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Multisubstituted *N*-fused heterocycles via transition metal-catalyzed cycloisomerization protocols

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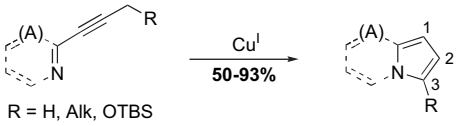
ABSTRACT

Two complementary protocols for assembly of multisubstituted *N*-fused heterocycles have been developed. It was demonstrated that 1,3-disubstituted *N*-fused heterocycles, including indolizines, pyrroloquinoxalines, and pyrrolothiazoles can easily be synthesized via an exceptionally mild and efficient method involving a novel silver-catalyzed cycloizomerization of propargyl-containing heterocycles. Alternatively, 1,2-disubstituted heterocycles can be accessed through the novel cascade transformation involving an alkyne–vinylidene isomerization with concomitant 1,2-shift of hydrogen, silyl, stannyl, or germyl groups. This mild and simple method allows for selective and highly efficient synthesis of indolizines, pyrroloisoquinolines, pyrroloquinoxalines, pyrrolopyrazines, and pyrrolothiazoles.

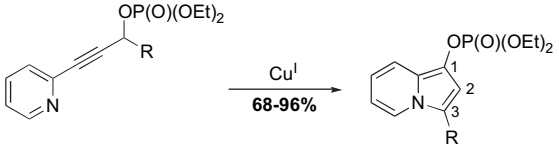
1. Introduction

Heteroaromatic molecules containing *N*-fused pyrrole unit, along with their partially or completely reduced analogues, are pharmaceutically significant scaffolds.[1,2] Structural fragments of this family are widely found in naturally occurring, as well as in synthetic biologically active molecules. Among diverse indolizine-containing biologically active molecules, the most prominent are: the potent topoisomerase I inhibitor, marine alkaloid Lamellarin D,[3,4] the anti-HIV integrase agent, Lamellarin α 20-sulfate,[5] 15-lipoxigenase,[6] and $sPLA_2$[7] inhibitors. More recently, the potent indolizine-containing cardiovascular agent[8] and anti-inflammatory CRTH2 receptor modulator[9] have also been reported. Although few routes toward fused pyrroloheterocycles exist,[10] there is a high demand for the effective and general methods for selective construction of heterocycles with alternative substitution pattern.

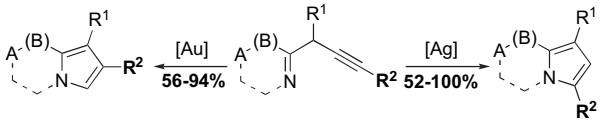
Recently, we reported two protocols for the synthesis of C-3 substituted and 1,3-disubstituted fused and non-fused pyrrole-containing heterocycles (Eqs. 1 and 2). The first approach, which operates via a copper-assisted cycloisomerization of conjugated alkynyl imines (Eq. 1), has been demonstrated to be very general and efficient for synthesis of C-3 monosubstituted heterocycles. This method, however, is not applicable for synthesis of C-2- and/or C-3-substituted heterocycles.[11] We also disclosed a set of cycloisomerization methodologies of imines and alkynyl ketones with concomitant acyloxy, phosphatyloxy, or sulfonyloxy group migration, which allows for the efficient synthesis of 1,3-disubstituted indolizines and other heterocycles (Eq. 2).[12]



R = H, Alk, OTBS (1)



(2)



(3)

R^2 = H, *Si*, *Sn*, *Ge* R^1 = OP(O)(OEt)$_2$, OTBS, OAc R^2 = H, Alk, Ar, Het, Alkenyl, Alkynyl

Aiming at the development of alternative methods toward heterocyclic units with different substitution pattern, as well as at expanding the scope of heterocyclic cores, we have developed two complementary protocols for cycloisomerization of propargyl-containing heterocycles (Eq. 3). These methods, being mild and

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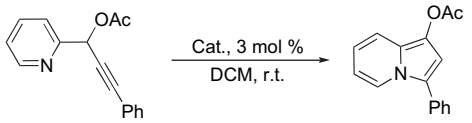
Table 1
Catalyst optimization for synthesis of 1,3-disubstituted heterocycles



1a **2a**

#	Catalyst	Reaction time	Yield, %[a]
1	CuI	3 h	77
2	*CuCl*	30 min	*83*
3	$AuCl_3$	30 min	71
4	*AuI*	3 h	*95*
5	$AlCl_3$	48 h	64[b]
6	$Sn(OTf)_2$	48 h	31
7	$Mg(OTf)_2$	48 h	52
8	$In(OTf)_2$	48 h	33
9	$PtCl_2$	48 h	41
10	$PdCl_2(PPh_3)_2$	30 min	61
11	$Pd(OAc)_2$	30 min	74
12	*$AgBF_4$*	30 min	*>99*
13	*$AgPF_6$*	30 min	*>99*
14	$AgSbF_6$	30 min	52
15	No catalyst	72 h	<20[c]

[a] GC–MS yields.
[b] 10 mol % of catalyst was used.
[c] Reaction was performed at 50 °C.

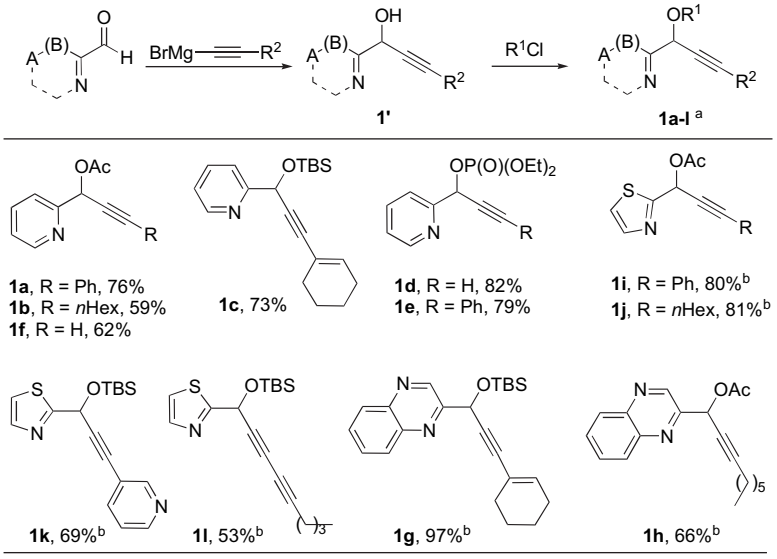
effective, allow for selective preparation of 1,3- or 1,2-disubstituted *N*-fused heterocycles. We demonstrated that in the presence of Ag, Cu or Au catalyst, 2-propagyl pyridines, quinoxalines, and thiazoles undergo smooth and facile cycloisomerization resulting in 1,3-disubstituted indolizines, pyrroloquinoxalines, and pyrrolothiazoles, in good to excellent yields.[13,14] In addition, we showed that 1,2-disubstituted heterocycles can be accessed via a novel alkyne–vinylidene isomerization cascade with concomitant 1,2-shift of various groups such as H, SiR_3, SnR_3, and even previously unknown migration of germyl group, and allows for the efficient synthesis of various fused pyrroloheterocycles functionalized at C-2 (Eq. 3).[15] Herein, we summarize our recent developments in this area, and provide a more detailed discussion of the scope and mechanisms of these novel transformations.

