OL | Organic Letters

Letter

Cite This: Org. Lett. XXXX, XXX, XXX−XXX

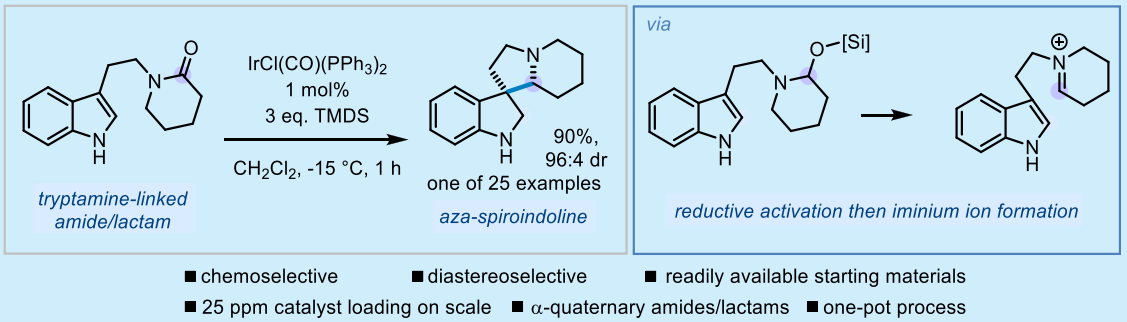
pubs.acs.org/OrgLett

Iridium-Catalyzed Aza-Spirocyclization of Indole-Tethered Amides: An Interrupted Pictet−Spengler Reaction

Pablo Gabriel, Alex W. Gregory, and Darren J. Dixon*

Department of Chemistry, University of Oxford, Chemistry Research Laboratory, 12 Mansfield Road, Oxford OX1 3TA, U.K.

Supporting Information



ABSTRACT: A mild, reductive spirocyclization of indole-linked amides and lactams for the efficient and selective synthesis of aza-spirocyclic indoline products is described. The catalytic reductive activation of tertiary amides or lactams by Vaska's complex with tetramethyldisiloxane as the terminal reductant allowed iminium ion formation, before a diastereoselective 5-endo-trig spirocyclization of the tethered indole moiety was triggered. Terminal reduction affords the aza-spiroindoline products in an overall highly chemoselective and diastereoselective one-pot process.

The aza-spiroindoline ring system is common to numerous bioactive compounds and natural products that are structurally and biologically relevant.[1] These range from the infamous poison strychnine **1**[2] to the potent anticancer compound vinblastine **2**.[3] Oxidized structural relatives include the spirooxindoles[4] of which horsefiline **3** is arguably the simplest, but well-known, member (Scheme 1a). The prevalence of this intricate ring system within important families of compounds continues to attract the development of new strategies and new methods for their efficient synthesis. Whereas tetrahydro-β-carbolines can be readily accessed by the classical Pictet−Spengler reaction, and its many variants, between tryptamine derivatives and aldehydes,[5] building the aza-spiroindoline core has proven to be more challenging due to the propensity for rearomatization.[6] Previous approaches have typically employed reactive electrophilic intermediates (imidoyl triflate **4a**,[6a−d] π-allyl cation **4b**,[6e,f] and *N*-acyl iminium **4c**[6g]) for accessing spirocyclic indolenines **5a**−**5c** (Scheme 1b). A subsequent reduction step after spirocyclization is, however, required to generate aza-spiroindoline **6**.

As part of our ongoing work toward structurally complex, sp^3-rich nitrogen-containing architectures based on an iridium-catalyzed reductive activation of amides and lactams,[7] we were drawn to the idea of developing a new approach to the aza-spiroindoline core. Our aim was to develop a direct and general strategy from readily available starting materials that, through the incorporation of multiple points of diversity in the products, could be applied to both drug discovery and library generation. Herein, we describe our findings.

Previous mechanistic studies on the Pictet−Spengler reaction have established the existence of a dynamic interplay among three isomeric cationic species [**8a**−**8c** (Scheme 2)],[8] prior to irreversible proton loss from 6-*endo*-trig cyclization intermediate **8b** to afford rearomatized tetrahydro-β-carboline **9**. We reasoned that the use of Vaska's catalyst **11** in conjunction with tetramethyldisiloxane reductant **12** on suitable indole-linked amide/lactam substrates not only would provide access to these cationic intermediates[9] but also could facilitate irreversible hydridic interception of the resulting spiroindolenium intermediate **8c**. If this pathway outcompeted the alternative 6-*endo*-*trig* pathway, reduced aza-spiroindoline **10**, the interrupted Pictet−Spengler product, would result.

To probe this concept, tryptamine-derived lactam **7a** was selected as a relevant model system and its reactivity toward Vaska's complex and various silanes was studied.

