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Gold/Lewis Acid Catalyzed Cycloisomerization/Diastereoselective [3 + 2] Cycloaddition Cascade: Synthesis of Diverse Nitrogen-Containing Spiro Heterocycles

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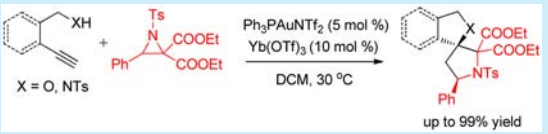
Supporting Information

ABSTRACT: A novel early and late transition-metal relay catalysis has been developed by combining a gold-catalyzed cycloisomerization and a $Yb(OTf)_3$-catalyzed diastereoselective [3 + 2] cycloaddition with aziridines in a selective C−C bond cleavage mode. Various biologically significant complex nitrogen-containing spiro heterocycles were rapidly constructed from readily available starting materials under mild conditions.



Nitrogen-containing spiro heterocycles served as an important structural unit in many bioactive natural products, pharmaceuticals, and agricultural chemicals (Figure 1). For instance, 7-(3-pyridinyl)-1,7-diazaspiro[4.4]nonane

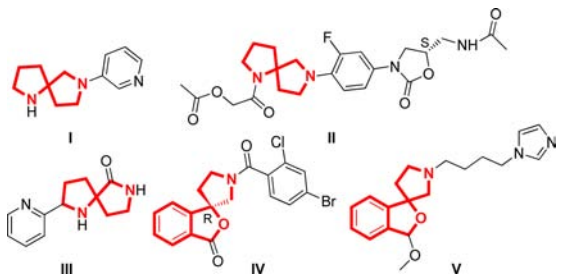


Figure 1. Bioactive compounds and pharmaceuticals containing spiro heterocycles.

analogue (**I**)[1] is used to treat the dysfunction of central and autonomic nervous systems. Their analogs were synthesized as novel ligands for nicotinic acetylcholine receptors (nAChR). 1,7-Diazaspiro[4.4]nonane analogues (**II**)[2] can also be served as antimicrobial agents. A spiro heterocycle (**III**)[3] can treat diseases and conditions mediated by modulation of voltage-gated sodium channels. The spiro lactone (**IV**)[4] is used as 11-β hydroxysteroid dehydrogenase type 1 inhibitors and mineralocorticoid receptor antagonists. The spiro heterocycle (**V**)[5] can act as σ_1 receptor ligands which are considered as promising drug candidates for the treatment of various neurological and psychiatric disorders, such as depression, anxiety, memory disorders, and Alzheimer's disease as well as alcohol and cocaine abuse. All these spiro heterocycles contain two five-membered rings with two nitrogen atoms or one nitrogen and one oxygen atom. Current synthetic routes to these compounds all require very long and tedious reaction steps.[1,5] Thus, efficient synthetic methodology development toward this structural target is in great demand. Herein we will report a bimetallic Lewis acid (Au (I) and Yb (III)) sequential catalyzed cascade reaction of alkynyl alcohols and amides with aziridines to access this type of spiro heterocycles.

Aziridine,[6] a versatile synthon in organic synthesis, was used as a masked 1,3-dipole to participate in [3 + 2] cycloaddition for the construction of five-membered nitrogen heterocycles. The most widely encountered reaction of aziridines is nucleophilic opening of the heterocyclic ring due to the reactivity of the strained C−N bonds.[7] The selective C−C bond cleavage has been rarely explored due to the relatively high energy barrier.[8] However, 2,2-diester aziridines favor C−C bond heterolytic cleavage in the presence of a Lewis acid, generating active transient azomethine ylide intermediates which can undergo a series of cycloaddition reactions with various dipolarophiles, such as alkenes and aldehyde.[9,10]

Recently, we developed a bimetallic relay catalysis strategy by a gold[11,12]-catalyzed cycloisomerization and a σ metal Lewis acid catalyzed [4 + 2] cycloaddition cascade reaction to synthesize fused or spiro aminals and ketals (Scheme 1).[13] Following this concept, the alkynyl alcohols or amides similarly underwent a gold-catalyzed 5-*exo*-*dig* intramolecular hydroxylation or hydroamination cyclization to afford the vinyl ether or enamide intermediate $\mathbf{M^1}$. Subsequent reaction with Lewis acid activated azomethine ylide $\mathbf{M^2}$ from 2,2-diester aziridines

