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Nitrogen-interrupted *halo*-Prins/*halo*-Nazarov fragment coupling cascade for the synthesis of indolines†

Aleksa Milosavljevic,[a] Connor Holt[ab] and Alison J. Frontier *[a]

The nitrogen-interrupted Nazarov cyclization can be a powerful method for the stereocontrolled synthesis of sp^3-rich *N*-heterocycles. However, due to the incompatibility between the basicity of nitrogen and the acidic reaction conditions, examples of this type of Nazarov cyclization are scarce. Herein, we report a one-pot nitrogen-interrupted *halo*-Prins/*halo*-Nazarov coupling cascade that joins two simple building blocks, an enyne and a carbonyl partner, to furnish functionalized cyclopenta[*b*]indolines with up to four contiguous stereocenters. For the first time, we provide a general method for the alkynyl *halo*-Prins reaction of ketones, thus enabling the formation of quaternary stereocenters. Additionally, we describe the outcomes of secondary alcohol enyne couplings, which exhibit helical chirality transfer. Furthermore, we investigate the impact of aniline enyne substituents on the reaction and evaluate the tolerance of different functional groups. Finally, we discuss the reaction mechanism and demonstrate various transformations of the prepared indoline scaffolds, highlighting their applicability in drug discovery campaigns.

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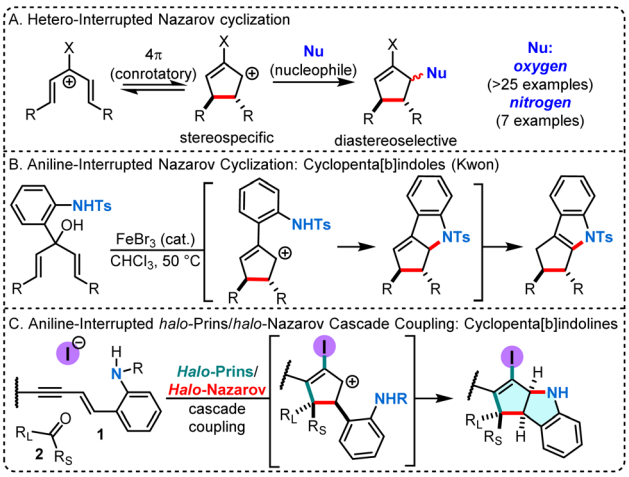
Introduction

Nitrogen heterocycles are highly valuable motifs in pharmaceutical chemistry, found in more than 75% of U.S. FDA-approved drugs.[1] Among them, simple indoles and pyrrolidines are two of the ten most frequently observed nitrogen-containing heterocyclic scaffolds.[2] Their more complex relatives, cyclopentannulated indoles and indolines, are part of Nature's large bioactive indole alkaloid family.[3] The cyclopenta[*b*]indoline scaffold is particularly attractive for drug discovery campaigns due to its molecular three-dimensionality, which has been associated with the reduction of off-target effects leading to toxicity.[4]

Interrupted Nazarov cyclization strategies are powerful methods for generating cyclopentanoid structures, providing rapid access to highly functionalized, stereochemically rich, three-dimensional scaffolds.[5] Stereospecific electrocyclization produces a cyclopentenyl cation that can be diastereoselectively trapped by various carbon and oxygen nucleophiles.[5] However, very few examples of nitrogen atom-interrupted Nazarov cyclization have been reported (Scheme 1A),[6] and only once been leveraged to build cyclopenta[*b*]indoles (Scheme 1B).[6g] In the context of our recent development of cascade cyclization sequences (*halo*-Prins coupling/interrupted *halo*-Nazarov cyclization),[7] we sought to design a system that could engage nitrogen in the interruption step. Herein, we describe an expedient strategy for the assembly of cyclopentannulated indolines from simple precursors **1** and **2**, featuring intramolecular capture of the intermediate *halo*-cyclopentenyl cation with an aniline moiety (Scheme 1C).



Scheme 1 Interrupted Nazarov cyclizations: application to the synthesis of *N*-heterocycles.

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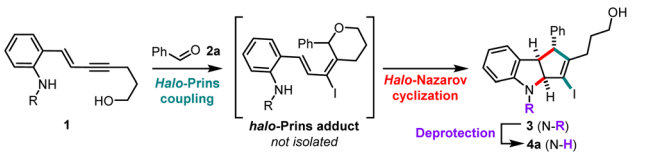
Nitrogen substitution