2. Results and discussion

2.1. Mild cycloisomerization of propargylic heterocycles

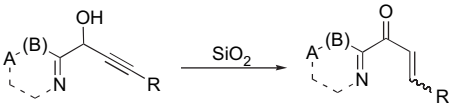
We anticipated that the triple bond of a propargyl-substituted heterocycle may be rendered reactive toward intramolecular nucleophilic attack of heterocyclic nitrogen by coordination of a π-phillic metal, such as Cu, Ag, or Au. First, we tested easily available propargylic derivative of pyridine **1a** under the previously elaborated copper/base-promoted cycloizomerization conditions.[11] It was found that **1a** underwent smooth cycloizomerization furnishing indolizine **2a** in good yield. Notably, the cycloisomerization of 'skipped' propargyl pyridine **1a** did not require elevated temperatures, as it was necessary for cycloisomerization of the conjugated substrates (Eq. 1). Thus, we were able to obtain **2** in good yield on performing the reaction at room temperature. Moreover, we found, that base is not required for this transformation, hence, it can be omitted, as well as dimethylacetamide solvent can be substituted with easier to handle dichloromethane. At the same time, the catalyst load was dropped from 30 to to 3 mol %. Employment of Cu(I) salts under these conditions resulted in a very facile conversion of **1a**, both copper iodide and chloride led to high yields of **2a**, affording 77 and 83% yields, respectively (Table 1). Gold catalysts were found to be efficient in this transformation, as well. Thus, Au(I) iodide and Au(III) chloride furnished **2a** in 71% and 95% yields, respectively, though the reaction was substantially slower. Contrary, only moderate yields of **2a** were obtained in the presence of other metals, such as Al, Sn, In, Mg, Pt, and Pd (Table 1). Recently, several reports appeared, which debated the role of eventual Brønsted acid as the true catalyst in transition metal-catalyzed transformations.[16] To address this issue, we tested this reaction in the presence of triflic acid, and found that only negligible amounts of **2a** were produced (entry 15). In contrast, switching to $AgBF_4$ and $AgPF_6$ led to virtually quantitative yields of **2a** (entries 12 and 13)!

The approach toward propargyl-substituted heterocycles **1**, including **1a** employed in our initial optimization, is general for all substrates (Scheme 1). This two-step procedure proved to be more efficient compared to the same sequence of steps performed in "one-pot". It was found, that upon column purification on silica gel, propargyl alcohols **1′** undergo facile isomerization into α,β-unsaturated ketones (Eq. 4),[17] therefore, compounds **1′** were used without additional purification in the next step. In a typical pro-



Scheme 1. Preparation of heterocycles **1**; (a) isolated yields over two steps; (b) isolated yields from **1′**.

cedure, heterocyclic aldehydes were treated with magnesium acetylides to afford the corresponding propargyl alcohols **1′**, which were further converted to acetyloxy-, phosphatyloxy-, or silyloxy-containing compounds **1** in good to very high yields (Scheme 1).

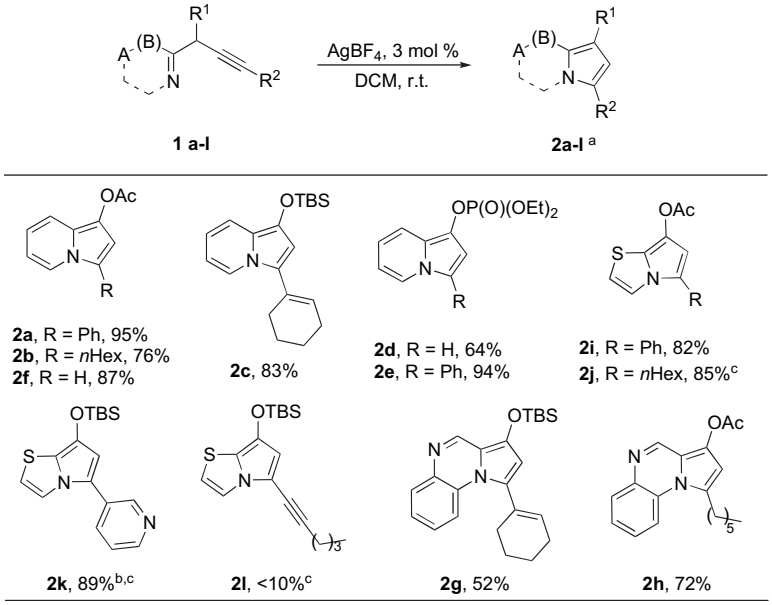


(4)