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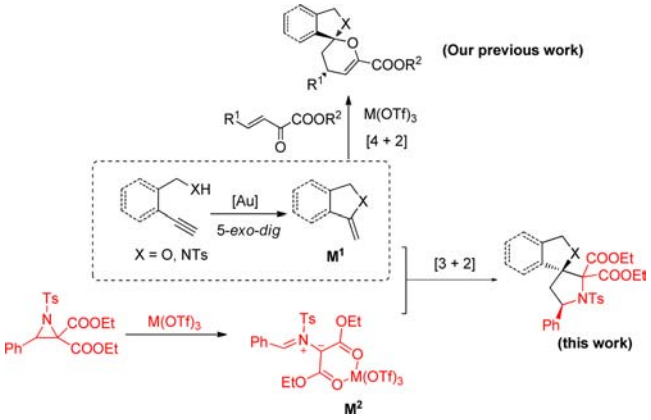
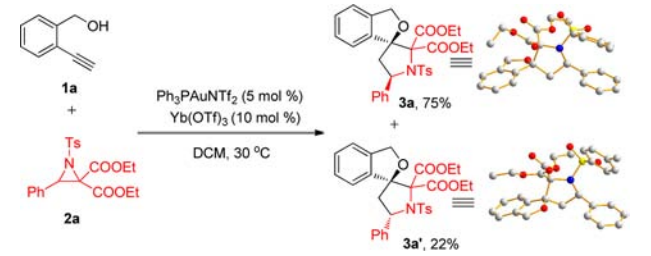
Scheme 1. Gold–Lewis Acid Relay Catalysis Approach toward Spiro Heterocycles



via C–C bond cleavage would form the expected spiro heterocycles (Scheme 1).

Alkynyl alcohol **1a** and diethyl 3-phenyl-1-tosylaziridine-2,2-dicarboxylate **2a** were chosen as the model substrates to test this hypothesis. To our delight, the target product **3a** was isolated in 75% yield together with its diastereoisomer **3a′** in 22% yield in the presence of $Ph_3PAuNTf_2$ and $Yb(OTf)_3$ in DCM at 30 °C (Scheme 2). The structures of both

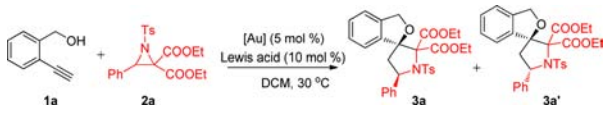
Scheme 2. Initial Formation of the Spiro-N,O-Heterocycles



diastereoisomers were unambiguously determined by single X-ray crystallography.[14] Inspired by the observed results, we continued to optimize the reaction conditions to improve the diastereoselectivity (Table 1). During this process, it was observed that when alkynyl alcohol **1a** was slowly injected into the reaction mixture, a much cleaner reaction system was obtained and the amount of major diastereoisomer **3a** increased. First, various transition metal catalysts such as $Y(OTf)_3$, $Yb(OTf)_3$, $Sc(OTf)_3$, $In(OTf)_3$, $Zn(OTf)_2$, and $Ni(ClO_4)_2$ were investigated. Among all of them, $Yb(OTf)_3$ was the optimal catalyst and the target product **3a** was obtained in almost quantitative yield as a single diastereomer (entry 2). Other metal catalysts gave lower yields or worse diastereoselectivities (entries 1–6). Other commonly used gold catalysts such as PPh_3AuCl/AgOTf and IPrAuCl/AgOTf gave relatively lower yields (entries 7, 8). Control experiments confirmed that both a gold catalyst and $Yb(OTf)_3$ are necessary in this reaction (entries 9, 10). Without the early transition metal, only a trace amount of the product was detected on TLC, and no product was formed without the gold catalyst. Finally we investigated other solvents such as THF and CH_3CN; very messy reactions were observed.

With the optimal reaction conditions in hand, we started to investigate the scope of aziridines in this reaction. As summarized in Scheme 3, a large variety of spiro-N,O-

