

EDGE ARTICLE

View Article Online
View Journal | View IssueCite this: *Chem. Sci.*, 2022, 13, 13836

All publication charges for this article have been paid for by the Royal Society of Chemistry

Received 25th August 2022
Accepted 4th November 2022

DOI: 10.1039/d2sc04750k

rsc.li/chemical-science

Alkynyl Prins carbocyclization cascades for the synthesis of linear-fused heterocyclic ring systems†

Jackson J. Hernandez and Alison J. Frontier *

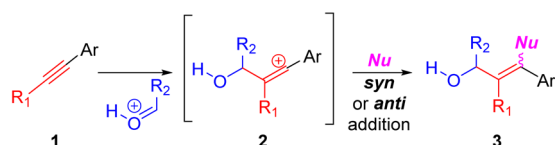
We report a Brønsted acid-catalyzed carbocyclization cascade, featuring condensation of an alcohol/sulfonamide with an aldehyde followed by an intramolecular three-component coupling involving an alkyne, an oxocarbenium/iminium ion, and an arene. A formal cycloaddition is embedded in the cationic cascade, which enables the synthesis of a wide range of fused heterotricycles. The diastereoselectivity of the cascade is studied using secondary alcohols/sulfonamides with different carbonyl partners. The described method results in the preparation of synthetically versatile scaffolds with ample opportunity for further derivatization at the resulting tetrasubstituted olefin, or by inclusion of other functionalizable motifs from the starting materials. It is worth noting that this chemistry also facilitates the synthesis of piperidines and 1,4-oxazepanes, as well as the inclusion of indoles and benzofurans, which are privileged motifs for medicinal chemistry. Herein we present the generality of this approach and some chemical transformations that can be achieved with our substrates.

Introduction

The development of methods that enable the synthesis of small molecules is essential for populating high throughput screening libraries used in drug discovery campaigns.¹ In particular, the preparation of synthetically versatile molecules that allow for differential functionalization around a polycyclic scaffold will help maximize diversity among derivatives and provide the ability to tune physicochemical properties.²

Alkyne-carbonyl coupling (Prins) reactions most commonly terminate with the capture of a presumed vinyl cation intermediate **2** with a nucleophile (Scheme 1).³

Without a means to control stereoselectivity or *E/Z* geometry, the synthetic utility of these reactions is limited. The most well-developed versions feature intramolecular alkyne-carbonyl couplings, with a water or a halide acting to capture the

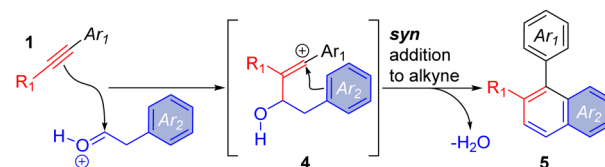
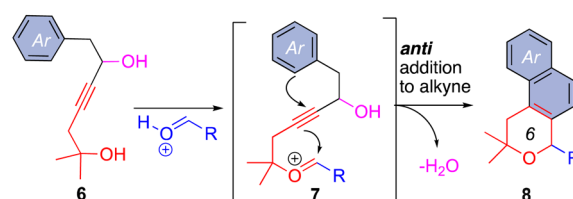


Nu = HOR, HNR₂, halide, or arene

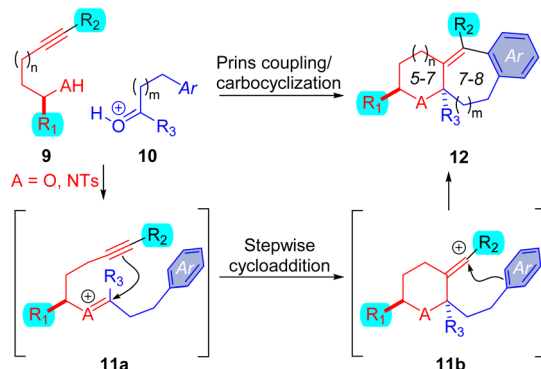
Scheme 1 Alkyne-carbonyl coupling (Prins) reactions. Nu = HOR, HNR₂, halide, or arene.

Department of Chemistry, University of Rochester, 120 Trustee Road, Rochester, New York 14611, USA. E-mail: alison.frontier@rochester.edu

† Electronic supplementary information (ESI) available. CCDC 2174699, 2174700, 2174702–2174704, 2176208 and 2195747. For ESI and crystallographic data in CIF or other electronic format see DOI: <https://doi.org/10.1039/d2sc04750k>

A. Stepwise [4+2] cycloaddition with **aromatization**B. Prins coupling/ cascade carbocyclization with **aromatization**

C. Stepwise Coupling/ Cycloaddition Cascade (syn addition to alkyne)



Scheme 2 Cascade Prins carbocyclizations. (A) Stepwise [4 + 2] cycloaddition with aromatization. (B) Prins coupling/cascade carbocyclization with aromatization. (C) Stepwise coupling/cycloaddition cascade (syn addition to alkyne).