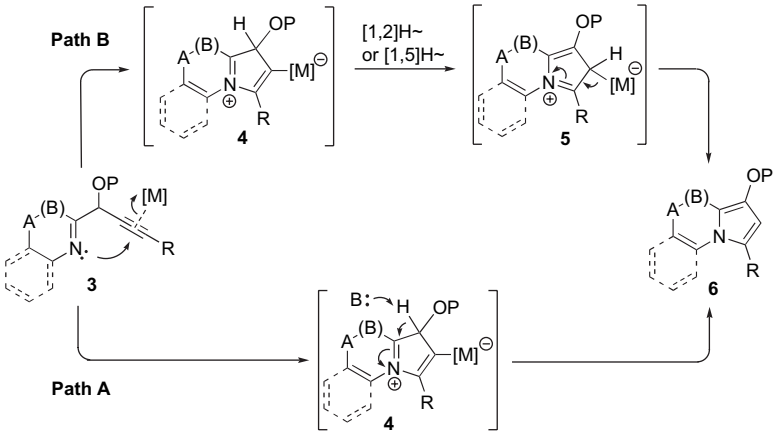
Next, the scope of this cycloisomerization has been examined. To this end, a series of propargyl-substituted heterocycles **1a**–**l** were synthesized and tested under the optimized conditions (Scheme 2). We were pleased to find, that acetyloxy-, diethylphosphatyloxy-, and O-TBS-protected propargylic substrates **1a**–**k**, possessing alkyl (**1b**, **1j**, **1l**, **1h**), aryl (**1a**, **1e**, **1i**), heteroaryl (**1k**), and alkenyl (**1c**, **1g**) substituents at the triple bond, as well as those possessing terminal alkyne moiety (**1f**, **1d**), underwent smooth cycloizomerization to give corresponding heterocycles **2a**–**k** in good to excellent yields (Scheme 2). In contrast, diyne-containing substrate **1l** furnished pyrrolothiazole **2l** in a very moderate yield. Of note, alkynyl *N*-fused heterocycles can be alternatively accessed via the recently developed direct C–H alkynylation approach.[18]

Further, the scope of this cycloisomerization with regard to the heterocyclic core was examined. It was found that disubstituted indolizines (**2a**–**f**), pyrroloquinoxalines (**2g**, **2h**), and pyrrolothiazoles (**2i**–**k**) can also be synthesized through this cycloisomerization in preparative yields (Scheme 2).

We propose the following mechanistic rationale for this novel cycloizomerization (Scheme 3). First, an intramolecular nucleophilic attack of the heterocyclic nitrogen[19] at the metal-activated-triple bond takes place (**3**) to produce zwitterionic adduct **4**, which then rearomatizes into the product **6** (Scheme 3). The rearomatization may proceed via two alternative pathways: through a proton transfer sequence (path **A**), or by a hydride shift (path **B**). In the deprotonation–protonation scenario, heterocyclic nitrogen of **3** would play a role of the base, as no other base is present in the reaction. Accordingly, we reasoned that if a deprotonation–protonation event, indeed, takes place (path **A**), a severe deuterium–hydrogen exchange in isotope-labeled substrate would be observed.[20] Conversely, if a hydride shift is the key step of the rearomatization (path **B**), a clean deuterium incorporation at C-2 of the product **6** would be expected.[21] To address this question, a deuterium-labeled propargyl pyridine **7** was subjected to the cycloisomerization conditions (Eq. 5).[22] A substantial proton–deuterium

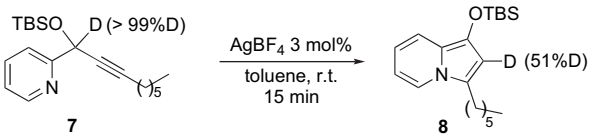


Scheme 2. Synthesis of 1,3-disubstituted *N*-fused pyrrole-containing heterocycles; (a) isolated yields; (b) 10% of catalyst was used; (c) reaction was performed at 40 °C.



Scheme 3.

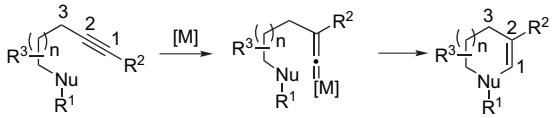
exchange (ca. 50%) was observed. It is believed that this observation strongly supports the deprotonation–protonation pathway **A**. Obviously, path **B** is in a contradiction with this result (Scheme 3).



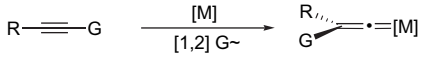
(5)

2.2. Gold-catalyzed cascade 1,2-migration/cycloisomerization

Encouraged by the successful development of cycloisomerization toward 1,3-disubstituted *N*-fused ring systems, we reasoned that propargylic heterocycles can serve as precursors for 1,2-disubstituted products as well, if *migratory* cycloisomerization[22] is achieved. Thus, we turned our attention to the development of an alternative cycloisomerization protocol, which would allow for a complementary substitution pattern at the fused pyrrole ring. Particularly, alkyne–vinylidene isomerization has drawn our attention. This rearrangement has long been recognized as a synthetically useful[23] and mechanistically interesting[24] transformation. In elegant series of works, McDonald employed this transformation as the key step in the efficient synthesis of oxygen, nitrogen, and sulfur-containing heterocycles, as well as in the synthesis of carbocycles (Eq. 6).[25] Moreover, it was exemplified by a number of research groups, that a 1,2-migration of certain groups can occur upon alkyne–vinylidene isomerization. For instance, Iwasawa and Miura[26] and Fürstner et al.[27] have shown that halogens undergo 1,2-shift in the presence of tungsten and gold complexes. Furthermore, Katayama demonstrated the Ru-catalyzed migration of silicon,[28] and Kawakami et al.[29] reported an analogous transformation with trialkyl tin (Eq. 7). Hence, we reasoned, that alkyne–vinylidene isomerization with a concurrent 1,2-shift of the groups other than hydrogen, can potentially be employed in the synthesis of heterocycles, though no such examples have been reported.

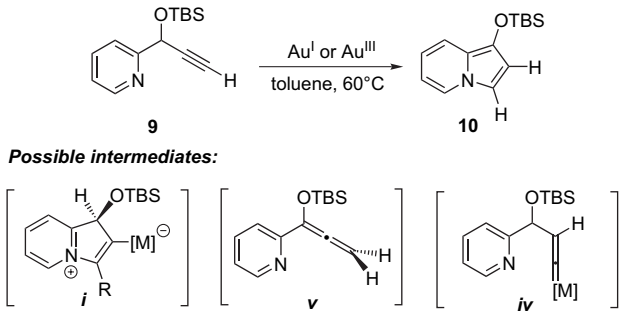


(6)



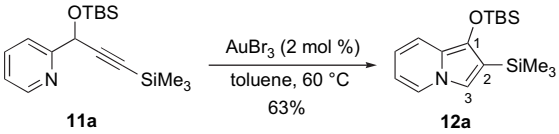
(7)

First, we turned our attention to the cycloisomerization of easily available skipped propargyl pyridine **9** (Scheme 4). Brief screening of transition metal catalysts revealed that **9**, in the presence of Au(I) or Au(III) catalyst,[30] underwent smooth cycloisomerization into C-1 monosubstituted indolizine **10**.[31] It is reasonable to propose that this transformation may operate through diverse mechanistic pathways: via a zwitterionic intermediate ***i***, similar to **4** (Scheme 1),[13] or, alternatively, through an allenyl intermediate ***v***, resulting from the formal 1,3-hydride shift.[11] Finally, the reaction may proceed via the gold–vinylidene intermediate ***iv*** (Scheme 4).



