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Gold-Catalyzed Unexpected Ring Transformation of Pyrimidodiazepine Derivatives

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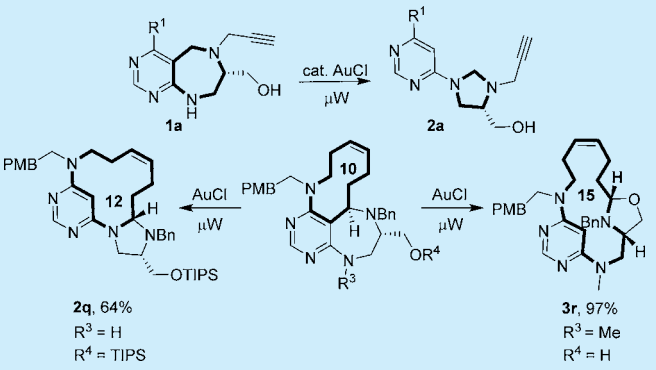
Supporting Information

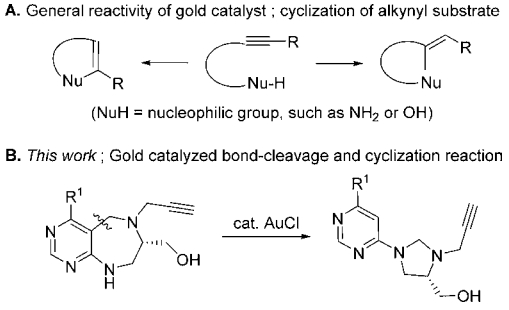
ABSTRACT: Pyrimidodiazepine derivatives underwent an unexpected gold-catalyzed retro-Mannich-type carbon−carbon bond cleavage and intramolecular nucleophilic cyclization. The pyrimidodiazepines bearing an alkyne moiety showed novel orthogonal reactivity in the presence of a gold catalyst, as opposed to the alkynophilicity that is commonly observed with gold catalysts. The ring transformation reaction of pyrimidodiazepines probably proceeds through an acyclic iminium intermediate. The potential of this synthetic method for the skeletal diversification of pyrimidine-containing macrocycles was also demonstrated.



The chemical and biological properties of privileged heterocycles are of continued interest because of the existence of these moieties in many bioactive natural products and FDA-approved pharmaceutical drugs.[1] Among them, pyrimidine has been extensively utilized in pharmaceutics as a key structural motif owing to its ability to mimic the structures and properties of nucleosides.[2] Pyrimidine and its derivatives exhibit diverse biological activities, including antibacterial,[3] antifungal,[4] antiviral,[5] and anticancer[6] properties.

Recently, we reported the synthesis of pyrimidine-containing polyheterocycles via the recombination of a pyrimidine ring with various heterocycles to expand molecular diversity using the privileged substructure-based diversity-oriented synthesis (pDOS) strategy.[7,8] We also showed that privileged structures serve as "chemical navigators" to efficiently access the bioactive chemical space.[8−10] Indeed, skeletal diversity has evolved as a key element in the design strategy for the construction of druglike small molecule libraries,[11] and there is a high demand for developing efficient methods to increase skeletal diversity. Thus, we have been pursuing new intramolecular transformations of pyrimidine-embedded polyheterocycles using transition-metal catalysts. In fact, transition-metal catalysis provides an efficient way to induce remarkable changes within molecular frameworks in a single step.[12] In particular, gold-catalyzed reactions have attracted much interest in organic synthesis because of the unique ability of gold catalysts to activate unsaturated carbon−carbon bonds so that they can react with various nucleophiles.[13] Gold catalysts have been widely used as selective alkynophiles for inter- and intramolecular nucleophilic reactions under mild conditions with excellent functional group tolerance to afford various heterocyclic products (Scheme 1A).[14]

Scheme 1. Unexpected Discovery of a Novel Gold-Catalyzed Reaction



As part of our continuing interest in the diversification of pyrimidine-embedded molecular frameworks, herein we report a novel synthetic method using a gold catalyst; this involves a retro-Mannich-type C−C bond cleavage in pyrimidodiazepines followed by intramolecular cyclization. The unique reactivity of the gold catalyst is mainly discussed. Under the AuCl-catalyzed microwave reaction conditions, the pyrimidodiazepine moiety can be transformed into imidazolidines, oxazinanes, and oxazolidines depending on the location and type of intramolecular nucleophiles through an iminium intermediate (Scheme 1B). This gold-catalyzed ring transformation can be used for the skeletal diversification of one pyrimidine-containing macrocycle to another in a single step at a late stage of synthesis. Moreover, this gold-catalyzed C−C bond cleavage occurs in preference to alkynophilic activation. To the best of our

