Lewis Acid-Catalyzed Diastereoselective Domino Reaction of Ene-Ynamide with Trimethylsilyl Cyanide to Construct Spiroindolines

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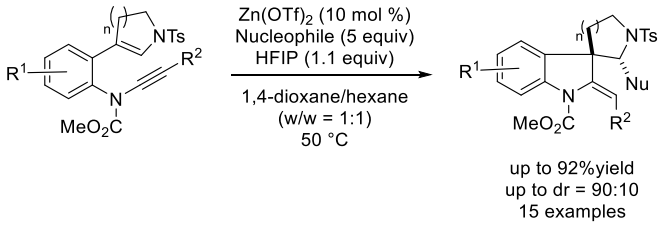
Supporting Information Placeholder



ABSTRACT: $Zn(OTf)_2$ catalyzed domino reaction of enamide-ynamides in the presence of trimethylsilyl cyanide as an external nucleophile to construct spirocyclic indolines was developed. This domino reaction involved cyclization of enamide to ynamide to generate 4',5'-dihydrospiro[indoline-3,3'-pyrrol]-1'-ium followed by cyanide addition to produce spiroindolopyrrolidines with good diastereoselectivity.

Spirocyclic pyrrolidinoindolines are privileged scaffolds found in bioactive alkaloids like coerulescine[1], uncarines[2], aspidospermidine[3] and strychnine[4], as well as pharmacology agents[5] (Figure 1). Because of their biological importance and structural features, spirocyclic pyrrolidinoindolines have been synthesized in several ways.[6]

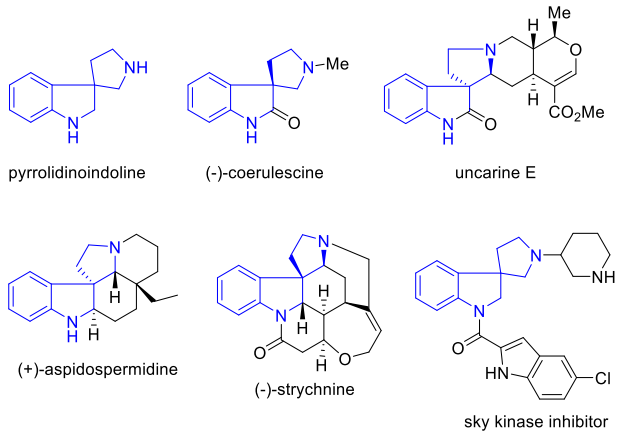
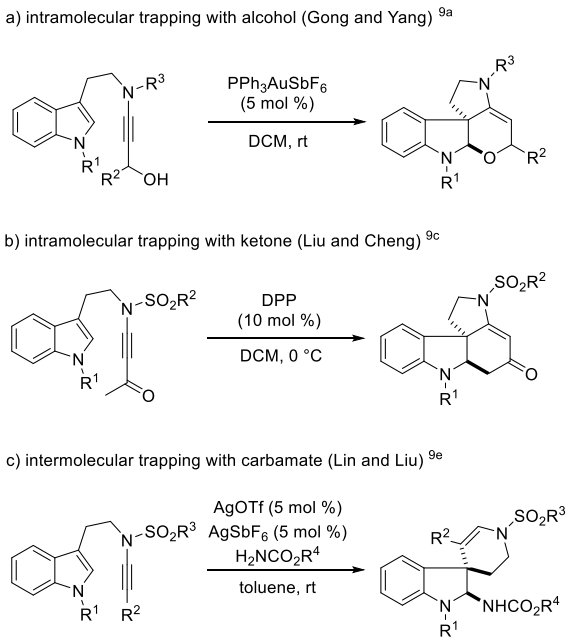


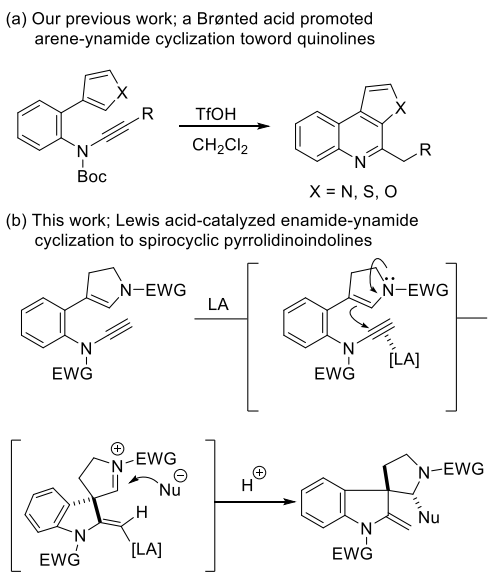
Figure 1. Representative spirocyclic pyrrolidinoindolines

