JOC The Journal of Organic Chemistry

Article

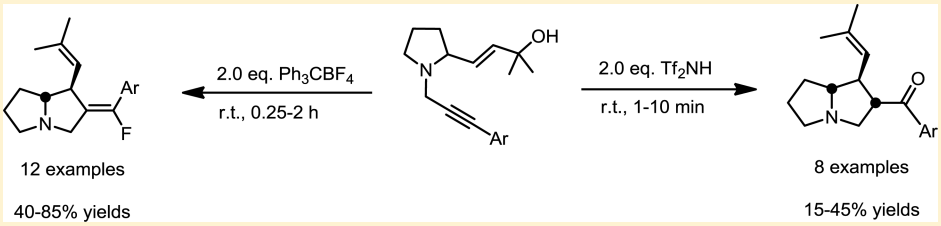
pubs.acs.org/joc

Diastereoselective Synthesis of Fluorine-Containing Pyrrolizidines via Triphenylcarbenium Tetrafluoroborate-Promoted Carbofluorination of *N*-3-Arylpropargylpyrrolidine-Tethered Tertiary Allylic Alcohols

Ming-Chang P. Yeh,* Hsiao-Feng Chen, Yu-Ya Huang, and Yu-Ting Weng

Department of Chemistry, National Taiwan Normal University, 88 Ding-Jou Road, Section 4, Taipei 11677, Taiwan, Republic of China

Supporting Information



ABSTRACT: Inexpensive and air stable triphenylcarbenium tetrafluoroborate efficiently promoted the carbofluorination of *N*-arylpropargylpyrrolidines bearing a tertiary allylic alcohol tether at the 2-position of the pyrrolidine ring to provide 1-isobutenyl-2-(fluoro(phenyl)methylenylhexahydro-1*H*-pyrrolizidines in a stereoselective fashion. When subjected to bis(trifluoromethane)-sulfonamide, the same substrates underwent cycloisomerization reaction within minutes to generate 1-isobutenyl-2-benzoylhexahydro-1*H*-pyrrolizidines with excellent stereoselectivity.

INTRODUCTION

The pyrrolizidine ring skeleton is present in a large number of naturally occurring nacine bases, many of which possess notable biological and pharmaceutical properties.[1] Many synthetic strategies have been developed for the construction of the pyrrolizidine ring scaffold including the intramolecular alkylation of *N*-chloroethylpyrrolidines with α,β-unsaturated esters,[2] the *N*-alkylation of pyrrolidines with alkyltosylates,[3] or alkylesters,[4] the radical cyclization reaction of *N*-allylstannane-pyrrolidine-2,5-diones,[5] the reaction of α-acylamino radicals with alkenyl tethers,[6] the SmI_2-mediated intramolecular ring closure of alkyl bromides with ynamides,[7] the Pd(II)-catalyzed intramolecular 1,2-aminoalkylation of conjugated 1,3-dienes,[8] the 1,3-dipolar cycloaddition of azomethane ylides with acrylates,[9] the [3 + 2]-cycloadditions of cyclic nitrones with alkenes[10] and the gold-catalyzed [3 + 2]-cycloaddition-enamine cyclization of iminoesters with acetylenes and dipolarophiles.[11] Encouraged by the diverse biological activities of pyrrolizidine derivatives and to expand our recently developed Lewis acid-promoted carbohalogenation reactions of alkynes with allylic alcohols,[12] we envisioned that *N*-3-arylpropargylpyrrolidine containing a tertiary allylic alcohol tether at the 2-position of the pyrrolidine ring would be a good candidate for a Lewis acid-assisted carbohalogenation reaction, which may lead to the formation of halogenated hexahydro-1*H*-pyrrolizidine derivatives. Herein, we report that triphenylcarbenium tetrafluoroborate (Ph_3CBF_4) features both Lewis acid character and the nucleophilic fluoride source for the carbofluorination of *N*-3-arylpropargylpyrrolidine-tethered tertiary allylic alcohols. It was suggested that *anti*-addition of a fluoride and the transient allylic carbonium ion, generated in situ from the reaction of tertiary allylic alcohols with the trityl cation, across the acetylene afforded the fluorinated pyrrolizidine derivatives in a stereoselective manner and in good yield. Furthermore, bis(trifluoromethane)sulfonamide (Tf_2NH) successfully performed the cycloisomerization reaction of the substrates in minutes, providing 1-isobutenyl-2-aroylhexahydro-1*H*-pyrrolizine derivatives with excellent stereoselectivity.

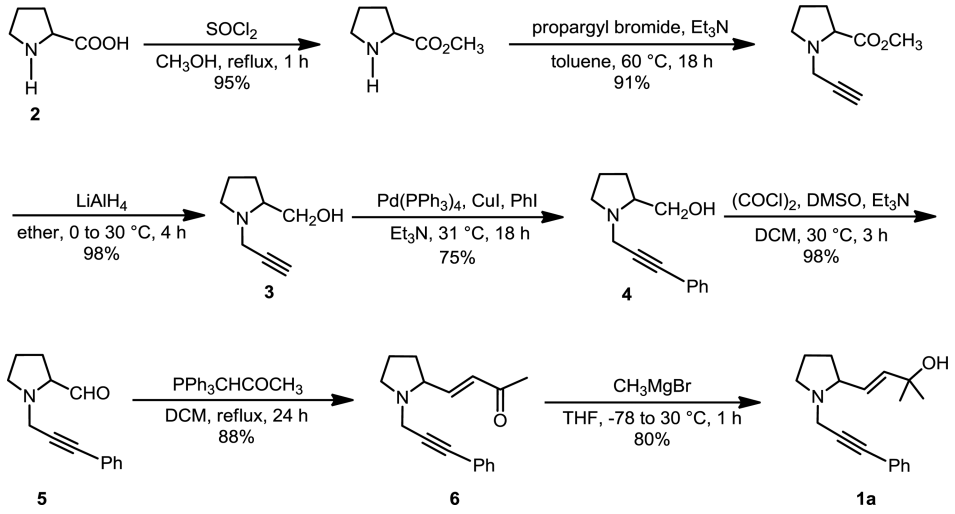
RESULTS AND DISCUSSION

The synthetic route for the preparation of the starting substrate **1a** is depicted in Scheme 1. Starting from commercial (±)-proline **2**, an esterification and propargylation sequence, followed by reduction of the resulting ester group with $LiAlH_4$ gave the corresponding alcohol **3** in 85% yield over the three steps. Following the Sonogashira protocol,[13] coupling the terminal alkyne of **3** with phenyl iodide afforded the coupling product **4** in 75% isolated yield. Swern oxidation of **4** provided the aldehyde **5**,[14] which was used for the next step without further purification. Next, a Wittig reaction employing 1-(triphenylphosphoranylidene)propan-2-one with **5**,[15] followed by addition of the methyl Grignard reagent to the resulting

Received: August 31, 2015

DOI: 10.1021/acs.joc.5b02025
J. Org. Chem. XXXX, XXX, XXX−XXX

Scheme 1. Synthesis of Starting Substrate 1a

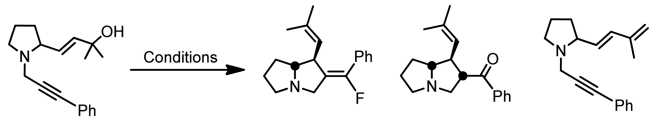


ketone furnished the desired starting substrate **1a** in 70% yield over the last two steps.

Initially, various Lewis acids were screened for their ability to promote the carbochlorination of **1a**. Chlorine-containing Lewis acids, including $FeCl_3$, $InCl_3$, $SnCl_2$, $AlCl_3$, and $TiCl_4$, failed to assist the carbochlorination reaction with **1a**. Delightfully, the use of 2.0 equiv of $BF_3{\cdot}OEt_2$ in 0.1 M of dichloromethane (DCM) with **1a** completed the carbofluorination reaction in 10 min, generating 1-isobutenyl-2-(fluoro(phenyl)methylenylhexahydro-1*H*-pyrrolizidine (**7a**) in 46% yield together with the cycloisomerization product 1-isobutenyl-2-benzoyl-hexahydro-1*H*-pyrrolizidine (**8a**) in 17% yield and a trace amount of the dehydration product **9a** (Table 1, entry 1). Importantly, both compounds **7a** and **8a** were isolated as the only stereomer. The relative stereochemistry of **7a** and **8a** as depicted were determined on the basis of NOESY experiments (see Supporting Information for details). As shown in Figure 1, for **7a**, the *cis* relationship between H-8 and the isobutenyl group was established since the NOE correlation is observed between H-8 and H-9. For **8a**, the NOE correlations between H-8 and H-9, and between H-8 and H-2 supports the *trans* relationship between H-8 and H-1 and the *cis* relationship between H-8 and H-2. In the transformation of **1a** into **7a**, $BF_3{\cdot}OEt_2$ acts as both the Lewis acid character and the nucleophilic fluoride source in the carbofluorination of the acetylene.[16] The relative stereochemistry may derive from *anti*-addition of the transient allylic carbonium ion from the less hindered *β*-face and the fluoride source across the acetylene. On the other hand, the minor product **8a** may arise from addition of BF_2OH and the allylic carbonium ion across the acetylene followed by an aqueous workup (Scheme 2).

Next, substrate **1a** was subjected to fluorine-containing Lewis acids, including $BF_3{\cdot}OEt_2$, Ph_3CBF_4, and Ph_3CPF_6, to search for optimal conditions for the carbofluorination reaction. The results are summarized in Table 1. Decreasing the concentration of **1a** to 0.01 or 0.0025 M in DCM with $BF_3{\cdot}OEt_2$ did not affect the cyclization reaction significantly and the desired product **7a** was isolated in 47% and 54% yield, respectively, (Table 1, entries 2 and 3). Switching the solvent from DCM to CH_3CN failed to provide the desired fluorination product **7a** and the dehydration product **9a** was isolated in 20% yield (Table 1, entry 4). Changing the Lewis acid and the fluoride source to Ph_3CBF_4 (2.0 equiv) in DCM at 0.1 M concentration,

Table 1. Optimizing of Reaction Conditions in the Carbofluorination of 1a with Fluorine-Containing Lewis Acids



1a 7a 8a 9a

					yield (%)[a]		
entry	reagent	loading (equiv)	solvent	time	7a	8a	9a
1	$BF_3{\cdot}OEt_2$	2	0.1 M DCM	10 min	46	17	1
2	$BF_3{\cdot}OEt_2$	2	0.01 M DCM	5 min	47	24	8
3	$BF_3{\cdot}OEt_2$	2	0.0025 M DCM	30 min	54	–	3
4	$BF_3{\cdot}OEt_2$	2	0.1 M CH_3CN	24 h	–	–	20
5	Ph_3CBF_4	2	0.1 M DCM	5 min	41	12	–
6	Ph_3CBF_4	2	0.01 M DCM	25 min	85	8	5
7[b]	Ph_3CBF_4	2	0.01 M DCM	6.5 h	43	8	2
8	Ph_3CBF_4	2	0.0025 M DCM	2.5 h	79	13	–
9	Ph_3CBF_4	1.2	0.01 M DCM	24 h	52	19	7
10	Ph_3CPF_6	2	0.0025 M DCM	20 h	–	4	30

[a]Yields obtained from column chromatography over silica gel. [b]The reaction was performed at 0 °C.

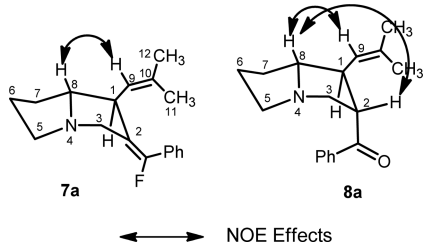
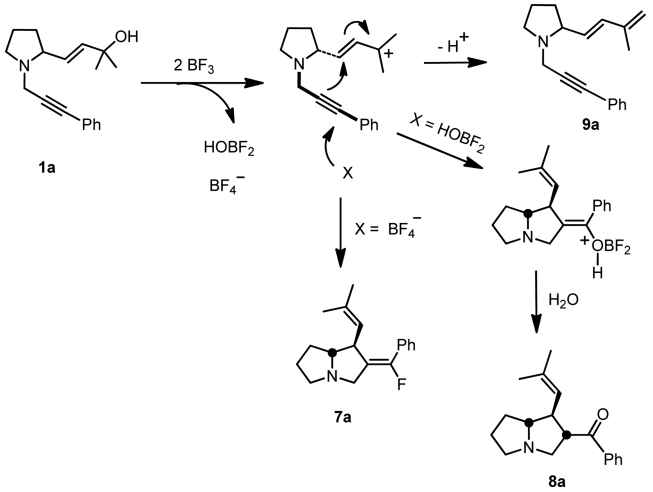


Figure 1. NOE interactions for **7a** and **8a**.

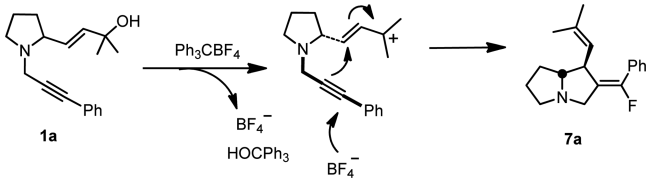
DOI: 10.1021/acs.joc.5b02025
J. Org. Chem. XXXX, XXX, XXX−XXX

Scheme 2. Suggested Reaction Paths for the Formation of 7a, 8a, and 9a from 1a with BF_3·OEt_2



1a gave **7a** and **8a** in 5 min and in 41 and 12% yield, respectively (Table 1, entry 5). Delightly, the use of 2.0 equiv of Ph_3CBF_4 at a concentration of 0.01 M in DCM completed the reaction within 30 min and afforded **7a** in 85% yield and the side products **8a** and **9a** in 8 and 5% yield, respectively (Table 1, entry 6). Conducting the reaction at 0 °C (Table 1, entry 7) or lowering the concentration of **1a** (Table 1, entry 8) did not improve the yield of **7a**. Furthermore, the use of 1.2 equiv of Ph_3CBF_4 at 0.01 M in DCM required a longer reaction time (24 h) to afford a 52% yield of the desired product **7a** (Table 1, entry 9). Unfortunately, switching the trityl cation source from Ph_3CBF_4 to Ph_3CPF_6 (Table 1, entry 10) gave predominantly the dehydration product **9a** in 30% yield and a trace amount of the cycloisomerization product **8a**. Therefore, the use of Ph_3CBF_4 (2.0 equiv) with **1a** at 0.01 M concentration in DCM under nitrogen (Table 1, entry 5) was the most efficient and was employed as the standard reaction conditions. It is important to state that reports on the use of the trityl cation (Ph_3C^+) to promote organic transformations have been limited to Mukaiyama aldol reactions,[17] Diels–Alder reactions,[18] Michael additions,[19] hydride abstractions from metal-alkene and -diene complexes,[20] dehydrogenation of polycyclic hydroaromatics,[21] and deprotection of ketone acetals.[22] Our current study reveals that Ph_3CBF_4 can behave as both the Lewis acid and the fluoride source in the carbofluorination of the *N*-3-arylpropargylpyrrolidine-tethered tertiary allylic alcohols, providing the fluorine-containing pyrrolizidine derivatives under mild reaction conditions in good yield and with high stereoselectivity (Scheme 3). Moreover, the use of the stable Ph_3CBF_4 powder is operationally easier than our previous method employing BF_3·OEt_2 for the carbofluorinaton of enynols.[12b] Recently, various fluorine-containing reagents including tetrafluoroborates been used both as a promotor

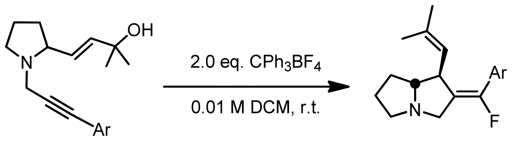
Scheme 3. Ph_3CBF_4-Promoted Formation of 7a from 1a



and the nucleophilic fluoride source in numerous organic transformations have been extensively studied.[23] It is worthy to mention that the fluorinated pyrrolizidines may have potential applications in medicinal chemistry since many monofluoroalkenes play an important role in pharmaceuticals.[24]

With optimized reaction conditions in hand, the scope of the carbofluorination reaction was investigated employing various aryl substituted alkynes using the standard reaction conditions. As can be seen from Table 2, substrates **1a–d** having an

