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Gold(I)-Catalyzed One-Pot Tandem Coupling/Cyclization: An Efficient Synthesis of Pyrrolo-/Pyrido[2,1-*b*]benzo[*d*][1,3]oxazin-1-ones

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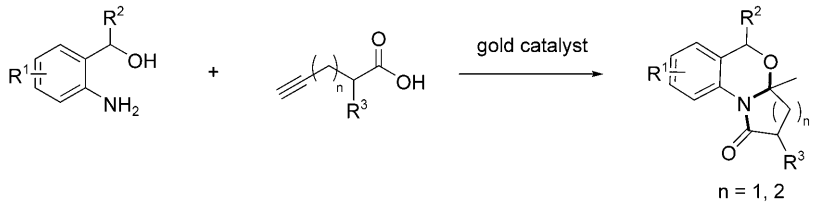
Abstract: A highly efficient method has been developed for the one-pot synthesis of multi-ring heterocyclic compounds such as pyrrolo-/pyrido[2,1-*b*]benzo[*d*][1,3]oxazin-1-ones from *o*-aminobenzyl alcohols *via* a gold(I)-catalyzed tandem coupling/cyclization reaction. Significantly, the strategy presents a straightforward and efficient approach to construct novel tricyclic or polycyclic molecular architectures in which two new C–N bonds and one C–O bond are formed in a one-pot reaction operation from two simple starting materials. Moreover, a broad spectrum of substrates can participate in the process effectively to produce the desired products in good yields.

Keywords: alkynes; gold; pyrrolo-/pyrido[2,1-*b*]benzo[*d*][1,3]oxazin-1-ones; tandem reactions

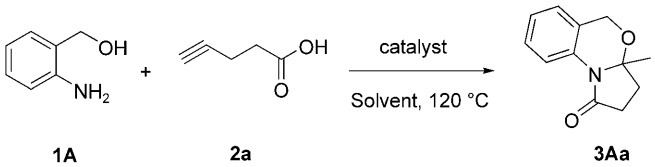
Owing to the prevalence of polycyclic heterocyclic compounds in medicinal chemistry and the fact that they are considered to be "privileged structures" in the pharmaceutical and agrochemical industries, the development of new and effective transition metal-catalyzed reactions for the synthesis of fused heterocycles is being actively researched for the purpose of obtaining novel bioactive lead compounds.[1] One of the most effective ways for forming such fused ring systems is to develop remarkably powerful domino reactions that enable multiple bond-forming and bond-cleavage events to occur in one synthetic operation.[2] Recently, gold-catalyzed tandem reactions have attracted considerable attention because of their ability to activate alkyne, alkene, and allene functionalities under mild conditions and at low catalyst loadings.[3] In spite of impressive progress, several significant limitations remain to be addressed, e.g., the vast majority of the reported cascade sequences employed an intramolecular reaction with a single starting material containing multiple functional groups strategically positioned along a chain, terminating with an alkyne functionality.[2a,4] Construction of complex fused heterocyclic multi-ring architectures *via* an intermolecular union of simple starting materials through a one-pot operation still represents significant synthetic challenges. To the best of our knowledge, there is no report on the cascade synthesis of pyrrolo-/pyrido[2,1-*b*]benzo[*d*][1,3] oxazin-1-ones from *o*-aminobenzyl alcohols and 4-pentynoic acid/5-hexynoic acid *via* a gold-catalyzed, one-pot domino process. In our ongoing efforts to develop new convenient and efficient approaches to the synthesis of potentially useful heterocyclic compounds with transition metal catalysts,[5] we herein report an efficient gold-catalyzed, one-pot tandem reaction protocol for the synthesis of highly substituted pyrrolo-/pyrido[2,1-*b*]benzo[*d*][1,3]oxazin-1-ones (Scheme 1).

Initially, we investigated the effectiveness of various gold catalysts and the optimum reaction conditions using *o*-aminophenylmethanol (**1A**) and 4-pentynoic acid (**2a**) as model substrates in a sealed tube. The results of these experiments are shown in Table 1, different gold catalysts such as $AuBr_3$, AuI, $AuCl(PPh_3)$, [Au{P(*t*-Bu)$_2$(*o*-biphenyl)}]Cl (Au^1 catalyst), [Au{P(*t*-Bu)$_2$(*o*-biphenyl)}{CH_3CN}]SbF_6 (Au^2 catalyst) and [Au{1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene}]Cl (Au^3 catalyst) were probed at 120 °C in THF. Among the catalysts tested, the Au^2 catalyst was



Scheme 1. Synthesis of pyrrolo-/pyrido[2,1-*b*]benzo[*d*][1,3]oxazin-1-ones.

