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Synthesis of Pyrrolo[1,2-*b*]isoquinolines via Gold(I)-Catalyzed Cyclization/Enyne Cycloisomerization/1,2-Migration Cascade

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Cite This: https://dx.doi.org/10.1021/acs.orglett.0c02310 Read Online

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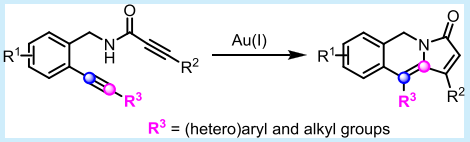
ABSTRACT: A gold(I)-catalyzed cascade transformation of *N*-alkynic 2-ynamides for the rapid and efficient synthesis of the indolizidine scaffold is developed. Through a sequential nucleophilic cyclization/enyne cycloisomerization/1,2-migration process, diverse pyrrolo[1,2-*b*]isoquinolines are obtained under mild conditions in a regiospecific and convergent manner. Various alkyl and aryl migrating groups are tolerated in this process. The electronic effect of the migrating group is comprehensively investigated. The study of the mechanism indicates that the pathway involving a gold carbenoid species is the main pathway and that the 1,2-migration of alkyl and aryl groups to the gold carbenoid occurs in an intramolecular fashion. This cascade reaction is also employed as the key step for the synthesis of a decumbenine B analogue.



Indolizidine and its derivatives represent an important class of nitrogen-containing heterocycles, because they are key structural cores in many pharmacologically active natural products (Figure 1),[1] such as septicine, antofine, tylophorine,

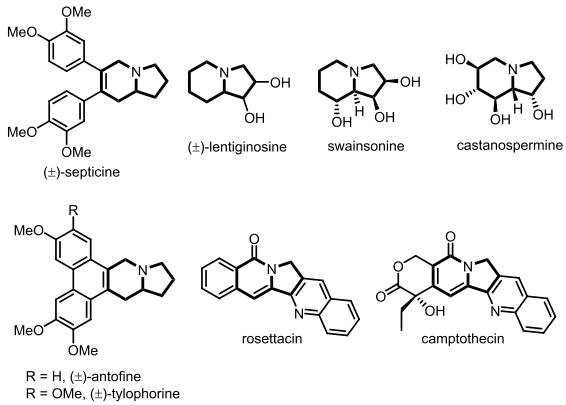


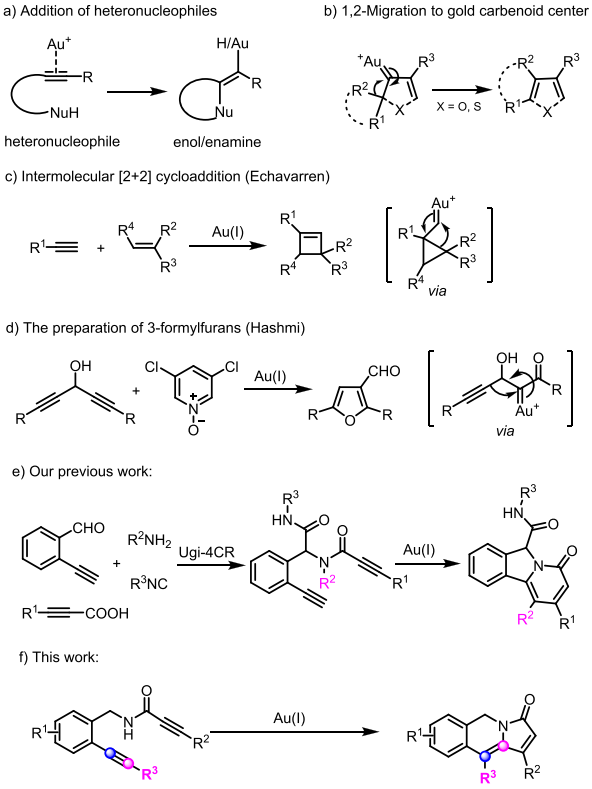
Figure 1. Representative bioactive natural products with an indolizidine scaffold.

camptothecin, rosettacin, lentiginosine, swainsonine, and castanospermine. Conventionally, the route for the construction of the indolizidine scaffold requires lengthy synthetic procedures and harsh conditions.[1] Therefore, the development of rapid, facile, and highly efficient approaches to the indolizidine scaffold is still of great interest.