Table 2. Ph_3CBF_4-Promoted Carbofluorination of 1



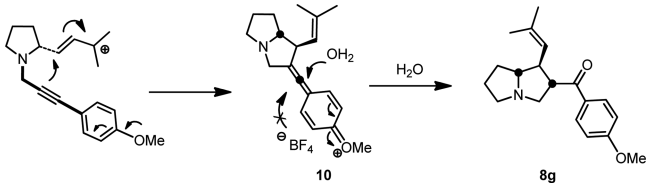
entry	Ar	substrate	time	product	yield (%)[a]
1	phenyl	**1a**	25 min	**7a**	85
2	3-methylphenyl	**1b**	30 min	**7b**	71
3	4-methylphenyl	**1c**	45 min	**7c**	50
4	4-biphenyl	**1d**	40 min	**7d**	40
5	1-naphthyl	**1e**	2.0 h	–	–[b]
6	3-methoxyphenyl	**1f**	10 min	**7f**	52
7	4-methoxyphenyl	**1g**	25 min	–	–[c]
8	3-trifluoromethylphenyl	**1h**	2.0 h	**7h**	55
9	3-carbethoxyphenyl	**1i**	1.0 h	**7i**	52
10	4-carbethoxyphenyl	**1j**	1.5 h	**7j**	48
11	3-nitrophenyl	**1k**	1.5 h	**7k**	50
12	4-nitrophenyl	**1l**	1 h	**7l**	58
13	4-chlorophenyl	**1m**	20 min	**7m**	60
14	4-bromophenyl	**1n**	1.0 h	**7n**	66
15	2-bromophenyl	**1o**	30 min	–	–[d]
16	2-nitrophenyl	**1p**	4.5 h	–	–
17	2-carbethoxyphenyl	**1q**	2 h	–	–[e]
18	3-thienyl	**1r**	40 min	**7r**	14

[a]Isolated yields obtained from column chromatography over silica gel. [b]Ketone **8e** was isolated in 40% yield. [c]Ketone **8g** was isolated in 52% yield. [d]Ketone **8o** was Isolated in 14% yield. [e]Lactone **11** was isolated in 46% yield.

electron-neutral aryl group on the acetylene afforded pyrrolizidine derivatives **7a–d** in 40–85% yields within a period of 45 min (Table 2, entries 1–4). Substrate **1e**, bearing a naphthyl-substituted alkyne, failed to produce any fluorinated pyrrolizidine but instead the cycloisomerization product **8e** was isolated as the major product in 40% yield (Table 2, entry 5). While **1f**, with an electron-donating methoxy group at the 3-position of the phenyl ring, afforded the desired product **7f** in 10 min in 52% yield (Table 2, entry 6), compound **1g**, with a C4-methoxyphenyl-substituted alkyne, cycloisomerized to the corresponding ketone **8g** in 52% yield and none of the desired fluorination product was isolated (Table 2, entry 7). The formation of **8g** from **1g** was suggested in Scheme 4. The initial formed tertiary allylic carbonium ion was attacked by the electron-rich (*p*-methoxyphenyl)alkynyl group to give the allenyl intermediate **10**. Addition of the tetrafluoroborate anion at the allenyl carbon center failed. Hydrolysis of the intermediate **10** provided ketone **8g**. Substrates possessing an electron withdrawing group, including a trifluoromethyl, ester, and nitro group on the phenyl ring (**1h–l**), were also effective in the carbofluorination and generated the fluorinated

DOI: 10.1021/acs.joc.5b02025
J. Org. Chem. XXXX, XXX, XXX–XXX

Scheme 4. Mechanism for the Formation of 8g from 1g



pyrrolizidines (**7h–l**) in 48–58% yields (Table 2, entries 8–12). Moreover, the presence of a halogen atom at the 4-position of the phenyl ring, **1m** and **1n**, did not influence the pyrrolizidines formation and the desired products, **7m** and **7n**, were isolated in 60 and 66% yield, respectively (Table 2, entries 13–14). Unfortunately, a substituent at the 2-position of the phenyl ring, (**1o–p**), inhibited the carbofluorination reaction (Table 2, entries 15–16). Compound **1o** gave the cycloisomerization product **8o** in only 14% isolated yield and **1p** gave a mixture of unidentified compounds. Apparently, the presence of a substituent at the C-2 position of the phenyl ring prevents BF_4^- from attacking at the acetylene carbon. This steric effect is consistent with that of the pyrrolidine-tethered naphthyl-substituted alkyne **1e**, which did not produce any desired fluorinated pyrrolizidine (Table 2, entry 5). Interestingly, substrate **1q** (Figure 2) bearing a carbethoxy group at the

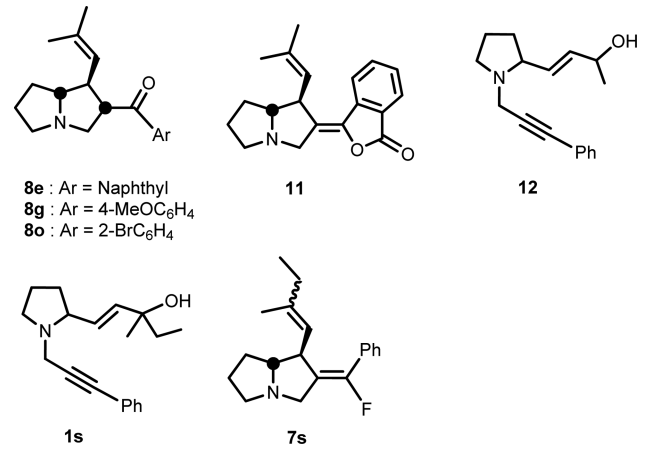
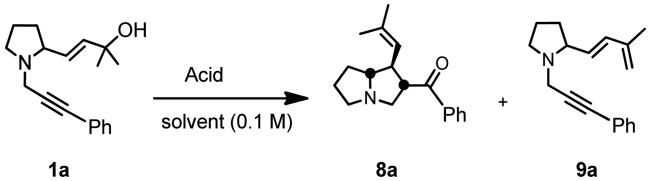


Figure 2. Structures of **8e**, **8g**, **8o**, **11–12**, **1s**, and **7s**.

2-position of the phenyl group afforded the azabicyclic lactone **11** in 46% isolated yield under the standard reaction conditions. In this process, *anti*-addition of the transient allylic carbonium ion and the proximal ester group across the acetylene afford the pyrrolizidine-tethered lactone **11**. The 3-thienyl-substituted alkyne **1r** also gave the desired cyclized product **7r**, albeit in only 14% yield (Table 2, entry 18). Attempts to carry out the carbofluorination of substrate **12** (Figure 2), bearing a secondary allyic alcohol, failed. Instead the oxidation product ketone **6** (Scheme 1) was isolated in 80% yield. The formation of the ketone from **12** is consistent with those of literature reports on oxidation of secondary allylic alcohols with trityl cations.[25] Unfortunately, attempts to synthesize a substrate bearing an *n*-butyl-substituted alkyne failed. Moreover, the tertiary allylic alcohol **1s**, substituted with a methyl and an ethyl group at the carbinol carbon, was subjected to the standard reaction conditions to give **7s** in 60% yield as a mixture of *Z* and *E* isomers (Figure 2).

Inspired by the work of Yamamoto on the TfOH-catalyzed cycloisomerization reaction of alkyne-tetherd tertiary alcohols,[26] we then concentrated our effort on searching for a suitable Brønsted acid and optimal reaction conditions in obtaining ketone **8a** from **1a**. The screening of the cycloisomerization reaction was carried out by treating **1a** with TfOH and Tf_2NH. The results are summarized in Table 3.

Table 3. Optimization of Cycloisomerization of 1a to 8a



1a **8a** **9a**

					yield (%)[a]	
entry	acid (equiv)	solvent	temp. (°C)	time	**8a**	**9a**
1	TfOH (0.1)	DCE	50	24 h	–	–
2	TfOH (0.1)	DCM	28	24 h	–	–
3	TfOH (2.0)	DCM	28	10 min	–	10
4	Tf_2NH (2.0)	DCM	28	1 min	45	7
5	Tf_2NH (1.2)	DCM	28	6 h	39	7
6	Tf_2NH (3.0)	DCM	28	1 min	29	–
7	Tf_2NH (2.0)	DCE	28	50 min	48	9
8[b]	Tf_2NH (2.0)	DCM	28	24 h	21	19
9	Tf_2NH (2.0)	DCM	0	5 min	32	5
10	Tf_2NH (2.0)	DCM	40	1 min	35	–
11	Tf_2NH (2.0)	Ether	28	10 h	8	72
12	Tf_2NH (2.0)	THF	28	40 h	–	58
13	Tf_2NH (2.0)	Toluene	28	24 h	–	–

[a]Yield obtained from column chromatography over silica gel. [b]Three drops of water were added.

Substrate **1a** was first treated with TfOH employing Yamamoto's protocol (0.1 equiv of TfOH in DCE), at 50 and 28 °C. After 24 h, only starting material **1a** was recovered without any evidence for the formation of **8a** at both temperatures (Table 3, entries 1–2). Increasing the amount of TfOH up to 2.0 equiv, **1a** gave the dehydration product **9a** in 10% yield (Table 3, entry 3). While employing 2.0 equiv of Tf_2NH in DCM delivered **8a** instantaneously in 45% isolated yield (Table 1, entry 4), the use of 1.2 equiv of Tf_2NH required longer reaction time (6 h) and gave only a 39% yield of **8a** (Table 3, entry 5). In both cases, the dehydration product **9a** was isolated in 7% yield in each case. It is important to state that, in this simple operation, three carbon stereocenters of **8a** are created; however, only the single stereoisomer shown was isolated. Moreover, the relative stereochemistry does not erode in this high acidic condition. Increasing Tf_2NH loading (Table 3 entry 6), changing the solvent system to dicholoroethane (DCE) (Table 3, entry 7) or addition of a small amount of water (Table 3, entry 8) into the reaction mixture did not improve the cycloisomerization reaction. No improvements were observed when the reaction was conducted in DCM at 0 or 40 °C (Table 3, entries 9–10). The use of ether gave **8a** in 8% yield (Table 3, entries 11). Furthermore, no desired product was obtained in THF or toluene (Table 3, entry 12–13). Therefore, the use of 2.0 equiv of Tf_2NH in DCM at 0.1 M concentration was chosen as the optimal conditions for transformation of **1** into ketone 8.

DOI: 10.1021/acs.joc.5b02025
J. Org. Chem. XXXX, XXX, XXX–XXX

With the optimized reaction conditions in hand (Table 3, entry 3), we further investigated the substrate scope of this cycloisomerization of **1a** using 2.0 equiv of Tf_2NH in DCM at room temperature. In general, substrates substituted with an electron-neutral or -rich aryl group at the alkyne were capable of transforming **1** into ketone **8** in minutes, albeit in 15−45% yields (Table 4, entries 1−6). Unfortunately, substrates **1i−j**, bearing an electron-withdrawing group on the phenyl ring, decomposed when subjected to Tf_2NH under the same reaction conditions. (Table 4, entries 7−8). Moreover, substrates **1m−o**, bearing a bromine or chlorine atom on the phenyl ring, were also successfully transformed into the corresponding ketones **8m−o** in 32−45%, respectively (Table 4, entries 9−11). The 3-theinyl-substituted alkyne **1r** also reacted with Tf_2NH to afford the corresponding ketone **8r** in 25% isolated yield (Table 4, entry 12).

Table 4. Tf_2NH-Promoted Cycloisomerization of 1 to 8

1 **8**

entry	Ar	substrate	time (min)	product	yield (%)[a]
1	phenyl	**1a**	1	**8a**	45
2	3-methylphenyl	**1b**	1	**8b**	36
3	4-methylphenyl	**1c**	1	**8c**	36
4	1-naphthyl	**1e**	5	**8e**	20
5	3-methoxyphenyl	**1f**	10	**8f**	30
6	4-methoxyphenyl	**1g**	1	**8g**	15
7	4-carbethoxyphenyl	**1j**	10	–	–
8	4-nitrophenyl	**1l**	5	–	–
9	4-chlorophenyl	**1m**	5	**8m**	45
10	4-bromophenyl	**1n**	5	**8n**	38
11	2-bromophenyl	**1o**	10	**8o**	32
12	3-thienyl	**1r**	1	**8r**	25

[a]Isolated yields obtained from column chromatography over silica gel.

In conclusion, a carbofluorination reaction of *N*-arylpropargylpyrrolidine- tethered tertiary allylic alcohols to afford fluorinated pyrrolizidines in an excellent stereoselective fashion is described. The procedure employs the inexpensive and air stable triphenylcarbenium tetrafluoroborate instead of the strong Lewis acid ($BF_3{\cdot}OEt_2$). Furthermore, 2-alkenyl-3-aroylpyrrolizidine derivatives are available with excellent stereoselectivity via cycloisomerization of the substrates employing bis(trifluoromethane)sulfonamide. Further studies on the extension of the present methods to the construction of other nitrogen-containing heterocycles are currently underway in our laboratory.

EXPERIMENTAL SECTION

General Considerations. All reactions were conducted in carefully dried glassware in an atmosphere of nitrogen. The addition of anhydrous solvents or liquid (regents) was performed with an oven-dried syringe or cannula through a septum. Solids were added under gentle stream of nitrogen. Solvents were predried by molecular sieves and then by passing through an Al_2O_3 column. Melting points were measured in open glass capillaries with an electronic apparatus and were uncorrected. Chromatographic purification was performed with flash column chromatography using silica P60, 40−63 m (230−400 mesh). ^1H nuclear magnetic resonance (NMR) spectra were recorded with 400 and 500 MHz spectrometers. Chemical shifts are given in parts per million (ppm) relative to Me_4Si (0.00 ppm) with either Me_4Si or the solvent residual peak ($CHCl_3$, 7.26 ppm) as internal standard. Coupling patterns are described by the following abbreviations: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet). Coupling costants (*J*) are given in Herz (Hz). ^{13}C NMR spectra were recorded with 100 and 125 MHz spectrometers using solvent $CDCl_3$ (77.0 ppm) as internal standard. Mass spectra were determined by using a spectrometer at a 70 eV ionization potential. Peaks are listed according to their mass/charge (*m*/*e*) value with percent relative abundance. High-resolution mass spectra were obtained with a double-focusing mass spectrometer.