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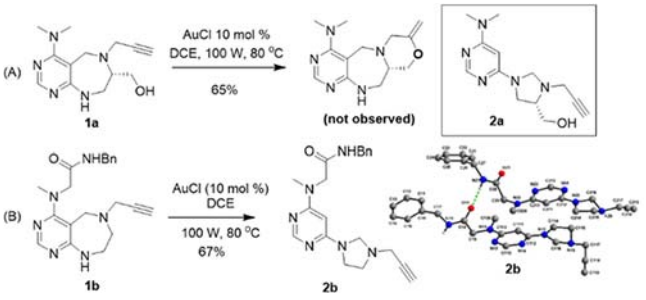
knowledge, no gold-catalyzed methodology with orthogonal reactivity of substrates in the presence of an terminal acetylene moiety has been reported.

We recently focused on the diversification of pyrimidodiazepine using the pDOS strategy[7,8] to construct various polyheterocyclic scaffolds for molecular diversity to systematically explore the protein−protein[8] and protein−DNA/RNA interactions.[9] During this exploration, we designed and synthesized substrate **1a** bearing a terminal acetylene group which can be activated by a gold catalyst; subsequent cyclization via the intramolecular nucleophilic attack of primary alcohol group would afford a fused morpholine moiety. However, we failed to obtain the fused morpholine moiety under typical gold-catalyzed reaction conditions using microwave irradiation (Scheme 2A). Instead, the terminal acetylene moiety was

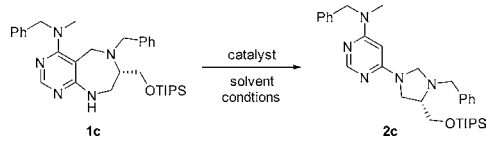
Scheme 2. Initial Discovery of a Novel Gold-Catalyzed Reaction



found to be intact by ^{1}H and ^{13}C NMR spectroscopy. Surprisingly, this unexpected product **2a** was a ring-contracted heterocycle containing an imidazolidine moiety, formed by gold-catalyzed C−C bond cleavage and subsequent intramolecular nucleophilic cyclization of the anilinic nitrogen. To confirm this transformation, we designed and tested **1b** containing a terminal acetylene group as substrate **1a** and no primary alcohol nucleophile. As shown in Scheme 2B, the imidazolidine-containing product **2b** was obtained with the terminal acetylene moiety intact, as determined by ^{1}H NMR spectroscopy. The exact structure of **2b** was confirmed by X-ray crystallography (see the Supporting Information).

Intrigued by this unexpected result, we attempted to optimize the gold-catalyzed transformation under various conditions (Table 1). The feasibility of this process was investigated using substrate **1c** without the terminal acetylene moiety and various coinage metal catalysts and conditions. First, **1c** was thermally activated in the presence of various gold and silver catalysts (entries 1−5). Among the tested coinage metal catalysts, AuCl showed the efficient transformation of **1c** to **2c**, but this thermal reaction was quite slow (23 h, entry 1). Although the reaction rate of $AuCl_3$ was faster than that of other catalysts, the reaction was not clean (entry 2). In the case of microwave-assisted activation, the reaction time was effectively reduced,[15] but the yield was also significantly decreased (entry 6). To solve this problem, different solvents were screened; the desired product **2c** was obtained in an excellent yield within a short reaction time when acetonitrile was used (entry 10). Model substrate **1c** contains two potential nucleophiles, anilinic nitrogen and TIPS-protected alcohol. To investigate the priority of two competing nucleophiles, the following experiment were performed by changing the reaction sequence (see Scheme S9). Based on this

