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ARTICLE

Stereoselective Synthesis of 3-Spiropiperidino Indolenines via S_N2-Type Ring Opening of Activated Aziridines with 1*H*-Indoles/Pd-Catalyzed Spirocyclization with Propargyl Carbonates

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3-Spiropiperidino indolenines have been synthesized via a novel Lewis acid-catalyzed S_N2-type ring opening of activated aziridines with 1*H*-indoles followed by Pd-catalyzed dearomative spirocyclization with propargyl carbonates in up to 88% yields. The step and pot-economic transformation comprises sequential C–C, C–N, and C–C bond forming steps generating two stereogenic centers including an all-carbon quaternary stereocenter to furnish the products in diastereomerically pure (dr >99:1) forms with excellent enantiomeric excess (ee up to >99%). The synthetic versatility of the strategy has been illustrated by converting the synthesized products into spirocyclic indolenine 2-piperidinones, dihydropiperidines, and 5-alkynylated piperidines.

3-Spiropiperidino indolenine is a privileged heterocyclic scaffold with exceptional pharmaceutical significance. It constitutes structural cores of several naturally-occurring alkaloids with valuable biological activities. Figure 1 shows a few such examples: **I** is a calcitonin gene-related peptide (CGRP) receptor antagonist for headache therapy,[1] **II** and **III** are 11β-hydroxysteroid dehydrogenase type-1 enzyme inhibitors useful in the treatment and prophylaxis of obesity and diabetes,[2] and (+)-koumine (**IV**) is the main alkaloid of *Gelsemium elegans* Benth. that is used as a folk medicine to treat migraines, neuralgia, sciatica, cancer, and various types of sores.[3]

Synthesis of spirocyclic indolenines[4] can be achieved by classical methodologies such as interruptive Fischer indolization employing arylhydrazines and cycloalkanecarbldehydes[5] or acid-mediated intramolecular cyclization of the corresponding arylhydrazones.[6] However, the most recent approach includes also spirocyclization of indoles with different electrophilic components including alkylation,[7] Pd/Ir/Ru-assisted addition to π-allyl intermediates derived from allylic acetates or carbonates,[8] intramolecular Michael/Mannich cascade reaction of indolyl methyl enones,[9] spirocyclization of *N*-arylisonicotinamides followed by hydrogenation and

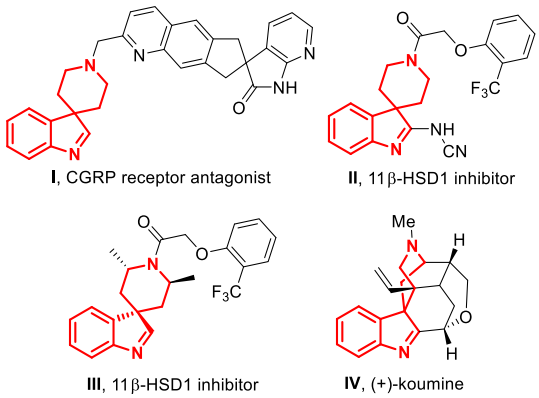

Figure 1. Biologically active 3-spiropiperidino indolenines.

reduction.[10] Other noteworthy routes involve intramolecular S_NAr reactions,[11] Ir-catalyzed allylic dearomatization of 2-iodoindoles,[12] Ag(I)-catalyzed intramolecular cycloisomerization of indolylcyclopropenes[13] etc. However, the few available methods for the synthesis of 3-spiropiperidino indolenines[8,12,13] suffer from limited substrate scope and functionalizability of the products as well as poor stereoselectivity.

In recent years, activated aziridines and azetidines have emerged as important building blocks in organic synthesis.[14] Our longstanding involvement in exploring and exploiting the area of Lewis acid (LA)-catalyzed S_N2-type ring-opening transformations of aziridines and azetidines has emanated several expedient methodologies such as ring-opening cyclization (ROC)[15] and domino ring-opening cyclization (DROC)[16] to directly access various aza-heterocycles. In this vein, we envisaged an effective and general stereoselective synthetic route to 3-spiropiperidino indolenines via LA-catalyzed ring opening of activated aziridines with 1*H*-indoles followed by Pd-catalyzed dearomative spirocyclization with propargyl carbonates. Herein, we report our preliminary results as a communication.

