Ag(I)/PPh_3-Catalyzed Diastereoselective Syntheses of the Spiro[indole-3,4'-piperidine] Scaffold and Its Derivatives via Chelation-Controlled Cycloisomerizations of Tryptamine-Ynamides

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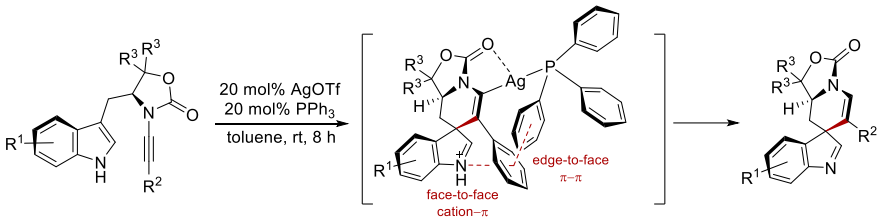
Supporting Information Placeholder



ABSTRACT: A Ag(I)/PPh_3-catalyzed chelation-controlled cycloisomerization of tryptamine-ynamide was developed to access the spiro[indole-3,4'-piperidine] scaffold. The asymmetric products with this scaffold were obtained through a diastereoselective synthesis via a chiral pool approach. Such a synthesis could be realized on a gram scale and derivatization of this scaffold afforded various derivatives. DFT calculations indicated that strong non-covalent effects between the substrate and catalyst/ligand complex stabilized the spiroindoleninium intermediate via cation-π-π interactions, leading to the diastereoselective syntheses of the asymmetric products.

Spiro[indole-3,4'-piperidine], as a significant scaffold of communesin[1] and koumine[2] indole alkaloids, has drawn much attention from the chemical and medicinal communities. The construction of the scaffold with a spirocyclic quaternary carbon center is rather difficult but it has been achieved in the total syntheses of a number of natural products and the development of synthetic methodologies (Figure 1).[3,4] Among those methods, metal-catalyzed cyclization of *N*-propargyl tryptamine is one of the most popular strategies.[4a,5] In particular, many cyclizations under gold catalysis have been developed in recent years.[5a–c] For example, in 2007, Echavarren and coworkers reported that *N*-sulfonyl-*N*-propargyl tryptamines with a methyl group at the C2-position could be cyclized under the catalysis of [JohnPhosAu(MeCN)]SbF_6, a Au(I) complex bearing bulky phosphane to give spiro 2-methyleneindolenenine.[5a] In 2017, Guinchard and coworkers developed a gold(I)-catalyzed approach to spiroindolenines with *N*-propargyl tryptamines bearing *N*-substituents such as propargyl, allyl, alkyl or benzyl groups.[5b] In 2020, Zhang and You collaborated on a gold-catalyzed dearomatization reaction of *N*-sulfonyl-*N*-propargyl tryptamines derivatives with substitutions at the 2-position to yield spiroindolenine.[5c] Besides gold catalysis, an example to access spiroindolenines reported in 2010 by You and coworkers involved an Ir-catalyzed allylic alkylation reaction of *N*-allyl tryptamine[4a] and that reported in 2021 by Breit and coworkers utilized a Rh-catalyzed stereoselective cyclization of 3-allenylindoles to generate spirocyclic indolenines[5d] (Scheme 1).

