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Synthesis of Six-Membered Spiro Azacyclic Oxindole Derivatives via a One-Pot Process of Umpolung Allylation/Aza-Prins Cyclization

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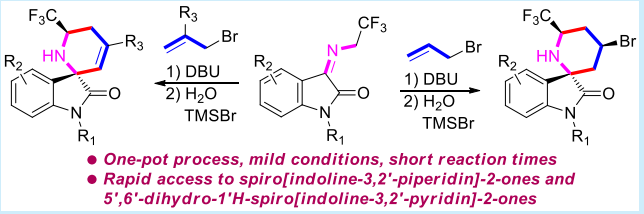
ABSTRACT: An unprecedented synthetic approach involving umpolung allylation/aza-Prins cyclization of *N*-2,2,2-trifluoroethylisatin ketimines is described. The reactions proceed smoothly with allyl bromide in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene, H_2O, and trimethylsilyl bromide; this one-pot protocol allows access to six-membered spiro azacyclic oxindole derivatives in good to excellent yields. Notably, while the general aza-Prins cyclization involves amines and aldehydes, the present synthetic strategy represents the first aza-Prins cyclization that utilizes the umpolung property of *N*-2,2,2-trifluoroethylisatin ketimines.



Spirooxindoles, which are prevalent in natural products,[1] are attractive target motifs owing to their diverse biological activities.[2] Among these molecules, spiro *N*-heterocyclic oxindoles exhibit important pharmacological activities such as IRAP inhibitory, SIRT1 inhibitory, antibreast cancer, antitumor, and antimalarial activities (Figure 1).[3] In addition, the trifluoromethyl group has been known to improve the metabolic stability, bioavailability, and lipophilicity of bioactive molecules.[4] Despite their importance, only a few synthetic methods that use *N*-2,2,2-trifluoroethylisatin ketimines have been developed for the construction of spiro *N*-heterocyclic oxindoles featuring CF_3 groups.[5]

Zhao and co-workers have accomplished the [3 + 3] cycloaddition of *N*-2,2,2-trifluoroethylisatin ketimines and *N*,*N*′-dialkyloxyureas in the presence of NaH and PhI(OH)(OTs) for the synthesis of spiro-1,3,5-triazinan-2-one oxindoles.[6] Azomethine ylides reacted with *N*,*N*′-dialkyloxy diaza-

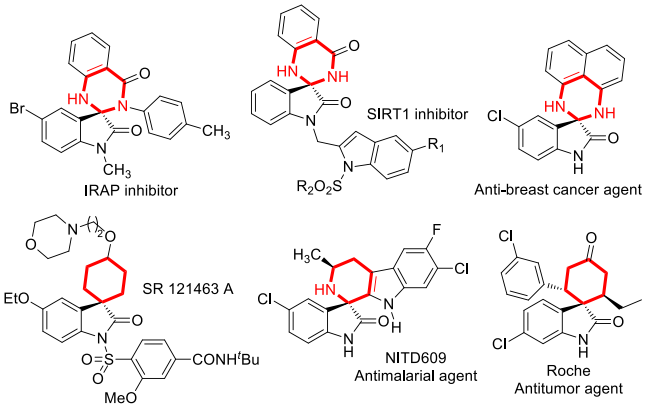
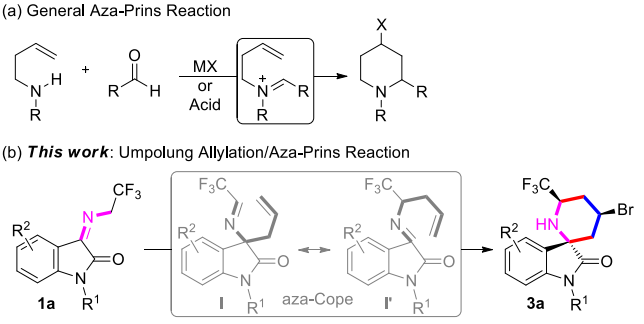


Figure 1. Representative examples of bioactive molecules containing the spirooxindole motif

Scheme 1. Synthetic Strategies for Spirooxindole Derivatives: (a) General Aza-Prins Reaction; (b) One-Pot Umpolung Allylation/Aza-Prins Reaction



allyl cations generated *in situ* in moderate yields. To the best of our knowledge, this is the only reported example of [3 + 3] cycloaddition of *N*-2,2,2-trifluoroethylisatin ketimines thus far. Consequently, a practical and efficient synthetic methodology for six-membered spiro azacyclic oxindole backbones remains.