To begin with, 2-phenyl-*N*-tosylaziridine (**1a**) was reacted with 2-phenyl-1*H*-indole (**2a**) in the presence of 10 mol % $LiClO_4$ in acetonitrile at 80 °C for 3 h[15c] and the corresponding ring-opened product **3a** was obtained as a single regioisomer in 92% yield. **3a** was subsequently treated with *tert*-butyl prop-2-yn-1-

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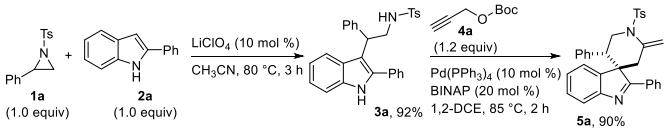
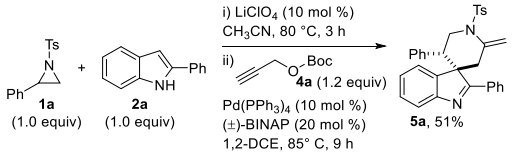
yl carbonate (**4a**) in the presence of 10 mol % $Pd(PPh_3)_4$ and 20 mol % (±)-BINAP in DCE at 85 °C and to our delight the desired 3-spiropiperidino indolenine **5a** was obtained with an exocyclic olefinic moiety at the 2-position of the piperidine ring in 90% yield in 2 h (Scheme 1).



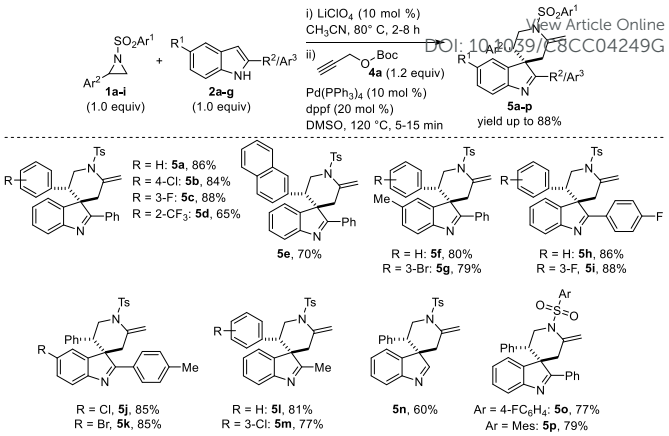
Scheme 1. Lewis acid-catalyzed S_N2-type ring opening of 2-phenyl-*N*-tosylaziridine with 2-phenyl-1*H*-indole followed by Pd-catalyzed dearomative spirocyclization

We subsequently achieved the pot-economy by conducting the ring opening of **1a** with **2a** in the presence of 10 mol % $LiClO_4$ in CH_3CN at 80 °C. Upon complete consumption of the starting materials, **4a** was added to the reaction mixture followed by the addition of 10 mol % $Pd(PPh_3)_4$ and 20 mol % (±)-BINAP in DCE and the temperature was elevated to 85 °C. The reaction completed in 9 h and **5a** was obtained in 51% overall yield (Scheme 2).



Scheme 2. One-pot synthesis of 3-spiropiperidino indolenine **5a**

The reaction conditions were optimized to obtain **5a** in an improved yield by screening several Pd catalysts, ligands, and solvents.[19] The best result was obtained with 10 mol % $Pd(PPh_3)_4$ and 20 mol % 1,1'-bis(diphenylphosphino)ferrocene (dppf) ligand in DMSO at 120 °C and in 5 min, **5a** was obtained in 86% yield. The approach was subsequently generalized by employing a diverse range of 2-aryl-*N*-tosylaziridines under the optimized reaction conditions. When 2-(4-chlorophenyl)-1-tosylaziridine (**1b**) was reacted with **2a** in the presence of 10 mol % $LiClO_4$ in acetonitrile at 80 °C for 3 h, the corresponding ring-opened product formed which thereafter underwent spirocyclization with **4a** to produce **5b** in 84% yield. Considering the importance and usefulness of the fluorinated[17] and trifluoromethylated[18] compounds in the pharmaceutical industry, we synthesized 3-spiropiperidino indolenines bearing various fluorine substituents. For this purpose, the 3-fluoro variant of the 2-aryl-*N*-tosylaziridine **1c** was treated with **2a** and **4a** under the optimized ROC conditions, and **5c** formed in 88% yield. Next, 1-tosyl-2-(2-(trifluoromethyl)phenyl)aziridine (**1d**) was reacted with **2a** and **4a** to obtain **5d** in 65% yield. To gauge the generality of the methodology in terms of stereoelectronic effect of the 2-aryl groups in the aziridine, 2-(naphthalen-2-yl)-1-tosylaziridine (**1e**) was reacted with **2a** and **5e** formed in 70% yield. We subsequently subjected various 2-ary-*N*-tosylaziridines and 2-aryl/alkyl substituted NH-free indoles to the optimized one-pot ROC conditions to further generalize the strategy. Electron-rich 5-methyl-2-phenyl-1*H*-indole (**2b**) was reacted with **1a** and **5f** formed in 80% yield within 15 min. The transformation was successful with 2-(3-bromophenyl)-*N*-tosylaziridine (**1f**) and **5g** was obtained in comparable yield (79%). Increase in the efficiency of the transformation was noted when 2-(4-fluorophenyl)-1*H*-indole (**2c**) was reacted with

