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Gold-Catalyzed Multicomponent Synthesis of Aminoindolizines from Aldehydes, Amines, and Alkynes under Solvent-Free Conditions or in Water

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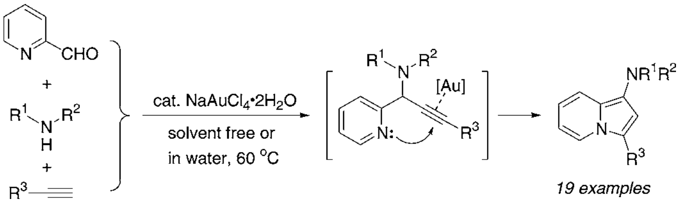
ABSTRACT



A gold(III)-catalyzed multicomponent coupling/cycloisomerization reaction of heteroaryl aldehydes, amines, and alkynes under solvent-free conditions or in water has been developed. This methodology provides rapid access to substituted aminoindolizines with high atom economy and high catalytic efficiency. Especially, the coupling of enantiomerically enriched amino acid derivatives produces the corresponding *N*-indolizine-incorporated amino acid derivatives without loss of enantiomeric purity.

One-pot multicomponent coupling reactions (MCRs) have attracted significant research interest in recent years.[1] Especially, multicomponent reactions with atom economy and the identification of catalytic procedures that can be run under solvent-free conditions or in water are ideal protocols for the development of environmentally friendly and economical advantageous chemical processes.[2] In the past decade, transition-metal-catalyzed C−N bond-forming reactions have become important methods for the preparation of nitrogen-containing heterocycles in both academic and pharmaceutical research areas.[3] Indolizines, which exhibit intriguing molecular structures featured by an *N*-bridgehead bicyclic ring system fused with both a π-excessive pyrrole and a π-deficient pyridine, have received much attention in recent years.[4] Many of the synthetic and natural indolizines have displayed important biological activities which can find a variety of applications in pharmaceutical use.[5] Among various synthetic approaches for indolizines, metal-catalyzed C−N bond-forming methodologies have proved to be versatile in terms of efficiency and of having a wide scope

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(1) For reviews, see (a) Posner, G. H. *Chem. Rev.* **1986**, *86*, 831. (b) Armstrong, R. W.; Combs, A. P.; Tempest, P. A.; Brown, S. D.; Keating, T. A. *Acc. Chem. Res.* **1996**, *29*, 123. (c) Bienaymé, H.; Hulme, C.; Oddon, G.; Schmitt, P.; *Chem.*−*Eur. J.* **2000**, *6*, 3321. (d) *Multicomponent Reactions*; Zhu, J., Bienaymé, H., Eds.; Wiley-VCH: Weinheim, 2005.

(2) For reviews on reactions in water or under solvent-free conditions, see (a) Li, C. J. *Chem. Rev.* **1993**, *93*, 2023. (b) Metzger, J. *Angew. Chem., Int. Ed.* **1998**, *37*, 2975. (c) Tanaka, K.; Toda, F. *Chem. Rev.* **2000**, *100*, 1025. (d) Li, C. J. *Chem. Rev.* **2005**, *105*, 3095. (e) Hobbs, H. R.; Thomas, N. R. *Chem. Rev.* **2007**, *107*, 2786.

(3) For reviews, see (a) Ojima, I. In *Comprehensive Organometallic Chemistry III*; Mingos, D. M., Crabtree, R. H., Eds.; Elsevier: Amsterdam, 2007; Vol. 10, pp 695−724. (b) Tsuji, J. *Palladium Reagents and Catalysis*; John Wiley & Sons: Chichester, 2004. (c) Nakamura, I.; Yamamoto, Y. *Chem. Rev.* **2004**, *104*, 2127. (d) Tsuji, J. *Transition Metal Reagents and Catalyst*; John Wiley & Sons Ltd.: New York, 2000.

(4) For reviews, see (a) The Structure, Reactions, Synthesis, and Uses of Heterocyclic Compounds. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R.; Rees, C. W., Eds.; Pergamon Press: Oxford, 1984; Vols. 1−8. (b) Flitsch, W. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon: Oxford, U.K., 1996; Vol. 8, p 237.

(5) For recent reviews, see (a) Micheal, J. P. *Alkaloids* **2001**, *55*, 91. (b) Micheal, J. P. *Nat. Prod. Rep.* **2002**, *19*, 742.