In accordance with the recent reductive functionalization reaction of amides,[10] a toluene solution of model substrate **7a** at room temperature was treated with Vaska's catalyst **11** and 2 equiv of TMDS **12** (Scheme 1). Very pleasingly, aza-spiroindoline **10a** was indeed obtained in 55% NMR yield after 60 min (Table 1, entry 1). The reaction was selective for the *syn* diastereoisomer (80:20 dr), and importantly, no sign of the Pictet−Spengler product was detectable. With this excellent proof of concept in hand, we turned to optimize the reaction for both yield and diastereoselectivity. In contrast to previous

Received: June 25, 2019

DOI: 10.1021/acs.orglett.9b02194
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 1. (a) Examples of Aza-Spiroindoline Ring Systems in Nature and (b) Known Aza-Spirocyclization Methodologies via Reactive Cationic Intermediates

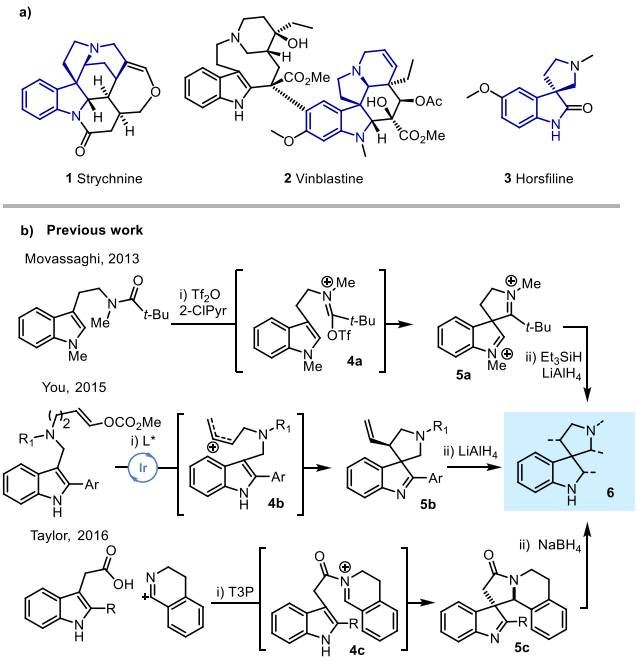
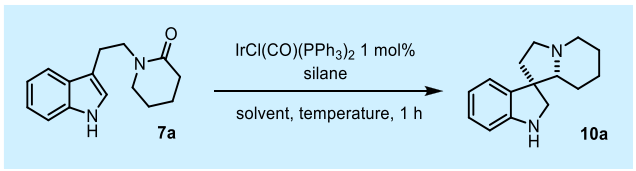


Table 1. Proof of Concept and Optimization Studies of Model System 7a



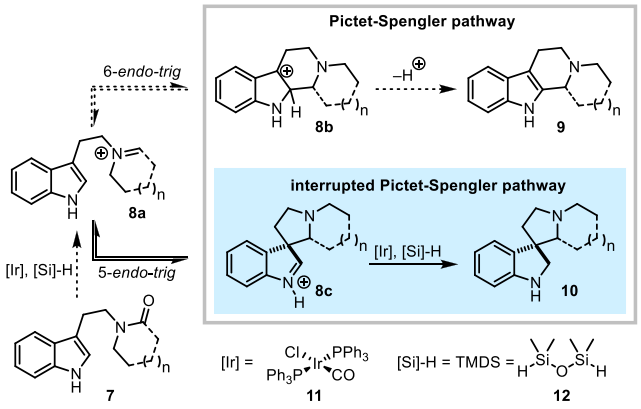
entry	solvent	silane (equiv)	temp	yield[a] (%)	dr[b]
1	toluene	TMDS (2)	rt	55	80:20
2	toluene	TMDS (3)	rt	77	80:20
3	toluene	$PhSiH_3$ (3)	rt	0	–
4	toluene	Ph_2SiH_2 (3)	rt	0	–
5	toluene	Et_3SiH (3)	rt	0	–
6	THF	TMDS (3)	rt	32	86:14
7	$CHCl_3$	TMDS (3)	rt	74	66:34
8	CH_2Cl_2	TMDS (3)	rt	93	90:10
9	CH_2Cl_2	TMDS (3)	0 °C	90	91:9
10	CH_2Cl_2	TMDS (3)	−15 °C	91	96:4

[a] ^{1}H NMR yield determined against *m*-nitro dimethylaniline as an internal standard. [b] Determined by ^{1}H NMR analysis of the crude product.

studies, 3 equiv of TMDS was required to reach full conversion (entry 2).[11] Recourse to other silanes proved to be ineffective (entries 3−5)[12] but a solvent screen identified dichloromethane as the best solvent, both for yield and for diastereocontrol.[13] Furthermore, excellent diastereoselectivity (96:4 dr) was achieved when the reaction temperature was decreased to −15 °C (entry 10).