Meanwhile, ynamides have received much attention as intriguing building blocks for nitrogen-containing product synthesis[7]. This synthon is specifically well suited for the synthesis of heterocyclic compounds via cyclization reactions.[8] As a result, there have been a few reports on the synthesis of spiroindolines using tryptamine-derived ynamides (Scheme 1).[9] However, during the synthesis of spiroindolines from tryptamine-derived ynamides, a carbon bond is formed at C-2 via rapid Wagner–Meerwein rearrangement. Previous research reports the requirement of intramolecular traps with an appropriate nucleophile to prevent this. Lin, Lie, and colleagues[9e] recently reported the synthesis of spiro[indoline-3,4'-pyridin]-2-yl carbamate via an $AgOTf/PPh_3$-catalyzed tandem cyclization of tryptamine-ynesulfonamides with an appropriately suitable external nucleophile, such as carbamate, to prevent rearrangement (Scheme 1c). However, only carbamate with appropriate acidity and nucleophilicity can be used as external nucleophile. We reported a Brønsted acid-promoted cyclization of arene-ynamide to give polycyclic quinolines and the total synthesis of natural products such as aplidiopsamine A as an application of this methodology (Scheme 2a).[10] In this reaction, the intramolecular electrophilic aromatic substitution of ynamide bearing (hetero)aromatic ring proceeds with a Brønsted acid to afford the quinoline skeleton. As a result, we predicted that if the aryl moiety is replaced with dihydropyrrole, cyclization of ynamide would proceed selectively from the 3-position of the dihydropyrrole, followed by nucleophilic addition on the resulting iminium to yield spiroindoline derivatives (Scheme 2b).

Scheme 1. Representative Tryptamine-derived Ynamide Cyclizations to Spirocyclic Indolines

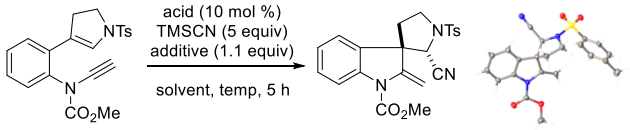


Scheme 2. Our previous work and Proposal for Spirocyclic Pyrrolidinoindolines Synthesis



We examined the cyclization reaction of enamide-ynamide **1a** with trimethylsilyl cyanide (TMSCN) as an external trapping reagent under several conditions (Table 1). When the reaction was carried out with stoichiometric amount of trifluoromethanesulfonic acid (TfOH) in CH_2Cl_2 at 23 °C under the same conditions as the previous work [10], the reaction proceeded well to give the desired spiroindoline **2a** in 91% yield albeit with low diastereoselectivity (dr = 60:40) (entry 1). When the reaction was carried out with a catalytic amount of TfOH (entry 2), only 11% of the yield of **2a** was obtained. Following that, we looked into the reaction with a catalytic amount of several Lewis acids and additives to inspect whether diastereoselectivity could be improved (entries 3-7). The use of zinc trifluoromethanesulfonate resulted in a low yield as well as low diastereoselectivity (entry 3). We investigated the effect of additional proton sources on Lewis acid turnover. Several studies have shown that 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) has a positive effect on chemical yield, but the diastereoselectivity has not improved (entries 3-5). Other Lewis acids, such as copper and scandium trifluoromethanesulfonate, produce lower yields (entries 6 and 7). The temperature has little effect as well (entry 8). Other solvents, including toluene, 1,4-dioxane, and hexane were investigated for the reaction (entries 8-11)[11]. The use of 1,4-dioxane increased diastereoselectivity (dr = 85:15) while maintaining the chemical yield (entry 10). Hexane produced the best results in terms of diastereoselectivity, albeit at a low yield (entry 11). We discovered that using 1,4-dioxane and hexane (v/v = 1/1) as mixed solvents yielded satisfactory results in terms of yield (85%) and diastereoselectivity (dr = 90:10) (entry 12)[12]. We conducted the domino reaction of **1a** to **2a** on a gram scale (entry 13). Moreover, product **2a** was obtained in 90% yield with good diastereoselectivity. Recrystallization of the diastereomixers allowed for the selective production of *anti*-**2a** (788 mg, 60% yield). Ambiguously the structure of *anti*-**2a** as a major diastereomer was revealed by X-ray analysis.