The well-established aza-Prins cyclization[7,8] is a stereoselective strategy for the synthesis of piperidines. Generally, the aza-Prins cyclization involves the condensation of homoallylic amines with aldehydes in the presence of a Lewis acid to generate iminium ions, which cyclize spontaneously through intramolecular nucleophilic attack from the olefin (Scheme 1a). Inspired by the aza-Prins cyclization, we

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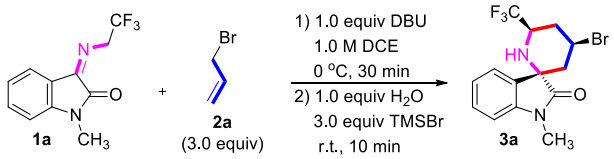
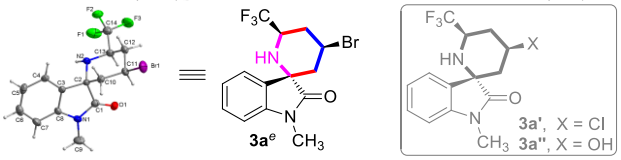
Table 1. Optimization of Reaction Conditions[a,e]

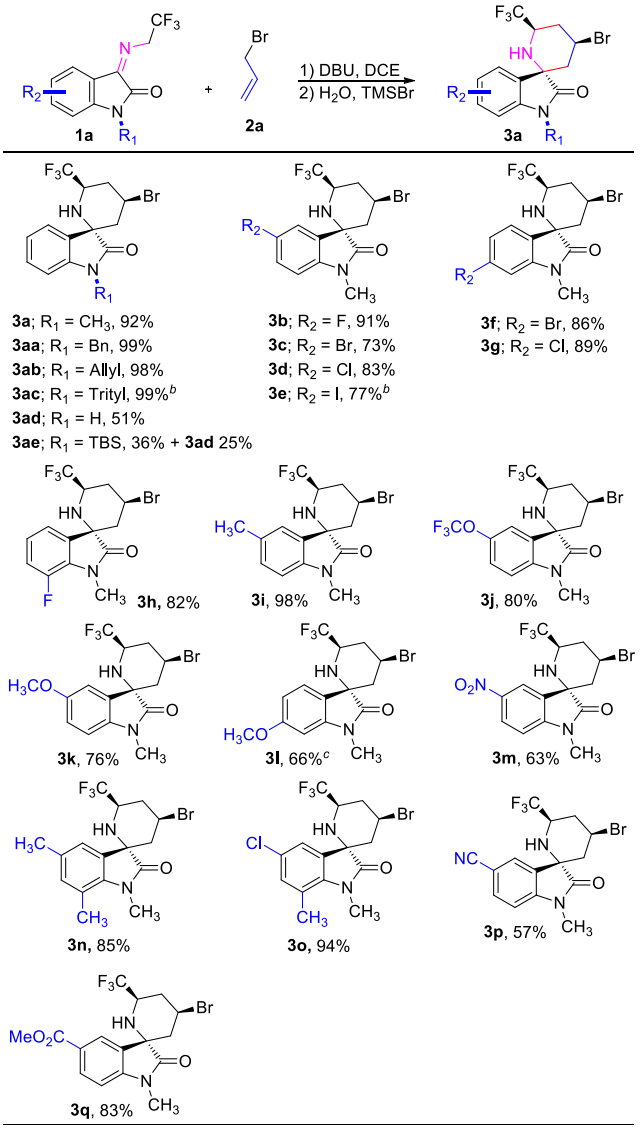


entry	variation from standard conditions	3a[b] (%)
1	$CHCl_3$, DCM, or CH_3CN/-10 °C/40 °C	89, 88, 82
2	−10 °C/40 °C	92
3[c]	−10 °C	92
4	none	92
5[c]	rt	80
6	without H_2O/−10 °C/40 °C, 48 h	59
7[d]	DCM/2.0 equiv TMSBr, 40 °C, 18 h	70
8	2.0 equiv **2a**	88
9	^{t}BuOK	trace
10	Cs_2CO_3	no reaction
11	$BF_3{\cdot}OEt_2$	75
12	TMSI, TMSOAc, or $InCl_3$	N.D.
13	TMSCl	11/7 (**3a′**)
14	TMSOTf	36/11 (**3a″**)
15	TESOTf	15/31 (**3a″**)
16	$TiCl_4$	14/32 (**3a′**)
17	$FeCl_3$	5/4 (**3a′**)
18	$Cu(OTf)_2$	0/4 (**3a″**)



[a]Reaction conditions: **1a** (0.1 mmol), **2a** (3.0 equiv), and DBU (1.0 equiv) in DCE (1.0 M), 0 °C, 30 min; then H_2O (1.0 equiv), TMSBr (3.0 equiv), rt, 10 min. [b]Isolated yield. [c]Temperature of the allylation step. [d]Temperature and time of the cyclization step. [e]The ellipsoids are drawn at the 50% probability level.

Scheme 2. Substrate Scope of Ketimines[a]



[a]Reaction conditions: **1a** (0.1 mmol), **2a** (3.0 equiv), and DBU (1.0 equiv) in DCE (1.0 M), 0 °C, 30 min; then H_2O (1.0 equiv), TMSBr (3.0 equiv), rt, 10 min. [b]30 min for the cyclization step. [c]−10 °C, 30 min for the allylation step and 40 °C, 12 h for the cyclization step.

envisioned that *N*-2,2,2-trifluoroethylisatin ketimine is a suitable substrate for the synthesis of six-membered spiro azacyclic oxindoles via an umpolung allylation/aza-Prins reaction (Scheme 1b). Unlike previous aza-Prins reactions, this synthetic method would take advantage of the umpolung property of *N*-2,2,2-trifluoroethylisatin ketimine.[9] Thus, we decided to investigate the umpolung allylation/aza-Prins reaction of *N*-2,2,2-trifluoroethylisatin ketimines in a one-pot process for the preparation of spiro[indoline-3,2′-piperidin]-2-ones. Herein, we report the first efficient and facile synthetic methodology that uses the umpolung allylation/aza-Prins reaction of *N*-2,2,2-trifluoroethylisatin ketimines to produce useful spiro[indoline-3,2′-piperidin]-2-ones and 5′,6′-dihydro-1′*H*-spiro[indoline-3,2′-pyridin]-2-ones.

