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Gold-Catalyzed Ring Expansion of Alkynyl Heterocycles through 1,2-Migration of an Endocyclic Carbon–Heteroatom Bond

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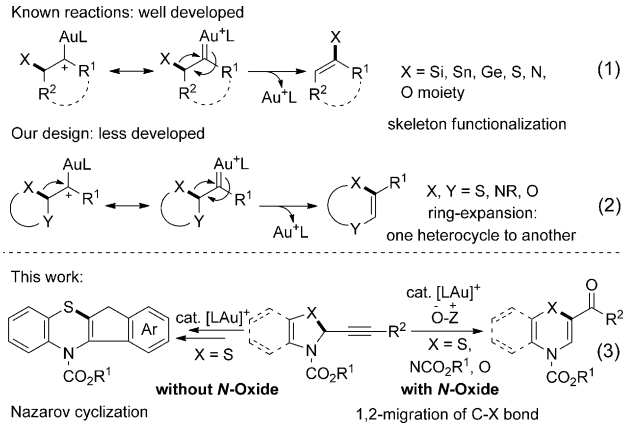
Abstract: A mild and efficient gold-catalyzed oxidative ring-expansion of a series of alkynyl heterocycles using pyridine-*N*-oxide as the oxidant has been developed, which affords highly valuable six- or seven-membered heterocycles with wide functional group toleration. The reaction consists of a regioselective oxidation and a chemoselective migration of an endocyclic carbon–heteroatom bond (favored over C–H migration) with the order of migratory aptitude for carbon–heteroatom bonds being C–S > C–N > C–O. In the absence of an oxidant, polycyclic products are readily constructed through a ring-expansion/Nazarov cyclization reaction sequence.



Scheme 1. Gold-catalyzed 1,2-heteroatom migration reactions.

Transformations that involve 1,2-heteroatom migrations have received considerable attention in recent years, since they are highly attractive for the rapid construction of diversely functionalized structures from easily available starting materials.[1–3] In this regard, gold-catalyzed 1,2-heteroatom migration reactions have been developed with remarkable improvements due to their relatively mild reaction conditions, high efficiencies, and high selectivities. These reactions usually involve metal vinylidene species, carbocations, metal carbenes, or electrophilic metal π-complexes.[2] For example, Fürstner disclosed a 1,2-iodine migration via formation of a metal vinylidene species,[2a,b] and Gevorgyan reported a 1,2-halogen migration via a halirenium intermediate.[2h] Silicon,[2i–l] tin,[2i,j] germanium,[2i,j] sulfur,[2m–o] nitrogen,[2p] and oxygen[2p] groups have been shown by several research groups to undergo 1,2-migration through gold–carbene intermediates. Although much progress has been achieved, most of these transformations proceed by 1,2-migration along an open-chain system or on a ring framework [Scheme 1, Eq. (1)], whereas 1,2-migrations of endocyclic C–heteroatom bonds that lead to ring expansion are quite rare [Scheme 1, Eq. (2)]. To our knowledge, among metal-catalyzed rearrangement reactions, this type of reaction has only been reported for gold-catalyzed 1,2-thio-migration of propargyl dithioacetals.[2n,o] The development of new methodologies for such transformations would be of great interest for producing one heterocycle from another. We recently described a gold-catalyzed oxidative ring expansion of 2-alkynyl-1,2-dihydropyridine and its analogues,[4] which proceeds by exclusive 1,2-migration of a vinyl or phenyl group. Inspired by this result, we envisioned that a 1,2-heteroatom migration from two-heteroatom-bearing alkynyl heterocycles would be desirable. Herein, we report a highly regioselective gold-catalyzed oxidative ring expansion of alkynyl heterocycles through 1,2-migration of endocyclic C–S, C–N, and C–O bonds, with pyridine *N*-oxide as the oxidant.[5] Interestingly, in the absence of *N*-oxide, a polycyclic ring system could be readily constructed by a gold-catalyzed ring-expansion/Nazarov cyclization sequence [Scheme 1, Eq. (3)].