Table 1. Optimization of the reaction conditions of tandem synthesis of **3Aa**.[a]



1A **2a** **3Aa**

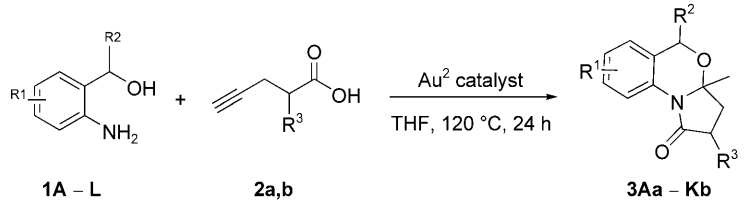
Entry	Catalyst system[b]	Solvent	Yield [%]
1	$AuBr_3$	THF	25[c]
2	AuI	THF	18[c]
3	$AuCl(PPh_3)$	THF	62[c]
4	Au^1 catalyst	THF	64[c]
5	Au^2 catalyst	THF	85[c]
6	Au^3 catalyst	THF	70[c]
7	**Au^2 catalyst**	**THF**	**91** (89[d])
8	–	THF	0
9	Au^2 catalyst/$AgSbF_6$	THF	45
10	Au^2 catalyst/$AgBF_4$	THF	50
11	Au^2 catalyst/TFA	THF	61
12	Au^2 catalyst/TsOH	THF	20
13	Au^2 catalyst	THF	72[e] (85[f])
14	Au^2 catalyst	THF	62[g] (88[h])
15	Au^2 catalyst	CH_2Cl_2	84
16	**Au^2 catalyst**	**Toluene**	**88**
17	Au^2 catalyst	Dioxane	34
18	Au^2 catalyst	CH_3CN	37
19	Au^2 catalyst	CH_3OH	40
20	Au^2 catalyst	H_2O	50
21	Au^2 catalyst	THF	90[i]
22	Au^2 catalyst	THF	58[j]

[a] **1A** (0.1 mmol), **2a** (0.25 mmol), Au catalyst (2 mol%), Ar protection.
[b] Au^1 catalyst = [Au{P(*t*-Bu)$_2$(*o*-biphenyl)}]Cl; Au^2 catalyst = [Au{P(*t*-Bu)$_2$(*o*-biphenyl)}{CH_3CN}]SbF_6; Au^3 catalyst = [Au{1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene}]Cl.
[c] Reaction performed in the presence of 5 mol% Au^2 catalyst.
[d] Reaction performed in the presence of 1 mol% Au^2 catalyst.
[e] The reaction time was prolonged to 48 h.
[f] The reaction time was shortened to 12 h.
[g] The reaction temperature was below 100 °C.
[h] The reaction temperature was 140 °C.
[i] Reaction performed without Ar protection.
[j] Reaction performed under M.W. irradiation.

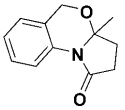
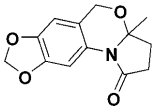
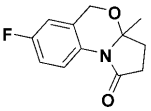
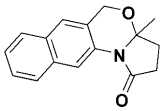
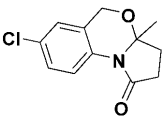
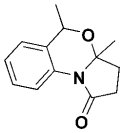
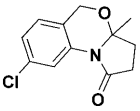
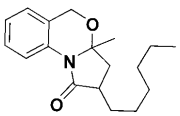
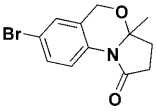
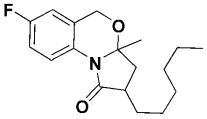
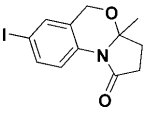
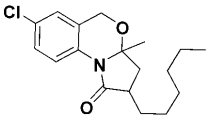
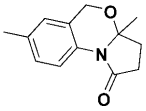
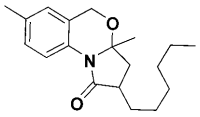
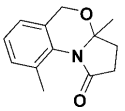
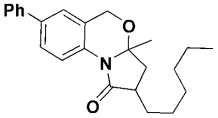
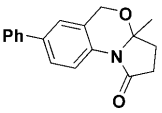
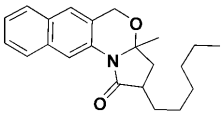
found to be the most effective (Table 1, entries 1–6). Meanwhile, the amount of Au^2 catalyst was also optimized. When the amount of catalyst was reduced to 2 mol%, it was found that a better yield was obtained. However, treatment with 1 mol% of the catalyst resulted in a slightly decreased yield relative to the treatment with 2 mol% of the catalyst (Table 1, entry 7). In addition, no desirable product was formed in the absence of the Au catalyst (Table 1, entry 8). Some Brønsted acids and protonic acids are usually used as a co-catalyst for gold catalysts. $AgSbF_6$, $AgBF_4$, TFA and TsOH were thus investigated as a co-catalyst, respectively, but no good results were obtained (Table 1, entries 9–12). The reaction time is an important factor for this reaction, the yield decreased considerably when the reaction time was prolonged to 48 h. A shorter reaction time (12 h) also led to a decrease in the yield of target compound **3Aa** (Table 1, entry 13). Besides, the reaction temperature was also found to be an important factor for this tandem transformation; for example, compound **3Aa** was obtained in 62% yield when the reaction temperature was reduced to below 100 °C. When the reaction temperature was increased to 140 °C the yield decreased (Table 1, entry 14). Subsequently, we screened different solvents, and the results showed that THF was the most effective solvent for this transformation (Table 1, entries 7 and 15–20). However, toluene also appears to be an effective reaction solvent (Table 1, entry16). Without Ar protection, the yield of **3Aa** was not affected drastically (Table 1, entry 21). Although this transformation was also performed under microwave irradiation, no improved yield was observed (Table 1, entry 22). Briefly, the optimum results were obtained when *o*-aminophenylmethanol (0.1 mmol, **1A**) and 4-pentynoic acid (0.25 mmol, **2a**) in THF were treated with 2 mol% of Au^2 catalyst in a sealed tube under Ar protection at 120 °C for 24 h.