10.1021/ol701886e CCC: $37.00

of application.[6] These include CuX-mediated cycloisomerization of alkynyl pyridines,[6a−d] Au-catalyzed 1,2-migration/cycloisomerization of propargylic substrates,[6e] and so forth. However, there are few reports concerning multicomponent synthesis of indolizines using transition metals.[7] Recently, we reported a Pd/Cu catalyzed one-pot synthesis of 3-aminoindolizines through the cascade coupling/cycloisomerization reactions of propargyl amines or amides with heteroaryl bromides.[8a] We have also described a Cu-catalyzed cycloisomerization or cyclization/1,2-migration of OAc-substituted propargylic pyridine or its derivatives to indolizines or indolizinones.[8b] During further studies for the construction of functionalized indolizines, we envisioned that 1-aminoindolizines **1** might be formed by metal-catalyzed cyclization of NR^1R^2-substituted propargylic pyridines, which could be accessed *in situ* via three-component coupling of aldehydes, alkynes, and amines by Mannich−Grignard type reactions (Figure 1). Recent works by Li[9] and others[10] have demonstrated that several kinds of metal catalysts could be realized for this type of coupling reaction. In this paper, we report a gold-catalyzed one-step synthetic route to 1,3-disubstituted indolizines under solvent-free conditions or in water, in which a gold catalyst was utilized as a single-pot catalyst to catalyze independent reactions in the same reaction vessel, and there was no need to isolate the intermediate of propargylic pyridines. Furthermore, the coupling of optically pure α-amino acid derivatives with aldehydes and alkynes produces the corresponding indolizines without loss of enantiomeric purity.

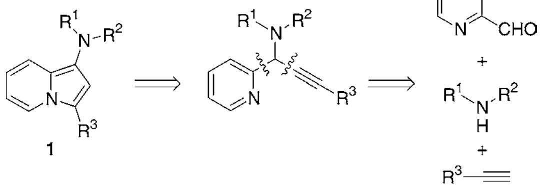
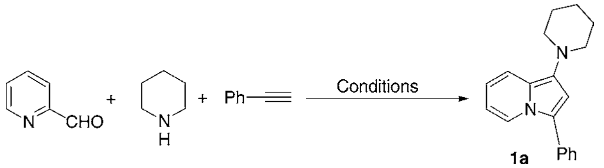


Figure 1. Multicomponent approach to aminoindolizines.

To test the hypothesis, we first examined the coupling reactions of pyridine-2-carboxaldehyde, piperidine, and phenylacetylene in the presence of various metal catalysts (Table 1). We found that, in the presence of 1 mol % $NaAuCl_4\cdot 2H_2O$, this three-component coupling/cycloisomerization reaction proceeded smoothly in water to afford the desired 3-phenyl-1-(piperidin-1-yl)indolizine **1a** in 85% yield after 3 h at 60 °C (Table 1, entry 3). $AuCl_3$[11] also showed good catalytic activity in water to afford 86% of **1a** (Table 1, entry 4). However, AuCl was found to be less effective and only 20% of **1a** was obtained (Table 1, entry 5). Interestingly, 95% of **1a** was achieved using 1 mol % $NaAuCl_4\cdot 2H_2O$ under solvent-free conditions at 60 °C within 1.5 h (Table 1, entry 7). In addition, the reactions could be performed at room temperature; however, a longer reaction time was required and lower product yields were observed (Table 1, entries 2 and 8). On the other hand, the use of copper catalysts could not give good results under the current conditions (Table 1, entries 9−11).

Table 1. Opitimization Studies for the Metal-Catalyzed Three-Component Coupling Reactions



entry	catalyst	solvent	temp/time	yield (%)[a,b]
1	2 mol % $NaAuCl_4\cdot 2H_2O$	H_2O	60 °C, 3 h	80
2	2 mol % $NaAuCl_4\cdot 2H_2O$	H_2O	rt, 5 days	38
3	1 mol % $NaAuCl_4\cdot 2H_2O$	H_2O	60 °C, 3 h	85[c]
4	2 mol % $AuCl_3$	H_2O	60 °C, 3 h	86
5	2 mol % AuCl	H_2O	60 °C, 12 h	20
6	2 mol % $NaAuCl_4\cdot 2H_2O$	–[d]	60 °C, 1.5 h	93[c]
7	1 mol % $NaAuCl_4\cdot 2H_2O$	–[d]	60 °C, 1.5 h	95[c]
8	1 mol % $NaAuCl_4\cdot 2H_2O$	–[d]	rt, 72 h	86[c]
9	5 mol % CuBr	H_2O	60 °C, 1.5 h	–[e]
10	5 mol % CuBr	–[d]	60 °C, 12 h	7[c]
11	10 mol % $Cu(OTf)_2$	H_2O	60 °C, 1.5 h	–[e]

[a] Pyridine-2-carboxaldehyde (1.0 mmol), piperidine (1.1 mmol), and phenylacetylene (1.5 mmol) were used. [b] Isolated yields based on aldehyde. [c] Phenylacetylene (1.2 mmol) was used. [d] Solvent-free. [e] Complicated reaction mixture was observed.

