Total Synthesis of (–)-Rauvomine B via a Strain-Promoted Intramolecular Cyclopropanation

Jake M. Aquilina,[a] Ankush Banerjee,[a] Gabriel N. Morais,[ab] Shuming Chen,*[b] and Myles W. Smith*[a]

[a]*Department of Biochemistry, UT Southwestern Medical Center, 5323 Harry Hines Blvd., Dallas, Texas 75390, United States*

[b]*Department of Chemistry and Biochemistry, Oberlin College, 119 Woodland St., Oberlin, Ohio 44074, United States*

Abstract. We describe the first total synthesis of the unusual cyclopropane-containing indole alkaloid (–)-rauvomine B via a strategy centered upon intramolecular cyclopropanation of a tetracyclic *N*-sulfonyl triazole. Preparation of this precursor evolved through two generations of synthesis, with the ultimately successful route involving a palladium-catalyzed stereospecific allylic amination, a *cis*-selective Pictet–Spengler reaction, and ring-closing metathesis as important bond-forming reactions. The key cyclopropanation step was found to be highly dependent on the structure and conformational strain of the indoloquinolizidine *N*-sulfonyl triazole precursor, the origins of which are explored computationally through DFT studies. Overall, our synthesis proceeds in 11 total steps and 2.4% yield from commercial materials.

Introduction:

The rauvomines (**1**–**7**) are a group of indole alkaloids recently isolated from *Rauvolfia vomitoria*, a small tree used in various traditional medicines which has proven to be a rich source of monoterpene indole alkaloids (MIAs).[1,2] Structurally, rauvomines A–G fall into the sarpagine class of MIAs (exemplified by **8**) but contain certain features that render them unique among this family.[3] For instance, while all rauvomines incorporate an additional C-19 methyl-bearing stereocenter found in a smaller subset of the class,[4] rauvomines A (**1**) and C (**3**) contain an alkyl chloride, an uncommon motif for terrestrial indole alkaloids.[5] Rauvomine B (**2**) is more unique still, with its proposed structure featuring a cyclopropane ring bridging its indoloquinolizidine unit, formed via an additional C–C bond between C-16 and C-20 in the typical sarpagine scaffold. To the best of our knowledge, this renders **2** one of only five natural MIAs (out of >3,000) to contain a cyclopropane.[6] From a synthetic perspective, its unique 6/5/6/6/3/5 hexacyclic ring system presents challenges not readily addressed via existing approaches to the sarpagine alkaloids. In addition, preliminary biological testing has shown rauvomine B (**2**) to be among the most active of its congeners in anti-inflammatory screens, displaying inhibition of RAW 264.7 macrophages (IC_{50} = 39.6 μM; positive control, celecoxib: IC_{50} = 34.3 μM).[1] Inspired by the unique structure of rauvomine B (**2**) and seeking to develop a new synthetic entry to the sarpagine family for further biological screening, we embarked upon a total synthesis of **2**.

The sarpagine alkaloids, as well as their biosynthetically related macroline and ajmaline congeners, have proven popular targets for the synthetic community based on their challenging structures and diverse biological properties. Such studies began with early (semi)syntheses by Sakai[7] and Magnus,[8] and were significantly expanded by numerous total syntheses reported by the Cook group and others over the subsequent three decades.[9–18] Continued interest in the family has been showcased in a series of creative approaches developed in the past five years.[19–26] Despite this rich body of work, synthetic approaches capable of addressing the particular structural challenges presented by rauvomines A–C (**1**–**3**) are yet to be developed. While the Cook group has developed an approach to the less common C-19 methyl-bearing sarpagines,[16] synthetic solutions to the alkyl chloride or cyclopropane motifs have not been reported to date. One preliminary study by the Lei group explicitly targets the rauvomine alkaloids.[27] While these authors are able to access the core sarpagan scaffold using established Pictet–Spengler (**9** → **10**) and Dieckmann (**10** → **11**) disconnections popularized by Cook, neither the C-19 stereocenter nor the cyclopropane or chloro motifs have yet been addressed.

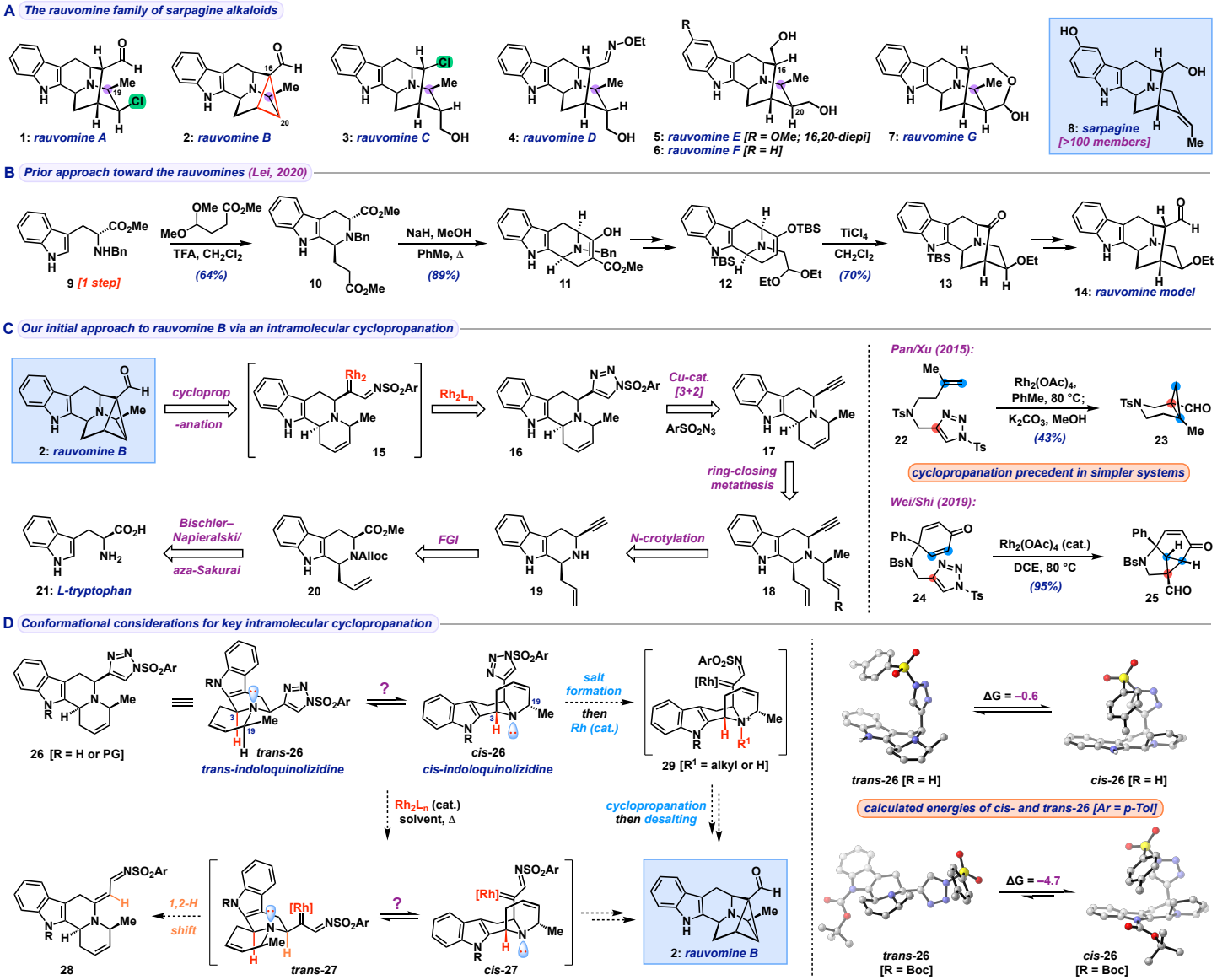


Figure 1. (**A**) The rauvomine family of structurally unusual indole alkaloids. (**B**) Prior synthetic efforts toward the rauvomines. (**C**) Our initial synthetic approach to rauvomine B (**2**) and literature precedent. (**D**) Conformational aspects for the key intramolecular cyclopropanation and DFT-calculated conformational preferences [energies in kcal/mol; hydrogen atoms omitted for clarity].