Initially, we used ketimine **1a**[6,10−14] as the standard substrate to screen various sets of reaction conditions with allyl bromide **2a**, and the results are summarized in Table 1. In the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 1.0 equiv), **1a** and **2a** (3.0 equiv) were reacted in $CHCl_3$ at −10 °C for 30 min; then H_2O (1.0 equiv) and trimethylsilyl bromide (TMSBr, 3.0 equiv) were added, and the reaction continued at 40 °C for 10 min. Gratifyingly, desired product **3a** was isolated in 89% yield; it was also obtained in 88%, 82%, and 92% yields when dichloromethane (DCM), CH_3CN, and dichloroethane (DCE), respectively, were used (entries 1 and 2). The structure of **3a** was confirmed by single-crystal X-ray diffraction analysis (CCDC 2053124). When the temperature of the cyclization step was lowered from 40 °C to room temperature or that of the allylation step was raised from −10 to 0 °C, the reaction afforded **3a** in very high yields (entries 3 and 4). In contrast, when the reaction was attempted with an allylation step at room temperature or without H_2O in the cyclization step, lower yields of **3a** were observed (entries 5 and 6). Interestingly, 1.0 equiv of H_2O critically affected the yield of the product. Furthermore, when 2.0 equiv of **2a** or TMSBr was utilized, **3a** was generated in yields of 88% and 70%, respectively (entries 7 and 8). Next, the use of various bases was examined; however, **3a** was not produced (entries 9 and 10). Additionally, various reagents that trigger aza-Prins cyclization other than TMSBr were investigated (entries 11−18). In the presence of $BF_3{\cdot}OEt_2$, **3a** was provided in yield of 75%, while no desired products were formed in the presence of TMSI, TMSOAc, or $InCl_3$. The expected allylation/aza-Prins reaction occurred when TMSCl,

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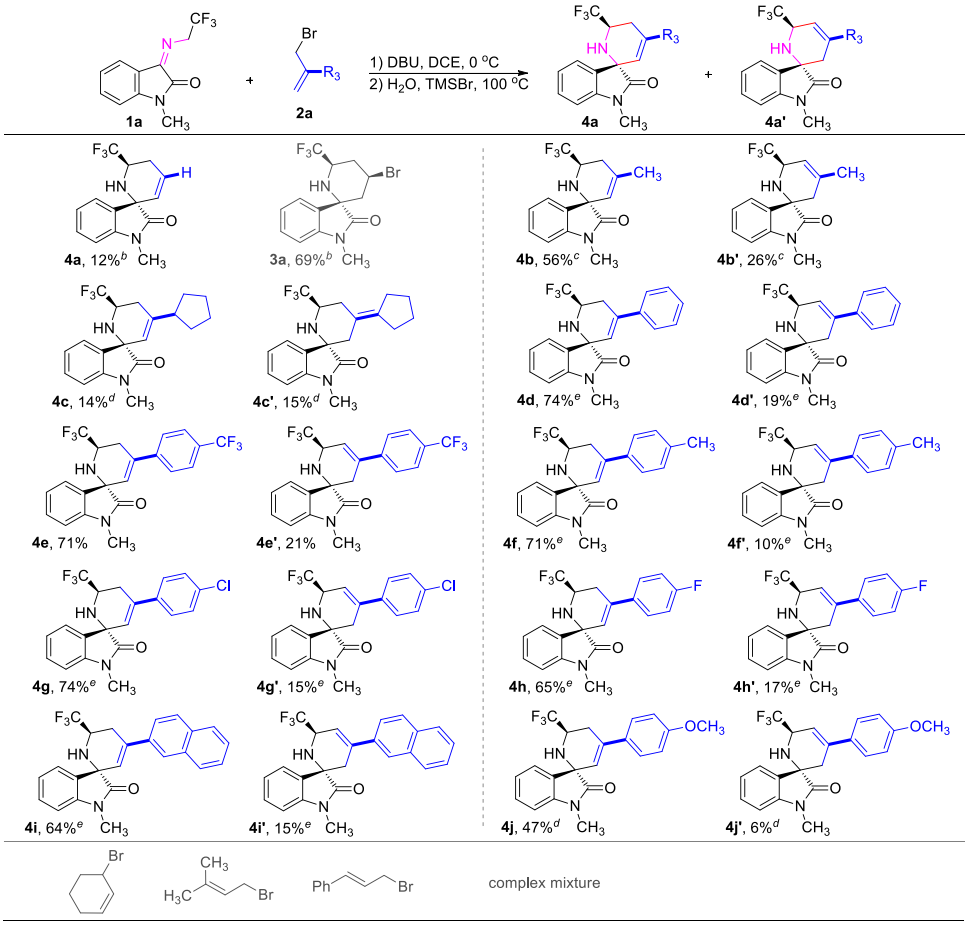
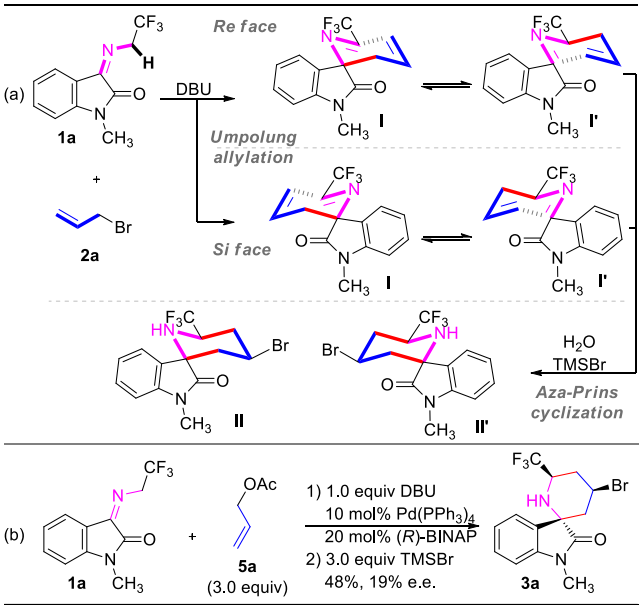
Scheme 3. Substrate Scope of Dihydro-1′*H*-spiro[indoline-3,2′-pyridin]-2-one Synthesis[a]