With optimized conditions established, the scope of the reaction with respect to the indole and the lactam moiety was explored. Variations to the indole aromatic ring revealed that both electron-withdrawing and electron-donating groups were

Scheme 2. Proposed Iridium-Catalyzed Interrupted Pictet−Spengler Reaction



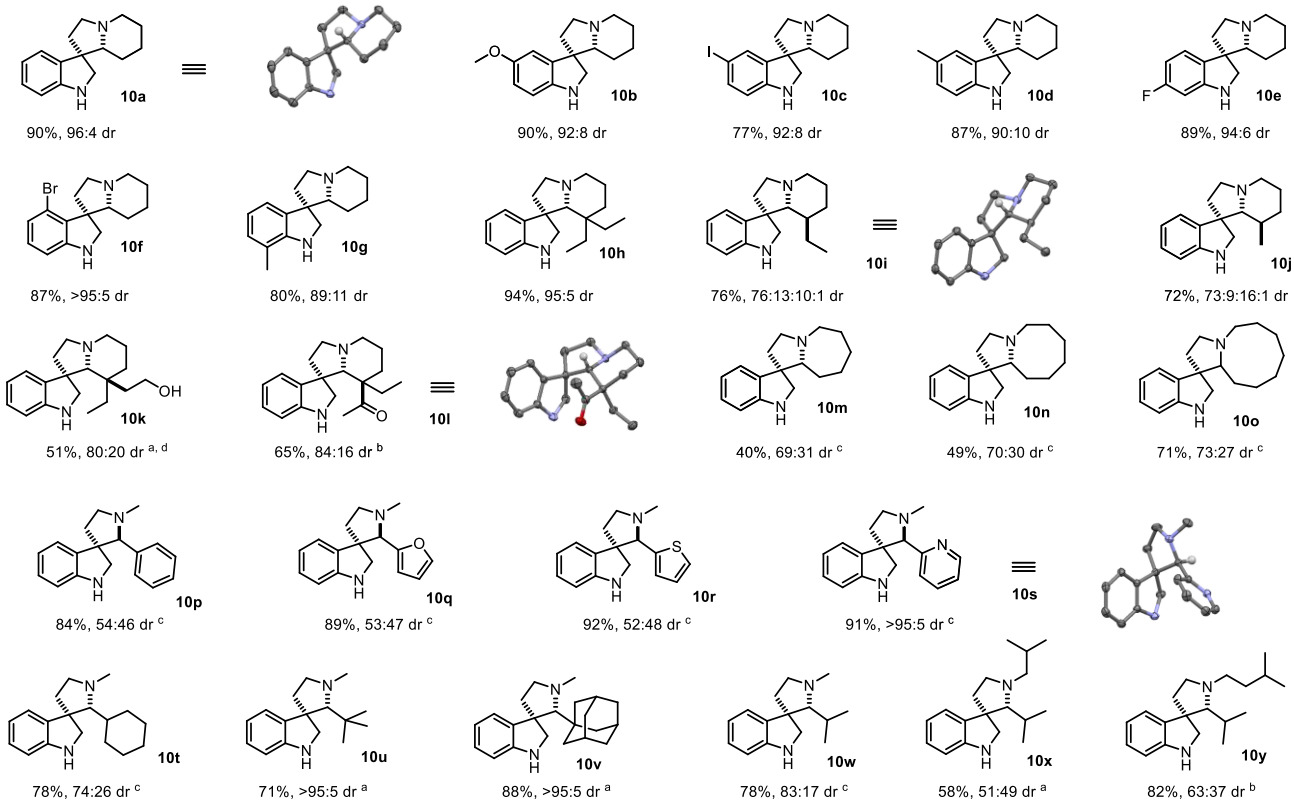
tolerated at positions 4−7 [**10b**−**10g** (Scheme 3)]. Exploiting the possibility of generating and trapping a nucleophilic lithium enolate of the lactam,[14] we could readily synthesize α-substituted starting materials and subject them to the reaction conditions. This extra stereocenter provided control over the relative configuration of the newly formed pyrrolidine ring (**10i** and **10j**). Attack of the cyclic iminium ion on the least hindered face gave predominantly *anti*-**10i**, as proven by single-crystal X-ray analysis. Substrates containing α-quaternary centers could also be cyclized (**10k** and **10l**), although the high steric hindrance demanded longer reaction times as well as increased catalyst loading. To showcase the chemoselectivity of the catalytic system, ketone **7l** was cyclized to give indoline **10l** in good yield, with the ketone carbonyl group remaining unaffected. Remarkably, no epimer at the α-quaternary center could be observed for this substrate or for primary alcohol **10k**. Medium-sized ring substrates derived from capro-, enantho-, and caprylolactam could be cyclized (**7m**−**7o** to **10m**−**10o**), albeit in slightly reduced yield and diastereoselectivity.[15]

Acyclic amides also underwent spirocyclization, and various aryl/heteroaryl (**10p**−**10s**) and sterically demanding amides (**10h** and **10t**−**10y**) were smoothly transformed into the desired indolines in good to excellent yields, showing the general applicability of this new methodology. Notably, pyridine **10s** was formed as a single *anti* diastereoisomer; its relative configuration was determined by single-crystal X-ray diffraction analysis. Interestingly, if substantial steric hindrance was introduced at the amide α-position, diastereoselectivity was improved to ≥95:5 dr (*t*-Bu **10u**, adamantyl **10v**, or α-diethyl **10h**) but at the expense of increased reaction time (24 h) and catalyst loading (5 mol %). Furthermore, branching at the relatively distant β-position of the alkyl chain on the nitrogen atom resulted in reduced reactivity and diastereocontrol (**10x**, 51:49 dr).[16]

