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One-Pot Double-Annulation Strategy for the Synthesis of Unusual Fused Bis-Heterocycles

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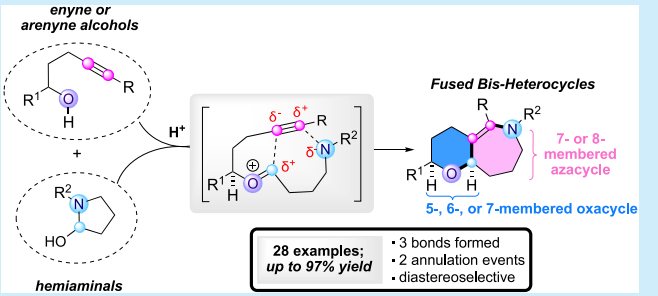
ABSTRACT: A novel metal-free double-annulation cascade for the construction of unusual fused heterocyclic systems is described. This simple protocol enables the sequential assembly of two rings in one pot from two simple precursors. Acidic conditions promote the condensation and the intramolecular alkynyl Prins reaction of an enyne or arenyne alcohol with a cyclic hemiaminal to form a five-, six-, or seven-membered oxacycle followed by a seven- or eight-membered azacycle. In this transformation, chemical complexity is rapidly generated with the formation of three new bonds (one C−O, one C−C, and one C−N) in one synthetic operation. The strategy is modular and relatively general, providing access to a series of unique fused bicyclic scaffolds.

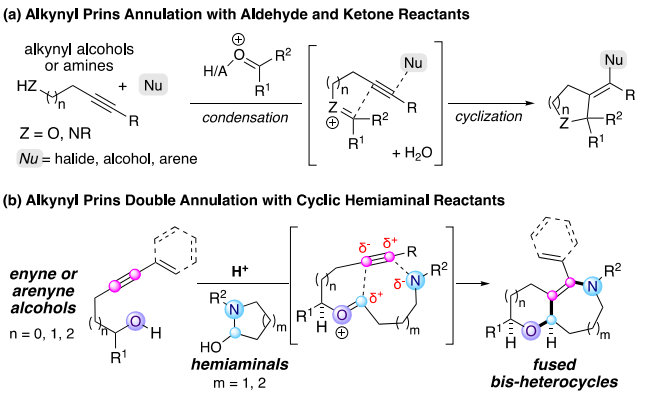


Small molecules with polycyclic structures are valuable in the context of drug discovery, especially if the ring system contains heteroatoms, a unique cyclic scaffold, and a high percentage of sp^3 stereogenic centers.[1] Numerous bioactive molecules contain seven- and eight-membered nitrogen heterocycles[2] or cyclic ethers.[3] However, these structural motifs can be difficult to access synthetically and thus represent a small percentage of compound libraries used in screening.[4] Furthermore, whereas elegant and creative approaches have been developed to build azepine and azocine rings within a carbocyclic array,[5] the assembly of fused, highly saturated heterocyclic ring systems is typically a multistep enterprise.

As evidenced by its extensive utility in the synthesis of a number of bioactive targets,[6] the alkynyl oxa-Prins and aza-Prins reactions serve as powerful and versatile methods for the preparation of complex dihydrofurans, -pyrans, -pyrrolidines, and -piperidines (Scheme 1a).[7] The acid-catalyzed condensation of alkynyl alcohols/amines with aldehydes or ketones, followed by the intramolecular cyclization of the alkyne onto an oxocarbenium/iminium intermediate and terminal nucleophilic capture, furnishes oxa- and azacycles. In recent years, arenes,[8] alcohols,[9] and halides[10] have all been demonstrated to be competent terminal nucleophiles for these cyclization reactions. Despite these advances, there is only one report describing an alkynyl Prins cyclization with a nitrogen atom as the terminal nucleophile,[11] and there are no applications that enable the *de novo* synthesis of fused bis-heterocycles.