To evaluate the scope of the proposed gold-catalyzed reaction, we attempted to investigate the cascade cyclization reaction by probing changes in both the substituted *o*-aminobenzyl alcohols and the alkynoic acids under the above-mentioned optimum reaction conditions (Table 2, entries 1–18). We found that a variety of substituted *o*-aminobenzyl alcohols participated in the process to afford products **3Aa**–**3Kb** with moderate to excellent yields (53–98%). The posi-

Table 2. One-pot tandem synthesis of **3** from 2-aminobenzyl alcohols in THF.[a]



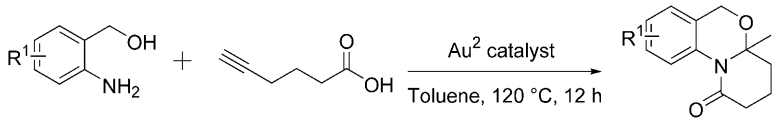
1A – L **2a,b** **3Aa – Kb**

Entry	Product		Yield [%]	Entry	Product		Yield [%]
1		**3Aa**	91	10		**3Ja**	69
2		**3Ba**	98	11		**3Ka**	96[c]
3		**3Ca**	86	12		**3La**	65 (5:1 *dr*)
4		**3Da**	53	13		**3Ab**	82 (1:1.1 *dr*)
5		**3Ea**	74	14		**3Bb**	97 (1:1.3 *dr*)
6		**3Fa**	61	15		**3Cb**	93 (1:1.2 *dr*)
7		**3Ga**	95	16		**3Gb**	95 (1:1.4 *dr*)
8		**3Ha**	57 (82[b])	17		**3Ib**	88 (1:1 *dr*)
9		**3Ia**	86	18		**3Kb**	94 (1.3:1 *dr*)

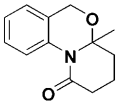
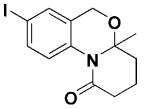
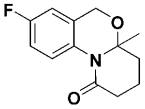
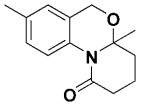
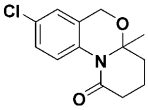
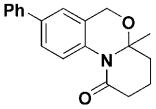
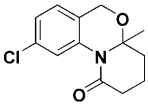
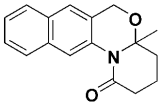
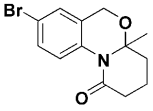
[a] **1A** (0.1 mmol), **2a** (0.25 mmol), Au^2 catalyst (2 mol%), THF (2–3 mL), Ar protection.
[b] Reaction performed in 2 mL of toluene.
[c] The reaction time was prolonged to 36 h.

tion and type of substituent on the *o*-aminobenzyl alcohols were found to be important impact factors for the yields of the target compounds (Table 2, entries 1–10). High yields were obtained when the 7-position of the *o*-aminobenzyl alcohol was substituted by F, Cl, Br, CH_3, or the phenyl group (Table 2, entries 2, 3, 5, 7 and 9) or when there was no substituent at the 7-position (Table 2, entry 1), respectively. Introduction of Cl and CH_3 at the 8- and 9-positions of *o*-aminobenzyl alcohol resulted in a drastic decrease in the yield of the product, respectively (Table 2, entries 4 and 8). However, treatment of 9-methyl-substituted *o*-aminobenzyl alcohol with 4-pentynoic acid in toluene afforded a good yield (Table 2, entry 8). (3-Aminonaphthalen-2-yl)methanol formed by the annelation of *o*-aminobenzyl alcohol was tolerated in the

