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Gold(I)-Catalyzed Intramolecular Hydroamination and Hydroalkoxylation of Alkynes: Access to Original Heterospirocycles

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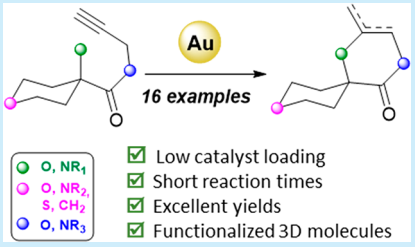
ABSTRACT: We report here a simple and robust gold-catalyzed annulation reaction, giving *N*- and *O*-spirocycles in good to excellent yields. We have prepared a library of protected amines and tertiary alcohols that give, upon cyclization with alkynes, a representative set of heterospirocycles and illustrate reaction compatibility with diverse functional groups. A change in catalytic activity is possible by modifying the solvent, and two original tricyclic spirocycles were synthesized in a tandem reaction.



Spirocycles are characterized by the presence of a fully substituted sp^3 carbon that defines a well-organized 3D orthogonal structure. They are attractive targets in the search for chemical diversity and as an escape from "flatland" in medicinal chemistry.[1−5] Different synthetic methodologies have been developed to generate these scaffolds, but their preparation remains challenging.[6−11] There are several common strategies available to construct the spirocyclic core,[12] and metal catalysis is one important option. The use of organometallic reagents generally avoids aggressive reaction conditions, reduces the risk of side reactions, and can remove certain reaction barriers while maintaining compatibility with most organic functions.

Gold catalysis has been widely used for the construction of carbon−carbon or carbon−heteroatom bonds over the past 15 years.[13−17] The gold-catalyzed activation of alkynes followed by inter- or intramolecular nucleophilic attack leads to a multitude of different chemical structures.[18,19] In particular, gold(I)-catalyzed hydroamination and hydroalkoxylation are both powerful methods for building new heterocycles.[20−22] Gold catalysis has changed the way chemists view reactivity and bond formation, giving access to a greater number of available nucleophilic partners, even those that are traditionally seen as non-nucleophilic.

In general, when a heteroatom is attached to a fully substituted carbon center, its reactivity is limited because of the hindered steric environment. Harsh conditions are often necessary for the heteroatom to engage in further reactions, in particular during ring formation to create a new spirocyclic center. To overcome this problem, we sought to develop a mild and efficient process that would both boost reactivity and promote intramolecular cyclization to form new functionalized heterospirocycles starting from tertiary alcohols and the corresponding protected amines. Although gold catalysis has been effectively used for spiroacetal formation,[23] reports of intramolecular gold-catalyzed ring formation with amines or alcohols attached to a fully substituted carbon center remain scarce when compared with their less hindered counterparts.[24−28] Literature examples are, in most cases, reserved to specific substrates with no further exploration.

As illustrated in Scheme 1 a−c, formal hydroxyalkoxylation or hydroamination reactions with alkynes have been described with both gold(I) and (III) catalysts, but hydration or further oxidation is always observed, either by the capture of the reactive intermediate or as a desired part of the reaction process.[29−31] In our work, the addition of various tertiary alcohols or protected amines to alkynes has been achieved without affecting the oxidation state of the newly formed spirocycle (Scheme 1 d).

We wish to report here the gold-catalyzed intramolecular hydroamination and hydroalkoxylation of alkynes with tertiary alcohols or protected amines to form new spirocycles. Starting from the general structure **I** containing a piperidine, a tetrahydro(thio)pyran ring, or a simple carbocyle, access to dihydro-pyrazinone and -oxazinone spirocycles with the general structure **II** was achieved (Scheme 1 d).

