

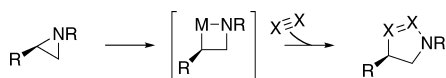
Cyclocarboamination of Alkynes with Aziridines: Synthesis of 2,3-Dihydropyrroles by a Catalyzed Formal [3 + 2] Cycloaddition

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The ability to make complex, high value synthetic targets in a step economical, practical, and green fashion depends heavily on the introduction of new reactions and new ways of thinking about bond construction that they inspire.¹ Guided by this view, we previously reported new two-, three-, and four-component cycloadditions (e.g., [5+2],^{2a} [5+2+1],^{2b} and [5+2+1+1]^{2c}) involving CC bond activation of a vinylcyclopropane by a metal catalyst and subsequent capture of the resultant metallacycle by one or more coreactants. Atom analogy suggests that similarly strained epoxides and aziridines could be analogously activated to generate metallaheterocycles from which heterocycles could be derived through coreactant insertions. The Alper group has provided support for this idea by showing that a phenyl aziridine can be converted to a β -lactam, through Rh(I) activation of a CN bond to form a metalla-azetidone followed by CO insertion.³ The corresponding alkyne insertion would represent a novel process for accessing 2,3-dihydropyrroles and, by extension, related heterocycles of value as synthetic building blocks,^{4a} therapeutic leads,^{4b} and materials.^{4c}

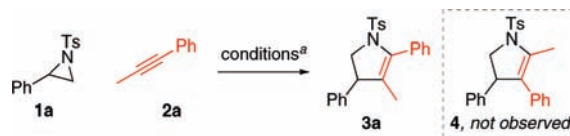


Previous methods for the synthesis of 2,3-dihydropyrroles include the ring closing metathesis of enamides,⁵ cyclization of sulfonamide anions and alkynyliodonium triflates,⁶ ring expansion of imino cyclopropanes and alkenyl aziridines,⁷ hydroamination,⁸ double *N*-alkenylation,⁹ iodoamidation,¹⁰ isomerization of 3,4-dihydropyrroles,¹¹ cycloadditions of nitro-olefins to isocyanoesters,¹² and reactions of 1-cyano or 1-nitro cyclopropyl ketones with aniline.¹³

When aziridine **1a** and alkyne **2a** were treated with a cationic Rh(I) catalyst generated from [RhCl(CO)₂]₂ and AgSbF₆, 2,3-dihydropyrrole **3a** was formed in 57% isolated yield as the only detectable regioisomer. However, a control experiment revealed that **3a** was also formed when AgSbF₆ was used without a Rh(I) catalyst (entries 1–2, Table 1). Moreover, similar results were obtained using only Sc(OTf)₃ (50%) or Zn(OTf)₂ (47%). These findings suggest a mechanism different from metal insertion, involving instead aziridine opening to a formal 1,3-dipole.¹⁴ This reactivity pattern has previously been observed with *N*-arylsulfonyl aziridines in reactions with alkenes,¹⁵ carbonyls,¹⁶ nitriles,¹⁷ and alkynyl tungsten complexes,¹⁸ but no examples of addition to unactivated alkynes such as **2a** have been reported. It is noteworthy that this Ag-catalyzed reaction avoids the use of stoichiometric BF₃·Et₂O reported for the addition of aziridines to alkenes and offers the additional benefit of being a room temperature process. The reaction can be scaled up by a factor of 20 (range studied) without significant loss in efficiency giving dihydropyrrole **3a** on a gram scale. On this scale, the concentration can be increased 2.5-fold and as little as 2 mol % catalyst gave full conversion. By slow addition of the aziridine, the amount of alkyne can be reduced to 1.5 equiv with only a minor decrease in yield (entry 4, Table 1).¹⁹

Based on these initial observations, we hypothesized that simple Bronsted acids could also catalyze this process, offering for certain

Table 1. Silver Catalyzed Cycloaddition of Aziridine **1a** to Alkyne **2a**



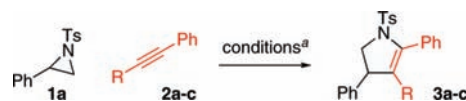
entry	catalyst (mol %)	alkyne, R (equiv)	solvent	product	isolated yield
1	AgSbF ₆ (5)	2a (3)	CH ₂ Cl ₂	3a	85%
2 ^b	AgSbF ₆ (5)	2a (3)	MeNO ₂	3a	65%
3 ^c	AgSbF ₆ (2)	2a (3)	CH ₂ Cl ₂	3a	82%, (1.2 g)
4 ^{c,d}	AgSbF ₆ (2)	2a (1.5)	CH ₂ Cl ₂	3a	73%

^a Conditions: Reaction run with 1.0 equiv of aziridine **1a** (0.1 M).

^b Reaction run at 40 °C. ^c The reaction was done on a 3.67 mM scale.

^d The aziridine (0.7 M in CH₂Cl₂) was added using a syringe pump over 8 h.

Table 2. Triflic Acid Catalyzed Cycloaddition of Aziridine **1a** to Alkynes




entry	alkyne, R (equiv)	solvent	product	isolated yield
1 ^b	2a , Me (2)	CH ₂ Cl ₂	3a	83%
2 ^c	2a , Me (3)	MeNO ₂	3a	78%
3 ^c	2b , Et (2)	CH ₂ Cl ₂	3b	89%
4 ^c	2c , Ph (2)	CH ₂ Cl ₂	3c	51%

^a Conditions: Reaction run with 1.0 equiv of aziridine **1a** (0.1 M), using 0.05 equiv of TfOH. ^b Reaction run at –15 °C. ^c Reaction run at 0 °C.

applications a metal-free alternative. Indeed, the use of triflic acid as catalyst provided **3a–c** in yields comparable to those obtained using Ag catalysis (Table 2). Both the silver and TfOH catalyzed reactions also proceed in nitromethane with only a minor drop in yield.