Our planned approach to rauvomine B (**2**) was built around a potentially powerful intramolecular cyclopropanation transform to simplify **2** back to *N*-sulfonyl-1,2,3-triazole precursor **16** (Figure 1C). In the forward direction, we planned to take advantage of chemistry developed by Fokin and Gevorgyan where *N*-sulfonyl triazoles can be converted into α-imino rhodium carbenes (e.g., **15**) in the presence of a dimeric Rh(II) carboxylate catalyst, which can subsequently effect cyclopropanation of alkenes.[28–30] *N*-sulfonyltriazole **16** can arise from a Cu-catalyzed [3+2] cycloaddition of a sulfonyl azide with alkyne **17**. **17** contains a tetracyclic indoloquinolizidine framework present in numerous MIA natural products, which we aimed to prepare via a combination of chiral pool and modern transition metal-catalyzed methods. Specifically, alkene **17** was seen to arise via ring-closing metathesis (RCM) of diene **18**, itself available via regio- and stereoselective *N*-crotylation controlled via a Ir- or Pd-catalysis of secondary amine **19**. We planned to access **19** by adapting a protocol developed by the Martin group towards a related tetrahydro-β-carboline.[31] Briefly, the alkyne of **19** could be installed via homologation of ester **20**, itself available via *cis*-selective aza-Sakurai reaction of an iminium ion ultimately derived from *L*-tryptophan (**21**) as an inexpensive chiral pool starting material.

A few aspects of the key cyclopropanation step warrant discussion. Although the Fokin–Gevorgyan transformation of *N*-sulfonyl-1,2,3-triazoles to α-imino carbenes has found some use in total synthesis,[32–35] to the best of our knowledge it is yet to be leveraged for cyclopropanation in natural product synthesis. Limited examples of intramolecular

cyclopropanations involving flexible substrates such as **22** and **24** have been reported by Xu[36] and Shi[37] (Figure 1C, right). While these reports provided encouragement, our proposed indoloquinolizidine system **26** presents a number of conformational complications that are projected to affect the feasibility of this key transannular transformation (Figure 1D). Firstly, indoloquinolizidine **26** can exist in either its *trans*- or *cis*-forms (*trans*- or *cis*-**26**) depending on the orientation of the nitrogen lone pair; interconversion between these two forms is possible by nitrogen inversion.[38,39] Presumably, these conformers can advance to the corresponding Rh carbenes *trans*-**27** and *cis*-**27** in the usual manner. At this stage, however, the reactive carbene is placed either proximal or distal to the piperidine alkene: in *cis*-**27**, cyclopropanation should be possible to an *N*-sulfonyl imine that can be hydrolyzed to give rauvomine B (**2**); in contrast, such a reaction in *trans*-**27** seems to be precluded and one might expect the known propensity for carbenes containing adjacent H-atoms to undergo 1,2-hydride shift to compete, providing **28**.[40,41] While typically *trans*-indoloquinolizidines are favored over their *cis*-forms, substituents can bias this preference significantly.[39] DFT calculations indeed predicted a 0.6 kcal/mol preference for *cis*-**26** over *trans*-**26** when the indole nitrogen is unsubstituted, which increased to 4.7 kcal/mol for its *N*-Boc congener (Figure 1D, right). The extent to which these preferences might translate to the derived carbenes **27**, impact the ensuing transition states, or whether efficient interconversion between the conformers would occur under the reaction conditions was less clear at the outset of our studies. With these complexities both challenging to predict and adding to the intrigue of the key step, we resolved to screen various forms of **26**, including conformationally-locked ammonium derivatives **29**, to explore the viability of this direct route to rauvomine B (**2**).

Results and Discussion:

Our synthesis began with the preparation of tricyclic secondary amine **19** (Figure 2A). Following the Martin precedent,[31] we were able to access multigram quantities of iminium salt **30** (67%). Treatment of **30** with AllocCl and NEt_3, followed by addition of methanol and additional NEt_3, gave hemiaminal ether **31**. While this compound proved difficult to obtain in analytically pure form due to its sensitivity to silica gel, after a quick purification it could be subjected to aza-Sakurai conditions with allyltrimethylsilane to arrive at *cis*-**20** stereoselectively (73%, 2 steps).[31] A one-pot DIBAL-H reduction and Ohira–Bestmann homologation then converted the ester **20** to the desired alkyne **32**. High-yielding *N*-Alloc deprotection of both **32** and **20** was possible under palladium catalysis. With secondary amines **19** and **33** in hand, we screened a number of *N*-crotylation conditions on both substrates[42] using a chiral Ir catalyst[43] and palladium catalysts[44] with symmetrical and non-symmetrical π-allyl precursors, and even simple halide/pseudohalide electrophiles without success (see Table S1 for details). We attribute the failure of these *N*-allylations with secondary electrophiles to the steric hindrance around the amine in **19**/**33**, with the flanking substituents likely oriented in a bis-equatorial fashion (**35**).[45]