Initial tests were carried out using the commercially available 4-*N*-Boc-amino-1-Cbz-piperidine-4-carboxylic acid functionalized with propargylamine. JohnPhosAu(MeCN)SbF_6 was chosen as the catalyst because acetonitrile is a relatively weak coordinating ligand and is easily displaced, thus avoiding the

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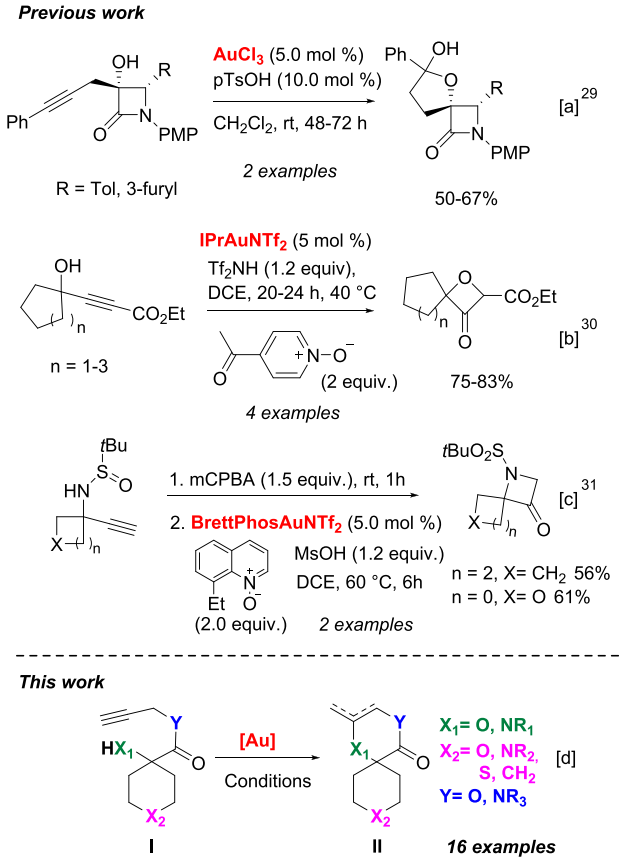
Scheme 1. (a−c) Gold-Catalyzed Heterospirocyclization in the Literature and (d) Our Proposed Methodology



use of silver salts to activate the catalytic species. To our disappointment, heating the secondary amide **1** in the presence of the gold complex gave the oxazoline derivative **2** in good yield (Scheme 2).[32] Using different gold catalysts such as $(Ph_3P)AuCl$ or JohnPhosAuCl gave the same results.

Scheme 2. Oxazoline Formation

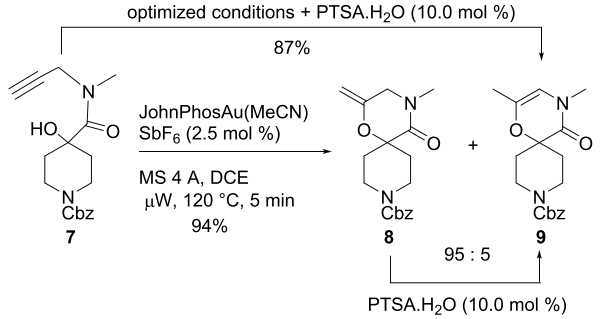
To avoid oxazoline formation due to tautomerization of the secondary amide, the corresponding *N*-methyl amide **3** was prepared. Conventional heating (80 °C) in the presence of 5.0 mol % of JohnPhosAu(MeCN)SbF_6 gave an 81% yield of the endocyclic product **5**. The presence of the exocyclic compound **4** was undetected (Table 1, entry 1). Even though our first reaction was successful, we felt that there was room for improvement, so we set out to optimize various reaction conditions such as the reaction length, catalyst, and loading. (See the SI for catalyst structures.)

A slight increase in yield was obtained by decreasing the reaction temperature to 40 °C (entry 2), but 24 h was necessary for the full conversion of the starting material. Microwave irradiation was then tested to shorten the reaction time, with spectacular results. Only 10 min at 120 °C was necessary to obtain 78% of the desired spirocycle (entry 3). Decreasing the reaction temperature, but for a longer period of time, gave the desired product in 88% yield (entry 4). Decreasing the catalyst loading to 2.5 mol % was possible, with no effect on the reaction efficiency (entry 5). Finally, the best results were obtained with a 2.5 mol % catalyst loading at 120 °C for only 5 min under microwave irradiation (entry 6). Different gold chloride catalysts were then tested, but the substrate conversion was poor in all cases (entries 7−9). In comparison, the presence of the weakly coordinating bis-(trifluoromethanesulfonyl)amide ligand (entry 10) gave the desired product in excellent yield, confirming our results in which highly coordinating anions are poorly reactive (entry 9 vs 10). The nature of the phosphine ligand was then modified (entries 11−13), with no significant difference in reactivity. We thus chose JohnPhosAu(MeCN)SbF_6 as the best catalyst with regard to both cost and availability. The potentially deactivating *tert*-butyloxycarbonyl (Boc) amino protecting group had no effect on the cyclization, and the presence of intermediate **4** was never observed in any of the reactions.