Representative Procedure for the Synthesis of Starting Compound 1. To a solution of (±)-proline **2** (3.45 g, 30.00 mmol) in dried MeOH (30 mL), thionyl chloride (3.93 g, 33.00 mmol) was added dropwise at 0 °C. The reaction mixture was stirred for 1 h under refluxing condition and then allowed to cool to room temperature. The solvent was removed in vacuo to afford a crude methyl pyrrolidine-2-carboxylate (5.02 g, 30.00 mmol, 95%). To a solution of methyl pyrrolidine-2-carboxylate (5.02 g, 30.00 mmol) in toluene (30 mL) were added Et_3N (9.2 mL) and propargyl bromide (4.64 g, 39.00 mmol). The reaction mixture was heated at 50 °C for 18 h before it was cooled to room temperature and quenched with aqueous $NaHCO_3$ solution (90 mL). The mixture was extracted with toluene (90 mL × 3). The combined organic extracts were washed with water (200 mL × 2) and brine (200 mL × 2). The organic layer was dried over $MgSO_4$ (15 g) and filtered. Solvent were evaporated under reduced pressure. The crude mixture was purified by flash column chromatography over silica gel (EtOAc/hexanes 1:3) to afford the corresponding methyl-1-(prop-2-yn-1-yl)- pyrrolidine-2-carboxylate (4.34 g, 25.96 mmol, 91%). To a 250 mL round-bottom flask, equipped with a stirring bar and a dropping funnel, under nitrogen at 0 °C were added lithium aluminum hydride (LAH, 1.97 g, 51.92 mmol) and dry Et_2O (130 mL). The methyl-1-(prop-2-yn-1-yl)pyrrolidine-2-carboxylate (4.34 g, 25.96 mmol) was added dropwise to the reaction at 0 °C. The reaction mixture was stirred at room temperature for 4 h. The solution was added a mixture of $NH_4Cl_{(aq)}$ (10 mL) and $NH_{3(aq)}$ (20 mL) to obtain a buffer solution (pH 8). The suspension was filtered through a bed of Celite, and the solid residue was washed with Et_2O. The filtrate was dried over $MgSO_4$ (15 g) and concentrated under reduced pressure in vacuo to afford the corresponding (1-(prop-2-yn-1-yl)pyrrolidin-2-yl)methanol **3** (3.61 g, 25.96 mmol, 98%). To a two-neck flask equipped with a stirring bar were added CuI (0.19 g, 1.04 mmol), PhI (6.36 g, 31.15 mmol), $Pd(PPh_3)_4$ (0.06 g, 0.52 mmol) and Et_3N (26 mL) under nitrogen. The mixture was allowed to stir at room temperature for 30 min followed by addition of (1-(prop-2-yn-1-yl)pyrrolidin-2-yl)methanol **3** (3.61 g, 25.96 mmol). The reaction mixture was stirred at room temperature for 8 h before quenching with aqueous NH_4Cl solution (30 mL). The resulting solution was extracted with CH_2Cl_2 (30 mL × 3). The combined organic extracts were washed with water (70 mL × 2) and brine (70 mL × 2). The organic layer was dried over $MgSO_4$ (15 g) and filtered. Solvent was evaporated under reduced pressure. The crude mixture was purified by flash column chromatography over silica gel (EtOAc/hexanes 1:1) to afford the corresponding product (1-(3-phenylprop-2-yn-1-yl)pyrrolidin-2- yl)methanol **4** (4.19 g, 19.47 mmol, 75%). Oxalyl chloride (2.77 g, 21.81 mmol) was added dropwise to a solution of dimethyl sulfoxide (DMSO, 3.41 g, 43.62 mmol) in CH_2Cl_2 (73 mL) at −78 °C. The reaction was allowed to stir at −78 °C for 15 min followed by addition of (1-(3-phenylprop-2-yn-1-yl)pyrrolidin-2-yl)-methanol **4** (3.1317 g, 14.54 mmol). After being stirred for 30 min, the reaction was allowed to warm to −50 °C followed by addition of Et_3N (14.2 mL). The reaction mixture was stirred at room temperature for 2 h before quenching with brine (30 mL). The resulting solution was extracted with CH_2Cl_2 (30 mL × 3). The combined organic extracts were washed (70 mL × 2) with water and brine (70 mL × 2). The filtrate was dried over $MgSO_4$ (15 g) and concentrated under reduced pressure in vacuo to afford the corresponding 1-(3-phenylprop-2-yn-1-yl)pyrrolidine-2-carbaldehyde **5** (3.10 g, 14.54 mmol, 98%). To a solution of 1-(3-phenylprop-2-yn-1-yl)pyrrolidine- 2-carbaldehyde **5**

DOI: 10.1021/acs.joc.5b02025
J. Org. Chem. XXXX, XXX, XXX−XXX

(3.10 g, 14.54 mmol) in CH_2Cl_2 (73 mL) was added 1-(triphenylphosphoranylidene)propan-2-one (6.94 g, 21.81 mmol). The reaction mixture was stirred for 24 h under refluxing condition before it cooled to room temperature, quenched with saturated brine (50 mL) and extracted with CH_2Cl_2 (50 mL × 3). The combined organic extracts were washed with water (70 mL × 2) and saturated brine (70 mL × 2). The filtrate was dried over $MgSO_4$ and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography over silica gel (EtOAc/hexanes 1:3) to afford the corresponding (*E*)-4-(1-(3-phenylprop-2-yn-1-yl)-pyrrolidin-2-yl)but-3-en-2-one **6** (3.20 g, 12.64 mmol, 88%). Methylmagnesium bromide (38 mL of a 1.0 M solution in THF, 37.91 mmol) was added dropwise over 30 min to a stirred solution of 4-(1-(3-phenylprop-2-yn-1-yl)pyrrolidin-2-yl)but-3-en-2-one **6** (3.20 g, 12.64 mmol) in dried THF (126 mL) at −78 °C under an nitrogen atmosphere. The mixture was stirred at room temperature for 1 h. After which time, the reaction mixture was quenched with water (30 mL) and extracted with EtOAc (30 mL × 3). The combined organic extracts were washed with water (70 mL × 2) and saturated brine (70 mL × 2). The filtrate was dried over $MgSO_4$ and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography over silica gel (EtOAc/hexanes 1:1) to afford the corresponding (*E*)-2-methyl-4-(1-(3-phenylprop- 2-yn-1-yl)pyrolidin-2-yl)but-3-en-2-ol (**1a**) (2.72 g, 10.11 mmol, 80%) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46−7.40 (m, 2H), 7.32−7.27 (m, 3H), 5.84 (d, *J* = 15.6 Hz, 1H), 5.52 (dd, *J* = 15.6, 8.4 Hz, 1H), 3.71 (d, *J* = 17.0 Hz, 1H), 3.46 (d, *J* = 17.0 Hz, 1H), 3.15 (td, *J* = 8.6, 2.8 Hz, 1H), 3.00 (q, *J* = 8.2 Hz, 1H), 2.63 (q, *J* = 8.9 Hz, 1H), 2.04−1.94 (m, 1H), 1.92−1.84 (m, 1H), 1.82−1.74 (m, 1H), 1.69−1.62 (m, 1H), 1.34 (s, 3H), 1.34 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 141.2, 131.6 (2C), 128.1 (2C), 128.0, 127.9, 123.2, 84.9, 84.7, 70.3, 64.4, 52.2, 41.0, 31.7, 29.7, 29.7, 22.0; IR (CH_2Cl_2) 3369, 2970, 2928, 2818, 2346, 2373, 1675, 1598, 1459, 1363, 1153, 974, 756 cm^{-1}; MS (ESI) *m*/*e* (%) 270.2 ([M + H]$^+$, 100), 262.2 (10); HRMS (ESI) calcd. for $C_{18}H_{24}NO$ [M + H]$^+$ 270.1858, found 270.1859.

*(1-(Prop-2-yn-1-yl)pyrrolidin-2-yl)methanol (**3**).* (3.61 g, 25.96 mmol, 98%). A colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.64 (dd, *J* = 11.0, 3.5 Hz, 1H), 3.53 (dd, *J* = 17.3, 2.3 Hz, 1H), 3.48−3.38 (m, 2H), 3.07−2.99 (m, 1H), 2.89−2.82 (m, 1H), 2.69 (q, *J* = 8.5 Hz, 1H), 2.44−2.29 (br s., 1H), 2.20 (t, *J* = 2.4 Hz, 1H), 1.98−1.84 (m, 1H), 1.84−1.68 (m, 4H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 79.1, 72.5, 62.3, 61.8, 53.2, 41.0, 27.5, 23.1; IR (CH_2Cl_2) 3491, 2970, 1230, 780, 699 cm^{-1}; MS (ESI) *m*/*e* (%) 140.1 ([M + H]$^+$, 100), 120.1 (25); HRMS (ESI) calcd. for $C_8H_{14}NO$ [M + H]$^+$ 140.0998, found 140.0997.

*(1-(3-Phenylprop-2-yn-1-yl)pyrrolidin-2-yl)methanol (**4**).* (3.61 g, 25.96 mmol, 75%). A yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48−7.38 (m, 2H), 7.36−7.27 (m, 3H), 3.78−3.68 (m, 2H), 3.65 (d, *J* = 17.3 Hz, 1H), 3.47 (dd, *J* = 11.0, 2.8 Hz, 1H), 3.14−3.06 (m, 1H), 2.98−2.91 (m, 1H), 2.78 (q, *J* = 8.5 Hz, 1H), 1.97−1.90 (m, 1H), 1.87−1.73 (m, 4H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 131.7 (2C), 128.3 (2C), 128.1, 123.1, 84.9, 84.8, 62.1, 61.9, 53.5, 41.8, 27.8, 23.5; IR (CH_2Cl_2) 3376, 2948, 1599, 1459, 1328 cm^{-1}; MS (ESI) *m*/*e* (%) 216.1 ([M + H]$^+$, 100); HRMS (ESI) calcd. for $C_{14}H_{18}NO$ [M + H]$^+$ 216.1388, found 216.1385.

*1-(3-Phenylprop-2-yn-1-yl)pyrrolidine-2-carbaldehyde (**5**).* (3.10 g, 14.54 mmol, 98%). A yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.59 (d, *J* = 3.3 Hz, 1H), 7.46−7.38 (m, 2H), 7.34−7.27 (m, 3H), 3.72 (d, *J* = 1.1 Hz, 2H), 3.26 (ddd, *J* = 9.3, 6.2, 3.4 Hz, 1H), 3.22−3.13 (m, 1H), 2.76 (q, *J* = 8.5 Hz, 1H), 2.13−2.02 (m, 1H), 2.00−1.84 (m, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 202.5, 131.6 (2C), 128.2 (2C), 128.2, 122.8, 85.2, 84.4, 69.7, 53.3, 43.0, 26.9, 24.0; IR (CH_2Cl_2) 2965, 2716, 1727, 1598, 1490 cm^{-1}; MS (ESI) *m*/*e* (%) 214.1 ([M + H]$^+$, 40), 166.7 (45), 148.8 (12), 102.1 (61), 91.0 (3); HRMS (ESI) calcd. for $C_{14}H_{16}NO$ [M + H]$^+$ 214.1232, found 214.1232.

*(E)-4-(1-(3-Phenylprop-2-yn-1-yl)pyrrolidin-2-yl)but-3-en-2-one (**6**).* (3.20 g, 12.64 mmol, 88%). A yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46−7.39 (m, 2H), 7.34−7.27 (m, 3H), 6.66 (dd, *J* = 16.0, 8.0 Hz, 1H), 6.22 (d, *J* = 15.9 Hz, 1H), 3.71 (d, *J* = 17.2 Hz, 1H), 3.52 (d, *J* = 17.1 Hz, 1H), 3.27 (q, *J* = 8.0 Hz, 1H), 3.21−3.12 (m, 1H), 2.74 (q, *J* = 8.8 Hz, 1H), 2.27 (s, 3H), 2.13−2.02 (m, 1H), 2.00−1.89 (m, 1H), 1.89−1.80 (m, 1H), 1.78−1.67 (m, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 198.5, 148.7, 132.0, 131.7 (2C), 128.2 (2C), 128.1, 123.0, 85.2, 84.3, 63.5, 52.6, 41.6, 31.8, 26.7, 22.7; IR (CH_2Cl_2) 2924, 2368, 2346, 1677, 1357, 1255, 978, 757 cm^{-1}; MS (ESI) *m*/*e* (%) 254.2 ([M + H]$^+$, 100); HRMS (ESI) calcd. for $C_{17}H_{20}NO$ [M + H]$^+$ 254.1542, found 254.1545.

*(E)-2-Methyl-4-(1-(3-(m-tolyl)prop-2-yn-1-yl)pyrrolidin-2-yl)but-3-en-2-ol (**1b**).* (0.26 g, 0.95 mmol, 70%). A yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27−7.21 (m, 2H), 7.18 (t, *J* = 7.5 Hz, 1H), 7.11 (d, *J* = 7.5 Hz, 1H), 5.84 (d, *J* = 15.6 Hz, 1H), 5.52 (dd, *J* = 15.5, 8.5 Hz, 1H), 3.70 (d, *J* = 16.7 Hz, 1H), 3.48 (d, *J* = 17.0 Hz, 1H), 3.13 (td, *J* = 8.8, 2.8 Hz, 1H), 3.03 (q, *J* = 8.2 Hz, 1H), 2.74−2.55 (m, 2H), 2.32 (s, 3H), 2.04−1.95 (m, 1H), 1.92−1.83 (m, 1H), 1.82−1.73 (m, 1H), 1.70−1.60 (m, 1H), 1.33 (s, 3H), 1.33 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 141.4, 137.8, 132.2, 128.8, 128.7, 128.1, 127.7, 123.0, 85.1, 84.2, 70.4, 64.4, 52.0, 40.9, 31.6, 29.8, 29.6, 22.0, 21.1; IR (CH_2Cl_2) 3369, 2970, 2926, 2346, 2224, 1945, 1602, 1459, 1361, 1234, 1153, 974, 891 cm^{-1}; MS (APCI) *m*/*e* (%) 284.2 ([M + H]$^+$, 100); HRMS (APCI) calcd. for $C_{19}H_{26}NO$ [M + H]$^+$ 284.2014, found 284.2018.

*(E)-2-Methyl-4-(1-(3-(p-tolyl)prop-2-yn-1-yl)pyrrolidin-2-yl)but-3-en-2-ol (**1c**).* (0.22 g, 0.77 mmol, 90%). A yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, *J* = 8.1 Hz, 2H), 7.11 (d, *J* = 8.0 Hz, 2H), 5.85 (d, *J* = 15.5 Hz, 1H), 5.53 (dd, *J* = 15.6, 8.5 Hz, 1H), 3.72 (d, *J* = 16.7 Hz, 1H), 3.48 (d, *J* = 17.0 Hz, 1H), 3.17 (td, *J* = 8.9, 2.8 Hz, 1H), 3.04 (q, *J* = 8.2 Hz, 1H), 2.67 (q, *J* = 8.9 Hz, 1H), 2.49 (br s., 1H), 2.34 (s, 3H), 2.04−1.94 (m, 1H), 1.93−1.84 (m, 1H), 1.83−1.73 (m, 1H), 1.71−1.62 (m, 1H), 1.34 (s, 3H), 1.33 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 141.7, 138.0, 131.5 (2C), 128.9 (2C), 127.2, 119.9, 85.1, 83.5, 70.3, 64.5, 51.9, 40.8, 31.5, 29.7, 29.5, 22.0, 21.3; IR (CH_2Cl_2) 3373, 2969, 2924, 2233, 1904, 1671, 1509, 1460, 1361, 1331, 1152, 974, 816 cm^{-1}; MS (APCI) *m*/*e* (%) 284.2 ([M + H]$^+$, 100), 194.2 (5); HRMS (APCI) calcd. for $C_{19}H_{26}NO$ [M + H]$^+$ 284.2014, found 284.2021.

*(E)-4-(1-(3-([1,1′-Biphenyl]-4-yl)prop-2-yn-1-yl)pyrrolidin-2-yl)-2-methylbut-3-en-2-ol (**1d**).* (0.20 g, 0.59 mmol, 39%). A yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60−7.57 (m, 2H), 7.54 (dd, *J* = 6.2, 2.0 Hz, 2H), 7.50 (dd, *J* = 6.6, 2.1 Hz, 2H), 7.44 (t, *J* = 7.2 Hz, 2H), 7.38−7.33 (m, 1H), 5.86 (d, *J* = 15.5 Hz, 1H), 5.53 (dd, *J* = 15.6, 8.5 Hz, 1H), 3.74 (d, *J* = 17.0 Hz, 1H), 3.49 (d, *J* = 17.0 Hz, 1H), 3.18 (td, *J* = 9.0, 2.8 Hz, 1H), 3.02 (q, *J* = 8.1 Hz, 1H), 2.65 (q, *J* = 8.9 Hz, 1H), 2.05−1.96 (m, 1H), 1.94−1.85 (m, 1H), 1.85−1.74 (m, 1H), 1.71−1.61 (m, 2H), 1.35 (s, 3H), 1.35 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 141.4, 140.8, 140.4, 132.1 (2C), 128.8 (2C), 127.9, 127.6, 127.0 (2C), 126.9 (2C), 122.1, 85.4, 84.8, 70.5, 64.6, 52.2, 41.1, 31.7, 29.8, 29.7, 22.1; IR (CH_2Cl_2) 3372, 2968, 2358, 2632, 1366, 1120, 975, 843, 764, 698 cm^{-1}; MS (ESI) *m*/*e* (%) 346.2 ([M + H]$^+$, 100), 342.1 (5), 304.1 (5); HRMS (ESI) calcd. for $C_{24}H_{28}NO$ [M + H]$^+$ 346.2171, found 346.2169.