Table 1. Optimization of Reaction Conditions[a]



entry	catalyst	conditions[b]	s.m. (%)[c]	product (%)[c]
1	AuCl	DCE, 80 °C, 23 h	-	96
2	$AuCl_3$	DCE, 80 °C, 2 h	-	83
3	$Au(PPh_3)OTf$	DCE, 80 °C, 20 h	95	-
4	$AgSbF_6$	DCE, 80 °C, 20 h	65	21
5	AgOTf	DCE, 80 °C, 20 h	87	-
6[d]	AuCl	DCE, 80 °C, 100 W, 30 min	82	14
7[d]	AuCl	$CHCl_3$, 80 °C, 100 W, 30 min	89	10
8[d]	AuCl	DMF, 80 °C, 100 W, 30 min	55	47
9[d]	AuCl	THF, 80 °C, 100 W, 30 min	96	-
10[d]	AuCl	ACN, 80 °C, 100 W, 30 min	-	95

[a]Reaction conditions: SM, catalyst (10 mol %), solvent (0.1 M). [b]DCE: 1,2-dichloroethane. DMF: dimethylformamide. THF: tetrahydrofuran. ACN: acetonitrile. [c]Yields determined by the ^{1}H NMR analysis of crude products using an internal standard (1,3,5-tri-MeO-C_6H_3). [d]Microwave conditions.

result, we confirmed that anilinic nitrogen has a higher priority over the alcoholic nucleophile when both are available.[19]

With the optimized conditions in hand, we performed a series of reactions to investigate the substrate scope of this gold-catalyzed ring transformation. As shown in Table 2, alkylamines and cyclic amines at the R^1 position were well tolerated, providing imidazolidine products in good-to-excellent yields. Diverse substituents on the secondary amine at the R^2 position were also tolerated, including alkynyl (**1a**, **1b**, and **1d**), allyl (**1e**), and benzyl (**1c**, **1g**, **1i**, and **1k**−**o**) as well as unmodified secondary amines (**1f**, **1h**, and **1j**). The ester moiety (**1h**) at the C-7 position and the silyl ether moiety (**1c**−**g** and **1i**−**k**) at the C-7 and C-8 positions of the pyrimidodiazepine provided the corresponding products in good yields. However, tosyl or carbonyl substituents at the R^2 position failed to provide the desired products, probably because of the electron-withdrawing nature of the substituents at the R^2 position for this reaction (data not shown). Next, the ability of alcohol nucleophile to form different types of heterocycles (Table 2, **1l**−**o**) was investigated. The primary alcohol substituents at the C-7 or C-8 position in the gold-catalyzed transformation of pyrimidodiazepine afforded either 1,3-oxazinanes (**3l** and **3m**) or oxazolidines (**4n** and **4o**), respectively. To decrease the nucleophilicity of aniline, electron-donating alkyl substituents as well as electron-withdrawing carbonyl substituents were introduced at the R^3 position. Notably, different reactive nucleophiles in pyrimidodiazepine **1** result in the diverse ring transformations, generating different heterocycles from the same skeleton.

Using the synthetic method for the pyrimidodiazepine core skeleton (see Scheme S6), various R^4 substituents were introduced at the C-5 position at the stage of the formation of iminium intermediate, generated by *N*-alkylation of **SI-4**, using Grignard reagents. The diastereomeric outcome of the alkyl substituents in **1p**−**s** varied due to the chiral environment generated by the TIPS-containing substituent at the C-7 position of the iminium intermediate.[8] As shown in Table 3, the diastereomeric ratio of the starting materials (**1p**−**s**) was influenced by the size of R^2 substituent at the N-6 position