Herein we describe a convenient, one-pot, metal-free double-annulation strategy for the rapid construction of complex heterocyclic scaffolds from simple precursors. When cyclic hemiaminals are employed as reactants in the alkynyl Prins reaction in replacement of carbonyl precursors, two rings and three new bonds are formed in a novel cationic reaction cascade, producing fused bis-heterocyclic scaffolds (Scheme 1b). Upon coupling to an alkynyl alcohol under acidic conditions, the hemiaminal moiety is transformed into a bifunctional intermediate that behaves like a pincer, reacting at one end of the alkyne as an electrophile and at the other as a

Scheme 1. Alkynyl Prins Reactions with (a) Aldehydes and Ketones (Known) and (b) Cyclic Hemiaminals in Double-Annulation Cascades (Previously Unknown)



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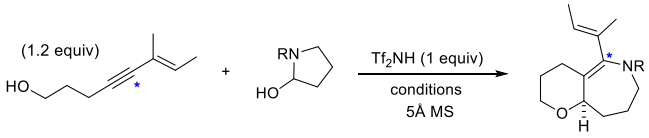
nucleophile. Novel oxacyclo[3,2-*c*]-azepine and -azocine systems are obtained from these cascades. As far as we are aware, bicyclic systems of this kind have not been previously synthesized or even described.

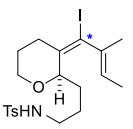
The study began when experiments in our laboratory focused on the alkynyl *halo*-Prins cyclization yielded an unexpected result.[12] The treatment of enyne **1a** with TBAI (2 equiv) and Tf_2NH (2.4 equiv) in the presence of Ts-protected hemiaminal **2** gave **3a** in 82% yield (Table 1, entry 1). The expected *halo*-Prins product (**4**) was not observed, indicating that intramolecular capture by the pendent sulfonamide is a highly favorable process and outcompetes intermolecular iodide incorporation at the distal enyne carbon (labeled * in Table 1).

Table 1. Optimization of the Double Annulation[a]

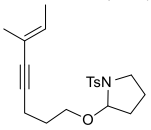


enyne **1a** hemiaminal **2**; **5-7** **3a**; **8-10a**

entry	R (hemiaminal)	solvent	product (yield)
1[b]	Ts (**2**)	$CHCl_3$	**3a** (82%)[c]
2	Ts (**2**)	$CHCl_3$	**3a** (91%)[d]
3	Boc (**5**)	DCM	**8a** (N/A)[e]
4	CBz (**6**)	DCM	**9a** (30%)
5	Ns (**7**)	DCM	**10a** (35%)
6	Ts (**2**)	MTBE	**3a** (33%)[f] + **8** (66%)
7[g]	Ts (**2**)	Et_2O	**3a** (44%)[d] + **8** (50%)
8[g]	Ts (**2**)	$CHCl_3$	**3a** (94%)
9	Ts (**2**)	DCM	**3a** (95%)
10[g]	Ts (**2**)	DCM	**3a** (97%)



iodo-Prins product (**4**)
not observed



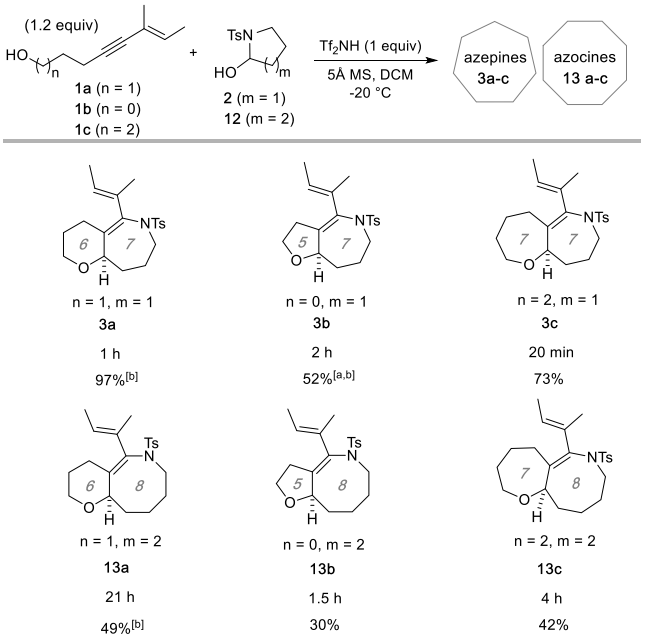
N,O-acetal (**11**)