Table 3. Gold-catalyzed one-pot synthesis of a broad spectrum of fused heterocycles **3**.[a]



1A – K **2c** **3Ac – Kc**

Entry	Product		Yield [%]	Entry	Product		Yield [%]
1		**3Ac**	73	6		**3Fc**	58
2		**3Bc**	77	7		**3Gc**	76
3		**3Cc**	66	8		**3Ic**	63
4		**3Dc**	60	9		**3Kc**	78
5		**3Ec**	65				

[a] **1A** (0.1 mmol), **2a** (0.25 mmol), Au^2 catalyst (2 mol%), toluene (2–3 mL), Ar protection.

reaction, but the reaction required a longer time (36 h) for full conversion (Table 2, entry 11). When sterically hindered groups were introduced adjacent to the hydroxy group of the *o*-aminobenzyl alcohol, the cyclization cascade was also successful and good yields were obtained (Table 2, entry 12). Furthermore, substitution of an alkyl group (*n*-hexyl group) into the alkynoic acid chain was also tolerated and excellent yields were observed (Table 2, entries 13–18).

Further experiments under the optimized reaction conditions demonstrated that the proposed reaction could be extended to generate pyrido[2,1-*b*]benzo[*d*]-[1,3]-oxazin-1-ones by the treatment of *o*-aminobenzyl alcohols with 5-hexynoic acid. Although good yields were observed in the above-mentioned experimental examples under the optimum conditions, we did not obtain the same good results when *o*-aminobenzyl alcohols were treated with 5-hexynoic acid in THF under the same catalyst conditions (data not shown). However, when this cascade cyclization reaction was performed in toluene with the same gold catalyst, good results were obtained. As shown in Table 3, *o*-aminobenzyl alcohols with substituents exhibiting steric and electronic properties are tolerated in the cascade reactions, and good yields were obtained (Table 3, entries 1–9). Therefore, this synthetic strategy is an alternative approach to the synthesis of novel polycyclic molecular architectures that could be potential 'privileged structures' in the pharmaceutical and agrochemical industries. The product **3Ea** was recrystallized from a solvent mixture of petroleum ether and ethyl acetate and was characterized with crystallography (Figure 1, see the Supporting Information for details).[6]

On the basis of our previous knowledge and the results of our present study, we propose a plausible mechanism for the construction of polycyclic hetero-

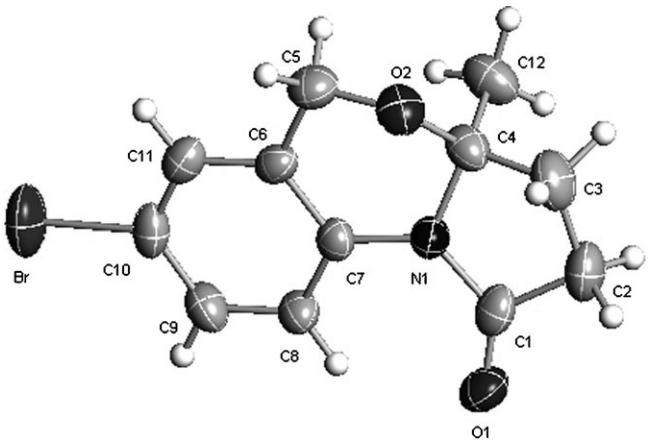
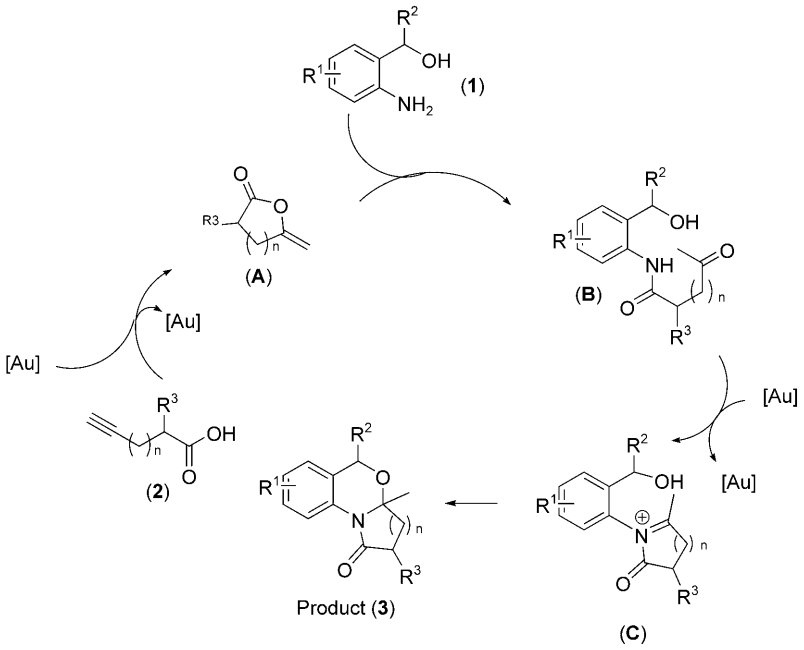