[a]Reaction conditions: **1a** (0.1 mmol), **2a** (1.5 equiv), and DBU (1.0 equiv) in DCE (1.0 M), 0 °C, 30 min; then H_2O (1.0 equiv), TMSBr (3.0 equiv), 100 °C, 1 h. [b]CH_3CN was used instead of DCE. [c]**2a** (3.0 equiv) was used; 12 h for the cyclization step. [d]Allyl tosylate was used instead of allyl bromide; rt for the cyclization step. [e]rt for the cyclization step.

Scheme 4. Proposed Reaction Mechanism



$TiCl_4$, or $FeCl_3$ was used, affording mixtures of **3a** and **3a′**, which were separated completely, in combined yields of 18%, 46%, and 9%, respectively. Similarly, when 3.0 equiv of TMSOTf or triethylsilyl triflate (TESOTf) was used, mixtures of **3a** and **3a″**, which were isolated by column chromatography, were obtained in combined yields of 47% and 46%, respectively. Finally, the reaction was attempted using $Cu(OTf)_2$, and a trace amount of **3a″** was observed.

With the optimal reaction conditions in hand, we explored the ketimine substrate scope, and the results are shown in Scheme 2. The reactions with *N*-protected ketimines featuring a benzyl, allyl, or trityl group gave excellent yields of 99%, 98%, and 99%, respectively (**3aa**−**3ac**). Unprotected ketimine **1ad**[6,10,12] reacted smoothly to generate **3ad** in a yield of 51%, while a mixture of **3ae** and **3ad** was obtained from *N*-*tert*-butyldimethylsilyl (TBS)-protected ketimine **1ae**[12] in a combined yield of 61%. 5-Halogen-substituted ketimines produced the corresponding products **3b**, **3c**, **3d**, and **3e** in 91%, 73%, 83%, and 77% yields, respectively. Similarly, the expected products **3f**, **3g**, and **3h** were furnished in good yields of 86%, 89%, and 82%, respectively, from 6-bromo-, 6-chloro-, and 7-fluoro-*N*-2,2,2-trifluoroethylisatin ketimines. The reactions of 5-methyl and 5-trifluoromethoxy ketimines **1i**[6,10−13] and **1j**[12] gave products **3i** and **3j** in 98% and 80% yields, respectively. In the case of *N*-2,2,2-trifluoroethylisatin ketimines with a methoxy group at the C5 or C6 position, the targeted products **3k** and **3l** were produced in good yields of 76% and 66%, respectively. The

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reaction with 5-electron-withdrawing group substituted ketimines **1m**,[10−12] **1p**, and **1q** led to the formation of the desired products **3m**, **3p**, and **3q** in 63%, 57%, and 83% yields, respectively. With disubstituted ketimines **1n**[12] and **1o**,[12] the corresponding products **3n** and **3o** were synthesized in excellent yields of 85% and 94%, respectively.