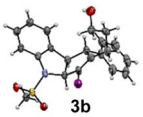
The investigation of the nitrogen-interrupted *halo*-Prins/*halo*-Nazarov cascade commenced with the reaction of the *N*-tosyl aniline enyne **1a** and benzaldehyde (**2a**). When these building blocks are exposed to triflic acid (TfOH) and tetrabutylammonium iodide (TBAI) in dichloromethane (DCM),[7] the *halo*-Prins coupling occurs smoothly. Subsequent addition of HFIP initiates the *halo*-Nazarov cascade and delivers the desired indoline **3a** in high yield (88%; Table 1, entry 1). This one-pot process extends well to the *N*-mesyl analog **1b**, producing the corresponding **3b** in 86% yield (entry 2). Unfortunately, it is not possible to remove these *N*-sulfonyl groups cleanly (see ESI† for details). In search of a more labile aniline protecting group, we tested carbamate analog **1c**, which cleanly transforms into **3c** in 84% yield (entry 3). However, the carbamate resists undergoing clean deprotection when one atmosphere of hydrogen is used under typical hydrogenolysis conditions. 2-(Trimethylsilyl)ethanesulfonyl group (SES) is designed for simple removal using fluoride reagents.[8] Indeed, when the coupling cascade is carried out using enyne **1d**, capture with aniline is realized, delivering the desired indoline **4a** after TBAF-mediated deprotection (50% yield overall, entry 4). Even better, the use of *N*-nosyl (2-nitrobenzenesulfonyl) enyne **1e** allows execution of three reactions in one-pot (*halo*-Prins coupling, *halo*-Nazarov cyclization, deprotection[9]), affording the *N*-unsubstituted indoline **4a** in 81% yield (entry 5).

The unprotected enyne **1f** cannot be converted into the desired indoline **4a** using the optimized conditions (Scheme 2). Instead, the *halo*-Prins product **3′f** is obtained, as an undesired imine adduct. No reaction is observed upon the subjection of **3′f** to the *halo*-Nazarov reaction conditions (in one-pot or in sequence).

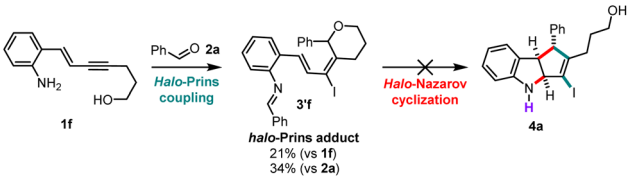
Table 1 Scope (enyne **1** aniline *N*-substitution)[a]



Entry	Aniline **1**	Indoline **3** (yield[b])	Indoline **4a** (yield[c])
1	**1a** (R = Ts)	**3a** (88%)	—[d]
2	**1b** (R = Ms)	**3b** (86%)	—[d]
3	**1c** (R = Cbz)	**3c** (84%)	—[d]
4	**1d** (R = SES)	**3d** (71%)	50%
5	**1e (R = Ns)**	**3e (74%)**	**81%**[e]


3b (X-Ray)

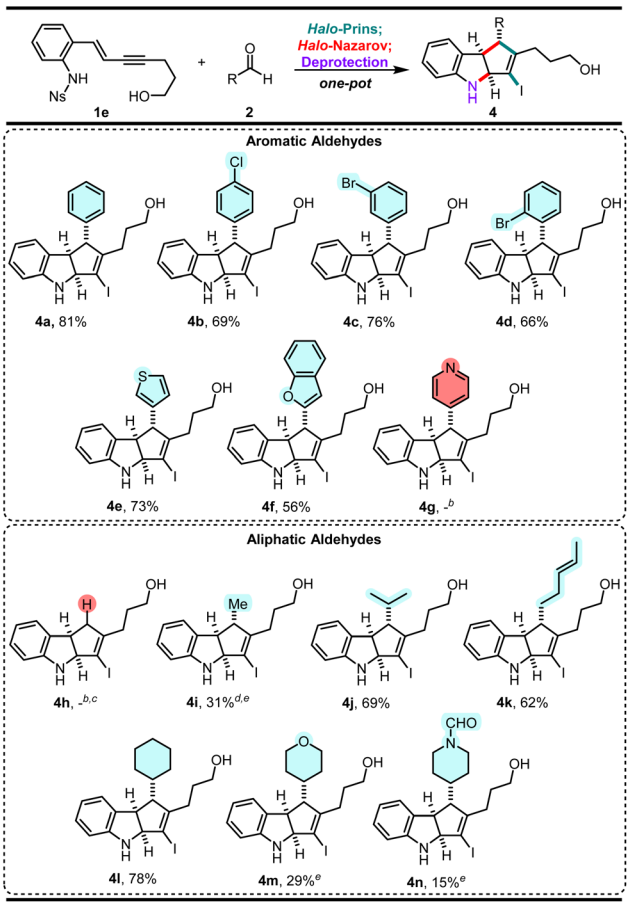
[a] One-pot reaction conditions: **1** (0.2 mmol), **2a** (1.2 equiv.), TBAI (1.2 equiv.), TfOH (1.25 equiv.), DCM, −40 °C to rt; then HFIP, 0 °C to rt; then deprotection (see ESI for details). [b] Isolated yield across two steps. [c] Isolated yield across three steps. [d] Removal of these *N*-groups was unsuccessful (see ESI for details). [e] One-pot *halo*-Prins/*halo*-Nazarov/deprotection.



Scheme 2 The behavior of the unprotected enyne **1f**.

