

Iridium-Catalyzed Aza-Spirocyclisation of Indole-Tethered Amides: an Interrupted Pictet-Spengler Reaction

Pablo Gabriel,[‡] Alex W. Gregory,[‡] Darren J. Dixon.^{‡,*}

[‡] Department of Chemistry, University of Oxford, Chemistry Research Laboratory, 12 Mansfield Road, Oxford, OX1 3TA, UK

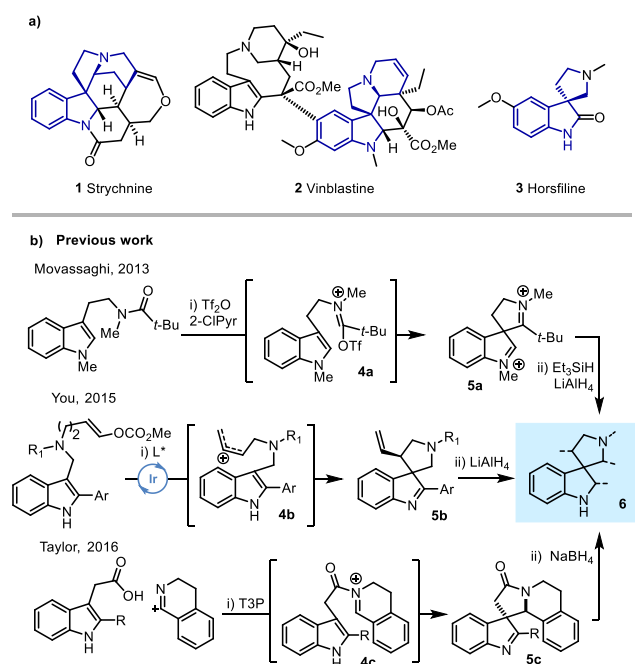
KEYWORDS Spirocyclisation, Iridium catalysed, Pictet-Spengler, Amide, Lactam, Reductive

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 of structural and biological relevance.¹ These range from the infamous poison strychnine **1**² to the potent anti-cancer compound vinblastine **2**.³ Oxidized structural relatives include the spirooxindoles⁴ of which horsefilline **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 -carboline 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 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} *N*-acyl iminium **4c**^{6g}) for accessing spirocyclic indolenines **5a-5c** (Scheme 1b). A subsequent reduction step after spirocyclization is however required to generate the aza-spiroindoline **6**.

As part of our ongoing work towards structurally complex, sp³-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 towards 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 wish to describe our findings.

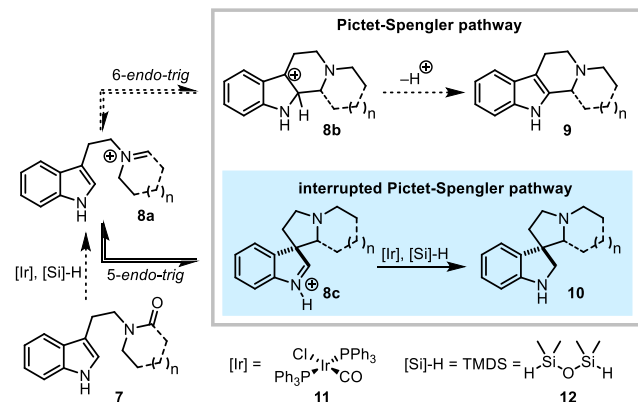
Scheme 1. a) Examples of aza-spiroindoline ring systems in nature, and b) known aza-spirocyclization methodologies via reactive cationic intermediates.



Previous mechanistic studies of the Pictet-Spengler reaction have established the existence of a dynamic interplay between three isomeric cationic species (**8a-c**, Scheme 2),⁸ prior to irreversible proton loss from 6-endo-trig cyclisation intermediate **8b** to afford re-aromatized 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 would not only provide access to these cationic intermediates,⁹ but

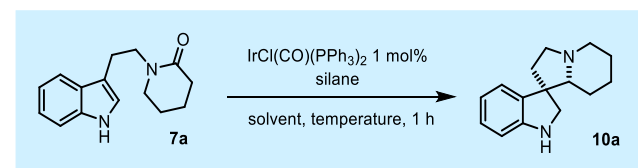
could also facilitate irreversible hydridic interception of the resulting spiroindolenium intermediate **8c**. If this pathway out-competed the alternative 6-*endo-trig* pathway, reduced aza-spiroindoline **10**, the interrupted Pictet-Spengler product, would result.