The Ag-catalyzed reaction accommodates a wide range of substrates, including internal and terminal aryl alkynes (Table 3). Significantly, in all cases, only one regioisomer is detected. A competition experiment involving the reaction of isosteric but electronically differentiated phenyl acetylenes with a limited amount of aziridine **1a** gave the relative product preference: 4-Me **3e** > 4-H **3d** > 4-F **3g**, consistent with capture of a cationic intermediate in the product forming step. Sterically encumbered products can also be accessed as evident from the formation of **3i**, which exhibits restricted vinyl–aryl bond rotation (~17 kcal/M) on the NMR time scale.


The reaction is not limited to aryl alkynes. It proceeds regioselectively with cyclopropylacetylene (**2k**) and 1-ethynylcyclohex-1-ene (**2l**) to give vinyl cyclopropane **3k** and diene **3l**, respectively (Table 4). Dialkyl substituted alkyne **2n** was unreactive using a Ag catalyst, but with Sc(OTf)₃, the corresponding dihydropyrrole **3n** was isolated, albeit in low yield. Basic functionalities including a methyl ether and a

Table 3. Cycloaddition between **1a** and Aryl Alkynes


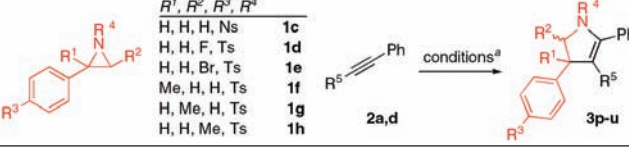
entry	alkyne, Ar, R	product	isolated yield
1	2b , Ph, Et	3b	80%
2	2d , Ph, H	3d	74%
3	2c , Ph, Ph	3c	54%
4	2e , 4-Me-Ph, H	3e	79%
5	2f , 4-Ph-Ph, H	3f	63%
6	2g , 4-F-Ph, H	3g	61%
7	2h , 1-C ₁₀ H ₇ , H	3h	53%
8	2i , 2-Me-Ph, Me	3i	41%

^a Conditions: Reaction run with 1.0 equiv of aziridine **1a** (0.1 M, CH₂Cl₂), and 3.0 equiv of alkyne using 0.05 equiv of AgSbF₆.

Table 4. Cycloaddition between **1a** and Various Alkynes


entry	alkyne, R ¹ , R ² (equiv)	product	isolated yield
1	2j , Ph, (CH ₂) ₂ OPiv, (3)	3j	72%
2	2k , <i>c</i> -Pr, H, (10)	3k	69%
3	2l ,  , H, (5)	3l	35%
4	2m , Ph, CH ₂ OMe, (3)	3m	36%
5 ^b	2n , C ₂ H ₅ , C ₂ H ₅ , (10)	3n	28%

^a Conditions: Reaction run with 1.0 equiv aziridine **1a** (0.1 M, CH₂Cl₂), using 0.05 equiv of AgSbF₆. ^b Sc(OTf)₃ (0.05 equiv) was used as catalyst.

Table 5. Cycloaddition with Various Aryl-Aziridines


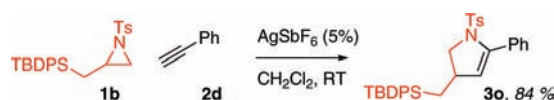
entry	aziridine	alkyne, R ⁵	product	dr	isolated yield
1	1c	2d , H	3p	-	82%
2	1d	2d , H	3q	-	84%
3	1e	2d , H	3r	-	68%
4	1f	2d , H	3s	-	71%
5	1g	2a , Me	3t	51:49	51%
6	1h	2a , Me	3u	-	65%

^a Conditions: Reaction run with 1.0 equiv of aziridine (0.1 M, CH₂Cl₂), and 3.0 equiv of alkyne using 0.05 equiv of AgSbF₆.

pivaloyl ester are compatible with Ag catalysis. The slow reaction of **2m** combined with a difficult purification accounts for the moderate yield of **3m**.

The reaction proceeds efficiently with a range of aryl aziridines (Table 5). Furthermore, *N*-nosyl-aziridine **1c** efficiently generated *N*-Ns-cycloadduct **3p**, providing options for *N*-protection and deprotection.²⁰ A carbamate analogue of **1a**, *N*-Boc 2-phenyl aziridine, was unreactive in the presence of AgSbF₆ up to 60 °C. Aryl,alkyl-substituted aziridines also participate efficiently in the reaction. 2-Methyl, 2-phenyl aziridine **1g** gave tetrasubstituted cycloadduct **3t** as an inseparable mixture of diastereomers. The homologous 2-methyl, 2-phenyl aziridine **1f** efficiently formed **3s** bearing an all-carbon quaternary stereocenter.

Finally, the process is not limited to arylaziridines. Aziridine **1b**, incorporating α -*tert*-butyl diphenylsilyl as a cation-stabilizing group,²¹

Scheme 1. Cycloaddition of α -Silyl Aziridine **1b** to **2d**

reacted with phenylacetylene under our standard conditions to form **3o** in 84% yield (Scheme 1).

In summary, a formal [3+2] cycloaddition between aziridines and nonactivated alkynes catalyzed by Lewis or Bronsted acids, to form 2,3-dihydropyrroles, is described. The reaction proceeds under mild conditions with a wide range of substrates, is scalable, uses low catalyst loadings, is highly regioselective and provides a variety of polysubstituted dihydropyrroles. Further studies are in progress.

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Supporting Information Available: Experimental details and characterization data for all new compounds. Author list for ref 4b. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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