In line with the observations of Taylor,[6g] we believe the origin of diastereoselectivity is likely facial recognition between the indole and the iminium ion in the key addition step (Scheme 5). Two possible diastereoisomers can arise from the spirocyclization step. In the *endo*-transition structure, steric repulsion would occur between any aliphatic cyclic or acyclic side chain and the indole ring, resulting in a higher-energy transition structure then in the *exo* case (Scheme 4, case 1). The observed diastereomeric ratios of the products are in agreement with these observations, particularly for bromo-substituted lactam **10f** where the proximity of the bromine atom appears to further enhance the

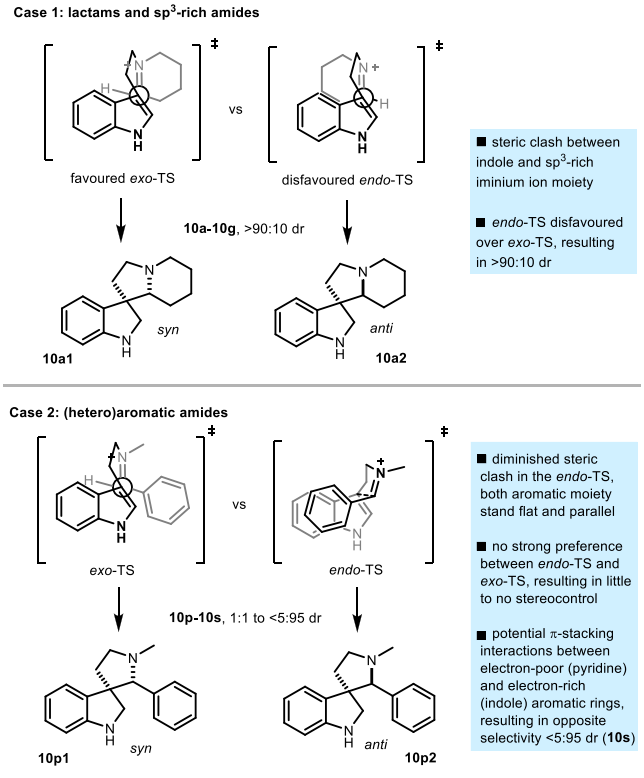
DOI: 10.1021/acs.orglett.9b02194
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 3. Scope of the Iridium-Catalyzed Reductive Spirocyclization Reaction[e]

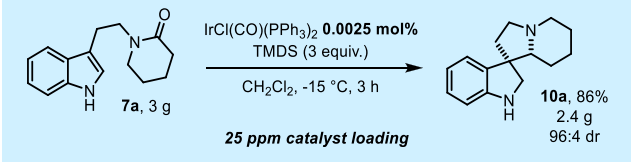


[a]With 5 mol % catalyst, rt, 24 h. [b]With 1 mol % catalyst, rt, 6 h. [c]With 1 mol % catalyst, rt, 1 h. [d]With 4 equiv of TMDS. [e]Standard conditions: 3 equiv of TMDS, 1 mol % catalyst, −15 °C, 1 h.

Scheme 4. Postulated Origins of Diastereocontrol



Scheme 5. Double-Digit Parts per Million Catalyst Loading on a Multigram Scale Reaction



diastereocontrol.[17] The seven-, eight-, and nine-membered lactams seem to lack the rigidity needed for the steric clash to hamper the addition. However, when the amide moiety was relatively flat [i.e., derived from (hetero)aromatic carboxylic acids, such as in **10p**−**10s**], the steric clash in the *endo*-transition structure would be minimized, thus reducing the differential in energy and resulting in almost no observed diastereocontrol (Scheme 4, case 2). In the case of pyridyl indoline **10s**, π-interactions between the electron-rich indole and the electron-poor pyridine ring are likely to lower the energy of the *endo*-transition structure even further when these rings are in the proximity of each other, giving rise to the exclusive formation of the *anti* diastereoisomer.

Moreover, when the lactam possesses an α-stereocenter, diastereofacial control can be observed. This control is only partial in the formation of α-alkyl **10i** and **10j**, as the addition of the indole is naturally, but imperfectly, directed to the face opposite the alkyl group. Substantial control at this position is however observed when a carbonyl or a primary alcohol is present (**10k** and **10l**). We believe this is due to a stabilization of

DOI: 10.1021/acs.orglett.9b02194
Org. Lett. XXXX, XXX, XXX−XXX

the vacant π-orbital of the iminium ion by the oxygen atom (neighboring group participation) completely directing the indole addition to the opposite face.

In addition to a broad scope, we also wanted to demonstrate practical scalability, with a particular emphasis on the catalyst loading. Following a series of investigations, we were pleased to find that subjecting 3 g of the simple tryptamine derived lactam **7a** to the same reaction conditions but with a catalyst loading of 25 ppm (240 μg) resulted in complete conversion to spirocyclic indoline **10a**.

