (43%). Also in this case, bulky
phosphine ligands such as L1 and L3 (L1=JohnPhos; L3=
XPhos; Figure 1) led to improved reactivity with a 5 mol% catalyst loading (entries 4 and 7). Ethanol (entry 5) and acetic
acid (entry 6) were the solvents of choice for the tricyclization
giving slightly improved yields, presumably due to promotion of proto−deauration.

The tricyclization was extended to other types of substrates
(Figure 3). The sterically hindered t−butyl group completely
interrupted the third cyclization, providing none of the desired product 14c. Instead, this reaction gave the bis-cyclization product of type 13a (Table 3). In contrast, all the aryl-substituted triyne substrates produced the desired tricyclization products 14d-h. The relatively low yields of 14h can be explained by the high coordinating ability of the electron-rich anisylalkyne moiety for the third cyclization, which might somewhat hinder the first and/or second cyclization step. Substitution effects for the aniline part were next examined (14i-k). A cyano group at the para position to the amino group significantly decreased the reactivity and led to formation of a considerable amount of a complex mixture of unidentified products. This was presumably because of the decreased nucleophilicity at the reaction site(s). A thiophene ring can be used as the junction part, with the reaction producing the corresponding fused thiophene 14l in 79% yield.

Next, tetra- and penta-cyclization of the polyyne-type anilines were investigated (Figure 4). To our delight, the reaction with L3AuCl/AgBF4 (L3=XPhos, Figure 1; 7.5–20 mol%) in EtOH produced the desired highly-fused carbazoles 15a and 16a in 86% and 68% yields. In these cases, a combination of XPhos and EtOH was more effective than the standard conditions for tricyclization (L1AuCl/AgBF4 and AcOH or EtOH). For example, tetracyclization with L1AuCl/AgBF4 (10 mol%) in EtOH for 29 h gave 15a in only 12% yield, along with the tricyclization intermediate (58%).

Interestingly, the pentacyclization product 16a was produced as a 2:1 mixture of stereoisomers. Tosylation of the isomeric mixture allows recrystallization and isolation of the major isomer. X-ray analysis of the tosylated major isomer 16b confirmed the assignment for this compound, with a strained polynaphthalene helix structure (Figure 5).

We believe that the second and further cyclization(s) proceed after proto-deauration of the vinyl gold intermediate as already shown in Scheme 4. This is supported by the reaction of plausible intermediates (Scheme 5): treatment of the monocyclization product 7a under the standard conditions quantitatively proceeded to afford the desired tricyclization product 6a. Similarly, exposure of the bis-cyclization intermediate 13a to the optimized reaction conditions afforded the tricyclization product in 90% yield. Combined with the reaction using insufficient loading of the catalyst to produce the intermediates such as 7a and 13a with recovered starting material, these results strongly support the reaction mechanism including stepwise hydroarylation/proto-deauration.

Following our reports, several related reactions have been reported by other research groups. Some important examples are shown in Scheme 6. In 2012, The Jin–Yamamoto group reported a gold-catalyzed bicyclization of bis(diynylaniline) derivatives 17, to produce new donor–acceptor materials 18.
Alabugin and co–workers reported the synthesis of benzofuran–fused chrysene derivative 21 based on the Sonogashira coupling followed by furan formation from triyne 20 with 2–iodophenol 19 and subsequent gold–catalyzed bicyclization.16 Quite recently, interesting regioselectivity in the gold–catalyzed hydroarylation was observed by Wang et al.17 They used benzoic acid–derived diynes 22 bearing a terminal alkyn moiety and obtained the bicyclization products 23. They proposed a mechanism that involves activation of the terminal alkyn by the cationic gold complex to promote a 5 exo–dig cyclization, which is followed by nucleophilic attack of the carboxy group.

From these observations, gold–catalyzed polycyclization of anilines and related compounds bearing a polyenic moiety shows significant potential for atom–economical construction of highly fused aromatic ring systems. The gold catalysts promote a third and fourth hydroarylation when using polypylene–type substrates to afford highly fused carbazoles. This reaction can be considered as the polypylene version of biogenetic polycyclization, in which the newly formed benzene ring(s) participates in the next cyclization to form multiple benzene rings.

3. Intermolecular Reactions of 1,2–DialkynylBenzene Derivatives

Based on our success with carbazole formation, we next attempted to use an initial intermolecular reaction of 1,2–dialkynylbenzenes to construct an internal nucleophilic functional group to carry out cyclization. We planned two strategies: naphthalene synthesis based on intermolecular nucleophilic addition, and pyrazole/indazole synthesis based on three–component coupling as shown below.