Aldehyde scope

Once we identified the optimal enyne **1e**, our goal was to demonstrate efficient synthesis of indoline scaffolds with structural features of value (Scheme 3).[10] Thus, we focused primarily on aldehydes containing halogens (that enable further cross-coupling strategies for functionalization), medicinally relevant fragments (heterocycles), and different alkyl groups (that increase three-dimensionality). Indolines **4b–4d**, bearing arenes with functional handles, form smoothly in 66–76% yield.



Scheme 3 Exploration of scope (aldehyde reactants **2**).[a] [a]Yields correspond to isolated yields of pure products across the three-step sequence (one-pot unless otherwise stated). [b]No product was observed. [c]Dimethoxymethane and 1,3,5-trioxane were used as formaldehyde surrogates. [d]1,1-Dimethoxyethane was used as an acetaldehyde surrogate. [e]The sequence was not done in one-pot (see ESI† for details).

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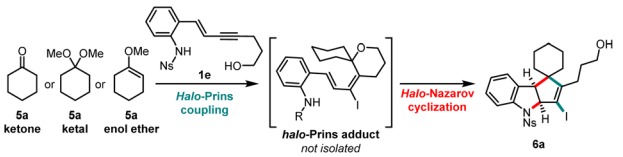
Heteroaromatic aldehydes containing a thiophene (**2e**) or a benzofuran (**2f**) core also afford the indolines **4e** and **4f** in good yields (73% and 56% yield, respectively). Unfortunately, the reaction of **1e** with pyridine-4-carbaldehyde is not successful, using either 1.2 or 2.4 equiv. of TfOH. Neither the desired product **4g** nor any of the expected intermediates were observed.

Next, we examined aliphatic aldehydes. Due to difficulties in handling neat formaldehyde and acetaldehyde, acetals were used as surrogates. Unfortunately, formaldehyde, in the form of dimethoxymethane or 1,3,5-trioxane,[11a] is not a suitable carbonyl partner, and cannot be incorporated into the scaffolds. On the other hand, 1,1-dimethoxyethane[11b] as the acetaldehyde surrogate reacts well, producing **4i** in a moderate 31% yield. We were pleased to observe that isobutyraldehyde performs just as well as aromatic aldehydes, successfully furnishing **4j** (69%). It was satisfying to observe that (*E*)-4-hexenal undergoes efficient reaction to yield **4k** (62%). There is no evidence of degradation of the alkene functionality under the reaction conditions. Surprisingly, much bulkier cyclohexanecarbaldehyde performs better than the smaller aliphatic aldehydes, smoothly affording **4l** in 78% yield. Heteroatom-containing cyclic aldehydes do not react as well as other aldehydes; they convert to the desired products **4m** and **4n** in diminished yields (29% and 15% respectively).

Ketone optimization and scope

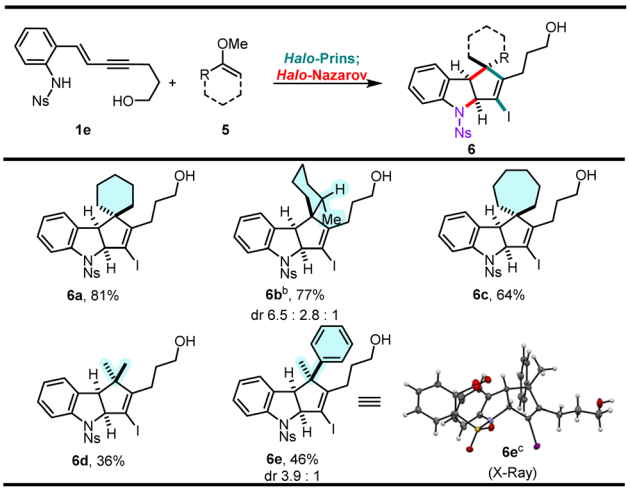
The engagement of ketones in the alkynyl Prins coupling is challenging, with limited reports in the literature.[12] Subjection of the ketone **5a** to the one-pot *halo*-Prins/*halo*-Nazarov conditions used for aldehydes leads to the formation of a complex mixture that is difficult to purify. However, a telescoped, two-step sequence greatly simplifies the subsequent isolation of the *halo*-Nazarov product **6a**. Using this method, we investigated the reactivity of ketone **5a**, along with its dimethyl ketal and methyl enol ether analogs (Table 2). The reactivity of the ketone and ketal is almost identical, and in each case, a higher yield of **6a** is observed with a larger excess of the carbonyl partner (entries 1–4). Methyl enol ether reacts faster, the reactions are cleaner, and the yield of **6a** is strikingly higher (entry 6) compared to the reactions in which the ketone or ketal are used. Furthermore, when reacted with secondary alcohol enynes, methyl enol ethers are the only ketone equivalents that produce *halo*-Prins and *halo*-Nazarov products in significant yields.[13] The use of methyl enol ethers is a broadly effective, general method for engaging ketones in the alkynyl *halo*-Prins coupling/cyclization.