In conclusion, an iridium(I)-catalyzed interrupted reductive Pictet−Spengler reaction giving access to complex azaspirocyclic indoline structures from readily available indole-linked lactams and amides has been developed. The reaction was shown to be highly chemoselective and diastereoselective at the newly formed contiguous stereocenters, and the very mild reductive conditions allowed for good functional group tolerance. Furthermore, the turnover number for the catalyst was in the range of at least 40000 when the reaction was performed on a gram scale.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02194.

Synthetic procedures and full characterization data of all compounds (PDF)

Accession Codes

CCDC 1906300−1906303 contain 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.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: darren.dixon@chem.ox.ac.uk.

ORCID

Pablo Gabriel: 0000-0002-3462-5151

Darren J. Dixon: 0000-0003-2456-5236

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors gratefully acknowledge the EPSRC (Leadership Fellowship to D.J.D., Studentship to A.W.G.) and AstraZeneca for funding. P.G. is grateful to the EPSRC Centre for Doctoral Training in Synthesis for Biology and Medicine (EP/L015838/1) for a studentship, generously supported by AstraZeneca, Diamond Light Source, Defence Science and Technology Laboratory, Evotec, GlaxoSmithKline, Janssen, Novartis, Pfizer, Syngenta, Takeda, UCB, and Vertex. The authors thank Prof. Robert Paton (Colorado State University, Fort Collins, CO) for helpful input into the mechanistic pathway. The authors thank Heyao Shi (University of Oxford) for X-ray structure determination and Dr. Amber L. Thompson and Dr. Kirsten E. Christensen (Oxford Chemical Crystallography Service) for X-ray mentoring and help.

■ REFERENCES

(1) (a) Zhu, X.; Zeng, X.; Sun, C.; Chen, S. Biosynthetic pathway of terpenoid indole alkaloids in Catharanthus roseus. *Front. Med.* **2014**, *8*, 285−293. (b) O'Connor, S. E. *Comprehensive Natural Products II*; Mander, L., Liu, H.-W., Eds.; Elsevier: Amsterdam, 2010; Vol. *1*, p 977. (c) Powell, N. A.; Kohrt, J. T.; Filipski, K. J.; Kaufman, M.; Sheehan, D.; Edmunds, J. E.; Delaney, A.; Wang, Y.; Bourbonais, F.; Lee, D.-Y.; Schwende, D.; Sun, F.; McConnell, P.; Catana, C.; Chen, H.; Ohren, J.; Perrin, L. A. Novel and selective spiroindoline-based inhibitors of sky kinase. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 190−193. (d) Zhu, X.-X.; Fan, Y.-Y.; Xu, L.; Liu, Q.-F.; Wu, J.-P.; Li, J.-Y.; Li, J.; Gao, K.; Yue, J.-M. Four Rearranged Indole Alkaloids from Alstonia scholaris. *Org. Lett.* **2019**, *21*, 1471−1474. (e) Yap, W.-S.; Gan, C.-Y.; Sim, K.-S.; Lim, S.-H.; Low, Y.-Y.; Kam, T.-S. Aspidofractinine and Eburnane Alkaloids from a North Borneo Kopsia. Ring-Contracted, Additional Ring-Fused, and Paucidactine-Type Aspidofractinine Alkaloids from K. pauciflora. *J. Nat. Prod.* **2016**, *79*, 230−239. (f) Nge, C.-E.; Chong, K.-W.; Thomas, N. F.; Lim, S.-H.; Low, Y.-Y.; Kam, T.-S. Ibogan, Aspidosperman, Vincamine, and Bisindole Alkaloids from a Malayan Tabernaemontana corymbosa: Iboga Alkaloids with C-20α Substitution. *J. Nat. Prod.* **2016**, *79*, 1388−1399. (g) Zlotos, D. P.; Tränkle, C.; Holzgrabe, U.; Gündisch, D.; Jensen, A. A. Semisynthetic Analogues of Toxiferine I and Their Pharmacological Properties at α7 nAChRs, Muscle-Type nAChRs, and the Allosteric Binding Site of Muscarinic M2 Receptors. *J. Nat. Prod.* **2014**, *77*, 2006−2013.

(2) Lawrence, D.; McLinskey, N.; Huff, J. S.; Holstege, C. P. In *Clinical Neurotoxicology, Syndromes, Substances, Environment*; Dobbs, M. R., Ed.; Elsevier: Amsterdam, 2009; pp 30−46.

(3) (a) Neuss, N.; Neuss, M. N. In *The Alkaloids*; Brossi, A., Suffness, M., Eds.; Academic: San Diego, 1990; Vol. *37*, pp 229−240. (b) Pearce, H. L. In *The Alkaloids*; Brossi, A., Suffness, M., Eds.; Academic: San Diego, 1990; Vol. *37*, pp 145−204. (c) Kuehne, M. E.; Marko, I. In *The Alkaloids*; Brossi, A., Suffness, M., Eds.; Academic: San Diego, 1990; Vol. *37*, pp 77−132.

