Alkynyl Prins and Alkynyl Aza-Prins Annulations: Scope and Synthetic Applications.

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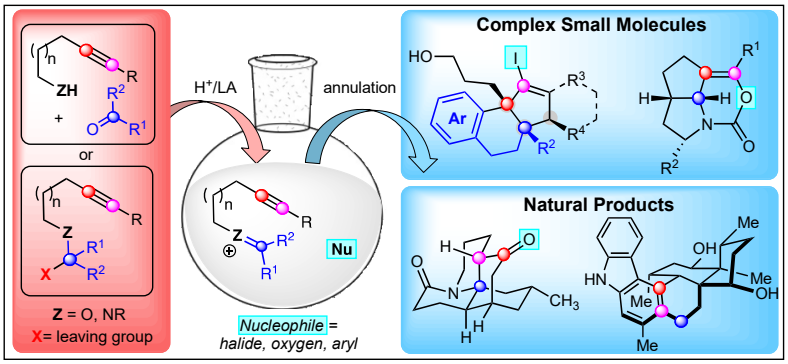

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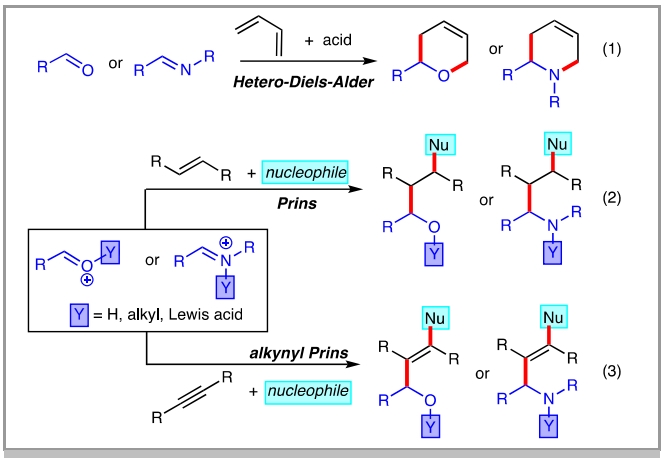
Abstract This review focuses on alkynyl Prins and alkynyl aza-Prins cyclization processes, which involve intramolecular coupling of an alkyne with either an oxocarbenium or iminium electrophile. The oxocarbenium or iminium species can be generated through condensation- or elimination-type processes, to achieve an overall bimolecular annulation that enables the synthesis of both oxygen- and nitrogen-containing saturated heterocycles with different ring sizes and substitution patterns. Also discussed are cascade processes in which alkynyl Prins heterocyclic adducts react to trigger subsequent pericyclic reactions, including [4+2] cycloadditions and Nazarov electrocyclizations, to rapidly construct complex small molecules. Finally, examples of the use of alkynyl Prins and alkynyl aza-Prins reactions in the synthesis of natural products is described. The review covers the literature through the end of 2019.

Key words Prins, annulations, cyclizations, natural products, oxacycles, azacycles, alkynes,

1. Introduction.

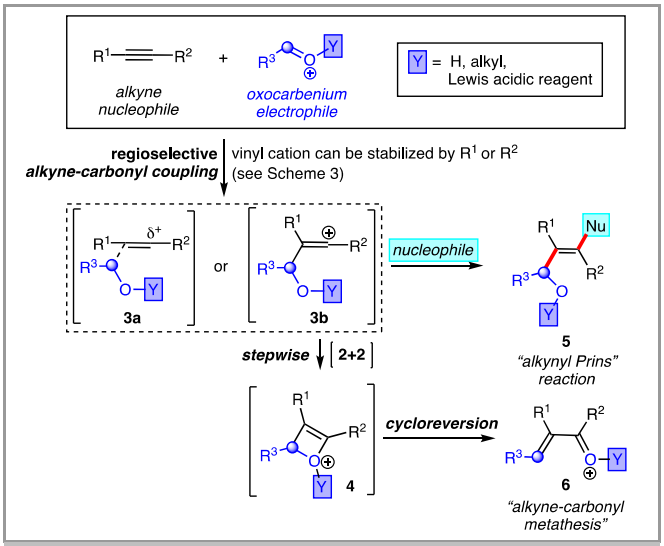
Bimolecular coupling reactions of complementary π-systems are some of the oldest, most extensively studied processes in organic synthesis. Hetero-Diels Alder reactions (diene plus C=O or C=NR) and Prins reactions[1] (alkene plus C=O or C=NR) are simple, powerful reactions that couple an alkene to an activated carbonyl or imine reactant, forging two new bonds in the process (Scheme 1, equations 1 and 2). Some "hetero-Diels Alder" reactions occur in a stepwise or asynchronous fashion, much like the Prins reaction. With careful design, both reactions can be induced to occur efficiently, diastereoselectively, and enantioselectively.[2] The chiral building blocks generated are valuable for the synthesis of molecules of interest to chemists in the pharmaceutical industry, and for other projects targeting complex bioactive compounds. While the coupling of an alkyne and a carbonyl derivative also belongs in this category (Scheme 1, equation 3), this reaction has been difficult to control (vide infra), limiting its synthetic utility. As such, it has been relegated to the sidelines for many years.



Scheme 1 Coupling reactions of π-nucleophiles with π -electrophiles

1.1 Alkyne-Carbonyl Coupling Pathways.

Lewis or Brønsted acids promote intermolecular coupling reactions of alkynes with carbonyl derivatives, including activated aldehydes,[3] acetals,[4] hemiketals[5] and imines.[6] Even ketones[7] and ketals[8] will couple when the process is intramolecular. Two new bonds are formed in these couplings, one at each carbon of the alkyne, through a type **3** intermediate (Scheme 2). The process most likely begins with attack of the more nucleophilic carbon of the alkyne onto the electrophilic oxocarbenium or iminium ion, with concomitant development of vinyl cation character at the other carbon of the alkyne (see **3**, Scheme 2). This idea is supported by the regioselectivity of this process, which is very sensitive to the electronic characteristics of the alkyne (*vide infra* for details) and is typically excellent. The drawback to the chemistry is the unpredictable behavior of the vinyl cation species **3**, which can engage in two different reaction pathways to afford products like **5** and/or **6** (Scheme 2). The partitioning between the pathways depends on the reactants and reagents employed, and selectivities vary from case to case.



Scheme 2 Alkyne-carbonyl coupling pathways

In one reaction pathway, vinyl cation **3b** undergoes intramolecular capture by the carbonyl oxygen in a stepwise [2+2] cycloaddition/ ring-opening sequence that affords enones **6** via oxetenes **4**. This overall transformation has been

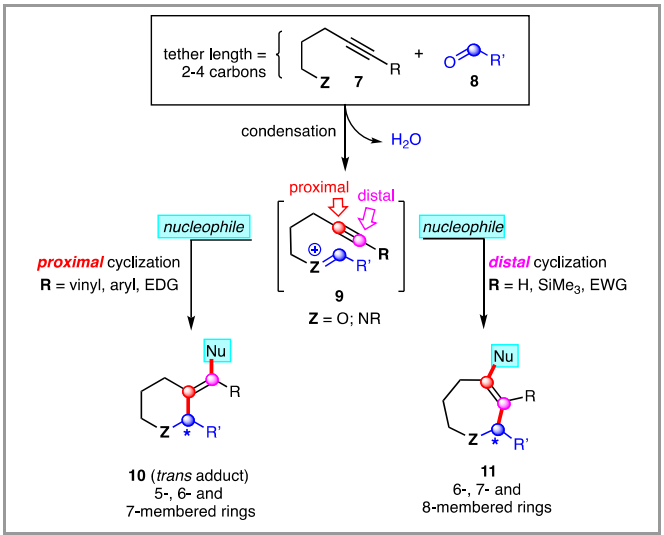
previously described as "alkyne-carbonyl metathesis,"[3e] and can be catalyzed by strong Lewis acids, Brønsted acids, iron(III) reagents, $AuCl_3$/ $AgSbF_6$, and $In(OTf)_3$.[3-4, 7a, 7b, 7d, 7g, 9]

In the other pathway, a nucleophile intercepts vinyl cation **3a** or **3b** to afford type **5** product. The net outcome of this transformation is analogous to a Prins reaction, and thus often termed an "alkynyl Prins" reaction. It is not clear whether the process is concerted (via developing cation **3a**) or stepwise (via discrete vinyl cation **3b**), and indeed may vary from case to case. A concerted process would result in the net *anti* addition of a nucleophile and a carbonyl derivative across the alkyne, and indeed, *anti* addition products dominate reaction mixtures.[5b, 8a, 10] When halide-containing Lewis acidic reagents are used to promote alkyne-carbonyl coupling, mixtures of alkynyl Prins reaction products **5** (Nu=halide) and metathesis products **6** are sometimes observed.[3c, 7g, 10a,11] Generally speaking, when alignment is favorable for the stepwise [2+2] pathway, it is difficult to suppress.

1.2 Coupling/Cyclization Cascades using the Alkynyl Prins Reaction.

When electronic and geometric reaction parameters are carefully controlled, it is possible to execute alkyne-carbonyl coupling sequences that that favor the alkynyl Prins pathway. One selective, synthetically useful strategy achieves the annulative coupling of two simple reactants (type **7** alkyne and an aldehyde **8**, Scheme 3). An initial condensation generates a cationic oxocarbenium or iminium intermediate **9**, aligned to cyclize through an intramolecular alkynyl Prins reaction, delivering ethers (Z=O) and amines (Z=NR) **10** or **11**. Importantly, the alkyne-carbonyl metathesis pathway (see **3b** to **6**; Scheme 2) is not available to intermediates **9**, and type **5** products are obtained exclusively. A chiral center (*) and three new bonds (C-Z, C-C and C-Nu; see **10**/**11**) are generated in the process. The reactions have been demonstrated to proceed with excellent regioselectivity (in the C-C bond-forming step) and stereoselectivity (in the C-Nu bond-forming step). Specific examples will follow in the body of the review.

Attack on the oxocarbenium/ iminium carbon by the proximal carbon of **7**, leading to type **10** products, occurs when alkyne substituent R is π-electron-donating, and thus able to stabilize the developing positive charge on the distal carbon. Complete regioselectivity in both inter- and intramolecular couplings are observed when R= aryl or alkenyl.[7g, 9d, 10, 12] Importantly, the metathesis pathway is ruled out when the alkyne is electronically primed to cyclize at the proximal carbon, as only the alkynyl Prins reaction is geometrically viable. In electronically symmetric type **7** alkynes (R= alkyl), the tether length has a strong influence on regioselectivity in the intramolecular alkynyl Prins reaction.[13] Regioselective cyclization at the distal carbon, generating type **11** products, is observed when R=H and R=SiR_3, where the alkyne substituents stabilize developing positive charge at the proximal carbon.[8] Thus, the tether imparts a degree of control and efficiency while generating adducts with appealing functional handles.



Scheme 3 Alkynyl Prins Annulation via a Condensation/Cyclization Cascade

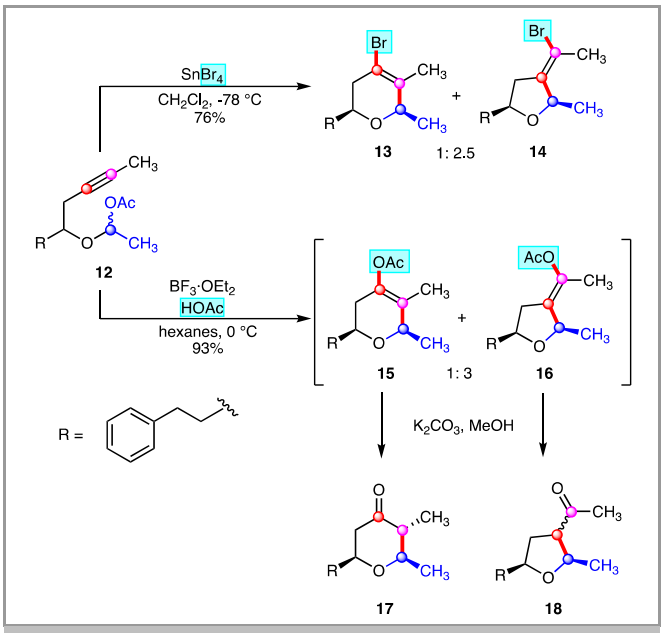
While reviews dedicated to the classical Prins reaction,[1] and the aza-Prins reaction[14] include sections describing the alkynyl Prins reaction, this represents the first review dedicated to the scope and synthetic utility of the alkynyl Prins and alkynyl aza-Prins reactions. We focus on alkynyl Prins annulations via type **9** intermediates (Scheme 3), which are especially selective and efficient. We also discuss applications to natural product syntheses, and the participation of alkynyl Prins adducts in cationic cascades as well as pericyclic reactions. We will describe the scope of electrophile (carbonyl derivative) and nucleophile (halide, arene, alcohol) partners capable of engaging the alkyne in these reaction sequences, to demonstrate the untapped potential of the reaction as a cyclization strategy.