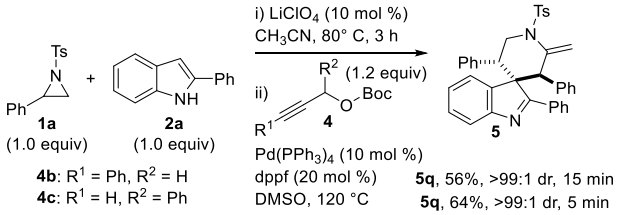


Scheme 3. Synthesis of 5′-Aryl-Substituted 3-Spiropiperidino Indolenines from 2-Arylaziridines

1a and **1c** separately in two different experiments, and the respective 3-spiropiperidino indolenines **5h** and **5i** were obtained in enhanced yields. Chloro (**2d**) and bromo substituents (**2e**) at the 5-position of the 2-*p*-tolyl-1*H*-indoles were well-accommodated in the strategy and the respective products **5j** and **5k** were obtained in excellent yields. When 2-methyl-1*H*-indole (**2f**) was reacted with **1a** and 2-(3-chlorophenyl)-*N*-tosylaziridine (**1g**), the respective products **5l** and **5m** formed in very high yields. Unsubstituted 1*H*-indole (**2g**) was also found to be a good candidate for the transformation which produced the corresponding 3-spiropiperidino indolenine **5n** in 60% yield. Notably, the various halogen groups appended around the molecular framework of **5** could naturally allow further synthetic elaborations to other biologically and synthetically significant compounds as demonstrated later in this paper. To study the electronic effect of the *N*-arylsulfonyl group on the strategy, 1-((4-fluorophenyl)sulfonyl)-2-phenylaziridine (**1h**) was exposed to the optimized reaction conditions with **2a** and **4a** and **5o** was obtained in 77% yield. On the other hand, when **1i** with a strong electron-donating mesityl group attached with the N-sulfonyl group was reacted with **2a** and **4a**, the corresponding product **5p** formed in marginally increased yield (79%). All the results are shown in Scheme 3.

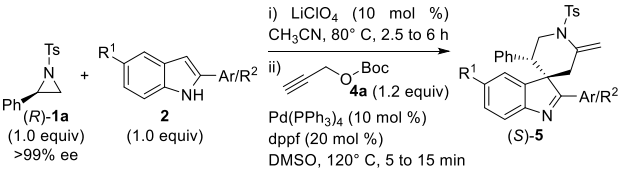
To gain a mechanistic insight, reactions were studied with phenyl- substituted propargyl carbonates. When ring opening of **1a** was carried out with **2a** followed by spirocyclization with *tert*-butyl (3-phenylprop-2-yn-1-yl) carbonate (**4b**), the corresponding 3′,5′-diphenyl-substituted 3-spiropiperidino indolenine **5q** was obtained as a single diastereomer in 56% yield (>99:1 dr, Scheme 4). When the experiment was revisited by employing **1a** and **2a** with the isomeric *tert*-butyl-(1-phenylprop-2-yn-1-yl) carbonate (**4c**), the formation of the same **5q** was also observed as a single diastereomer, in slightly enhanced yield (64%, >99:1 dr).[19] The relative stereochemistry of the two phenyl groups at the 3′ and 5′-positions of **5q** was found to be *trans* as determined by nuclear Overhauser effect (NOE) experiments.[19]

The synthetic significance of the strategy was further demonstrated by the synthesis of enantioenriched 3-spiropiperidino indolenines by reacting enantiopure activated aziridine (*R*)-**1a** (>99% ee) with a range of substituted 2-