Table 1. Optimization of Reaction Conditions with 1a[a]



x-ray of *anti*-**2a** CCDC 2168857

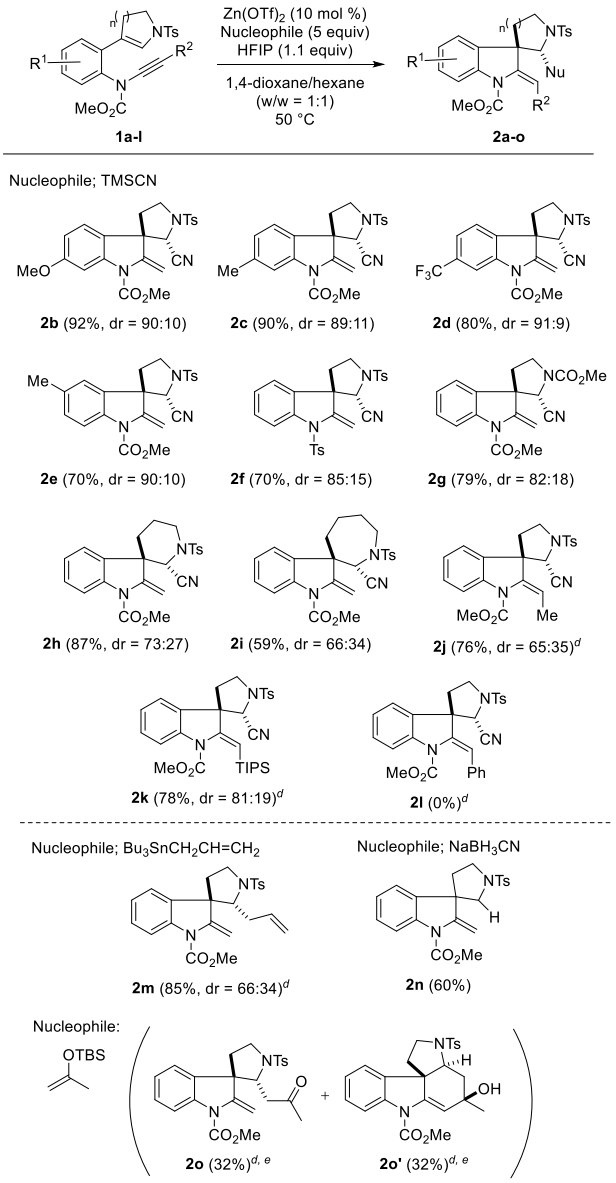
Entry	Temp (°C)	acid	solvent	additive	Yield[b] (%)	dr[c]
1	23	TfOH[d]	CH_2Cl_2	none	91	60:40
2	23	TfOH	CH_2Cl_2	none	11	60:40
3	23	$Zn(OTf)_2$	CH_2Cl_2	none	22	55:45
4	23	$Zn(OTf)_2$	CH_2Cl_2	*t*BuOH	75	60:40
5	23	$Zn(OTf)_2$	CH_2Cl_2	HFIP[e]	79	60:40
6	23	$Cu(OTf)_2$	CH_2Cl_2	HFIP	65	55:45
7	23	$Sc(OTf)_3$	CH_2Cl_2	HFIP	40	55:45
8	50	$Zn(OTf)_2$	DCE	HFIP	85	65:35
9	50	$Zn(OTf)_2$	toluene	HFIP	47	80:20
10	50	$Zn(OTf)_2$	dioxane	HFIP	77	85:15
11	50	$Zn(OTf)_2$	hexane	HFIP	9	90:10
12	50	$Zn(OTf)_2$	dioxane/ hexane	HFIP	85	90:10
13[f]	50	$Zn(OTf)_2$	dioxane/ hexane	HFIP	90	90:10

[a]Reaction conditions: **1a** (0.1 mmol), acid (10 mol %), additive (1.1 equiv), TMSCN (5.0 equiv.) in solvent (0.1 M). [b]Isolated yields. [c]determined by crude ^{1}H-NMR. [d]1.1 equivalent of TfOH was used. [e]HFIP = 1,1,1,3,3,3-hexafluoro-2-propanol. [f] 2.77 mmol (1.1 g) scale.