2. Alkynyl Prins Annulation (Oxocarbenium Electrophiles)

In the following sections, we describe alkynyl Prins annulations with oxocarbenium electrophiles. The examples in sections 2.2-2.6 are divided according to the differences in the termination step, which is either capture with a nucleophile, or elimination.

2.1 Early Work

In 2001, Rychnovsky and co-workers reported the alkynyl Prins cyclization of α-acetoxyethers **12** promoted tin(IV) and BF_3 Lewis acids (Scheme 4).[15] Subjection of **12** to $SnBr_4$ in DCM at -78 °C produces a 1:2.5 ratio of distal to proximal bromine-incorporated cyclization products **13** and **14** in 76% yield. As an extension to this method, a 1:3 mixture of regioisomeric acetate-trapped cyclization products **15** and **16** are generated using a mixture of acetic acid and $BF_3{\cdot}OEt_2$ in hexanes at 0 °C. Basic workup (K_2CO_3, MeOH) of the reaction mixture affords endo- and exocyclic ketones **17** and **18** respectively in 93% yield.



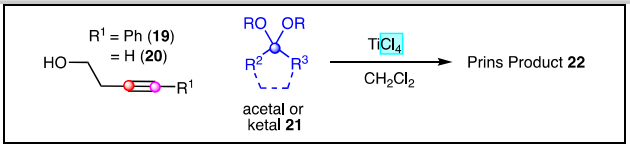
Scheme 4 Alkynyl Prins cyclization of α-acetoxyether **12** with $SnBr_4$ and $BF_3{\cdot}OEt_2$/AcOH.

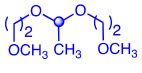
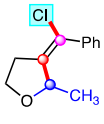
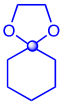
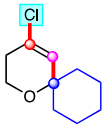
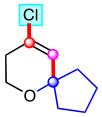
2.2. Halide as Terminal Nucleophile

a. Condensation of homopropargyl alcohols with acetals and ketals In 1989, Thompson and co-workers reported a $TiCl_4$-mediated alkynyl halo-Prins cyclization of homopropargyl alcohols **19**/**20** with acetals and ketals **21** via a transacetalization-cyclization sequence. [16]

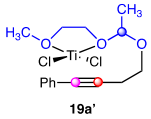
Reaction of 4-phenyl-3-butyn-1-ol **19** with methoxyethoxymethyl (MEM) acetal **21a** at 0°C in CH_2Cl_2 efficiently produces proximal cyclization product **22a** in 90% yield as an 83:17 mixture of *E*/*Z* isomers (Table 1, entry 1). Cyclization of ethylene glycol-protected ketones **21b** and **21c** furnished distal cyclization products **22b** and **22c** in comparatively lower yields when reacted with 3-butyn-1-ol **20** (entries 2 and 3). The exceptional cyclization efficiency of MEM acetal **21a** was surmised to be due to favorable bidentate coordination of alkyl ether motif to the titanium center, consequently generating a more reactive/electrophilic mixed acetal species **19a'** in situ (see footnote "b").

Table 1 $TiCl_4$-promoted Transacetalization-Cyclization Sequence



Entry	Alkyne	Acetal/Ketal	Conditions	Product	Yield
1	**19**	 **21a**	0 °C, 0.8 h	 **22a**	90%[a,b] (*E*/Z: 83:17)
2	**20**	 **21b**	22 °C, 4 h 0 °C, 4 h	 **22b**	23% 52%
3	**20**	 **21c**	0 °C, 6 h	 **22c**	<10%

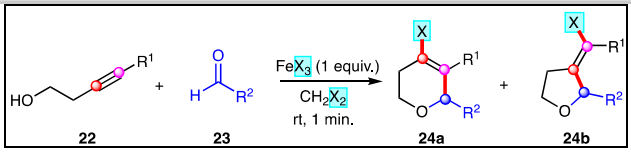
[a] Product **22a** shown as major *E* isomer.
[b] Higher yields are attributed to a favorable bidentate binding mode as shown in **19a'**


19a'

b. Condensation of homopropargyl alcohols with aldehydes and ketones. Several groups have studied the alkynyl Prins reaction of homopropargyl alcohols with aldehydes and ketones. These studies are described in this section, and a graphical summary is provided in Scheme 3.

In 2003, Martin and co-workers reported the Prins cyclization of homopropargylic alcohols **22** and aldehydes **23** using stoichiometric FeX_3 (X=Cl,Br) halides salts (Table 2). [17] Aliphatic and aromatic aldehydes efficiently cyclize, furnishing Prins products **24a**/**24b** in good to excellent yields (75-98%). Substitution at the distal terminus of the alkyne heavily influences the regioselectivity of terminal nucleophile addition. When $FeCl_3$ was used as the Lewis acid promoter, terminal alkyne **22a** underwent cyclization with aliphatic and aromatic aldehydes (R^1 = H) to distal cyclization product **24a** as the major product (entries 1-4). Implementation of $FeBr_3$ as the Lewis acid furnished the corresponding bromo-Prins product **24a** in high yields, although with the accompaniment of chlorine-trapped contamination products derived from metal-solvent halide exchange (entries 5-7). In contrast to terminal alkyne cases, implementation of internal alkyne **22b** (R^1 = Me) results in an inversion of regioselectivity in halide addition, as a product 65:35 ratio of **24b** to **24a** was isolated when $FeCl_3$ was used as the promoter (entry 8).

Table 2 Fe(III)-promoted Prins cyclization of homopropargylic alcohols and aldehydes to produce 2-alkyl-3-halo-5,6-dihydro-2*H*-pyrans.



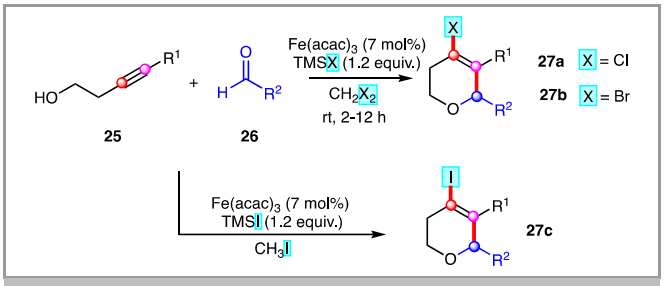
Entry	R^1	R^2	X	Ratio 24a : 24b	Yield
1	H (**20a**)	*c*-C_6H_{11}	Cl	100:1	80
2	H (**20a**)	*i*-Bu			90
3	H (**20a**)	Ph			30
4	H (**20a**)	Bn			75
5	H (**20a**)	*i*-Bu	Br	-[a]	98
6	H (**20a**)	*c*-C_6H_{11}		-[a]	93
7	H (**20a**)	Bn		-[a]	92
8	Me (**22b**)	*n*-C_6H_{12}	Cl	35:65	80

[a]Contamination of product with chlorine-trapped Prins product.

In a follow-up report in 2009, a catalytic Prins protocol of homopropargyl alcohols **25** and aldehydes **26** was disclosed by Padron and co-workers, relying upon cooperative catalysis between Fe(III) metals and trimethylsilyl halides (Scheme 5).[18]

Implementation of 7 mol% $Fe(acac)_3$ catalyst and 1.2 equivalents of TMSX (X = Cl, Br) as the halide donor in the matched halogenated solvent (CH_2Cl_2 or CH_2Br_2) affords chloro- and bromo-Prins products **27a** and **27b** in CH_2Cl_2 and CH_2Br_2 respectively. It was found that matching of the halide donor and halogenated solvent was critical to the transformation as mismatched solvent-TMSX combinations produced complex mixtures of chlorine- and bromine-incorporated Prins products.

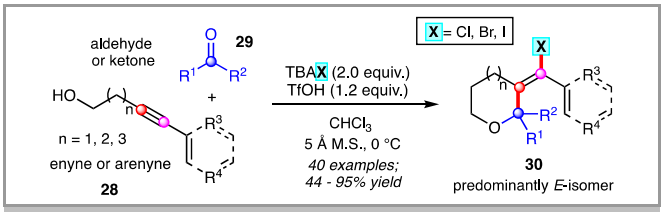
Conveniently, the methodology can be extended to the construction of iodo-Prins cyclization products **27c** via the usage of catalytic $Fe(acac)_3$ and trimethylsilyl iodide (TMSI) in methyl iodide as the solvent. Notably, a similar method was released by Yadav for the synthesis of iodo-Prins adducts involving in situ TMSI formation using a mixture of TMSCl and sodium iodide. [19]



Scheme 5 Fe(III)-catalyzed alkynyl Prins cyclization of homopropargyl alcohols **25** and aldehydes **26** to furnish Prins product **27**.

Nitrogen heterocycles can also be synthesized in this way starting from homopropargyl tosylamines, as will be discussed in Section 4.2 (Scheme 22).

In two successive reports, our research group reported the development and servicing of an alkynyl halo-Prins annulation of enyne or arenyne alcohols **28** and aldehydes or ketones **29** for the syntheses of spirocyclic halo-cyclopentenes[20] and halo-indenes[21], respectively (vide supra; Scheme 13). A combination of triflic acid (TfOH), soluble tetrabutylammonium halide salts (TBAX; X = Cl, Br, I), and 5Å molecular sieves as the dehydrating agent efficiently generates chloro-, bromo-, and iodo-Prins products **30** in moderate to excellent yields (44-95%), accompanied by excellent *E*/*Z* ratios (Scheme 6). The synthetic utility of this transformation is later discussed in Section 3.2.

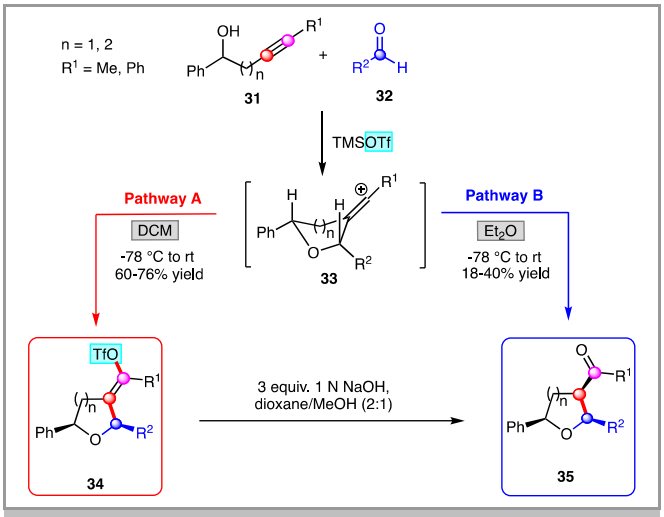


Scheme 6 TfOH-promoted alkynyl Prins cyclization for the synthesis of **30**.

2.3 Oxygen as Terminal Nucleophile

In 2008, Cho and co-workers reported a TMSOTf-mediated alkynyl Prins cyclization of secondary alkynyl alcohols **31** and aldehydes **32** for the chemodivergent synthesis of exocyclic vinyl triflates **34** and 3-acetyl-substituted ethers **35** (Scheme 7).[22]

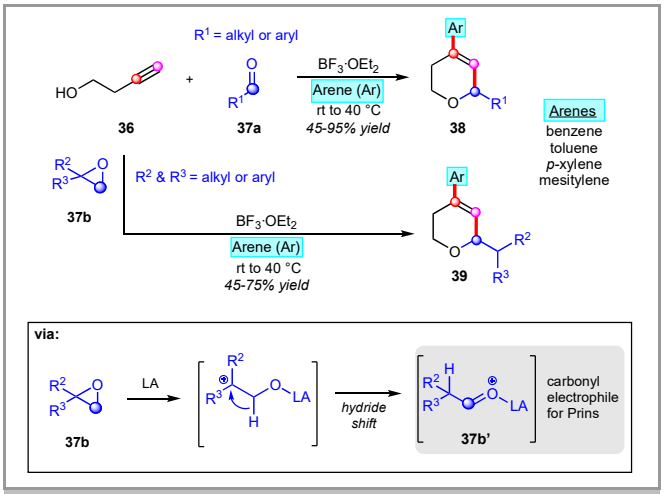
Stereoselective proximal cyclization of **31** and **32** produces vinyl cation intermediate **33**. The fate of the vinyl cation intermediate is strongly influenced by the solvent conditions employed. When DCM is used as the reaction solvent, triflate-incorporated Prins product **34** is generated exclusively (Pathway A). However, in Et_2O, 3-acetyl substituted ether **35** is observed exclusively by the way of a hydrolysis pathway (Pathway B). Futhermore, **35** may be accessed via basic hydrolysis of **34** using 3 equivalents of 1N sodium hydroxide in a 2:1 mixture of dioxane and methanol.