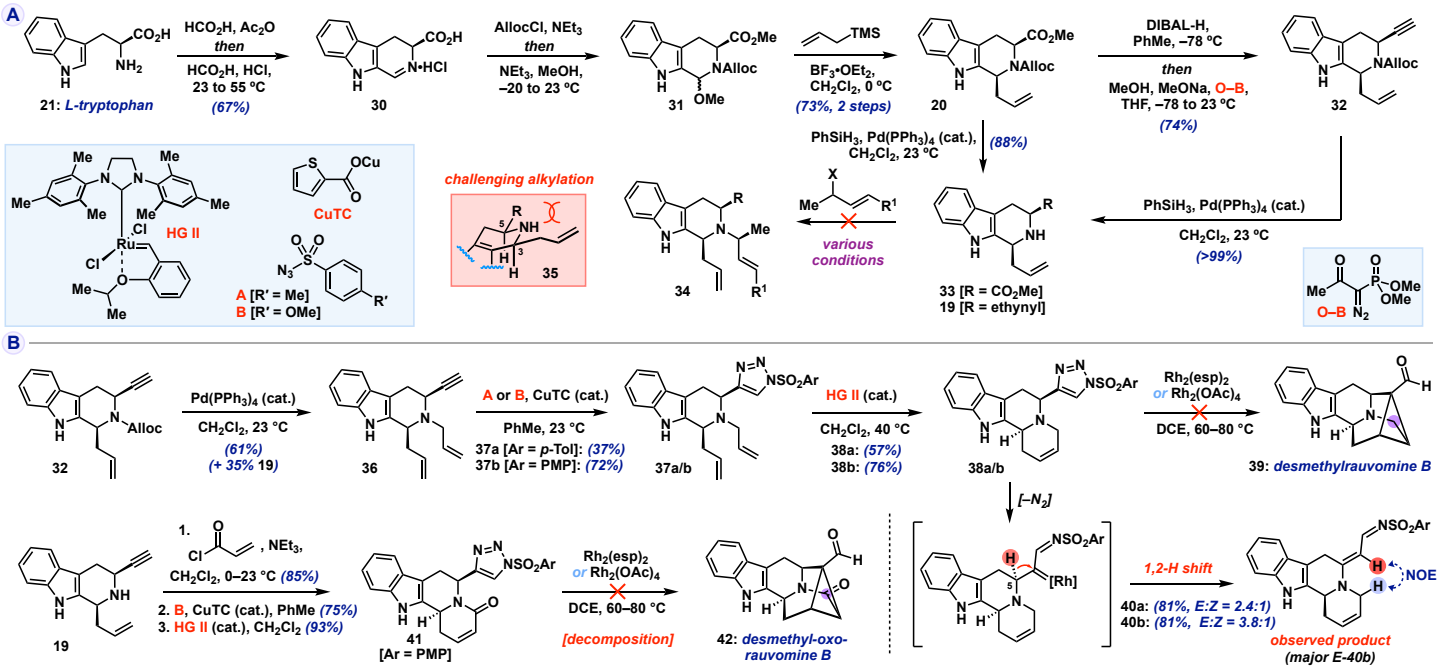


Figure 2. (**A**) Preparation and unsuccessful *N*-crotylation of tetracyclic secondary amines **19** and **33**. (**B**) Exploration of the key cyclopropanation in the C19-desmethyl series.

Despite our failure to engage a secondary alkyl electrophile with hindered secondary amines **19** and **33**, we were able to install a less hindered allyl unit using the *N*-Alloc group as a latent allyl source (Figure 2B).[46] In the event, decarboxylation of **32** under $Pd(PPh_3)_4$ catalysis in the absence of an allyl trap delivered *N*-allylamine **36** (61%, with 35% of **19**). **36** presented an opportunity to explore the key cyclopropanation in the context of a desmethyl model system, potentially leading to desmethylrauvomine B (**39**). Intermediate **36** could be advanced via Cu-catalyzed triazole formation with either tosyl azide or 4-methoxyphenylsulfonyl azide to provide **37a** (37%) and **37b** (72%), respectively. Ring-closing metathesis proceeded smoothly using Hoveyda–Grubbs II catalyst (HG II) providing cyclopropanation precursors **38a** (57%) and **38b** (76%). Subjecting triazoles **38a/b** to several standard rhodium-catalyzed conditions at elevated temperature unfortunately led to none of the desired cyclopropane **39** in either imine or aldehyde form. Instead, 1,2-H shift products **40a** and **40b** were formed as an *E*/*Z*-mixture in good yields (major *E*-isomer of **40b** assigned by NOE studies). As mentioned above, such reactivity of Rh carbenes bearing α-H substituents is well precedented and, despite efforts to optimize these transformations towards the desired cyclopropane product **39**, no success was found. We additionally prepared an unsaturated lactam analogue **41** via *N*-acryloylation to probe whether changing the electronics[37] of the alkene might impact the selectivity for cyclopropanation; unfortunately, **41** simply led to decomposition when subjected to the same cyclopropanation conditions.

At something of an impasse, we reasoned that any further studies of the key cyclopropanation step should be conducted on the intact rauvomine B precursor (**16**, Figure 1), given that subtle effects on the conformational preferences engendered by the C-19 methyl stereocenter might be crucial to the success of this key step. Thus, we reworked our current approach to alkyne precursor **17** to enable the attachment of a secondary *N*-alkyl unit (Figure 3A). The key adjustment was to switch the order of tetrahydro-β-carboline formation and *N*-crotylation steps, a maneuver that would transpose the previously elusive *N*-crotylation onto the less hindered primary amine of tryptophan methyl ester (**45**) to yield secondary amine **44**, followed by a Pictet–Spengler reaction to **43** under *cis*-selective conditions developed by the Cook group.[47] The *trans*-selective Pictet–Spengler reaction of tryptophan-derived secondary amines has been utilized extensively in indole alkaloid synthesis, including of many sarpagine members, but application of its *cis*-selective variant is yet to be reported.