Table 2 Optimization of the *halo*-Prins/*halo*-Nazarov coupling cascade for the formation of ketone-derived indolines[a]



Entry	Carbonyl partner **5a**	Equiv.	Indoline **6a** (yield[b])
1	Ketone	1.2	42%[c]
2		2.0	61%
3	Ketal	1.2	44%[c]
4		2.0	61%
5	**Enol ether**	1.2	49%[c]
6		**2.0**	**81%**

[a] Reaction conditions: **1e** (0.1 mmol), **5a** (equiv. in the table), TBAI (2.0 equiv.), TfOH (1.2 equiv.), DCM, −40 °C; then TfOH (0.2 equiv.), DCM/HFIP (10 : 1 v/v), 0 °C. [b] Yield corresponds to the isolated yield of pure product **6a** across two steps. [c] Enyne **1e** was partially consumed.



Scheme 4 Exploration of scope (ketones masked as methyl enol ethers **5**).[a] [a]Yields correspond to isolated yields of pure products across two steps. Diastereomeric ratios (dr) were determined from ^{1}H NMR. [b]Stereochemistry of the major diastereomer is tentatively assigned. [c]X-Ray structure of the major diastereomer of **6e** (recrystallized from the mixture).[15]

With the optimized conditions in hand, we briefly explored the scope of the ketone-derived cyclopenta[*b*]indolines (Scheme 4). The enol ether of an unsymmetrical cyclic ketone (2-methylcyclohexanone, **5b**) reacts well, producing an inseparable mixture of diastereomers (major diastereomer is tentatively assigned as **6b**). Enol ethers of larger-sized cyclic ketones can also be engaged, as shown by the facile formation of **6c**. Enol ethers of acyclic ketones do not behave as well as the cyclic ones and lower yields of the desired products are observed. Both acetone and acetophenone methyl enol ethers give the desired indoline scaffolds **6d** and **6e**, respectively; the latter as an inseparable mixture of diastereomers. Interestingly, the major diastereomer of **6e** is the result of a conrotatory cyclization of a pentadienyl cation in which the phenyl group is located "in" and the methyl group "out".[14]

Aniline substitution

To explore the effect of the aniline enyne substitution on the *halo*-Prins/*halo*-Nazarov reactivity, enynes **1g–1i** were prepared and subjected to the one-pot reaction conditions (Scheme 5). The

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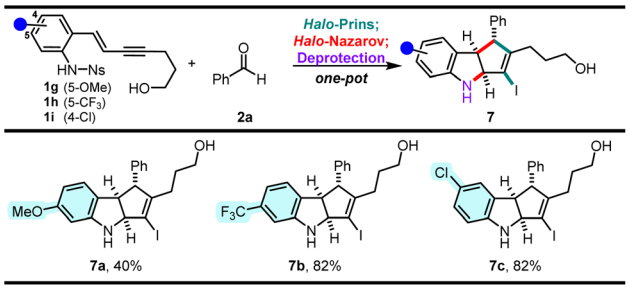


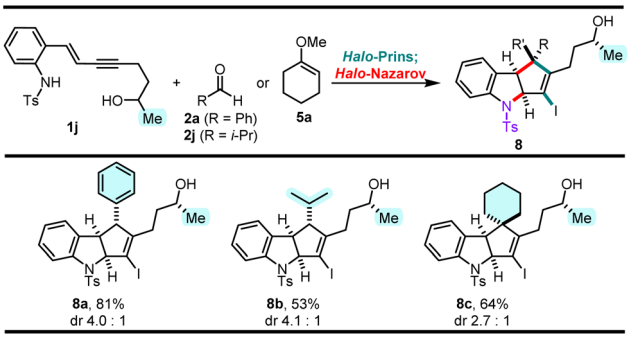
Scheme 5 Effect of the aniline (ring) substitution on the *halo*-Prins/*halo*-Nazarov reaction cascade.[a] [a]Yields correspond to the isolated yields of pure products across three steps in one-pot.

methoxy-substituted enyne **1g** requires careful control of the reaction conditions, as it reacts erratically to give **7a** in a diminished 40% yield.[16] Conversely, the trifluoromethyl-substituted enyne **1h** and the chloro-substituted enyne **1i** produce the desired **7b** and **7c** smoothly in 82% yield. Chloroindoline **7c** is of particular value as it introduces a new functional handle for further transformations.

Secondary alcohols

It was previously discovered that the *halo*-Prins/*halo*-Nazarov coupling cascades proceed *via* a conrotatory cyclization of helically chiral pentadienyl cations.[7c] Furthermore, helical preorganization of the pentadienyl cation, dictated by the stereochemical elements present in the enyne, can transfer the chirality to the *halo*-Nazarov product, leading to partial or complete diastereoselectivity in the cationic cascade.[17]

To investigate this phenomenon in our system, we prepared the enyne secondary[18] alcohol **1j** and coupled it with three stereochemically and electronically different carbonyl partners (Scheme 6). Benzaldehyde **2a** reacts smoothly and affords the desired product **8a** in 81% yield, in a 4.0 : 1 dr. On the other hand, isobutyraldehyde **2j** reacts more sluggishly than **2a**, giving **8b** in 53% yield, with a similar 4.1 : 1 dr. Lastly, cyclohexanone methyl enol ether **5a** couples with **1j**, albeit with a slower rate compared to the coupling with **1e**, and affords **8c** in 64% yield, in a 2.7 : 1 dr. This is the first example of the chirality transfer observed in the formation of ketone-derived *halo*-Nazarov products.