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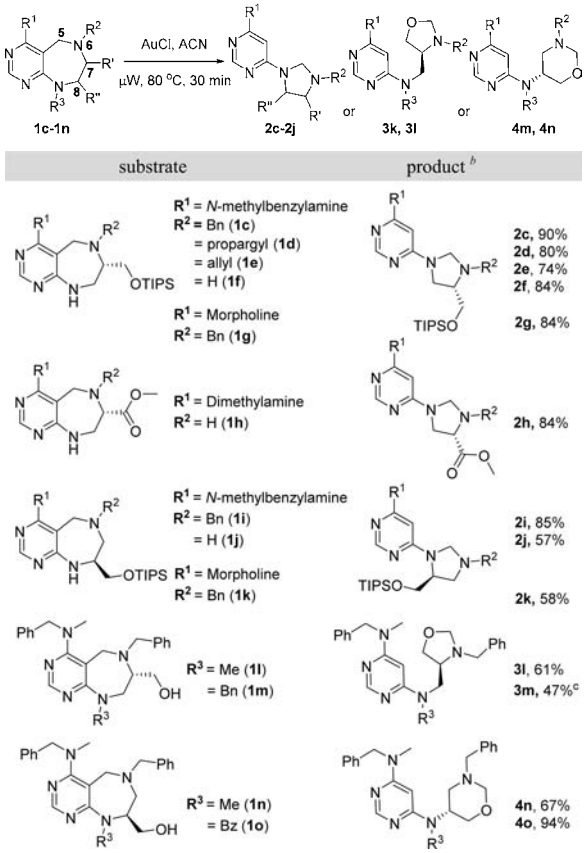
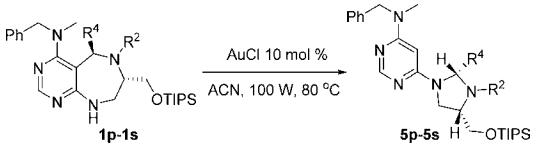
Table 2. Substrate Scope of Gold-Catalyzed Ring Transformation Reaction[a]



[a]Reaction conditions: SM, AuCl (10 mol %), ACN (0.1 M), microwave, 100 W, 80 °C, 30 min. [b]Yield of the isolated product. [c]Based on recovered starting materials.

Table 3. Steric Effects of R^2 and R^4 Substituents on Diastereomeric Ratio

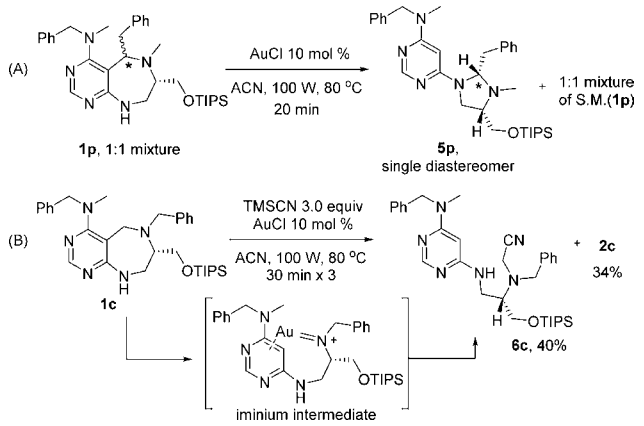


entry	R^4	R^2	SM dr ratio[b]	pdt dr ratio[b]	yield[c] (%)
1	Bn	Me (**1p**)	4:1	≫99:1	**5p**, 72
2	Bn	Bn (**1q**)	3.6:1	≫99:1	**5q**, 81
3	Me	Bn (**1r**)	2.7:1	2:1	**5r**, 70
4	Me	Me (**1s**)	3.6:1	1.21:1	**5s**, 92

[a]Reaction conditions: SM, AuCl (10 mol %), ACN (0.1 M), microwave, 100 W, 80 °C. [b]Diastereomeric ratio was determined by ^{1}H NMR analysis. [c]Yield of the isolated product.

owing to the facial selectivity of Grignard reagents. After the preparation of a full matrix of either methyl or benzyl substituents at the C-5 and N-6 positions, the gold-catalyzed ring transformation reaction was performed. Surprisingly, a single product (**5p** and **5q**) was observed from a 4:1 mixture of **1p** and 3.6:1 mixture of **1q**, respectively, in good yield and excellent diastereoselectivity under the optimized reaction conditions. However, the corresponding diastereoselectivity decreased when the size of the R^4 substituent at the C-5 position was smaller (methyl instead of benzyl) in the case of **1r** and **1s**. To understand the mechanistic origin of this diastereoselectivity, the reactivity of gold-catalyzed ring transformation was further investigated using a 1:1 mixture of pyrimidodiazepine substrate **1p** containing benzyl and methyl moieties at the C-5 and N-6 position, respectively. When this gold-catalyzed reaction of **1p** was quenched prior to its full conversion, the desired imidazolidine **5p** was obtained as a single diastereomer, and the remaining starting material **1p** was obtained as a 1:1 mixture as confirmed by crude ^{1}H NMR spectroscopy (Scheme 3A). This