Scheme 4. Diastereoselective Synthesis of 3-Spiropiperidino Indolenines from 2-Phenyl-*N*-tosylaziridine and Substituted Propargyl Carbonates

aryl/alkyl-1*H*-indoles. While 2-phenyl and 2-methyl-1*H*-indoles **2a** and **2f** furnished the respective products (*S*)-**5a** and (*S*)-**5l** with excellent enantiomeric excesses (99% ee), the substituted 2-aryl indoles **2b–d** produced the corresponding products (*S*)-**5f** (98% ee), (*S*)-**5h** (98% ee), and (*S*)-**5j** (95% ee) with slightly reduced optical purity (Scheme 5) which is probably due to the partial racemization of the starting enantiopure aziridine via ring-opening by indole followed by bond rotation and cyclization back to the other enantiomer of the aziridine. Another possibility: the ring-opening product may undergo another S_N2 attack by indole itself giving rise to the other enantiomer of the ring-opening product. We do believe that these two processes are responsible for reduced ee in these cases depending on the nucleophilicity of different indoles.[20]

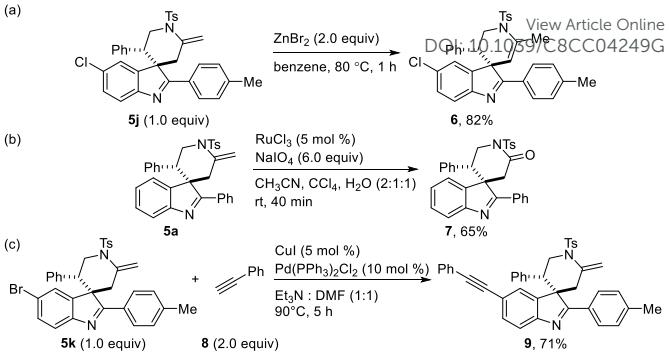


R1, Ar/R2: H, Ph, (*S*)-**5a**, 99% ee; Me, Ph, (*S*)-**5f**, 98% ee; H, 4-FC_6H_4, (*S*)-**5h**, 98% ee; Cl, *p*-Tol, (*S*)-**5j**, 95% ee; H, Me, (*S*)-**5l**, 99% ee

Scheme 5. Enantiospecific synthesis of 3-spiropiperidino indolenines from enantiopure 2-phenyl-*N*-tosylaziridine.

We envisaged a novel strategy to convert the synthesized 3-spiropiperidino indolenines into the isomeric dihydropyridines[21] by Lewis acid-catalyzed isomerization of the exocyclic double bond. Therefore, when **5j** was treated with 2.0 equiv of zinc(II) bromide in benzene at 80 °C for 1 h, the corresponding 3-spirodihydropyridino indolenine **6** formed in excellent yield (82%, Scheme 6a). We directed our subsequent efforts to construct 3-spiropiperidino indoleninone framework that could be useful as versatile synthetic precursors for other privileged heterocycles[22] from the synthesized 3-spiropiperidino indolenines by the oxidative cleavage of the exocyclic C=C bond. Accordingly, when **5a** was treated with 5 mol % ruthenium(III) chloride and 6.0 equiv of sodium periodate in a CH_3CN, CCl_4 and H_2O solvent system (2:1:1) at room temperature for 40 min,[23] the corresponding 3-spiropiperidino indoleninone **7** formed in 65% yield (Scheme 6b). We next attached a highly functionalizable 'alkyne arm'[24] to the synthesized 3-spiropiperidino indolenines by subjecting **5k** to the classic Sonogashira coupling reaction conditions[25] along with phenyl acetylene (**8**) in the presence of 5 mol % CuI and 10 mol % $Pd(PPh_3)_2Cl_2$ in 1:1 triethylamine and DMF solvent system at 90 °C for 5 h. Gratifyingly, we observed the formation of the corresponding coupling product **9** in 71% yield (Scheme 6c).