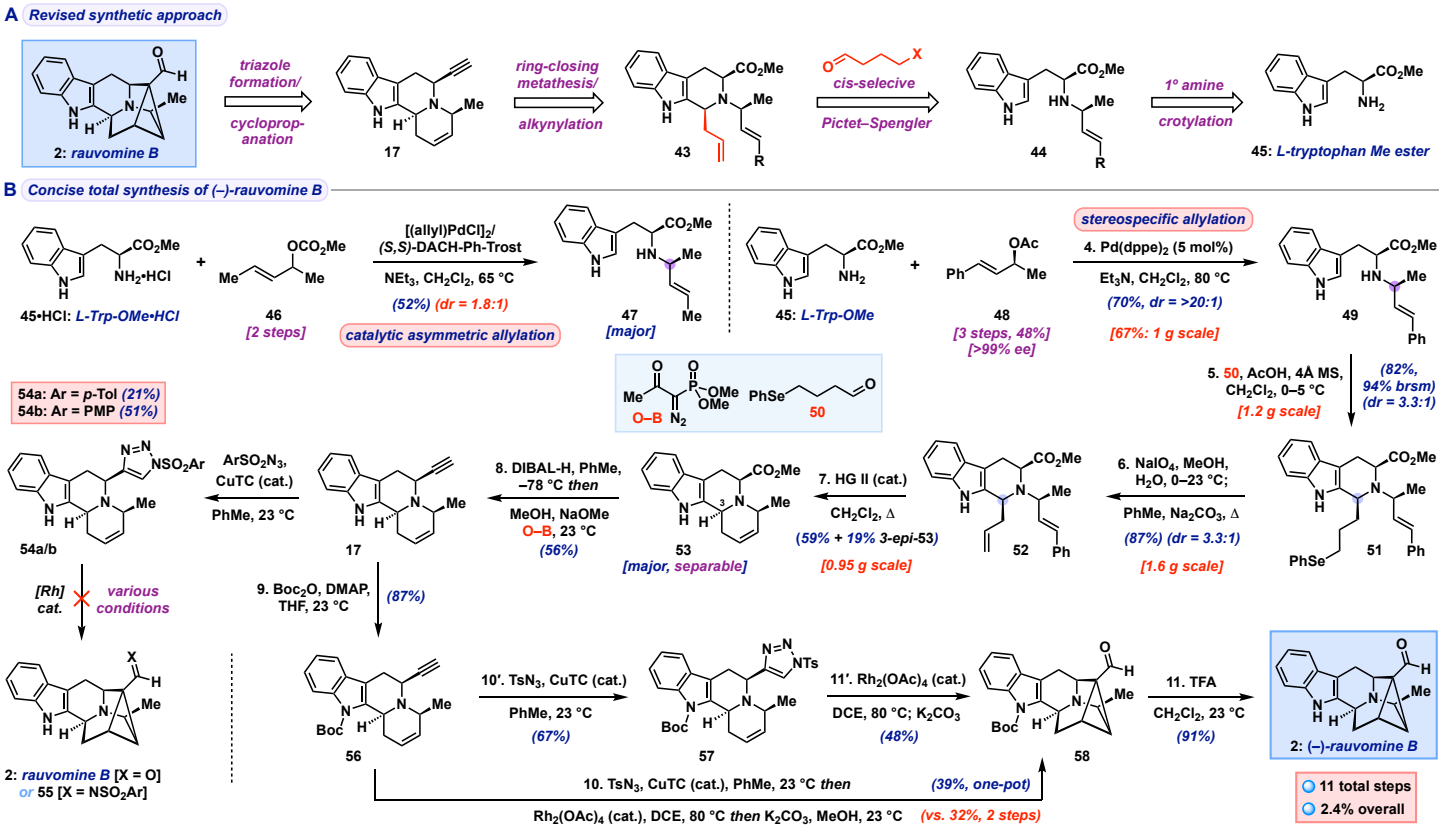


Figure 3. (**A**) Revised retrosynthetic approach to rauvomine B (**2**). (**B**) Successful asymmetric total synthesis of (–)-**2**.

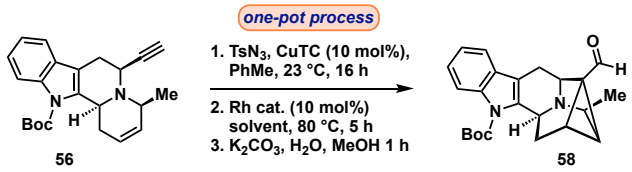
Initial efforts involving branch-selective *N*-crotylation under recently described chiral Ir-catalyst-controlled conditions, only delivered the desired product in low yields (<10%) in our hands.[48] We therefore explored Pd-catalyzed asymmetric allylic amination using symmetrical π-allyl precursor **46**[49] based on close precedent reported by Trost.[50] Using a modification of their conditions we were able to obtain desired product **44**, albeit with only moderate diastereoselection

(52%, dr = 1.8:1). This low level of stereoselectivity is consistent with observations made by Trost that our desired stereochemical outcome represents the mismatched case between the chirality of the (*S*,*S*)-DACH-Ph-Trost/Pd catalyst and L-tryptophan methyl ester (**45**). While further screening of non-commercial chiral ligands may have improved the selectivity,[51] we sought a more straightforward solution. We therefore investigated stereospecific *N*-alkylation using an enantioenriched allylic electrophile. While several possibilities were investigated, the most fruitful proved to be a palladium-catalyzed allylic alkylation using enantioenriched allylic acetate **48**. This species, available in three steps in essentially enantiopure form (48%, >99% ee) via a facile enzymatic resolution,[52] is known to undergo regioselective substitution at the methyl-bearing carbon (rather than the benzylic position) as would be required in the current case.[53] As noted in many seminal contributions, the stereospecifity of such processes depends on the nature of the Pd-catalyst involved. Consistent with these studies,[53,54] catalysts bearing monodentate ligands led to ablation of the stereochemistry (e.g., $Pd(PPh_3)_4$: dr = 1:1); subsequent screening of bidentate ligands with Pd_2dba_3 showed varying degrees of stereospecificity (dr = 3:1 – >20:1) depending on the ligand (see Table S2). Ultimately, we found that the preformed catalyst $Pd(dppe)_2$[54] provided perfect stereoretention and good yield (82% ^{1}H NMR yield, dr = >20:1) on screening scale; scale-up to preparative scale retained this level of stereospecificity along with a serviceable isolated yield of **49** (70%; gram-scale: 67%).

With reliable access to stereopure **49**, we could engage this secondary amine in a Pictet–Spengler reaction under Cook's *cis*-selective conditions[47] using known aldehyde **50**[55] as a masked 3-butenal fragment. Pleasingly, these conditions (AcOH, 4Å MS, CH_2Cl_2, 0–5 °C) led to tetrahydro-β-carboline **51** (82%) as an inseparable 3.3:1 diastereomeric mixture favoring the desired diastereomer *cis*-**51**. Oxidative elimination of the phenylseleno group in **51** under conditions reported by Gaich[56] unveiled the diene **52** (87%, dr = 3.3:1) required for RCM. This cyclization occurred smoothly, delivering now separable diastereomers **53** (59%) and 3-*epi*-**53** (19%). Major diastereomer **53** could be advanced via the same one-pot homologation described earlier to alkyne **17**, followed by CuTC-catalyzed triazole formation with two sulfonyl azides to give *N*-tosyltriazole **54a** (21%) and *N*-(*p*-methoxyphenyl)sulfonyl **54b** (51%).

Cyclopropanation precursors **54a/b** bear the all carbons of the natural product as well as the C-19 methyl stereocenter and might lead directly to rauvomine B (**2**) after imine hydrolysis. Disappointingly, we once again observed either no reaction, decomposition, or 1,2-hydride shift products as the sole identifiable species under a range of conditions; in no case was **2** or its precursor imine **55** observed (see Table S3). This led us to screen the effect of indole *N*-protection on the cyclopropanation pathway, in the hope that either intermediate/product stability or the energetics of the competing pathways might be beneficially affected. Boc protection of the indole nitrogen gave alkyne **56**, which in turn led to *N*-tosyltriazole **57** (67%) after [3+2] cycloaddition with TsN_3. Upon testing *N*-Boc protected **57** under similar conditions to **54a/b**, we were pleased to find that desired cyclopropane **58** could be formed in moderate yield. Ultimately, after screening a number of Rh-catalysts, solvents, and in situ hydrolyses, we found that treatment of **56** with $Rh_2(OAc)_4$ (10 mol%) in DCE at 80 °C for 5 h, followed by imine hydrolysis with K_2CO_3/MeOH[28] in the same pot was able to provide *N*-Boc rauvomine B (**57**) in 48% yield (see Table S4 for optimization). Since during our studies *N*-tosyl triazole substrates had been susceptible to detosylation during purification, we speculated that a one-pot process[27] might increase overall efficiency. After some optimization, involving balancing equivalents of sulfonyl azide and the loading of both catalysts (Table 1), this indeed proved to be the case: initial CuTC-catalyzed triazole formation in PhMe, followed by concentration and application of the same $Rh_2(OAc)_4$-catalyzed cyclopropanation in DCE and in situ hydrolysis gave **57** in 39% yield (entry 14; vs 32% overall for the 2-step process). *N*-Boc rauvomine B (**57**) was then deprotected under standard conditions (TFA, CH_2Cl_2) to deliver rauvomine B (**2**) in excellent yield (91%), completing a 11-step total synthesis (longest linear sequence from commercial benzylideneacetone) of the natural product in 2.4% overall yield. Spectroscopic data for our synthetic rauvomine B matched well with that of the natural material; the optical rotation of **2** also was in excellent agreement with the isolation report $\{[\alpha]^{25}_D = -94.1$ (c = 0.42, $CHCl_3$); lit.:

Table 1. Optimization of one-pot intramolecular cyclopropanation.