We then applied the optimized conditions to the corresponding oxygenated substrate **7**, made in four steps, and a 58% yield from the commercially available 1-(benzyloxycarbonyl)-4-piperidinone. (See the SI for the detailed synthesis of **7**.)

In this case, the formation of two alkene regioisomers was observed in 94% overall yield as a clean mixture (Scheme 3).

Scheme 3. Spirocyclization with a Tertiary Hydroxyl Group



We were surprised to find that the major reaction product was the exomethylene derivative **8**, as determined by ^1H NMR. The separation of the isomers by column chromatography gave a 74% isolated yield of **8**, with the remaining amount being a mixture of the two compounds. A shorter reaction time (1 or 2 min) was ineffective in suppressing the small amount of isomerized product **9** formed. Moreover, we also found that compound **8** was easily transformed into **9** when treated with *p*-toluenesulfonic acid ($PTSA{\cdot}H_2O$) (10.0 mol %) at rt (total conversion after 5 min). This led us to perform the reaction in the presence of PTSA to provoke double-bond migration *in situ*, giving the endo isomer **9** as the unique product in 87% isolated yield.

To evaluate the observed microwave effect, we subjected compound **7** to our optimized conditions in a sealed tube at 120 °C in a preheated heating block. Conventional heating was less efficient, with only a 78% conversion and a 55% isolated yield.

The crystallization of regioisomer **9** gave us the opportunity to prove its structure by X-ray analysis. The ORTEP

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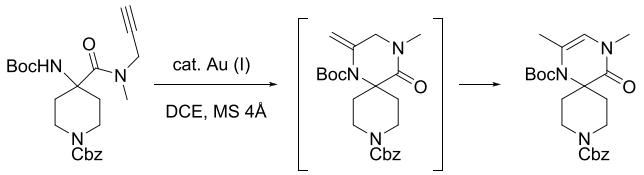
Table 1. Optimization of Au-Catalyzed Cyclization and Catalyst Screening



3 4 5

entry	temp (°C)[a]	time[b]	cat. (mol %)	conv. (%)[c]	yield (%)
1	Δ, 80	16 h	JohnPhosAu (MeCN)SbF_6 (5)	100	81
2	Δ, 40	24 h	JohnPhosAu (MeCN)SbF_6 (5)	100	90
3	120	10	JohnPhosAu (MeCN)SbF_6 (5)	100	78
4	80	20	JohnPhosAu (MeCN)SbF_6 (5)	100	88
5	80	20	JohnPhosAu (MeCN)SbF_6 (2.5)	100	90
6	120	5	JohnPhosAu (MeCN)SbF_6 (2.5)	100	92
7	120	5	$AuCl_3$ (2.5)	21	n.d.[d]
8	120	5	PPh_3AuCl (2.5)	5	n.d.
9	120	5	JohnPhosAuCl (2.5)	64	n.d.
10	120	5	JohnPhosAuNTf_2 (2.5)	100	92
11	120	5	SPhosAu (MeCN)SbF_6 (2.5)	100	90
12	120	5	*t*-BuXPhosAu (MeCN)SbF_6 (2.5)	100	89
13	120	5	*t*-BuBrettPhos Au(MeCN)SbF_6 (2.5)	100	90

[a] μW irradiation unless otherwise indicated. [b] Time in minutes unless otherwise indicated. [c] Determined by ^1H NMR analysis. [d] n.d., not determined.

representation (Figure 1) clearly shows an oxazinone moiety linked by a fully substituted carbon to a piperidine moiety in