Scheme 4.

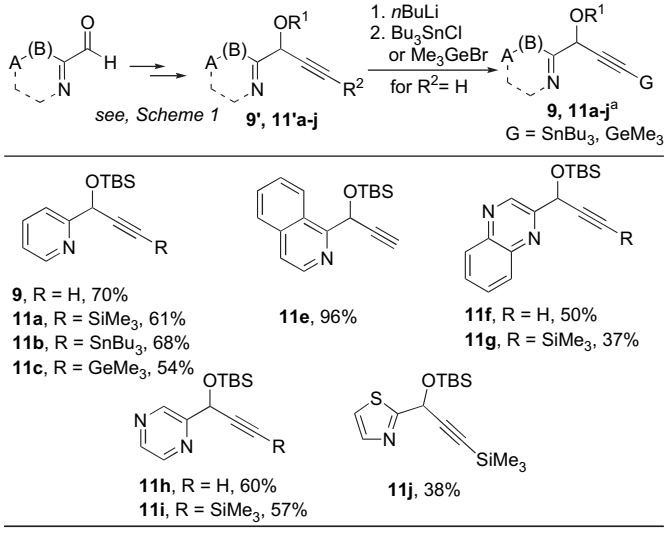
In order to elucidate if this reaction, indeed, can proceed via a vinylidene intermediate ***iv***, we examined cycloisomerization of TMS-substituted propargyl pyridine **11a** in the presence of Au catalyst. A prototropic isomerization through intermediate ***v***,[32] as well as formation of a zwitterionic intermediate ***i***, would result in the formation of C-3-silyl indolizine, whereas C-2-substituted isomer would be the expected product if the alkyne–vinylidene isomerization takes place. After initial experimentation, it was found that **11a** in the presence of $AuBr_3$ (2.0 mol %) in toluene at 50 °C underwent smooth cycloisomerization to afford indolizine **12a** with TMS group residing at the C-2 as the sole regioisomer in 63% yield (Eq. 8). Employment of Cu(I) salts led to trace amount of products, whereas various Ag, Pt, and Pd sources tested did not catalyzed this reaction at all. Of note, the C-2 position in indolizines, as well as in related fused heterocycles, has long been considered as 'unfunctionalizable', as a substituent generally has to be introduced prior to cyclization.[10]



(8)

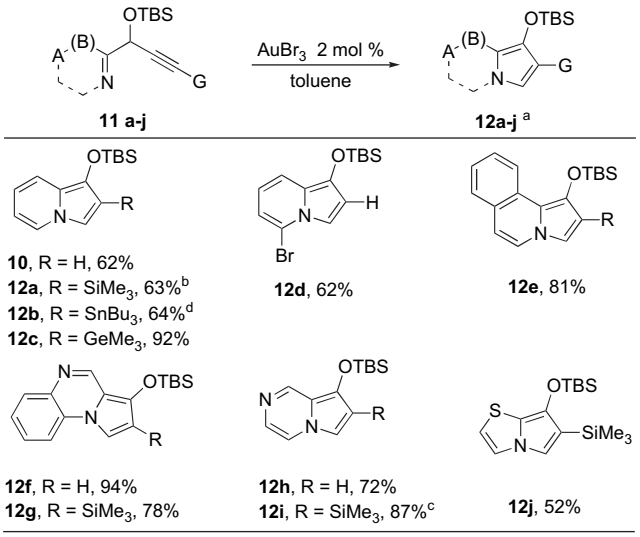
To examine the scope of this novel cascade migratory cycloisomerization, a series of substrates have been prepared (Scheme 5). Thus, H- and TMS-containing propargyl heterocycles were prepared using the protocol discussed above (Scheme 1). Whereas, stannyl and germyl groups have been installed by deprotonation of the terminal alkynes **11**′ furnishing lithium acetylides, which were quenched with stannyl and germyl halides to form compounds **11b** and **11c**, respectively (Scheme 5).

Next, migratory cycloisomerization of **11a**–**j** in the presence of gold catalysts was examined. Thus, similarly to the silyl-containing substrate **11a**, its stannyl counterpart **11b** underwent smooth cycloisomerization to afford 2-stannyl indolizine **12b**.[29] It was also found that previously unprecedented 1,2-migration of a germyl group can occur: cyclization of the corresponding propargylic



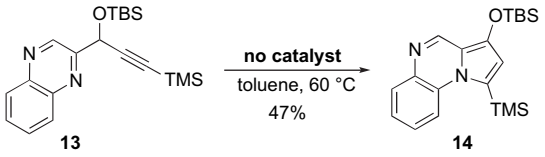
Scheme 5. (a) Isolated yields over two steps.

substrate **11c** furnished 2-germyl indolizine **12c** in excellent yield. It was also demonstrated that this protocol is efficient for construction of other related *N*-fused heterocyclic systems, such as pyrroloisoquinoline (**12e**), quinoxaline (**12f**, **12g**), pyrazine (**12h**, **12i**), and thiazole (**12j**). The corresponding substrates **11e–j** reacted smoothly, producing fused bicyclic and tricyclic molecules in good to excellent yields (Scheme 6).



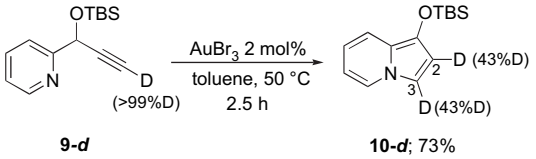
Scheme 6. Synthesis of 1,2-disubstituted *N*-fused pyrrole-containing heterocycles; (a) isolated yields; (b) NMR yield; (c) yields over two steps; (d) AuCl was used as a catalyst.

Additionally, this transformation was tested under catalyst-free conditions. It was found that in the absence of gold catalyst, propargylic substrate **13** at 60 °C underwent thermal cycloisomerization into **14**, expectably, with no 1,2-silicon shift (Eq. 9).