Scheme 2. Proposed iridium-catalyzed interrupted Pictet-Spengler reaction.



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

Table 1. Proof of concept and optimization studies on model system **7a.**



entry	solvent	silane (equiv.)	temperature	yield [a]	dr ^[b]
1	toluene	TMDS (2)	r.t.	55%	80:20
2	toluene	TMDS (3)	r.t.	77%	80:20
3	toluene	PhSiH ₃ (3)	r.t.	0%	-
4	toluene	Ph ₂ SiH ₂ (3)	r.t.	0%	-
5	toluene	Et ₃ SiH (3)	r.t.	0%	-
6	THF	TMDS (3)	r.t.	32%	86:14
7	CHCl ₃	TMDS (3)	r.t.	74%	66:34
8	CH ₂ Cl ₂	TMDS (3)	r.t.	93%	90:10
9	CH ₂ Cl ₂	TMDS (3)	0 °C	90%	91:9
10	CH ₂ Cl ₂	TMDS (3)	-15 °C	91%	96:4

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

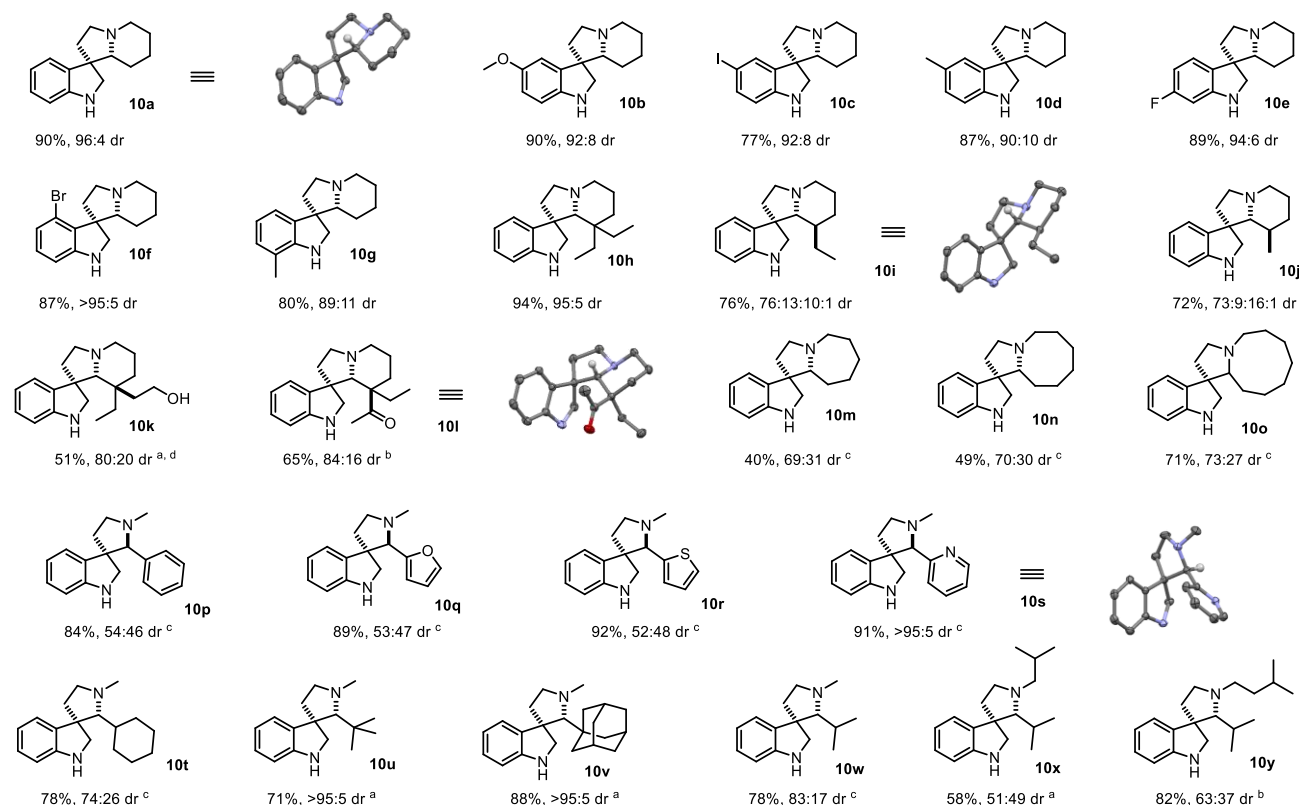
Aligned to recent reductive functionalization reaction of amides,¹⁰ a toluene solution of the model substrate **7a** at room temperature was treated with Vaska's catalyst **11** and