As illustrated in Table 2, this multicomponent process can be readily diversified through combinations of a range of heteroaryl aldehydes, amines, and alkynes. With respect to amines, cyclic amines afforded moderate to excellent yields of indolizines (Table 2, entries 1−6 and 12). For example, pyrrolidine and morpholine led to 1,3-disubstituted indoliz-

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(6) (a) Kel'in, A. V.; Sromek, A. W.; Gevorgyan, V. *J. Am. Chem. Soc.* **2001**, *123*, 2074. (b) Kim, J. T.; Gevorgyan, V. *Org. Lett.* **2002**, *4*, 4697. (c) Kim, J. T.; Butt, J.; Gevorgyan, V. *J. Org. Chem.* **2004**, *69*, 5638. (d) Kim, J. T.; Gevorgyan, V. *J. Org. Chem.* **2005**, *70*, 2054. (e) Seregin, I. V.; Gevorgyan, V. *J. Am. Chem. Soc.* **2006**, *128*, 12050. (f) Smith, C. R.; Bunnelle, E. M.; Rhodes, A. J.; Sarpong, R. *Org. Lett.* **2007**, *9*, 1169.

(7) (a) Ohsawa, A.; Abe, Y.; Igeta, H. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 3273. (b) For a coupling/1,3-dipolar cycloaddition sequence to indolizines, see Rotaru, A. V.; Druta, I. D.; Oeser, T.; Müller, T. J. J. *Helv. Chim. Acta* **2005**, *88*, 1798.

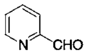
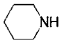
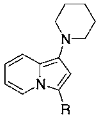
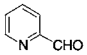
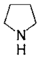
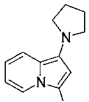
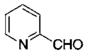
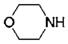
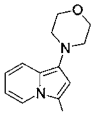
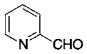
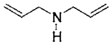
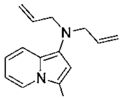
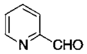
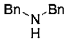
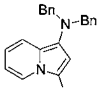
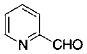
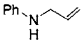
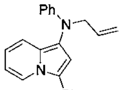
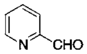
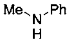
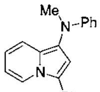
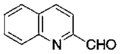
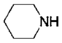
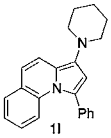
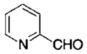
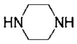
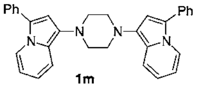
(8) (a) Liu, Y. H.; Song, Z. Q.; Yan, B. *Org. Lett.* **2007**, *9*, 409. (b) Yan, B.; Zhou, Y. B.; Zhang, H.; Chen, J. J.; Liu, Y, H. *J. Org. Chem.*, published online Aug 25, http://dx.doi.org/10.1021/jo070983j.

(9) (a) Li, C. J.; Wei, C. M. *Chem. Commun.* **2002**, 268. (b) Wei, C. M.; Li, C. J. *J. Am. Chem. Soc.* **2002**, *124*, 5638. (c) Wei, C. M.; Li, C. J. *J. Am. Chem. Soc.* **2003**, *125*, 9584. (d) Wei, C. M.; Li, Z. G.; Li, C. J. *Org. Lett.* **2003**, *5*, 4473. (e) Huang, B. S.; Yao, X. Q.; Li, C. J. *Adv. Synth. Catal.* **2006**, *348*, 1528.

(10) (a) Gommermann, N.; Koradin, C.; Polbom, K.; Knochel, P.; *Angew. Chem., Int. Ed.* **2003**, *42*, 5763. (b) Lo, V. K.; Liu, Y. G.; Wong, M. K.; Che, C. M. *Org. Lett.* **2006**, *8*, 1529. (c) Kantam, M. L.; Prakash, B. V.; Reddy, C. R. V.; Sreedhar, B. *Synlett* **2005**, 2329. (d) Shi, L.; Tu, Y. Q.; Wang, M.; Zhang, F. M.; Fan, C. A. *Org. Lett.* **2004**, *6*, 1001. (e) Choudary, B. M.; Sridhar, Ch.; Kantam, M. L.; Sreedhar, B. *Tetrahedron Lett.* **2004**, *45*, 7319.