Initially, we focused on the possible ring-expansion reaction of *N*-CO_2Me-protected 2-alkynyl-2,3-dihydrobenzo[*d*]thiazole **1a** in the presence of various gold catalysts with pyridine *N*-oxide as the oxidant (Table 1). To our delight, various commonly used gold catalysts, such as [PPh_3AuNTf_2], [PPh_3AuSbF_6], [PPh_3AuOTf], and [IPrAuNTf$_2$] [IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene], catalyzed the desired transformation efficiently, furnishing **2a** in high yields.[6] The results implied that the reaction proceeds through highly selective migration of the endocyclic C–X bond or heteroatom group; 1,2-S migration occurred preferentially and no 1,2-H or 1,2-N migration took place. The higher migratory aptitude of the thio group over H and N groups might attribute to the facile formation of the thiiranium ion intermediate. We next examined the substrate scope of this oxidative ring expansion to benzothiazines, with 2 mol% [PPh_3AuNTf_2] as the catalyst. 1,2-S migration

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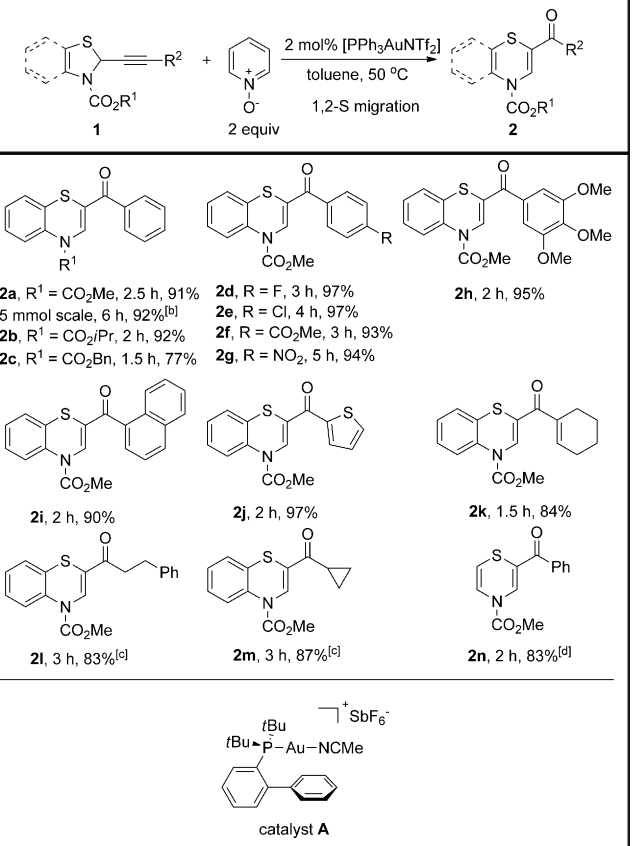
Table 1. Gold-catalyzed synthesis of benzo[*b*][1,4]thiazines.[a]