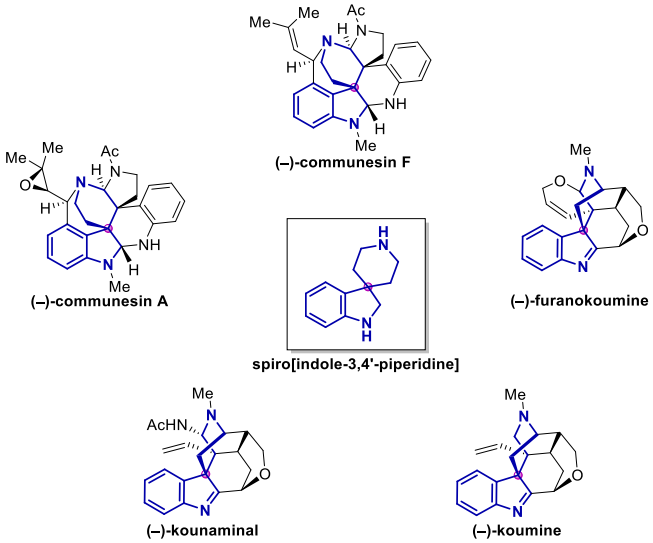


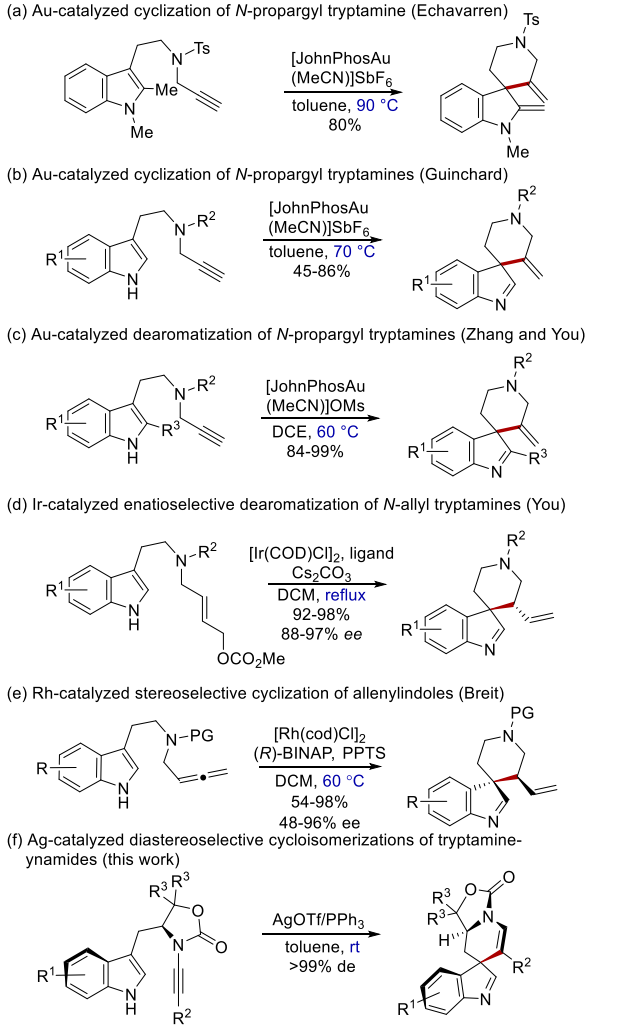
Figure 1. Natural products containing spiro[indole-3,4'-piperidine] scaffold.

The importance of tryptamine-ynamides as versatile building blocks in organic synthesis, especially in the construction of indoline scaffolds, has been established by many elegant pioneering works due to the development of synthetic methods

of tryptamine-ynamide.[6] Most cases reported to date relied on the electron-donating ability of nitrogen, leading to the regioselective addition of nucleophiles to the α-carbons of ynamides and the formation of spiro[indole-3,3'-pyrrolidine].[6a,b,d,e,i] Ye and our group reported the opposite regioselectivity via a umpolung-type additions of indole to ynamides controlled by the chelating group of nitrogen under the catalysis of metal such as copper and silver salts, resulting in formation of azepino[4,5-*b*]indole derivatives.[6f,7]

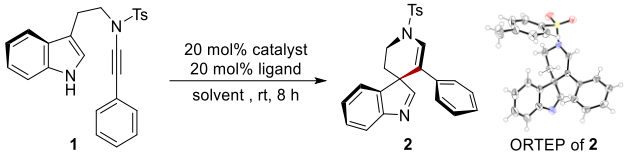
Herein, a Ag(I)/PPh_3-catalyzed chelation-controlled diastereoselective cycloisomerization of tryptamine-ynamide to access spiro[indole-3,4'-piperidine] was reported. It was shown that it could tolerate a wide range of substitutions under mild conditions. It was worth noting that this cyclization of tryptamine-ynamide substrates could proceed smoothly at room temperature, which was milder than those of the substrates bearing alkyne, alkene and allene as shown in Scheme 1 due to the higher reactivity of ynamide.