[a]Reaction conditions: Hemiaminal (**2**, **5**−**7**) (0.20 mmol), enyne **1a** (0.24 mmol), 5 Å MS, and solvent (0.1 M) were reacted with Tf_2NH (0.2 mmol) at −20 °C for 5 h or until the consumption of *N,O*-acetal **8** was observed by TLC (see the SI). [b]2.4 equiv of Tf_2NH, 2 equiv of TBAI used. [c]**3a** was isolated as a mixture of E/Z isomers (19:1). [d]**3a** was isolated as a mixture of E/Z isomers (10:1). [e]Decomposition of reaction mixture observed. [f]**3a** isolated as a mixture of E/Z isomers (5:1). [g]0.25 equiv of Tf_2NH used.

When the halide donor is omitted, bicycle **3a** is obtained in 91% yield as a 10:1 mixture of E/Z isomers (Table 1, entry 2), and the reaction can be conducted using lower loadings of both the promoter and enyne. Further optimization with respect to the reaction conditions and the scope of the hemiaminal was carried out, as shown in Table 1. A solvent screen (refer to the SI for comprehensive screening) with Ts-protected hemiaminal **2** reveals that halogenated solvents furnish the cyclization product **3a** most efficiently (entries 1 and 7−9). The reaction is sluggish in ethereal solvents and does not readily progress beyond *N,O*-acetal **11** (entries 6 and 7). However, if **11** is resubjected to the annulation conditions in a halogenated solvent, then smooth conversion to **3a** is observed. Boc-protected hemiaminal **5** decomposes under the reaction conditions (entry 2), whereas carboxybenzyl (CBz)- and nosyl (Ns)-protected hemiaminals **6** and **7** readily participate in the annulation with **1a** but inefficiently (entries 4 and 5). The reaction can also be carried out using a substoichiometric amount of acid (0.25 equiv instead of 1.0 equiv of Tf_2NH), in either chloroform or methylene chloride to afford cyclization products in excellent yield (compare entries 8 and 10 with entry 9). The reaction conditions in entries 9 and 10 were identified as optimal.

On the basis of the Table 1 findings, we chose to focus on *N*-tosyl hemiaminal reactants. We next studied alkynyl alcohols and hemiaminals with different tether lengths (*n* and *m*; see Scheme 2).[13] The method is reasonably general, enabling the synthesis of six different types of ring systems (Scheme 2). Under standard acid conditions, the double annulation can be executed with hemiaminal **2** (*m* = 1) and enynes **1a**−**c** (*n* = 0, 1, or 2), furnishing [6,7]-, [5,7]-, and [7,7]-fused bicyclic systems **3a**, **3b**, and **3c**, respectively, in good to excellent yields.

Scheme 2. Synthesis of Fused Ring Systems with the Cyclization Protocol



[a]0.25 equiv of Tf_2NH used. [b]$CHCl_3$ used as the reaction solvent.

Annulation with six-membered hemiaminal **12** (*m* = 2) enables the assembly of oxacyclo[3,2-*c*]-azocines **13a**−**c**, although efficiency is reduced (Scheme 2). With a three-carbon tether (enyne alcohol **1a**, *n* = 1), smooth cyclization occurs, affording **13a** in 49% yield. With a shorter tether (enyne **1b**; *n* = 0), the reaction is less efficient but still delivers the [5,8]-fused system **13b** in 30% yield. A longer tether (**1c**, *n* = 2) provides access to **13c**, containing a [7,8]-fused bicyclic system, in 42% yield. As we worked to characterize these novel oxacyclo[3,2-*c*]-azepines and azocines, we discovered that all of these molecules exhibit complex conformational profiles at room temperature, judging by the ^1H NMR spectroscopic analysis (see the SI).[14]