Next, encouraged by these results, we focused our attention on the scope of the allyl bromides as coupling partners (Scheme 3). When the reaction of methyl-substituted allyl bromide **2b** was conducted, a mixture of at least four compounds was detected. It was attributed to the formation of a mixture of diastereomers due to a quaternary center at the C4 and C2 positions of the piperidine backbone and to a trace amount of tetrahydropyridine triggered by DBU. To avoid the difficult separation of the mixture and complicacy, reaction temperatures ranging from 60 to 100 °C were examined for the aza-Prins cyclization step. At 100 °C, spiro *N*-heterocyclic oxindoles **4b** and **4b′**, which were isolated using column chromatography, with carbon−carbon double bonds in the six-membered rings were generated in yields of 56% and 26%, respectively. Using the optimal reaction conditions, the reaction of ketimine **1a** with **2a** was attempted, affording **4a** and **3a** in yields of 12%, and 69%, respectively. Cyclopentyl-substituted allyl tosylate **2c**[15] was converted to the products **4c** and **4c′** in 14% and 15% yields, respectively. The expected products **4d** and **4d′** were obtained in a combined yield of 93% from phenyl-substituted allyl bromide. In contrast to the alkyl groups, the phenyl group enhanced the reaction, and this was attributed to the construction of a fully conjugated styrene moiety in the structure of the product. When **1a** was treated with **2e**[16,17] or **2f**,[16−19] mixtures of regioisomers **4e** and **4e′** and regioisomers **4f** and **4f′** were formed in combined yields of 92% and 81%, respectively. *p*-Chlorophenyl- and *p*-fluorophenyl-substituted allyl bromides **2g**[16−19] and **2h**[17−19] were tolerated, and they yielded the adducts **4g** and **4g′** and adducts **4h** and **4h′** in combined yields of 89% and 82%, respectively. In the case of polyaromatic substituted allyl bromide **2i**,[16,19] the corresponding products **4i** and **4i′** were prepared in yields of 64% and 15%, respectively. The reaction with **2j**[20] led to give the products **4j** and **4j′** in a combined yield of 53%. Allyl bromides with a variety of substituents at the C1 position could not be converted to the anticipated products owing to steric hindrance.

Based on the experimental results, a possible reaction mechanism, depicted in Scheme 4, was proposed for the synthesis of **3a** from ketimine **1a** via umpolung allylation/aza-Prins cyclization. Hydrogen on the carbon atom adjacent to the CF_3 group in ketimine **1a** is abstracted by DBU to generate an 2-azaallyl anion, which reacts with allyl bromide (Scheme 4a). Interestingly, the 2-azaallyl anion furnishes intermediates **I** and **I′** in a ratio of 1:0.2, according to ^{1}H NMR spectroscopy. This result showed well-known umpolung reactivity[9a,b,21] of ketimine **1a**, which acts as a nucleophile through the imine carbon on either the *Re*- or *Si*-face. In addition, some 2-azaallyl anions spontaneously undergo aza-Cope rearrangement to produce **I′** or allylation occurs at the nucleophilic carbon adjacent to the CF_3 group. Finally, the intermediates **I** and **I′** transform into the desired products **II** and **II′** through aza-Prins cyclization in the presence of H_2O and TMSBr. Remarkably, water does not react with intermediates **I** and **I′** as a nucleophile; thus, we assume that water either solubilizes the iminium bromide generated from DBU to prevent whatever hampers the reaction[22] or activates TMSBr to accelerate aza-Prins cyclization.[23] Furthermore, preliminary studies have shown that chiral phosphine ligands, such as (*R*)-BINAP, affect the desymmetrization of **1a** with promising levels of enantioselectivity (Scheme 4b, 19% enantiomeric excess (ee)). This result suggests that umpolung allylation/aza-Prins cyclization is amenable to an asymmetric catalysis system, and this research is underway.

In conclusion, we have demonstrated the first umpolung allylation/aza-Prins cyclization of *N*-2,2,2-trifluoroethylisatin ketimines for the syntheses of spiro[indoline-3,2′-piperidin]-2-ones and 5′,6′-dihydro-1′*H*-spiro[indoline-3,2′-pyridin]-2-ones in a one-pot process. The six-membered spiro azacyclic oxindole framework, which is found often in natural products and pharmaceuticals, is considered as an important structure that requires facile synthetic routes toward the development of new drug candidates because of the bioactivity of compounds possessing this motif. The developed protocol, which grants access to this crucial scaffold, features a single-step process with broad functional group tolerance under transition-metal free conditions. Moreover, a new [3 + 3] cycloaddition strategy involving aza-Prins cyclization and utilizing the umpolung reactivity of ketimines was established, enabling the construction of six-membered spiro azacyclic oxindoles. This aza-Prins cyclization differs clearly from the general version, which involves an amine, aldehyde, and acid. Further investigations for controlling the enantioselectivity are ongoing.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00292.

Experimental procedures, characterization data, and copies of all ^{1}H and ^{13}C NMR spectra for all isolated compounds (PDF)

Accession Codes

CCDC 2053124 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Lin, H.; Danishefsky, S. J. Gelsemine: A Thought-Provoking Target for Total Synthesis. *Angew. Chem., Int. Ed.* **2003**, *42*, 36−51. (b) Galliford, C. V.; Scheidt, K. A. Pyrrolidinyl-Spirooxindole Natural Products as Inspirations for the Development of Potential Therapeutic Agents. *Angew. Chem., Int. Ed.* **2007**, *46*, 8748−8758.

(2) (a) Venkatesan, H.; Davis, M. C.; Altas, Y.; Snyder, J. P.; Liotta, D. C. Total Synthesis of SR 121463 A, a Highly Potent and Selective Vasopressin V2 Receptor Antagonist. *J. Org. Chem.* **2001**, *66*, 3653−3661. (b) Lo, M. M.-C.; Neumann, C. S.; Nagayama, S.; Perlstein, E. O.; Schreiber, S. L. A Library of Spirooxindoles Based on a Stereoselective Three-Component Coupling Reaction. *J. Am. Chem. Soc.* **2004**, *126*, 16077−16086. (c) Kotha, S.; Deb, A. C.; Lahiri, K.; Manivannan, E. Selected Synthetic Strategies to Spirocyclics. *Synthesis* **2009**, *2009*, 165−193.