Scheme 7 Chemodivergent synthesis of exocyclic vinyl triflate **34** and 3-acetyl-substituted ethers **35** via a TMSOTf-promoted alkynyl Prins cyclization.

2.4 Arene as Terminal Nucleophile (Intermolecular)

Saikia and co-workers reported a Friedel-Crafts-terminated alkynyl Prins cyclization of aldehydes **37a** and epoxides **37b** with 3-butyn-1-ol **36** using $BF_3{\cdot}OEt_2$ in aromatic solvents (Scheme 8).[23]



Scheme 8 Friedel-Crafts-terminated alkynyl Prins cyclization of homopropargyl alcohol **36** with aldehydes **37a** and epoxides **37b**.

Aryl and aliphatic aldehydes **37a** perform well under the reaction conditions, affording Prins products in 45-95% yield, albeit lower yields were obtained with the implementation of aliphatic ketones (not shown). Benzene, as well as toluene, *p*-xylene, and mesitylene readily produced Prins products under the described reaction conditions, although no cyclization products were observed in the case of highly electron-rich arenes such as anisole

and 1,3,5-trimethoxybenzene due to competitive dehydrative processes.

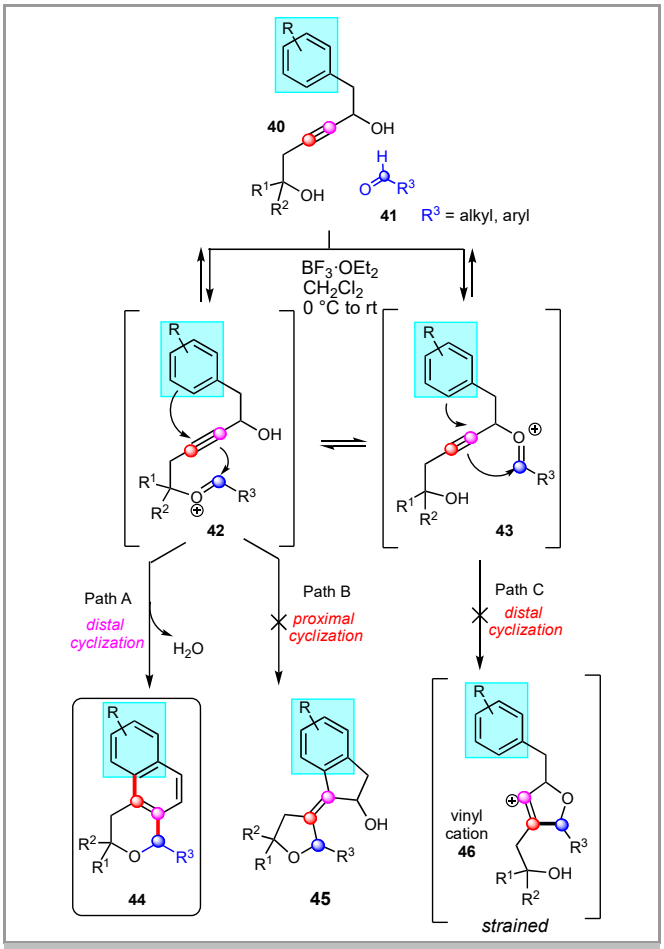
It was also demonstrated that unsymmetrical epoxides such as **37b** can serve as useful aldehyde surrogates for the generation of Prins cyclized products under Lewis acidic conditions. Epoxide ring opening of **37b** to a stabilized tertiary cation, followed by a 1,2-hydride, shift generates the active carbonyl (oxocarbenium) electrophile **37b'** for cyclization affording Prins product **39** in 45-75% yield.

2.5 Arenes as Terminal Nucleophile (Intramolecular)

In 2013, Hinkle and co-workers reported the expedient synthesis of 3,4-dihydro-2*H*-benzo[*f*]isochromenes **44** using a BF_3-promoted cascade cyclization sequence of aryl-tethered diol **40** and aryl and aliphatic aldehydes **41** (Scheme 9).[24] The cascade sequence involves an alkynyl Prins cyclization, Friedel-Crafts alkylation and dehydration/aromatization to afford product **44**.

To rationalize the formation of Prins product **44**, three distinct mechanistic pathways were composed by the authors as presented in Scheme 9. Lewis acid-promoted condensation of **41** with the tertiary or secondary alcohol of **40** is conjectured to produce an equilibrating mixture of oxocarbenium intermediates, **42** and **43**, respectively. Distal cyclization of oxocarbenium **42** with terminal Friedel-Crafts alkylation/aromatization affords isochromene product **44** (Path A). Alternatively, oxocarbenium **42** may proceed through a proximal cyclization pathway to produce **45** via Path B, although no products corresponding to **45** were observed. To rationalize the exclusive formation of **44** versus **45**, the authors suggest that inductive withdrawal of electron density by the oxygen atom at the propargylic position results in the preferential development of positive charge at the proximal (red) carbon rather than the distal (pink) one. Path C which involves Prins cyclization of oxocarbenium intermediate **43** is hypothesized to be disfavored due to the formation of a highly strained endocyclic vinyl cation **46**.[25]

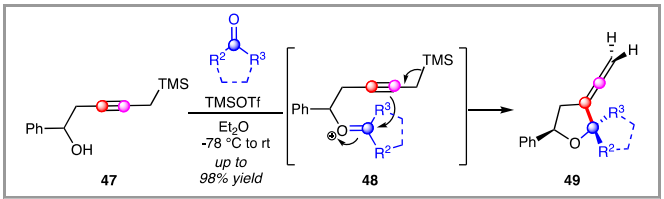
A follow-up report involving this method was later released in 2017 involving stereochemical studies involving enantio- and diastereoselective cyclizations of diols of type **40**.[26]



Scheme 9 One-pot $BF_3{\cdot}OEt_2$-initiated cascade in construction of tricyclic scaffolds.

2.6 Cyclizations Terminated by Elimination

In 2005, Cho and co-workers described the synthesis 3-vinylidene tetrahydrofurans **49** using a TMSOTf-promoted Prins cyclization of propargyl silanes of type **47** and aldehydes or ketones (Scheme 10). [27]



Scheme 10 TMSOTf-mediated synthesis of 2-substituted-3-vinylidene tetrahydropyrans **49** from propargyl silanes **47**.

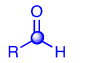
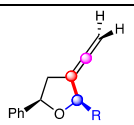
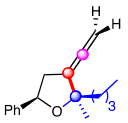
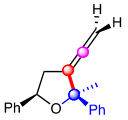
Condensation of alcohol **47** and aldehyde or ketone in the presence of TMSOTf generates oxocarbenium ion **48** in which proximal cyclization and silane elimination affords 3-vinylidene motifs such as **49** in up to 98% yield.

Other Lewis acids, such as $SnCl_4$, $BF_3{\cdot}Et_2O$, and $InCl_3$ were determined to be sufficient promoters for this transformation, albeit **49** was produced in comparatively lower yields. As shown in Table 3, Prins cyclization of aldehydes proceed with high stereoselectivity, producing *cis*-2,5-subsitututed tetrahydrofurans **49a** as the exclusive product in moderate to nearly quantitative yields (entry 1). [28] Similarly, asymmetric

ketones such as 2-hexanone and acetophenone efficiently cyclize in a stereoselective fashion to afford 2-quaternary substituted furans **49b** and **49c** in a 1.5: 1 and 7:1 *cis* to *trans* ratio respectively, in which the larger substituent shares a *cis* relationship with respect to the 5-phenyl substituent in the major isomer as shown (entries 2 and 3). The more pronounced stereoselectivity in entry 3 may be attributed to the markedly dissimilar steric bulk of the carbonyl substituents (Me versus phenyl), in which the larger substituent exhibits preference for pseudo-equatorial placement in the five-membered transition state.[29]

It is worth mentioning that a similar Prins cyclization method for the synthesis of 2-substituted tetrahydropyrans from propargyl silane and aldehyde precursors was reported by Furman et al. [30]

Table 3 Prins Cyclization of **47** with various Carbonyl Sources

Entry	Carbonyl	Product	Yield	*cis/trans*
1	R = alkyl, aryl 	 **49a**	58-98%	only *cis*
2		 **49b**	90%	1.5:1[a]
3		 **49c**	55%	7:1[a]

[a]Major *cis* stereoisomer shown.

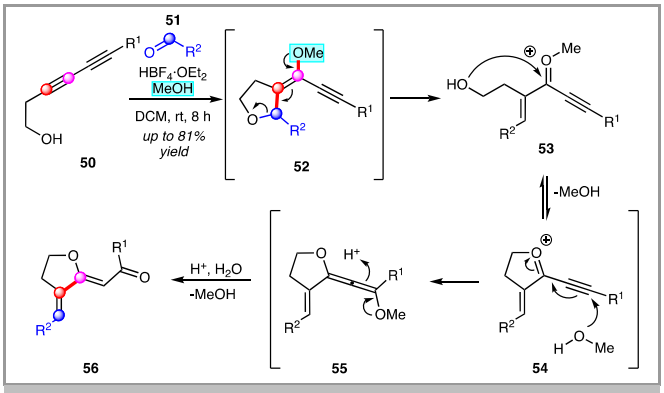
3. Synthetic Utility of Alkynyl Prins Annulation

In this section, we will highlight applications of the alkynyl Prins cyclization. The adducts can be induced to undergo further transformations, participating in cycloaddition and electrocyclization processes, for example (Sections 3.1 – 3.2). In this way, the generated Prins adducts represent a launching point for synthetic methods that build complex small molecules. The alkynyl Prins cyclization can also be used as a strategy in the synthesis of natural products, as described in Section 3.3.

3.1. Alkynyl Prins-mediated Synthesis of Dienes for a [4+2] Cycloaddition-Oxidation Sequence

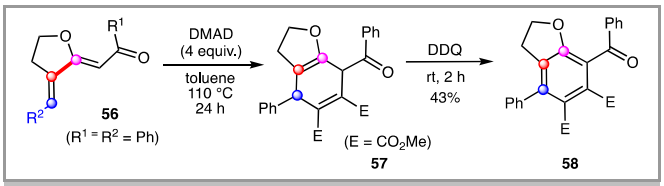
In 2018, Saito reported a Prins-mediated domino synthesis of dienes of type **56** from diynols **50** and aldehydes **56** using $HBF_4{\cdot}OEt_2$.[31] The mechanism for this transformation is described in Scheme 11. Distal cyclization of diynol **50** and aldehyde **51** with trapping by methanol generates Prins intermediate **52** which undergoes subsequent ring opening ionization to oxocarbenium intermediate **53**.[32] From intermediate **53**, transacetalization followed by MeOH addition to **54** produces allenolate **55** which upon protonation furnishes diene **56**.

A multitude of aryl- and alkyl-terminated diyne analogues (R^1 = EDG-Ar, EWG-Ar, C_4H_9) yield domino product **56** in satisfactory yields under the reaction conditions. Additionally, aryl, aliphatic and unsaturated aldehydes were well tolerated and afford **56** in high efficiency (up to 81%).



Scheme 11 Prins-mediated domino synthesis of diene **56** from 3,5-diynols **50** and aldehydes **51** using $HBF_4{\cdot}OEt_2$.

From diene **56**, 2,3-dihydrobenzofurans such as **58** may be synthesized via a [4+2] cycloaddition-oxidation sequence. Diels-Alder reaction of diene **56** with dimethyl acetylenedicarboxylate (DMAD) at 110 °C for 24 hours produces 1,4-cyclohexadiene **57** which upon oxidative treatment with 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) yields dihydrobenzofuran **58** in 43% yield (Scheme 12).



Scheme 12 Cycloaddition-oxidation sequence for the generation of **58**.