(4) For a review of the use of spirooxindoles as scaffolds in anticancer agents, see: Yu, B.; Yu, D.-Q.; Liu, H.-M. Spirooxindoles: Promising scaffolds for anticancer agents. *Eur. J. Med. Chem.* **2015**, *97*, 673−698.

(5) (a) Kovvuri, J.; Nagaraju, B.; Lakshma Nayak, V.; Akunuri, R.; Rao, M. P. N.; Ajitha, A.; Nagesh, N.; Kamal, A. Design, synthesis and biological evaluation of new β-carboline-bisindole compounds as DNA binding, photocleavage agents and topoisomerase I inhibitors. *Eur. J. Med. Chem.* **2018**, *143*, 1563−1577. (b) Yu, Q.; Guo, P.; Jian, J.; Chen, Y.; Xu, J. Nine-step total synthesis of (−)-strychnofoline. *Chem. Commun.* **2018**, *54*, 1125−1128. (c) Kayhan, J.; Wanner, M. J.; Ingemann, S.; van Maarseveen, J. H.; Hiemstra, H. Consecutive Pictet−Spengler Condensations toward Bioactive 8-Benzylprotoberberines: Highly Selective Total Syntheses of (+)-Javaberine A, (+)-Javaberine B, and (−)-Latifolian A. *Eur. J. Org. Chem.* **2016**, *2016*, 3705−3708. (d) Gremmen, C.; Willemse, B.; Wanner, M. J.; Koomen, G.-J. Enantiopure Tetrahydro-β -carbolines via Pictet−Spengler Reactions with N-Sulfinyl Tryptamines. *Org. Lett.* **2000**, *2*, 1955−1958. (e) Seayad, J.; Seayad, A. M.; List, B. Catalytic Asymmetric Pictet-Spengler Reaction. *J. Am. Chem. Soc.* **2006**, *128*, 1086−1087. (f) Wang, S.-G.; Xia, Z.-L.; Xu, R.-Q.; Liu, X.-J.; Zheng, C.; You, S.-L. Construction of Chiral Tetrahydro-β-Carbolines: Asymmetric Pictet−Spengler Reaction of Indolyl Dihydropyridines. *Angew. Chem., Int. Ed.* **2017**, *56*, 7440−7443.

(6) For other aza-spiroindoline syntheses, see: (a) Medley, J. W.; Movassaghi, M. Synthesis of Spirocyclic Indolines by Interruption of the Bischler Napieralski Reaction. *Org. Lett.* **2013**, *15* (14), 3614−3617. (b) White, K. L.; Mewald, M.; Movassaghi, M. Direct Observation of Intermediates Involved in the Interruption oft he Bischler-Napieralski Reaction. *J. Org. Chem.* **2015**, *80*, 7403−7411. (c) Antropow, A. H.; Garcia, N. R.; White, K. L.; Movassaghi, M. Enantioselective Synthesis of (−)-Vallesine: Late-Stage C17-Oxidation via Complex Indole Boronation. *Org. Lett.* **2018**, *20*, 3647−3650. (d) Medley, J. W.; Movassaghi, M. A Concise and Versatile Double-Cyclization Strategy for the Highly Stereoselective Synthesis and Arylative Dimerization of Aspidosperma Alkaloids. *Angew. Chem., Int. Ed.* **2012**, *51*, 4572−4576.

DOI: 10.1021/acs.orglett.9b02194
Org. Lett. XXXX, XXX, XXX−XXX

(e) Zhuo, C.-X.; Zhou, Y.; Cheng, Q.; Huang, L.; You, S.-L. Enantioselective Construction of Spiroindolines with Three Contiguous Stereogenic Centers and Chiral Tryptamine Derivatives via Reactive Spiroindolenine Intermediates. *Angew. Chem., Int. Ed.* **2015**, *54*, 14146−14149. For a method to rearomatize aza-spiroindolines into Pictet−Spengler-like products, see: (f) Wu, Q.-F.; Zheng, C.; Zhuo, C.-X.; You, S.-L. Highly efficient synthesis and stereoselective migration reactions of chiral five-membered azaspiroindolenines: scope and mechanistic understanding. *Chem. Sci.* **2016**, *7*, 4453−4459. For methods using more reactive acyl iminium ions, nitrilium ions, N-sulfonyl iminium ions, or triflyl imidates, see: (g) Chambers, S. J.; Coulthard, G.; Unsworth, W. P.; O'Brien, P.; Taylor, R. J. K. From Heteroaromatic Acids and Imines to Azaspirocycles: Stereoselective Synthesis and 3D Shape Analysis. *Chem. - Eur. J.* **2016**, *22*, 6496−6500. (h) Li, Y.; Zhang, Q.; Du, Q.; Zhai, H. Rh-Catalyzed [3 + 2] Cycloaddition of 1-Sulfonyl-1,2,3-triazoles: Access to the Framework of Aspidosperma and Kopsia Indole Alkaloids. *Org. Lett.* **2016**, *18*, 4076−4079. (i) Saya, J. M.; Roose, T. R.; Peek, J. J.; Weijers, B.; de Waal, T. J. S.; Vande Velde, C. M. L.; Orru, R. V. A.; Ruijter, E. Iodospirocyclization of Tryptamine-Derived Isocyanides: Formal Total Synthesis of Aspidofractinine. *Angew. Chem., Int. Ed.* **2018**, *57*, 15232−15236. (j) Saya, J. M.; Oppelaar, B.; Cioc, R. C.; van der Heijden, G.; Vande Velde, C. M. L.; Orru, R. V. A.; Ruijter, E. Synthesis of polycyclic spiroindolines by highly diastereoselective interrupted Ugi cascade reactions of 3-(2-isocyanoethyl)indoles. *Chem. Commun.* **2016**, *52*, 12482−12485. (k) Delgado, R.; Blakey, S. B. Cascade Annulation Reactions To Access the Structural Cores of Stereochemically Unusual Strychnos Alkaloids. *Eur. J. Org. Chem.* **2009**, *2009*, 1506−1510.