intermediate cation **2**.⁴ Our lab has recently been engaged in the development of alkynyl Prins coupling methods: Prins terminated by halide,⁵ aza-Prins terminated by halide,⁶ and Prins annulation terminated with sulfonamide.⁷ More rarely, the vinyl cation intermediate can be trapped with an arene nucleophile, terminating the Prins coupling with C–C rather than C–heteroatom bond formation. Intermolecular C–C bond formation (*cf.* Scheme 1; **Nu** = arene) is only successful when the arene reactant is in large excess (as solvent).⁸

Examples of intramolecular arene capture are limited to those shown in Scheme 2. Stepwise [4 + 2] cycloaddition processes generate functionalized naphthalenes **5** (Scheme 2A),⁹ and cationic cascades developed by Hinkle *et al.* generate benzo[*f*]isochromenes **8** (Scheme 2B).¹⁰ These two types of carbocyclizations employ simple (phenyl) arenes as the terminating nucleophile and eliminate H₂O (*via* **4** and **7**) to generate a naphthalene moiety.

In this paper, we describe a carbocyclization cascade that generates fused polycyclic adducts **12** (Scheme 2C). Condensation of readily available building blocks **9** and **10** generates an oxocarbenium or iminium ion **11a**, aligned with an alkyne and an arene such that a formal cycloaddition occurs diastereoselectively. As indicated in Scheme 2C, the broad scope of the one-step process enables variation of ring size, at R₁, R₂, R₃, and in the arene ring. The scaffolds represent a novel structure class, offering entry into new polycyclic chemical space.

Optimization of the Prins cascade carbocyclization

Optimization experiments for this reaction were done using arenynol alcohol **9a** and aldehyde **10a**, with an electron-rich nucleophilic tether (Table 1). Substoichiometric amounts of trifluoromethanesulfonic acid (TfOH) are sufficient to promote the cyclization to afford **12a**. This, in combination with 5 Å molecular sieves (MS) in a solvent mixture of dichloromethane (DCM) and 1,1,1,3,3,3-hexafluoropropan-2-ol (HFIP) results in optimal yields (see Table 1). HFIP was chosen as cosolvent due to its

demonstrated ability to stabilize carbocationic intermediates.¹¹ Omission of the HFIP gives the desired product **12a** in 40% yield, as well as unreacted aldehyde, acetal (resulting from condensation of the aldehyde with two molecules of arenynol alcohol; see ESI† for details), and other unidentifiable byproducts (Table 1, entry 1). Lowering the TfOH loading to 10 mol% gives good yields for **12a** (entry 2), however, since other substrates required more acid for full consumption of the starting material, we chose 20 mol% TfOH as part of our standard conditions. Reduction of the amount of HFIP by half gives 78% yield of cyclized product **12a** (entry 3). Using bis(trifluoromethane)sulfonamide (Tf₂NH) instead of TfOH also affords the desired product in good yields (entry 4). Finally, exclusion of molecular sieves leads to sluggish reactions where the starting material is never fully consumed, even after warming to room temperature (entry 5).

Substrate scope

Using these optimized conditions, the alkyne and carbonyl scope was explored. Electron-rich, neutral, and deficient arenynol alcohols react cleanly to give fused products **12a–12g** in good to excellent yields (Scheme 3). Enyne alcohols work as well to afford products **12h–12j** in good yields. An internal alkyne engages to give product **12k** in 64% yield, although 40 mol% of TfOH and stirring at room temperature is required for the reaction to go to completion, otherwise the acetal of **10a** is isolated (see ESI†). Although electron deficient arenynes engage well in this chemistry, 4-cyanoarenynol (a more basic functional group) is not tolerated. Similarly, tests with a terminal alkyne, bromoalkyne, alkynylsilane, and diyne also result in the formation of complex mixtures (see ESI†).

Aldehyde **10** (with Ar = *m*-methoxyphenyl) reacts well to give cycloaddition product **12c** as a 1.7 : 1 mixture of the *para/ortho*-trapped product in 94% combined yield. Aldehyde **10** (with Ar = Ph) also traps well to give **12d** in 89% yield. Even an electron-deficient arene engages to give **12e**, albeit in 31% yield. Different tether lengths of the alcohol work without any negative impact on the yield, giving access to five-membered oxacycle **12l** in 92% yield, and seven-membered oxacycle **12m** in 82% yields. Eight-membered carbocycle formation is also feasible under the reaction conditions to give product **12n** *via* a formal [6 + 2] pathway, albeit in lower yields. Ketone **10** (R₁ = Me) also reacts to afford [5 + 2] adduct **12o**, although in only 20% yield. Using the dimethyl ketal of **10** (R₁ = Me) instead brings this yield up to 48% (Scheme 3).