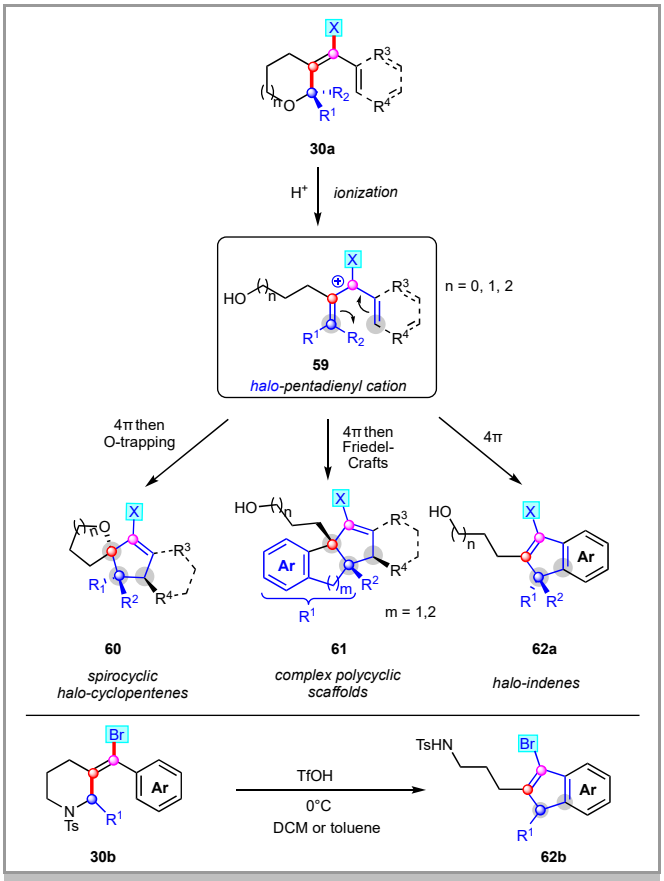
3.2. Alkynyl Prins Cyclization Adducts as Nazarov Cyclization Precursors

Alkynyl Prins adducts can be ionized to generate pentadienyl cation intermediates, which then undergo 4π electrocyclization. These cascades have been reported sporadically during studies focused on stepwise [2+2] cycloaddition sequences,[3c, 7g] and have recently taken center stage in the development of Nazarov cyclization sequences.

Our research group has recently discovered that alkynyl Prins adducts may serve as a platform for *halo*-Nazarov-initated cascade reactions for complex molecule synthesis (Scheme 13).[20-21, 33] Ring-opening ionization of Prins adduct **30a** unveils halopentadienyl cation of type **59**, which may be leveraged for the rapid construction of diverse molecular skeletons depending on starting materials employed. In one scenario, halopentadienyl cation **59** undergoes a 4π conrotatory (halo-Nazarov) electrocyclization followed by trapping by the pendant alcohol to produce spirocyclic halo-cyclopentenes such as **60** with high diastereoselectivity. In another case, electrocyclic ring closure of **59** followed by Friedel-Crafts alkylation from aryl-tethered Prins precursors (R^1 = CH_nAr) effectively afford complex polycycles

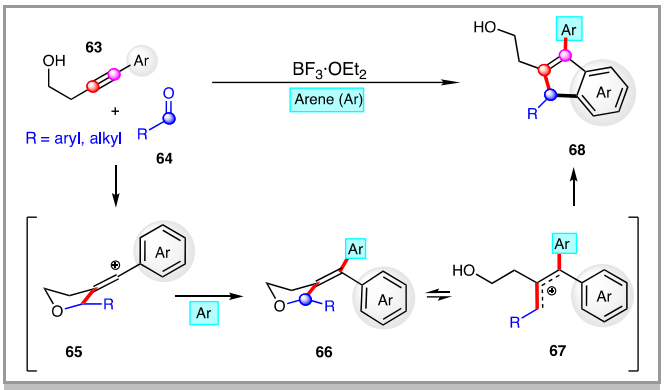
such as **61**. Lastly, when R^3/R^4=aryl, 4π electrocyclization readily produces halo-indene **62a**.

Furthermore, in 2019, Hou demonstrated that Prins-derived 4-(bromomethylene)-piperidines such as **30b** may similarly proceed through a halo-Nazarov using TfOH at 0 °C to furnish 3-bromoindenes **62b**. [34]



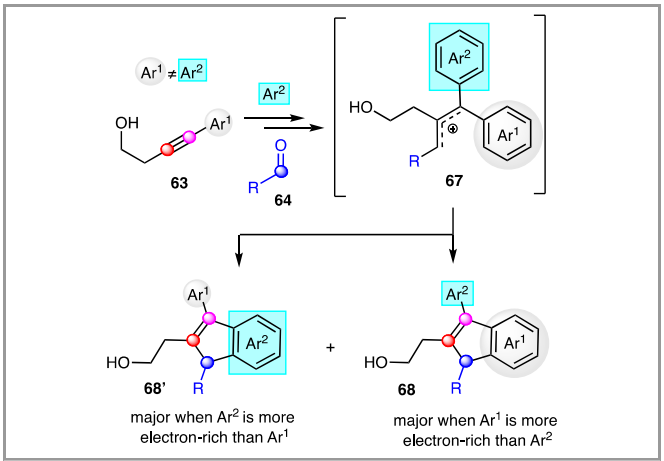
Scheme 13 Synthetic utility of alkynyl halo-Prins precursor **30** for halo-Nazarov-mediated cascade reactions.

In a previous report, Hou et al. discovered that the synthesis of indenes **68** may be achieved through a Prins-mediated cascade sequence involving arenyne alcohols **63** and aromatic or aliphatic aldehydes **64** using $BF_3{\cdot}OEt_2$ in aromatic solvents (Scheme 14).[35] The general mechanism for this transformation is described in Scheme 14 below. Proximal cyclization of **63** and **64** produces exocyclic vinyl cation **65**, which is captured in a Friedel-Crafts fashion to produce an equilibrating mixture of non-ionized and ionized intermediates, **66** and **67** respectively. Nazarov cyclization of allyl cation **67** terminates the cascade sequence and furnishes indene **68**.



Scheme 14 Synthesis of Indene **68** via $BF_3{\cdot}OEt_2$-mediated Nazarov cacasade sequence in aromatic solvents.

Benzene as well as other electron rich solvents (*p*-xylene and 1,4-dimethoxybenzene) serve as viable aromatic solvents in this transformation. Indeed, the electronic profiles of the employed arenyne alcohol (Ar^1) and solvent (Ar^2) vastly influence cyclization selectivity. Indene **68** is observed as the major product when arenyne **63** (Ar^1) is more electron-rich than the solvent employed (Ar^2). Conversely, indene **68'** is observed as the major product when the solvent employed (Ar^2) is more electron-rich than the starting arenyne **63** (Scheme 15).



Scheme 15 Product distribution of indene **68/68'** in the presence of dissimilar aryl groups ($Ar^1 \neq Ar^2$).

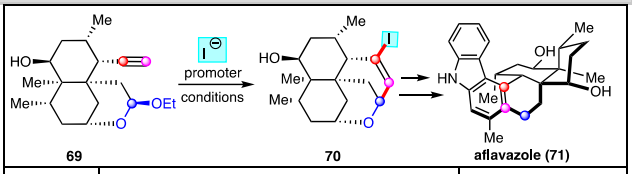
3.3. Alkynyl Prins Cyclizations in Natural Product Synthesis

Li and coworkers demonstrated an elegant total synthesis of aflavazole **71**, which capitalized upon an AlI_3-promoted alkynyl Prins cyclization.[36] Conditions for the synthesis of Prins substrate **70** from α-ethoxy acetal **69** are described in Table 4.

A combination of Bronsted acid and halide salts failed to produce **70**, even at elevated temperatures (entry 1). Trimethylsilyl iodide furnished Prins product **70** in rather low yield (entry 2), albeit implementation of iodo-Prins cyclization conditions previously disclosed by Padron[18] results in higher yield of **70** (entry 3). Similarly, other promoters such as SnI_4 and TiI_4 and GaI_3 afford **70** in comparatively low yields (entries 4, 5, and 8). Excess amounts (6 equivalents) of AlI_3 proved be optimal for this transformation, affording Prins product **70** in the highest yields in toluene (entries 7 & 8).

Isolation of iodo-Prins adduct **70** set the stage for the construction of the sterically congested indole diterpenoid, aflavazole **71**, in four subsequent steps.

Table 4 Screened conditions for the iodo-Prins cyclization of **69**.



69 **70** **aflavazole (71)**

Entry	Promoter/Conditions	**70** (%)
1	Bu_4NI (5 equiv.), CSA (2 equiv.), MeCN, 22 °C	0[a]
2	TMSI (5 equiv.), toluene, -10 °C	12
3	$Fe(acac)_3$ (20 mol%), TMSI (3 equiv.), MeI, 22°C	43
4	SnI_4 (6 equiv.), CH_2Cl_2, 22 °C	0
5	TiI_4 (6 equiv.), CH_2Cl_2, -40 °C	32
6	AlI_3 (6 equiv.), CH_2Cl_2, -78 °C	51
7	AlI_3 (6 equiv.), toluene, -78 °C	68
8	GaI_3 (6 equiv.), toluene, -40 °C	42

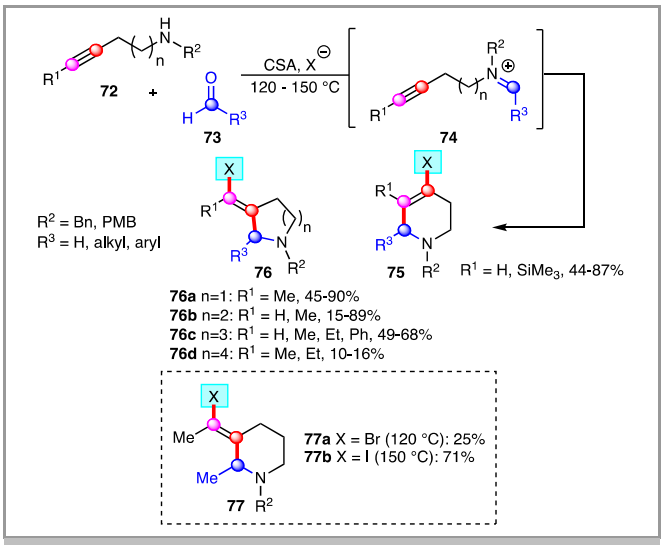
[a] Decomposition observed at elevated temperatures.

4. Alkynyl Aza-Prins Annulation

The alkynyl Prins cyclization can also be applied to substrates bearing nitrogen-containing electrophiles. In general, the electrophiles involved in this subset of the alkynyl Prins reaction can be grouped into two types: iminium or activated iminium ions. Iminium electrophiles are typically generated through condensation of an amine and a carbonyl partner or cleavage of an *N,O*-acetal precursor, whereas activated iminium ions are formed *in situ* by ionization of a leaving group. Activated iminium ions are rendered more electrophilic due to the electron-withdrawing nature of their *N*-acyl or *N*-sulfonyl protecting groups. The most common terminal nucleophiles are halides; however, examples of other terminal nucleophiles such as azide, thiocyanate, triflate, water, and even acetonitrile have been reported. This section will outline the development of this reaction and its applications in total synthesis.