(7) (a) Gregory, A. W.; Chambers, A.; Hawkins, A.; Jakubec, P.; Dixon, D. J. Iridium-Catalyzed Reductive Nitro-Mannich Cyclization. *Chem. - Eur. J.* **2015**, *21*, 111−114. (b) Tan, P. W.; Seayad, J.; Dixon, D. J. Expeditious and Divergent Total Syntheses of Aspidosperma Alkaloids Exploiting Iridium(I)-Catalysed Generation of Reactive Enamine Intermediates. *Angew. Chem., Int. Ed.* **2016**, *55*, 13436−13440. (c) Fuentes de Arriba, A. L.; Lenci, E.; Sonawane, M.; Formery, O.; Dixon, D. J. Iridium-Catalyzed Reductive Strecker Reaction for Late-Stage Amide and Lactam Cyanation. *Angew. Chem., Int. Ed.* **2017**, *56*, 3655−3659. (d) Xie, L.-G.; Dixon, D. J. Tertiary amine synthesis via reductive coupling of amides with Grignard reagents. *Chem. Sci.* **2017**, *8*, 7492−7497. (e) Xie, L.-G.; Dixon, D. J. Iridium-catalyzed reductive Ugi-type reactions of tertiary amides. *Nat. Commun.* **2018**, *9*, 2841.

(8) (a) Maresh, J. J.; Giddings, L.-A.; Friedrich, A.; Loris, E. A.; Panjikar, S.; Trout, B. L.; Stöckigt, J.; Peters, B.; O'Connor, S. Strictosidine Synthase: Mechanism of a Pictet-Spengler Catalyzing Enzyme. *J. Am. Chem. Soc.* **2008**, *130*, 710−723. (b) Klausen, R. S.; Kennedy, C. R.; Hyde, A. M.; Jacobsen, E. N. Chiral Thioureas Promote Enantioselective Pictet−Spengler Cyclization by Stabilizing Every Intermediate and Transition State in the Carboxylic Acid-Catalyzed Reaction. *J. Am. Chem. Soc.* **2017**, *139*, 12299−12309. (c) Zheng, C.; Xia, Z.-L.; You, S.-L. Unified Mechanistic Understandings of Pictet-Spengler Reactions. *Chem.* **2018**, *4*, 1952−1966.

(9) Previous work by our group has established that both iminium and enamine species can be accessed via reductive activation. Their fate depends on the nature of the reaction partner and conditions (see ref 7, in particular refs 7a−c).