*(E)-2-Methyl-4-(1-(3-(naphthalen-1-yl)prop-2-yn-1-yl)pyrrolidin-2-yl)but-3-en-2-ol (**1e**).* (0.64 g, 2.02 mmol, 80%). A yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (d, *J* = 8.3 Hz, 1H), 7.83 (d, *J* = 8.1 Hz, 1H), 7.80 (d, *J* = 8.3 Hz, 1H), 7.67 (dd, *J* = 7.1, 0.9 Hz, 1H), 7.58−7.54 (m, 1H), 7.52−7.48 (m, 1H), 7.40 (t, *J* = 7.7 Hz, 1H), 5.90 (d, *J* = 15.5 Hz, 1H), 5.58 (dd, *J* = 15.6, 8.6 Hz, 1H), 3.88 (d, *J* = 17.1 Hz, 1H), 3.68 (d, *J* = 17.1 Hz, 1H), 3.21 (td, *J* = 8.8, 2.8 Hz, 1H), 3.15 (q, *J* = 8.2 Hz, 1H), 2.78 (q, *J* = 8.8 Hz, 1H), 2.05−1.96 (m, 1H), 1.95−1.85 (m, 1H), 1.85−1.76 (m, 1H), 1.73−1.64 (m, 1H), 1.35 (s, 3H), 1.34 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 141.7, 133.3, 133.1, 130.5, 128.4, 128.2, 127.5, 126.6, 126.3, 126.0, 125.1, 120.8, 89.4, 83.0, 70.4, 64.5, 52.0, 41.1, 31.6, 29.8, 29.6, 22.0; IR (CH_2Cl_2) 3365, 3058, 2969, 2935, 2816, 2227, 1932, 1812, 1689, 1586, 1507, 1424, 1395, 1359, 1330, 1153, 973, 799, 774 cm^{-1}; MS (ESI) *m*/*e* (%) 320.2 ([M + H]$^+$, 100), 284.2 (5), 266.2 (5); HRMS (ESI) calcd. for $C_{22}H_{26}NO$ [M + H]$^+$ 320.2014, found 320.2012.

*(E)-4-(1-(3-(3-Methoxyphenyl)prop-2-yn-1-yl)pyrrolidin-2-yl)-2-methylbut-3-en-2-ol (**1f**).* (0.19 g, 0.64 mmol, 70%). A yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (t, *J* = 7.9 Hz, 1H), 7.03 (d, *J* = 7.6 Hz, 1H), 6.99−6.95 (m, 1H), 6.86 (dd, *J* = 8.2, 2.6 Hz, 1H), 5.85 (d, *J*

DOI: 10.1021/acs.joc.5b02025
J. Org. Chem. XXXX, XXX, XXX−XXX

= 15.4 Hz, 1H), 5.54 (dd, *J* = 15.5, 8.5 Hz, 1H), 3.80 (s, 3H), 3.73 (d, *J* = 17.2 Hz, 1H), 3.48 (d, *J* = 17.0 Hz, 1H), 3.18 (td, *J* = 8.9, 2.7 Hz, 1H), 3.03 (q, *J* = 8.1 Hz, 1H), 2.66 (q, *J* = 8.8 Hz, 1H), 2.03−1.97 (m, 1H), 1.93−1.85 (m, 1H), 1.82−1.75 (m, 1H), 1.72−1.65 (m, 1H), 1.34 (s, 3H), 1.34 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 159.2, 141.3, 129.3, 127.9, 124.2, 124.2, 116.6, 114.5, 84.7, 84.7, 70.5, 64.6, 55.2, 52.2, 41.1, 31.7, 29.8, 29.7, 22.1; IR (CH_2Cl_2) 3364, 2969, 2366, 1603, 1463, 1360, 1318, 1288, 1203, 1162, 1045, 976 cm^{-1}; MS (ESI) *m*/*e* (%) 300.2 ($[M + H]^+$, 100); HRMS (ESI) calcd. for $C_{19}H_{26}NO_2$ $[M + H]^+$ 300.1964, found 300.1964.

*(E)-4-(1-(3-(4-Methoxyphenyl)prop-2-yn-1-yl)pyrrolidin-2-yl)-2-methylbut-3-en-2-ol (**1g**).* (0.20 g, 0.68 mmol, 43%). A yellow oil: ^1H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, *J* = 8.8 Hz, 2H), 6.83 (d, *J* = 8.8 Hz, 2H), 5.84 (d, *J* = 15.6 Hz, 1H), 5.52 (dd, *J* = 15.5, 8.4 Hz, 1H), 3.81 (s, 3H), 3.70 (d, *J* = 16.9 Hz, 1H), 3.45 (d, *J* = 17.0 Hz, 1H), 3.16 (td, *J* = 8.9, 2.7 Hz, 1H), 3.01 (q, *J* = 8.2 Hz, 1H), 2.63 (q, *J* = 8.9 Hz, 1H), 2.23 (br s., 1H), 2.03−1.95 (m, 1H), 1.92−1.83 (m, 1H), 1.81−1.74 (m, 1H), 1.70−1.63 (m, 1H), 1.34 (s, 3H), 1.33 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 159.3, 141.6, 133.0 (2C), 127.4, 115.2, 113.7 (2C), 84.7, 82.9, 70.2, 64.4, 55.1, 51.9, 40.9, 31.5, 29.7, 29.5, 21.9; IR (CH_2Cl_2) 3374, 2968, 2932, 2872, 2838, 2228, 1607, 1509, 1291, 1248, 1152, 1033, 832 cm^{-1}; MS (ESI) *m*/*e* (%) 300.2 ($[M + H]^+$, 100), 284.2 (15), 279.3 (5), 246.2 (10); HRMS (ESI) calcd. for $C_{19}H_{26}NO_2$ $[M + H]^+$ 300.1964, found 300.1956.

*(E)-2-Methyl-4-(1-(3-(3-(trifluoromethyl)phenyl)prop-2-yn-1-yl)-pyrrolidin-2-yl)but-3-en-2-ol (**1h**).* (1.13 g, 4.29 mmol, 87%). A yellow oil: ^1H NMR (400 MHz, $CDCl_3$) δ 7.68 (s, 1H), 7.59 (d, *J* = 7.7 Hz, 1H), 7.55 (d, *J* = 7.9 Hz, 1H), 7.42 (t, *J* = 7.8 Hz, 1H), 5.84 (d, *J* = 15.6 Hz, 1H), 5.52 (dd, *J* = 15.6, 8.5 Hz, 1H), 3.73 (d, *J* = 17.2 Hz, 1H), 3.45 (d, *J* = 17.1 Hz, 1H), 3.17 (td, *J* = 8.7, 2.8 Hz, 1H), 2.98 (q, *J* = 8.2 Hz, 1H), 2.61 (q, *J* = 8.9 Hz, 1H), 2.05−1.96 (m, 1H), 1.93−1.84 (m, 1H), 1.84−1.75 (m, 1H), 1.72−1.61 (m, 2H), 1.35 (s, 3H), 1.34 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 141.3, 134.8, 130.9 (q, *J* = 32.6 Hz),128.8, 128.5 (q, *J* = 3.7 Hz), 128.1, 124.5 (q, *J* = 3.7 Hz), 124.2, 123.7 (q, *J* = 272.4 Hz), 86.9, 83.3, 70.6, 64.7, 52.4, 41.1, 31.8, 29.8, 29.7, 22.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ −63.9; IR (CH_2Cl_2) 3372, 2970, 2826, 2961, 1638, 1334, 1166, 1129, 1094, 974, 902, 801, 696 cm^{-1}; MS (ESI) *m*/*e* (%) 338.2 ($[M + H]^+$, 100), 330.2 (5), 284.1 (5); HRMS (ESI) calcd. for $C_{19}H_{23}NOF_3$ $[M + H]^+$ 338.1732, found 338.1723.

*(E)-Ethyl 3-(3-(2-(3-hydroxy-3-methylbut-1-en-1-yl)pyrrolidin-1-yl)prop-1-yn-1- yl)benzoate (**1i**).* (0.26 g, 0.75 mmol, 50%). A yellow oil: ^1H NMR (400 MHz, $CDCl_3$) δ 8.10 (t, *J* = 1.8 Hz, 1H), 7.97 (dt, *J* = 7.8, 1.3 Hz, 1H), 7.60 (dt, *J* = 7.7, 1.2 Hz, 1H), 7.37 (t, *J* = 7.8 Hz, 1H), 5.85 (d, *J* = 15.5 Hz, 1H), 5.52 (dd, *J* = 15.5, 8.4 Hz, 1H), 4.38 (q, *J* = 7.0 Hz, 2H), 3.72 (d, *J* = 17.0 Hz, 1H), 3.46 (d, *J* = 17.0 Hz, 1H), 3.15 (td, *J* = 8.8, 2.7 Hz, 1H), 2.99 (q, *J* = 8.2 Hz, 1H), 2.62 (q, *J* = 8.9 Hz, 1H), 2.15 (br s., 1H), 2.04−1.95 (m, 1H), 1.92−1.84 (m, 1H), 1.83−1.75 (m, 1H), 1.70−1.61 (m, 1H), 1.40 (t, *J* = 7.1 Hz, 3H), 1.34 (s, 3H), 1.34 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 166.0, 141.2, 135.8, 132.8, 130.7, 129.0, 128.3, 128.1, 123.7, 86.0, 83.8, 70.6, 64.6, 61.2, 52.4, 41.2, 31.8, 29.8, 29.7, 22.1, 14.3; IR (CH_2Cl_2) 3384, 2971, 2941, 2430, 2196, 1721, 1367, 1293, 1225, 1105, 974, 754 cm^{-1}; MS (ESI) *m*/*e* (%) 342.2 ($[M + H]^+$, 100), 229.1 (10), 143.1 (5); HRMS (ESI) calcd. for $C_{21}H_{28}NO_3$ $[M + H]^+$ 342.2069, found 342.2065.

*(E)-Ethyl 4-(3-(2-(3-hydroxy-3-methylbut-1-en-1-yl)pyrrolidin-1-yl)prop-1-yn-1- yl)benzoate (**1j**).* (0.22 g, 0.65 mmol, 43%). A yellow oil: ^1H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, *J* = 8.1 Hz, 2H), 7.48 (d, *J* = 8.2 Hz, 2H), 5.84 (d, *J* = 15.5 Hz, 1H), 5.52 (dd, *J* = 15.6, 8.4 Hz, 1H), 4.38 (q, *J* = 7.1 Hz, 2H), 3.74 (d, *J* = 17.1 Hz, 1H), 3.47 (d, *J* = 17.1 Hz, 1H), 3.17 (td, *J* = 8.7, 2.7 Hz, 1H), 2.98 (q, *J* = 8.2 Hz, 1H), 2.61 (q, *J* = 8.8 Hz, 1H), 2.05−1.96 (m, 1H), 1.92−1.84 (m, 1H), 1.83−1.73 (m, 1H), 1.70−1.56 (m, 2H), 1.39 (t, *J* = 7.2 Hz, 3H), 1.34 (s, 3H), 1.34 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 166.1, 141.2, 131.6 (2C), 129.7, 129.4 (2C), 128.1, 127.9, 88.3, 84.2, 70.6, 64.7, 61.1, 52.5, 41.3, 31.8, 29.8, 29.7, 22.1, 14.3; IR (CH_2Cl_2) 3396, 2964, 2194, 1719, 1629, 1365, 1307, 1274, 1106, 767, 740 cm^{-1}; MS (ESI) *m*/*e* (%) 342.2 ($[M + H]^+$, 100); HRMS (ESI) calcd. for $C_{21}H_{28}NO_3$ $[M + H]^+$ 342.2069, found 342.2068.

*(E)-2-Methyl-4-(1-(3-(3-nitrophenyl)prop-2-yn-1-yl)pyrrolidin-2-yl)but-3-en-2-ol (**1k**).* (0.40 g, 1.28 mmol, 85%). A yellow oil: ^1H NMR (400 MHz, $CDCl_3$) δ 8.27 (s, 1H), 8.18−8.11 (m, 1H), 7.73 (d, *J* = 7.7 Hz, 1H), 7.49 (t, *J* = 8.0 Hz, 1H), 5.84 (d, *J* = 15.7 Hz, 1H), 5.52 (dd, *J* = 15.6, 8.4 Hz, 1H), 3.75 (d, *J* = 17.1 Hz, 1H), 3.47 (d, *J* = 17.1 Hz, 1H), 3.18 (td, *J* = 8.6, 2.7 Hz, 1H), 2.97 (q, *J* = 8.2 Hz, 1H), 2.61 (q, *J* = 8.8 Hz, 1H), 2.07−1.97 (m, 1H), 1.94−1.85 (m, 1H), 1.83−1.76 (m, 1H), 1.71−1.64 (m, 1H), 1.35 (s, 3H), 1.35 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 148.1, 141.3, 137.4, 129.2, 128.0, 126.5, 125.1, 122.7, 88.2, 82.5, 70.6, 64.8, 52.5, 41.1, 31.8, 29.9, 29.7, 22.1; IR (CH_2Cl_2) 2256, 2967, 2944, 1981, 1531, 1351, 1155, 1105, 974, 736 cm^{-1}; MS (ESI) *m*/*e* (%) 315.2 ($[M + H]^+$, 100); HRMS (ESI) calcd. for $C_{18}H_{23}N_2O_3$ $[M + H]^+$ 315.1709, found 315.1705.

*(E)-2-Methyl-4-(1-(3-(4-nitrophenyl)prop-2-yn-1-yl)pyrrolidin-2-yl)but-3-en-2-ol (**1l**).* (0.42 g, 1.35 mmol, 90%). A yellow oil: ^1H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, *J* = 8.7 Hz, 2H), 7.56 (d, *J* = 8.7 Hz, 2H), 5.84 (d, *J* = 15.5 Hz, 1H), 5.52 (dd, *J* = 15.6, 8.4 Hz, 1H), 3.76 (d, *J* = 17.2 Hz, 1H), 3.47 (d, *J* = 17.2 Hz, 1H), 3.18 (td, *J* = 8.9, 2.6 Hz, 1H), 2.96 (q, *J* = 8.2 Hz, 1H), 2.59 (q, *J* = 8.9 Hz, 1H), 2.06−1.96 (m, 1H), 1.94−1.85 (m, 1H), 1.84−1.76 (m, 1H), 1.71−1.58 (m, 2H), 1.35 (s, 3H), 1.34 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 147.0, 141.4, 132.4 (2C), 130.2, 128.0, 123.5 (2C), 91.2, 83.1, 70.6, 64.9, 52.5, 41.3, 31.8, 29.9, 29.7, 22.1; IR (CH_2Cl_2) 3354, 2968, 2875, 2828, 2360, 2232, 1966, 1594, 1518, 1343, 1107, 854, 750 cm^{-1}; MS (ESI) *m*/*e* (%) 315.2 ($[M + H]^+$, 100); HRMS (ESI) calcd. for $C_{18}H_{23}N_2O_3$ $[M + H]^+$ 315.1709, found 315.1700.

*(E)-4-(1-(3-(4-Chlorophenyl)prop-2-yn-1-yl)pyrrolidin-2-yl)-2-methylbut-3-en-2-ol (**1m**).* (0.95 g, 3.09 mmol, 72%). A yellow oil: ^1H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, *J* = 8.5 Hz, 2H), 7.27 (d, *J* = 8.6 Hz, 2H), 5.83 (d, *J* = 15.5 Hz, 1H), 5.51 (dd, *J* = 15.6, 8.4 Hz, 1H), 3.70 (d, *J* = 17.0 Hz, 1H), 3.43 (d, *J* = 17.0 Hz, 1H), 3.15 (td, *J* = 8.7, 2.7 Hz, 1H), 2.96 (q, *J* = 8.2 Hz, 1H), 2.59 (q, *J* = 8.8 Hz, 1H), 2.04−1.95 (m, 1H), 1.92−1.83 (m, 1H), 1.82−1.73 (m, 1H), 1.69−1.61 (m, 1H), 1.34 (s, 3H), 1.33 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 141.2, 133.9, 132.9 (2C), 128.5 (2C), 128.1, 121.7, 86.1, 83.6, 70.5, 64.7, 52.4, 41.2, 31.7, 29.8, 29.7, 22.1; IR (CH_2Cl_2) 3357, 2968, 2875, 2827, 2901, 2644, 1489, 1363, 1151, 1091, 827, 754, 740 cm^{-1}; MS (ESI) *m*/*e* (%) 306.1 ($[M + 2 + H]^+$, 30), 304.1 ($[M + H]^+$, 100), 296.1 (5), 264.1 (5); HRMS (ESI) calcd. for $C_{18}H_{23}NOCl$ $[M + H]^+$ 304.1468, found 304.1463.