4.1 Iminium Electrophiles

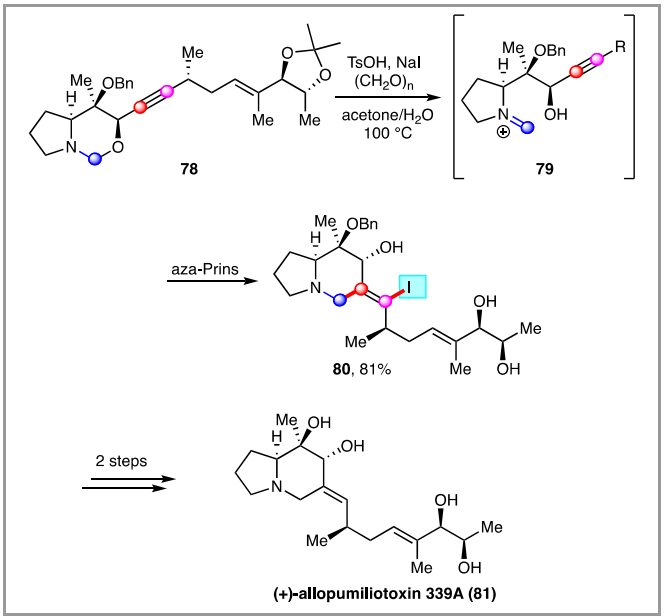
The pioneering studies of Overman in 1988 focused on the cyclization of alkynes with iminium ions in the presence of terminal nucleophiles such as halides, azide, or thiocyanate anions (Scheme 16).[37] Interestingly, the group found that without the terminal nucleophile, the electrophilic cyclization reactions do not occur. Like the oxa-alkynyl Prins reactions discussed in earlier sections, the regioselectivity of the cyclization (*proximal* or *distal* mode) can be altered by changing the tether length and the substituents on the alkyne. For the shortest tethers (n = 1; Scheme 16), proximal cyclization is preferred with an alkyne bearing a methyl substituent as in **76a**. However, distal cyclization is preferred for products **75** when the alkyne bears a hydrogen or TMS group. For the longer tether lengths ($n \geq 2$, products **76** and **77**), the proximal mode is exclusively observed, and the reaction occurs stereoselectively to generate the *E*-isomer. Overman later demonstrated that this reaction can be used to access seven- and eight-membered nitrogen heterocycles **76c-d**, although low yields were reported for the latter.[38]



Scheme 16 Aza-alkynyl Prins cyclization (iminium ion generated *in situ*)

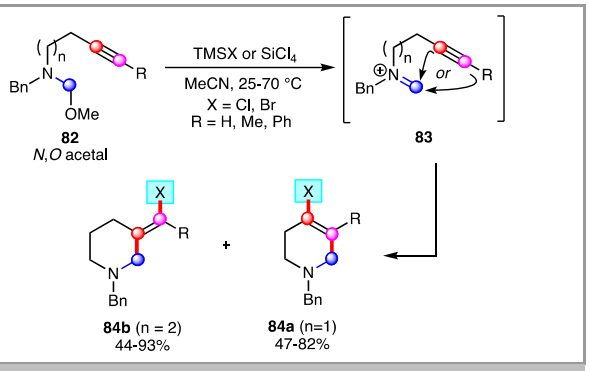
Overman and coworkers then expanded the aldehyde substrate scope in a subsequent study.[39] These reactions are conducted in acetonitrile solvent at temperatures between 120 – 150 °C in the presence of an alkyne and tetrabutylammonium iodide (TBAI). Notably, TBAB is not as effective as TBAI in these cyclizations (Scheme 16). Similarly, terminal alkynes and iminium ions derived from benzaldehyde result in lower yields for the aza-alkynyl Prins reaction.

This methodology was then utilized by Overman and coworkers as the key step of the first total synthesis of (+)-allopumiliotoxin 339A,[40] and subsequent syntheses of (+)-allopumiliotoxin 267A and (+)-allopumiliotoxin 323B' (Scheme 17).[41,42] The formaldiminium electrophile **79** is revealed *in situ* by acidic cleavage of cyclopentaoxazine **78**, conditions which also reveal the 1,2-diol. This process cleanly affords the alkynyl aza-Prins adduct **80** in 81% yield.



Scheme 17 Aza-alkynyl Prins as the Key Step en route to (+)-allopumiliotoxin 339A

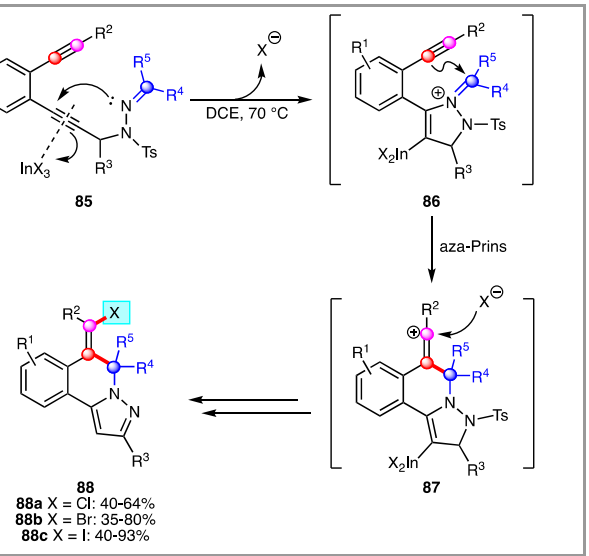
Overman and Murata later disclosed a general method of incorporating either chloride or bromide into aza-Prins adducts under anhydrous conditions.[43] Rather than condensing formaldehyde with an amine substrate, a preformed *N,O*-acetal **82** is treated with TMSX (X = Cl, Br) or $SiCl_4$ in acetonitrile (Scheme 18).



Scheme 18 Removal of *N,O*-acetal to Form Iminium Electrophile *in situ*

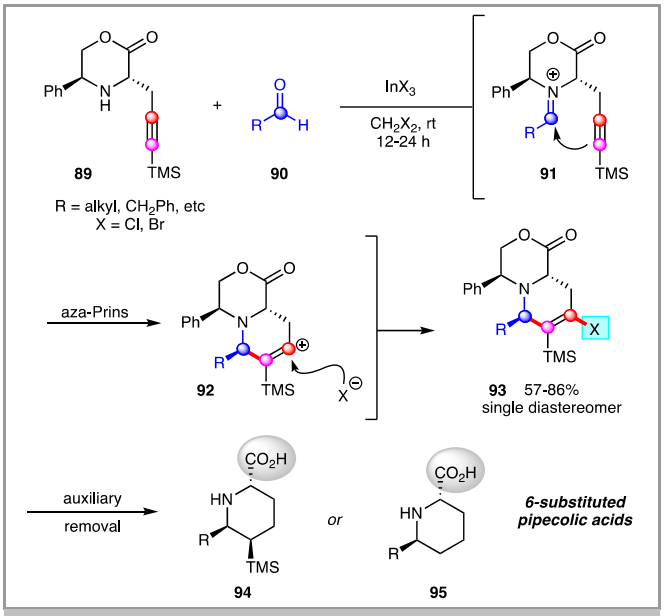
Under these conditions, the cyclization proceeds efficiently at room temperature for internal alkynes but requires elevated temperature for terminal alkynes. Only the (*E*)-alkylidene stereoisomer **84b** is observed when the terminal substituent of the alkyne is H or Me, whereas 6-7% of the (*Z*)-alkylidene stereoisomer is isolated when the terminal substituent is phenyl. With the shortest tether (n=1), distal cyclization of this *N,O*-acetal affords endocyclic adducts **84a** in similar yields.

Zhan and coworkers reported a cascade sequence involving an alkynyl aza-Prins reaction as one of the key steps in forming functionalized 5,6-dihydropyrazolo[5,1-*a*]isoquinolines (Scheme 19).[44]



Scheme 19 Indium-promoted aza-Prins cascade sequence

The reactions are promoted by stoichiometric InX_3 (X = Cl, Br, I) in the presence of hydrazones that are derived from aldehydes and ketones. Electrophilic activation of alkyne **85** by InX_3 promotes nucleophilic addition of the tethered hydrazone to generate this unique iminium electrophile **86** that is then trapped by the proximal carbon of the adjacent alkyne. Furthermore, vinyl chlorides, bromides, and iodides can all be formed; however, the yield and rate of this cascade sequence is optimal with iodide as the terminal nucleophile. This observation is in line with previous work by Overman (Scheme 16, product **77**). Dobbs et. al. recently disclosed the first asymmetric variant of the alkynyl aza-Prins reaction (Scheme 20). Substrates bearing a pendent amine functionalized with a newly-developed chiral auxiliary undergo cyclization to achieve the diastereoselective synthesis of substituted piperidines and pipecolic acids.[45] Notably, chiral Lewis acid complexes did not affect enantioinduction, either through condensation of the amine and aldehyde partner or with a preformed imine. Consequently, it was proposed that the Lewis acid is only involved in imine formation and does not provide a chiral environment for the cyclization event. Using $InCl_3$ or $InBr_3$, aza-Prins adducts **93** can be prepared from aldehydes, acetals, or epoxides as single diastereomers.

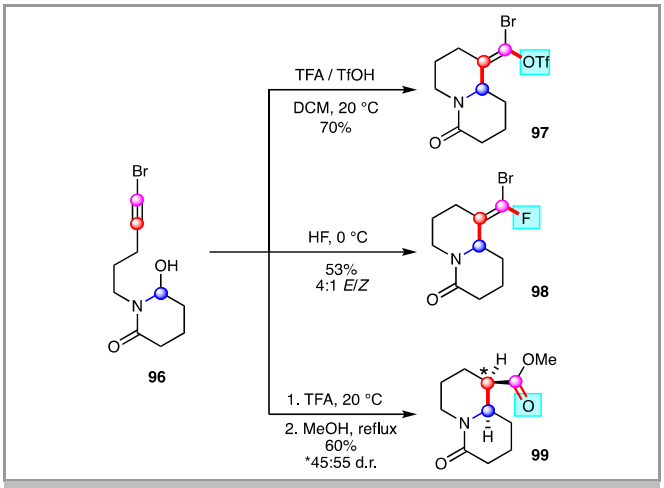


Scheme 20 Diastereoselective alkynyl aza-Prins reaction using a chiral auxiliary

Aliphatic aldehydes or acetals reportedly work best under these optimized conditions, while benzaldehyde does not afford any desired product. Lower yields are observed for acetal and epoxide precursors, but all products are isolated as single diastereomers relative to the chiral auxiliary. The auxiliary can then be removed in high yields using Pearlman's catalyst to afford functionalized, enantiopure pipecolic acids **94** or **95**.

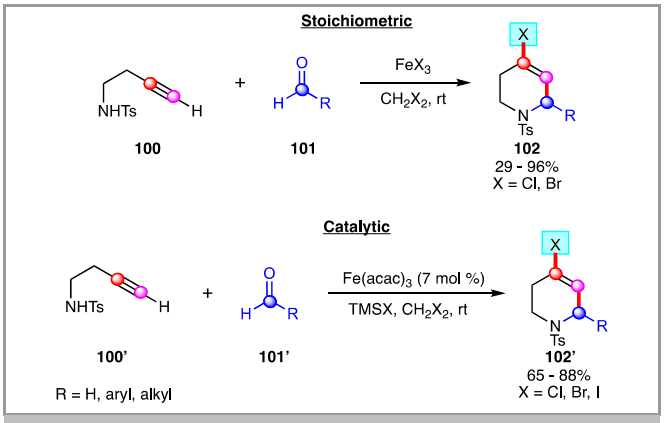
4.2 Activated Iminium Electrophiles

Gesson and coworkers explored the behavior of 1-bromoalkynes as nucleophiles for an aza-Prins cyclization with *N*-acyliminium electrophiles as part of a formal synthesis of lupinine and epilupinine (Scheme 21).[46] When a combination of TFA and TfOH is used, bromoenol triflate **97** is isolated as a single isomer in 70% yield. Interestingly, when anhydrous HF is used as the promoter, the intermediate vinyl cation is trapped by fluoride to afford a 4:1 (*E*/*Z*) mixture of bromofluoro isomers **98** in 53% combined yield. When **96** is treated with TFA and then refluxing methanol, ester **99** is obtained in 60% yield, presumably through hydrolysis of the intermediate trifluoroacetate-trapped aza-Prins product.