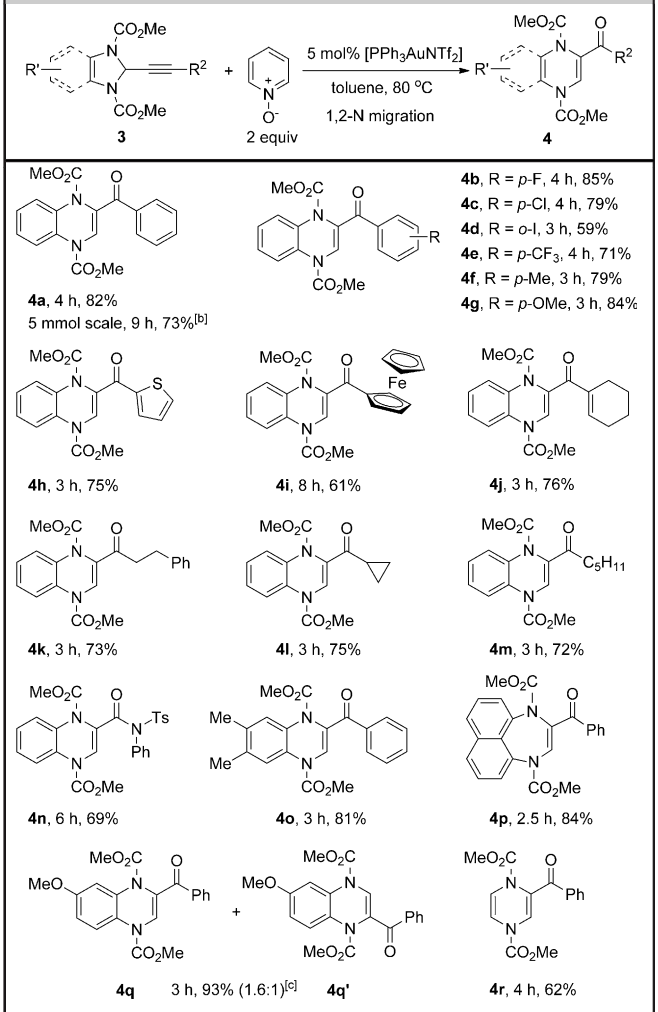


[a] Yields refer to isolated products. [b] 1 mol% $[PPh_3AuNTf_2]$. [c] 5 mol% $[PPh_3AuNTf_2]$, 80 °C. [d] 5 mol% catalyst **A** and 2.0 equivalents of 8-methylquinoline *N*-oxide.

products were obtained exclusively in all cases and isolated in good to excellent yields (Table 1). Besides the *N*-CO_2Me-protected substrates, *N*-CO_2*i*Pr- and *N*-CO_2Bn-protected substrates also underwent the reaction smoothly to give **2b** and **2c** in 92% and 77% yields, respectively. For aryl-substituted alkynes, both electron-deficient (*p*-F, *p*-Cl, *p*-CO_2Me, and even strongly electron-withdrawing *p*-NO_2) and electron-rich aryl alkynes [3,4,5-$(MeO)_3$] were well suited, furnishing the corresponding products **2d**–**h** in 93–97% yields. Substrate possessing a 2-thienyl group was efficiently converted into **2j** in 97% yield. The method also worked well with the substrate bearing an alkenyl group at the alkyne terminus, and the desired **2k** was obtained in 84% yield. In addition, alkyl-substituted alkynes (e.g., phenylethyl, cyclopropyl) were efficiently transformed into benzothiazines **2l** and **2m** in 83% and 87% yields, respectively, at 80 °C. In the case of monocyclic methyl 2-(phenylethynyl)thiazole-3(2*H*)-carboxylate **1n**, no desired ring expansion product was formed under the standard reaction conditions. However, the reaction proceeded smoothly when [JohnPhos(MeCN)$AuSbF_6$] (catalyst **A**) was used as the catalyst in the presence of 8-methylquinoline *N*-oxide as the oxidant, furnishing **2n** in 83% yield. The structures of benzothiazine products were unambiguously confirmed by X-ray crystal analyses of **2h** and **2k**.[7]

Encouraged by the above results, we next attempted to examine the possible 1,2-N migration of 2-alkynyl-2,3-dihydro-1*H*-benzo[*d*]imidazoles **3**. 1,2-N migration reactions are quite rare in gold catalysis. Davies and co-workers recently reported a gold-catalyzed synthesis of indenes accompanied by 1,2-migration of an exocyclic sulfonamide group through C–N bond cleavage of the ynamides.[2p] As expected, the ring expansion of **3** to 1,4-dihydroquinoxaline **4** occurred efficiently, catalyzed by 5 mol% $[PPh_3AuNTf_2]$ at 80 °C, indicating that 1,2-N migration indeed took place during the process (Table 2). A wide

Table 2. Gold-catalyzed synthesis of 1,4-dihydroquinoxalines.[a]

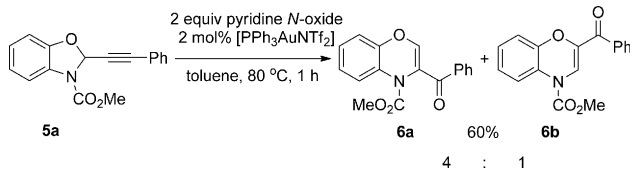


[a] Yields refer to isolated products. [b] 2 mol% $[PPh_3AuNTf_2]$. [c] Major isomer unknown.