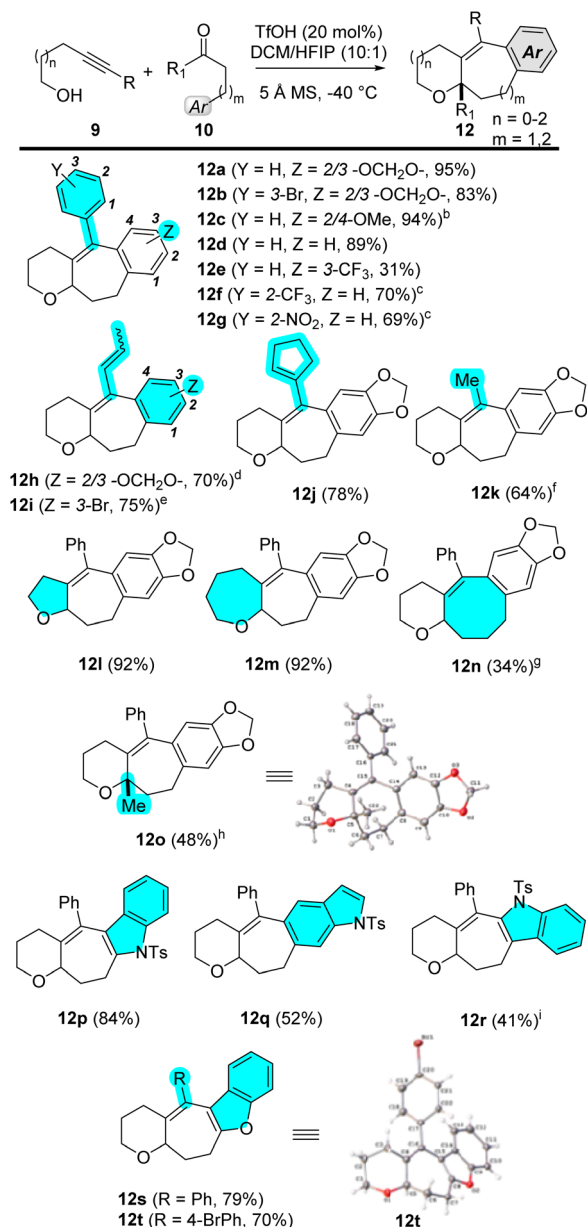
Heteroaromatic nucleophiles also react smoothly under these conditions. Tosyl indole aldehydes engage well to afford products **12p**, **12q**, and **12r** in 84, 52, and 41% yields, respectively. Product **12r** is obtained as a 1 : 1 mixture of conformers. We hypothesize that these conformers arise from steric interactions between the tosyl protecting group and the phenyl ring on the cycloheptene (Scheme 3). This hypothesis is supported by the fact that, upon detosylation of the indole, a single product is observed (see ESI†). Benzofuran aldehydes give **12s** (79% yield) and **12t** (70% yield). When *N*-methyl, or deprotected indoles are subjected to the reaction conditions, the aldehyde undergoes decomposition, and no Prins product is formed (see ESI†).¹²

Table 1 Optimization of the alkynyl Prins carbocyclization

Entry	Deviations from standard conditions	Isolated % yield
1	No HFIP added	40
2	10 mol% TfOH	87
3	20 : 1 DCM/HFIP	78
4	Tf ₂ NH (no TfOH)	90
5 ^b	No MS	48 ^c

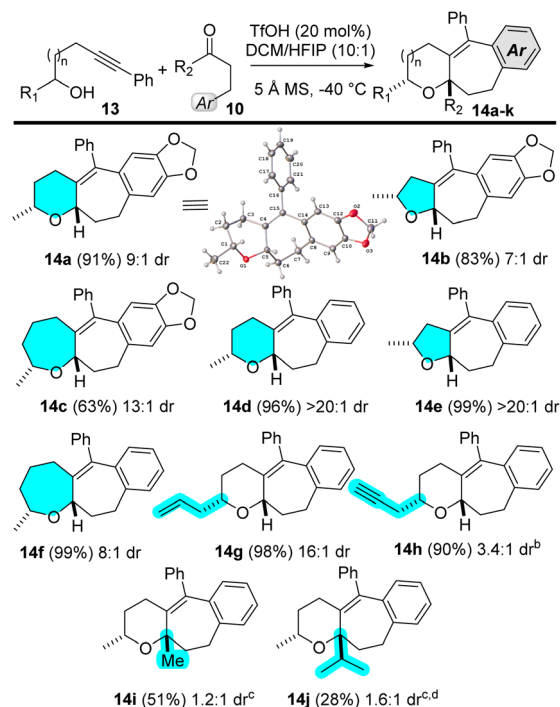
^a 300 mg of 5 Å MS used per 1.0 mmol of limiting reagent **10a**. ^b No MS added, warmed up to room temperature. ^c Some starting material recovered.