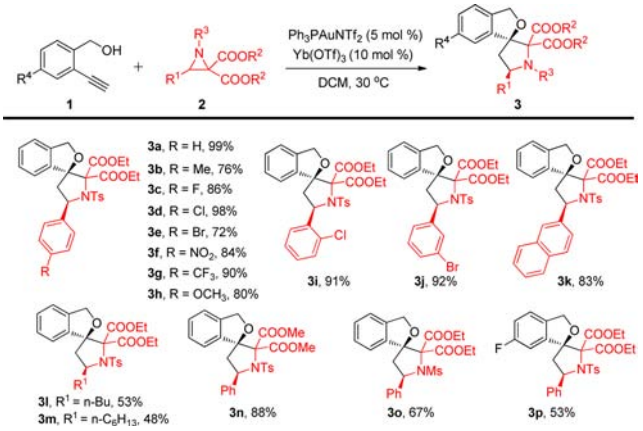
Table 1. Optimization of Reaction Conditions[a]



	catalyst		yield[b] (%)	
entry	A	B	3a	3a′
1	$Ph_3PAuNTf_2$	$Y(OTf)_3$	61	37
2	**$Ph_3PAuNTf_2$**	**$Yb(OTf)_3$**	**99**	**trace**
3	$Ph_3PAuNTf_2$	$Sc(OTf)_3$	54	trace
4	$Ph_3PAuNTf_2$	$In(OTf)_3$	98	trace
5	$Ph_3PAuNTf_2$	$Zn(OTf)_2$	26	40
6	$Ph_3PAuNTf_2$	$Ni(ClO_4)_2{\cdot}6H_2O$	73	trace
7	Ph_3PAuCl/AgOTf	$Yb(OTf)_3$	77	22
8	IPrAuCl/AgOTf	$Yb(OTf)_3$	91	trace
9	$Ph_3PAuNTf_2$	–	trace	0
10	–	$Yb(OTf)_3$	0	0

[a]Reaction conditions: To a mixture of **2a** (0.12 mmol), [Au] (5 mol %), catalyst B (10 mol %), 4 Å M.S. (80 mg) in dry DCM (1 mL) was injected a solution of **1a** (0.1 mmol) in DCM (1 mL) by a syringe pump in 0.5 h, and then the system was stirred at 30 °C for another 0.5 h. [b]Isolated yields were reported.

Scheme 3. Substrate Scope of Aziridines to Spiro N,O-Heterocycles[a]



[a]Reaction conditions: **2** (0.12 mmol), $Ph_3PAuNTf_2$ (5 mol %), $Yb(OTf)_3$ (10 mol %), 4 Å M.S. (80 mg) in dry DCM (1 mL) were added to a solution of **1** (0.1 mmol) in dry DCM (1 mL) by a syringe pump in 0.5 h at 30 °C, followed by stirring for another 0.5 h; isolated yield.

heterocycles were synthesized in good to excellent yields with excellent diastereoselectivities. For the *para*-substituted substrates, the reaction afforded the desired products in 72–99% yields (**3a–3h**). Various halogens, such as F, Cl, and Br, electron-withdrawing groups such as NO_2 and CF_3, and electron-donating groups such as CH_3 and CH_3O were all tolerated in this reaction. Substituents at the *ortho* or *meta* position did not affect this reaction, giving the corresponding products in excellent yields (**3i**, **3j**). A substrate bearing a 2-naphthyl group was also a suitable substrate for this transformation (**3k**). By switching the aromatic aziridines to aliphatic substrates, the desired products could also be obtained in moderate yields (**3l**, **3m**). Both 2,2-dimethyl ester and *N*-methylsulfonyl substituted aziridines could also react smoothly to afford the target products in good yields (**3n**, **3o**). A fluorine substituted alkynyl alcohol could also afford the desired product

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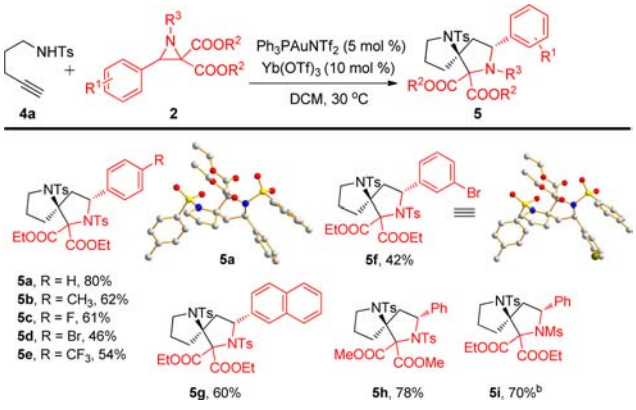
3p in an acceptable yield. It should be noted that all these reaction were completed in 1 h and the diastereoselectivity was very good.