These experiments indicate that an alkynyl alcohol with a three-carbon tether is ideal, and the five-membered Ts-protected hemiaminal (**2**) gives the best results in the double annulation. Our investigation of scope continued with testing a

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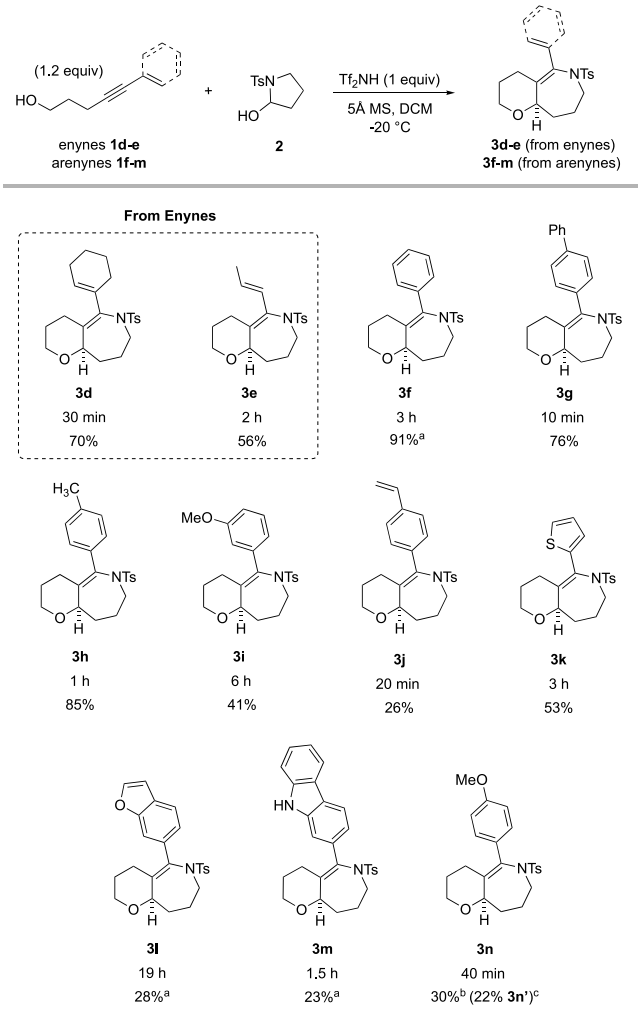
Scheme 3. Enyne and Arenyne Substrate Scope



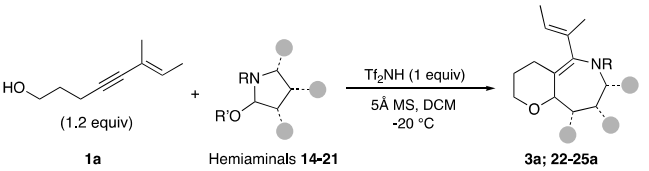
[a]0.25 equiv of Tf_2NH used. [b]2.0 equiv Tf_2NH used. [c]Dihydropyran side product observed; see the SI.

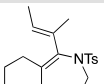
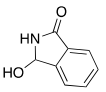
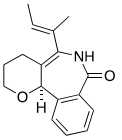
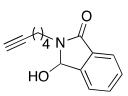
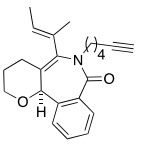
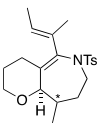
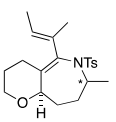
series of enyne and arenyne alcohols **1** with **2** as the hemiaminal partner (Scheme 3). Enyne partners (**1d,e**) react smoothly to provide **3d,e** in 70 and 56% yield, respectively. Arenyne alcohols **1f−m** also provide azepines **3f−m** with varying annulation efficiencies, but annulation is not successful with electron-deficient arenynes.[15] Electron-rich, *para*-methoxy-substituted arenyne **1n** produces the desired azepine **3n** in 30% yield along with an unexpected product, dihydropyran **3n′** in 22% yield.[16] Clearly, the electronic character of the arenyne partner has a strong impact on the annulation efficiency.