Scheme 3 Substrate scope for alkynyl oxa-Prins carbocyclization. (a) Conditions: to a mixture of 9, 10, and molecular sieves in DCM/HFIP at $-40\text{ }^{\circ}\text{C}$ was added TfOH, dropwise. Stir at $-40\text{ }^{\circ}\text{C}$ until all starting material is consumed by TLC (b) 1.7 : 1 *p/o*-trapped (c) warmed to $0\text{ }^{\circ}\text{C}$ 1 hour after adding TfOH, then to room temperature (d) 6.3 : 1 *E/Z* (e) 7.9 : 1 *E/Z* (f) 40 mol% TfOH added at $-40\text{ }^{\circ}\text{C}$, then warmed to room temperature after an hour (g) 40 mol% TfOH added at $-40\text{ }^{\circ}\text{C}$, then to $0\text{ }^{\circ}\text{C}$ after an hour (h) 1.5 equiv. of corresponding dimethyl ketal 10 ($R_1 = \text{Me}$) used with 1.0 equiv. of alcohol 9a (i) 1 : 1 mixture of conformers.

The alkynyl Prins reaction of secondary alcohols with aldehydes is known to proceed diastereoselectively.^{4g} In a previous paper from our group, we demonstrated that the oxa-Prins reaction with an enantioenriched alcohol like **13** produces enantioenriched Prins adducts.⁷ Scheme 4 shows the diastereoselectivity of our Prins coupling/cycloaddition approach, using secondary alcohols **13** and aldehydes or ketals **10** ($R_2 = \text{Me}$, ¹Pr). As evidenced with cases **14a** through **14f**, secondary



Scheme 4 Diastereoselective Prins carbocyclizations with secondary alcohol reactants. (a) Conditions: to a mixture of **13**, **10**, and molecular sieves in DCM/HFIP at $-40\text{ }^{\circ}\text{C}$ was added TfOH, dropwise. Stir at $-40\text{ }^{\circ}\text{C}$ until all starting material is consumed by TLC. (b) Reported dr was observed for 0.2 mmol scale reaction. At 1.0 mmol scale, dr went down to 2.8 : 1. (c) Dimethyl ketal of corresponding ketone used (d) Reaction warmed up to $0\text{ }^{\circ}\text{C}$ after 24 h until all the alcohol was consumed.

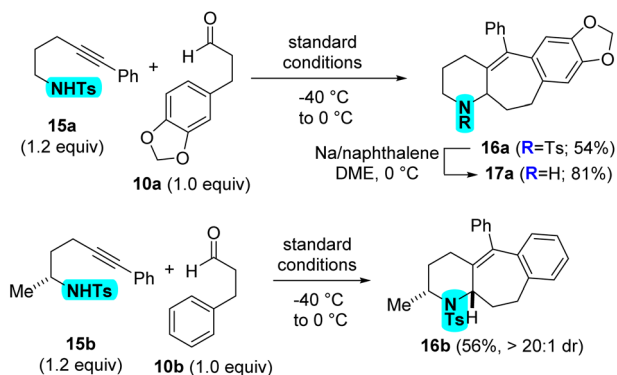
alcohols **13** react well with aldehydes to give five-, six-, and seven-membered oxacycles in excellent yields and good diastereoselectivities. With a homoallylic alcohol, cycloaddition product **14g** is generated in excellent yield and 16 : 1 dr. The diastereoselectivity is lower with a homopropargylic alcohol, which gives **14h** (3.4 : 1 dr).

The Prins carbocyclization of secondary alcohol **13a** and dimethyl ketal **10** ($R_2 = \text{Me}$) gives Prins product **14i** (51% yield), with virtually no diastereoselectivity. Replacing the methyl with a bulkier isopropyl group makes the reaction sluggish, delivering cycloaddition product **14j** in 28% yield as a 1.6 : 1 mixture of diastereomers.¹³

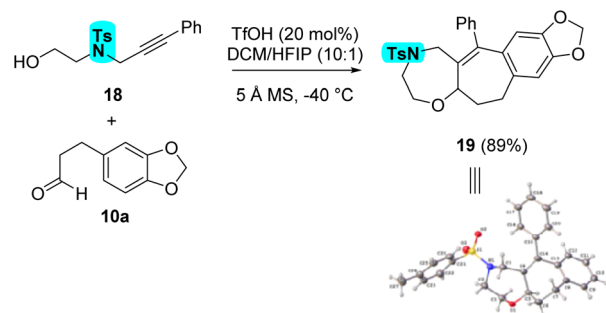
Synthesis of linear-fused N-heterocyclic systems

Furthermore, it was exciting to discover that the reaction conditions translate to the preparation of piperidines from sulfonamides **15** (Scheme 5). The reaction performs well for alpha-primary sulfonamide **15a** to give tosyl-protected piperidine **16a** in 54% yield. Starting with alpha-secondary sulfonamide **15b** leads to the diastereoselective formation of piperidine **16b** in 56% yield and >20 : 1 dr. The tosyl protecting group of **16a** can be removed using sodium naphthalenide to afford piperidine **17a** in 81% yield.

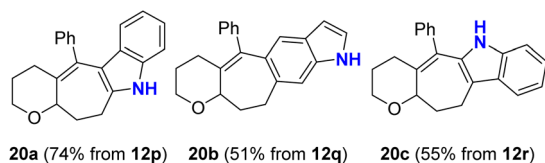




Scheme 5 Carbocyclization for synthesis of fused piperidines.