(3) (a) Engen, K.; Sävmarker, J.; Rosenström, U.; Wannberg, J.; Lundbäck, T.; Jenmalm-Jensen, A.; Larhed, M. Microwave Heated Flow Synthesis of Spiro-oxindole Dihydroquinazolinone Based IRAP Inhibitors. *Org. Process Res. Dev.* **2014**, *18*, 1582−1588. (b) Rambabu, D.; Raja, G.; Sreenivas, B. Y.; Seerapu, G. P. K.; Kumar, K. L.; Deora, G. S.; Haldar, D.; Rao, M. V. B.; Pal, M. Spiro heterocycles as potential inhibitors of SIRT1: Pd/C-mediated synthesis of novel *N*-indolylmethyl spiroindoline-3,2′-quinazolines. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 1351−1357. (c) Arya, K.; Dandia, A. Regioselective Synthesis of Biologically Important Scaffold Spiro [Indole-Perimidines]: An Antitumor Agents. *Lett. Org. Chem.* **2007**, *4*, 378−383. (d) Ashton, T. D.; Devine, S. M.; Möhrle, J. J.; Laleu, B.; Burrows, J. N.; Charman, S. A.; Creek, D. J.; Sleebs, B. E. The Development Process for Discovery and Clinical Advancement of Modern Antimalarials. *J. Med. Chem.* **2019**, *62*, 10526−10562. (e) Chang, M.-Y.; Pai, C.-L.; Kung, Y.-H. Synthesis of (±)-coerulescine and a formal synthesis of (±)-horsfiline. *Tetrahedron Lett.* **2005**, *46*, 8463−8465. (f) Serradeil-Le Gal, C.; Lacour, C.; Valette, G.; Garcia, G.; Foulon, L.; Galindo, G.; Bankir, L.; Pouzet, B.; Guillon, G.; Barberis, C.; Chicot, D.; Jard, S.; Vilain, P.; Garcia, C.; Marty, E.; Raufaste, D.; Brossard, G.; Nisato, D.; Maffrand, J. P.; Le Fur, G. Characterization of SR 121463A, a highly potent and selective, orally active vasopressin V2 receptor antagonist. *J. Clin. Invest.* **1996**, *98*, 2729−2738. (g) Beccalli, E. M.; Clerici, F.; Gelmi, M. L. A new synthetic procedure to spiro[cyclohexane-1,3′-indoline]-2′,4-diones. *Tetrahedron* **2003**, *59*, 4615−4622. (h) Liu, J.-J.; Zhang, Z. Spiroindolinone derivatives. (Hoffmann-LaRoche AG) PCT Int. Appl. WO2008/055812, 2008.

(4) (a) Smits, R.; Cadicamo, C. D.; Burger, K.; Koksch, B. Synthetic strategies to α-trifluoromethyl and α-difluoromethyl substituted α-amino acids. *Chem. Soc. Rev.* **2008**, *37*, 1727−1739. (b) Wang, J.; Sanchez-Rosello, M.; Acena, J. L.; del Pozo, C.; Sorochinsky, A. E.; Fustero, S.; Soloshonok, V. A.; Liu, H. Fluorine in Pharmaceutical Industry: Fluorine-Containing Drugs Introduced to the Market in the Last Decade (2001−2011). *Chem. Rev.* **2014**, *114*, 2432−2506. (c) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. Fluorine in medicinal chemistry. *Chem. Soc. Rev.* **2008**, *37*, 320−330. (d) Liang, T.; Neumann, C. N.; Ritter, T. Introduction of Fluorine and Fluorine-Containing Functional Groups. *Angew. Chem., Int. Ed.* **2013**, *52*, 8214−8264. (e) Merino, E.; Nevado, C. Addition of CF_3 across unsaturated moieties: a powerful functionalization tool. *Chem. Soc. Rev.* **2014**, *43*, 6598−6608. (f) Egami, H.; Sodeoka, M. Trifluoromethylation of Alkenes with Concomitant Introduction of Additional Functional Groups. *Angew. Chem., Int. Ed.* **2014**, *53*, 8294−8308. (g) Besset, T.; Poisson, T.; Pannecoucke, X. Recent Progress in Direct Introduction of Fluorinated Groups on Alkenes and Alkynes by means of C-H Bond Functionalization. *Chem. - Eur. J.* **2014**, *20*, 16830−16845.

(5) Gui, H.-Z.; Wei, Y.; Shi, M. Recent Advances in the Construction of Trifluoromethyl-Containing Spirooxindoles through Cycloaddition Reactions. *Chem. - Asian J.* **2020**, *15*, 1225−1233.

(6) Zhao, H.-W.; Guo, J.-M.; Wang, L.-R.; Ding, W.-Q.; Tang, Z.; Song, X.-Q.; Wu, H.-H.; Fan, X.-Z.; Bi, X.-F. Diastereoselective formal [3 + 3] cycloaddition of isatin-based α-(trifluoromethyl)imines with *N,N*′-dialkyloxyureas. *Org. Chem. Front.* **2019**, *6*, 3891−3895.