Scheme 21 *N*-acyliminium ion cyclization with bromoalkyne nucleophile

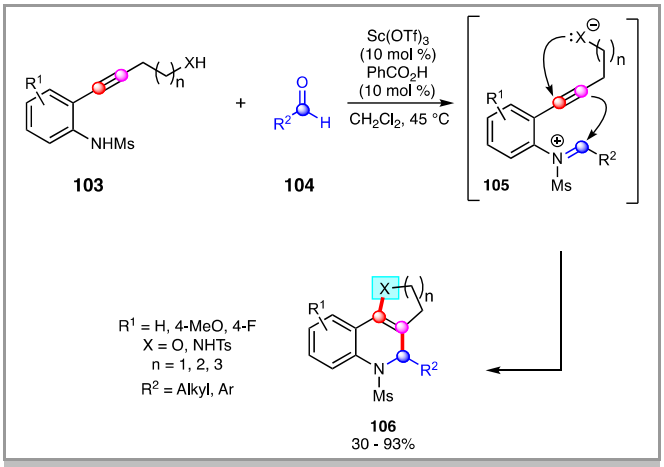
Padrón and coworkers reported the synthesis of tetrahydropyridine derivatives through a stoichiometric iron (III)-promoted aza-Prins reaction (Scheme 22).[47] Homopropargyl tosylamine **100** can be efficiently coupled with a variety of aldehydes under mild reaction conditions to undergo distal cyclization, affording azacycles **102**.[47-48]



Scheme 22 Stoichiometric and Catalytic Iron-Promoted Aza-Alkynyl Prins

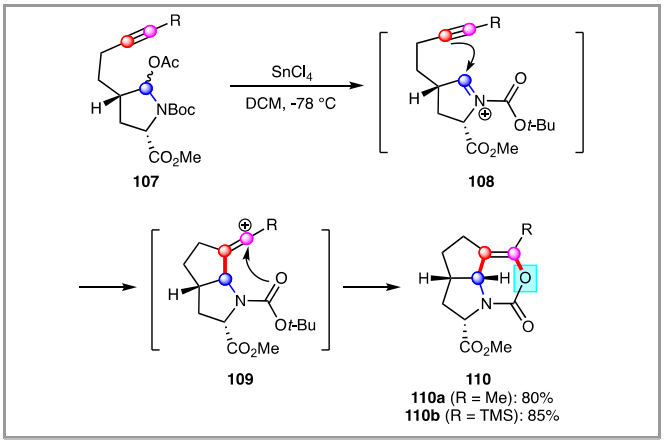
Padrón later disclosed a catalytic variant of this transformation, using an $Fe(acac)_3$ system in combination with a trimethylsilyl halide to efficiently construct nitrogen-containing heterocycles.[18] Using these conditions, it is possible to incorporate chloride, bromide, and iodide into these aza-Prins products with moderate to excellent yields under very mild reaction conditions (Scheme 22). Use of catalytic FeX_3 instead of $Fe(acac)_3$ gives similar results; however, $Fe(acac)_3$ is easier to handle as it is less hygroscopic. This work was extended in 2010 by Padrón in a subsequent study that includes other *N*-sulfonyl protecting groups and their impact on further synthetic modifications of the aza-Prins products.[14a] Similar methodology with internal alkynes has also been recently developed (see Scheme 13).[34]

Ma and coworkers demonstrated the coupling of *o*-alkynylanilines with a variety of aldehydes to generate 1,2-dihydroquinolines **106** through an alkynyl Prins / intramolecular termination cascade sequence (Scheme 23).[49] Condensation under Lewis acidic conditions leads to distal cyclization onto iminium **105**, followed by intramolecular trapping of the developing vinyl cation with the terminal heteroatom nucleophile. In cases where the aromatic aldehyde contains electron-withdrawing substituents, $PhCO_2H$ aids in the formation of the iminium ion.



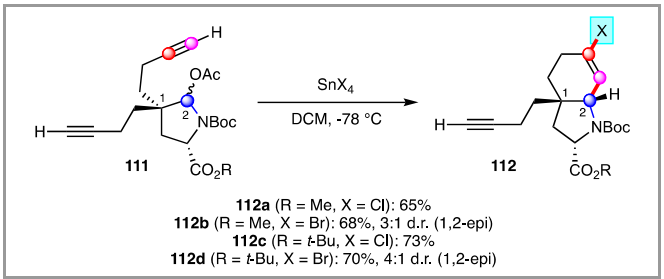
Scheme 23 Cascade aza-Prins with trapping of an internal nucleophile

Hanessian and coworkers conducted an extensive examination of alkynyl aza-Prins cyclizations of *N*-acyloxyiminium ions with both terminal and internal alkynes (Schemes 24 and 25).[50] Either $SnCl_4$ or $SnBr_4$ can ionize the acetoxy lactam to generate the *N*-acyloxyiminium intermediate, which suffers intramolecular attack by alkyne nucleophiles. Substrates **107** with a single internal alkyne undergo proximal cyclization to afford dihydrooxazinones **110** in high yields. In these cases, the terminating nucleophile is the *N*-Boc protecting group.



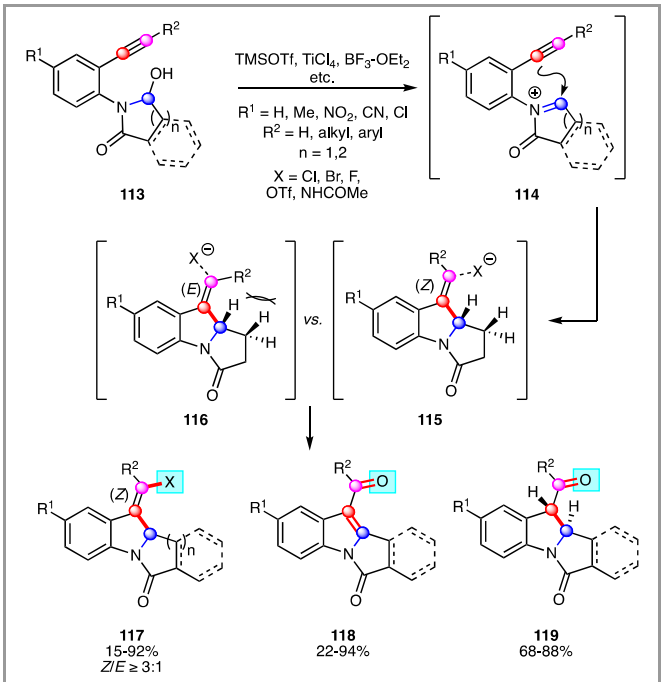
Scheme 24 Alkynyl aza-Prins of *N*-acyliminium ion with internal trapping of the *N*-Boc group

Substrates with the bis-alkynyl substitution pattern undergo distal cyclization with terminal alkynes, affording 6-halooctahydroindoles **112**. However, varying results are observed depending on the terminal nucleophile and ester substituent (Scheme 25). When **111** is ionized with $SnCl_4$, single diastereomers are observed for products **112a,c** whereas diastereomeric mixtures are observed for products **112b,d** after ionization with $SnBr_4$. In cases where diastereomers are observed, improved diastereomeric ratios are achieved when the methyl ester is replaced with a *tert*-butyl ester (up to 4:1 dr).



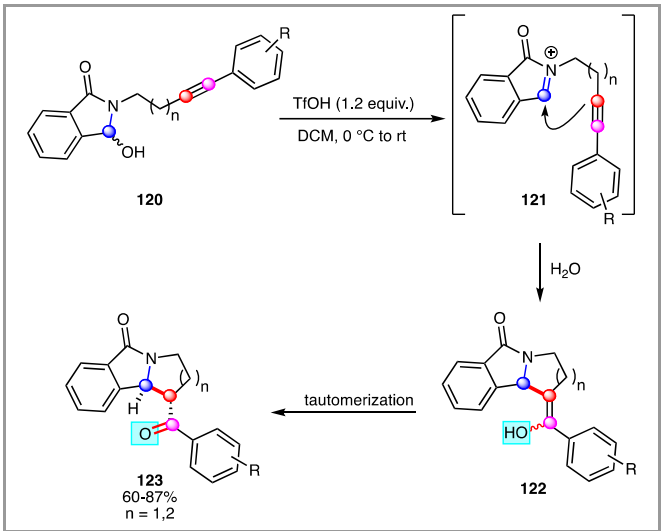
Scheme 25 *N*-acyliminium ion cyclization with a terminal alkyne nucleophile

The *N*-acyliminium electrophile has also been exploited in the development of methodology that constructs *N*-fused indole, indoline, and indolylidine derivatives (Scheme 26).[51] Gharpure and coworkers demonstrated that a variety of *N*-fused indoles **117-119** can be synthesized depending on the promoter used as well as the terminal nucleophile (halides, triflate, acetonitrile). One benefit noted by the authors is that vinyl fluorides are easily prepared using BF_3 as the Lewis acid. Contrary to much of the literature that has been surveyed thus far, the group reported the *Z* isomer as the predominant product (*Z*/*E* 3:1 up to ≥20:1), which the authors rationalized by invoking $A^{1,3}$ strain between R^2 and the amide skeleton (see **115** vs. **116**).



Scheme 26 *N*-acyliminium ion cyclization with trapping of various nucleophiles

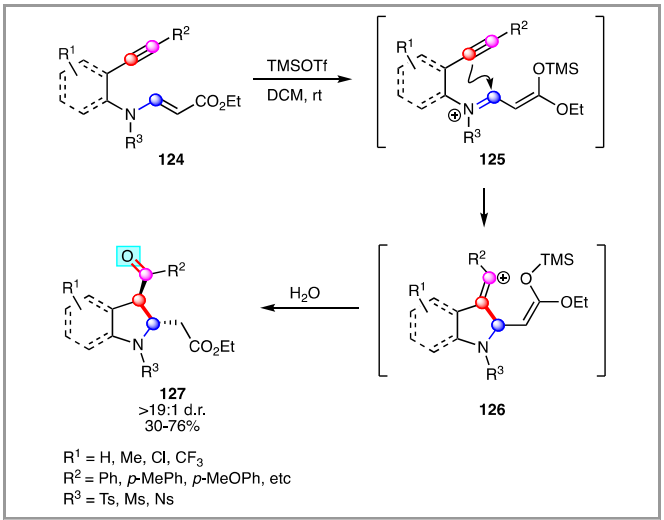
Saikia and coworkers successfully access the pyrrolo- and pyridoisoindolone skeletons **123** through an intramolecular alkynyl aza-Prins cyclization of type **121** *N*-acyliminium electrophiles (Scheme 27).[52] Ionization of carbinol lactams **120** results in *in situ* formation of the *N*-acyliminium ion **121**, which is then attacked in a proximal fashion by the alkyne to generate a vinyl cation that is then trapped with water. The enol ether intermediate **122** tautomerizes to produce a variety of aza-Prins adducts **123** diastereoselectively with respect to the two stereogenic centers indicated by the blue and red spheres.



Scheme 27 *N*-acyliminium ion cyclization followed by trapping with water

No reaction is observed when the aromatic ring attached to the alkyne contains strong electron-withdrawing substituents, and terminal or alkyl-substituted alkynes do not react under the optimized conditions. However, various electron-donating groups are tolerated on the aromatic ring, and Saikia rationalizes these observations as a result of the substituent's ability to stabilize the intermediate vinyl cation.

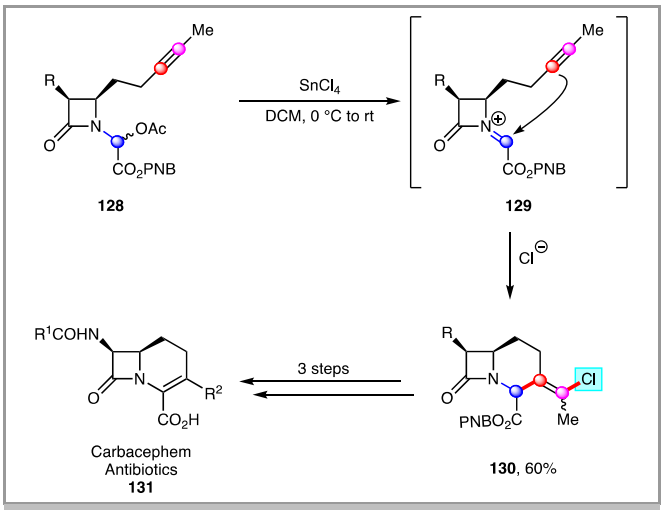
Gharpure and colleagues reported an alkynyl aza-Prins cyclization that utilizes vinylogous carbamates to generate the activated iminium electrophile. In the presence of TMSOTf as the Lewis acid, the vinylogous carbamate reacts to form iminium **125**, which is then trapped by the proximal carbon of the alkyne (Scheme 28).[53] Subsequent hydrolysis of intermediate **126** affords indolines **127** in excellent diastereoselectivity and yields. Similar chemistry by Gharpure has also been accomplished with oxocarbenium electrophiles.[54]



Scheme 28 Alkynyl aza-Prins of a vinylogous carbamate

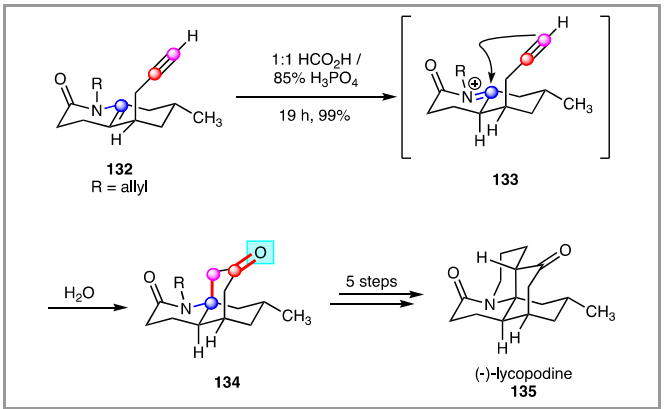
5. Alkynyl Aza-Prins Cyclizations in Natural Product Synthesis

Overman and colleagues employed a halide-terminated *N*-acyliminium cyclization as the key step in their synthesis of functionalized carbacephem antibiotics (Scheme 29).[55] Remarkably, the reaction proceeds in 60% yield under Lewis acidic conditions, despite the presence of additional functional groups in the substrate. The aza-Prins adduct **130** was then converted to the target carbacephem antibiotics in only three additional steps.