On the basis of the experimental observations, a plausible mechanism for the formation of 3-spiropiperidino indolenines has been provided in Scheme 7. At first, the Lewis acid



Scheme 6. Lewis acid-catalyzed isomerization of 3-Spiropiperidino Indolenine to 3-Spirodihydropyridino Indolenine.

co-ordinates with the nitrogen of the aziridine **1** (or with the sulfonyl oxygen) to generate a highly reactive intermediate **A**. The indole nucleophile attacks the benzylic position of **A** in an S_N2 fashion to generate **B** that subsequently rearomatizes to generate the corresponding ring-opened product **3**. In the next step, the propargyl carbonate **4** and Pd(0) catalyst get involve in a decarboxylative oxidative addition reaction to form the cationic Pd-allenyl species **C**. The in-situ generated *tert*-butoxide anion deprotonates the N–H of the sulfonamide group of **3** leading to the anionic species **D**. Next, the negatively charged nitrogen of the sulfonamide group attacks the central carbon of Pd-allene **C** to form the Pd-carbenoid species **E** that subsequently undergo proton migration to form the corresponding Pd-π-allyl species **F**. Subsequent spirocyclization from the indolyl-C3 center and reductive elimination generate the desired 3-spiropiperidino indolenine **5** and Pd(0) reenters into the catalytic cycle. Now, the formation of **5q** from the reactions of aziridine **1a** and 1*H*-indole **2a** with the isomeric phenyl-substituted propargyl carbonates **4b** and **4c** could only be explained by the presence of a common intermediate **F** due to its delocalized nature. The concomitant spirocyclization from the indolyl-C3 center must take place at the more stable benzylic position of the Pd-π-allyl species **F**. Formation of the *cis* diastereomer of **5q** would result in severe steric congestion between 2-Ph and 3'-Ph groups which is absent in the trans diastereomer. Hence, both transformations exclusively favor the formation of the trans diastereomer **5q** (Scheme 7).

To conclude, we have developed a highly valued transformation for the synthesis of a wide range of 3-spiropiperidino indolenines possessing an exocyclic olefinic moiety at the 2-position of the piperidine ring via one-pot Lewis acid catalyzed S_N2-type ring opening of activated aziridines with 2-substituted 1*H*-indoles followed by Pd-catalyzed spirocyclization with propargyl carbonates. The high yields, excellent diastereo- and enantiospecificity and the wide substrate scope of the synthesized products underscore the utility and efficiency of the transformation. We strongly believe that the methodology will be useful in synthetic organic and medicinal chemistry for the construction of such spirocyclic aza-heterocycles of biological relevance.

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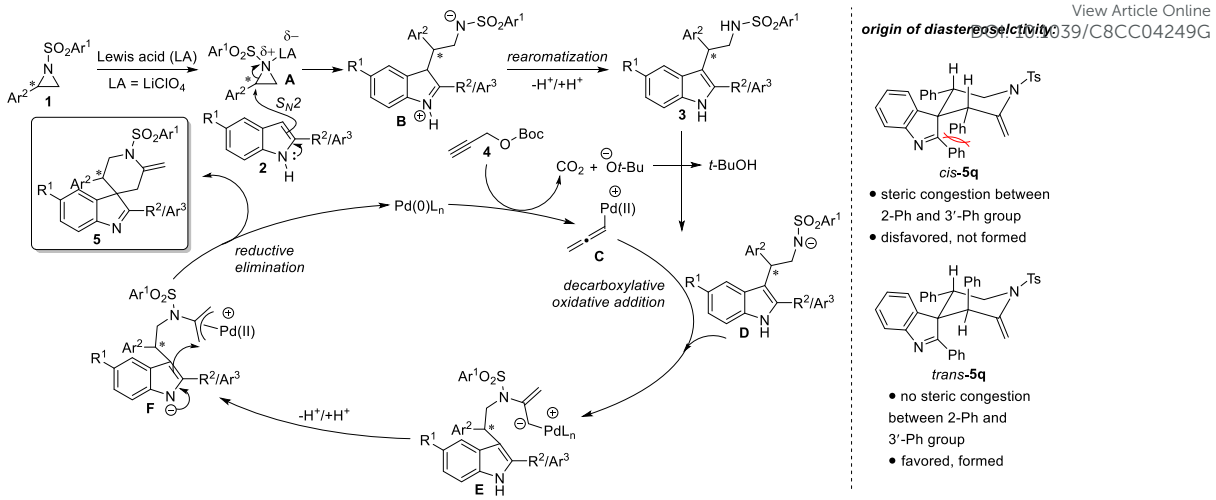

Scheme 7. Plausible mechanistic pathway for the synthesis of 3-spiropiperidino indolenines from activated aziridines via ring opening with 1*H*-indoles followed by dearomatizing spirocyclization with propargyl carbonate.

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