Gold Catalysis

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A Diversity-Oriented Approach to Spiroindolines: Post-Ugi Gold-Catalyzed Diastereoselective Domino Cyclization**

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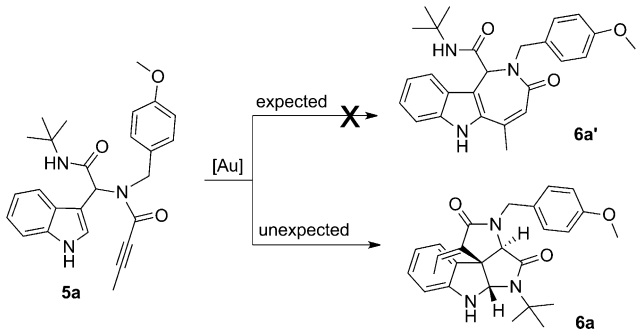
Gold-catalyzed carbocyclization and heteroannulation strategies have recently attracted much attention owing to the selective and efficient activation of the C≡C bond towards a wide range of nucleophiles that these methods provide.[1] Domino approaches involving gold-catalysis lead to complex heterocyclic compounds under exceedingly mild reaction conditions.[2] Although gold-catalyzed approaches are rising to prominence, they suffer in terms of diversity and procedural length. Multistep sequences are usually required for assembling the starting material for cyclization. We have recently reported a concise route to indoloazocines by a sequential Ugi/gold-catalyzed intramolecular hydroarylation approach.[3] Inspired by these findings and as a result of our continued synthetic interest in the indole core,[4] multicomponent reactions[5] and transition metal-catalysis,[6] we have developed a post-Ugi gold-catalyzed domino cyclization method to generate spiroindolines.

The Ugi four-component reaction (4-CR)[7] of indole-3-carboxaldehyde (**1a**) with *p*-methoxybenzyl amine (**2a**), 2-butynoic acid (**3a**) and *tert*-butyl isonitrile (**4a**) in methanol at 50 °C gave Ugi-adduct **5a** in 71 % yield. When this was treated with 5 mol % of Au[PPh_3]OTf (OTf = trifluoromethanesulfonate) in $CDCl_3$ at RT, the expected outcome of the reaction was indoloazepinone **6a′** through an *endo*-dig cyclization[1m,n,3] followed by rearrangement (Scheme 1). Surprisingly, an *exo*-dig cyclization followed by intramolecular trapping of the spiro intermediate occurred instead, resulting in the diastereoselective formation of tetracyclic spiroindoline **6a** in 61 % yield (Scheme 1).



Scheme 1. Unexpected gold-catalyzed domino cyclization.

This observation was remarkable, as the attack on the α-position of an alkyne conjugated with an amide is rare, and trapping of the spiro intermediate by a sterically hindered *tert*-butyl amide is rather unexpected, as was the diastereoselectivity observed. Spiroindolines[8] are prominent molecular motifs that are frequently encountered among the large family of alkaloids; for example, it is present in communesines[8,9] and perophoramidines[8,10] (Figure 1), which display distinct pharmacological properties.[8–10] These fused polycyclic systems, which feature quaternary stereocenters, present a nontrivial challenge for organic chemists to develop synthetic approaches.[11]

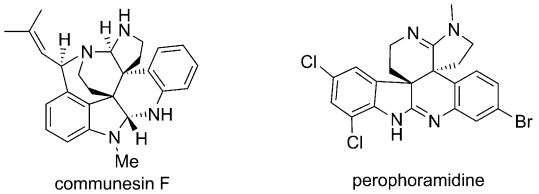


Figure 1. Naturally occurring polycyclic spiroindolines.

First, we optimized the conditions for this domino cyclization (Table 1). Whereas Au(X-Phos) with different counter ions (X-Phos = 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl) did not improve the yield, AuCl, $AuCl_3$, and Au(PPh_3)Cl gave almost no conversion (Table 1, entries 2–7). Reaction with Au(PPh_3)SbF_6 afforded an improved yield of 75 % in merely 2 h (Table 1, entry 8). Replacing SbF_6^- with other counterions, or using [MeCN(JohnPhos)Au^I]SbF_6 (JohnPhos = (2-biphenyl)di-*tert*-butylphosphine) did not give better results (Table 1, entries 9–11).