Scheme 6 Prins carbocyclization for synthesis of 1,4-oxazepanes.

Scheme 7 Deprotection of *N*-Ts indole substrates.

It is also possible to prepare 1,4-oxazepane **19** in 89% yield from alcohol **18**, using the standard reaction conditions (Scheme 6). A single crystal x-ray structure confirmed the identity of the cycloadduct.

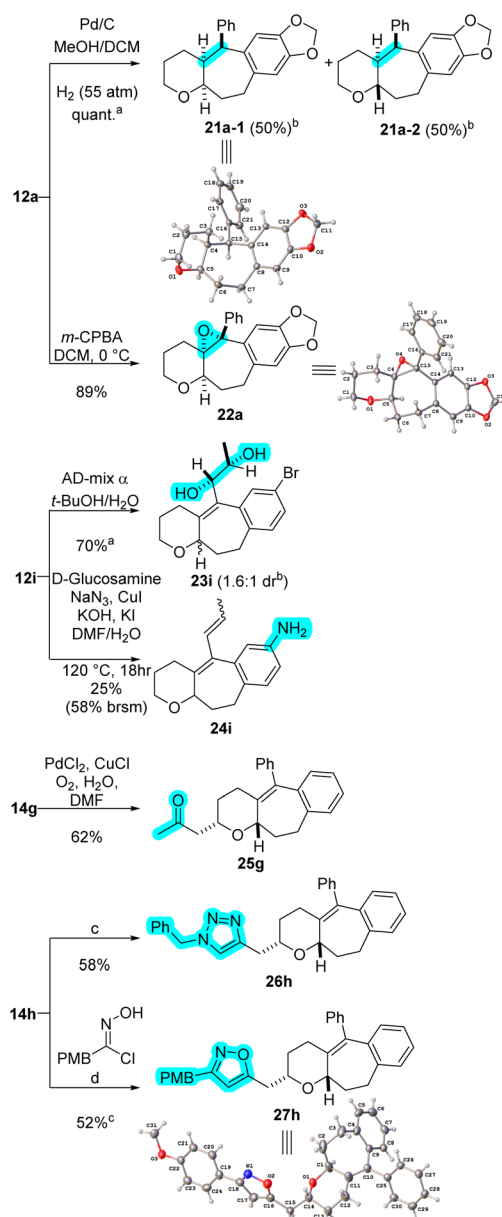
Finally, we focused on unmasking *N*-Ts indoles **12p**, **12q**, and **12r** to access the *N*-H indole motif, which is ubiquitous among bioactive natural products and drug targets.¹⁴ In these cases, detosylation occurred smoothly upon treatment with potassium *tert*-butoxide (3 equiv.) in DMSO, providing access to the target scaffolds **20a–c** as shown (Scheme 7).¹⁵

Diversification of polycyclic adducts

The synthetic versatility of products **12** and **14** can be exploited to give access to new chemical space. Scheme 8 shows examples of some chemical transformations that can be done to enhance the complexity of these scaffolds. Hydrogenation of the tetra-substituted olefin in **12a** occurs using palladium on carbon (Pd/C) and gives quantitative yields of **21a** as a 1 : 1 mixture of diastereomers that can be separated by column chromatography.

Hydrogenation of **14a** gives the corresponding hydrogenated product as a 5 : 1 mixture of inseparable diastereomers (see ESI†). Oxidation of **14a** with *m*-CPBA delivers epoxide **22a** in 89% yield, with no purification required.

The olefin in **12i** can be oxidized with AD-mix α to give diol **23i** as a 1.6 : 1 mixture of diastereomers that can be separated by column chromatography. The aryl bromide is a potential functional handle for subsequent cross-coupling operation. Aniline derivative **24i**, for example, was obtained in 25% yield (58% based on recovered starting material) after a copper-mediated amination.¹⁶



Scheme 8 Diversification of cycloadducts. (a) Combined yield of two diastereomers (b) dr determined based on isolated yields of separable diastereoisomers (c) BnNH_2 , Cu powder, $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$, sodium ascorbate, $\text{H}_2\text{O}/t\text{-BuOH}$, rt. (d) Cu powder, $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$, NaHCO_3 , $\text{H}_2\text{O}/t\text{-BuOH}$, rt.



Subjection of cycloadduct **14g** (bearing a pendent alkene) to Wacker oxidation conditions gives ketone **25g** in good yields.¹⁷ Finally, applying [3 + 2] cycloaddition strategies to cycloadduct **14h** (bearing a pendent alkyne) enables efficient introduction of interesting heterocycles such as triazole **26h** and isoxazole **27h**.¹⁸

Conclusions

In summary, alkynyl Prins coupling/carbocyclization sequences have been developed for the diastereoselective preparation of novel polycyclic systems. The linear-fused ring arrays contain a saturated heterocyclic ring, a seven- or eight-membered carbocycle, and an aromatic or heteroaromatic ring. In the presence of substoichiometric amounts of acid, this method couples two simple building blocks (an aldehyde and an alkynyl alcohol) in a cascade sequence, forging three new bonds (one C–O; two C–C) and two new rings in one pot.