(7) For reviews, see: (a) Olier, C.; Kaafarani, M.; Gastaldi, S.; Bertrand, M. P. Synthesis of tetrahydropyrans and related heterocycles *via* Prins cyclization; extension to aza-Prins cyclization. *Tetrahedron* **2010**, *66*, 413−445. (b) Pastor, I. M.; Yus, M. Focused Update on the Prins Reaction and the Prins Cyclization. *Curr. Org. Chem.* **2012**, *16*, 1277−1312.

(8) For recent selected examples, see (a) Osawa, C.; Tateyama, M.; Miura, K.; Tayama, E.; Iwamoto, H.; Hasegawa, E. An Effective Procedure to Promote Aza−Prins Cyclization Reactions Employing a Combination of Ferric Chloride and an Imidazolium Salt in Benzotrifluoride. *Heterocycles* **2012**, *86*, 1211−1226. (b) Clarisse, D.; Pelotier, B.; Fache, F. Solvent-Free, Metal-Free, Aza-Prins Cyclization: Unprecedented Access to δ-Sultams. *Chem. - Eur. J.* **2013**, *19*, 857−860. (c) Taheri, A.; Quinn, R. J.; Krasavin, M. Naturally occurring scaffolds for compound library design: convenient access to bis-aryl-1-azaadamantanes carrying a vicinal amino alcohol motif. *Tetrahedron Lett.* **2014**, *55*, 5390−5393. (d) Sun, Y.; Chen, P.; Zhang, D.; Baunach, M.; Hertweck, C.; Li, A. Bioinspired Total Synthesis of Sespenine. *Angew. Chem., Int. Ed.* **2014**, *53*, 9012−9016. (e) Nallasivam, J. L.; Fernandes, R. A. A Cascade Aza-Cope/Aza-Prins Cyclization Leading to Piperidine Derivatives. *Eur. J. Org. Chem.* **2015**, *2015*, 2012−2022. (f) Okoromoba, O. E.; Hammond, G. B.; Xu, B. Preparation of Fluorinated Tetrahydropyrans and Piperidines using a New Nucleophilic Fluorination Reagent DMPU/HF. *Org. Lett.* **2015**, *17*, 3975−3977. (g) Chio, F. K. I.; Guesne, S. J. J.; Hassall, L.; McGuire, T.; Dobbs, A. P. Synthesis of Azabicycles *via* Cascade Aza-Prins Reactions: Accessing the Indolizidine and Quinolizidine Cores. *J. Org. Chem.* **2015**, *80*, 9868−9880. (h) Durel, V.; Lalli, C.; Roisnel, T.; Weghe, P. Synergistic Effect of the $TiCl_4$/*p*-TsOH Promoter System on the Aza-Prins Cyclization. *J. Org. Chem.* **2016**, *81*, 849−859. (i) Liu, G.-Q.; Cui, B.; Xu, R.; Li, Y.-M. Preparation of trans-2-Substituted-4-halopiperidines and *cis*-2-Substituted-4-halotetrahydropyrans *via* $AlCl_3$-Catalyzed Prins Reaction. *J. Org. Chem.* **2016**, *81*, 5144−5161. (j) Ma, D.; Zhong, Z.; Liu, Z.; Zhang, M.; Xu, S.; Xu, D.; Song, D.; Xie, X.; She, X. Protecting-Group-Free Total Synthesis of (−)-Lycopodine *via* Phosphoric Acid Promoted Alkyne Aza-Prins Cyclization. *Org. Lett.* **2016**, *18*, 4328−4331. (k) Katamura, T.; Shimizu, T.; Mutoh, Y.; Saito, S. Synthesis of Tricyclic Benzazocines by Aza-Prins Reaction. *Org. Lett.* **2017**, *19*, 266−269. (l) Mittapalli, R. R.; Guesne, S. J. J.; Parker, R. J.; Klooster, W. T.; Coles, S. J.; Skidmore, J.; Dobbs, A. P. The Asymmetric Aza-silyl-Prins Reaction: Synthesis of Enantiopure Piperidines. *Org. Lett.* **2019**, *21*, 350−355.

(9) (a) Shi, L.-M.; Sun, X.-S.; Shen, C.; Wang, Z.-F.; Tao, H.-Y.; Wang, C.-J. Catalytic Asymmetric Synthesis of α-Trifluoromethyl Homoallylic Amines *via* Umpolung Allylation/2-Aza-Cope Rearrangement: Stereoselectivity and Mechanistic Insight. *Org. Lett.* **2019**, *21*, 4842−4848. (b) Sun, X.-S.; Wang, X.-H.; Tao, H.-Y.; Weia, L.; Wang, C.-J. Catalytic Asymmetric Synthesis of Quaternary Trifluoromethyl α- to ε-Amino Acid Derivatives *via* Umpolung Allylation/2-aza-Cope Rearrangement. *Chem. Sci.* **2020**, *11*, 10984−10990. (c) Shen, C.; Wang, R.-Q.; Wei, L.; Wang, Z.-F.; Tao, H.-Y.; Wang, C.-J. Catalytic Asymmetric Umpolung Allylation/2-Aza-Cope Rearrangement for the Construction of α-Tetrasubstituted α-Trifluoromethyl Homoallylic Amines. *Org. Lett.* **2019**, *21*, 6940−6945.