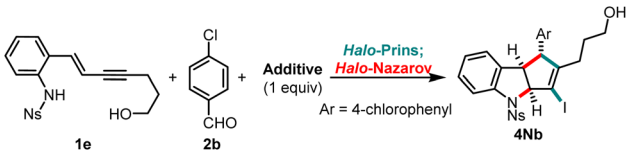
Scheme 6 Effect of a secondary (alcohol) enyne on the diastereoselectivity of the *halo*-Prins/*halo*-Nazarov coupling cascade.[a] [a]Yields correspond to isolated yields of pure products across two steps. Diastereomeric ratios were determined by normal-phase HPLC separation. Structures of major diastereomers are tentatively assigned according to ref. 7c.

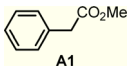
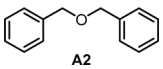
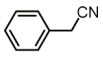
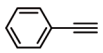
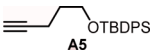
Functional group compatibility

A functional group robustness screen, developed by Glorius *et al.*, is a convenient method for the rapid assessment of the compatibility of functional groups with the reactions of interest.[19] In this method, the reaction is performed in the presence of one equivalent of an additive containing the functional group of interest, and the outcome of the reaction is analyzed using an appropriate analytical method. This approach effectively "decouples" the functional group from the alteration of steric and electronic properties of the substrates, which can often lead to erroneous conclusions.

Using this method, we analyzed the effect of six common functional groups on the *halo*-Prins/*halo*-Nazarov coupling cascade that forms the indoline **4Nb** (Table 3). The effect of additives on the reaction was monitored using TLC analysis, and the yield of **4Nb** was quantified using quantitative ^{1}H NMR (qNMR). In the absence of any additives, the reaction proceeds smoothly and forms the desired product in 91% yield (entry 1). The reaction is unaffected by methyl phenylacetate **A1**, and the desired product is obtained in 90% yield (entry 2). No evidence

Table 3 Effect of additives containing various functional groups on the *halo*-Prins/*halo*-Nazarov cascade



Entry	Additive[a] (1 equiv.)	Indoline **4Nb** (NMR yield[b])
1	None	91%[c]
2	 **A1**	90%
3	 **A2**	83%
4	 **A3**	81%
5	 **A4**	58%[d]
6	 **A5**	54%[e]

[a] Additive was added to the reaction mixture prior to the addition of TfOH (to initiate the cascade). [b] NMR yields were obtained using trichloroethylene as the internal standard. [c] Isolated yield of **4Nb** is 91%. [d] Isolated yield of **4Nb** is 58%. Partial consumption of **A4** was observed (*via* TLC). [e] Isolated yield of **4Nb** is 55%. Partial consumption of **A5** and the formation of 4-pentyn-1-ol was observed (*via* TLC).

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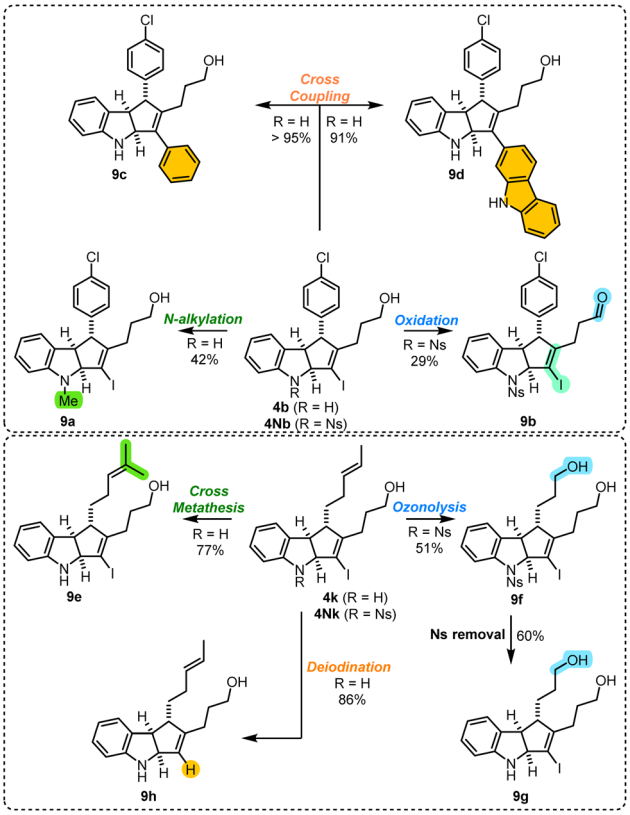
of transesterification is observed in the qNMR. The presence of dibenzyl ether **A2** and benzyl cyanide **A3** has a slight deleterious effect on the reaction, and the indoline is obtained in 81–83% yield (entries 2 and 3). On the other hand, phenylacetylene **A4** undergoes partial conversion leading to the unselective formation of a mixture of products (entry 5). However, the formation of the desired indoline **4Nb** is still observed, albeit with a diminished 58% yield. A comparable result is obtained with the *t*-butyldiphenylsilyl ether of 4-pentyn-1-ol (**A5**), leading to the formation of the product in 54% yield (entry 6). In this case, however, desilylation is also observed.