The polycyclic small molecules described here represent a new structure class.¹⁹ The multiple sites available for easy diversification should enable synthesis of derivatives that extend into new areas of chemical space. Thus, the method can offer access to a diverse library of compounds different from any that have been prepared and tested before. If the molecules exhibit biological activity, the simple synthetic procedure will allow for rapid preparation of analogs for follow-up studies. Ongoing work includes the exploration of an asymmetric carbocyclization, expanding the scope of the aza-Prins variant of the reaction, and exploring other means of trapping the vinyl cation intermediate.

Data availability

All of the related experimental and computational data are provided in the ESI.†

Author contributions

A. J. F. and J. J. H. designed the research study and prepared the manuscript. All the experiments, product characterization, and computational studies were performed by J. J. Hernandez.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We thank the NSF (CHE-1900050 and CHE- 2154854) for funding this study. J. J. H acknowledges the NIGMS (1F31GM142259-01A1) for fellowship support. We thank Dr W. W. Brennessel (Dept. of Chemistry, University of Rochester) for running X-ray crystallography analyses and the NSF (CHE-1725028) for funding our X-ray diffractometer. We also thank Kevin Wells, the University of Rochester Mass Spectrometry Resource Laboratory, and are thankful for the NIH instrument grant

(S10OD021486). We also thank Aleksa Milosavljevic (Dep. Of Chemistry, University of Rochester) for helpful discussions.

Notes and references

- (a) S. Dandapani and L. A. Marcaurelle, Grand Challenge Commentary: Accessing new chemical space for 'undruggable' targets, *Nat. Chem. Biol.*, 2010, **6**, 861–863; (b) M. Follmann, H. Briem, A. Steinmeyer, A. Hillisch, M. H. Schmitt, H. Haning and H. Meier, An approach towards enhancement of a screening library: The Next Generation Library Initiative (NGLI) at Bayer — against all odds?, *Drug Discov.*, 2019, **24**, 668–672; (c) A. Barker, J. G. Kettle, T. Nowak and J. E. Pease, Expanding medicinal chemistry space, *Drug Discov.*, 2013, **18**, 298–304; (d) M. Garcia-Castro, S. Zimmermann, M. G. Sankar and K. Kumar, Scaffold Diversity Synthesis and Its Application in Probe and Drug Discovery, *Angew. Chem., Int. Ed.*, 2016, **55**, 7586–7605.
- (a) P. Ertl, S. Jelfs, J. Mühlbacher, A. Schuffenhauer and P. Selzer, Quest for the Rings. In Silico Exploration of Ring Universe to Identify Novel Bioactive Heteroaromatic Scaffolds, *J. Med. Chem.*, 2006, **49**, 4568–4573; (b) I. P. Silvestri and P. J. J. Colbon, The Growing Importance of Chirality in 3D Chemical Space Exploration and Modern Drug Discovery Approaches for Hit-ID, *ACS Med. Chem. Lett.*, 2021, **12**, 1220–1229.
- (a) S. Abdul-Rashed, C. Holt and A. J. Frontier, Alkynyl Prins and Alkynyl Aza-Prins Annulations: Scope and Synthetic Applications, *Synth*, 2020, **52**, 1991–2007; (b) P. Padmaja, P. N. Reddy and B. V. Subba Reddy, Tandem Prins cyclizations for the construction of oxygen containing heterocycles, *Org. Biomol. Chem.*, 2020, **18**, 7514–7532.
- (a) J. J. Jaber, K. Mitsui and S. D. Rychnovsky, Stereoselectivity and Regioselectivity in the Segment-Coupling Prins Cyclization, *J. Org. Chem.*, 2001, **66**, 4679–4686; (b) P. O. Miranda, D. D. Díaz, J. I. Padrón, J. Bermejo and V. S. Martín, Iron (III)-Catalyzed Prins-Type Cyclization Using Homopropargylic Alcohol: A Method for the Synthesis of 2-Alkyl-4-halo-5,6-dihydro-2H-pyrans, *Org. Lett.*, 2003, **5**, 1979–1982; (c) P. O. Miranda, D. D. Díaz, J. I. Padrón, M. A. Ramírez and V. S. Martín, Fe (III) Halides as Effective Catalysts in Carbon–Carbon Bond Formation: Synthesis of 1,5-Dihalo-1,4-dienes, α,β -Unsaturated Ketones, and Cyclic Ethers, *J. Org. Chem.*, 2005, **70**, 57–62; (d) P. O. Miranda, M. A. Ramírez, V. S. Martín and J. I. Padrón, Factors Controlling the Alkyne Prins Cyclization: The Stability of Dihydropyranyl Cations, *Chem.-Eur. J.*, 2008, **14**, 6260–6268; (e) P. O. Miranda, R. M. Carballo, V. S. Martín and J. I. Padrón, A New Catalytic Prins Cyclization Leading to Oxa- and Azacycles, *Org. Lett.*, 2009, **11**, 357–360; (f) G. Sabitha, K. B. Reddy, M. Bhikshapathi and J. S. Yadav, TMSI mediated Prins-type cyclization of ketones with homoallylic and homopropargylic alcohol: synthesis of 2,2-disubstituted-, spirocyclic-4-iodo-tetrahydropyrans and 5,6-dihydro-2H-pyrans, *Tetrahedron Lett.*, 2006, **47**, 2807–2810;