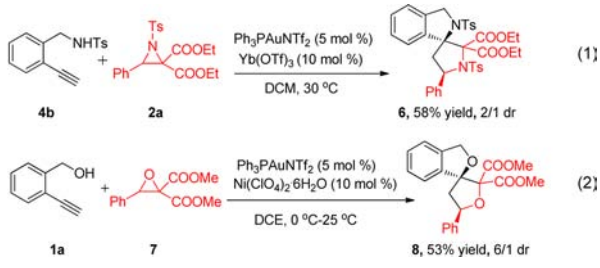
Switching from alkynyl alcohols to alkynyl amides, a similar reaction with aziridine 2 is possible to obtain spiro-N,N-heterocycles. As illustrated in Scheme 4, when alkynyl amide 4a

Scheme 4. Substrate Scope of Aziridines to Spiro *N,N*-Heterocycles[a]



[a]Reaction conditions: 4a (0.1 mmol), 2 (0.12 mmol), $Ph_3PAuNTf_2$ (5 mol %), $Yb(OTf)_3$ (10 mol %), 4 Å M.S. (80 mg) in dry DCM (1 mL) was stirred for 1.5−2 h at 30 °C; isolated yield. [b]dr = 9:1.

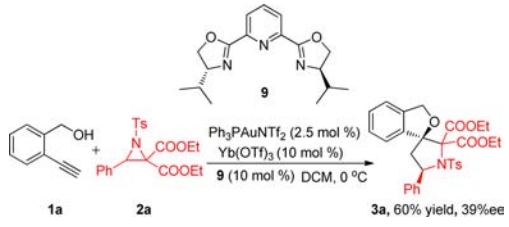
and aziridine 2a were subjected to standard conditions, the desired spiro heterocycle 5a was isolated in 80% yield. This reaction also proceeded with excellent diastereoselectivity. This structure of 5a was also confirmed by single X-ray analysis.[14] Slow injection of amide 4a into the reaction system could not improve the reaction yield. Then the scope of various aziridines was also tested (Scheme 4). The electronic effect of substituents at the *para* position of the aromatic ring of aziridines was evaluated (5a−5e). This reaction tolerated both electron-withdrawing and -donating groups. Both 2,2-dimethyl ester and *N*-methylsulfonyl subsituted aziridines are also amenable to this transformation, providing corresponding products in good yields (5h, 5i). In addition, alkynyl amide 4b was also a suitable substrate for this reaction, generating tricyclic spiro compound 6 in 58% yield with moderate diastereoselectivity (eq 1).



Moreover, application of oxirane[15] in this reaction is possible to build up spiro oxygen-containing heterocycles. However, a very messy reaction system was observed under the standard conditions when $Yb(OTf)_3$ was used as a σ metal Lewis acid. After optimization of reaction conditions (for details, see Supporting Information (SI)), the target spiro product 8 could be obtained in 53% yield with 6/1 dr using $Ni(ClO_4)_2$ as the Lewis acid and DCE as solvent (eq 2).

Asymmetric bimetallic relay catalysis is more challenging because of ligand/metal compatibility issues.[16] Since the first gold-catalyzed cycloisomerization does not produce chiral centers, introducing chiral ligands onto the Lewis acid $Yb(OTf)_3$ is possible to realize the asymmetric variant of this reaction. After screening of various of chiral nitrogen ligands (for details, see SI), the highest 39% ee was obtained using the commercial available isopropyl pybox 9 as chiral ligands (Scheme 5). Although the enantioselectivity was only moderate at the present stage, it still demonstrates that an asymmetric reaction is feasible by using an appropriate chiral ligand.

Scheme 5. Catalytic Enantioselective Reaction to Nonracemic Spiro Heterocycles



In summary, we have developed a highly diastereoselective cascade reaction by using a bimetallic gold(I)/Lewis acid relay catalysis strategy. Diverse spiro nitrogen-containing heterocycles were efficiently synthesized from aziridines and alkynyl alcohols and amides under very mild conditions, which demonstrated the advantage of this strategy in building up molecular complexity from simple starting materials. This combination of a π-acid with another σ metal Lewis acid will find more applications in other diversity oriented syntheses.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02253.

Experimental detailes, crystal structure of 3a, 3a′, 5a, 5f, and characterization data (PDF)
Crystallographic data for 3a (CIF)
Crystallographic data for 3a′ (CIF)
Crystallographic data for 5a (CIF)
Crystallographic data for 5f (CIF)

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Notes

The authors declare no competing financial interest.

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(14) CCDC 1496916−1496919 (**3a**, **3a′**, **5a**, **5f**) contain the supplementary crystallographic data for this paper. 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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