Product transformations

Lastly, we explored various transformations that further diversify prepared scaffolds, using **4b**/**4Nb** and **4k**/**4Nk** as model substrates (Scheme 7).[20] *N*-Alkylation of the indoline **4b** can be achieved using reductive amination conditions, giving *N*-methyl indoline **9a** in 42% yield. Efforts to achieve alcohol oxidation using *in situ* prepared RuO_4 produce aldehyde **9b** from *N*-nosyl **4Nb** in 29% yield, whereas insoluble material is obtained from unprotected indoline **4b**. Suzuki–Miyaura cross-coupling showed complete chemoselectivity for the vinylic iodide over aryl chloride, effortlessly furnishing **9c** and **9d** in >90% yields. The pendant olefin of **4k** readily engages in olefin cross metathesis, affording the terpene-like product **9e** in 77% yield. In contrast, ozonolysis of unprotected indoline **4k** produced insoluble material. However, this is not the case with the *N*-nosyl **4Nk**, which gives the diol **9f** readily after a reductive workup. The nosyl group was cleanly removed to give **9g**, and the reduced yield can be attributed to the challenges associated with the isolation of the significantly more polar dihydroxy indoline. Finally, a lithium–halogen exchange procedure leads to smooth deiodination to form the vinylic iodide **9h**.



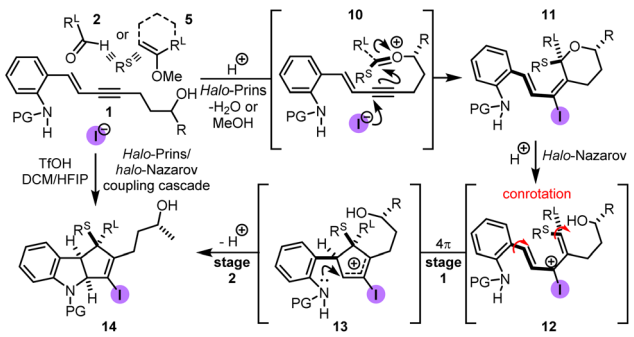
Scheme 7 Transformations of the cyclopenta[*b*]indoline scaffolds.[a] [a]Reaction conditions: *N*-alkylation (**9a**): **4b**, HCHO (aq.), AcOH, $NaCNBH_3$, rt. Oxidation (**9b**): **4Nb**, $RuCl_3$ hydrate, $NaIO_4$, $MeCN/H_2O$, 0 °C to rt. Cross coupling (**9c**): **4b**, $PhB(OH)_2$, $Pd(PPh_3)_4$, Na_2CO_3 (aq.), toluene, EtOH, 80 °C. Cross coupling (**9d**): **4b**, (9*H*-carbazol-2-yl) boronic acid pinacol ester, $Pd(PPh_3)_4$, K_2CO_3, 1,4-dioxane, water, 100 °C. Cross metathesis (**9e**): **4k**, 2-methyl-2-butene, HG-II catalyst, toluene, 60 °C. Ozonolysis (**9f**): **4Nk**, pyridine, DCM, O_3/O_2 gas mixture, −78 °C; then MeOH, $NaBH_4$, 0 °C. Ns removal (**9g**): **9f**, $HSCH_2CO_2H$, K_2CO_3, MeOH, 0 °C to rt. Deiodination (**9h**): **4k**, THF, *t*-BuLi, −78 to −40 °C. Yields refer to isolated yields of pure products.

Mechanism

The proposed mechanism for the *halo*-Prins/*halo*-Nazarov coupling cascade is depicted in Scheme 8.[21] Upon Brønsted acid-mediated condensation of aniline-containing enyne **1** with the aldehyde **2** or enol ether **5**, oxycarbenium intermediate **10** is formed. This intermediate undergoes cyclization to afford the *halo*-Prins product **11**. This product may be isolated or the cascade can be continued by the addition of HFIP. This results in the ionization of the labile C–O bond and formation of the 3-*halo* pentadienyl cation **12**, which transforms *via* a 4π conrotatory electrocyclization (stage 1) into the *halo*-cyclopentenyl cation **13**. Finally, this cation is captured by the nitrogen atom (stage 2) to afford the *halo*-Nazarov product **14**. In case when **1** is a secondary alcohol, its stereogenic center controls the helical conformation of the non-planar U-shaped pentadienyl cation **12**. The observed diastereoselectivity of the products is a result of the competing rates of electrocyclization and helical epimerization.

DFT calculations were performed to gain further insight into the energetics of the *halo*-Nazarov cyclization and the results are depicted in Fig. 1. The *N*-mesyl analog of **4i** was chosen for this case study to minimize the computational time.