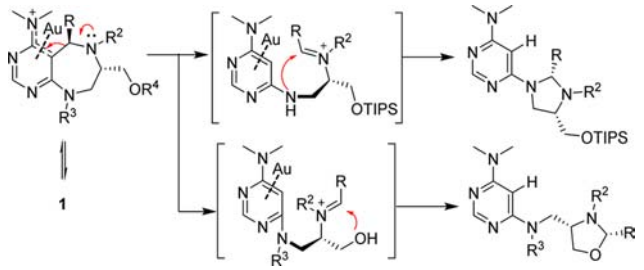
Scheme 3. Experimental Investigation To Elucidate the Reaction Mechanism of Gold-Catalyzed Ring Transformation



observation indicates that the gold-catalyzed reaction occurred through the formation of an identical intermediate from both the diastereomeric starting materials with the same reaction rate followed by the intramolecular nucleophilic addition of anilinic nitrogen to afford the desired product **5p** as a single diastereomer.

On the basis of these experimental results, a probable mechanism of this gold-catalyzed ring transformation involving an iminium intermediate is proposed (Scheme 4).[16] Strongly

Scheme 4. Plausible Mechanism of Gold-Catalyzed Ring Transformation of Pyrimidodiazepine



nucleophilic trimethylsilyl cyanide (TMSCN) was added to trap the acyclic iminium intermediate of the gold-catalyzed reaction of **1c**; the CN-trapped product **6c** was observed along with the desired imidazolidine product **2c** (Scheme 3B).[19] Therefore, it can be concluded that this AuCl-catalyzed ring transformation of pyrimidodiazepine is mediated via the in situ generation of an acyclic iminium intermediate through gold-catalyzed ring opening[17] and subsequent intramolecular nucleophilic cyclization. The stereochemical enrichment of this unusual gold-catalyzed reaction can be attributed to the retro-Mannich-type cleavage of C−C bond,[18] followed by the face-selective trapping of iminium intermediates (Scheme 4).

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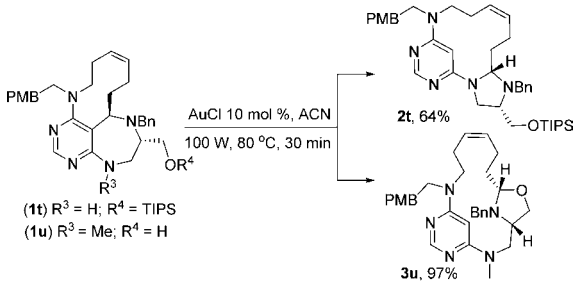
To demonstrate the potential of this synthetic method, the gold-catalyzed reaction was used to transform medium-sized rings into larger macrocycles at the last stage of synthesis for skeletal diversification (Scheme 5). The starting materials (**1t** and **1u**) were prepared using our standard synthetic methods including olefin metathesis (Scheme S7).[8] The 10-membered pyrimidodiazepines (**1t** and **1u**) were subjected to the gold-catalyzed reaction, allowing the ring enlargement to 12-membered **2t** and 15-membered **3u** via the intramolecular nucleophilic cyclization with aniline and alcohol nucleophiles, respectively. It is noteworthy that significantly different macrocycles were obtained from the same skeleton simply by switching the reactive nucleophiles. The stereochemical configuration of **2t** and **3u** was confirmed by 2D NOESY NMR analysis.[19]

Scheme 5. Synthetic Utility of This Method



In conclusion, a novel orthogonal gold-catalyzed ring transformation method was developed for pyrimidodiazepine derivatives in the presence of an alkyne moiety. This gold-catalyzed reaction is mediated by the in situ generation of acyclic iminium intermediates via unusual C−C bond cleavage and subsequent nucleophilic cyclization. The formation of imidazolidine, oxazolidine, and oxazinane derivatives depends on the type of intramolecular nucleophiles in pyrimidodiazepines. The stereochemical enrichment of this gold-catalyzed reaction is probably caused by the facial selectivity of iminium intermediates. This synthetic method was successfully used to synthesize two different types of macrocycles from the same skeleton. This method provides a highly concise and effective protocol to synthesize novel drug candidates with diverse structures. Further investigations on the mechanistic details of this gold-catalyzed reaction are currently underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03520.

Additional supporting figures and tables, detailed experimental procedures, synthetic schemes, spectroscopic data, and full characterization data of all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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