Scheme 1. Reported Strategies and Our Strategy to Spiro[indole-3,4'-piperidine]



First, substrate **1** was prepared via a copper-catalyzed coupling reaction to screen the reaction conditions.[6f] According to our previous study, PPh_3 was an excellent ligand by combining with silver salts in catalyzing the cycloisomerizations of tryptamine-ynamides.[8] Therefore, different silver salts (20 mol%) were examined in the presence of PPh_3 (20 mol%) using toluene as the solvent at room temperature for 8 h, in which the combination of AgOTf/PPh_3 afforded the spiro[indole-3,4'-piperidine] **2** with the best yield (Table 1, entries 1–4). The structure of the product **2** was determined by ^1H and ^{13}C NMR spectroscopies and single-crystal X-ray diffraction (CCDC 2104911). When the loadings of the catalyst and the ligand were decreased to 5 mol% and 10 mol%, the yields of the reaction dropped dramatically (Table 2, entries 5 and 6). The yield remained unchanged when 30 mol% of AgOTf/PPh_3 was utilized (Table 1, entry 7). In contrast, the yield dropped by 15% in the absence of PPh_3, suggesting that the ligand played an important role in the reaction (Table 1, entry 8). A blank control experiment was performed by removing silver triflate, which afforded no products. It indicated that silver triflate was the true catalytic species for this cyclization (Table 1, entry 9). However, increasing the loading of PPh_3 to 40 mol% had an adverse effect on the catalytic ability of the catalyst, possibly due to the over coordination of the ligand with the silver catalyst (Table 1, entry 10). Screening of solvents revealed that toluene was still the best one among the solvents examined such as THF, DCM and MeCN (Table 1, entries 11–13). Finally, the optimal condition was determined as to stir the substrate in toluene under the catalysis of 20 mol% AgOTf/20 mol% PPh_3 at room temperature for 8 h.

Table 1. Screening of Reaction Conditions[a]



entry	catalyst	ligand	solvent	yield (%)
1	$AgBF_4$	PPh_3	toluene	75
2	$AgSbF_6$	PPh_3	toluene	76
3	$AgNTf_2$	PPh_3	toluene	80
4	AgOTf	PPh_3	toluene	81
5	AgOTf	PPh_3	toluene	34[b]
6	AgOTf	PPh_3	toluene	45[c]
7	AgOTf	PPh_3	toluene	82[d]
8	AgOTf	–	toluene	66
9	–	PPh_3	toluene	0
10	AgOTf	PPh_3	toluene	53[e]
11	AgOTf	PPh_3	THF	60
12	AgOTf	PPh_3	DCM	66
13	AgOTf	PPh_3	MeCN	53