range of aryl-, alkenyl-, and alkyl-substituted alkynes underwent the reaction efficiently, leading to 1,4-dihydroquinoxalines **4** in good to high yields within short reaction times. For aryl-substituted alkynes, a wide variety of functional groups on aryl rings were well tolerated. The electronic nature of the aryl ring had little influence on the product yields. Ferrocenyl-substituted **3i** also worked for this reaction, affording **4i** in 61% yield. The reactions with alkenyl- or alkyl-substituted alkynes

were satisfactory, producing the desired products **4j–m** in 72–76% yields. Substrate **3n**, with an ynamide moiety, was also well suited, providing **4n** in 69% yield. In addition, the reaction could be applied to the synthesis of 7-membered diazepine **4p** in 84% yield. When 5-methoxy-substituted benzo[*d*]imidazole **3q** was employed, a mixture of two regioisomers **4q** and **4q′** was formed in a combined yield of 93%, indicating that both NCO_2Me groups migrated during the reaction. Gratifyingly, the monocyclic 2,3-dihydro-1*H*-imidazole **3r** was successfully converted into the 1,4-dihydropyrazine **4r** in 62% yield. It should be noted that substrate **3s**, in which one of the *N*-CO_2Me groups was replaced with an *N*-methyl group, did not react cleanly. These results indicate that the protecting group also plays an important role in this reaction. The practicality of this method was demonstrated by gram-scale synthesis of **2a** and **4a** (see Tables 1 and 2), which were obtained in 92% and 73% yields, respectively.

To better understand the comparative migratory aptitudes of O and NR groups, we next synthesized 2-alkynyl-2,3-dihydrobenzo[*d*]oxazole **5a**. The gold-catalyzed oxidative reaction of **5a** afforded a mixture of ring-expanded products **6a** and **6b** in 4:1 ratio (Scheme 2). The results indicated that both the

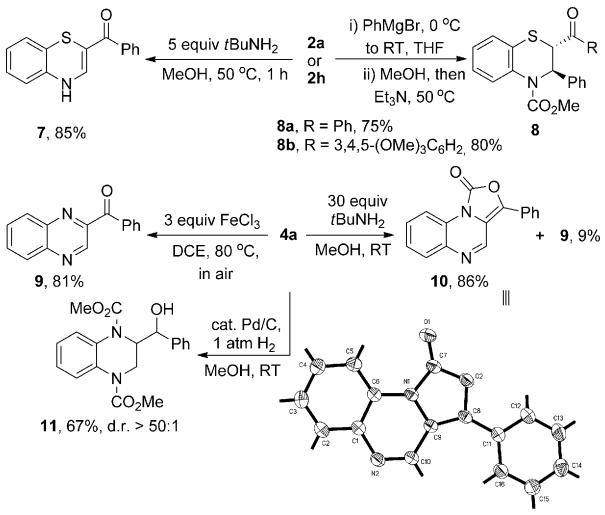


Scheme 2. Gold-catalyzed ring-expansion of 2-alkynyl-2,3-dihydrobenzo-[*d*]oxazole.

O and the NCO_2Me group migrated during the reaction process, and that NCO_2Me has higher migratory aptitude than O. Based on the above results, we summarized that the order of migratory aptitude was C–S > C–N > C–O under the present reaction conditions.

The ketone-functionalized products could be transformed into a variety of valuable building blocks (Scheme 3). For example, **2a** could be deprotected efficiently to give **7**. Michael addition of **2a** or **2h** with Grignard reagent followed by treatment with base afforded *trans*-3,4-dihydro-2*H*-benzo[*b*][1,4]thiazine **8a** or **8b** as a single diastereoisomer.[8] **4a** could be converted into aromatized quinoxaline **9** by treatment with $FeCl_3$. Interestingly, stirring of **4a** in the presence of *t*$BuNH_2$ in MeOH produced fused tricyclic heterocycle **10** in 86% yield. **10** exhibited strong fluorescence in solution, which might be ascribed to its nearly planar structure. In addition, hydrogenation of **4a** provided **11** in 67% yield.