- (g) S. N. Chavre, H. Choo, J. H. Cha, A. N. Pae, K. I. Choi and Y. S. Cho, 5-Exocyclic Products, 2,3,5-Trisubstituted Tetrahydrofurans via Prins-Type Cyclization, *Org. Lett.*, 2006, **8**, 3617–3619; (h) S. N. Chavre, H. Choo, J. K. Lee, A. N. Pae, Y. Kim and Y. S. Cho, 5- and 6-Exocyclic Products, cis-2,3,5-Trisubstituted Tetrahydrofurans, and cis-2,3,6-Trisubstituted Tetrahydropyrans via Prins-Type Cyclization, *J. Org. Chem.*, 2008, **73**, 7467–7471.
- 5 (a) G. Alachouzos and A. J. Frontier, Diastereoselective Construction of Densely Functionalized 1-Halocyclopentenes Using an Alkynyl Halo-Prins/Halo-Nazarov Cyclization Strategy, *Angew. Chem., Int. Ed.*, 2017, **56**, 15030–15034; (b) G. Alachouzos and A. J. Frontier, Cationic Cascade for Building Complex Polycyclic Molecules from Simple Precursors: Diastereoselective Installation of Three Contiguous Stereogenic Centers in a One-Pot Process, *J. Am. Chem. Soc.*, 2019, **141**, 118–122; (c) C. Holt, G. Alachouzos and A. J. Frontier, Leveraging the Halo-Nazarov Cyclization for the Chemodivergent Assembly of Functionalized Haloindenes and Indanones, *J. Am. Chem. Soc.*, 2019, **141**, 5461–5469; (d) G. Alachouzos, C. Holt and A. J. Frontier, Stereochemical Relay through a Cationic Intermediate: Helical Preorganization Dictates Direction of Conrotation in the halo-Nazarov Cyclization, *Org. Lett.*, 2020, **22**, 4010–4015.
- 6 J. J. Hernandez and A. J. Frontier, Synthesis of Spirocyclic Isoindolones Using an Alkynyl aza-Prins/Oxidative halo-Nazarov Cyclization Sequence, *Org. Lett.*, 2021, **23**, 1782–1786.
- 7 S. Abdul-Rashed, G. Alachouzos, W. W. Brennessel and A. J. Frontier, One-Pot Double-Annulation Strategy for the Synthesis of Unusual Fused Bis-Heterocycles, *Org. Lett.*, 2020, **22**, 4350–4354.
- 8 (a) U. C. Reddy and A. K. Saikia, One-Pot, Three-Component Synthesis of 4-Aryl-5,6-dihydropyran via Prins-Friedel-Crafts Reaction, *Synlett*, 2010, **2010**, 1027–1032; (b) T. Kotipalli and D.-R. Hou, Synthesis of Indenes by a BF₃·OEt₂-Mediated, One-Pot Reaction of Aryl Homopropargyl Alcohols, Aldehydes, and Arenes, *Org. Lett.*, 2018, **20**, 4787–4790.
- 9 (a) G. S. Viswanathan, M. Wang and C. J. Li, A highly regioselective synthesis of polysubstituted naphthalene derivatives through gallium trichloride catalyzed alkyne-aldehyde coupling, *Angew. Chem.*, 2002, **114**, 2242–2245; (b) Z.-Q. Wang, Y. Liang, Y. Lei, M.-B. Zhou and J.-H. Li, Iron-catalyzed annulations of 2-(2-alkynyl)phenoxy-1-arylethanones leading to substituted naphthalen-1-ols, *Chem. Commun.*, 2009, 5242–5244; (c) S. Ponra, M. R. Vitale, V. Michelet and V. Ratovelomanana-Vidal, HNTf₂-Catalyzed Regioselective Preparation of Polysubstituted Naphthalene Derivatives Through Alkyne-Aldehyde Coupling, *J. Org. Chem.*, 2015, **80**, 3250–3257; (d) V. Gudla, M. Sudheer, C. J. Rao, P. D. Sanasi and V. R. Battula, Triflic acid catalysed regioselective synthesis of substituted naphthalenes by benzannulation of carbonyls with alkynes, *Tetrahedron*, 2021, **90**, 132214; (e) A. K. Sahu, R. Unnava, B. K. Behera and A. K. Saikia, Synthesis of dibenzocyclohepta[1,2-a]naphthalene derivatives from phenylacetaldehyde and alkynyl benzyl alcohols via sequential electrophilic addition and double Friedel-Crafts reactions, *Org. Biomol. Chem.*, 2021, **19**, 2430–2435.