Entry	*TsN_3* (equiv)	*Rh Catalyst*	*Solvent* (step 2)	*Yield* (%)[a]
1	1.1	$Rh_2(OAc)_4$	DCE	16[b]
2	1.3	$Rh_2(OAc)_4$	DCE	22[b]
3	1.3	$Rh_2(OAc)_4$	DCE	31
4	1.3	$Rh_2(OAc)_4$	DCE	26[c]
5	1.3	$Rh_2(OAc)_4$	PhMe	30
6	1.3	$Rh_2(esp)_2$	DCE	23
7	1.3	$Rh_2(oct)_4$	DCE	trace
8	1.3	$Rh_2(TFA)_4$	DCE	ND
9	1.3	$Rh(OCOPh_3)_2$	DCE	14
10	1.5	$Rh_2(OAc)_4$	DCE	19
11	1.3	$Rh_2(OAc)_4$	DCE	21[d]
12	1.3	$Rh_2(OAc)_4$	PhMe	18[d]
13	1.5	$Rh_2(OAc)_4$	DCE	24[e]
14	*1.3*	*$Rh_2(OAc)_4$*	*DCE*	*39[f]*
15	1.3	$Rh_2(OAc)_4$	DCE	37[g]

[a]Reactions were carried out on ~10 mg scale, isolated yield; [b]without step 3; [c]step 3 continued for 5 h; [d]step 1 was conducted at 35 °C; [e]7.5 mol% catayst was used; [f]step 2 was carried out at 100 °C for 3 h; [g]step 2 was carried out at 120 °C for 2 h.

$[\alpha]^{20}_{D} = -95.6$ (c = 0.8, $CHCl_3$)},[1] confirming the absolute configuration of the natural product based on the known chirality of L-tryptophan methyl ester (**45**).

With the synthesis complete, we turned our attention to investigating the origins of the divergent reactivity of *N*-H vs *N*-Boc indole triazoles **54a/b** and **57** in the key cyclopropanation step. Specifically, we sought to probe the relative energetic barriers for this desired pathway vs the competing 1,2-H shift (observed with **53a** and the desmethyl substrates **38a/b**) via DFT calculations (Figure 4). Our calculated free energy diagram (Figure 4A) revealed the differential impact of Boc substitution on the cyclopropanation vs 1,2-H shift pathways. After ***cis*-26** and ***trans*-26** are transformed into their corresponding Rh carbene forms **A**/**A′** and **B**/**B′**, respectively, our calculations indicated that they would be funneled towards the low-energy aziridinium ylide resting state **C**/**C′** via near-barrierless ring closure. Ring-opening of aziridinium ylide **C**/**C′** is necessary in order to undergo cyclopropanation (via **TS-1**/**TS-1′**) or 1,2-H shift (via **TS-2**/**TS-2′**; see Figure 4B for calculated structures). While the 1,2-H shift proceeds with similar activation barriers for the *N*-H and *N*-Boc aziridinium ylides (17.6 and 16.3 kcal/mol, respectively), the cyclopropanation barrier was calculated to be 6.9 kcal/mol lower for the *N*-Boc aziridinium ylide **C** than its *N*–H analogue **C′**. As a result, cyclopropanation ($\Delta G^{\ddagger}$ = 14.9 kcal/mol) is overall more favorable than 1,2-shift ($\Delta G^{\ddagger}$ = 16.3 kcal/mol) for the *N*-Boc derivative, while 1,2-shift ($\Delta G^{\ddagger}$ = 17.6 kcal/mol) is predicted to dominate over cyclopropanation ($\Delta G^{\ddagger}$ = 21.8 kcal/mol) in the *N*-H system, consistent with experimentally observed reaction outcomes.

To further explain why the *N*-Boc protecting group tipped the kinetics vastly in favor of cyclopropanation, we closely examined the calculated geometries of **C**/**C'** and **TS-1**/**TS-1'** (Figure 4C). We found that in the *N*-Boc aziridinium ylide **C**, severe allylic-type strain forces the Boc protecting group out of plane with respect to the indole ring system (with an O=C–N–C dihedral angle of 9.8°), while also pushing the C-3 substituent up into more of a pseudoaxial orientation. The effect of this strain on the geometry of **C** is particularly evident when superimposed upon its *N*-H analogue **C′**. In the cyclopropanation transition state **TS-1**, the conformational changes required for the alkene to approach the Rh carbene moiety – which includes positioning the C-3 substituent completely pseudoaxial – also happen to be the perfect antidote to the allylic-type strain. This allows the Boc group to become almost completely coplanar with the indole system with an O=C–N–C dihedral angle of only 0.5°. In other words, the cyclopropanation barrier in the *N*-Boc system is greatly diminished due to its resting state (**C**) being selectively destabilized by allylic-type strain compared to its transition state (**TS-1**).