(9)

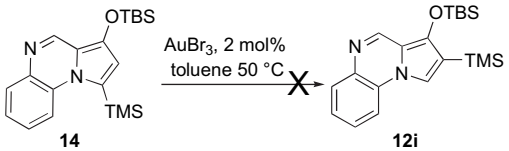
The mechanism of the gold-catalyzed cascade transformation can be rationalized as following (Scheme 7). First, alkyne **9** undergoes isomerization to form vinylidene intermediate ***iv*** (Scheme 4). A nucleophilic attack of the nitrogen lone pair at the vinylidene carbon results in the formation of zwitterion **15**, which can either undergo a sequence of 1,2-hydride shifts (path **A**), or proton transfer processes (path **B**), to give **12**. In order to verify, which pathway operates, we examined cycloisomerization of deuterium-labeled propargyl pyridine **9-*d***, under the standard cycloisomerization conditions (Eq. 10). The reaction produced indolizine **10-*d*** with equal distribution of deuterium between positions C-2 and C-3, thus strongly supporting path **A** (Scheme 7).[33] Logically, equal distribution of the deuterium between positions C-2 and C-3 is possible via the path **A** if there is no H/D kinetic isotope effect in the transformation **16** to **12**. Obviously, path **B** cannot explain the observed scrambling of deuterium at C-2.



Scheme 7.

(10)

Furthermore, we considered a possibility of Au-catalyzed 1,2-trimethylsilyl shift, which may occur after cyclization.[34] However, the test experiment with **14**, an isomer of pyrroloquinoxaline **12i**, ruled out this possibility (Eq. 11).



(11)

3. Conclusions

Two complementary protocols for the preparation of multisubstituted *N*-fused heterocycles have been developed. It was demonstrated that 1,3-disubstituted *N*-fused heterocycles, including indolizines, pyrroloquinoxalines, and pyrrolothiazoles can be easily prepared via an exceptionally mild, and efficient method involving a novel silver-catalyzed cycloizomerization of propargyl-containing heterocycles. Alternatively, 1,2-disubstituted heterocycles can be accessed through the Au-catalyzed cascade cycloisomerization of propargylic derivatives of *N*-containing heterocycles into pyrrole-fused heterocycles. This cascade transformation involves 1,2-migration of silyl, stannyl, and germyl groups. This mild and simple method allows for selective and highly efficient synthesis of indolizines, pyrroloisoquinolines, pyrroloquinoxalines, pyrrolopyrazines, and pyrrolothiazoles, not available via existing cycloisomerization techniques.

4. Experimental

4.1. General

NMR spectra were recorded on Bruker Avance DRX-500 (500 MHz) and DPX-400 (400 MHz) instruments. GC/MS analyses were performed on a Hewlett Packard Model 6890 GC interfaced to a Hewlett Packard Model 5973 mass selective detector (15 m×0.25 mm capillary column, HP-5MS). Column chromatography was carried out employing Silicycle silica gel (43–60 μm). HRMS (EI) analysis was performed on a JEOL GCmate II instrument. All manipulations with transition metal catalysts were conducted under inert atmosphere using a combination of glovebox and standard Schlenk techniques. Anhydrous toluene, tetrahydrofuran, and dichloromethane, purchased from Aldrich, were additionally purified on PureSolv PS-400-4 by Innovative Technology, Inc. purification system. All other chemicals and solvents were purchased from Aldrich, Fisher, Acros Organics, TCI, and Alfa Aesar and used without additional purification.

4.2. General procedures for Ag-catalyzed cycloisomerization

In a glovebox under nitrogen atmosphere, to a 5.0 mL Wheaton microreactor equipped with a spin vane and screw cap with a PTFE faced silicone septum was added 3–10 mol % of $AgBF_4$. The microreactor was removed from the glovebox, propargyl heterocycles **1a–l** and anhydrous toluene (0.10 M) were successively added and the mixture was stirred until completion (as monitored by TLC and/or GC/MS). The solvent was removed under reduced pressure and the residue was purified using flash-column chromatography using hexane or hexane/ethyl acetate mixture as eluent to afford pure fused pyrroloheterocycles **2a–2l**.

*4.2.1. 1-(Acetyloxy)-3-(phenyl)indolizine (**2a**)*

^{1}H NMR (500.13 MHz, $CDCl_3$) δ ppm 8.18 (1H, d, J=7.3 Hz), 7.56 (2H, dd, J=8.3, 1.3 Hz), 7.44–7.50 (2H, m), 7.32–7.37 (1H, m), 7.29 (1H, d, J=9.0 Hz), 6.83 (1H, s), 6.65 (1H, dd, J=9.2, 6.4 Hz), 6.44 (1H, dd, J=8.4, 6.4 Hz), 2.37 (3H, s); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ ppm 172.4, 131.8, 128.9, 128.1, 127.3, 123.0, 122.0, 121.6, 116.5, 116.3, 110.9, 109.5, 106.6, 20.9.

*4.2.2. 1-(Acetyloxy)-3-(hexyl)indolizine (**2b**)*

^{1}H NMR (500.13 MHz, $CDCl_3$) δ ppm 7.61 (1H, d, J=7.0 Hz), 7.22 (1H, d, J=9.1 Hz), 6.56 (1H, dd, J=9.1, 6.4 Hz), 6.53 (1H, s), 6.45 (1H, dd, J=8.5, 7.0 Hz), 2.76 (2H, d, J=7.6 Hz), 2.34 (3H, s), 1.66–1.79 (2H, m), 1.37–1.49 (2H, m), 1.29–1.37 (4H, m), 0.90 (3H, t, J=5.6 Hz); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ ppm 167.3, 121.5, 121.0, 120.9, 116.0, 114.8, 110.0, 110.0, 104.4, 31.6, 29.2, 27.1, 25.8, 22.6, 20.9, 14.1. HREIMS m/z 259.1575, calcd for $C_{16}H_{21}NO_2$ 259.1572.

*4.2.3. 1-((tert-Butyldimethyl)silanyloxy)-3-(cyclohexenyl)-indolizine (**2c**)*

^{1}H NMR (500.13 MHz, $CDCl_3$) δ ppm 8.03 (1H, d, J=7.9 Hz), 7.24 (1H, d, J=9.1 Hz), 6.35 (1H, dd, J=8.9, 6.3 Hz), 6.27 (1H, dd, J=7.0, 5.7 Hz), 6.03 (1H, t, J=3.8 Hz), 2.29–2.38 (2H, m), 2.20–2.30 (2H, m), 1.75–1.85 (2H, m), 1.65–1.75 (2H, m), 1.02 (9H, s), 0.19 (6H, s); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ ppm 132.2, 128.9, 124.9, 122.5, 121.9, 120.8, 117.0, 112.7, 109.7, 103.3, 29.1, 25.8, 25.5, 23.0, 22.2, 18.2, −4.5. HREIMS m/z 327.2010, calcd for $C_{20}H_{29}NOSi$ 327.2018.