2 equivalents of TMDS **12** (Scheme 1). Very pleasingly, aza-spiroindoline **10a** was indeed obtained in 55% NMR yield after 60 minutes (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 studies, 3 equivalents of TMDS was required to obtain full conversion (entry 2).¹¹ Recourse to other silanes proved ineffective (entry 3-5)¹² but a solvent screen identified dichloromethane as the best solvent, both for yield and diastereocontrol.¹³ Furthermore, excellent diastereoselectivity (96:4 dr) was achieved when the reaction temperature was lowered to -15 °C (entry 9 & 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 tolerated at the 4-, 5-, 6- and 7-positions (**10b-10g**, Scheme 3). Exploiting the possibility to generate and trap a nucleophilic lithium enolate of the lactam,¹⁴ α -substituted starting materials could be readily synthesized and subjected to the reaction conditions. This extra stereocentre provided control over the relative configuration of the newly formed pyrrolidine ring (**10i-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-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 caprylactam 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 yield 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 hinderance was introduced at the amide α -position, diastereoselectivity was improved to $\geq 95:5$ 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

Scheme 3. Scope of the iridium-catalyzed reductive spirocyclization reaction.

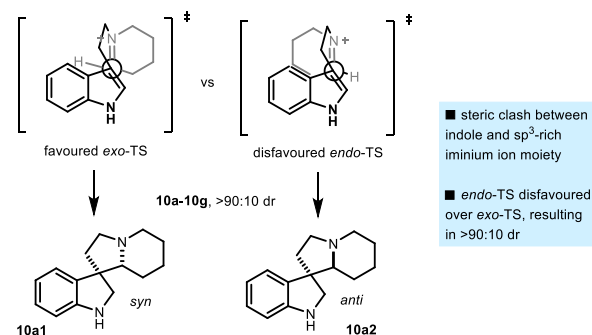


Standard conditions: 3 equiv. TMDS, 1 mol % catalyst, -15 °C, 1 h, ^a 5 mol % catalyst, rt, 24 h, ^b 1 mol % catalyst, rt, 6 h, ^c 1 mol % catalyst, rt, 1 h, ^d 4 equiv. TMDS.

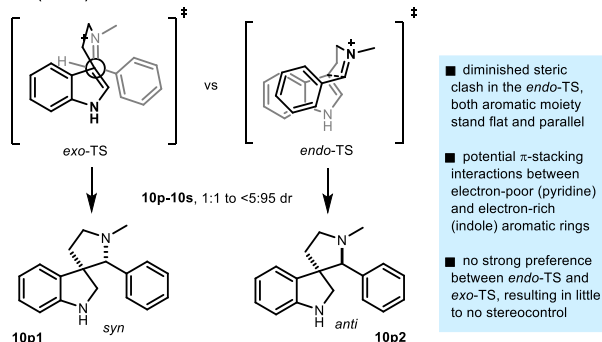
In line with the observations of Taylor,^{6g} we believe the origin of diastereoselectivity is likely due to facial recognition between the indole and the iminium ion in the key addition step (Scheme 5). Two possible diastereoisomers can arise from the spirocyclization step. In the *endo*-transition structure, steric repulsion would occur between any aliphatic cyclic or acyclic side-chain and the indole ring, resulting in a higher energy transition structure than 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 diastereocontrol.¹⁷ The 7-, 8- and 9-membered lactams seem to lack the rigidity needed for the steric clash to hamper the addition. However, when the amide moiety was relatively flat (*ie* 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 the 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 close proximity, giving rise to the exclusive formation of the *anti* diastereoisomer.