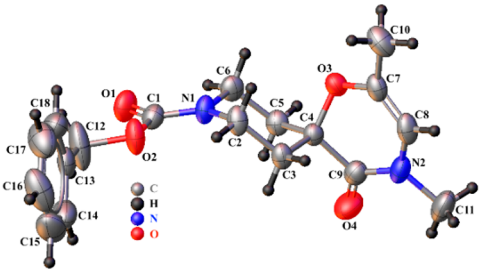


Figure 1. ORTEP representation of compound **9**.

chair conformation with the oxygen atom in the axial position. The oxazinone ring is not planar due to a significant deviation from the mean plane of the C4 and O3 atoms.

With these results in hand, we wished to generalize this quick and efficient gold-catalyzed spirocyclization to other nitrogen- and oxygen-containing substrates of type **I**. (See the SI for the preparation of the starting amides **10**–**22**.) A catalytic amount of PTSA·H_2O was systematically added in the oxygen series to favor double-bond migration and give only one product.

The desired *N*-spirocycles were obtained in good to excellent yields (Figure 2). The use of *N*-Boc protected substrates gave the corresponding endocyclic double bonds in all cases, whereas protection with a *p*-toluenesulfonyl group led to the exclusive formation of an exocyclic double bond (**29**). For this substrate, a reduced reactivity was also observed, as microwave irradiation for 2 h was necessary for a complete conversion with a total of 5% mol JohnPhosAu(MeCN)SbF_6. This lack of reactivity can most likely be explained by the electron-withdrawing nature of the amino protecting group (Tosyl vs Boc). Heterospirocyclization was compatible with the presence of sulfur atoms, although with a substantially longer reaction time of 2.5 h, to give the desired product **25** in

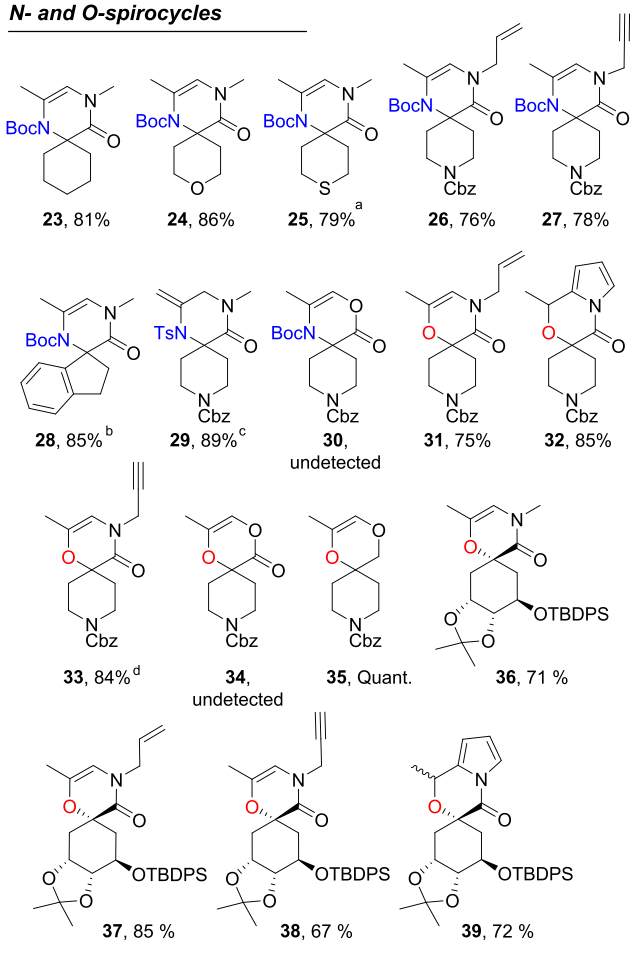


Figure 2. Substrate scope of the heterospirocyclization reaction.

79% yield. A slight decrease in yield was also observed when the starting substrates contained multiple bonds (final compounds **26** and **27**).