Figure 1. X-ray crystallographic structure of **3Ea**.



Scheme 2. A plausible mechanism.

cyclic frameworks. As shown in Scheme 2, alkynoic acids were first activated by gold(I) catalyst to generate cyclic activated enol lactone intermediates **A**,[7] which were then attacked by an amino group of the *o*-aminobenzyl alcohols **1** to form ammonolysis products. The resulting keto amide **B** underwent gold-catalyzed *N*-acyliminium ion formation/cyclization and was converted into the transition state **C**. Finally, nucleophilic attack by the hydroxy group yielded the final product **3**.[8]

In summary, we have developed an efficient method for one-pot synthesis of multi-ring heterocyclic compounds such as pyrrolo-/pyrido[2,1-*b*]benzo-[*d*][1,3]oxazin-1-ones from *o*-aminobenzyl alcohols *via* a gold(I)-catalyzed tandem coupling/cyclization reaction. This reaction is atom economic and has high functional group tolerance. Significantly, the strategy presents a straightforward and efficient approach to construct novel tricyclic molecular architectures in which several carbon-nitrogen and carbon-oxygen bonds are formed in a one-pot reaction operation from two simple starting materials. We expect that these potential "privileged structures" will find wide applications in related medicinal chemistry. Further, one-pot reaction cascade sequences catalyzed by single and/or multiple catalytic entities are under investigation and the results will be reported in due course.

Experimental Section

General Procedure for Synthesis of 3Aa (Table 2, entry 1)

To a solution of 4-pentynoic acid (1.25 mmol) in dry THF (3 mL) was added the Au^2 catalyst (2 mol%). After stirring for 10 min at room temperature under Ar protection, *o*-aminobenzyl alcohol (0.5 mmol) was added. Subsequently, the reaction vial was sealed under Ar protection and the mixture was heated to 120 °C for 24 h. Then, the cold mixture was concentrated under vacuum, the resulting residue was purified by flash column chromatography (petroleum ether/ethyl acetate = 4/1) to afford the expected tricyclic heterocyclic product **3Aa**.

The characterization data obtained for **3Aa** are as follows: ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 8.29$ (d, $J = 8.1$ Hz, 1H), 7.29 (d, $J = 7.5$ Hz, 1H), 7.11 (m, 1H), 7.05 (d, $J = 6.9$ Hz, 1H), 5.03 (d, $J = 15.2$ Hz, 1H), 4.86 (d, $J = 15.3$ Hz, 1H), 2.60 (m, 2H), 2.23 (m, 2H), 1.43 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 171.3$, 132.8, 127.5, 124.1, 124.0, 123.0, 120.4, 90.0, 62.8, 33.0, 30.2, 21.2; LR-MS (EI): $m/z = 203$ (M^+); HR-MS (EI): $m/z = 203.0946$, calcd. for $C_{12}H_{13}NO_2$ (M^+): 203.0946.

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[6] CCDC 755261 contains the supplementary crystallographic data for **3Ea**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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[8] To further explore the proposed mechanism, we have treated one of commercially available intermediates A (*alpha-angelica lactone*) from Scheme 2 with *o*-aminobenzyl alcohol under the above optimal reaction conditions, and the desired product **3Aa** was obtained in 90% yield. ***Synthetic procedure:*** To a solution of alpha-angelica lactone (1.25 mmol) in dry THF (3 mL) were added Au^2 catalyst (2 mol%), and *o*-aminobenzyl alcohol (0.5 mmol) was added. Subsequently, the reaction vial was sealed under Ar protection and the mixture was heated to 120 °C for 24 h. The cold mixture was concentrated under vacuum, and the resulting residue was purified by flash column chromatography (petroleum ether/ethyl acetate = 4/1) to afford the expected product **3Aa**.