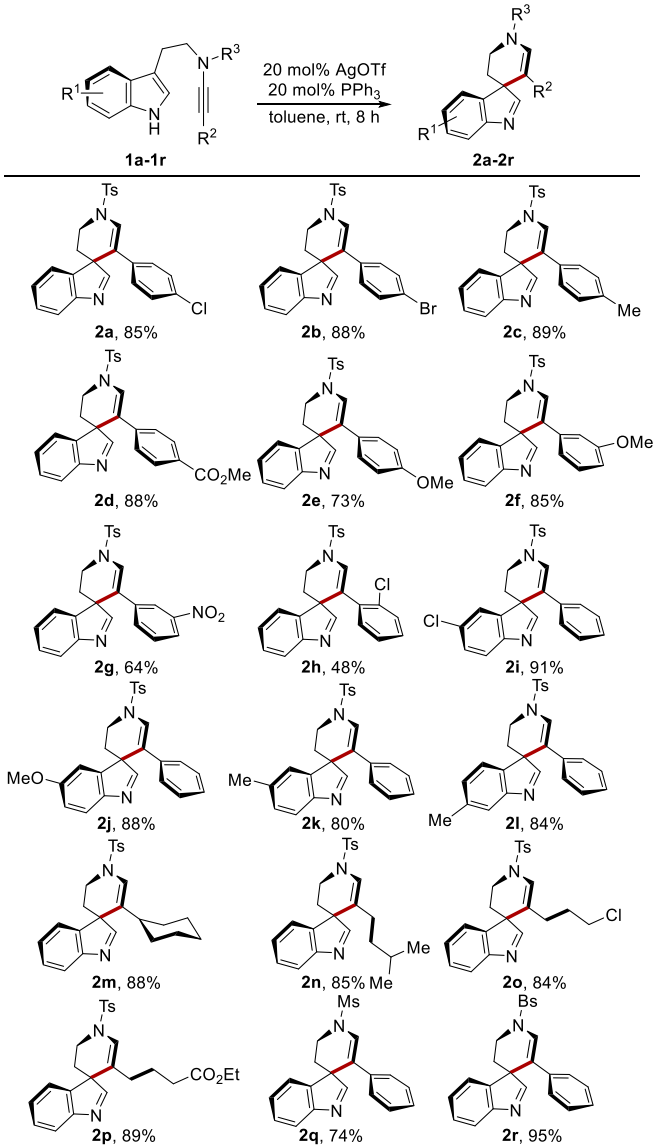
[a]Isolated yields and the ORTEP of **2** is shown with 50% probability ellipsoids.; [b]5 mol% AgOTf and 5 mol% PPh_3 were used; [c]10 mol% AgOTf and 0 mol% PPh_3 were used; [d]30 mol% AgOTf and 30 mol% PPh_3 were used; [e]40 mol% PPh_3 were used.

Next, the substrate scope of this cycloisomerization was examined by synthesizing a series of substituted substrates of tryptamine-ynamides. Under the optimal condition, all the substrates examined gave acceptable yields as shown in Scheme 2. The reactions proceeded smoothly to provide the desired products in moderate yields when the substitutions on the phenyl ring connected to the alkyl group were either electron-donating or electron-withdrawing groups (Scheme 2, **2a**–**2h**). The reactions of the substrates with substituted phenyl ring on indole also proceeded very well (Scheme 2, **2i**–**2l**). The substrates with alkyl substitutions on the alkyl moiety also gave excellent yields, although the reaction time had to be extended to 12 h (Scheme 2, **2m**–**2p**). The protective groups on the nitrogen of ynamide could be changed into mesylate or *p*-

bromobenzenesulfonyl without losing the efficiency of the cycloisomerization (Scheme 2, **2q**–**2r**).

After achieving the racemic syntheses of spiro[indole-3,4'-piperidine] derivatives, we proceeded to the diastereoselective syntheses of these spiro[indole-3,4'-piperidine] derivatives via a chiral pool strategy.[9] The chiral substrates **3a–3n** were prepared from commercially available L-tryptophan via a series of functional group transformations (see supporting information for more details). When the chiral substrates were subjected to the optimal conditions obtained in Table 1, the desired spiro[indole-3,4'-piperidine] products **4a–4n** were generated diastereoselectively as single isomers. The substitutions (R^3) on oxazolidin-2-one were examined by synthesizing substrates with hydrogen, methyl, ethyl and phenyl groups. All the synthetic substrates afforded the products with satisfactory yields (Scheme 3, **4a**–**4d**). The structure and stereochemistry of product **4a** were confirmed by NMR spectroscopy and the single-crystal X-ray diffraction (**4a**, CCDC 2104928). The substrates with different substitutions (R^2) on the alkyne were then examined. The reaction proceeded smoothly regardless of the substrates with