*4.2.4. 1-(Diethylphosphatoxy)indolizine (**2d**)*

^{1}H NMR (500.13 MHz, $CDCl_3$) δ ppm 7.72 (1H, d, J=7.0 Hz), 7.39 (1H, d, J=9.1 Hz), 7.06 (1H, d, J=2.2 Hz), 6.69 (1H, d, J=2.9 Hz), 6.58 (1H, dd, J=9.4, 6.4 Hz), 6.38 (1H, dd, J=8.5, 2.2 Hz), 4.21 (4H, q, J=8.2 Hz), 1.34 (6H, t, J=7.0 Hz); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ ppm 130.8, 128.8, 124.6, 116.2, 116.0, 110.4, 108.5, 105.2, 64.5, 16.1. HREIMS m/z 269.0816, calcd for $C_{12}H_{16}NO_4P$ 269.0817.

*4.2.5. 1-(Diethylphosphatoxy)-3-(phenyl)indolizine (**2e**)*

^{1}H NMR (500.13 MHz, acetone-d_6) δ ppm 8.26 (1H, d, J=7.3 Hz), 7.55–7.63 (2H, m), 7.45–7.53 (3H, m), 7.37 (1H, d, J=6.5 Hz), 6.85 (1H, s), 6.70 (1H, dd, J=8.2, 7.3 Hz), 6.53 (1H, dd, J=7.0, 6.4 Hz), 4.22 (4H, q, J=4.0 Hz), 1.32 (6H, t, J=7.0 Hz); ^{13}C NMR (125.76 MHz, acetone-d_6) δ ppm 131.6, 129.0, 127.8, 127.3, 121.5, 121.4, 116.4, 116.3, 111.2, 105.4, 105.4, 64.2, 64.1, 15.6, 15.6. HREIMS m/z 345.1131, calcd for $C_{18}H_{20}NO_4P$ 345.1130.

*4.2.6. 1-(Acetyloxy)indolizine (**2f**)*

^{1}H NMR (500.13 MHz, $CDCl_3$) δ ppm 7.75 (1H, d, J=7.0 Hz), 7.22 (1H, d, J=9.1 Hz), 7.14 (1H, d, J=2.9 Hz), 6.72 (1H, d, J=2.9 Hz), 6.60 (1H, dd, J=9.1, 6.4 Hz), 6.41 (1H, dd, J=7.0, 5.6 Hz), 2.34 (3H, s); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ ppm 169.5, 124.8, 116.4, 115.9, 115.7, 110.4, 110.1, 109.0, 106.3, 20.9. HREIMS m/z 175.0634, calcd for $C_{10}H_9NO_2$ 175.0633.

*4.2.7. 1-(Cyclohexenyl)-3-((tert-butyldimethyl)-silanyloxy)pyrrolo[1,2]quinoxaline (**2g**)*

^{1}H NMR (500.13 MHz, $CDCl_3$) δ ppm 8.63 (1H, s), 7.97 (1H, d, J=4.7 Hz), 7.82 (1H, d, J=5.0 Hz), 7.28–7.38 (2H, m), 6.10 (1H, s), 5.99–6.08 (1H, m), 2.17–2.34 (3H, m), 1.68–1.90 (5H, m), 1.03 (9H, s), 0.25 (6H, s); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ ppm 143.7, 139.5, 137.4, 131.9, 131.8, 130.7, 129.2, 129.1, 126.3, 124.4, 116.6, 116.1, 109.5, 105.7, 28.9, 25.6, 25.5, 22.5, 21.7, 18.2, −4.5. HREIMS m/z 378.2125, calcd for $C_{23}H_{30}N_2OSi$ 378.2127.

*4.2.8. 1-(Hexyl)-3-(acetyloxy)pyrrolo[1,2]quinoxaline (**2h**)*

^{1}H NMR (500.13 MHz, $CDCl_3$) δ ppm 8.65 (1H, s), 8.08 (1H, d, J=8.2 Hz), 7.92 (1H, d, J=7.6 Hz), 7.35–7.53 (2H, m), 6.68 (1H, s), 3.08–3.33 (2H, m), 2.39 (3H, s), 1.72–1.95 (2H, m), 1.43–1.60 (2H, m), 1.27–1.44 (4H, m), 0.91 (3H, t, J=7.02 Hz); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ ppm 168.6, 142.8, 137.5, 132.8, 131.6, 130.1, 129.4, 127.0, 124.9, 116.6, 116.1, 106.4, 31.6, 30.8, 29.1, 28.1, 22.5, 21.0, 14.0. HREIMS m/z 310.1693, calcd for $C_{19}H_{22}N_2O_2$ 310.1681.

*4.2.9. 5-(Phenyl)-7-(acetyloxy)pyrrolo[1,2]thiazole (**2i**)*

^{1}H NMR (500.13 MHz, $CDCl_3$) δ ppm 7.63 (1H, d, J=4.2 Hz), 7.45–7.50 (2H, m), 7.39–7.45 (2H, m), 7.24–7.32 (1H, m), 6.63 (1H, d, J=4.2 Hz), 6.54 (1H, s), 2.31 (3H, s); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ ppm 168.1, 132.4, 128.9, 126.7, 126.2, 122.5, 119.2, 119.0, 119.0, 112.3, 105.4, 20.8. HREIMS m/z 257.0500, calcd for $C_{14}H_{11}NO_2S$ 257.0511.

*4.2.10. 5-(Hexyl)-7-(acetyloxy)pyrrolo[1,2]thiazole (**2j**)*

^{1}H NMR (500.13 MHz, $CDCl_3$) δ ppm 7.16 (1H, d, J=4.2 Hz), 6.54 (1H, d, J=4.2 Hz), 6.11 (1H, s), 2.58–2.72 (2H, m), 2.26 (3H, s), 1.57–1.67 (2H, m), 1.34–1.42 (2H, m), 1.26–1.34 (2H, m), 0.89 (3H, t, J=6.9 Hz); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ ppm 168.2, 127.7, 121.9, 117.7, 115.3, 111.3, 103.7, 31.6, 28.9, 28.3, 26.8, 22.6, 20.8, 14.1. HREIMS m/z 265.1130, calcd for $C_{14}H_{19}NO_2S$ 265.1137.