Scheme 4. Postulated origins of diastereocontrol.

Case 1: lactams and sp³-rich amides

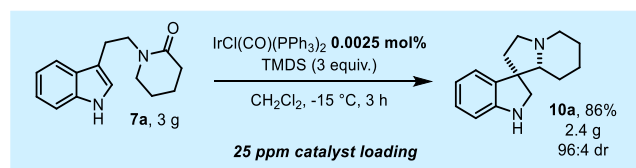


Case 2: (hetero)aromatic amides



Moreover, when the carbon in the α -position of the lactam carbonyl is bearing stereogenic information (**10i-10l**), control arising from this stereocentre 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, 10l**). We believe this is due to a stabilization of the vacant π -orbital of the iminium ion by the oxygen atom (neighboring group participation) completely directing the indole addition to the opposite face.

Scheme 5. Double-digit ppm catalyst loading on a multigram scale reaction.



In addition to having 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 grams 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 the 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 stereocentres, and the very mild reductive conditions allowed for good functional group tolerance. Furthermore, the TON for the catalyst has been proven to be in the range of at least 40 000 when the reaction was performed on gram-scale.

ASSOCIATED CONTENT

The Supporting Information is available free of charge on the ACS Publications website. Synthetic procedures and full characterization data of compounds (PDF).

Crystallographic data for **10a** (CCDC 1906300)

Crystallographic data for **10i** (CCDC 1906301)

Crystallographic data for **10l** (CCDC 1906302)

Crystallographic data for **10s** (CCDC 1906303)

AUTHOR INFORMATION

Corresponding Author

*darren.dixon@chem.ox.ac.uk

ACKNOWLEDGMENT

We 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. We thank Prof. Robert Paton (Colorado State University) for helpful input into the mechanistic pathway. We 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

- (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*, Vol.1 (Eds.: L. Mander, H.-W. Liu), Elsevier, Amsterdam, **2010**, p.977; (c) Powell, N. A.; Kohrt, J. T.; Filipinski, K. J.; Kaufman, M.; Sheehan, D.; Edmunds, J. E.; Delaney, A.; Wang, Y.; Bourbonnais, 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. Alstonlarsines A-D, 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.; Tomas, 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-20 α Substitution. *J. Nat. Prod.* **2016**, *79*, 1388-1399; (g) Zlotos, D. P.; Tränkle, C.; Holzgrabe, U.; Gündisch, D.; Jensen, A. A. Semi-synthetic Analogues of Toxiferine I and Their Pharmacological Properties at $\alpha 7$ 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* (Eds.: M.R. Dobbs), Elsevier, Amsterdam, **2009**, pp30-46.
- (3) (a) Neuss, N.; Neuss, M. N. in *The Alkaloids*, (Eds.: A. Brossi, M. Suffness), Academic, San Diego, CA, **1990**, Vol. 37, pp 229-240; (b) Pearce, H. L. in *The Alkaloids*, (Eds.: A. Brossi, M. Suffness), Academic, San Diego, CA, **1990**, Vol. 37, pp 145-204; (c) Kuehne, M. E.; Marko, I. in *The Alkaloids* (Eds.: A. Brossi, M. Suffness), Academic, San Diego, CA, **1990**, Vol. 37, pp 77-132.
- (4) For a review on the use of spirooxindole 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**, 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 a method to make aza-spiroindolines, 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 of the 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; (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 in 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, nitrilium ions, N-sulfonyl iminium 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**, 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. Stric-tosidine Synthase: Mechanism of a Pictet–Spengler Catalyzing En-zyme. *J. Am. Chem. Soc.* **2008**, 130, 710–723; (b) Klausen, R. S.; Ken-nedy, C.; Rose, A. M. Hyde, Jacobsen, E. N. Chiral Thioureas Pro-mote 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 Understand-ings of Pictet Spengler Reactions. *Chem.* **2018**, 4, 1952–1966.