*(E)-4-(1-(3-(4-Bromophenyl)prop-2-yn-1-yl)pyrrolidin-2-yl)-2-methylbut-3-en-2-ol (**1n**).* (0.93 g, 2.66 mmol, 93%). A yellow oil: ^1H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, *J* = 8.4 Hz, 2H), 7.29 (d, *J* = 8.4 Hz, 2H), 5.83 (d, *J* = 15.7 Hz, 1H), 5.51 (dd, *J* = 15.6, 8.4 Hz, 1H), 3.70 (d, *J* = 17.0 Hz, 1H), 3.42 (d, *J* = 17.0 Hz, 1H), 3.16 (td, *J* = 8.6, 2.7 Hz, 1H), 2.96 (q, *J* = 8.2 Hz, 1H), 2.59 (q, *J* = 8.9 Hz, 1H), 2.04−1.95 (m, 1H), 1.91−1.83 (m, 1H), 1.82−1.74 (m, 1H), 1.69−1.56 (m, 2H), 1.34 (s, 3H), 1.34 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 141.2, 133.2 (2C), 131.5 (2C), 128.2, 122.2, 122.1, 86.4, 83.7, 70.5, 64.7, 52.4, 41.2, 31.8, 29.8, 29.7, 22.1; IR (CH_2Cl_2) 3372, 2970, 2875, 2816, 1654, 1485, 1460, 1359, 1330, 1151, 973, 823 cm^{-1}; MS (ESI) *m*/*e* (%) 350.1 ($[M + 2 + H]^+$, 100), 348.1 ($[M + H]^+$, 100), 194.1 (10); HR-MS (ESI) calcd. for $C_{18}H_{23}NOBr$ $[M + H]^+$ 348.0963, found 348.0966.

*(E)-4-(1-(3-(2-Bromophenyl)prop-2-yn-1-yl)pyrrolidin-2-yl)-2-methylbut-3-en-2-ol (**1o**).* (0.83 g, 2.39 mmol, 77%). A yellow oil: ^1H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 8.1 Hz, 1H), 7.46 (dd, *J* = 7.6, 1.4 Hz, 1H), 7.25 (td, *J* = 7.6, 1.3 Hz, 1H), 7.18−7.12 (m, 1H), 5.89 (d, *J* = 15.6 Hz, 1H), 5.51 (dd, *J* = 15.6, 8.5 Hz, 1H), 3.76 (d, *J* = 17.2 Hz, 1H), 3.59 (d, *J* = 17.2 Hz, 1H), 3.18−3.10 (m, 2H), 2.77 (q, *J* = 8.8 Hz, 1H), 2.04−1.96 (m, 1H), 1.92−1.84 (m, 1H), 1.82−1.75 (m, 1H), 1.69−1.62 (m, 1H), 1.34 (s, 3H), 1.34 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 141.3, 133.5, 132.3, 129.1, 128.1, 126.9, 125.4 (2C), 89.9, 83.4, 70.6, 64.0, 52.0, 40.9, 31.8, 29.8, 29.7, 22.2; IR (CH_2Cl_2) 3370, 2970, 2942, 2359, 1930, 1803, 1469, 1360, 1153, 947, 754 cm^{-1}; MS (ESI) *m*/*e* (%) 350.1 ($[M + 2 + H]^+$, 95), 348.1 ($[M + H]^+$, 100), 341.1 (5), 145.0 (10); HRMS (ESI) calcd. for $C_{18}H_{23}NOBr$ $[M + H]^+$ 348.0963, found 348.0955.

*(E)-2-Methyl-4-(1-(3-(2-nitrophenyl)prop-2-yn-1-yl)pyrrolidin-2-yl)but-3-en-2-ol (**1p**).* (0.37 g, 1.19 mmol, 79%). A yellow oil: ^1H

DOI: 10.1021/acs.joc.5b02025
J. Org. Chem. XXXX, XXX, XXX−XXX

NMR (400 MHz, $CDCl_3$) δ 8.01 (d, J = 8.2 Hz, 1H), 7.62 (d, J = 7.6 Hz, 1H), 7.56 (t, J = 7.5 Hz, 1H), 7.44 (t, J = 7.9 Hz, 1H), 5.88 (d, J = 15.5 Hz, 1H), 5.50 (dd, J = 15.5, 8.4 Hz, 1H), 3.78 (d, J = 17.4 Hz, 1H), 3.59 (d, J = 17.4 Hz, 1H), 3.17−3.05 (m, 2H), 2.72 (q, J = 8.8 Hz, 1H), 2.07−1.98 (m, 1H), 1.92−1.84 (m, 1H), 1.84−1.77 (m, 1H), 1.70−1.60 (m, 2H), 1.35 (s, 3H), 1.34 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 150.0, 141.4, 134.9, 132.6, 128.4, 128.0, 124.5, 118.6, 94.0, 80.1, 70.6, 64.2, 52.1, 41.1, 31.8, 29.8, 29.7, 22.2; IR (CH_2Cl_2) 3383, 2967, 2876, 2419, 1545, 1525, 1351, 1143, 980, 741 cm^{-1}; MS (ESI) m/e (%) 315.2 ($[M + H]^+$, 100), 229.1 (10), 143.1 (5); HRMS (ESI) calcd. for $C_{18}H_{23}N_2O_3$ $[M + H]^+$ 315.1709, found 315.1700.

*(E)-Ethyl 2-(3-(2-(3-hydroxy-3-methylbut-1-en-1-yl)pyrrolidin-1-yl)prop-1-yn-1- yl)benzoate (**1q**).* (0.31 g, 1.81 mmol, 60%). A yellow oil: ^1H NMR (400 MHz, $CDCl_3$) δ 7.90 (dd, J = 7.8, 1.1 Hz, 1H), 7.55 (dd, J = 7.8, 0.9 Hz, 1H), 7.44 (td, J = 7.5, 1.4 Hz, 1H), 7.34 (td, J = 7.7, 1.3 Hz, 1H), 5.89 (d, J = 15.6 Hz, 1H), 5.53 (dd, J = 15.5, 8.4 Hz, 1H), 4.38 (q, J = 7.1 Hz, 2H), 3.77 (d, J = 17.1 Hz, 1H), 3.57 (d, J = 17.2 Hz, 1H), 3.17 (td, J = 8.6, 2.8 Hz, 1H), 3.09 (q, J = 8.2 Hz, 1H), 2.71 (q, J = 8.9 Hz, 1H), 2.05−1.95 (m, 1H), 1.92−1.83 (m, 1H), 1.83−1.76 (m, 1H), 1.71−1.63 (m, 2H), 1.40 (t, J = 7.2 Hz, 3H), 1.34 (s, 3H), 1.34 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 166.3, 141.4, 134.4, 132.4, 131.4, 130.0, 128.1, 127.6, 123.7, 90.4, 83.4, 70.6, 64.5, 61.1, 52.3, 41.3, 31.8, 29.8, 29.6, 22.2, 14.3; IR (CH_2Cl_2) 3404, 2969, 2427, 2195, 1966, 1720, 1460, 1365, 1276, 1080, 974, 756, 740 cm^{-1}; MS (ESI) m/e (%) 342.2 ($[M + H]^+$, 100); HRMS (ESI) calcd. for $C_{21}H_{28}NO_3$ $[M + H]^+$ 342.2069, found 342.2065.

*(E)-2-Methyl-4-(1-(3-(thiophen-3-yl)prop-2-yn-1-yl)pyrrolidin-2-yl)but-3-en-2-ol (**1r**).* (1.02 g, 3.72 mmol, 80%). A brown oil: ^1H NMR (400 MHz, $CDCl_3$) δ 7.42−7.39 (m, 1H), 7.25 (dd, J = 5.0, 3.1 Hz, 1H), 7.10 (dd, J = 4.9, 0.9 Hz, 1H), 5.83 (d, J = 15.5 Hz, 1H), 5.51 (dd, J = 15.6, 8.4 Hz, 1H), 3.69 (d, J = 17.2 Hz, 1H), 3.42 (d, J = 17.0 Hz, 1H) 3.14 (td, J = 8.8, 2.6 Hz, 1H), 2.96 (q, J = 8.2 Hz, 1H), 2.60 (q, J = 8.9 Hz, 1H), 2.02−1.94 (m, 1H), 1.91−1.82 (m, 1H), 1.80−1.73 (m, 1H), 1.68−1.61 (m, 1H), 1.55 (br s., 1H), 1.34 (s, 3H), 1.33 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 141.1, 130.0, 128.3, 128.2, 125.1, 122.3, 84.6, 79.7, 70.5, 64.6, 52.4, 41.2, 31.8, 29.8, 29.7, 22.1; IR (CH_2Cl_2) 3386, 2970, 2822, 2338, 2231, 1676, 1459, 1359, 1148, 974, 780 cm^{-1}; MS (ESI) m/e (%) 276.5 ($[M + H]^+$, 100), 121.4 (2); HRMS (ESI) calcd. for $C_{16}H_{22}NOS$ $[M + H]^+$ 276.1422, found 276.1421.

*(E)-3-Methyl-1-(1-(3-phenylprop-2-yn-1-yl)pyrrolidin-2-yl)pent-1-en-3-ol (**1s**).* (0.16 g, 0.55 mmol, 55%). Compound **1s** was obtained as a mixture of diastereomers. A yellow oil: ^1H NMR (400 MHz, $CDCl_3$) δ 7.46−7.40 (m, 2H + 2H′), 7.32−7.27 (m, 3H + 3H′), 5.75 (d, J = 15.7 Hz, 1H), 5.74 (d, J = 15.8 Hz, 1H′), 5.52 (dd, J = 15.6, 8.4 Hz, 1H), 5.50 (dd, J = 15.7, 8.5 Hz, 1H′), 3.72 (d, J = 17.0 Hz, 1H), 3.72 (d, J = 17.0 Hz, 1H′), 3.48 (d, J = 17.0 Hz, 1H), 3.47 (d, J = 16.9 Hz, 1H′), 3.17−3.11 (m, 1H + 1H′), 3.06−2.98 (m, 1H + 1H′), 2.64 (q, J = 8.8 Hz, 1H), 2.64 (q, J = 8.8 Hz, 1H′), 2.04−1.94 (m, 1H + 1H′), 1.91−1.82 (m, 1H + 1H′), 1.82−1.74 (m, 1H + 1H′), 1.69−1.61 (m, 1H + 1H′), 1.61−1.54 (m, 2H + 2H′), 1.53−1.39 (br s., 1H + 1H′), 1.30 (s, 3H), 1.28 (s, 3H′), 0.90 (t, J = 7.4 Hz, 3H), 0.89 (t, J = 7.5 Hz, 3H′); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 140.0, 139.9, 131.7 (2C), 129.2, 129.1, 128.2 (2C), 127.9, 123.3, 84.9, 84.7, 73.0, 72.9, 64.6, 52.3, 52.2, 41.1, 35.2, 35.2, 31.9, 27.5, 27.3, 22.1, 8.4, 8.3; IR (CH_2Cl_2) 3406, 2967, 2329, 2231, 1598, 1460, 1367, 1151, 976, 756, 692 cm^{-1}; MS (ESI) m/e (%) 284.7 ($[M + H]^+$, 100), 268.4 (4); HRMS (ESI) calcd. for $C_{19}H_{26}NO$ $[M + H]^+$ 284.2014, found 284.2013.

General Experimental Procedure for Ph_3CBF_4-Promoted Carbofluorination of (*E*)-2-Methyl-4-(1-(3-phenyprop-2-yn-1-yl)pyrrolidin-2-yl)but-3-en-2-ol (1a). *Synthesis of (1S*,7aR*,Z)-2-(Fluoro(phenyl)methylene)-1-(2-methylprop-1-en-1- yl)hexahydro-1H-pyrrolizine (**7a**).* To a solution of Ph_3CBF_4 (0.17 g, 0.52 mmol) in CH_2Cl_2 (26 mL) was added **1a** (70 mg, 0.26 mmol) at room temperature under nitrogen. The mixture was stirred for 25 min until **1a** was disappeared as monitored by TLC. The reaction mixture was quenched with saturated $NaHCO_3$ (10 mL). The resulting mixture was extracted with DCM (3 × 30 mL). The organic phase was dried over MgSO4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (EtOAc/hexanes = 1:1) to give of **7a** (0.06 g, 0.22 mmol, 85%) as a yellow oil: ^1H NMR (600 MHz, $CDCl_3$) δ 7.40−7.37 (m, 2H), 7.34−7.28 (m, 3H), 5.01 (dt, J = 9.6, 1.3 Hz, 1H), 4.04 (d, J = 16.1 Hz, 1H), 3.82 (dd, J = 16.1, 3.0 Hz, 1H), 3.47−3.42 (m, 1H), 3.35 (q, J = 5.3 Hz, 1H), 3.22−3.15 (m, 1H), 2.67 (dt, J = 10.0, 8.1 Hz, 1H), 2.12−2.05 (m, 1H), 2.00−1.92 (m, 1H), 1.91−1.83 (m, 1H), 1.64 (d, J = 1.3 Hz, 3H), 1.63−1.59 (m, 1H), 1.58 (d, J = 1.3 Hz, 3H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 151.5 (d, J = 239.7 Hz), 132.5, 132.0 (d, J = 29.6 Hz), 128.4, 127.7 (2C), 127.0 (d, J = 6.1 Hz, 2C), 125.0, 122.1 (d, J = 21.3 Hz), 73.9, 55.4 (d, J = 5.4 Hz), 54.2, 45.5 (d, J = 3.3 Hz), 29.8, 25.5, 24.5, 18.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ −103.5; IR (CH_2Cl_2) 3404, 2908, 2847, 2541, 2358, 1702, 1600, 1443, 1375, 1272, 1051, 924 cm^{-1}; MS (ESI) m/e (%) 272.2 ($[M + H]^+$, 100), 268.2 (10), 221.2 (10); HRMS (ESI) calcd. for $C_{18}H_{23}FN$ $[M + H]^+$ 272.1815, found 272.1823.

(1S,7aR*,Z)-2-(Fluoro(m-tolyl)methylene)-1-(2-methylprop-1-en-1-yl)hexahydro-1H-pyrrolizine (**7b**).* The crude residue obtained from the reaction of **1b** (73 mg, 0.26 mmol) with Ph_3CBF_4 (0.17 g, 0.52 mmol) in CH_2Cl_2 (26 mL) was purified by flash column chromatography to give **7b** (53 mg, 0.18 mmol, 71%) as a yellow oil: ^1H NMR (400 MHz, $CDCl_3$) δ 7.24−7.18 (m, 3H), 7.13−7.07 (m, 1H), 5.04 (d, J = 9.7 Hz, 1H), 3.95 (d, J = 15.6 Hz, 1H), 3.77 (dd, J = 16.1, 2.9 Hz, 1H), 3.47−3.37 (m, 1H), 3.30−3.21 (m, 1H), 3.13−3.00 (m, 1H), 2.69−2.56 (m, 1H), 2.33 (s, 3H), 2.09−2.00 (m, 1H), 1.99−1.89 (m, 1H), 1.86−1.78 (m, 1H), 1.66 (d, J = 1.1 Hz, 3H), 1.63−1.56 (m, 4H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 151.2 (d, J = 238.2 Hz), 137.3, 132.2 (d, J = 29.5 Hz), 131.8, 129.0, 127.6, 127.6 (d, J = 5.6 Hz), 125.7, 123.9 (d, J = 6.2 Hz), 122.8 (d, J = 21.5 Hz), 73.8, 55.5 (d, J = 5.2 Hz), 54.0, 45.6 (d, J = 3.2 Hz), 29.8, 25.5, 24.5, 21.4, 18.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ −104.7; IR (CH_2Cl_2) 3754, 2967, 2375, 1686, 1376, 1123, 1050, 927 cm^{-1}; MS (ESI) m/e (%), 286.2 ($[M + H]^+$, 100), 282.2 (5), 221.2 (5); HRMS (ESI) calcd. for $C_{19}H_{25}FN$ $[M + H]^+$ 286.1971, found 286.1963.