Recently, gold-catalyzed cascade transformations are emerging as important atom- and step-economical synthetic strategies for the preparation of complex heterocycles,[2] which are not easily synthesized by conventional approaches. Following this principle, through the combination with heteronucleophiles, the gold-catalyzed intramolecular cascade cyclization could be enhanced by the employment of *in situ* generated reactive enol/enamine species (Scheme 1a).[3] In addition, gold-catalyzed annulations involving gold carbene or vinylidene species have received much attention,[4] since these intermediates could undergo various interesting and valuable reactions, such as C−H bond insertion,[5] 1,2-migration, cyclopropanation,[6] cyclization rearrangement,[7] and hydride shift.[8] Among them, the 1,2-migration of alkyl and aryl groups to an adjacent gold carbenoid center serves as an efficient approach for the construction of functionalized carbocycles and heterocycles (Scheme 1b).[9] One example of them was reported by Echavarren in 2010, who developed a gold(I)-catalyzed intermolecular [2 + 2] cycloaddition of terminal alkynes with alkenes for the synthesis of cyclobutenes (Scheme 1c).[9h] Subsequently, Hashmi described an efficient method for the preparation of 3-formylfurans by a gold(I)-catalyzed oxidation/1,2-alkynyl migration/cyclization cascade (Scheme 1d).[9i] However, the incorporation of a 1,2-migration of an alkyl or aryl group in a gold-catalyzed cascade reaction for the synthesis of novel complex polycyclic scaffolds is rare.[10] Recently, we developed a gold-catalyzed annulation of Ugi adducts for the preparation of structurally complex polyheterocycles via a cascade nucleophilic cyclization/intramolecular 1,3-migration/1,5-enyne cycloisomerization process (Scheme 1e).[11a] Within our studies on gold-catalyzed cascade reactions for the construction of complex polycyclic scaffolds,[11] we herein report an unprecedented gold-catalyzed cascade annulation of *N*-alkynic 2-ynamides for the rapid and efficient

Received: July 11, 2020

Scheme 1. Gold(I)-Catalyzed Addition of Heteronucleophiles As Well As 1,2-Migration and This Approach

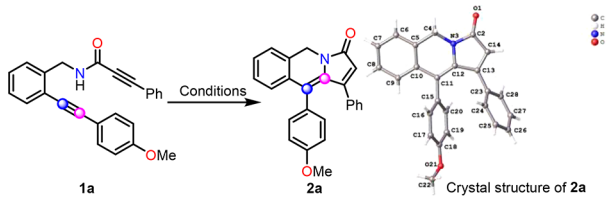


construction of diverse indolizidine scaffolds (Scheme 1f). Through the tandem nucleophilic cyclization/enyne cycloisomerization/1,2-migration sequence, the regiospecific and convergent synthesis of pyrrolo[1,2-*b*]isoquinolines are achieved under mild conditions.

Our studies commenced by examining the gold(I)-catalyzed 1,2-aryl migration of **1a**. Screening of various gold catalysts (Table 1, entries 1−9) revealed that *in situ* generated JohnPhosAuOTf is the most efficient one (entry 5). Employing JohnPhosAuCl with other chloride scavengers such as $AgNTf_2$, $AgSbF_6$, $AgBF_4$, or Ag_2CO_3 assured that $AgNTf_2$ is the best one (entries 10−13). To our delight, the reaction worked well at room temperature delivering product **2a** in 89% yield (entry 14). The structure of **2a** has been confirmed by X-ray diffraction (CCDC 2007683).

After optimization of the reaction conditions, various substrates were subjected to this process to examine the scope and limitations (Scheme 2). We first examined the substituent effect (R^1) of the migrating phenyl group. Both the *ortho* and *meta*-methoxyl phenyl appeared to be a good migrating group, delivering the corresponding products in 81% and 82% yields (**2b** and **2c**). The substrate with a *para*-dimethylamine phenyl showed complete conversion in 3 h delivering the product in 33% yield (**2d**). Other electron-donating groups, such as methyl, *n*-pentyl, and *tert*-butyl in the *para* position of the migrating phenyl group, gave complete conversion in 6 h at rt with moderate to good yields (**2e**−**2i**). However, substrates with an electron-withdrawing group on the migrating phenyl group hardly gave complete conversion at rt. Whe the temperature was increased to 60 °C for 3 h, substrates bearing a *para*-fluoro or a *para*-chlorophenyl group

Table 1. Optimization of the Conditions[a]