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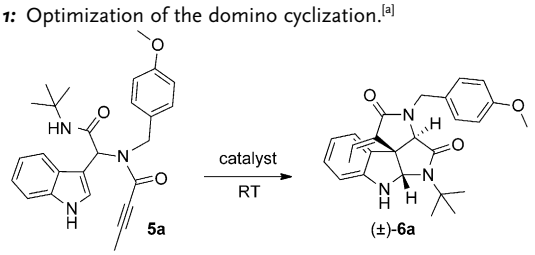
Table 1: Optimization of the domino cyclization.[a]



Entry	Catalyst	Solvent	*t* [h]	% Conversion[b] (% Yield)
1	$Au(PPh_3)OTf$	$CDCl_3$	3	100 (61)
2	$Au(X\text{-}Phos)SbF_6$	$CDCl_3$	3	100 (59)
3	$Au(X\text{-}Phos)BF_4$	$CDCl_3$	20	40
4	$Au(X\text{-}Phos)NTf_2$	$CDCl_3$	20	100 (67)
5	AuCl	$CDCl_3$	20	0
6	$AuCl_3$	$CDCl_3$	20	trace
7	$Au(PPh_3)Cl$	$CDCl_3$	20	0
8	**$Au(PPh_3)SbF_6$**	**$CDCl_3$**	**2**	**100 (75)**
9	$Au(PPh_3)BF_4$	$CDCl_3$	20	20
10	$Au(PPh_3)NTf_2$	$CDCl_3$	20	100 (64)
11	$[MeCN(JohnPhos)Au^I]SbF_6$	$CDCl_3$	20	100 (62)
12	AgOTf	$CDCl_3$	20	35
13	$AgSbF_6$	$CDCl_3$	20	50
14[c]	$Au(PPh_3)SbF_6$	$CDCl_3$	0.5	100 (72)
15[d]	$Au(PPh_3)SbF_6$	$CDCl_3$	0.25	100 (58)[e]
16[f]	$Au(PPh_3)SbF_6$	$CDCl_3$	20	50
17	$Au(PPh_3)SbF_6$	CD_2Cl_2	3	100 (70)
18	$Au(PPh_3)SbF_6$	CD_3CN	20	80
19	$Au(PPh_3)SbF_6$	$[D_8]THF$	20	trace
20	$Au(PPh_3)SbF_6$	MeOD	2	100 (46)[e]

[a] Unless otherwise noted, all reactions were run with **5a** (0.1 mmol) and a catalyst loading of 5 mol% in a screw-cap vial at RT. [b] Conversion based on ^1H NMR analysis; yields given in parentheses are yields of isolated products. [c] Reaction at 50°C. [d] Reaction at 100°C. [e] Unidentified by-products were formed. [f] Catalyst loading of 2 mol%. JohnPhos = (2-biphenyl)di-*tert*-butylphosphine, Tf = trifluoromethanesulfonyl, X-Phos = 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl.

Experiments with AgOTf and $AgSbF_6$ resulted in only moderate yields (Table 1, entries 12 and 13). Reaction with the hitherto best catalyst system, $Au(PPh_3)SbF_6$, at 50°C reduced the time for reaction completion to 30 min with a slightly diminished yield, whereas increasing the temperature to 100°C decreased the yield to 58% (Table 1, entries 14 and 15). A lower catalyst loading of 2 mol% resulted in only 50% conversion after 20 h. Changing the solvent did not give better results (Table 1, entries 16–20).

To evaluate the scope and limitations of our optimized method (Table 1, entry 8), different Ugi adducts were synthesized from indole-3-carboxaldehyde in good to excellent yields, and subjected to the domino cyclization reaction (Table 2). Various substituents on the alkyne, isonitrile, indole, and amine groups are tolerated (Table 2, entries 1–4, 7–9). In the case of bulky substituents on the alkyne, such as *p*-methoxyphenyl and *iso*-propyl, the yields decreased to 50% and 57%, respectively (Table 2, entries 5 and 6). Methyl substitution at the 2-position of the indole core completely inhibited the cyclization, and the starting material was quantitatively recovered (Table 2, entry 10).

The application of D-(+)-1-phenylethylamine in the Ugi reaction resulted in an inseparable 1:1 mixture of diastereoisomers. When subjected to the domino cyclization, two diastereoisomeric spiroindolines **6la** (35%) and **6lb** (25%) were formed in a combined yield of 79% (Table 2, entry 11). A tosyl group on the indole nitrogen strongly diminished the nucleophilicity of this core and hence no cyclized product could be observed (Table 2, entry 12). The structure of compound **6a** was unambiguously assigned by X-ray crystallography (Figure 2).[12]

The observed diastereoselecitivity of the reaction can be easily explained by the mechanism (Scheme 2).[13] After the activation of the triple bond of Ugi adduct (*R*)-**5a** by cationic gold, the nucleophilic attack at the 3-position of the indole can occur from two sides. If the attack occurs from the back side of the indole core, intermediate **B** is formed. However, trapping of the intermediate iminium ion in **B** by the secondary amide, is sterically impossible. As a result, the newly formed spiro-ring reopens to intermediate **A**. In contrast, when the attack occurs from the front side of the indole core, which results in spiro intermediate **C**, trapping of the iminium ion is possible and spiroindoline **6a** is formed, which possesses two newly formed chiral centers (*S*,*S*; Scheme 2).