(1S,7aR*,Z)-2-(Fluoro(p-tolyl)methylene)-1-(2-methylprop-1-en-1-yl)hexahydro-1H-pyrrolizine (**7c**).* The crude residue obtained from the reaction of **1c** (0.0737 g, 0.26 mmol) with Ph_3CBF_4 (0.17 g, 0.52 mmol) in CH_2Cl_2 (26 mL) was purified by flash column chromatography to give **7c** (37 mg, 0.13 mmol, 50%) as a yellow oil: ^1H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, J = 8.2 Hz, 2H), 7.12 (d, J = 8.1 Hz, 2H), 5.02 (dt, J = 9.6, 1.4 Hz, 1H), 3.94 (dt, J = 16.3, 2.2 Hz, 1H), 3.75 (dd, J = 16.1, 3.1 Hz, 1H), 3.45−3.36 (m, 1H), 3.28−3.19 (m, 1H), 3.05 (ddd, J = 10.2, 8.0, 4.2 Hz, 1H), 2.62 (dt, J = 10.1, 8.0 Hz, 1H), 2.35 (s, 3H), 2.07−1.98 (m, 1H), 1.98−1.86 (m, 1H), 1.85−1.77 (m, 1H), 1.65 (d, J = 1.1 Hz, 3H), 1.62−1.54 (m, 4H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 151.2 (d, J = 237.6 Hz), 138.1, 131.8, 129.5 (d, J = 30.1 Hz), 128.4 (2C), 126,7 (d, J = 6.1 Hz, 2C), 125.7, 122.3 (d, J = 21.7 Hz), 73.8, 55.5 (d, J = 5.2 Hz), 54.0, 45.7 (d, J = 3.7 Hz), 29.8, 25.5, 24.5, 21.3, 18.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ −105.0; IR (CH_2Cl_2) 2971, 2929, 2474, 1671, 1607, 1449, 1375, 1297, 1109, 823 cm^{-1}; MS (ESI) m/e (%) 286.2 ($[M + H]^+$, 100), 276.1 (5); HRMS (ESI) calcd. for $C_{19}H_{25}FN$ $[M + H]^+$ 286.1971, found 286.1972.

(1S,7aR*,Z)-2-([1,1′-Biphenyl]-4-ylfluoromethylene)-1-(2-methylprop-1-en-1-yl)hexahydro-1H-pyrrolizine (**7d**).* The crude residue obtained from the reaction of **1d** (90 mg, 0.26 mmol) with Ph_3CBF_4 (0.17 g, 0.52 mmol) in CH_2Cl_2 (26 mL) was purified by flash column chromatography to give **7d** (36 mg, 0.10 mmol, 40%) as a yellow oil: ^1H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, J = 7.2 Hz, 2H), 7.56 (d, J = 8.2 Hz, 2H), 7.48−7.43 (m, 4H), 7.39−7.34 (m, 1H), 5.06 (d, J = 9.6 Hz, 1H), 4.05 (d, J = 16.2 Hz, 1H), 3.83 (dd, J = 16.2, 2.9 Hz, 1H), 3.53−3.45 (m, 1H), 3.41−3.32 (m, 1H), 3.23−3.13 (m, 1H), 2.67 (dt, J = 10.0, 8.1 Hz, 1H), 2.15−2.05 (m, 1H), 2.02−1.92 (m, 1H), 1.91−1.83 (m, 1H), 1.69 (d, J = 0.7 Hz, 3H), 1.67−1.60 (m, 4H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 151.2 (d, J = 238.8 Hz), 141.1, 140.4, 132.5, 131.0 (d, J = 29.6 Hz), 128.8 (2C), 127.6, 127.3 (d, J = 6.1 Hz, 2C), 127.0 (2C), 126.4 (2C), 125.2, 122.5 (d, J = 22.1 Hz), 73.8, 55.4 (d, J = 5.5 Hz), 54.1, 45.6 (d, J = 3.4 Hz), 29.9, 25.5, 24.5, 18.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ −98.3; IR (CH_2Cl_2) 2923, 2345, 2654, 1447, 1379, 1265, 1077, 845, 734, 699 cm^{-1}; MS (ESI) m/e (%) 348.2 ($[M + H]^+$, 100), 328.3 (5); HRMS (ESI) calcd. for $C_{24}H_{27}FN$ $[M + H]^+$ 348.2128, found 348.2129.

DOI: 10.1021/acs.joc.5b02025
J. Org. Chem. XXXX, XXX, XXX−XXX

(1S,7aR*,Z*)-2-(Fluoro(3-methoxyphenyl)methylene)-1-(2-methylprop-1-en-1-yl)hexahydro-1H-pyrrolizine (**7f**).* The crude residue obtained from the reaction of **1f** (78 mg, 0.26 mmol) with Ph_3CBF_4 (0.17 g, 0.52 mmol) in CH_2Cl_2 (26 mL) was purified by flash column chromatography to give **7f** (41 mg, 0.14 mmol, 52%) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (t, J = 7.9 Hz, 1H), 7.02−6.94 (m, 2H), 6.89 (dd, J = 8.3, 2.4 Hz, 1H), 5.13 (d, J = 9.4 Hz, 1H), 4.23 (d, J = 16.1 Hz, 1H), 3.89 (dd, J = 15.9, 2.7 Hz, 1H), 3.80 (s, 3H), 3.68−3.63 (m, 1H), 3.55−3.44 (m, 2H), 2.75 (dt, J = 10.8, 8.1 Hz, 1H), 2.25−2.16 (m, 1H), 2.03−1.92 (m, 2H), 1.71−1.61 (m, 7H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 159.3, 152.3 (d, J = 243.4 Hz), 133.8, 132.6 (d, J = 28.7 Hz), 129.0, 124.1, 119.5 (d, J = 6.0 Hz), 119.1 (d, J = 17.9 Hz), 114.6, 112.8 (d, J = 6.0 Hz), 73.3, 55.3, 54.5 (d, J = 6.3 Hz), 54.4, 45.1 (d, J = 3.4 Hz), 30.4, 25.5, 24.5, 18.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ −98.6; IR (CH_2Cl_2) 3050, 2929, 2966, 2415, 2348, 2305, 1680, 1600, 1581, 1453, 1433, 1290, 1228, 1044, 736 cm^{-1}; MS (APCI) m/e (%) 302.2 ([M + H]$^+$, 100); HRMS (APCI): calcd. for $C_{19}H_{25}FNO$ [M + H]$^+$ 302.1920, found 302.1912.

(1S,7aR*,Z)-2-(Fluoro(3-(trifluoromethyl)phenyl)methylene)-1-(2-methylprop-1-en-1-yl)hexahydro-1H-pyrrolizine (**7h**).* The crude residue obtained from the reaction of **1h** (88 mg, 0.26 mmol) with Ph_3CBF_4 (0.17 g, 0.52 mmol) in CH_2Cl_2 (26 mL) was purified by flash column chromatography to give **7h** (49 mg, 0.14 mmol, 55%) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (s,1H), 7.59 (d, J = 7.8 Hz, 1H), 7.54 (d, J = 7.9 Hz, 1H), 7.45 (t, J = 7.8 Hz, 1H), 4.95 (dt, J = 9.4, 1.4 Hz, 1H), 4.00 (dt, J = 16.6, 2.2 Hz, 1H), 3.81 (dd, J = 16.6, 3.2 Hz, 1H), 3.49−3.38 (m, 1H), 3.28 (q, J = 5.5 Hz, 1H), 3.09 (ddd, J = 10.1, 8.0, 4.0 Hz, 1H), 2.62 (dt, J = 10.0, 8.0 Hz, 1H), 2.12−2.03 (m, 1H), 2.02−1.92 (m, 1H), 1.90−1.82 (m, 1H), 1.71−1.60 (m, 4H), 1.58 (d, J = 0.9 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 149.6 (d, J = 237.3 Hz), 133.3, 132.9 (d, J = 30.6 Hz), 130.2 (q, J = 32.3 Hz), 129.7 (d, J = 6.1 Hz), 128.3, 125.6 (d, J = 21.0 Hz), 124.8, 124.8 (q, J = 3.7 Hz), 124.0 (q, J = 272.4 Hz), 123.9 (qd, J = 7.7, 3.9 Hz), 74.1, 55.7 (d, J = 5.3 Hz), 53.9, 45.5 (d, J = 3.2 Hz), 29.6, 25.3, 24.4, 18.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ −63.6, −105.8; IR (CH_2Cl_2) 2154, 1642, 1265, 723 cm^{-1}. MS (EI) m/e (%) 339.2 (M$^+$, 100), 270.1 (18), 256.0 (16), 201.1 (13); HRMS (ESI) calcd. for $C_{19}H_{21}NF_4$ [M]$^+$ 339.1610, found 339.1611.

Ethyl 3-((Z)-Fluoro((1S,7aR*)-1-(2-methylprop-1-en-1-yl)-tetrahydro-1H-pyrrolizin- 2(3H)-ylidene)methyl)benzoate (**7i**).* The crude residue obtained from the reaction of **1i** (89 mg, 0.26 mmol) with Ph_3CBF_4 (0.17 g, 0.52 mmol) in CH_2Cl_2 (26 mL) was purified by flash column chromatography to give **7i** (46 mg, 0.14 mmol, 52%) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (t, J = 1.8 Hz, 1H), 7.96 (dt, J = 7.8, 1.2 Hz, 1H), 7.58−7.52 (m, 1H), 7.38 (t, J = 7.8 Hz, 1H), 4.90 (dt, J = 9.5, 1.2 Hz, 1H), 4.39 (q, J = 7.0 Hz, 2H), 3.98 (dt, J = 16.4, 2.3 Hz, 1H), 3.79 (dd, J = 16.7, 3.3 Hz, 1H), 3.51−3.41 (m, 1H), 3.29−3.19 (m, 1H), 3.08 (ddd, J = 10.1, 8.0, 4.0 Hz, 1H), 2.63 (dt, J = 10.0, 8.1 Hz, 1H), 2.10−2.01 (m, 1H), 1.99−1.92 (m, 1H), 1.87−1.82 (m, 1H), 1.69−1.61 (m, 4H), 1.53 (d, J = 1.0 Hz, 3H), 1.40 (t, J = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 166.1, 150.2 (d, J = 238.7 Hz), 133.0, 132.4 (d, J = 30.2 Hz), 131.1 (d, J = 5.7 Hz), 130.1, 129.3, 128.2 (d, J = 6.1 Hz), 127.7, 124.6, 124.1 (d, J = 21.0 Hz), 73.7, 61.0, 55.3 (d, J = 5.2 Hz), 53.9, 45.3 (d, J = 3.2 Hz), 29.6, 25.4, 24.3, 18.1, 14.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ −104.5; IR (CH_2Cl_2) 2930, 2430, 1637, 1309, 1106, 739 cm^{-1}; MS (ESI) m/e (%) 344.2 ([M + H]$^+$, 100), 279.2 (10); HRMS (ESI) calcd. for $C_{21}H_{27}FNO_2$ [M + H]$^+$ 344.2026, found 344.2026.

Ethyl 4-((Z)-Fluoro((1S,7aR*)-1-(2-methylprop-1-en-1-yl)-tetrahydro-1H-pyrrolizin- 2(3H)-ylidene)methyl)benzoate (**7j**).* The crude residue obtained from the reaction of **1j** (89 mg, 0.26 mmol) with Ph_3CBF_4 (0.17 g, 0.52 mmol) in CH_2Cl_2 (26 mL) was purified by flash column chromatography to give **7j** (43 mg, 0.12 mmol, 48%) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, J = 8.4 Hz, 2H), 7.45 (d, J = 8.4 Hz, 2H), 4.98 (d, J = 9.6 Hz, 1H), 4.39 (q, J = 7.1 Hz, 2H), 3.98 (d, J = 16.6 Hz, 1H), 3.81 (dd, J = 16.6, 3.0 Hz, 1H), 3.51−3.42 (m, 1H), 3.27 (q, J = 5.3 Hz, 1H), 3.14−3.02 (m, 1H), 2.67−2.56 (m, 1H), 2.10−2.02 (m, 1H), 2.00−1.89 (m, 1H), 1.89−1.79 (m, 1H), 1.71 (s, 3H), 1.67−1.56 (m, 4H), 1.40 (t, J = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 166.1, 150.5 (d, J = 239.0 Hz), 136.0 (d, J = 29.3 Hz), 133.0, 130.0, 129.3, 128.9 (2C), 126.6 (d, J = 6.5 Hz, 2C), 124.5, 73.8, 61.1, 55.6 (d, J = 5.5 Hz), 54.1, 45.6 (d, J = 2.9 Hz), 29.8, 25.5, 24.4, 28.2, 14.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ −105.4; IR (CH_2Cl_2) 2936, 2475, 1719, 1366, 1277, 1106, 1080, 773, 739 cm^{-1}; MS (ESI) m/e (%) 344.2 ([M + H]$^+$, 100); HRMS (ESI) calcd. for $C_{21}H_{27}FNO_2$ [M + H]$^+$ 344.2026, found 344.2031.

(1S,7aR*,Z)-2-(Fluoro(3-nitrophenyl)methylene)-1-(2-methylprop-1-en-1-yl)hexahydro-1H-pyrrolizine (**7k**).* The crude residue obtained from the reaction of **1k** (82 mg, 0.26 mmol) with Ph_3CBF_4 (0.17 g, 0.52 mmol) in CH_2Cl_2 (26 mL) was purified by flash column chromatography to give **7k** (41 mg, 0.13 mmol, 50%) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (t, J = 1.8 Hz, 1H), 8.14 (ddd, J = 8.3, 2.2, 1.0 Hz, 1H), 7.73 (dt, J = 7.9, 1.2 Hz, 1H), 7.50 (t, J = 8.1 Hz, 1H), 4.97−4.90 (m, 1H), 4.01 (dt, J = 16.7, 2.4 Hz, 1H), 3.84 (dd, J = 16.9, 3.4 Hz, 1H), 3.52−3.45 (m, 1H), 3.33−3.26 (m, 1H), 3.10 (ddd, J = 10.1, 8.0, 4.0 Hz, 1H), 2.62 (dt, J = 10.0, 8.0 Hz, 1H), 2.14−2.05 (m, 1H), 2.03−1.94 (m, 1H), 1.92−1.83 (m, 1H), 1.73−1.65 (m, 4H), 1.59 (d, J = 1.2 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 148.8 (d, J = 237.8 Hz), 147.9, 134.3, 133.6 (d, J = 31.1 Hz), 132.2 (d, J = 6.1 Hz), 128.8, 126.6 (d, J = 19.5 Hz), 124.1, 122.9, 122.2 (d, J = 7.0 Hz), 74.2, 55.7 (d, J = 5.4 Hz), 53.9, 45.5 (d, J = 2.8 Hz), 29.6, 25.5, 24.4, 18.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ −106.4; IR (CH_2Cl_2) 2920, 2610, 2224, 1738, 1531, 1090, 923 cm^{-1}; MS (ESI) m/e (%) 317.2 ([M + H]$^+$, 100); HRMS (ESI) calcd. for $C_{18}H_{22}FN_2O_2$ [M + H]$^+$ 317.1665, found 317.1666.