Entry	Catalyst	Solvent	T (°C)	Time (h)	Yield of **2a** (%)[b]
1	AuCl	DCE	60	12	0
2	$AuCl_3$	DCE	60	12	0
3	$Ph_3PAuCl/AgOTf$	DCE	60	12	39
4	IPrAuCl/AgOTf	DCE	60	12	71
5	JohnPhosAuCl/AgOTf	DCE	60	12	81
6	$(tBuP)_3AuCl/AgOTf$	DCE	60	12	56
7	**Cat. A**/AgOTf	DCE	60	12	55
8	**Cat. B**/AgOTf	DCE	60	12	52
9	**Cat. C**/AgOTf	DCE	60	12	49
10	JohnPhosAuCl/$AgNTf_2$	DCE	60	12	89
11	JohnPhosAuCl/$AgSbF_6$	DCE	60	12	61
12	JohnPhosAuCl/$AgBF_4$	DCE	60	12	43
13	JohnPhosAuCl/Ag_2CO_3	DCE	60	12	45
14	JohnPhosAuCl/$AgNTf_2$	DCE	rt	3	89

[a]All reactions were run with 0.05 mmol of Ugi adduct **1a**, 5 mol % catalyst, and 1.0 mL of DCE in a sealed flask. [b]Isolated yields **Cat. A**: Chloro[2-di-*tert*-butyl(2′,4′,6′-triisopropylbiphenyl)phophine]gold-(I); **Cat. B**: Chloro[2-(dicyclohexylphosphino)biphenyl]gold(I); **Cat. C**: Chloro[di(1-adamantyl)-2-dimethylaminophenylphosphine]gold-(I).

gave complete conversion with moderate yields (**2j** and **2k**). Notably, a *para*-trifluoromethyl phenyl group also underwent the migration, although delivering the product in a low 39% yield (**2l**).

With a 6′-methoxylnaphtyl migrating group, the reaction smoothly delivered the target product in 85% yield at rt for 3 h (**2m**). The substrate with thiophenyl as the migrating group had to be heated to 60 °C for 3 h, leading to the corresponding product in 68% yield (**2n**). Due to steric effects, the substrate bearing a *tert*-butyl as the migrating group could not deliver the target product even when heated at 100 °C (**2o**). To our delight, when the reaction was performed at 60 °C, both the cyclohexyl (**2p**) and the cyclopropyl (**2q**), having a secondary sp^3 migrating carbon, performed well. Encouraged by these results, we next tried substrate bearing a benzyl as the migrating group. This substrate could give the corresponding product in 43% yield at 60 °C for 3 h (**2r**). We also tried a substrate with a cyclohexmethyl, i.e., a primary sp^3 carbon as the migrating group. Under the same conditions, product **2s** was isolated in 41% yield. We further evaluated the substrate with a terminal alkyne to test whether hydrogen could perform as a migrating group (**2t**). However, we did not obtain the expected product **2t**. Next, the scope of this reaction was further explored using substrates bearing different R^2 substituents. Various alkyl (**2u**−**2w**), aryl (**2y**−**2z**), and heteroaryl (**2x**) groups performed well. Finally, we examined the effect of the benzylamine substituents (R^3 and R^4).

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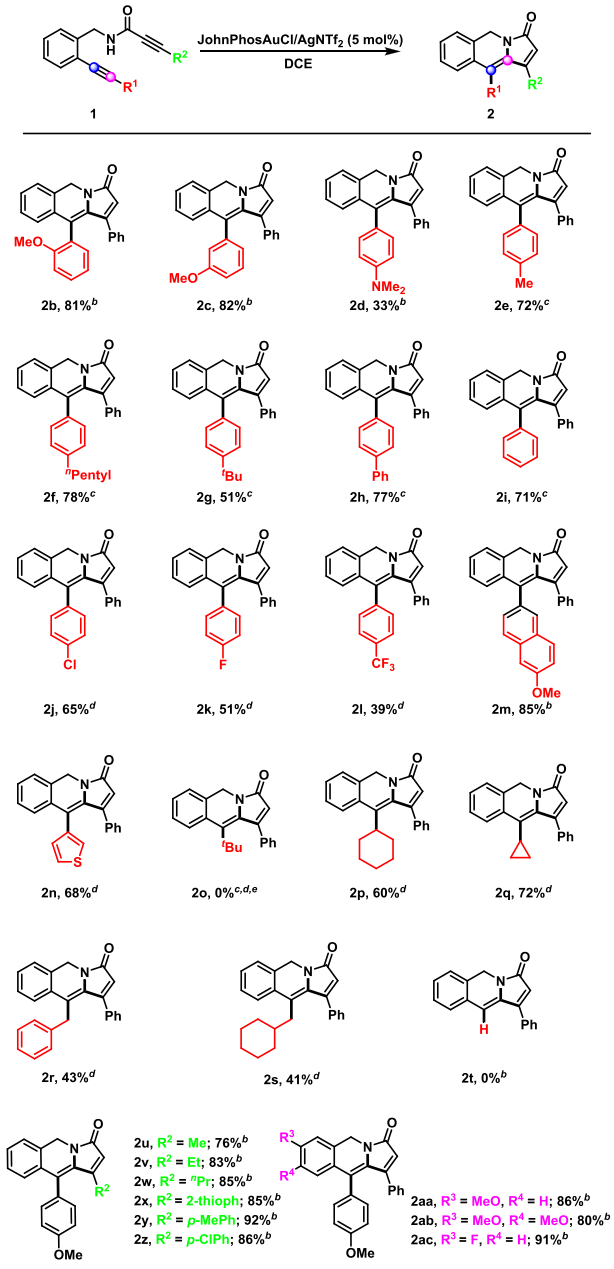
Scheme 2. Reaction Scope[a]