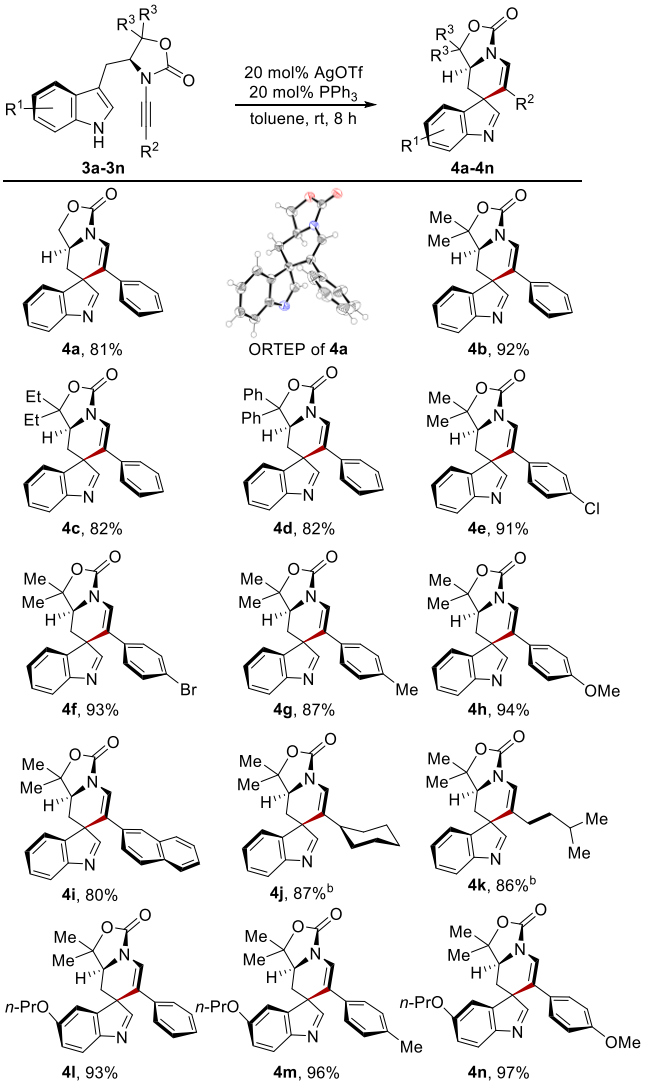
Scheme 2. Substrate Scope for the Syntheses of Spiro[indole -3,4'-piperidine] Derivatives



electron-withdrawing or electron-donating substituent phenyl on the alkyne (Scheme 3, **4e**–**4h**). The substrates with naphthalene and alkyl substitutions on the alkyne were also examined and provided the corresponding products with acceptable yields (Scheme 3, **4i**–**4k**).

The mechanism of the reaction was proposed based on the current experimental data and the literature[6f,h,7,8] as follows (Scheme 4). In the beginning, the complex **3b-1** was formed upon treating substrate **3b** with the cationic gold(I) species. The activated alkyne was then attacked by the C3 carbon atom of the indole under the control of the chiral oxazolidin-2-one moiety to give the spiroindoleninium intermediate **3b-2** diastereoselectively. Release of the catalyst by an intramolecular desilver protonation produced the spiroindolenine product **4b**. By examining the optimized geometries of intermediates **3b-1** and **3b-2**, it was observed that the iminium cation, the phenyl group connected to the alkynyl group, and the phenyl groups from PPh_3 were all within proximity of forming extensive non-covalent interactions. Therefore, a cation-π-π model was proposed to explain those interactions[6h,10] and it was corroborated by DFT calculations