3.1 Naphthalene Synthesis Based on Intermolecular Nucleophilic Addition

Our concept for the naphthalene synthesis is shown in Scheme 7. In these intermolecular reactions using external nucleophiles, a regioselectivity issue arises, i.e. which of the two regioisomeric products 25A and 25B predominates (path A/A’ vs. path B/B’). We expected that diynes bearing a terminal alkyn (R2=H) would be promising substrates for this naphthalene synthesis: regioselective nucleophilic addition by the external nucleophile onto the terminal alkyn would produce the intermediate G bearing a nucleophilic enamine or enol ether moiety, which will then react with the activated triple bond to produce the naphthalene derivatives 25B (R2=H) in a regioselective manner.

Initially, we investigated the reaction of 24a with several gold catalysts for the naphthalene formation using ethanol as the external nucleophile/solvent (Table 4, entries 1–6), and found that a gold carbene complex IPraAuCl shows better reactivity (entries 5 and 6) than complexes with phosphine ligands. Decreasing the loading of EtOH improved the yields slightly (50%, entry 7), probably by suppressing side reactions with excess EtOH. Interestingly, the most efficient conversion was observed by decreasing the loading of catalyst (2 mol%, entry 8).

Under these conditions, the reactions of some other nucleophiles were also examined (Figure 6). When using N–methylalanines as the external nucleophile, the desired products 25A–f were obtained in good to excellent yields (>92%) via nucleophilic carbon–nitrogen bond formation. Similarly, a protected hydrazine can be used to produce 25b in 77% yield.

**Scheme 5.** Cyclization of plausible intermediates

**Scheme 6.** Related reactions recently reported by other groups.15,17

**Scheme 7.** Our concept: intermolecular nucleophilic addition and carbocyclization.
The reaction with pyrrole and indole as carbon nucleophiles afforded the desired biaryl products 25i-k via nucleophilic C=C bond formation. For the diynes, an alkyl substitution on the alkyn (25i) and electron-withdrawing/donating substituents on the benzene ring (25m and 25n) were tolerated. This reaction can be applied to benzoazepine and benzo furan synthesis (25o and 25p), although the benzo furan formation was less efficient (35% yield) even using an increased amount (10 mol%) of the catalyst.

A plausible catalytic cycle for naphthalene formation is shown in Scheme 8: (1) regioselective intermolecular nucleophilic addition onto the terminal alkyn of 24a as depicted in H, (2) deauration of I by intra- or intermolecular proton transfer, (3) intramolecular nucleophilic addition of the resulting enol ether intermediate J, and (4) aromatization involving intra- or intermolecular proton transfer (as shown in K) leading to the naphthalenes 25a. We speculated that a dual activation mechanism through formation of a gold acetylide intermediate would be another possible pathway, where two gold fragments are used for the activation of the terminal alkyne (π-activation and σ-coordination). However, this possibility was ruled out as the major pathway in collaboration study with the Hashmi group: the reaction of acetylide 24a with 2 mol% of IPrAuCl/AgOTf in the presence of EtOH gave monoaurated benzopentalene species 26a (Scheme 9). Even if the reaction of 24a with EtOH (1.1 equiv) was carried out in the presence of HBF₄·OEt₂ (1 equiv) without using the gold catalyst, only a trace amount of 25a (4%) was produced. It is worth mentioning that when N-methylaniline, a stronger nucleophile, was used in the same reaction instead of EtOH, the formation of a significant amount of the naphthalene derivative 25d was observed (42%).

The labeling experiments shown in Scheme 10 support well the proposed catalytic cycle. The reaction of the labeled substrate 24a-d (93% d) with EtOH (10 equiv) under the standard conditions gave the corresponding naphthalene with loss of deuterium labeling (≤10% d, eq 1). This suggests that the proton at the alkyn terminal is efficiently exchanged in the reac-

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**Table 4. Optimization of the reaction conditions.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Au catalyst (mol%)</th>
<th>Solvent</th>
<th>T (°C)</th>
<th>Time (min)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph₂IPrAuCl/AgOTf (5)</td>
<td>EtOH</td>
<td>80</td>
<td>1.5</td>
<td>36</td>
</tr>
<tr>
<td>2</td>
<td>Ph₂IPrAuCl/AgOTf (5)</td>
<td>EtOH</td>
<td>80</td>
<td>0.5</td>
<td>30</td>
</tr>
<tr>
<td>3</td>
<td>L1IPrAuCl/AgNTf₂ (6)</td>
<td>EtOH</td>
<td>rt</td>
<td>0.5</td>
<td>15</td>
</tr>
<tr>
<td>4</td>
<td>L3IPrAuCl/AgNTf₂ (5)</td>
<td>EtOH</td>
<td>rt</td>
<td>24 &lt;8</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>L3IPrAuCl/AgNTf₂ (5)</td>
<td>EtOH</td>
<td>80</td>
<td>0.25</td>
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<td>EtOH</td>
<td>80</td>
<td>1.0</td>
<td>44</td>
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<tr>
<td>7</td>
<td>L3IPrAuCl/AgNTf₂ (5)</td>
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<td>50</td>
<td>4.0</td>
<td>50</td>
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<tr>
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<td>DCE</td>
<td>50</td>
<td>2.0</td>
<td>61</td>
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</table>

* The structures of L1, L3 and IPr are shown in Figure 1. 1.1 Equiv of EtOH was used.