The results reveal several key observations: the 4π electrocyclization is rapid ($\Delta G^{\ddagger}_{15/16} = 6.1$) and irreversible ($\Delta G^{\ddagger}_{16/15} = 22.1$), thus it is the diastereo determining step; the



Scheme 8 Proposed mechanism for the *halo*-Prins/*halo*-Nazarov coupling cascade.

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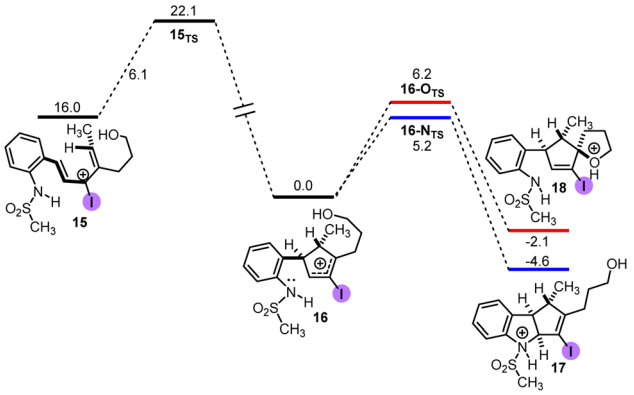

Fig. 1 Computational study (M06-2x/Def2-TZVP, SMD = DCM, free energies in kcal mol^{-1}) of the nitrogen-interrupted *halo*-Nazarov cyclization.

barriers for the heteroatom trappings (either nitrogen or oxygen) are low in both directions, implying that these processes are fast and reversible; the nitrogen trapping is kinetically and thermodynamically preferred over the oxygen trapping ($\Delta\Delta G^{\ddagger} = 1.0$ and $\Delta\Delta G = 2.5$, both in favor of the nitrogen trapping).

Conclusions

In conclusion, we have developed an efficient method for the synthesis of stereochemically complex cyclopenta[*b*]indolines from two simple precursors. Using a nitrogen-interrupted *halo*-Prins/*halo*-Nazarov coupling cascade strategy, four new bonds and two new rings, along with up to four contiguous stereogenic centers are forged. Synthesized products contain up to four distinct functionalities, including an aniline, alcohol, and vinyl iodide, which were demonstrated to perform well under a variety of transformations. The methodology possesses broad functional group tolerance, although some reactive and Lewis basic groups give products in diminished yields. Additionally, computational studies were used to provide further insight into the energetics of the *halo*-Nazarov cyclization and to explain the selectivity in the intramolecular capture of the *halo*-cyclopentenyl cation with the nitrogen atom.

Data availability

All data associated with this publication are provided in the ESI.†

Author contributions

AM synthesized and characterized most of the compounds, carried out qNMR and HPLC studies, completed all DFT calculations and contributed to manuscript writing. CH synthesized and characterized the rest of the compounds. AJF conceived and supervised the project and contributed to manuscript writing.

Conflicts of interest

There are no conflicts to declare.

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Notes and references

1 N. Kerru, L. Gummidi, S. Maddila, K. K. Gangu and S. B. Jonnalagadda, *Molecules*, 2020, **25**, 1909.
2 E. Vitaku, D. T. Smith and J. T. Njardarson, *J. Med. Chem.*, 2014, **57**, 10257.
3 T. Vivekanand, B. Satpathi, S. K. Bankar and S. S. V. S. V. Ramasastry, *RSC Adv.*, 2018, **8**, 18576and references therein.
4 F. Lovering, *MedChemComm*, 2013, **4**, 515.
5 Two extensive reviews on the interrupted Nazarov cyclizations have been published(*a*) A. V. Yadykov and V. Z. Shirinian, *Adv. Synth. Catal.*, 2020, **362**, 702; (*b*) T. N. Grant, C. J. Rieder and F. G. West, *Chem. Commun.*, 2009, 5676. Additionally, an account describing advances in this field by our group has been published, see (*c*) A. J. Frontier and J. J. Hernandez, *Acc. Chem. Res.*, 2020, **53**, 1822.
6 To the extent of our knowledge, this is the list of all nitrogen-interrupted Nazarov cyclizations reported so far(*a*) F. Dhoro and M. A. Tius, *J. Am. Chem. Soc.*, 2005, **127**, 12472; (*b*) A. Rostami, Y. Wang, A. M. Arif, R. McDonald and F. G. West, *Org. Lett.*, 2007, **9**, 703; (*c*) F. Dhoro, T. E. Kristensen, V. Stockmann, G. P. A. Yap and M. A. Tius, *J. Am. Chem. Soc.*, 2007, **129**, 7256; (*d*) D. Song, A. Rostami and F. G. West, *J. Am. Chem. Soc.*, 2007, **129**, 12019; (*e*) O. Scadeng, M. J. Ferguson and F. G. West, *Org. Lett.*, 2011, **13**, 114; (*f*) R. William, W. L. Leng, S. Wang and X.-W. Liu, *Chem. Sci.*, 2016, **7**, 1100; (*g*) Z. Wang, X. Xu, Z. Gu, W. Feng, H. Qian, Z. Li, X. Sun and O. Kwon, *Chem. Commun.*, 2016, **52**, 2811.
7 (*a*) G. Alachouzos and A. J. Frontier, *Angew. Chem., Int. Ed.*, 2017, **56**, 15030; (*b*) G. Alachouzos and A. J. Frontier, *J. Am. Chem. Soc.*, 2019, **141**, 118; (*c*) G. Alachouzos, C. Holt and A. J. Frontier, *Org. Lett.*, 2020, **22**, 4010.
8 P. Ribière, V. Declerck, J. Martinez and F. Lamaty, *Chem. Rev.*, 2006, **106**, 2249.
9 S. P. Miller, Y.-L. Zhong, Z. Liu, M. Simeone, N. Yasuda, J. Limanto, Z. Chen, J. Lynch and V. Capodanno, *Org. Lett.*, 2014, **16**, 174.