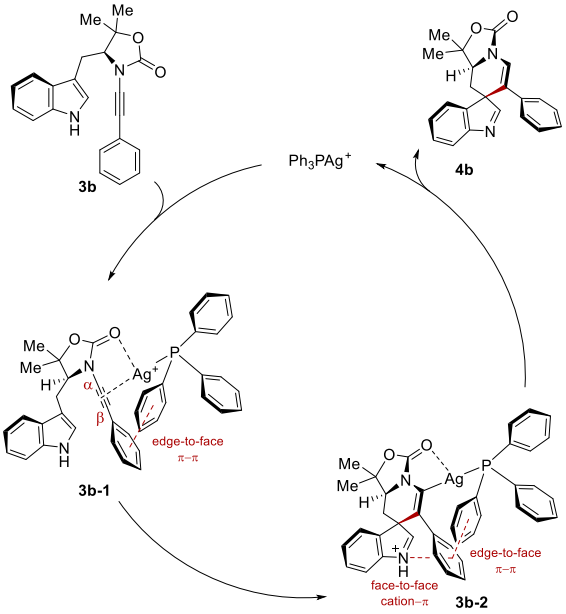
Scheme 3. Substrate Scope for the Diastereoselective Syntheses of Spiro[indole-3,4'-piperidine] Derivatives[a]



[a]The ORTEP of **4a** is shown with 50% probability ellipsoids.
[b]The reaction was performed for 12 h.

(Figure 2). It was shown that a silver ion was coordinated with the alkyne and the oxygen atom of the carbonyl group, forming complex **3b-1'** when the ligand PPh_3 was not added (Figure 2a). As a result, the positive charge was still mainly concentrated on the silver ion as seen from its electrostatic potential surface, making it highly reactive but less stable. When PPh_3 was added, complex **3b-1** was formed, introducing an edge-to-face π-π interaction between two phenyl groups. The concentrated positive charge on the silver atom was delocalized to the neighboring PPh_3 via electron redistribution, making it more evenly distributed therefore more stable (Figure 2b). The distance between the two phenyl groups was 5.69 Å, within the range of those experimental and computational results of typical edge-to-face π-π interactions.[6h] The same interactions were observed for intermediates **3b-2'** and **3b-2** with an extra layer of interaction between the positively charged indole nitrogen atom and the phenyl group in the middle. The cation-π interaction was distinctly visible from the electrostatic surface potential in Figure 2c and 2d. Such cation-π-π interactions provided further stability to the complex, allowing smooth leaving of the catalysts to produce **4b**.

Scheme 4. Proposed Mechanism of the Reaction



To achieve a scalable synthesis of the spiro[indole-3,4'-piperidine] for further applications in discovering structurally novel compounds, the reaction was performed on a gram scale without changing any conditions, affording the product successfully in 91% yield (Scheme 5).

The scalable synthesis of the spiro[indole-3,4'-piperidine] **4b** and its potentially modifiable imine moiety in structure inspired us to develop some protocols for further structural derivatizations. As shown in Scheme 6, under the catalysis of *L*-camphorsulfonic acid (*L*-CSA), the spirocyclic compound **4b**, as a significant building block could be transformed into azepino[4,5-*b*]indole derivative **5** via a Wagner-Meerwein rearrangement in 92% yield. When the product **4b** was subjected to $NaBH_4$ in refluxed MeOH, the imine group was readily reduced into amine to afford the product **6** in high yields. When the substrate was treated by $NaBH_4$ followed by the addition of formaldehyde and $NaBH_3CN$ in the presence of acetic acid, the product **7** was obtained in 51% yield via a reductive benzylation on the nitrogen of indole. When the imine was subjected to a sequential nucleophilic addition by TMSCN and hydrolysis condition, the amide product **8** was formed in 97% yield.