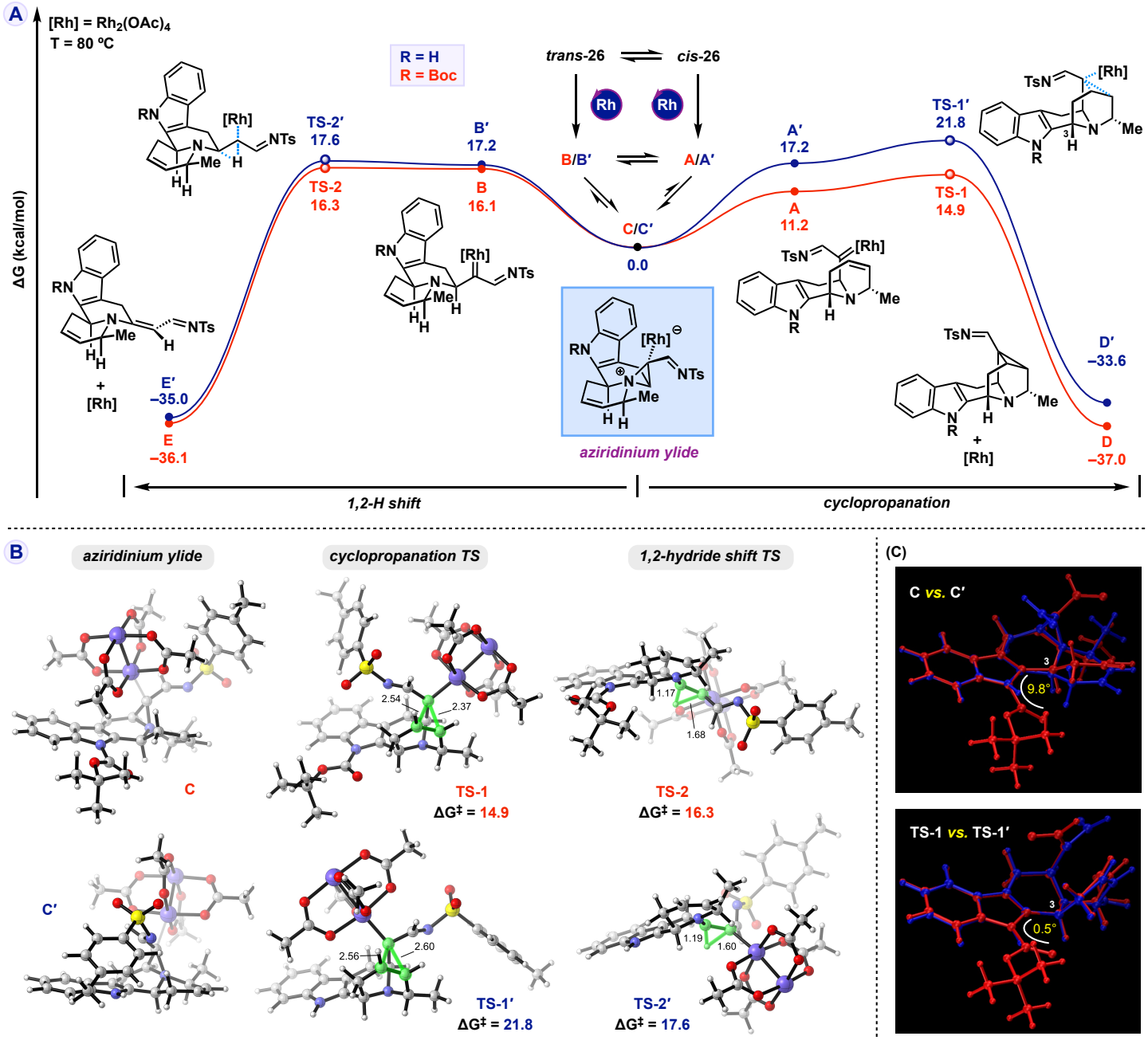


Figure 4. (**A**) Calculated free energy diagram. Free energies were obtained at the M06-D3/def2-TZVPP–SDD(Rh), SMD(DCE)//B3LYP-D3/def2-SVP–SDD(Rh) level of theory with the exception of the transition states, which were calculated at the M06-D3/def2-TZVPP–SDD(Rh), SMD(DCE)//B3LYP/def2-SVP–SDD(Rh) level of theory. (**B**) Calculated structures of key intermediates and transition states (TSs). Free energies are in kcal/mol. Interatomic distances are in Å. (**C**) Superimposed structures (red: R = Boc, blue: R = H) of key intermediates and TSs. The O=C–N–C dihedral angle in the R = Boc structure is marked in degrees. $Rh_2(OAc)_4$ and Ts groups are omitted for clarity.

Conclusions:

In summary, we have described the first total synthesis of the structurally unusual monoterpene indole alkaloid (–)-rauvomine B (**2**) via a concise approach leveraging intramolecular cyclopropanation of an indoloquinolizidine *N*-sulfonyltriazole. The successful execution of this key transformation, marking its first use in total synthesis, proved to be very sensitive to substrate structure. In particular, we have found through detailed DFT investigations that the reaction proceeds via an unusual aziridinium ylide resting state, which, when bearing an indole *N*-Boc substituent, is selectively destabilized to favor the cyclopropanation transition state over a 1,2-H shift that predominates for its *N*-H congener. With ready access to enantiopure (–)-rauvomine B, future studies will explore its biological properties in detail. Additionally,

generalization of the developed strategy to the synthesis of other sarpargine alkaloids, including other rauvomines, via regioselective cyclopropane cleavage will be pursued.

Author Information:

Corresponding Authors:

*shuming.chen@oberlin.edu
*myles.smith@utsouthwestern.edu

Acknowledgements:

This work was financially supported by UT Southwestern through the W. W. Caruth Jr. Scholarship, the Welch Foundation (I-2045), American Cancer Society Institutional Research Grant (IRG-21-142-16), and Cancer Center Support Grant (P30CA142543) (to M.W.S). S. C. is grateful to Oberlin College for financial support. DFT calculations were performed using the SCIURus, the Oberlin College HPC cluster (NSF MRI 1427949), as well as computing resources through allocation CHE210088 from the Advanced Cyberinfrastructure Coordination Ecosystem: Services & Support (ACCESS) program (NSF #2138259, #2138286, #2138307, #2137603, and #2138296). We thank the Tambar, Ready, Qin, DeBrabander, Chen, and Falck groups (UT Southwestern) for generous access to equipment and chemicals. We are grateful to Dr. Feng Lin, Dr. Hamid Baniasadi, and Dr. Vincent Lynch (UT Austin) for assistance with NMR studies, high-resolution mass spectrometry, and X-ray crystallographic analysis, respectively.

References:

1. Zeng, J.; Zhang, D.-B.; Zhou, P.-P.; Zhang, Q.-L.; Zhao, L.; Chen, J.-J.; Gao, K. Rauvomines A and B, Two Monoterpenoid Indole Alkaloids from *Rauvolfia vomitoria*. *Org. Lett.* **2017**, *19*, 3998–4001.
2. Zhan, G.; Miao, R.; Zhang, F.; Hao, Y.; Zhang, Y.; Zhang, Y.; Khurm, M.; Zhang, X.; Guo, Z. Peraksine derivatives with potential anti-inflammatory activities from the stems of *Rauvolfia vomitoria*. *Fitoterapia* **2020**, *146*, 104704.
3. Namjoshi, O. A.; Cook, J. M. (2016). Sarpagine and Related Alkaloids. In Hans-Joachim Knölker (Ed.), *The Alkaloids: Chemistry and Biology* (pp. 63–169), Volume 76. Academic Press.
4. Rahman, M. T.; Cook, J. M. (2020). The C-19 methyl substituted sarpagine-macroline-ajmaline alkaloids: Diversity, occurrence, bioactivity, and synthesis. In Atta-Ur-Rahman (Ed.), *Studies in Natural Products Chemistry* (pp. 1–57), Volume 64. Elsevier.
5. Gribble, G. W. A Survey of Recently Discovered Naturally Occurring Organohalogen Compounds. *J. Nat. Prod.* **2024**, *87*, 1285–1305.
6. Lundurines A–D represent the only other cyclopropane-containing MIAs, see: Kirillova, M. S.; Miloserdov, F. M.; Echavarren, A. M. Total syntheses of pyrroloazocine indole alkaloids: challenges and reaction discovery. *Org. Chem. Front.* **2018**, *5*, 273–287.
7. Takayama, H.; Kitajima, M.; Wongseripipatana, S.; Sakai, S. Partial synthesis and the absolute configuration of two new *Gelsemium* alkaloids, koumidine and (19Z)-taberpsychine *J. Chem. Soc., Perkin Trans. 1* **1989**, 1075–1076.
8. Magnus, P.; Mugrage, B.; DeLuca, M. R.; Cain, G. A. Studies on *Gelsemium* Alkaloids. Total Synthesis of (+)-Koumine, (+)-Taberpsychine, and (+)-Koumidine. *J. Am. Chem. Soc.* **1990**, *112*, 5220–5230.
9. Yu, P.; Cook, J. M. Enantiospecific Total Synthesis of the Sarpagine Related Indole Alkaloids Talpinine and Talcarpine: The Oxyanion−Cope Approach. *J. Org. Chem.* **1998**, *63*, 9160–9161.
10. Li, J.; Wang, T.; Yu, P.; Peterson, A.; Weber, R.; Soerens, D.; Grubisha, D.; Bennett, D.; Cook, J. M. General Approach for the Synthesis of Ajmaline/Sarpagine Indole Alkaloids: Enantiospecific Total Synthesis of (+)-Ajmaline, Alkaloid G, and Norsuaveoline via the Asymmetric Pictet–Spengler Reaction. *J. Am. Chem. Soc.* **1999,** *121,* 6998−7010.
11. Liu, X.; Cook, J. M. General Approach for the Synthesis of Sarpagine/Macroline Indole Alkaloids. Enantiospecific Total Synthesis of the Indole Alkaloid Trinervine. *Org. Lett.* **2001**, *3*, 4023−4026.
12. Deiters, A.; Chen, K.; C. Eary, C. T.; Martin, S. F. Biomimetic Entry to the Sarpagan Family of Indole Alkaloids: Total Synthesis of (+)-Geissoschizine and (+)-*N*-Methylvellosimine. *J. Am. Chem. Soc.* **2003**, *125*, 4541−4550.
13. Sarma, P. V. V. S.; Cook, J. M. Enantiospecific Synthesis of (+)-N_a-Methylpericyclivine and (–)-N_a-Methylakuammidine as Well as the Ring-A Oxygenated Natural Products, (+)-10-Methoxy N_a-Methylpericyclivine and 10-Hydroxy N_a-Methylpericyclivine. *Org. Lett.* **2006**, *8*, 1017−1020.