(1S,7aR*,Z)-2-(Fluoro(4-nitrophenyl)methylene)-1-(2-methylprop-1-en-1-yl)hexahydro-1H-pyrrolizine (**7l**).* The crude residue obtained from the reaction of **1l** (82 mg, 0.26 mmol) with Ph_3CBF_4 (0.17 g, 0.52 mmol) in CH_2Cl_2 (26 mL) was purified by flash column chromatography to give **7l** (48 mg, 0.15 mmol, 58%) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, J = 8.8 Hz, 2H), 7.56 (d, J = 9.0 Hz, 2H), 5.01−4.92 (m, 1H), 4.03 (dt, J = 16.9, 2.4 Hz, 1H), 3.86 (dd, J = 16.9, 3.2 Hz, 1H), 3.53−3.46 (m, 1H), 3.36−3.28 (m, 1H), 3.11 (ddd, J = 10.2, 8.0, 4.1, 1H), 2.63 (dt, J = 10.1, 8.1 Hz, 1H), 2.17−2.07 (m, 1H), 2.04−1.95 (m, 1H), 1.94−1.85 (m, 1H), 1.76 (d, J = 1.2 Hz, 3H), 1.71−1.64 (m, 1H), 1.62 (d, J = 1.1 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 149.1 (d, J = 237.3 Hz), 147.0, 138.1 (d, J = 29.8 Hz), 133.3, 128.9 (d, J = 20.7 Hz), 127.3 (d, J = 6.7 Hz, 2C), 124.4, 122.9 (2C), 74.1, 56.0 (d, J = 5.3 Hz), 53.9, 45.9 (d, J = 2.7 Hz), 29.7 (d, J = 5.7 Hz), 25.5, 24.3, 18.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ −106.9; IR (CH_2Cl_2) 2928, 2853, 2527, 2246, 1734, 1521, 1346, 1091, 950, 855 cm^{-1}; MS (ESI) m/e (%) 317.2 ([M + H]$^+$, 100), 297.2 (20); HRMS (ESI) calcd. for $C_{18}H_{22}FN_2O_2$ [M + H]$^+$ 317.1665, found 317.1668.

(1S,7aR*,Z)-2-((4-Chlorophenyl)fluoromethylene)-1-(2-methylprop-1-en-1-yl)hexahydro-1H-pyrrolizine (**7m**).* The crude residue obtained from the reaction of **1m** (79 mg, 0.26 mmol) with Ph_3CBF_4 (0.17 g, 0.52 mmol) in CH_2Cl_2 (26 mL) was purified by flash column chromatography to give **7m** (48 mg, 0.16 mmol, 60%) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, J = 8.8 Hz, 2H), 7.28 (d, J = 8.8 Hz, 2H), 4.95 (d, J = 9.6 Hz, 1H), 3.94 (dt, J = 16.4, 2.0 Hz, 1H), 3.76 (dd, J = 16.3, 3.1 Hz, 1H), 3.43−3.34 (m, 1H), 3.28−3.19 (m, 1H), 3.06 (ddd, J = 10.2, 8.0, 4.0 Hz, 1H), 2.60 (dt, J = 10.0, 8.0 Hz, 1H), 2.10−2.00 (m, 1H), 1.99−1.89 (m, 1H), 1.87−1.79 (m, 1H), 1.66 (d, J = 0.8 Hz, 3H), 1.64−1.57 (m, 4H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 150.0 (d, J = 237.5 Hz), 134.0, 132.4, 130.7 (d, J = 30 0.4 Hz), 128.2 (d, J = 6.1 Hz, 2C), 127.8 (2C), 125.1, 124.2 (d, J = 21.2 Hz), 73.9, 55.6 (d, J = 5.1 Hz), 53.9, 45.6 (d, J = 3.4 Hz), 29.7, 25.5, 24.4, 18.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ −105.3; IR (CH_2Cl_2) 2922, 2197, 1974, 1655, 1382, 1091, 739 cm^{-1}; MS (ESI) m/e (%) 308.1 ([M + 2 + H]$^+$, 25), 306.1 ([M + H]$^+$, 100), 302.1 (5); HRMS (ESI) calcd. for $C_{18}H_{22}ClFN$ [M + H]$^+$ 306.1425, found 306.1418.

(1S,7aR*,Z)-2-((4-Bromophenyl)fluoromethylene)-1-(2-methylprop-1-en-1-yl)hexahydro-1H-pyrrolizine (**7n**).* The crude residue obtained from the reaction of **1n** (91 mg, 0.26 mmol) with Ph_3CBF_4 (0.17 g, 0.52 mmol) in CH_2Cl_2 (26 mL) was purified by flash column chromatography to give **7n** (60 mg, 0.17 mmol, 66%) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, J = 8.5 Hz, 2H), 7.25 (d, J = 8.6 Hz, 2H), 4.96 (d, J = 9.6 Hz, 1H), 3.94 (dt, J = 16.4, 2.2 Hz, 1H), 3.76 (dd, J = 16.4, 3.1 Hz, 1H), 3.43−3.33 (m, 1H), 3.30−3.21 (m,

DOI: 10.1021/acs.joc.5b02025
J. Org. Chem. XXXX, XXX, XXX−XXX

1H), 3.08 (ddd, J = 10.3, 8.1, 4.1 Hz, 1H), 2.60 (dt, J = 9.9, 8.2 Hz, 1H), 2.10−2.01 (m, 1H), 1.99−1.89 (m, 1H), 1.88−1.79 (m, 1H), 1.66 (d, J = 0.7 Hz, 3H), 1.64−1.5 (m, 4H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 150.1 (d, J = 237.8 Hz), 132.4, 131.1 (d, J = 30.3 Hz), 130.8 (2C), 128.4 (d, J = 6.1 Hz, 2C), 125.1, 124.2 (d, J = 21.2 Hz), 122.3, 73.8, 55.6 (d, J = 5.1 Hz), 54.0, 45.6 (d, J = 3.2 Hz), 29.7, 25.5, 24.4, 18.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ −105.6; IR (CH_2Cl_2) 2967, 2929, 2538, 1912, 1686, 1676, 1487, 1446, 1395, 1287, 1160, 1091, 1010, 828 cm^{-1}; MS (ESI) m/e (%) 352.1 ($[M + 2 + H]^+$, 100), 350.1 ($[M + H]^+$, 100), 311.2 (5); HRMS (ESI) calcd. for $C_{18}H_{22}BrFN$ $[M + H]^+$ 350.0920, found 350.0913.

(1S,7aR*,Z)-2-(Fluoro(thiophen-3-yl)methylene)-1-(2-methylprop-1-en-1-yl)hexahydro-1H-pyrrolizine (**7r**).* The crude residue obtained from the reaction of **1r** (83 mg, 0.30 mmol) with Ph_3CBF_4 (0.20 g, 0.60 mmol) in CH_2Cl_2 (30 mL) was purified by flash column chromatography to give **7r** (11 mg, 0.04 mmol, 14%) as a brown oil: ^1H NMR (400 MHz, $CDCl_3$) δ 7.32−7.31 (m, 1H), 7.27−7.24 (m, 1H), 7.14 (d, J = 5.1, 1.1 Hz, 1H), 5.14 (d, J = 9.2 Hz, 1H), 3.91 (dt, J = 16.2, 2.3 Hz, 1H), 3.74 (dd, J = 16.0, 3.1 Hz, 1H), 3.41−3.37 (m, 1H), 3.30−3.25 (m, 1H), 3.03 (ddd, J = 10.3, 8.0, 4.3 Hz, 1H), 2.59 (dt, J = 10.2, 7.8 Hz, 1H), 2.11−2.03 (m, 1H), 1.97−1.88 (m, 1H), 1.85−1.77 (m, 1H), 1.72 (d, J = 1.1 Hz, 3H), 1.67 (d, J = 1.0 Hz, 3H), 1.66−1.60 (m, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 148.2 (d, J = 234.2 Hz), 133.8 (d, J = 33.6 Hz), 132.0, 126.2 (d, J = 1.4 Hz), 126.0 (d, J = 5.3 Hz), 124.9, 122.9 (d, J = 6.7 Hz), 122.1 (d, J = 21.1 Hz), 74.1, 55.2 (d, J = 4.7 Hz), 53.8, 45.7 (d, J = 3.7 Hz), 30.1, 25.6, 24.4, 18.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ −104.7; IR (CH_2Cl_2) 3712, 2925, 2435, 1673, 1446, 1376, 1246, 1188, 1090, 838, 789 cm^{-1}; MS (ESI) m/e (%), 278.5 ($[M + H]^+$, 100); HRMS (ESI) calcd. for $C_{16}H_{21}NFS$ $[M + H]^+$ 278.1379, found 278.1378.

(1S,7aR*,Z)-2-(Fluoro(phenyl)methylene)-1-(2-methylbut-1-en-1-yl)hexahydro-1H-pyrrolizine (**7s**).* The crude residue obtained from the reaction of **1s** (85 mg, 0.30 mmol) with Ph_3CBF_4 (0.20 g, 0.60 mmol) in CH_2Cl_2 (30 mL) was purified by flash column chromatography to give **7s** (52 mg, 0.18 mmol, 60%) as a mixture of E and Z isomers: ^1H NMR (400 MHz, $CDCl_3$) δ 7.44−7.36 (m, 2H + 2H′), 7.34−7.26 (m, 3H + 3H′), 5.03 (d, J = 9.5 Hz, 1H′), 5.00−4.94 (m, 1H), 4.02−3.92 (m, 1H + 1H′), 3.78 (dd, J = 16.2, 3.1 Hz, 1H), 3.76 (dd, J = 16.1, 3.2 Hz, 1H′), 3.48−3.42 (m, 1H + 1H′), 3.29−3.22 (m, 1H + 1H′), 3.12−3.05 (m, 1H + 1H′), 2.63 (dt, J = 10.0, 8.0 Hz, 1H + 1H′), 2.21−1.97 (m, 2H + 2H′), 1.97−1.90 (m, 1H + 1H′), 1.89−1.80 (m, 2H + 2H′), 1.66−1.59 (m, 4H), 1.59−1.54 (m, 4H′), 0.99 (t, J = 7.6 Hz, 3H′), 0.97 (t, J = 7.5 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 151.1 (d, J = 238.3 Hz), 151.1 (d, J = 238.1 Hz), 137.4, 137.3, 132.3 (d, J = 29.6 Hz), 132.3 (d, J = 30.0 Hz), 128.2, 128.2, 127.7 (2C), 127.7 (2C), 127.0 (d, J = 5.9 Hz, 2C), 127.0 (d, J = 5.8 Hz, 2C), 125.3, 124.0, 123.3 (d, J = 21.6 Hz), 73.9, 73.8, 55.5 (d, J = 5.2 Hz), 55.4 (d, J = 5.6 Hz), 54.1, 54.0, 45.4 (d, J = 3.6 Hz), 45.3 (d, J = 3.8 Hz), 32.2, 29.9, 29.8, 24.9, 24.5, 24.4, 22.4, 16.3, 12.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ −104.5, −104.6; IR (CH_2Cl_2) 3357, 2966, 1684, 1446, 1272, 1051, 766, 696 cm^{-1}; MS (ESI) m/e (%), 286.6 ($[M + H]^+$, 100); HRMS (ESI) calcd. for $C_{19}H_{25}NF$ $[M + H]^+$ 286.1971, found 286.1973.

General Experimental for the $NHTf_2$-Promoted Cycloisomerization of (*E*)-2-Methyl-4-(1-(3-phenylprop-2-yn-1-yl)-pyrrolidin-2-yl)but-3-en-2-ol (1a). *Synthesis of ((1S*,2S*,7aR*)-1-(2-Methylprop-1-en-1-yl)hexahydro-1H-pyrrolizin-2-yl)(phenyl)-methanone (**8a**).* A solution of **1a** (0.0700 g, 0.26 mmol) in CH_2Cl_2 (2.6 mL) was added $NHTf_2$ (0.15 g, 0.52 mmol). The mixture was stirred for 1 min until all **1a** was disappeared as monitored by TLC. The reaction mixture was quenched with saturated $NaHCO_3$ (10 mL). The resulting mixture was extracted with DCM (3 × 30 mL). The organic phase was dried over MgSO4, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (EtOAc/hexanes = 2:1) gave **8a** (31 mg, 0.10 mmol, 45%) as a yellow oil: ^1H NMR (400 MHz, $CDCl_3$) δ 7.93−7.91 (m, 2H), 7.55 (tt, J = 7.4, 1.3 Hz, 1H), 7.46−7.43 (m, 2H), 5.01−4.98 (m, 1H), 3.96 (td, J = 10.0, 7.6 Hz, 1H), 3.56 (dd, J = 10.2, 7.6 Hz, 1H), 3.46−3.42 (m, 1H), 3.07−3.01 (m, 2H), 2.90 (t, J = 10.1 Hz, 1H), 2.78−2.74 (m, 1H), 2.03−1.82 (m, 3H), 1.68−1.64 (m, 1H), 1.59 (d, J = 1.3 Hz, 3H), 1.53 (d, J = 1.3 Hz, 3H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 199.9, 137.1, 135.1, 133.1, 128.5 (2C), 128.5 (2C), 124.2, 71.7, 58.3, 54.9, 54.6, 48.6, 29.9, 25.7, 25.2, 18.2; IR (CH_2Cl_2) 2923, 2854, 1676, 1596, 1443, 1375, 1241, 1221, 1097, 998, 834 cm^{-1}; MS (ESI) m/e (%) 270.2 ($[M + H]^+$, 100), 268.2 (5); HRMS (ESI) calcd. for $C_{18}H_{24}NO$ $[M + H]^+$ 270.1858, found 270.1862.

((1S,2S*,7aR*)-1-(2-Methylprop-1-en-1-yl)hexahydro-1H-pyrrolizin-2-yl)(m-tolyl)methanone (**8b**).* The solution of **1b** (74 mg, 0.26 mmol) in CH_2Cl_2 (2.6 mL) was added $NHTf_2$ (0.15 g, 0.52 mmol). The crude mixture was purified by flash column chromatography to give **8b** (27 mg, 0.09 mmol, 36%) as a yellow oil: ^1H NMR (400 MHz, $CDCl_3$) δ 7.75−7.70 (m, 2H), 7.38−7.30 (m, 2H), 5.03−4.96 (m, 1H), 3.96 (td, J = 10.0, 7.6 Hz, 1H), 3.55 (dd, J = 10.2, 7.6 Hz, 1H), 3.46−3.41 (m, 1H), 3.08−3.00 (m, 2H), 2.86 (t, J = 10.1 Hz, 1H), 2.78−2.72 (m, 1H), 2.40 (s, 3H), 2.04−1.91 (m, 2H), 1.89−1.81 (m, 1H), 1.71−1.65 (m, 1H), 1.60 (d, J = 1.0 Hz, 3H), 1.54 (d, J = 1.0 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 200.1, 138.3, 137.2, 135.0, 133,9, 129,1, 128.4, 125.7, 124.3, 71.6, 58.3, 54.8, 54.7, 48.5, 30.0, 25.8, 25.2, 21.3, 18.2; IR (CH_2Cl_2) 3406, 2969, 2924, 2536, 2484, 2377, 2347, 1677, 1445, 1376, 1260, 1182, 1162, 1023, 999, 731, 683 cm^{-1}; MS (ESI) m/e (%) 284.2 ($[M + H]^+$, 100); HRMS (ESI) calcd. for $C_{19}H_{26}NO$ $[M + H]^+$ 284.2014, found 284.2012.

((1S,2S*,7aR*)-1-(2-Methylprop-1-en-1-yl)hexahydro-1H-pyrrolizin-2-yl)(p-tolyl)methanone (**8c**).* The solution of **1c** (74 mg, 0.26 mmol) in CH_2Cl_2 (2.6 mL) was added $NHTf_2$ (0.15 g, 0.52 mmol). The crude mixture was purified by flash column chromatography to give **8c** (27 mg, 0.09 mmol, 36%) as a yellow oil: ^1H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, J = 8.3 Hz, 2H), 7.24 (d, J = 8.1 Hz, 2H), 5.00−4.96 (m, 1H), 3.89 (td, J = 9.9, 7.6 Hz, 1H), 3.47 (dd, J = 10.0, 7.6 Hz, 1H), 3.35−3.30 (m, 1H), 3.03 (q, J = 9.7 Hz, 1H), 2.99−2.93 (m, 1H), 2.82 (t, J = 9.9 Hz, 1H), 2.73−2.67 (m, 1H), 2.40 (s, 3H), 1.98−1.86 (m, 2H), 1.84−1.76 (m, 1H), 1.68−1.61 (m, 1H), 1.60 (d, J = 1.0 Hz, 3H), 1.55 (d, J = 1.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 199.9, 143.8, 134.9, 134.4, 129.1 (2C), 128.6 (2C), 125.0, 71.8, 58.7, 55.0 (2C), 48.5, 30.1, 25.8, 25.3, 21.6, 18.2; IR (CH_2Cl_2) 2964, 2927, 2690, 2357, 1982, 1674, 1597, 1578, 1448, 1377, 1250, 1185, 1069, 1002, 704 cm^{-1}; MS (ESI) m/e (%) 284.2 ($[M + H]^+$, 100), 270.2 (15); HRMS (ESI) calcd. for $C_{19}H_{26}NO$ $[M + H]^+$ 284.2014, 284.2006.