The substrate scope of the cyclization reaction was achieved under the optimized reaction conditions (Table 1, entry 12), and the results are summarized in Scheme 3. The substrates **1b-e** with electron-donating and -withdrawing group substituted on the phenyl ring produced the desired

products **2b-e** in high yields with high diastereoselectivities. Changing the protecting groups on both enamide and ynamide to tosyl or methyl carbamates had no effect on the reaction (**2f** and **2g**). The different ring size of enamides were investigated. The six and seven-membered rings are appropriate for obtaining the desired products (**2h** and **2i**). The substituents on a terminal posi-

Scheme 3. Substrate Scope[a-c]

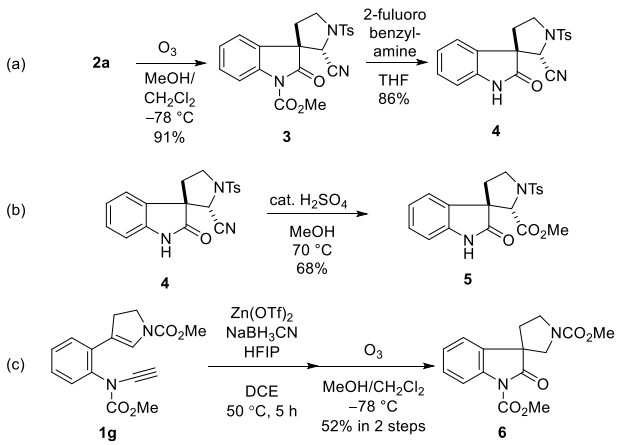


[a]Reaction conditions: **1a** (0.1 mmol), $Zn(OTf)_2$ (10 mol %), HFIP (1.1 equiv.), nucleophile (5.0 equiv.) in 1,4-dioxane/hexane (v/v = 1/1, 0.1 M). [b]Isolated yields. [c]diastereomer ratio was determined by crude ^{1}H-NMR. [d]1,2-dichloroethane as a solvent. [e]quenched with TBAF for deprotection of silyl group

tion of ynamide were investigated. However, when dioxane/hexane mixed solvents were used for the reaction of **1j**, the reaction rate was extremely slow resulting in a decreased yield (**2j**, 15% yield, dr = 90:10). The use of 1,2-dichloroethane resulted in high yield of **2j** with moderate diastereoselectivity (76%, dr = 65:35). The nuclear Overhauser effect (NOE) correlations were used to determine the *Z* geometry of the methyl group of **2j**.[13] The substrate **1k** bearing bulkier TIPS group on the terminal position of ynamide gave the product **2k** with good diastereoselectivity (79% yield, dr =81:19). The use of **1l** bearing phenyl group, somehow, gave complex mixtures. We investigated alternative external trapping reagents for the reaction with **1a**. The reaction with allyltributylstannane yielded the desired product of **2m** in high yield with moderate diastereoselectivity. The use of sodium cycnoborohydride resulted in good yield of the reducing product **2n**. The use of acetone derived *tert*-butyldimethylsilyl enol ether as an external nucleophile resulted tricyclic spiroindoline **2o** (32%) and tetracyclic indoline **2o'** (32%) obtained by cyclization from enamide.

Finally, we put product **2** through its paces under several conditions (Scheme 4). Ozonolysis of *anti*-**2a** proceeded well to afford oxindole **3** in 91% yield. Deprotection of methylcarbamate with 2-fluorobenzylamine afforded oxindole **4**.[14] Further derivatization of cyano group in **4**, such as esterification was conducted to afford ester **5** in 68% yield. Finally, we applied our methodology to produce **1g** of known spiroindoline **6** which can be converted to coerulescine (*see* Figure 1) as reported by Suárez-Castillo group[15].

Scheme 4. Further Derivatization of the Product 2



In summary, we developed an efficient method for Lewis acid-catalyzed domino cyclization of enamide-ynamides **1** with external nucleophiles to yield spiroindolopyrrolidine derivatives **2** with high diastereoselectivity. We also demonstrated additional application of the obtained product, such as formal natural product synthesis. Our laboratory is currently working on asymmetric synthesis of this reaction.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experiment procedures, supplemental figure, and copies of ^{1}H and ^{13}C NMR spectra (PDF)
crystallographic information for **2a** and **2o** (CIF)

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Notes

The authors declare no competing financial interest.

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(12) See the Supporting Information for more details of the optimized conditions and initial results of asymmetric reactions with chiral ligands.

(13) See the Supporting Information.

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