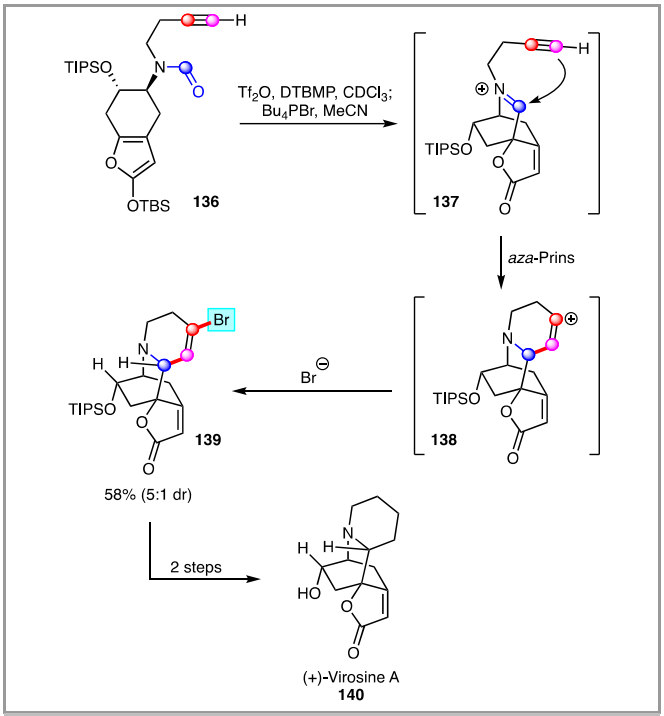
Scheme 29 *N*-acyliminium ion cyclization to access substituted carbacephem antibiotics

She and coworkers used the alkynyl aza-Prins cyclization as the key step of their total synthesis of (-)-lycopodine **135** (Scheme 30).[56] Beginning with **132**, the aza-Prins reaction is initiated under aqueous acidic conditions by protonation of the enamide moiety to reveal the *N*-acyl iminium electrophile **133**. This species then undergoes distal cyclization by the nucleophilic alkyne. Subsequent trapping of the vinyl cation with water followed by tautomerization to ketone **134** occurs in a remarkable 99% yield.



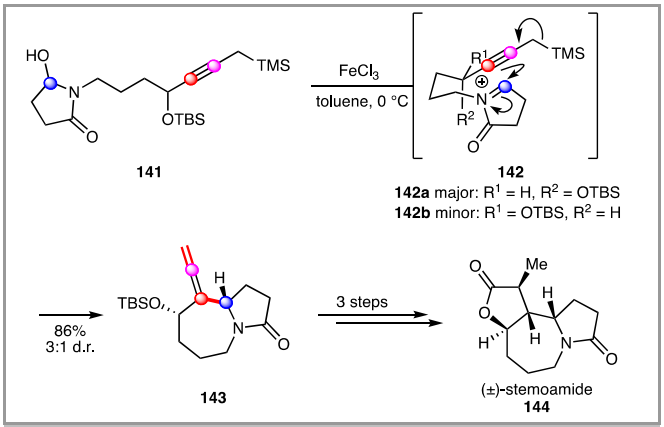
Scheme 30 Alkynyl aza-Prins as the key step toward the synthesis of (-)-lycopodine

Bélanger utilized a unique Vilsmeier-Haack / aza alkynyl-Prins cascade cyclization sequence to construct the azabicyclo[2.2.2]octane core of (+)-virosine A (Scheme 31).[57] The silyl enol ether engages in an intramolecular Vilsmeier-Haack cyclization after activation of formamide **136** with triflic anhydride. This process generates the iminium electrophile **137** necessary for the alkynyl Prins cyclization. After the addition of bromide as the terminal nucleophile, the alkynyl Prins adduct **139** is obtained in 58% yield in a 5:1 diastereomeric ratio (with respect to the stereogenic center indicated by the blue sphere).



Scheme 31 Asymmetric synthesis of (+)-virosine A

Hong and coworkers executed an alkynyl aza-Prins reaction as a key step in the total synthesis of (±)-stemoamide (Scheme 32).[58]



Scheme 32 Alkynyl aza-Prins of *N*-acyliminium ion as the key step toward the synthesis of (±)-stemoamide

In this case, the cascade cyclization of the propargyl silane reactant begins with *in situ* generation of *N*-acyliminium ion **142** by ionization of carbinol lactam **141** with $FeCl_3$. **142** then engages in proximal cyclization by the alkyne, and this sequence is terminated by desilylative elimination to generate allene **143** in excellent yield. This unique termination pathway has also been employed for oxygen electrophiles (Scheme 10). Although moderate diastereoselectivity is observed in the final product,

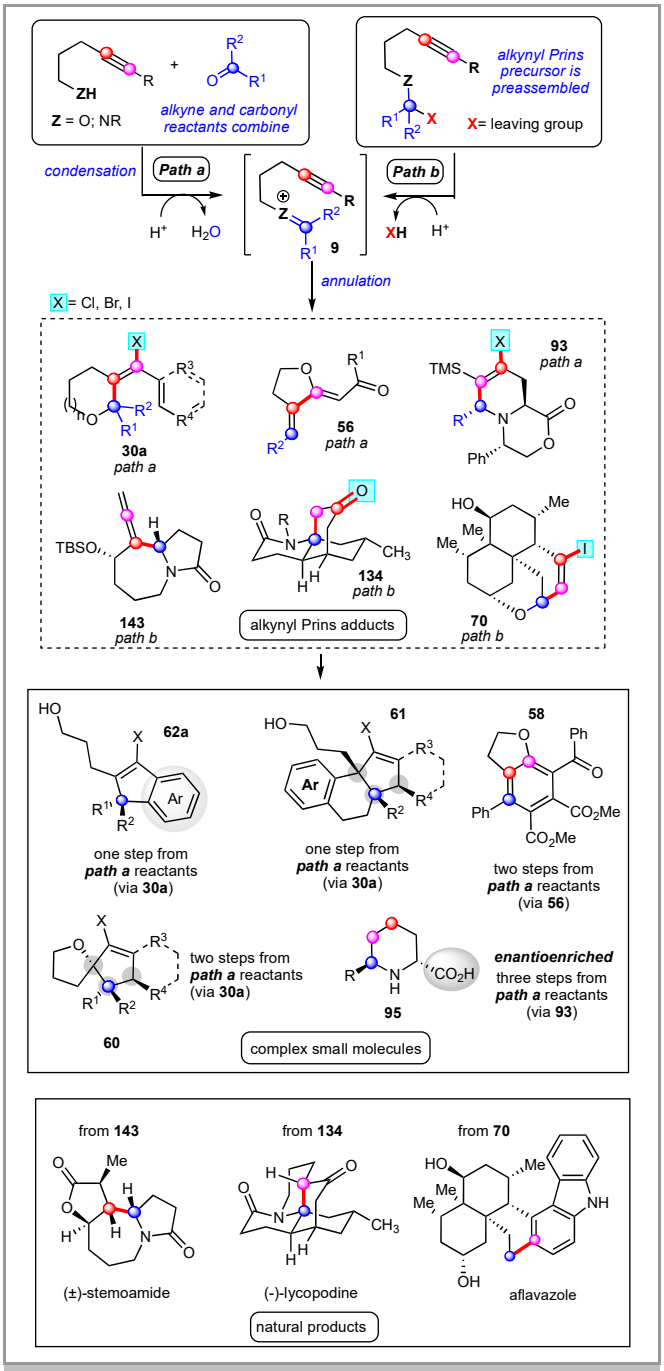
the efficient formation of this carbon skeleton in one operation using the alkynyl Prins reaction is impressive.

6. Summary and Outlook

A wide range of methods have been developed that capitalize upon annulative alkynyl Prins reactions. In these strategies, the condensation of two simple precursors enables facile cyclization, with formation of a total of three new bonds (one C-Z, where Z= O or NR; one C-C. and one C-Nu; Scheme 3, vide supra). The alkyne can be viewed as a lynchpin, reacting at one end with a tethered cationic oxocarbenium or iminium ion, and at the other end with a weakly nucleophilic species, such as a halide ion, an alcohol or an arene. As this review outlines, these cyclizations consistently occur with high efficiency, regio- and stereoselectivity. Especially appealing are annulations in which simple condensation couples two reactants *in situ* prior to the cyclization step. This strategy offers direct access to alkynyl Prins and aza-Prins annulation adducts, through cationic intermediate **9** (Scheme 33 below). The facility of these coupling/ cyclization sequences is an underappreciated feature of this reaction manifold.

These methods enable the synthesis of both oxygen- and nitrogen-containing saturated heterocycles with different ring sizes and substitution patterns. Furthermore, alkynyl Prins adducts have been used as a launching point for subsequent pericyclic reactions, including [4+2] cycloadditions and Nazarov electrocyclizations, to rapidly construct complex small molecules (Scheme 33). For example, compounds **60**, **60a**, and **61** can be prepared in one or two steps from the alkyne and carbonyl reactants in Path A, through the intermediacy of **30a**. In this way, alkynyl Prins chemistry assembles simple precursors into functional group arrays primed for additional reactions, which offers exciting opportunities for the design of novel cascade sequences.

Finally, while the alkynyl Prins reaction has served as a valuable transformation in a number of natural product syntheses, very few of these have employed the condensation/ annulation technique that is the focus of this review. This observation is surprising, given the useful carbon-carbon disconnection provided by this method and the ability to build a new ring through condensation of an aldehyde onto the pendent alcohol or amine of a complex molecule. Given all of these promising applications, alkynyl Prins cyclizations have received very little attention from the synthetic community. It is also important to note that examples of enantioselective alkynyl Prins and alkynyl aza-Prins reactions are missing from the synthetic arsenal. Therefore, this chemistry presents great opportunities for further reaction development, and should ultimately provide valuable new tools for solving problems in organic synthesis.



Scheme 33 Summation of Alkynyl Prins Annulation Methods for complex small molecule and natural product synthesis.