- 10 (a) R. J. Hinkle and S. E. Lewis, Atom Economical, One-Pot, Three-Reaction Cascade to Novel Tricyclic 2,4-Dihydro-1H-benzo[f]isochromenes, *Org. Lett.*, 2013, **15**, 4070–4073; (b) R. J. Hinkle, Y. Chen, C. P. Nofi and S. E. Lewis, Electronic effects on a one-pot aromatization cascade involving alkynyl-Prins cyclization, Friedel-Crafts alkylation and dehydration to tricyclic benzo[f]isochromenes, *Org. Biomol. Chem.*, 2017, **15**, 7584–7593; (c) R. J. Hinkle, D. J. Speer, B. B. Carnell, B. L. Kanter and R. D. Pike, Mild, Modular, and Convergent Synthesis of Helical Naphtho[2,1-c]chromenes via a Multistep Cyclization/Aromatization Cascade Sequence, *J. Org. Chem.*, 2019, **84**, 15633–15641.
- 11 (a) V. D. Vuković, E. Richmond, E. Wolf and J. Moran, Catalytic Friedel-Crafts Reactions of Highly Electronically Deactivated Benzylic Alcohols, *Angew. Chem., Int. Ed.*, 2017, **56**, 3085–3089; (b) F. Noël, V. D. Vuković, J. Yi, E. Richmond, P. Kravljanić and J. Moran, Catalytic Synthesis of Trifluoromethylated Allenes, Indenes, Chromenes, and Olefins from Propargylic Alcohols in HFIP, *J. Org. Chem.*, 2019, **84**, 15926–15947; (c) I. Colomer, A. E. R. Chamberlain, M. B. Haughey and T. J. Donohoe, Hexafluoroisopropanol as a highly versatile solvent, *Nat. Rev. Chem.*, 2017, **1**, 1–12; (d) H. F. Motiwala, A. M. Armaly, J. G. Cacioppo, T. C. Coombs, K. R. K. Koehn, V. M. Norwood and J. Aubé, HFIP in Organic Synthesis, *Chem. Rev.*, 2022, **122**, 12544–12747.
- 12 Subjecting the aldehyde to the reaction conditions (in the absence of alcohol **9**) leads to decomposition of the aldehyde.
- 13 Stereochemical assignment in **14i** and **14j** is tentative, based on aldehyde behavior and x-ray structure for **14a**.
- 14 (a) M. A. Corsello, J. Kim and N. K. Garg, Indole diterpenoid natural products as the inspiration for new synthetic methods and strategies, *Chem. Sci.*, 2017, **8**, 5836–5844; (b) W. Gul and M. T. Hamann, Indole alkaloid marine natural products: An established source of cancer drug leads with considerable promise for the control of parasitic, neurological and other diseases, *Life Sci.*, 2005, **78**, 442–453; (c) J. Vaca, F. Salazar, A. Ortiz and E. Sansineña, Indole alkaloid derivatives as building blocks of natural products from *Bacillus thuringiensis* and *Bacillus velezensis* and their antibacterial and antifungal activity study, *J. Antibiot.*, 2020, **73**, 798–802.
- 15 M. D. Heredia, W. D. Guerra, S. M. Barolo, S. J. Fornasier, R. A. Rossi and M. E. Budén, Transition-Metal-Free and Visible-Light-Mediated Desulfonylation and Dehalogenation Reactions: Hantzsch Ester Anion as Electron and Hydrogen Atom Donor, *J. Org. Chem.*, 2020, **85**, 13481–13494.
- 16 R. J. Lundgren, B. D. Peters, P. G. Alsabeh and M. A. P. Stradiotto, N-Ligand for Palladium-Catalyzed Ammonia Arylation: Coupling of Deactivated Aryl



- Chlorides, Chemoselective Arylations, and Room Temperature Reactions, *Angew. Chem., Int. Ed.*, 2010, **49**, 4071–4074.
- 17 A. Zúñiga, M. Pérez, G. Pazos, G. Gómez and Y. Fall, A Concise, Enantioselective Synthesis of (+)-Decarestrictine L from Tri-O-acetyl-d-glucal, *Synthesis*, 2010, 2446–2450.
- 18 F. Himo, T. Lovell, R. Hilgraf, V. V. Rostovtsev, L. Noodleman, K. B. Sharpless and V. V. Fokin, Copper(I)-Catalyzed Synthesis of Azoles. DFT Study Predicts Unprecedented Reactivity and Intermediates, *J. Am. Chem. Soc.*, 2005, **127**, 210–216.
- 19 A PubChem search of the general scaffold reported yields no similar structures at a 95% Tanimoto threshold. At 90% Tanimoto threshold 180 hits are observed, all of which lack the tricyclic core (most of them are not even bicyclic). There is only one report where a similar tricycle is observed as a minor byproduct (*Chem. Commun.*, 2015, **51**, 10318–10321.).