(11) For $AuCl_3$ catalyzed coupling of aldehydes, amines, and alkynes to propargylamines, see ref 9c.

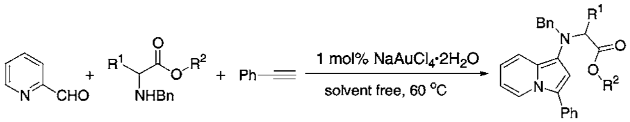
Table 2. Gold-Catalyzed Three-Component Coupling Reactions to Aminoindolizines

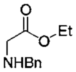
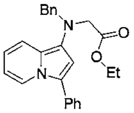
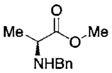
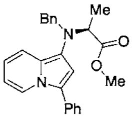
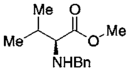
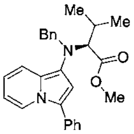
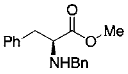
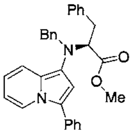
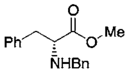
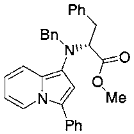
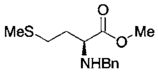
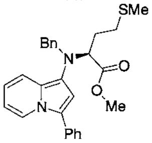
entry	ArCHO	amine	alkyne	product	yield(%)[a,b,c]
			R—≡		
1			R = p-ClC$_6$H$_4$	**1b**	88
2			R = p-MeOC$_6$H$_4$	**1c**	95 (8 h, 64)
3			R = C_6H_{13}	**1d**	66
4			R = CH_2CH_2OH	**1e**	54
5			Ph—≡	 **1f**	68 (7 h, 40)
6			Ph—≡	 **1g**	96 (1 h, 71)
7			Ph—≡	 **1h**	91 (2 h, 87)
8			Ph—≡	 **1i**	98 (45 min, 88)
9			Ph—≡	 **1j**	31
10			Ph—≡	 **1k**	28 (3.5 h, 30)
11			Ph—≡	 **1l**	74 (2 h, 92)
12			Ph—≡	 **1m**	52 (3 h, 65)[d]

[a] Unless noted, all the reactions were carried out at 60 °C for 1−4 h using aldehyde (1.0 mmol), amine (1.1 mmol), alkyne (1.2 mmol), and 1 mol % $NaAuCl_4 \cdot 2H_2O$ under solvent-free conditions. [b] Isolated yields based on aldehyde. [c] The results of the same reaction (reaction time and yields) carried out in water are listed in the parentheses. [d] 0.55 equiv of piperazine was used.

ines **1f** and **1g** in 68% and 96% yields, respectively (Table 2, entries 5 and 6). Diallylamine and dibenzylamine also gave products **1h** and **1i** in excellent yields (91% for **1h** and 98% for **1i**). However, the yields were low with allylphenylamine and methylphenylamine (Table 2, entries 9 and 10). It should be noted that while the current catalyst is quite effective for some secondary amines, however, the substrates of primary amines such as $PhNH_2$ could not be used for this reaction. In this case, only a complicated reaction mixture was observed. Aryl alkynes, whenever with electron-deficient or electron-donating groups, displayed high reactivities (Table 2, entries 1 and 2). Alkyl alkynes such as 1-octyne or functionalized alkyne could also be successfully incorporated into the indolizine products (Table 2, entries 3 and 4). Employing 2-quinolinecarboxaldehyde proceeded well to generate benz[*e*]indolizine **1l** in 74% yield (Table 2, entry 11). The use of piperazine as an amine afforded bridged indolizine **1m** in 52% yield (Table 2, entry 12). We also investigated the same reactions in water (the results are listed in parentheses). These reactions revealed that the current three-component reactions also occurred smoothly in water at 60 °C; however, in most cases, the yields were lower than those obtained under solvent-free conditions.