14. Yin, W.; Ma, J.; Rivas, F. M.; Cook, J. M. First Enantiospecific Total Synthesis of the Important Biogenetic Intermediates, (+)-Polyneuridine and (+)-Polyneuridine Aldehyde, as Well as 16-*Epi*-vellosimine and Macusine A. *Org. Lett.* **2007**, *9*, 295−298.
15. Edwankar, C. R.; Edwankar, R. V.; Deschamps, J. R.; Cook, J. M. Nature-Inspired Stereospecific Total Synthesis of *P*-(+)-Dispegatrine and Four Other Monomeric Sarpagine Indole Alkaloids. *Angew. Chem. Int. Ed*. **2012**, *51*, 11762–11765.
16. Edwankar, R. V.; Edwankar, C. R.; Deschamps, J. R.; Cook, J. M. General Strategy for Synthesis of C-19 Methyl-Substituted *Sarpagine/Macroline/Ajmaline* Indole Alkaloids Including Total Synthesis of 19(*S*),20(*R*)-Dihydroperaksine, 19(*S*),20(*R*)-Dihydroperaksine-17-al, and Peraksine. *J. Org. Chem.* **2014**, *79*, 10030–10048.
17. Krüger, S.; Gaich, T. Enantioselective, Protecting-Group-Free Total Synthesis of Sarpagine Alkaloids–A Generalized Approach. *Angew. Chem. Int. Ed*. **2015**, *54*, 315–317.
18. Kitajima, M.; Watanabe, K.; Maeda, H.; Kogure, N.; Takayama, H. Asymmetric Total Synthesis of Sarpagine-Related Indole Alkaloids Hydroxygardnerine, Hydroxygardnutine, Gardnerine, (*E*)-16-*epi*-Normacusine B, and Koumine. *Org. Lett*. **2016**, *18*, 1912−1915.
19. Yang, Z.; Tan, Q.; Jiang, Y.; Yang, J.; Su, X.; Qiao, Z.; Zhou, W.; He, L.; Qiu, H.; Zhang, M. Asymmetric Total Synthesis of Sarpagine and Koumine Alkaloids. *Angew. Chem. Int. Ed*. **2021**, *60*, 13105 –13111.
20. Zhu, J.; Zhang, C.; Liu, L.; Xue, C.; Cai, Y.; Liu, X.-Y.; Xue, F.; Qin, Y. Total Synthesis of Sarpagine Alkaloid (–)-Normacusine B. *Org. Lett.* **2022**, *24*, 3515−3520.
21. Chen, W.; Ma, Y.; He, W.; Wu, Y.; Huang, Y.; Zhang, Y.; Tian, H.; Wei, K.; Yang, X.; Zhang, H. Structure Units Oriented Approach towards Collective Synthesis of Sarpagine-Ajmaline-Koumine Type Alkaloids. *Nat. Commun.* **2022**, *13*, 908.
22. Zhang, Y.; Zhang, L.; Qi, X. Oxidative Coupling Approach to Sarpagine Alkaloids: Total Synthesis of (–)-Trinervine, Vellosimine, (+)-Normacusine B, and (–)-Alstomutinine C. *Angew. Chem. Int. Ed*. **2023**, *62*, e202304435.
23. Chatinovska, B.; Gegevičius, R.; Orentas, E. A Short Synthesis of Vellosimine and Its Derivatives. *J. Org. Chem.* **2023**, *88*, 9569−9573.
24. Qiu, H.; Fei, X.; Yang, J.; Qiao, Z.; Yuan, S.; Zhang, H.; He, L.; Zhang, M. A Bischler-Napieralski and Homo-Mannich Sequence Enables Diversified Syntheses of Sarpagine Alkaloids and Analogues. *Nat. Commun.* **2023**, *14*, 5560.
25. Zou, H.; Yan, J.; Zhang, X.; Wu, X.; Huo, J.; Xu, Y.; Xie, W. Asymmetric Synthesis of (+)-Vellosimine Enabled by a Sequential Nucleophilic Addition/Cyclization Process. *Org. Lett*. **2023**, 25, 8215−8219.
26. Cheng, W. F.; Ma, S.; Lai, Y. T.; Cheung, Y. T.; Akkarasereenon, K.; Zhou, Y.; Tong, R. $BiBr_3$-Mediated Intramolecular Aza-Prins Cyclization of Aza-Achmatowicz Rearrangement Products: Asymmetric Total Synthesis of Suaveoline and Sarpagine Alkaloids. *Angew. Chem. Int. Ed.* **2023**, *62*, e202311671.
27. Wu, B.; Jiang, Z.-J.; Tang, J.; Gao, Z.; Liang, H.; Tang, B.; Chen, J.; Lei, K. Total synthesis study of rauvomines A and B: construction of the pentacyclic core structure. *Org. Chem. Front.* **2020,** *7*, 1685–1689.
28. Horneff, T.; Chuprakov, S.; Chernyak, N.; Gevorgyan, V.; Fokin, V. V. Rhodium-Catalyzed Transannulation of 1,2,3-Triazoles with Nitriles. *J. Am. Chem. Soc.* **2008**, *130*, 14972–14974
29. Chuprakov, S.; Kwok, S. W.; Zhang, L.; Lercher, L.; Fokin, V. V. Rhodium-Catalyzed Enantioselective Cyclopropanation of Olefins with *N*-Sulfonyl 1,2,3-Triazoles. *J. Am. Chem. Soc.* **2009**, *131*, 18034–18035.
30. For an independent proposal of a similar approach that did not proceed beyond unsuccessful model studies, see: Jones, K. D. (2020). The Development of Transition Metal Catalysed Methodologies for Efficient Chemical Synthesis. University of Western Australia, Perth, Australia.
31. Neipp, C. E.; Martin, S. F. Synthesis of Bridged Azabicyclic Structures via Ring-Closing Olefin Metathesis. *J. Org. Chem.* **2003**, *68*, 8867–8878.
32. Fu, J.; Shen, H.; Chang, Y.; Li, C.; Gong, J.; Yang, Z. Concise Stereoselective Synthesis of Oxaspirocycles with 1-Tosyl-1,2,3-triazoles: Application to the Total Syntheses of (±)-Tuberostemospiroline and (±)-Stemona-lactam R. *Chem. Eur. J.* **2014**, *20*, 12881–12888.
33. Duan, S.; Xue, B.; Meng, H. Ye, Z.; Xu, Z.-F. Li, C.-Y. Rhodium(II)-Catalyzed [4+3] Cyclization of Triazoles with Indole Derivatives and Its Application in the Total Synthesis of (±)-Aurantioclavine. *Chin. J. Chem.* **2021**, *39*, 1145–1152.
34. Hou, B.-L.; Wong, J. J.; Lv, N.; Wang, Y.-Q.; Houk, K. N.; Li, C.-C. Facile Generation of Bridged Medium-Sized Polycyclic Systems by Rhodium-Catalysed Intramolecular (3+2) Dipolar Cycloadditions. *Nat. Commun.* **2021**, *12*, 5239.
35. Gunawan, N.; Nutt, M. J.; Bissember, A. C.; Smith, J. A.; Stewart, S. G. *N*-Tosyl-1,2,3 triazoles as Scaffolds for Morpholines: The Total Synthesis of (–)-Chelonin A. *Synlett* **2023**, *34*, 1524–1528.
36. Pan, X.-H.; Jiang, P.; Jia, Z.-H.; Xu, K.; Cao, J.; Chen, C.; Shen, M.-H.; Xu, H.-D. Expedient catalytic construction of azabicyclo[4.1.0]/[5.1.0] carbaldehydes via intramolecular cyclopropanation. *Tetrahedron* **2015**, *71*, 5124–5129.