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10 Reactivity of aldehydes with different electronics in the *halo*-Prins/*halo*-Nazarov reactions has already been evaluated, *e.g.* compounds **4j–4l** in C. Holt, G. Alachouzos and A. J. Frontier, *J. Am. Chem. Soc.*, 2019, **141**, 5461.

11 (*a*) A. B. Concepcion, H. Yamamoto, R. K. Boeckman Jr, K. F. Biegasiewicz and D. J. Tusch, in *Encycl. Reag. Org. Synth.*, John Wiley & Sons, Ltd, 2018; (*b*) M. J. Taschner, in *Encycl. Reag. Org. Synth.*, John Wiley & Sons, Ltd, 2001.

12 S. Abdul-Rashed, C. Holt and A. J. Frontier, *Synthesis*, 2020, **52**, 1991 and references therein.

13 In an independent project, we have discovered that methyl enol ethers of 4-aryl-2-butanones (4-aryl-2-methoxy-1-butenes) are the only ketone equivalents that undergo the alkynyl *halo*-Prins coupling with secondary (enyne) alcohols in an efficient manner (≥60% yields). Ketones were found to be unreactive and dimethyl ketals gave the desired *halo*-Prins adducts in low yields (≈30% yields).

14 The terminology is defined in ref. 7b (Scheme 6). This outcome is unusual, as the corresponding *A*-values for the phenyl and methyl group (3.0 *vs.* 1.7, respectively) imply that the bulkier group (phenyl) would prefer to be positioned "out", which would produce the opposite epimer (epi-**6e**) as the major diastereomer.

15 While an X-ray structure of a single diastereomer from a mixture cannot be used as a rationale for the structure determination of the major diastereomer, 2D-NOESY can, and this data is presented in the ESI (see pages S110–S111†).

16 If the temperature of the cold bath used for the reaction is not well maintained (*i.e.* if the *halo*-Prins reaction is let to warm up above 0 °C), a complex mixture of side products forms, further diminishing the yield of the desired **7a**. This is not the case with other enynes, which are well-behaved and do not require precise control of the reaction conditions.

17 Additionally, as shown in ref. 7c, this strategy can be used for the synthesis of enantiopure products (without a need for chiral separation). Starting with an enantiopure secondary alcohol enyne, the obtained *halo*-Nazarov product mixture can be separated and the stereocenter originating from the secondary alcohol can be removed (*via* oxidative or reductive methods). Such obtained products would be enantiomers, with one enantiomer in excess compared to the other.

18 Tertiary alcohols were deemed to be outside of the scope of the manuscript, as the ionization of the *halo*-Prins intermediate is expected to produce side-products originating from the competitive ionization that forms a tertiary carbocation.

19 K. D. Collins and F. Glorius, *Nat. Chem.*, 2013, **5**, 597.

20 Procedures for the transformations were obtained from the following publications: (*a*) D. Ma, G. Tang and A. P. Kozikowski, *Org. Lett.*, 2002, **4**, 2377. (Eschweiler–Clarke reaction); (*b*) L. Shi, K. Meyer and M. F. Greaney, *Angew. Chem., Int. Ed.*, 2010, **49**, 9250. (Oxidation); (*c*) K. F. Johnson E. A. Schneider, B. P. Schumacher, A. Ellern, J. D. Scanlon and L. M. Stanley, *Chem.–Eur. J.*, 2016, **22**, 15619. (Suzuki–Miyaura reaction for the preparation of **8c**); (*d*) N. Mace, A. R. Thornton and S. B. Blakey, *Angew. Chem., Int. Ed.*, 2013, **52**, 5836. (Suzuki–Miyaura reaction for the preparation of **8d**); (*e*) A. Sytniczuk, A. Kajetanowicz and K. Grela, *Catal. Sci. Technol.*, 2017, **7**, 1284. (Cross metathesis with 2-methyl-2-butene); (*f*) R. Willand-Charnley, T. J. Fisher, B. M. Johnson and P. H. Dussault, *Org. Lett.*, 2012, **14**, 2242. (Ozonolysis); (*g*) S. Xu, K. Hirano and M. Miura, *Org. Lett.*, 2020, **22**, 9059. (Halogen–lithium exchange).

21 This mechanism is analogous to the previously reported mechanisms for the *halo*-Prins/*halo*-Nazarov cascades, see ref. 7.