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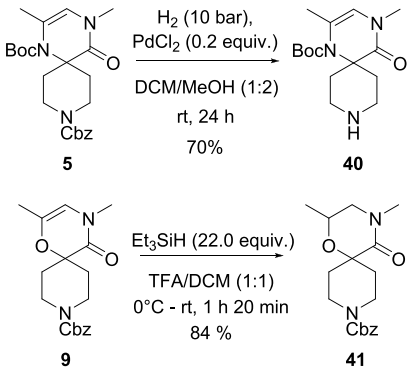
We performed the cyclization with amide **3** on a 1.0 mmol scale using our optimized conditions. For practical purposes, linked to the use of microwave irradiation and the limit imposed by the size of the microreactors, it was carried out at a concentration of 0.08 M. To our satisfaction, the spirocycle **5** was obtained in an excellent 98% yield. In a second larger scale reaction (2.6 mmol), increasing the reaction concentration to 0.26 M was successfully achieved while simultaneously decreasing the catalyst loading to only 1.0 mol %. Once again, we observed no changes in outcome or yield (96%). One real advantage of our process is that microwave irradiation is only 5 min on whatever scale performed for the majority of our substrates. Cyclization is also independent of the reaction concentration, and no intermolecular side reactions occur.

Extending the scope of the reaction in the oxygen series gave the *N*-allyl derivative (**31**) in moderate yield (Figure 2). The use of a dipropargyl-substituted amide led to a unique tricyclic structure, which was obtained in good yield through a double *in situ* cyclization process (**32**). The corresponding endo product (**33**) could be prepared by performing the reaction in DMF, which presumably reduces the catalytic efficiency by complexation of the gold catalyst. One limitation that we found in both series was the absence of cyclization when an ester was present in the starting material (**30** and **34**). Surprisingly, the unreacted esters were fully recovered in both cases. This constraint was lifted with the removal of the carbonyl group and the use of a simple ether, which gave compound **35** quantitatively.

We then decided to apply the spirocyclization reaction to a more complex chiral substrate. Several amide derivatives were prepared from a protected quinic acid derivative in good yields. (See the SI for the preparation of starting compounds.) Cyclization was performed in the presence of a catalytic amount of PTSA·H_2O in all cases to give the corresponding spirocycles **36**–**39**. No racemization of the chiral quaternary stereocenter was observed (^{1}H NMR), and the tricyclic product **39** was obtained as a separable mixture of diastereomers.

Our next steps were devoted to further transforming our molecules through the selective deprotection of the amino groups or double-bond reduction. The hydrogenation of compound **5** in the presence of palladium chloride allowed the removal of the benzyl carbamate in 70% yield, with no observed reduction of the double bond (Scheme 4). Conventional alkene reduction methods (H_2, Pd/C, or Pt) were unsuccessful, with the recovery of the unreacted starting material. Ionic conditions were then tried, and whereas the use of triethylsilane/trifluoroacetic acid failed with compound **5**, it proved to be successful starting from spirocycle **9**.[33] The desired spiromorpholinone **41** was isolated in 84% yield.

Scheme 4. Protecting Group Removal and Double-Bond Reduction



In conclusion, we have developed a spirocyclization reaction based on the intramolecular gold-catalyzed hydroamination and hydroalkoxylation of alkynes. Both tertiary alcohols and protected amines react to form new heterospirocycles in good to excellent yields under microwave irradiation in only a few minutes with low catalyst loading. We have prepared a small library of spirocycles containing dihydro-pyrazinone and -oxazinone cores, with no further oxidation of the final product. Gram quantities were also prepared in a practical and robust manner with an even lower catalyst loading. We have likewise proven the compatibility of the method toward asymmetric centers as well as common protective groups. As an added bonus, a tandem reaction to give unique tricyclic spirocycles (**32** and **39**) was observed, and the catalyst reactivity could be altered using DMF as a coordinating solvent. Further reactions such as isomerization, reduction, and selective deprotection increase the significance of the present work and offer possibilities for the use of these spirocyles as candidates to increase molecular diversity in medicinal chemistry.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02070.

Experimental procedures and ^{1}H NMR and ^{13}C NMR for all compounds (PDF)

Accession Codes

CCDC 2009173 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Author Contributions

[‖]K.E.S. and H.M. contributed equally.

Notes

The authors declare no competing financial interest.

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