*4.2.11. 5-(3-Pyridyl)-7-((tert-butyldimethyl)-silanyloxy)pyrrolo[1,2]thiazole (**2k**)*

^{1}H NMR (500.13 MHz, $CDCl_3$) δ ppm 8.74 (1H, s), 8.44 (1H, d, J=3.7 Hz), 7.73 (1H, d, J=7.9 Hz), 7.58 (1H, d, J=4.2 Hz), 7.31 (1H, dd, J=7.8, 4.9 Hz), 6.64 (1H, d, J=3.5 Hz), 6.35 (1H, s), 1.01 (9H, s), 0.23 (6H, s); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ ppm 146.6, 146.4, 134.2, 132.4, 129.1, 123.7, 118.8, 118.4, 118.1, 111.8, 106.6, 25.7, 18.1, −4.4. HREIMS m/z 324.1660, calcd for $C_{19}H_{24}N_2OSi$ 324.1658.

4.3. General procedures for Au-catalyzed cycloisomerization

In a glovebox under nitrogen atmosphere, to a 3.0 mL Wheaton microreactor equipped with a spin vane and screw cap with a PTFE faced silicone septum was added 2 mol % of $AuBr_3$. The microreactor was removed from the glovebox, propargylic heterocycle **9** or **11a–j** and anhydrous toluene (0.5 M) were successively added and the mixture was stirred until completion (as monitored by TLC and/or GC/MS). The solvent was removed under reduced pressure and the residue was purified using flash-column chromatography using hexane as eluent to afford pure fused pyrroloheterocycles **10**, **12a–j**.

*4.3.1. 1-((tert-Butyldimethyl)silanyloxy)indolizine (**10**)*

Prepared in 62% yield. ^{1}H NMR (500.13 MHz, acetone-d_6) δ 7.87 (1H, d, J=7.0 Hz), 7.24 (1H, d, J=9.2 Hz), 7.17 (1H, d, J=1.8 Hz), 6.42 (1H, dd, J=9.0, 6.4 Hz), 6.36 (1H, d, J=2.6 Hz), 6.29 (1H, dd, J=6.7, 6.7 Hz), 1.04 (9H, s), 0.20 (6H, s); ^{13}C NMR (125.76 MHz, acetone-d_6) δ 133.1, 126.3, 122.7, 117.9, 115.1, 111.0, 109.6, 106.1, 26.9, 19.4, −3.7. HREIMS calcd for $C_{14}H_{21}NOSi$ [M^+]: 247.1392. Found: 247.1392.

*4.3.2. 1-(tert-Butyldimethyl)silanyloxy-2-(trimethylsilyl)indolizine (**12a**)*

Prepared in 63% yield for two steps. ^{1}H NMR (500.13 MHz, acetone-d_6) δ 7.84 (1H, d, J=7.2 Hz), 7.23 (1H, d, J=9.9 Hz), 7.17 (1H, s),

6.39 (1H, dd, J=10.2, 6.3 Hz), 6.25 (1H, dd, J=7.3, 6.2 Hz), 1.09 (9H, s), 0.32 (9H, s), 0.22 (6H, s); ^{13}C NMR (125.76 MHz, acetone-d_6) δ 137.1, 125.4, 122.2, 117.7, 115.1, 114.4, 110.2, 26.4, 18.8, 0.4, −3.1. HREIMS calcd for $C_{17}H_{29}NOSi_2$ [M^+]: 319.1788. Found: 319.1782.

*4.3.3. 1-(tert-Butyldimethyl)silanyloxy-2-(tributylstannyl)indolizine (**12b**)*

Prepared in 64% yield for two steps (by NMR). ^{1}H NMR (500.13 MHz, benzene-d_6) δ 7.36 (1H, d, J=9.0 Hz), 7.08 (1H, d, J=7.0 Hz), 6.80 (1H, s), 6.22 (1H, dd, J=9.5, 6.8 Hz), 5.90 (1H, dd, J=7.5, 6.4 Hz), 1.67–1.79 (6H, m), 1.42–1.51 (6H, m), 1.25–1.32 (6H, m), 1.14 (9H, s), 0.93–1.01 (9H, m), 0.21 (6H, s); ^{13}C NMR (125.76 MHz, benzene-d_6) δ 124.2, 117.2, 115.5, 114.4, 113.5, 109.2, 29.7, 27.8, 26.2, 18.4, 13.9, 10.5, 2.1, −3.7. MS m/z (relative intensity) 537 (M^+, 84), 480 ($M^+-{}^t$Bu, 80), 368 ($M^+-3{}^n$Bu, 210); $C_{26}H_{47}NOSiSn$.

*4.3.4. 1-(tert-Butyldimethyl)silanyloxy-2-(trimethylgermyl)indolizine (**12c**)*

Prepared in 92% (0.75 mmol) yield. ^{1}H NMR (500.13 MHz, acetone-d_6) δ 7.85 (1H, d, J=7.0 Hz), 7.22 (1H, d, J=9.1 Hz), 7.12 (1H, s), 6.40 (1H, dd, J=9.1, 6.4 Hz), 6.25 (1H, dd, J=7.2, 6.4 Hz), 1.08 (9H, s), 0.44 (9H, s), 0.20 (6H, s); ^{13}C NMR (125.76 MHz, acetone-d_6) δ 129.8, 125.5, 122.5, 117.7, 114.5, 114.0, 110.1, 105.6, 26.6, 0.1, −3.2. HREIMS calcd for $C_{17}H_{29}GeNOSi$ [M^+]: 365.1230. Found: 365.1244.

*4.3.5. 1-(tert-Butyldimethyl)-silanyloxy-5-bromo-indolizine (**12d**)*

Prepared in 62% yield. ^{1}H NMR (500.13 MHz, $CDCl_3$) δ 7.31 (1H, d, J=9.9 Hz), 7.28 (1H, d, J=2.3 Hz), 6.64 (1H, d, J=6.8 Hz), 6.46 (1H, d, J=2.9 Hz), 6.34 (1H, dd, J=8.9, 6.9 Hz), 1.03 (9H, s), 0.20 (6H, s); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 133.6, 123.7, 115.7, 114.2, 113.7, 113.4, 108.8, 105.4, 25.7, 18.1, −4.6. HREIMS calcd for $C_{14}H_{20}BrNOSi$ [M^+]: 325.0498. Found: 325.0501.