Considering the inherent nucleophilicity of the heteroatom, it may attack the gold-coordinated alkyne directly to trigger a ring-expansion reaction. To investigate this point, the alkynyl S,N-heterocycle **1** was treated with gold-catalyst only to probe the new possibility (Table 3). To our surprise, , catalysis by 5 mol% [PPh_3AuNTf_2] afforded polycyclic product **12**, albeit

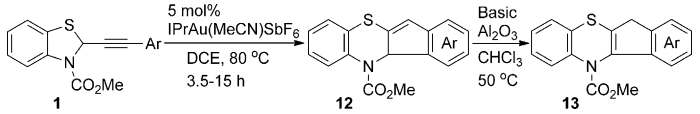


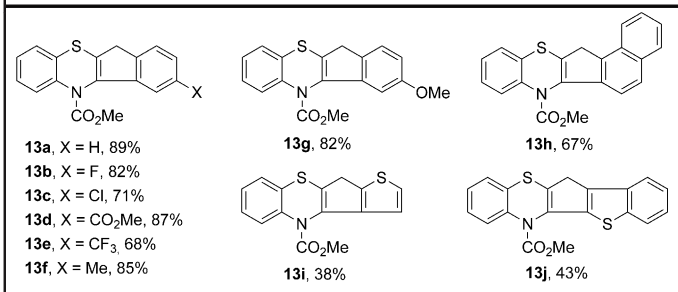
Scheme 3. Transformations of ring-expanded products.

with a low yield of 31% in the case of **12a**. The results implied that a gold–carbene intermediate might be generated during the process. After much effort, we found that the use of 5 mol% [IPrAu(MeCN)SbF_6] under dilute reaction conditions (0.015 M) gave the best results[6] and was applicable to a wide range of substrates. Due to the instability of **12** in most cases, it was further converted into the double-bond-isomerized product **13** in the presence of basic Al_2O_3 (Table 3).[9] This reaction could not be achieved in the cases of substrates **3** and **5**. The reaction showed excellent scope with respect to aryl alkynes and good to high yields were obtained in all cases. Heteroaryl substituents, such as 2-thienyl or 3-benzothienyl, could also be incorporated into the polycyclic products.

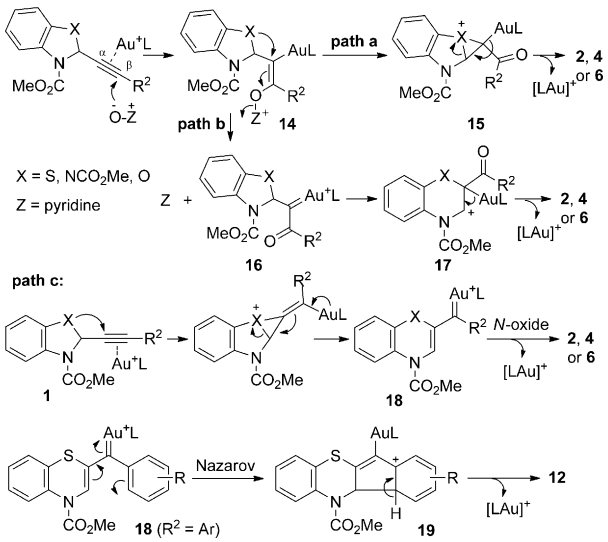
We propose the following reaction mechanism for these ring-expansion reactions (Scheme 4). The reaction is initiated by regioselective attack of the *N*-oxide at the β-carbon of the gold-activated alkyne to afford vinylgold intermediate **14**. The regioselectivity may be caused by the inductive effect of the heteroatom groups,[10] which renders the β-carbon more electrophilic. Nucleophilic attack of heteroatom X on the vinylgold

Table 3. Gold-catalyzed synthesis of polycyclic ring products **13**.[a]



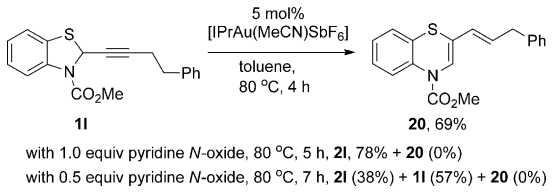


[a] Yields refer to isolated products.