We next evaluated a series of cyclic hemiaminal adducts **14−21** in the annulation with enyne alcohol **1a** (Table 2).

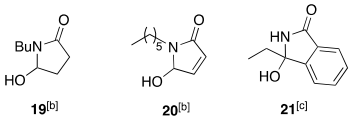
When methyl ether **14** is subjected to the reaction conditions, azepine **3a** is obtained, albeit in yields lower than its corresponding hemiaminal analogue **2** (55 vs 91%, compare Scheme 3). Phthalimide derivatives **15** (R = H) and **16** (R = alkyl) react smoothly, producing tricycles **22a** and **23a** in 52 and 72% yield, respectively. Diastereomeric mixtures of α- and γ-methylated hemiaminals **17** and **18** cyclize to afford azepine **24a** in 69% yield (1.5:1 dr) and **25a** in 65% yield (2:1 dr). Complex mixtures were obtained when *N*-alkyl-substituted succinimide **19** and maleimide derivative **20** were subjected to the reaction conditions. Lastly, whereas coupling to tetrasubstituted phthalimide **21** did not occur, neither did decomposition, as **21** was recovered intact from the reaction mixture.

Table 2. Scope and Limitations: Hemiaminal Reactants



Entry	Hemiaminal	Product	*t*	Yield [%]
1	 **14**	 **3a**	25 min	55
2	 **15**	 **22a**	7 h	52
3	 **16**	 **23a**	28 h	72
4	 **17** (1.5:1 dr)	 **24a**	20 min	69[a] (1.5:1 dr)
5	 **18** (2 : 1 dr)	 **25a**	25 min	65[a] (2:1 dr)

Other Hemiaminal Precursors



[a]0.25 equiv of Tf_2NH used. [b]Hemiaminal **20** decomposed under reaction conditions. [c]Hemiaminal **21** was not consumed under reaction conditions.

Alkynyl Prins cyclizations with secondary alcohol reactants are known to proceed with high diastereoselectivity, producing *cis*-2,6-disubstituted dihydropyrans.[17] On the basis of this precedent, we expected the double annulations to proceed diastereoselectively when using secondary alcohols in place of primary alcohols. Indeed, as illustrated in Scheme 4, subjecting racemic secondary alcohol reactants (±)-**1o−t** to optimized reaction conditions (0.25 equiv of Tf_2NH at −20 °C) delivers fused azepine systems **3o−t** in good yields and as single diastereomers in every case. The X-ray crystallographic analysis of **3q** (see the SI) confirms the cis relationship between the substituents at the two- and six-positions of the dihydropyranyl subunit. Finally, we demonstrate that enantioenriched azepines can be synthesized from nonracemic chiral secondary alcohols.

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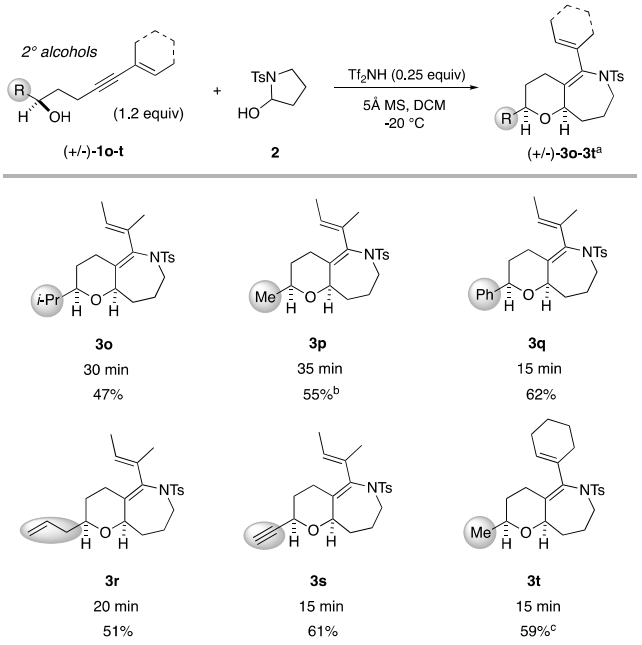
Scheme 4. Diastereoselective Cyclization of Secondary Alcohols