Thus, the chiral center already present in the Ugi adduct, diastereoselectively directs the domino cyclization. To the best of our knowledge, this is the first report of the synthesis of spiroindolines by a domino cyclization involving a "branched-handed" pre-cyclization architecture (Figure 3).[2,11]

In conclusion, we have developed a diversity-oriented approach to the synthesis of complex spiroindolines from readily available starting materials. The first step, the Ugi-4CR, generates diversity, and the second step, an efficient

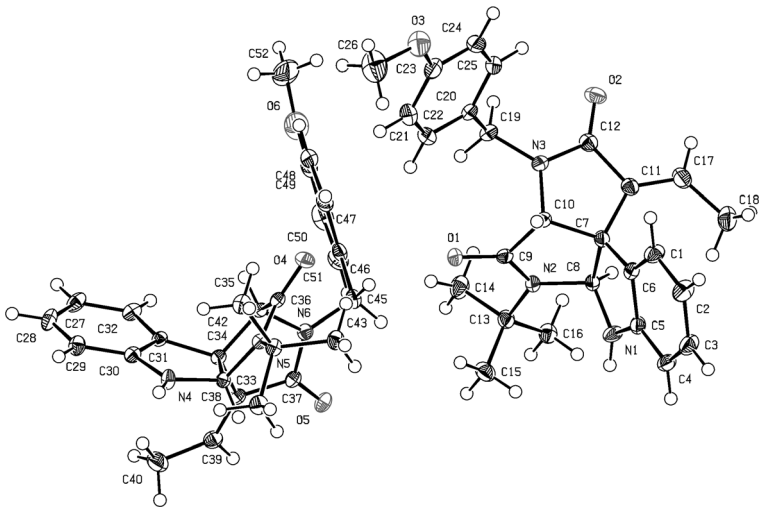
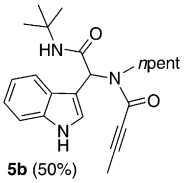
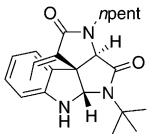
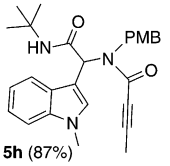
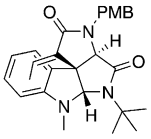
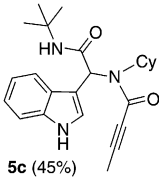
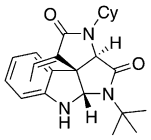
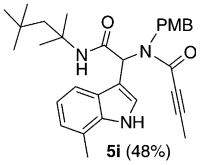
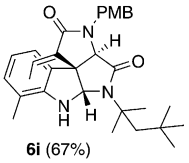
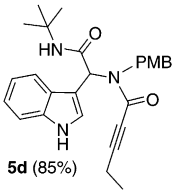
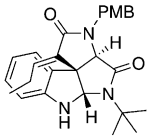
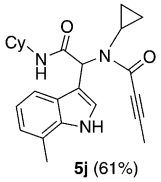
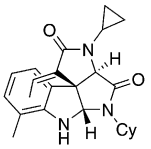
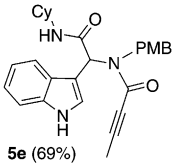
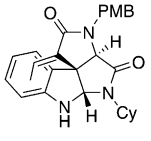
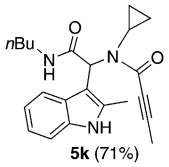
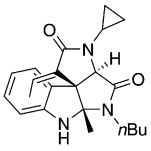
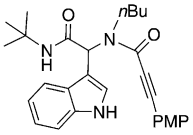
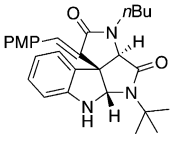
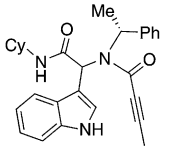
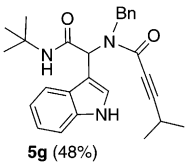
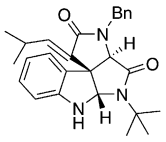
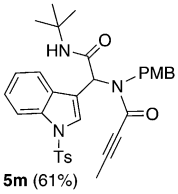
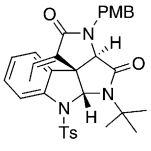
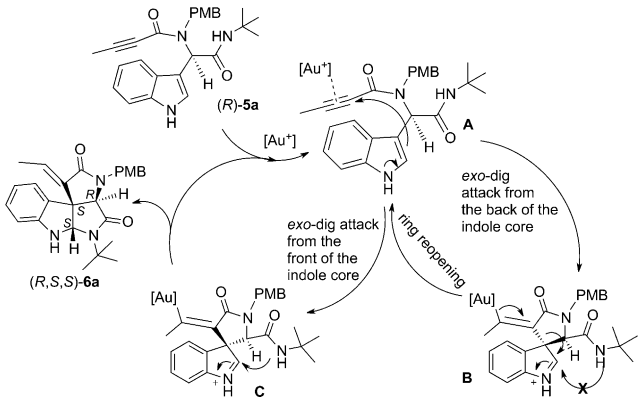