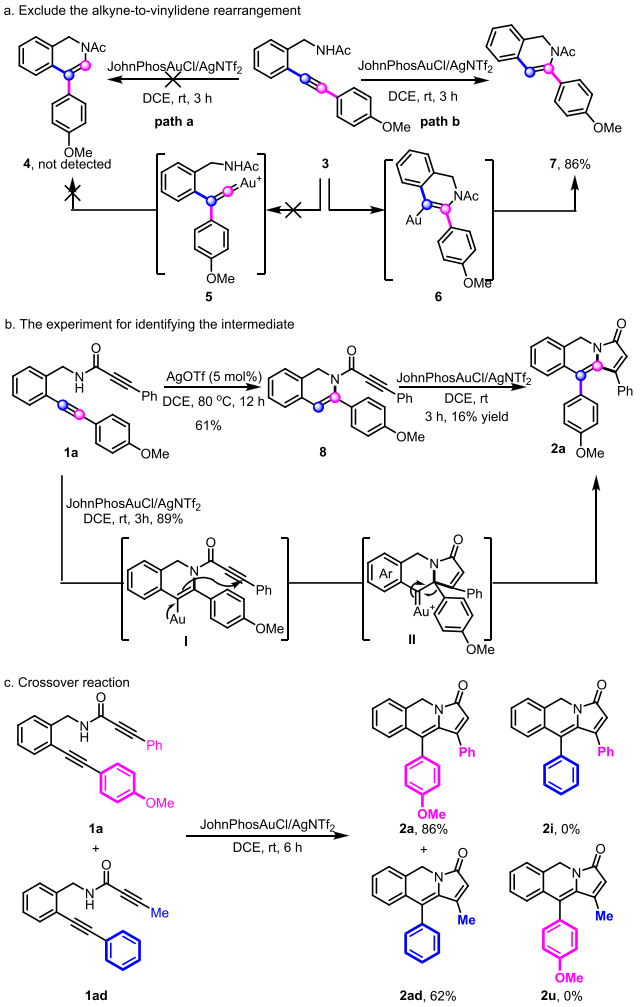


[a]All reactions were run with 0.1 mmol of Ugi adduct **1a**–**1ac**, 5 mol % of JohnPhosAuCl/$AgNTf_2$, and 2.0 mL of DCE in a sealed flask. [b]The reaction was conducted at rt for 3 h. [c]The reaction was conducted at rt for 6 h. [d]The reaction was conducted at 60 °C for 3 h. [e]The reaction was conducted at 100 °C for 3 h.

Substrates with electron-donating (**2aa** and **2ab**) or electron-withdrawing (**2ac**) substituents delivered the desired products in high yield employing the standard conditions.

To investigate the mechanism of this reaction, various control experiments were performed. When compound **3** was used under the standard conditions, product **7** was obtained in 86% yield, whereas no **4** was observed (Scheme 3a). These results suggest that the addition of heteronucleophile to alkyne is the first step, rather than a vinylidene rearrangement.[12] We also employed compound **8** under the standard conditions (Scheme 3b). Only 16% of **2a** was isolated, which indicates that probably two pathways are involved in the formation of **2a**

Scheme 3. Mechanistic Study



[a]The reactions were run on a 0.1 mmol scale with 5 mol % of JohnPhosAuCl/$AgNTf_2$ and 2.0 mL of DCE at rt in a sealed flask. The result was detected with ^{1}H NMR; yields were isolated yields.

from **1a** and that compound **8** is only an intermediate of a minor pathway. Moreover, a crossover reaction was performed using a 1:1 mixture of **1a** and **1ad** under standard conditions (Scheme 3c). The corresponding products **2a** and **2ad** were observed in 86% and 62% yield, respectively. However, crossover products **2i** and **2u** were not detected. This result indicates that the 1,2-migration of an alkyl or aryl group in this cascade process follows an intramolecular approach.