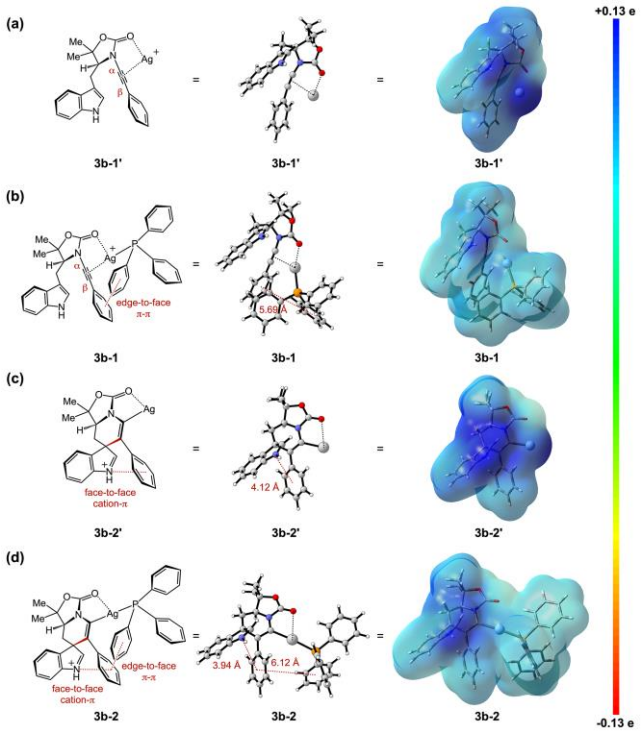
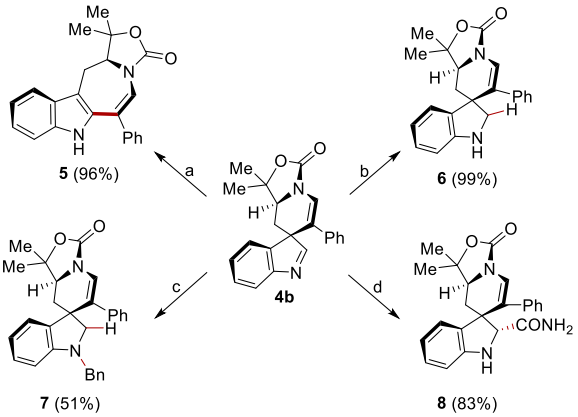


Figure 2. Proposed model of the cation-π-π interactions. 2D representations (left), 3D representations (middle), and 3D representations with electrostatic potential surfaces.

Scheme 5. Gram-Scale Synthesis of Spiro[indole-3,4'-piperidine]

Scheme 6. Derivatization of Spiro[indole-3,4'-piperidine]



a. *L*-CSA, DCM, rt. b. $NaBH_4$, MeOH, reflux. c. $NaBH_4$, MeOH; then PhCHO, AcOH, $NaBH_3CN$. d. TMSCN, K_2CO_3, MeOH, rt; then H_2O_2.

In summary, the Ag(I)/PPh_3-catalyzed chelation-controlled cycloisomerizations of tryptamine-ynamides via a umpolung-type addition to generate spiro[indole-3,4'-piperidine] skeleton were developed. The diastereoselective syntheses of

spiro[indole-3,4'-piperidine] derivatives were accomplished through a chiral pool strategy and gram-scale synthesis of the target scaffold was also achieved. This methodology enabled the collection of compound libraries containing the spiro[indole-3,4'-piperidine] scaffold for potential discovery of bioactive molecules through biological evaluations. DFT calculations of the intermediates of the reaction revealed that the cation-π-π interactions between the substrate and the catalyst/ligand complex was responsible for the stereoselectivity of the diastereoselective syntheses. The unique cation-π-π interactions in Ag(I)/Ph_3P-catalyzed cycloisomerizations provided an excellent example for predicting and interpreting the extensive non-covalent interactions in Ag(I)/Ph_3P-catalyzed transformations and possibly other related reactions. Applications of this methodology in medicinal chemistry and syntheses of relevant indole alkaloids are in progress in our laboratory and will be reported in due course.

ASSOCIATED CONTENT

Supporting Information

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

Experimental procedures, single-crystal X-ray analysis, computational data and compound characterization data (PDF)

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Author Contributions

All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

The research was supported by the Natural Science Foundation of China (Grant Number 21977073), Liaoning BaiQianWan Talents Program and Liaoning Revitalization Talents Program to Y. L. and by the Educational Department of Liaoning Province (Grant Number 2020LJC07) to B. L. The authors were grateful for the program for the innovative research team of the Ministry of Education and the program for the Liaoning innovative research team in university.

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