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**Figure 6.** Substrate scope for naphthalene formation. Reaction conditions: IPrAuCl/AgOTf (2 mol%), nucleophile (1.1 equiv), DCE, 50 °C. a) 5 equiv of n-BuOH or t-BuOH were used. The catalyst loading was increased to 10 mol%.
over the D shift in the deauration reaction. The need for multi-mediates, frequent cyclization proceeded smoothly under the standard 2014/10/22 9:48:01 de is useful for the that electron poor or rich phenylacetylenes (substrate, Scheme 8).

We expected, bicyclization of triyne–type substrate 27 proceeded well and gave the chrysene derivatives 28a, b (Scheme 11). The reaction is believed to proceed through intermolecular nucleophilic addition and intramolecular double carbocyclization. These observations demonstrate the inter/intramolecular nucleophilic addition cascade is useful for the construction of various types of benzene rings.

Scheme 11. Application to consecutive cyclization.

3.2 Dihydropyrazole/indazole Synthesis Based on Mannich–Type Three–Component Reaction

Pyrazoles are important class of compounds, exhibiting a variety of biological activities. Although a number of approaches to pyrazoles have been developed, sometimes, and especially for poly-substituted derivatives, suffer from the need for multi-step processes, a limited substituent scope, and/or regioselectivity issues in substitution of the two adjacent nitrogen atoms. To address these drawbacks we next designed an intermolecular reaction based on three-component annulation. As shown in Scheme 12, a Mannich–type three-component coupling of alkyne, aldehyde/ketone, and hydrazine would give a propargyl hydrazine intermediate, which could be converted to the pyrazole by transition-metal catalyzed cyclization. This reaction would provide a diversity-oriented synthetic method for pyrazole derivatives, in which all the reaction components are incorporated in the newly–formed ring. Use of 1,2-dialkynylenzene would lead to direct construction of benz–fused indazoles.

Scheme 12. Our concept: three-component dihydropyrazole synthesis

Initial investigations focused on the search for suitable catalysts and solvents for the reaction using phenylacetylene, isobutyraldehyde, and a protected hydrazine (BocNH–NH2). In this case as well, gold IPr complex (2 mol%) in the presence of AgOTf (2 mol%) in DCE efficiently catalyzed the reaction to give the pyrazole 29a in 96% yield (Figure 7). Examination of the substrate scope using other alkynes and hydrazine has revealed that electron poor or rich phenylacetylenes (29b and 29c), aliphatic alkynes (29d), and phenylhydrazine (29e) can all be used. Similarly, aromatic aldehydes (29f–h), and even aliphatic ketones (29i and 29j) can be used to the reaction, affording the desired annulation products. In some cases, slightly modified reaction conditions (5 mol% catalyst loading or AcOH as the solvent) were employed to promote the reaction when using less reactive components such as aromatic aldehydes and ketones.

Figure 7. Substrate scope for dihydropyrazole formation. Reaction conditions: alkyne (1–2 equiv), aldehyde/ketone (1.2–2 equiv), hydrazine (1 equiv), IPrAuCl/AgOTf (2 mol%), DCE, rt or 50 °C. *AcOH was used as the solvent. †The catalyst loading was increased to 5 mol%.

We turned our attention to cascade cyclization using diynes 24 as the alkyne component (Scheme 13). Our expectation was that 6–endo–dиг cyclization of the presumed intermediate 34 would produce benzene–fused dihydroidazoles 32. To our delight, the three–component annulation of 24, 30, and 31 and subsequent cyclization proceeded smoothly under the standard reaction conditions to provide 32 in 65–84% yields.

A medicinal chemistry application of this pyrazole synthesis is shown in Figure 8. Protein kinase CK2 is a potential tar-
get for cancer treatment, because CK2 is overexpressed in a wide variety of tumors. Based on the pyrazole-type CK2 inhibitor identified by our group, various benzo[\textit{g}]indazole and pyrazoloindole derivatives were prepared using our gold-catalyzed annihilation reactions. Evaluation of their CK2 inhibitory activities revealed that the benzoindazole and pyrazoloindole showed potent inhibitory activities toward CK2α (IC\textsubscript{50} 0.039 \textbullet 0.058 \textmu M) and CK2α' (IC\textsubscript{50} 0.019 \textbullet 0.028 \textmu M). It is worth noting that pyrazoloindole derivatives such as could also be prepared via three-component annulation using 1-azido-2-ethynylbenzene as the alkyne component followed by ruthenium-catalyzed C–H amination of the resulting azide derivative. Thus, our pyrazole synthesis is a promising method for identification of novel drug candidates.