(10) (a) Motoyama, Y.; Aoki, M.; Takaoka, N.; Aoto, R.; Nagashima, H. Highly efficient synthesis of aldenamines from carboxamides by iridium-catalyzed silane-reduction/dehydration under mild conditions. *Chem. Commun.* **2009**, *12*, 1574−1576. (b) Nakajima, M.; Sato, T.; Chida, N. Iridium-Catalyzed Chemoselective Reductive Nucleophilic Addition to N-Methoxyamides. *Org. Lett.* **2015**, *17*, 1696−1699. (c) Nakayama, Y.; Maeda, Y.; Kotatsu, M.; Sekiya, R.; Ichiki, M.; Sato, T.; Chida, N. Enantioselective Total Synthesis of (+)-Neostenine. *Chem. - Eur. J.* **2016**, *22*, 3300−3303. (d) Yoritate, M.; Takahashi, Y.; Tajima, H.; Ogihara, C.; Yokoyama, T.; Soda, Y.; Oishi, T.; Sato, T.; Chida, N. Unified Total Synthesis of Stemoamide-Type Alkaloids by Chemoselective Assembly of Five-Membered Building Blocks. *J. Am. Chem. Soc.* **2017**, *139*, 18386−18391. (e) Yamamoto, S.; Komiya, Y.; Kobayashi, A.; Minamikawa, R.; Oishi, T.; Sato, T.; Chida, N. Asymmetric Total Synthesis of Fasicularin by Chiral N-Alkoxyamide Strategy. *Org. Lett.* **2019**, *21*, 1868−1871. (f) Gammack Yamagata, A. D.; Dixon, D. J. Enantioselective Construction of the ABCDE Pentacyclic Core of the Strychnos Alkaloids. *Org. Lett.* **2017**, *19*, 1894−1897. (g) Huang, P.-Q.; Ou, W.; Han, F. Chemoselective reductive alkynylation of tertiary amides by Ir and Cu(I) bis-metal sequential catalysis. *Chem. Commun.* **2016**, *52*, 11967−11970. (h) Katahara, S.; Kobayashi, S.; Fujita, K.; Matsumoto, T.; Sato, T.; Chida, N. An Iridium-Catalyzed Reductive Approach to Nitrones from N-Hydroxyamides. *J. Am. Chem. Soc.* **2016**, *138* (16), 5246−5249. (i) Yang, Z.-P.; Lu, G.-S.; Ye, J.-L.; Huang, P.-Q. Ir-catalyzed chemoselective reduction of *β*-amido esters: A versatile approach to *β*-enamino esters. *Tetrahedron* **2019**, *75* (12), 1624−1631. (j) Une, Y.; Tahara, A.; Miyamoto, Y.; Sunada, Y.; Nagashima, H. Iridium-PPh3 Catalysts for Conversion of Amides to Enamines. *Organometallics* **2019**, *38*, 852−862. (k) Hu, X.-N.; Shen, T.-L.; Cai, D.-C.; Zheng, J.-F.; Huang, P.-Q. Iridium-Catalysed Reductive Coupling Reaction of Tertiary Lactams/Amides with Isocyanoacetates. *Org. Chem. Front.* **2018**, *5*, 2051−2056. For the reductive functionalization of secondary amides, see: (l) Ou, W.; Han, F.; Hu, X.-N.; Chen, H.; Huang, P.-Q. Iridium-catalyzed Reductive Alkylations of Secondary Amides. *Angew. Chem., Int. Ed.* **2018**, *57*, 11354−11358. (m) Takahashi, Y.; Yoshii, R.; Sato, T.; Chida, N. Iridium-Catalyzed Reductive Nucleophilic Addition to Secondary Amides. *Org. Lett.* **2018**, *20*, 5705−5708.

(11) Transient silylation of the indoline nitrogen was observed, consuming a further equivalent of the silane. $^{1}H-^{31}Si$ HMBC proved the existence of this N−Si bond when the reaction was carried out in an NMR tube (see the Supporting Information). However, a control experiment on 3-methyl indole (skatole) showed that the silylation is not occurring on the indole N−H under the reaction conditions, thus indicating that it must be taking place on either indolenium **8c** or indoline product **10**.

(12) Previous studies have found a "dual-silane" effect making TMDS a more effective silane reducing agent. See: (a) Hanada, S.; Motoyama, Y.; Nagashima, H. Dual Si−H effects in platinum-catalyzed silane reduction of carboxamides leading to a practical synthetic process of tertiary-amines involving self-encapsulation of the catalyst species into the insoluble silicone resin formed. *Tetrahedron Lett.* **2006**, *47*, 6173−6177. (b) Pesti, J.; Larson, G. L. Tetramethyldisiloxane: A Practical Organosilane Reducing Agent. *Org. Process Res. Dev.* **2016**, *20*, 1164−1181.

(13) The concentration had little effect on the yield or diastereoselectivity.

(14) Double deprotonation of model substrate **7a** with LDA followed by alkylation with alkyl iodides afforded *α*-alkylated products **7h**−**7j**. For similar strategies, see: (a) Amat, M.; Ramos, C.; Pérez, M.; Molins, E.; Florindo, P.; Santos, M. M. M.; Bosch, J. Enantioselective formal synthesis of *ent*-rhynchophylline and *ent*-isorhynchophylline. *Chem. Commun.* **2013**, *49*, 1954−1956. (b) Herrmann, J. L.; Kieczykowski, G. R.; Normandin, S. E.; Schlessinger, R. H. High yield stereospecific total syntheses of Eburnamonine and Eburnamine. *Tetrahedron Lett.* **1976**, 801−804.

(15) For these substrates, the major reaction byproduct was the saturated cyclic amine. The reason for the loss of diastereoselectivity is unclear, but could be attributed to the greater flexibilty of the seven-, eight-, and nine-membered rings lowering the steric clash in the *endo*-TS.

(16) We postulate that with groups bulkier than a N-Me, the increased steric clash with the alkyl chain of the iminium ion increases the energy of the *exo*-TS relative to that of the *endo*-TS, hence reducing the diastereoselectivity.

(17) This method is complementary to those developed by Taylor (ref 6g) and Movassaghi (ref 6a) as the opposite diastereoselectivity is observed.

DOI: 10.1021/acs.orglett.9b02194
Org. Lett. XXXX, XXX, XXX−XXX