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References

1. (a) Arundale, E.; Mikeska, L. A. *Chem. Rev.* **1952,** 51, 505-555; (b) Snider, B. B., The Prins and Carbonyl Ene Reactions. In *Comprehensive Organic Synthesis*, Snider, B. B., Ed. Pergamon Press: Oxford, 1991; Vol. 2, pp 527-561; (c) Pastor, I. M.; Yus, M. *Curr. Org. Chem.* **2007,** 11, 925-957; (d) Pastor, I. M.; Yus, M. *Curr. Org. Chem.* **2012,** 16, 1277-1312; (e) Snider, B. B., Prins Reactions and Carbonyl, Imine, and Thiocarbonyl Ene Reactions. In *Comprehensive Organic Synthesis II. vol 2*, Elsevier: 2014; Vol. 2, pp 148-191.
2. (a) Waldmann, H. *Synthesis* **1994**, 535-551; (b) Jorgensen, K. A. *Angew. Chem., Int. Ed.* **2000,** 39, 3558-3588; (c) Liu, L.; Kaib, P. S. J.; Tap, A.; List, B. *J. Am. Chem. Soc.* **2016,** 138, 10822-10825; (d) Xie, Y.; Cheng, G.-J.; Lee, S.; Kaib, P. S. J.; Thiel, W.; List, B. *J. Am. Chem. Soc.* **2016,** 138, 14538-14541.
3. (a) Rodini, D. J.; Snider, B. B. *Tetrahedron Lett.* **1980,** 21, 3857-3860; (b) Hayashi, A.; Yamaguchi, M.; Hirama, M. *Synlett* **1995,** 1995, 195-196; (c) Viswanathan, G. S.; Li, C.-J. *Tetrahedron Lett.* **2002,** 43, 1613-1615; (d) Kabalka, G. W.; Ju, Y.; Wu, Z. *The Journal of organic chemistry* **2003,** 68, 7915-7917; (e) Rhee, J. U.; Krische, M. J. *Org. Lett.* **2005,** 7, 2493-2495; (f) Saito, A.; Umakoshi, M.; Yagyu, N.; Hanzawa, Y. *Org. Lett.* **2008,** 10, 1783-1785; (g) Park, J. Y.; Ullapu, P. R.; Choo, H.; Lee, J. K.; Min, S.-J.; Pae, A. N.; Kim, Y.; Baek, D.-J.; Cho, Y. S. *Eur. J. Org. Chem.* **2008,** 2008, 5461-5469; (h) Balamurugan, R.; Gudla, V. *Org. Lett.* **2009,** 11, 3116-3119; (i) Saito, A.; Kasai, J.; Odaira, Y.; Fukaya, H.; Hanzawa, Y. *The Journal of organic chemistry* **2009,** 74, 5644-5647; (j) Miura, K.; Yamamoto, K.; Yamanobe, A.; Ito, K.; Kinoshita, H.; Ichikawa, J.; Hosomi, A. *Chem. Lett.* **2010,** 39, 766-767; (k) Okamoto, N.; Takeda, K.; Ishikura, M.; Yanada, R. *The Journal of organic chemistry* **2011,** 76, 9139-9143; (l) Wang, N.; Cai, S.; Zhou, C.; Lu, P.; Wang, Y. *Tetrahedron* **2013,** 69, 647-652; (m) Masuyama, Y.; Takamura, W.; Suzuki, N. *Eur. J. Org. Chem.* **2013,** 2013, 8033-8038.
4. (a) Zhu, L.; Xi, Z.-G.; Lv, J.; Luo, S. *Org. Lett.* **2013,** 15, 4496-4499; (b) Manojveer, S.; Balamurugan, R. *Chem. Commun.* **2014,** 50, 9925-9928; (c) Ehle, A.; Morris, M.; Klebon, B.; Yap, G.; Watson, M. *Synlett* **2015**.
5. (a) Tanabe, Y. *Bull. Chem. Soc. Jpn.* **1994,** 67, 3309-3313; (b) Tatina, M.; Kusunuru, A. K.; Yousuf, S. K.; Mukherjee, D. *Chem. Commun.* **2013,** 49, 11409.
6. Saito, A.; Kasai, J.; Konishi, T.; Hanzawa, Y. *The Journal of organic chemistry* **2010,** 75, 6980-6982.
7. (a) Jin, T.; Yamamoto, Y. *Org. Lett.* **2007,** 9, 5259-5262; (b) Jin, T.; Yamamoto, Y. *Org. Lett.* **2008,** 10, 3137-3139; (c) Jin, T.; Yang, F.; Liu, C.; Yamamoto, Y. *Chem. Commun.* **2009**, 3533; (d) Liu, L.; Wei, L.; Zhang, J. *Adv. Synth. Catal.* **2010,** 352, 1920-1924; (e) Liu, L.-P.; Malhotra, D.; Jin, Z.; Paton, R. S.; Houk, K. N.; Hammond, G. B. *Chemistry - A European Journal* **2011,** 17, 10690-10699; (f) Lin, M.-N.; Wu, S.-H.; Yeh, M. C. P. *Adv. Synth. Catal.* **2011,** 353, 3290-3294; (g) Yeh, M. C. P.; Lin, M.-N.; Hsu, C.-H.; Liang, C.-J. *The Journal of organic chemistry* **2013,** 78, 12381-12396.
8. (a) Balog, A.; Geib, S. V.; Curran, D. P. *J. Org. Chem.* **1995,** 60, 345-352; (b) Lin, H.-Y.; Causey, R.; Garcia, G. E.; Snider, B. B. *The Journal of organic chemistry* **2012,** 77, 7143-7156.
9. (a) González-Rodríguez, C.; Escalante, L.; Varela, J. s. A.; Castedo, L.; Saá, C. *Org. Lett.* **2009,** 11, 1531-1533; (b) Yamamoto, Y.; Gridnev, I. D.; Patil, N. T.; Jin, T. *Chem. Commun.* **2009**, 5075; (c) Escalante, L.; González-Rodríguez, C.; Varela, J. s. A.; Saá, C. *Angew. Chem. Int. Ed. Engl.* **2012,** 51, 12316-12320; (d) Zheng, D.; Gong, W.; Ma, Z.; Ma, B.; Zhao, X.; Xie, Z.; Li, Y. *Tetrahedron Lett.* **2011,** 52, 314-317.
10. (a) Xu, T.; Yang, Q.; Li, D.; Dong, J.; Yu, Z.; Li, Y. *Chemistry - A European Journal* **2010,** 16, 9264-9272; (b) Xu, T.; Yu, Z.; Wang, L. *Org. Lett.* **2009,** 11, 2113-2116; (c) Takami, K.; Yorimitsu, H.; Shinokubo, H.; Matsubara, S.; Oshima, K. *Synlett* **2001,** 2001, 0293-0295.
11. It is worth noting that distinguishing between the alkynyl Prins pathway and the alkyne-carbonyl metathesis pathway can be difficult if oxygen nucleophiles are present, as both pathways may give enone products 6 upon hydrolytic workup.]
12. Kim, Y.-H.; Lee, K.-Y.; Oh, C.-Y.; Yang, J.-G.; Ham, W.-H. *Tetrahedron Lett.* **2002,** 43, 837-841.
13. Abd-El-Aziz, A. S.; Bernardin, S. *Coord. Chem. Rev.* **2000,** 203, 219-67.
14. (a) Carballo, R. M.; Valdomir, G.; Purino, M.; Martin, V. S.; Padrón, J. I. *Eur. J. Org. Chem.* **2010,** 2010, 2304-2313; (b) Subba Reddy, B. V.; Nair, P. N.; Antony, A.; Lalli, C.; Grée, R. *Eur. J. Org. Chem.* **2017,** 2017, 1805-1819.
15. Jaber, J. J.; Mitsui, K.; Rychnovsky, S. D. *The Journal of organic chemistry* **2001,** 66, 4679-4686.
16. Nikolic, N. A.; Gonda, E.; Longford, C. P. D.; Lane, N. T.; Thompson, D. W. *The Journal of organic chemistry* **1989,** 54, 2748-2751.
17. Miranda, P. O.; Díaz, D. D.; Padrón, J. I.; Bermejo, J.; Martin, V. S. *Org. Lett.* **2003,** 5, 1979-1982.
18. Miranda, P. O.; Carballo, R. M.; Martin, V. S.; Padrón, J. I. *Org. Lett.* **2009,** 11, 357-360.
19. Sabitha, G.; Reddy, K. B.; Bhikshapathi, M.; Yadav, J. S. *Tetrahedron Lett.* **2006,** 47, 2807-2810.
20. Alachouzos, G.; Frontier, A. J. *Angew. Chem. Int. Ed. Engl.* **2017,** 56, 15030-15034.
21. Holt, C.; Alachouzos, G.; Frontier, A. J. *J. Am. Chem. Soc.* **2019,** 141, 5461-5469.
22. Chavre, S. N.; Choo, H.; Lee, J. K.; Pae, A. N.; Kim, Y.; Cho, Y. S. *The Journal of organic chemistry* **2008,** 73, 7467-7471.
23. Saikia, A.; Reddy, U. *Synlett* **2010,** 2010, 1027-1032.
24. Hinkle, R. J.; Chen, Y.; Nofi, C. P.; Lewis, S. E. *Org Biomol Chem* **2017,** 15, 7584-7593.
25. Mayr, H.; Schneider, R.; Wilhelm, D.; Schleyer, P. v. R. *J. Org. Chem.* **1981,** 46, 5336-5340.
26. Hinkle, R. J.; Chen, Y.; Nofi, C. P.; Lewis, S. E. *Organic & Biomolecular Chemistry* **2017,** 15, 7584-7593.
27. Shin, C.; Chavre, S. N.; Pae, A. N.; Cha, J. H.; Koh, H. Y.; Chang, M. H.; Choi, J. H.; Cho, Y. S. *Org. Lett.* **2005,** 7, 3283-3285.
28. Please see referenced article for the full synthetic scope.
29. See Scheme 7 for clarification.
30. Dziedzic, M.; Lipner, G.; Furman, B. *Tetrahedron Lett.* **2005,** 46, 6861-6863.
31. Kato, M.; Saito, A. *Org. Lett.* **2018,** 20, 4709-4712.
32. 53 may be isolated as the corresponding keto-alcohol following hydrolytic workup at low temperatures
33. Alachouzos, G.; Frontier, A. J. *J. Am. Chem. Soc.* **2019,** 141, 118-122.

34. Kotipalli, T.; Hou, D. R. *Asian J. Org. Chem.* **2019,** 8, 1561-1571.
35. Kotipalli, T.; Hou, D.-R. *Org. Lett.* **2018,** 20, 4787-4790.
36. Li, H.; Chen, Q.; Lu, Z.; Li, A. *J. Am. Chem. Soc.* **2016,** 138, 15555-15558.
37. Overman, L. E.; Sharp, M. J. *J. Am. Chem. Soc.* **1988,** 110, 612-614.
38. Overman, L. E.; Rodriguez-Campos, I. M. *Synlett* **1992,** 1992, 995-996.
39. Overman, L. E.; Sarkar, A. K. *Tetrahedron Lett.* **1992,** 33, 4103-4106.
40. Overman, L. E.; Robinson, L. A.; Zablocki, J. *J. Am. Chem. Soc.* **1992,** 114, 368-369.
41. Lin, N.-H.; Overman, L. E.; Rabinowitz, M. H.; Robinson, L. A.; Sharp, M. J.; Zablocki, J. *J. Am. Chem. Soc.* **1996,** 118, 9062-9072.
42. Caderas, C.; Lett, R.; Overman, L. E.; Rabinowitz, M. H.; Robinson, L. A.; Sharp, M. J.; Zablocki, J. *J. Am. Chem. Soc.* **1996,** 118, 9073-9082.
43. Murata, Y.; Overman, L. E. *Heterocycles* **1996,** 42, 549-553.
44. Li, R.-H.; Ding, C.-K.; Jiang, Y.-N.; Ding, Z.-C.; An, X.-M.; Tang, H.-T.; Jing, Q.-W.; Zhan, Z.-P. *Org. Lett.* **2016,** 18, 1666-1669.
45. Mittapalli, R. R.; Guesné, S. J. J.; Parker, R. J.; Klooster, W. T.; Coles, S. J.; Skidmore, J.; Dobbs, A. P. *Org. Lett.* **2019,** 21, 350-355.
46. Gesson, J. P.; Jacquesy, J. C.; Rambaud, D. *Tetrahedron Lett.* **1992,** 33, 3633-3636.
47. Carballo, R. M.; Ramírez, M. A.; Rodríguez, M. L.; Martin, V. S.; Padrón, J. I. *Org. Lett.* **2006,** 8, 3837-3840.
48. Miranda, P. O.; Carballo, R. M.; Ramírez, M. A.; Martin, V. S.; Padrón, J. I. *Arkivoc* **2007**, 331-343.
49. Zhu, C.; Ma, S. *Angewandte Chemie (International ed. in English)* **2014,** 53, 13532-13535.
50. Hanessian, S.; Tremblay, M.; Marzi, M.; Del Valle, J. R. *The Journal of organic chemistry* **2005,** 70, 5070-5085.
51. Gharpure, S. J.; Shelke, Y. G.; Kumar, D. P. *Org. Lett.* **2015,** 17, 1926-1929.
52. Das, M.; Saikia, A. K. *The Journal of organic chemistry* **2018,** 83, 6178-6185.
53. Gharpure, S. J.; Prasath, V.; Kumar, V. *Chem. Commun.* **2015,** 51, 13623-13626.
54. Gharpure, S. J.; Prasath, V. *Journal of Chemical Sciences* **2011,** 123, 943-949.
55. Metais, E.; Overman, L. E.; Rodriguez, M. I.; Stearns, B. A. *J. Org. Chem.* **1997,** 62, 9210-9216.
56. Ma, D.; Zhong, Z.; Liu, Z.; Zhang, M.; Xu, S.; Xu, D.; Song, D.; Xie, X.; She, X. *Org. Lett.* **2016,** 18, 4328-4331.
57. Bélanger, G.; Dupuis, M.; Larouche-Gauthier, R. *J. Org. Chem.* **2012,** 77, 3215-3221.
58. Wang, Y.; Zhu, L.; Zhang, Y.; Hong, R. *Angew. Chem. Int. Ed.* **2011,** 50, 2787-2790.

Biosketches

	Alison Frontier pursued graduate studies at Columbia University with Samuel Danishefsky, earning her PhD in 1999. After postdoctoral work with Barry Trost at Stanford University, she began her independent career at the University of Rochester in 2002, and where she is now Professor of Chemistry. Her research interests focus on synthetic organic chemistry, and the pursuit of both target synthesis and the development of new cyclization methods. Students in her group are pursuing novel strategies for the synthesis of bioactive, structurally interesting natural products, as well as the development of pericyclic reactions and multistep cationic cyclization cascades. She has been especially active in the development of new variants of the Nazarov electrocyclization.

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