(10) Ma, M.; Zhu, Y.; Sun, Q.; Li, X.; Su, J.; Zhao, L.; Zhao, Y.; Qiu, S.; Yan, W.; Wang, K.; Wang, R. The Asymmetric Synthesis of CF_3-containing Spiro[pyrrolidin-3,2′-oxindole] through the Organocatalytic 1, 3-dipolar Cycloaddition Reaction. *Chem. Commun.* **2015**, *51*, 8789−8792.

(11) Wu, X. Y.; Gao, Y. N.; Shi, M. Phosphine-Catalyzed [3 + 2] Annulation of *N*-2,2,2-Trifluoroethylisatin Ketimines with γ-Substi-

https://dx.doi.org/10.1021/acs.orglett.1c00292
Org. Lett. 2021, 23, 1510−1515

tuted Allenoates: Synthesis of Spiro[indoline-3,2′-pyrrole]. *Eur. J. Org. Chem.* **2019**, *2019*, 1620−1626.
(12) Ryu, H.; Seo, J.; Ko, H. M. Synthesis of Spiro[oxindole-3,2′-pyrrolidine] Derivatives from Benzynes and Azomethine Ylides through 1,3-Dipolar Cycloaddition Reactions. *J. Org. Chem.* **2018**, *83*, 14102−14109.
(13) Zou, C.; Han, Y. E.; Zeng, C.; Zhang, T. Y.; Ye, J.; Song, G. Remote regioselective organocatalytic asymmetric [3 + 2] cycloaddition of *N*-2,2,2-trifluoroethyl isatin ketimines with cyclic 2,4-dienones. *Chin. Chem. Lett.* **2020**, *31*, 377−380.
(14) (a) Niu, B.; Wu, X. Y.; Shi, M. Palladium-Catalyzed Diastereoselective Formal [5 + 3] Cycloaddition for the Construction of Spirooxindoles Fused with an Eight-Membered Ring. *Org. Lett.* **2019**, *21*, 4859−4863. (b) Zhao, H.-W.; Wang, L.-R.; Ding, W.-Q.; Guo, J.-M.; Tang, Z.; Song, X.-Q.; Wu, H.-H.; Fan, X.-Z.; Bi, X.-F.; Zhong, Q.-D. Formal [5 + 3] Cycloaddition between Isatin-Based α-(Trifluoromethyl)imine Ylides and Vinyloxiranes: Diastereoselective Access to Medium-Heterocycle-Fused Spirooxindoles. *Synlett* **2021**, *32*, 57−62.
(15) Zhao, Y.; Jiang, X.; Yeung, Y. Y. Catalytic, Enantioselective, and Highly Chemoselective Bromocyclization of Olefinic Dicarbonyl Compounds. *Angew. Chem., Int. Ed.* **2013**, *52*, 8597−8601.
(16) Garzan, A.; Jaganathan, A.; Marzijarani, N. S.; Yousefi, R.; Whitehead, D. C.; Jackson, J. E.; Borhan, B. Solvent-Dependent Enantiodivergence in the Chlorocyclization of Unsaturated Carbamates. *Chem. - Eur. J.* **2013**, *19*, 9015−9021.
(17) Xu, A.; Yang, S.; Ding, Z. $PhI(OAc)_2$-mediated oxidative rearrangement of allylic amides: efficient synthesis of oxazoles and β-keto amides. *Org. Chem. Front.* **2020**, *7*, 69−72.
(18) Pratsch, G.; Overman, L. E. Synthesis of 2,5-Diaryl-1,5-dienes from Allylic Bromides Using Visible-Light Photoredox Catalysis. *J. Org. Chem.* **2015**, *80*, 11388−11397.
(19) Yang, X.; Tsui, G. C. Copper-Mediated Trifluoromethylation−Allylation of Arynes. *Org. Lett.* **2018**, *20*, 1179−1182.
(20) Gassman, P. G.; Harrington, C. K. Effect of the α-Trifluoromethyl Moiety on the Solvolysis of Allylic Sulfonates. *J. Org. Chem.* **1984**, *49*, 2258−2273.
(21) Onyeagusi, C. I.; Shao, X.; Malcolmson, S. J. Enantio- and Diastereoselective Synthesis of Homoallylic α-Trifluoromethyl Amines by Catalytic Hydroalkylation of Dienes. *Org. Lett.* **2020**, *22*, 1681−1685.
(22) (a) Friedrich, E. C.; DeLucca, G. Interhalogen-catalyzed cleavages of ethers and esters with trimethylsilyl bromide or chloride. *J. Org. Chem.* **1983**, *48*, 1678−1682. (b) Verma, S. K.; Acharya, B. N.; Ghorpade, R.; Pratap, A.; Kaushik, M. P. A DBU-diheteroaryl halide adduct as fastest *N*-diheteroarylating agent. *RSC Adv.* **2013**, *3*, 18783−18786.
(23) Jin, F.; Yang, T.; Song, X.-R.; Bai, J.; Yang, R.; Ding, H.; Xiao, Q. TMSBr-Promoted Cascade Cyclization of *ortho*-Propynol Phenyl Azides for the Synthesis of 4-Bromo Quinolines and Its Applications. *Molecules* **2019**, *24*, 3999−4014.

https://dx.doi.org/10.1021/acs.orglett.1c00292
Org. Lett. 2021, 23, 1510−1515