For demonstrating the synthetic utility of this process, we performed the gram scale reaction of **1a** (Scheme 4). The reaction time was extended to 6 h, resulting in the formation of **2a** in a yield of 85%. Cleavage of the amide bond of **2a** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) afforded the α,β-unsaturated ester **9** in 90% yield. Selective reduction of ester **9** delivered the allylic alcohol **10**, which is a decumbenine B analogue.[13]

Based on our observations and previous reports,[5] a plausible mechanism[14] for this gold(I)-catalyzed transformation of *N*-alkynic 2-ynamides is depicted in Scheme 5. Substrate **1** undergoes sequential alkyne coordination and nucleophilic cyclization in a six-*endo*-dig fashion, delivering intermediate **B**. Cycloisomerization of **B** generates the gold carbenoid intermediate **C**. Subsequent 1,2-migration of the alkyl or aryl

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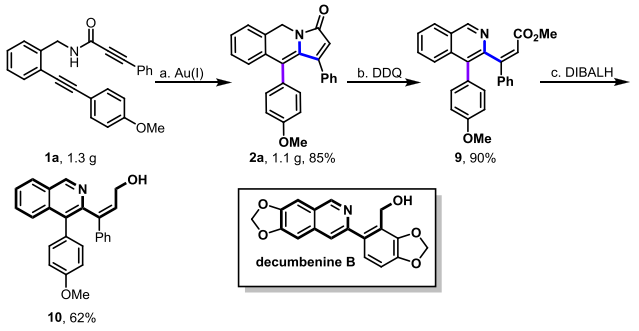
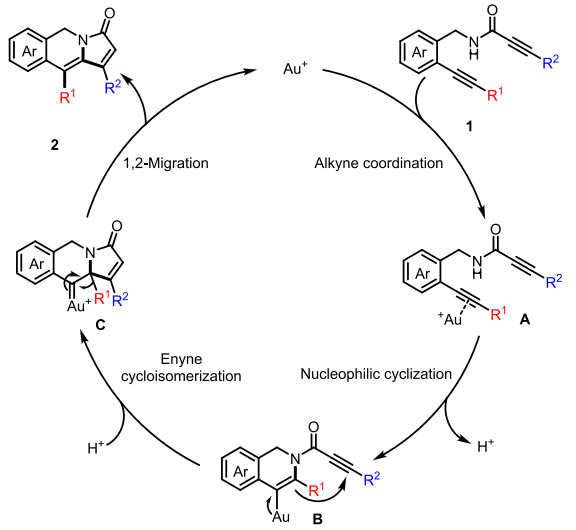
Scheme 4. Gram Scale Reaction and the Transformation of 2a



[a](a) JohnPhosAuCl/$AgNTf_2$, DCE, rt, 6 h. (b) DDQ (1.1 equiv), MeOH, reflux, 2 h. (c) DIBAL-H 1 M in hexane (3.0 equiv), THF, −78 °C to rt, 6 h.

Scheme 5. Proposed Mechanism



group delivers the product **2** and releases the gold(I) catalyst for the next cycle.

In summary, we have successfully developed a gold(I)-catalyzed cascade transformation of *N*-alkynic 2-ynamides for the rapid and efficient synthesis of the indolizidine scaffold in a regiospecific and convergent manner. *Via* a tandem nucleophilic cyclization/enyne cycloisomerization/1,2-migration sequence, various pyrrolo[1,2-*b*]isoquinolines are obtained in moderate to good yields under mild conditions. Various alkyl and aryl migrating groups are compatible in this reaction, such as aryl, heteroaryl, and alkyl groups. The mechanistic study shows that the pathway involving a gold carbenoid species is the main pathway and that the 1,2-migration of alkyl and aryl groups to the gold carbenoid occurs in an intramolecular manner. Moreover, this method could be used as the key step for the synthesis of a decumbenine B analogue.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02310.

Detailed information on experimental procedures, characterization data, and crystallographic and spectroscopic data (PDF)

Accession Codes

CCDC 2007683 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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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Liangliang Song appreciates the Postdoctoral Mandate (PDM) of KU Leuven. The authors are thankful to the F.W.O. [Fund for Scientific Research-Flanders (Belgium)], the Research Fund of the University of Leuven (KU Leuven), and the support of RUDN University Program 5-100 for financial support.

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