Scheme 4. Proposed reaction mechanism.

moiety in **14** leads to three-membered intermediate **15**, which undergoes ring opening to give the desired products **2**, **4**, and **6** (path a). Alternatively (path b), gold–carbene **16** might be generated through fragmentation; subsequent ring-expansion followed by elimination of the metal furnishes the final products. Path c involves first the formation of gold–carbene intermediate **18**,[2n,o] followed by oxidation. In this oxidative ring expansion, gold–carbene species **16** may not be involved, since if it were generated, an alkene product would possibly be formed through competing and highly favorable 1,2-C–H insertion from the ring side, as indicated in many gold-catalyzed reactions involving alkyl-substituted gold–carbene species.[5e,i,-l, 10a, 11] However, no such product was detected in our case. It is also unlikely to involve the formation of gold–carbene **18** in the course of oxidation. It was reported that, in the presence of *N*-oxide, 1,2-C–H insertion of gold–carbene intermediate with an alkyl substituent was much faster than oxidation.[11] In our reaction system, no alkene products were formed during the oxidation of the alkyl-substituted alkynes, indicating that this reaction pathway is less likely. Moreover, It was found that the gold-catalyzed reaction of **1l** in the absence of *N*-oxide afforded alkene **20**, formed by 1,2-C–H insertion of the gold–carbene intermediate **18** in 69% yield (Scheme 5). When the reaction of alkyl alkyne **1l** was carried out in the presence of less than one equivalent of *N*-oxide as the oxidant, no alkene product **20** was observed (Scheme 5).[12] If the reaction goes through path c, **20** should be formed, since the reactions leading to both the oxidation product **2l** and alkene **20** proceeds through the common intermediate **18**. Furthermore, when alkene **20** was subjected to the reaction conditions given in Scheme 5 in the presence of one equivalent of pyridine *N*-oxide, no oxidation product **2l** was observed. Therefore, it appears that path a is the most favorable pathway. In the absence of an oxidant, Nazarov cyclization of gold–carbene intermediate **18** leads to the fused-ring products **12** (Scheme 4). Our results indicate that the reaction pathway can be altered by adding *N*-oxide.[5e]



Scheme 5. Control experiments.

In summary, we have developed a mild and efficient gold-catalyzed oxidative ring-expansion of a series of alkynyl heterocycles. These unprecedented tandem reactions feature regioselective oxidation and chemoselective migration of an endocyclic C–X bond, favored over that of C–H, with the order of migratory aptitude being C–S > C–N > C–O. In the absence of an oxidant, polycyclic products could be constructed through a ring-expansion/Nazarov cyclization sequence. The current methodology may serve as a new and general protocol for the synthesis of heterocycles from other heterocycles. Further investigations on the detailed reaction mechanism and applications of this chemistry are in progress.

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Keywords: alkynes · gold · heterocycles · homogeneous catalysis · ring expansion

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[6] For details, see the Supporting Information.

[7] CCDC 1048280 (**1h**), 1048282 (**2h**), 1048279 (**2k**), 1048285 (**3a**), 1048281 (**4a**), 1048283 (**8b**), 1048284 (**10**), and 1420754 (**13a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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[11] a) B. Lu, C. Li, L. Zhang, *J. Am. Chem. Soc.* **2010**, *132*, 14070; b) A similar result was also found when diphenylsulfoxide was used as the oxidant, see: C. A. Witham, P. Mauleón, N. D. Shapiro, B. D. Sherry, F. Dean Toste, *J. Am. Chem. Soc.* **2007**, *129*, 5838.

[12] The use of [PPh_3AuNTf_2] as the catalyst afforded similar results. Likewise, treatment of aryl-substituted alkyne **1a** with 5 mol% of [PPh_3AuNTf_2] and 0.5 equivalents of pyridine *N*-oxide in toluene at 80 °C resulted in the formation of **2a** alongside some remnant **1a**, with no Nazarov cyclization product observed. The results also indicate that path c is disfavored. For details, see the Supporting Information.

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