(9) Previous work in our group has established that both imin-ium and enamine species are accessible via reductive activation. Their fate depends on the nature of the reaction partner and con-ditions (see reference 7, in particular 7a–7c).

(10) (a) Motoyama, Y.; Aoki, M.; Takaoka, N.; Aoto, R.; Na-gashima, H. Highly efficient synthesis of aldenamines from car-boxamides by iridium-catalyzed silane-reduction/dehydration under mild conditions. *Chem. Commun.* **2009**, 12, 1574–1576; (b) Nakajima, M.; Sato, T.; Chida, N. Iridium-Catalyzed Chemoselec-tive 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) Yoritake, M.; Takahashi, Y.; Tajima, H.; Ogi-hara, 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.; Mina-mikawa, R.; Oishi, T.; Sato, T.; Chida, N. Asymmetric Total Synthe-sis of Fascicularin by Chiral N-Alkoxyamide Strategy. *Org. Lett.* **2019**, 21, 1868–1871 (f) Gammack Yamagata, A. D.; Dixon, D. J. En-antioselective 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 ter-tiary 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-Cata-lyzed 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. *Tetrahed-ron*, **2018**, 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. Iri-dium-Catalysed Reductive Coupling Reaction of Tertiary Lactams/Amides with Isocynoacetates. *Org. Chem. Front.* **2018**, 5, 2051–2056. For the reductive functionalisation 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) Takashi, 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. ¹H–³Si HMBC pro-ved the existence of this N–Si bond when the reaction was carried out in an NMR tube, see Supporting Information. However, a con-trol 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 either on 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-cat-alyzed silane reduction of carboxamides leading to a practical syn-thetic 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, 1161-1181.

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

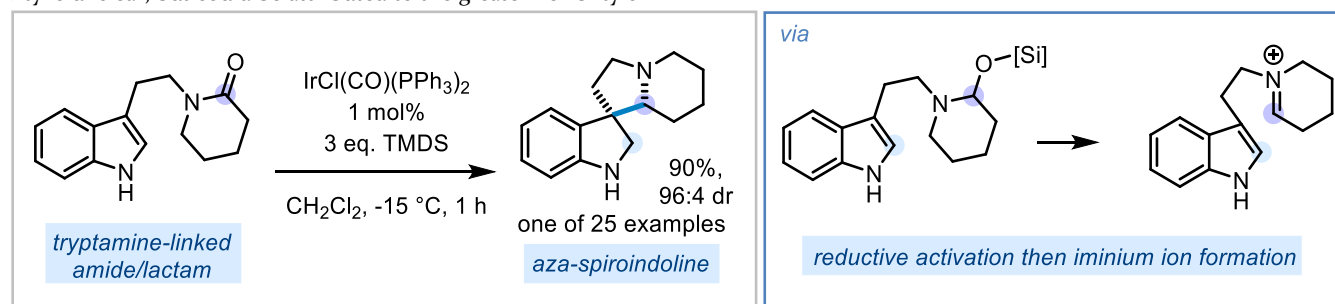
(14) Double deprotonation of the model substrate **7a** with LDA, followed by alkylation with alkyl iodides afforded the α -alkylated products **7h**, **7i**, and **7j**. For similar strategies, see: (a) Amat, M.; Ramos, C.; Pérez, M.; Molins, E.; Florindo, P.; Santos, M. M. M.; Bosch, J. Enantioselective formal synthesis of *ent*-rhynchophylline and *ent*-isorhynchophylline. *Chem. Commun.* **2013**, 49, 1954-1956; (b) Herrmann, J. L.; Kieczkowski, G. R.; Normandin, S. E.; Schlessinger, R. H. High yield stereospecific total syntheses of Eburnamine and Eburnamine. *Tetrahedron Lett.* **1976**, 11, 801-804.

(15) For these substrates, the major reaction by-product was the saturated cyclic amine. The reason for the loss in diastereoselectivity is unclear, but could be attributed to the greater flexibility of

the 7-, 8-, and 9-membered rings allowing a decrease of 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 the *endo*-TS, hence reducing the diastereoselectivity.

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



- chemoselective ■ diastereoselective ■ readily available starting materials
- 25 ppm catalyst loading on scale ■ α -quaternary amides/lactams ■ one-pot process