37. Zhu, C.-Z.; Wei, Y.; Shi, M. Rhodium(II)-catalyzed divergent intramolecular tandem cyclization of *N*- or *O*-tethered cyclohexa-2,5-dienones with 1-sulfonyl-1,2,3-triazole: synthesis of cyclopropa[*cd*]indole and benzofuran derivatives. *Org. Chem. Front.* **2019**, *6*, 2884–2891.
38. Uskokovic, M.; Bruderer, H.; von Planta, C.; Williams, T.; Brossi, A. The Nuclear Magnetic Resonance Spectra of the Angular Proton in Benzo[*a*]- and Indolo[*a*]quinolizidines. *J. Am. Chem. Soc.* **1964**, *86*, 3364–3367.
39. Eckermann, R.; Gaich, T. The Double-Bond Configuration of Corynanthean Alkaloids and Its Impact on Monoterpenoid Indole Alkaloid Biosynthesis. *Chem. Eur. J.* **2016**, *22*, 5749–5755.
40. Zhang, Z.; Shi, W.; Zhang, J.; Zhang, B.; Liu, B.; Liu, Y.; Fan, B.; Xiao, F.; Xu, F.; Wang, J. Rh(II)-catalyzed reaction of α-diazocarbonyl compounds bearing β-trichloroacetylamino substituent: C–H insertion versus 1,2-H shift. *Chem. Asian J.* **2010**, *5*, 1112–1119.
41. For 1,2-H shift products from *N*-sulfonyl triazoles, see: Makarov, A. S.; Uchuskin, M. G.; Hashmi, A. S. K. Intramolecular azavinyl carbene-triggered rearrangement of furans. *Chem. Sci.* **2019**, *10*, 8583–8588.
42. The corresponding *N*-sulfonyl triazole and indole *N*-Boc variants of **19** were also screened in the alkylations without success.
43. Jung, W.-O.; Yoo, M.; Migliozzi, M. M.; Zbieg, J. R.; Stivala, C. E.; Krische, M. J. Regio- and Enantioselective Iridium-Catalyzed Amination of Alkyl-Substituted Allylic Acetates with Secondary Amines. *Org. Lett.* **2022**, *24*, 441–445.
44. Dubovyk, I.; Watson, I. D. G.; Yudin, A. K. Chasing the Proton Culprit from Palladium-Catalyzed Allylic Amination. *J. Am. Chem. Soc.* **2007**, *129*, 14172–14173.
45. For a similar *cis*-disubstituted secondary amine adopting this conformation as determined by X-ray analysis, see: Alberch, L.; Bailey, P. D.; Clingan, P. D.; Mills, T. J.; Price, R. A.; Pritchard, R. G. The *cis*-Specific Pictet−Spengler Reaction. *Eur. J. Org. Chem.* **2004**, 1887–1890.
46. Attempts to prepare the corresponding carbamate incorporating a symmetrical secondary allylic electrophile proved unsuccessful (see SI).
47. Rahman, M. T.; Cook, J. M. Unprecedented Stereocontrol in the Synthesis of 1,2,3-Trisubstituted Tetrahydro-β-carbolines through an Asymmetric Pictet–Spengler Reaction towards Sarpagine-Type Indole Alkaloids. *Eur. J. Org. Chem.* **2018**, 3224–3229.
48. Meza, A. T.; Wurm, T.; Smith, L.; Kim, S. W.; Zbieg, J. R.; Stivala, C. E.; Michael J. Krische, M. J. Amphiphilic π-Allyliridium *C*,*O*-Benzoates Enable Regio- and Enantioselective Amination of Branched Allylic Acetates Bearing Linear Alkyl Groups. *J. Am. Chem. Soc.* **2018**, *140*, 1275–1279.
49. Braun M.; Meier, T.; Laicher, F.; Meletis, P.; Fidan, M. Palladium-Catalyzed Diastereoselective and Enantioselective Allylic Alkylations of Ketone Enolates. *Adv. Synth. Catal.* **2008**, *350*, 303–314.
50. Trost, B. M.; Calkins, T. L. Oertelt, C.; Zambrano, J. Catalyst controlled diastereoselective *N*-alkylations of α-amino esters *Tetrahedron Lett.* **1998**, *39*, 1713–1716.
51. Dohmen, S.; Reiher, M.; Albat, D.; Akyol, S.; Barone, M.; Neudörfl, J.-M.; Kühne, R.; Schmalz, H.-G. Pd-Catalyzed Asymmetric N-Allylation of Amino Acid Esters with Exceptional Levels of Catalyst Control: Stereo-Divergent Synthesis of ProM-15 and Related Bicyclic Dipeptide Mimetics. *Chem. Eur. J.* **2020**, *26*, 3049–3053.
52. Quirin, C.; Kazmaier, U. Stereoselective Synthesis of β-Branched Phenylalanine Derivatives via Chelate-Claisen Rearrangement. *Synthesis* **2009**, 1725–1731.
53. Murahashi, S.; Taniguchi, Y.; Imada, Y.; Tanigawa, Y. Palladium(0)-catalyzed azidation of allyl esters. Selective synthesis of allyl azides, primary allylamines, and related compounds. *J. Org. Chem.* **1989**, *54*, 3292–3303.
54. Granberg, K. L.; Jan E. Bäckvall, J. E. Isomerization of (π-Allyl)palladium Complexes via Nucleophilic Displacement by Palladium(0). A Common Mechanism in Palladium(0)-Catalyzed Allylic Substitution. *J. Am. Chem. Soc.* **1992**, *114*, 6858–6863.
55. Becker, J.; Butt, L.; von Kiedrowski, V.; Mischler, E.; Quentin. F.; Hiersemann, M. Catalytic Asymmetric Claisen Rearrangement of Gosteli-Type Allyl Vinyl Ethers: Total Synthesis of (–)-9,10-Dihydroecklonialactone B. *J. Org. Chem.* **2014**, *79*, 3040–3051.
56. Eckermann, R.; Breunig, M.; Gaich, T. Formal Total Synthesis of (±)-Strictamine by [2,3]-Sigmatropic Stevens Rearrangements. *Eur. J. Org. Chem.* **2017**, *23*, 3938–3949.