Table 3. Au-Catalyzed Coupling Reactions of Pyridine-2-Carboxaldehyde, Amino Acid Derivatives, and Alkyne under Solvent-Free Conditions



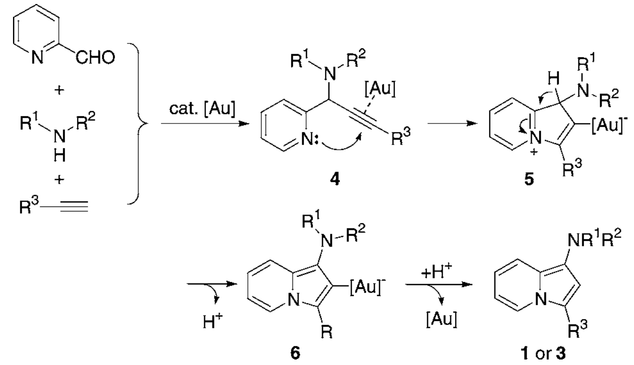
entry	amino acid derivatives[a]	time	product		yield(%)[b,c]	ee (%)[d]
1	 **2a**	1.5 h		**3a**	86[e]	–
2	 **2b**	6 h		**3b**	85	>99
3	 **2c**	5 h		**3c**	85	>99
4	 **2d**	6 h		**3d**	78[f]	>99[g]
5	 **2e**	6 h		**3e**	72	>99[g]
6	 **2f**	12 h		**3f**	52	>99[g,h]

[a] All of the chiral substrates are >99% ee as determined by chiral-column HPLC. [b] Unless noted, all the reactions were carried out at 60 °C using aldehyde (1.0 mmol), amine (1.1 mmol), alkyne (1.2 mmol), and 1 mol % $NaAuCl_4 \cdot 2H_2O$. [c] Isolated yields based on aldehyde. [d] Determined by chiral-column HPLC. [e] 70% of **3a** was obtained under the conditions in water for 1.5 h. [f] 43% of **3d** was obtained under the conditions in water for 25 h. [g] 1.0 mmol amine was used. [h] 5 mol % $NaAuCl_4 \cdot 2H_2O$ was used.

Arylation of complex amines, especially optically pure amines, has drawn much attention in recent years.[12] α-Amino acids are useful building blocks in organic synthesis, and chiral *N*-aryl-α-amino acids are common core structures for a number of synthetically challenging and medicinally important agents.[13] The above methodology may provide a new class of *N*-indolizine-incorporated α-amino acid derivatives with high enantiomeric purity, which may find potential utilities in pharmacological areas. We then applied the Au-catalyzed protocol to the coupling of amino acid derivatives with 2-pyridyl aldehyde and alkynes. First, we checked the reaction of *N*-benzyl-glycine ethyl ester **2a** under solvent-free conditions. It was found that the desired indolizine **3a** was rapidly formed in 86% yield at 60 °C for 1.5 h (Table 3, entry 1). The use of *N*-benzyl-L-alanine methyl ester **2b** resulted in the formation of **3b** in 85% yield without any racemization, as determined by chiral-column HPLC analysis (Table 3, entry 2). The coupling reactions were also tested with other common amino acid derivatives (Table 3, entries 3−6). In all cases, the products were found to be >99% enantiometric excess (ee) with a yield range from 52 to 85%. Thus, we could conclude that the present conditions were mild enough to avoid the racemization of either the starting materials or the products. In addition, the functionalities of esters and thioethers were well tolerated during the reactions. The reactions could also be performed in water to generate the corresponding products **3a** and **3d** in 70% and 43% yields, respectively, as depicted in Table 3 (footnotes *e* and *f*).

We propose the following mechanism for the formation of aminoindolizines, which is analogous to Cu-catalyzed cycloisomerization of OAc-substituted propargylic pyridines (Scheme 1).[8b] First, a gold-catalyzed three-component coupling of pyridine-2-carboxaldehyde, amine, and alkyne occurred to afford NR^1R^2-substituted propargylic pyridine **4** via a Mannich−Grignard reaction.[9c] Coordination of the triple bond in alkyne **4** to the gold catalyst enhances the electrophilicity of the alkyne, and the subsequent nucleophilic attack of the nitrogen lone pair would produce the cation **5**, which undergoes deprotonation followed by demetalation to afford indolizines.

Scheme 1



In summary, we have developed a Au-catalyzed multicomponent coupling/cycloisomerization reaction of heteroaryl aldehydes, amines, and alkynes under solvent-free conditions or in water. This methodology provides rapid access to substituted aminoindolizines with high atom economy and high catalytic efficiency. Especially, the coupling of enantiomerically enriched amino acid derivatives produces the corresponding *N*-indolizine-incorporated amino acid derivatives without loss of enantiomeric purity. Further studies to extend the scope and synthetic utility for this Au-catalyzed cascade reaction and the employment of amino acid derivatives as amine substrates for the multicomponent reactions are in progress in our laboratory.

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Supporting Information Available: Experimental details and spectroscopic characterization of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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