Figure 2. Crystal structure of compound **6a**. Thermal ellipsoids set at 50% probability.[12]

Table 2: Scope and limitations of domino cyclization to form spiroindolines.[a]

Entry	Ugi adduct **5**	Spiroindolines (±)-**6**	Entry	Ugi adduct **5**	Spiroindolines (±)-**6**
1	 **5b** (50%)	 **6b** (80%)	7	 **5h** (87%)	 **6h** (73%)
2	 **5c** (45%)	 **6c** (79%)	8	 **5i** (48%)	 **6i** (67%)
3	 **5d** (85%)	 **6d** (77%)	9	 **5j** (61%)	 **6j** (65%)
4	 **5e** (69%)	 **6e** (70%)	10	 **5k** (71%)	 **6k** (0%)
5	 **5f** (53%)	 **6f** (50%)	11	 **5l** (47%, d.r.=1:1)[b]	**6la** (35%)[c] **6lb** (25%)[c]
6	 **5g** (48%)	 **6g** (57%)	12	 **5m** (61%)	 **6m** (0%)

[a] All reactions were run with **5** (0.2 mmol) in a screw-cap vial at RT. [b] Inseparable mixture of diastereoisomers. [c] Yield of pure diastereoisomer. The combined yield was 79% (d.r. = 1:1). Bn = benzyl, Cy = cyclohexyl, PMB = *p*-methoxybenzyl, PMP = *p*-methoxyphenyl, Ts = *p*-toluenesulfonyl.



Scheme 2. Proposed mechanism for the diastereoselective domino cyclization to spiroindolines. PMB = *p*-methoxybenzyl.

gold(I)-catalyzed diastereoselective domino cyclization under mild reaction conditions, results in the formation of the spiroindolines. The unprecedented application of "branched-handed" pre-cyclization architecture, the unexpected selec-

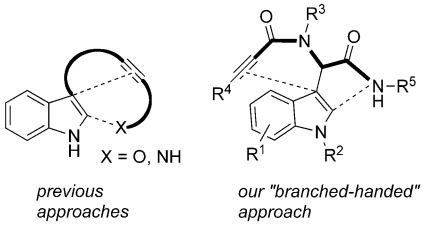


Figure 3. "Branched-handed" pre-cyclization architecture.

tive *exo*-attack of the indole on the propargylic amide, and the unique diastereoselectivity (control of three chiral centers) are the merits of this protocol. Further studies on ring expansion[14] and the application of this method to the synthesis of naturally occurring spiroindolines are currently under investigation.

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Keywords: alkynes · gold · indoles · spiroindolines · Ugi

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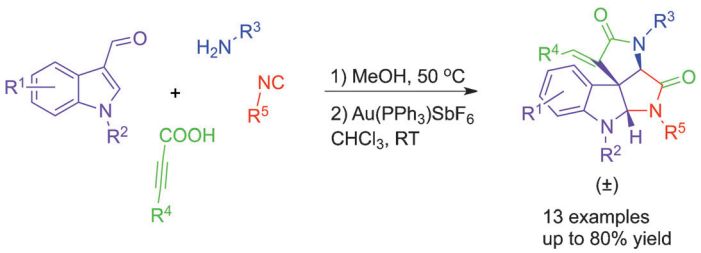
[14] Upon changing the components of the Ugi 4-CR (the amine as an alkyne source instead of the carboxylic acid) the resulting Ugi adduct, when treated with $Au(PPh_3)SbF_6$ (5 mol%) and TFA (1 equiv), formed a 65:35 mixture of the 6-*endo*- and 5-*exo*-compounds (formed by cyclization of the indole on the propargylic amide). Further optimization of this process is under current investigation.

Communications

Gold Catalysis

S. G. Modha, A. Kumar, D. D. Vachhani, J. Jacobs, S. K. Sharma, V. S. Parmar, L. Van Meervelt, E. V. Van der Eycken* _____ ■■■■–■■■■

A Diversity-Oriented Approach to Spiroindolines: Post-Ugi Gold-Catalyzed Diastereoselective Domino Cyclization



Caught "Spiro" handed: A diversity-oriented approach comprised of an Ugi four-component reaction and a diastereoselective gold(I)-catalyzed domino cyclization for the generation of complex spiroindolines under mild conditions has been developed. Variously substituted spiroindolines were synthesized in good to excellent yields and with complete diastereoselectivity.