*4.3.6. 1-((tert-Butyldimethyl)silanyloxy)pyrrolo[2,1-a]isoquinoline (**12e**)*

Prepared in 81% yield. ^{1}H NMR (500.13 MHz, $CDCl_3$) δ 8.45 (1H, d, J=8.07 Hz), 7.46 (1H, d, J=7.3 Hz), 7.44 (1H, dd, J=10.7, 8.0 Hz), 7.42 (1H, dd, J=11.0, 8.3 Hz), 7.23 (1H, d, 5.0 Hz), 6.95 (1H, d, J=2.9 Hz), 6.50 (1H, d, J=7.3 Hz), 6.31 (1H, d, J=2.9 Hz), 1.10 (9H, s), 0.30 (6H, s); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 136.8, 127.5, 127.1, 126.6, 126.3, 124.8, 124.4, 122.4, 115.9, 110.6, 110.5, 103.9, 26.2, 18.5, −3.9. HREIMS calcd for $C_{18}H_{23}NOSi$ [M^+]: 297.1549. Found: 297.1536.

*4.3.7. 3-((tert-Butyldimethyl)-silanyloxy)pyrrolo[1,2]quinoxaline (**12f**)*

Prepared in 94% yield. ^{1}H NMR (500.13 MHz, $CDCl_3$) δ 8.68 (1H, s), 7.83 (1H, d, J=7.9 Hz), 7.7 (5H, d, J=8.0 Hz), 7.58 (5H, d, J=2.9 Hz), 7.38 (1H, dd, J=8.0, 1.6 Hz), 7.34 (1H, dd, J=7.9, 1.5 Hz), 6.32 (1H, d, J=2.9 Hz), 1.02 (9H, s), 0.22 (6H, s); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 143.6, 139.7, 136.1, 129.7, 127.6, 127.2, 124.8, 116.0, 112.8, 110.8, 109.4, 104.6, 25.6, 18.2, −4.7. HREIMS calcd for $C_{17}H_{22}N_2OSi$ [M^+]: 298.1501. Found: 298.1503.

*4.3.8. 2-(Trimethylsilyl)-3-((tert-butyldimethyl)-silanyloxy)pyrrolo[1,2]quinoxaline (**12g**)*

Prepared in 78% yield. ^{1}H NMR (500.13 MHz, $CDCl_3$) δ 8.69 (1H, s), 7.82 (1H, d, J=7.7 Hz), 7.75 (1H, d, J=8.3 Hz), 7.60 (1H, s), 7.44 (1H, d, J=8.1 Hz), 7.36 (1H, d, J=8.0 Hz), 7.26 (1H, s), 1.09 (9H, s), 0.35 (9H, s), 0.27 (6H, s); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 144.7, 144.4, 136.1, 129.8, 127.8, 127.6, 125.2, 117.0, 116.8, 115.1, 113.1, 26.2, 25.9, 0.2, −3.3. HREIMS calcd for $C_{20}H_{30}N_2OSi_2$ [M^+]: 370.1897. Found: 370.1893.

*4.3.9. 8-((tert-Butyldimethyl)silanyloxy)pyrrolo[1,2]pyrazine (**12h**)*

Prepared in 72% yield. ^{1}H NMR (500.13 MHz, $CDCl_3$) δ 8.64 (1H, s), 7.47 (1H, d, J=5.0 Hz), 7.23 (1H, d, J=5.0 Hz), 7.07 (1H, d, J=2.8 Hz), 6.30 (1H, d, J=2.6 Hz), 0.99 (9H, s), 0.18 (6H, s); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 143.6, 136.5, 126.7, 118.5, 117.4, 111.1, 105.1, 25.9, 18.3, −4.5. HREIMS calcd for $C_{13}H_{20}N_2OSi$ [M^+]: 248.1345. Found: 248.1347.

*4.3.10. 7-(Trimethylsilyl)-8-((tert-butyldimethyl)-silanyloxy)pyrrolo[1,2]pyrazine (**12i**)*

Prepared in 87% yield. ^{1}H NMR (500.13 MHz, $CDCl_3$) δ 8.63 (1H, s), 7.46 (1H, d, J=5.0 Hz), 7.18 (3H, d, J=5.0 Hz), 7.06 (1H, s), 1.05 (9H, s), 0.30 (9H, s), 0.23 (6H, s); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 144.0, 140.8, 126.2, 118.7, 117.0, 116.6, 115.2, 25.9, 18.3, −0.1, −3.6. HREIMS calcd for $C_{16}H_{28}N_2OSi_2$ [M^+]: 320.1740. Found: 320.1741.

*4.3.11. 6-(Trimethylsilyl)-7-((tert-butyldimethyl)-silanyloxy)pyrrolo[1,2]thiazole (**12j**)*

Prepared in 56% yield. ^{1}H NMR (500.13 MHz, $CDCl_3$) δ 7.11 (1H, d, J=4.2 Hz), 6.86 (1H, s), 6.44 (1H, d, J=4.2 Hz), 1.02 (9H, s), 0.27 (6H, s), 0.26 (9H, s); ^{13}C NMR (125.76 MHz, $CDCl_3$), δ 137.2, 119.5, 117.1, 113.4, 112.3, 110.6, 25.9, 25.7, 18.0, −0.2, −3.4. HREIMS calcd for $C_{15}H_{27}NOSSi_2$ [M^+]: 325.1352. Found: 325.1347.

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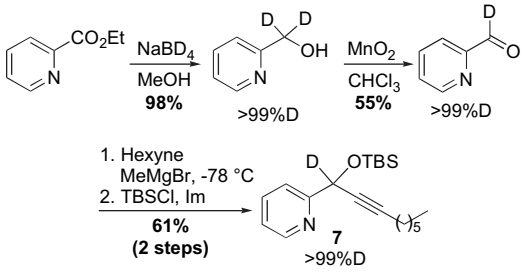
22. Deuterium-labeled propargylic substrate **7** was prepared via the following sequence of steps.



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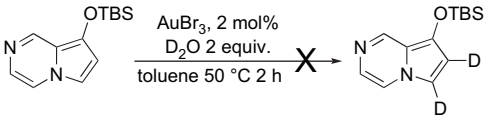
31. Au(I) is most likely the active catalyst. In the case of employment of $AuBr_3$ as a precatalyst, the latter can be reduced into Au(I) species via various redox processes. See, Ref. 30b.
32. For discussion on Au-catalyzed propargyl–allenyl prototropic isomerization, see Ref. 10c.
33. Control experiment indicated no proton–deuterium scrambling in the cyclized product.



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