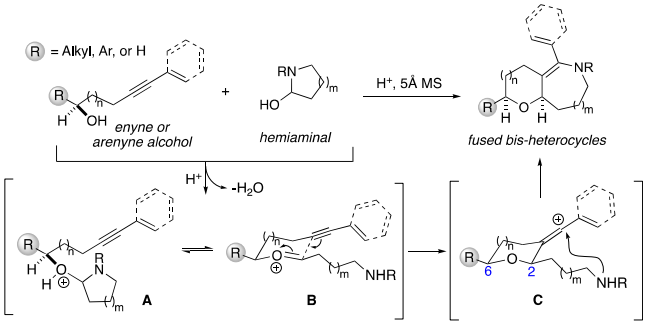


[a]Diastereoselectivity was >19:1 for all annulations: A single diastereoisomer was observed by ^{1}H NMR. [b]With reactant (*S*)-**1o** (>99:1 er), **3o** is isolated in 54% yield with >19:1 dr and >99:1 er (chiral HPLC analysis). [c]Reaction performed at −40 °C.

Specifically, the annulative coupling of (*S*)-**1p** (>99:1 er) and **2** delivers azepine (*S*)-**3p** as a single enantiomer (>99:1 er) and diastereomer (>99:1 dr) in 54% yield (Scheme 4, footnote b).

A mechanistic hypothesis for the double annulation is offered in Scheme 5. Dehydrative coupling of the enyne or arenyne alcohol with a hemiaminal under Brønsted acidic conditions presumably affords protonated *N*,*O*-acetal species **A**, in equilibrium with oxocarbenium intermediate **B**.

Scheme 5. Proposed Mechanism for the Alkynyl Prins Double-Annulation Sequence



Subsequent regio- and diastereocontrolled alkynyl Prins cyclization produces stabilized vinyl cation intermediate **C**, with 2,6-*cis* stereochemistry in the dihydropyran ring. Lastly, capture of vinyl cation **C** by the pendent amide furnishes the fused bis-heterocyclic system.

Annulation works best with enynes and arenynes within a specific reactivity window. With electron-deficient arenynes, no annulation products are observed, whereas with electron-releasing arenynes, annulation succeeds, but lower yields are observed (Scheme 3). From these observations, we can conclude that annulations proceed smoothly provided that the alkyne is both (a) nucleophilic enough to attack the tethered oxocarbenium electrophile (see intermediate **B**, Scheme 5) and (b) not so reactive that competing pathways derail the cascade cyclization process.

With regard to the hemiaminal substrate scope, cyclization seems to occur smoothly only when the C−N bond of the *N*,*O*-acetal intermediate is polarized enough to support efficient ring opening (**A** to **B**; Scheme 5). Two classes of hemiaminal partners behave well in the sequence: sulfonamide-substituted hemiaminals (**2** and **12**) and phthalimide derivatives (**15** and **16**), whereas experiments with other hemiaminal precursors **19**−**21** give either recovered starting material or decomposition under the reaction conditions.

In summary, we have developed a metal-free double-annulation protocol that provides facile access to a novel class of fused bis-heterocycles. Two simple reactants (enyne or arenyne alcohols and hemiaminals) are exposed to acidic conditions, forging two rings in one synthetic operation. The protocol is modular and convenient and rapidly generates chemical complexity while assembling a series of previously unknown oxacyclo[3,2-*c*]-azepine and -azocine scaffolds.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01351.

Experimental procedures and compound characterization data (PDF)

Accession Codes

CCDC 1997678−1997680 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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