4. Biscyclization of (Azido)ynamides: Indoloquinoline Synthesis

The final reaction discussed in this account is indoloquinoline synthesis based on gold-catalyzed cascade cyclization of (azido)ynamides, developed in 2014. In 2005, Toste et al. reported the use of azide as an effective nitrine equivalent for the generation of a gold-carbeneoid species in their synthesis of pyroles (Scheme 14, eq 1). Following on from this pioneering work, Gagosz\textsuperscript{7b} and Zhang\textsuperscript{7c} independently reported the development of a novel method for the synthesis of indoles from alkynyl azides by the reaction of alcohols or arynes with gold-carbeneoids (eq 2). In contrast to these studies, there had been no reports in the literature to date pertaining to the reactivity of ynamides with azides under gold catalysis.

The gold-catalyzed reaction of (azido)ynamides has significant potential for direct construction of the indoloquinoline framework found in numerous bioactive natural products (Figure 9). Thus, it was envisaged that the gold-catalyzed reaction of (azido)ynamide 38 would lead to the formation of an \textalpha-amidino gold-carbeneoid 39 (Scheme 15). This intermediate could be used to produce various indoloquinolines and related compounds 40–42 through an intramolecular trapping reaction. For example, the reaction of the carbeneoid 39 with an allylsilane or simple alkene moiety would give terminal alkene 40 or cyclopropane 41, respectively. Furthermore, direct arylation of the gold carbeneoid 39 would lead to fused indole 42.

After screening of gold catalysts, silver salts, reaction solvents and temperature using (Z)-allylsilane 38\textsubscript{8a} (Scheme 16,
R=H), we found that a combination of 1 mol% L4AuCl/AgOTf (L4=[(4-CF3)C6H4]2P) in nitromethane provided the highest level of activity with 40a being formed in 94% yield. The corresponding (E)-allylsilane resulted in the formation of the same product 40a in 95% yield. The (azido)ynamide bearing a trifluoromethyl group at the para-position to the azido group reacted much less efficiently, and gave the corresponding product 40c in only 60% yield. This is presumably because of decreased nucleophilicity of the azide group. In other cases, the substituent effect on the aryl azide moiety was less significant. It should be noted that this reaction represents the first example of the use of allylsilane as a nucleophilic trapping agent for the capture of a gold-carbenoid species.

Scheme 16. The reaction terminated with allylsilane. *(E)*-allylsilane was used. The catalyst loading was increased to 2 mol%.

We then moved on to investigate the cascade cyclization terminated with cyclopropanation (Scheme 17). As expected, ynamides 38B, which had a phenyl or n-butyl group as one of their alkene substituents, provided the corresponding cyclopropanes 41 in good to excellent yields. These reactions were found to be stereospecific and provided different products depending on the geometry of the alkene. The resulting cyclopropanes 41 easily underwent stereoselective ring-opening reaction at the carbon bearing the R group, upon exposure to EtOH/TsOH, NaN₃/NH₄Cl, or TMSCl. Thus, this cyclopropanation reaction would be useful for stereoselective synthesis of indoloquinoline derivatives bearing oxygen, nitrogen, or halogen functional groups at the α-position of the side chain.

Our preliminary investigations on the cascade reaction using direct arylation are shown in Scheme 18. As expected, the (azido)ynamides 38C bearing an aryl group as the trapping functional group underwent a cascade cyclization reaction to give the azocine- or azepine-fused pentacyclic indoles 42a and 42b, respectively, in moderate yields. Thus, a variety of different carbon–carbon multiple bonds can be used for this reaction, including allylsilanes, simple alkenes and arenes, which will provide a new method for the synthesis of biologically interesting α-carboline and indoloquinoline-type compounds.

Scheme 18. The reaction terminated with direct arylation.

5. Conclusion

As described, gold-catalyzed cascade reactions are useful for the synthesis of various heterocyclic compounds. Notable is that most of the reactions shown in this account are highly atom economical: carbazole synthesis (100%), naphthalene synthesis (100%), pyrazole/indazole synthesis (only H₂O as waste), and indoloquinoline synthesis (only N₂ as waste). Further efforts to develop new types of cascade cyclizations especially using conjugated diynes, as well as synthetic application to biologically–active compounds including alkaloid syntheses are underway in our laboratory.

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References and Notes


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