((1S,2S*,7aR*)-1-(2-Methylprop-1-en-1-yl)hexahydro-1H-pyrrolizin-2-yl) (naphthalen-1-yl)methanone (**8e**).* The solution of **1e** (83 mg, 0.26 mmol) in CH_2Cl_2 (2.6 mL) was added $NHTf_2$ (0.15 g, 0.52 mmol). The crude mixture was purified by flash column chromatography to give **8e** (17 mg, 0.05 mmol, 20%) as a yellow oil: ^1H NMR (400 MHz, $CDCl_3$) δ 8.42 (dd, J = 8.4, 0.9 Hz, 1H), 7.96 (d, J = 8.2 Hz, 1H), 7.88−7.85 (m, 1H), 7.76 (dd, J = 7.2, 1.0 Hz, 1H), 7.58−7.46 (m, 3H), 4.97−4.92 (m, 1H), 3.94 (td, J = 10.0, 7.5 Hz, 1H), 3.53 (dd, J = 10.1, 7.5 Hz, 1H), 3.38−3.33 (m, 1H), 3.11−2.97 (m, 3H), 2.78 (dt, J = 10.5, 6.4 Hz, 1H), 2.03−1.81 (m, 3H), 1.69−1.64 (m, 1H), 1.52 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 204.5, 137.0, 134.7, 133.8, 132.3, 130.0, 128.3, 127.7, 127.4, 126.4, 125.6, 124.5, 124.5, 124.3, 71.7, 58.9, 58.4, 55.1, 49.3, 30.0, 25.7, 25.3, 18.2; IR (CH_2Cl_2) 3367, 3049, 2970, 2925, 2437, 2359, 1681, 1506, 1445, 1376, 1266, 1244, 1179, 1111, 1043, 804 cm^{-1}; MS (ESI) m/e (%) 320.2 ($[M + H]^+$, 100), 311.2 (5); HRMS (ESI) calcd. for $C_{22}H_{26}NO$ $[M + H]^+$ 320.2014, found 320.2013.

(3-Methoxyphenyl)((1S,2S*,7aR*)-1-(2-methylprop-1-en-1-yl)-hexahydro-1H-pyrrolizin-2-yl)methanone (**8f**).* The solution of **1f** (78 mg, 0.26 mmol) in CH_2Cl_2 (2.6 mL) was added $NHTf_2$ (0.15 g, 0.52 mmol). The crude mixture was purified by flash column chromatography to give **8f** (23 mg, 0.08 mmol, 30%) as a yellow oil: ^1H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, J = 7.6 Hz, 1H), 7.46−7.45 (m, 1H), 7.35 (t, J = 7.9 Hz, 1H), 7.10 (dd, J = 8.2, 2.6 Hz, 1H), 4.99 (d, J = 9.7 Hz, 1H), 3.90 (td, J = 9.9, 7.6 Hz, 1H), 3.85 (s, 3H), 3.50 (dd, J = 10.0, 7.8 Hz, 1H), 3.37−3.32 (m, 1H), 3.04 (q, J = 9.5 Hz, 1H), 3.00−2.95 (m, 1H), 2.83 (t, J = 10.0 Hz, 1H), 2.74−2.68 (m, 1H), 2.00−1.87 (m, 2H), 1.84−1.77 (m, 1H), 1.66−1.62 (m, 1H), 1.61 (s, 3H), 1.56 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 200.1, 159.8, 138.7, 134.6, 129.4, 124.8, 121.2, 119.7, 112.5, 71.7, 58.6, 55.4, 55.2, 55.0, 48.5, 30.1, 25.8, 25.2, 18.2; IR (CH_2Cl_2) 2961, 2934, 2348,

DOI: 10.1021/acs.joc.5b02025
J. Org. Chem. XXXX, XXX, XXX−XXX

1678, 1596, 1582, 1450, 1430, 1287, 1262, 1195, 1044, 825, 796, 739 cm^{-1}; MS (ESI) *m/e* (%) 300.2 ([M + H]$^+$, 100); HRMS (ESI) calcd. for $C_{19}H_{26}NO_2$ [M + H]$^+$ 300.1964, found 300.1972.

(4-Methoxyphenyl)((1S,2S*,7aR*)-1-(2-methylprop-1-en-1-yl)-hexahydro-1H-pyrrolizin-2-yl)methanone (**8g**).* The solution of **1g** (78 mg, 0.26 mmol) in CH_2Cl_2 (2.6 mL) was added $NHTf_2$ (0.15 g, 0.52 mmol). The crude mixture was purified by flash column chromatography to give **8g** (18 mg, 0.04 mmol, 15%) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.8 Hz, 2H), 6.92 (d, *J* = 8.9 Hz, 2H), 5.00 (d, *J* = 9.7 Hz, 1H), 3.94 (dt, *J* = 10.1, 7.5 Hz, 1H), 3.87 (s, 3H), 3.58 (dd, *J* = 10.2, 7.4 Hz, 1H), 3.54−3.49 (m, 1H), 3.13−3.07 (m, 1H), 3 03 (q, *J* = 9.7 Hz, 1H), 2.92 (t, *J* = 10.3 Hz, 1H), 2.83−2.77 (m, 1H), 2.04−1.86 (m, 3H), 1.75−1.65 (m, 1H), 1.59 (s, 3H), 1.51 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 197.8, 163.7, 135.5, 130.9 (2C), 130.1, 123.8, 113.7 (2C), 71.7, 58.2, 55.5, 54.8, 53.8, 48.7, 29.9, 25.7, 25.1, 18.2; IR (CH_2Cl_2) 3841, 2939, 2358, 2030, 1662, 1600, 1575, 1512, 1459, 1422, 1379, 1310, 1253, 1172, 1027, 847 cm^{-1}; MS (ESI) *m/e* (%) 300.2 ([M + H]$^+$, 100); HRMS (ESI) calcd. for $C_{19}H_{26}NO_2$ [M + H]$^+$ 300.1964, found 300.1956.

(4-Chlorophenyl)((1S,2S*,7aR*)-1-(2-methylprop-1-en-1-yl)-hexahydro-1H-pyrrolizin-2-yl)methanone (**8m**).* The solution of **1m** (79 mg, 0.26 mmol) in CH_2Cl_2 (2.6 mL) was added $NHTf_2$ (0.15 g, 0.52 mmol). The crude mixture was purified by flash column chromatography to give **8m** (36 mg, 0.12 mmol, 45%) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.6 Hz, 2H), 7.42 (d, *J* = 8.5 Hz, 2H), 4.98 (d, *J* = 9.7 Hz, 1H), 3.86 (dt, *J* = 9.8, 7.6 Hz, 1H), 3.46 (dd, *J* = 10.0, 7.7 Hz, 1H), 3.37−3.32 (m, 1H), 3.02−2.95 (m, 2H), 2.86 (t, *J* = 9.9 Hz, 1H), 2.47−2.68 (m, 1H), 1.98−1.86 (m, 2H), 1.85−1.78 (m, 1H), 1.65−1.60 (m, 1H), 1.60 (s, 3H), 1.52 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 199.2, 139.6, 135.6, 134.9, 129.9 (2C),128.8 (2C), 124.6, 71.8, 58.3, 55.0 (2C), 48.8, 30.1, 25.8, 25.2, 18.2; IR (CH_2Cl_2) 3390, 2930, 2196, 1662, 1589, 1382, 1909, 1010, 841, 740 cm^{-1}; MS (ESI) *m/e* (%)306.1 ([M + 2+ H]$^+$, 25), 304.1 ([M + H]$^+$, 100); HR-MS (ESI) calcd. for $C_{18}H_{23}ClNO$ [M + H]$^+$ 304.1468, found 304.1460.

(4-Bromophenyl)((1S,2S*,7aR*)-1-(2-methylprop-1-en-1-yl)-hexahydro-1H-pyrrolizin-2-yl)methanone (**8n**).* The solution of **1n** (91 mg, 0.26 mmol) in CH_2Cl_2 (2.6 mL) was added $NHTf_2$ (0.15 g, 0.52 mmol). The crude mixture was purified by flash column chromatography to give **8n** (34 mg, 0.10 mmol, 38%) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79−7.76 (m, 2H), 7.60−7.57 (m, 2H), 5.00−4.95 (m, 1H), 3.85 (tr, *J* = 9.8, 7.6 Hz, 1H), 3.46 (dd, *J* = 9.7, 7.8 Hz, 1H), 3.38−3.32 (m, 1H), 3.02−2.95 (m, 2H), 2.86 (t, *J* = 9.8 Hz, 1H), 2.74−2.68 (m, 1H), 1.98−1.75 (m, 3H), 1.67−1.57 (m, 1H), 1.60 (d, *J* = 0.8 Hz, 3H), 1.52 (d, *J* = 0.8 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 199.2, 135.9, 135.1, 131.7 (2C), 130.0 (2C), 128.4, 124.2, 71.6, 58.1, 54.9, 54.6, 48.8, 30.0, 25.7, 25.1, 18.2; IR (CH_2Cl_2) 3404, 2922, 2547, 2359, 2345, 1959, 1676, 1585, 1400, 1251, 1105, 1071, 1009, 840, 739 cm^{-1}; MS (ESI) *m/e* (%) 350.1 ([M + 2+ H]$^+$, 100), 348.1 ([M + H]$^+$, 100); HRMS (ESI) calcd. for $C_{18}H_{23}BrNO$ [M + H]$^+$ 348.0963, found 348.0958.

(2-Bromophenyl)((1S,2S*,7aR*)-1-(2-methylprop-1-en-1-yl)-hexahydro-1H-pyrrolizin-2-yl)methanone (**8o**).* The solution of **1o** (91 mg, 0.26 mmol) in CH_2Cl_2 (2.6 mL) was added $NHTf_2$ (0.15 g, 0.52 mmol). The crude mixture was purified by flash column chromatography to give **8o** (29 mg, 0.08 mmol, 32%) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (dd, *J* = 7.9, 1.0 Hz, 1H), 7.33 (td, *J* = 7.5, 1.0 Hz, 1H), 7.28−7.22 (m, 2H), 4.91−4.84 (m, 1H), 3.78 (td, *J* = 10.0, 7.5 Hz, 1H), 3.50 (dd, *J* = 10.1, 7.4 Hz, 1H), 3.31−3.26 (m, 1H), 3.04−2.96 (m, 2H), 2.91 (q, *J* = 9.8 Hz, 1H), 2.77−2.72 (m, 1H), 2.00−1.79 (m, 3H), 1.65−1.60 (m, 1H), 1.59 (d, *J* = 1.0 Hz, 3H), 1.57 (d, *J* = 1.0 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 204.3, 142.0, 134.8, 133.5, 131.5, 128.4, 127.1, 124.0, 119.0, 71.6, 58.8, 57.5, 55.0, 49.7, 29.8, 25.7, 25.1, 18.3; IR (CH_2Cl_2) 2929, 2538, 2691, 1431, 1380, 1053, 764, 740 cm^{-1}; MS (ESI) *m/e* (%) 350.1 ([M + 2+ H]$^+$, 100), 348.1 ([M + H]$^+$, 100), 298.2 (5); HRMS (ESI) calcd. for $C_{18}H_{23}BrNO$ [M + H]$^+$ 348.0963, found 348.0962.

((1S,2S*,7aR*)-1-(2-Methylprop-1-en-1-yl)hexahydro-1H-pyrrolizin-2-yl) (thiophen-3-yl)methanone (**8r**).* The solution of **1r** (72 mg, 0.26 mmol) in CH_2Cl_2 (2.6 mL) was added $NHTf_2$ (0.15 g, 0.52 mmol). The crude mixture was purified by flash column chromatography to give **8r** (18 mg, 0.065 mmol, 25%) as a brown oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (dd, *J* = 2.8, 1.2 Hz, 1H), 7.53 (dd, *J* = 5.3, 1.3 Hz, 1H), 7.29 (dd, *J* = 5.2, 3.0 Hz, 1H), 5.02−5.00 (m, 1H), 3.71 (td, *J* = 9.9, 7.6 Hz, 1H), 3.49−3.42 (m, 1H), 3.36−3.29 (m, 1H), 3.02−2.93 (m, 2H), 2.89 (t, *J* = 9.9 Hz, 1H), 2.71 (dt, *J* = 10.2, 6.2 Hz, 1H), 1.99−1.87 (m, 2H), 1.87−1.76 (m, 1H), 1.65−1.60 (m, 4H), 1.52 (d, *J* = 1.1 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 194.4, 142.8, 134.8, 132.6, 127.2, 126.1, 124.8, 71.8, 58.3, 56.9, 54.9, 48.7, 30.1, 25.8, 18.2; IR (CH_2Cl_2) 3103, 2938, 1668, 1511, 1417, 1244, 1182, 1101, 834, 749 cm^{-1}; MS (ESI) *m/e* (%), 276.5 ([M + H]$^+$, 100), 258.4 (3); HRMS (ESI) calcd. for $C_{16}H_{22}NOS$ [M + H]$^+$ 276.1422, found 276.1420.

*(E)-2-(3-Methylbuta-1,3-dien-1-yl)-1-(3-phenylprop-2-yn-1-yl)-pyrrolidine (**9a**).* The crude mixture was purified by flash column chromatography to give **9a** (29 mg, 0.08 mmol, 32%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47−7.41 (m, 2H), 7.33−7.29 (m, 3H), 6.34 (d, *J* = 15.6 Hz, 1H), 5.55 (dd, *J* = 15.5, 8.7 Hz, 1H), 4.98 (s, 2H), 3.75 (d, *J* = 17.0 Hz, 1H), 3.51 (d, *J* = 17.0 Hz, 1H), 3.24−3.13 (m, 2H), 2.75−2.67 (m, 1H), 2.08−1.99 (m, 1H), 1.97−1.89 (m, 1H), 1.87 (s, 3H), 1.85−1.77 (m, 1H), 1.76−1.67 (m, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 141.6, 136.1, 131.7, 130.1, 128.3, 128.2, 123.0, 116.5, 85.4, 84.0, 65.4, 52.0, 41.1, 31.8, 22.1, 18.6; IR (CH_2Cl_2) 2980, 2540, 1440, 1001, 764, 740 cm^{-1}; MS (ESI) *m/e* (%) 252.2 ([M + H]$^+$, 100), 199.0 (5), 190.0 (5), 176.1 (5); HRMS (ESI) calcd. for $C_{18}H_{22}N$ [M + H]$^+$ 252.1752, found 252.1749.

(Z)-3-((1S,7aR*)-1-(2-Methylprop-1-en-1-yl)tetrahydro-1H-pyrrolizin-2(3H)-ylidene)isobenzofuran-1(3H)-one (**11**).* The crude residue obtained from the reaction of **1q** (89 mg, 0.26 mmol) with Ph_3CBF_4 (0.17 g, 0.52 mmol) in CH_2Cl_2 (26 mL) was purified by flash column chromatography to give **11** (31 mg, 0.10 mmol, 40%) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94−7.87 (m, 1H), 7.68−7.60 (m, 1H), 7.53−7.44 (m, 2H), 5.25−5.16 (m, 1H), 4.09 (dd, *J* = 17.4, 2.1 Hz, 1H), 3.99 (d, *J* = 17.3 Hz, 1H), 3.69−3.61 (m, 1H), 3.40 (dt, *J* = 7.2, 4.8 Hz, 1H), 3.07 (ddd, *J* = 10.3, 7.8, 4.1 Hz, 1H), 2.56 (dt, *J* = 10.2, 7.9 Hz, 1H), 2.23−2.14 (m, 1H), 2.01−1.93 (m, 1H), 1.92−1.84 (m, 4H), 1.80−1.73 (m, 4H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 166.9, 140.2, 138.0, 134.0, 133.0, 129.7, 128.8, 125.4, 125.3, 125.1, 123.1, 74.3, 56.9, 53.5, 46.0, 30.1, 25.5, 24.4, 18.6; IR (CH_2Cl_2) 2954, 2929, 2430, 2048, 1845, 1776, 1641, 1446, 1380, 1273, 1033, 764 cm^{-1}; MS (ESI) *m/e* (%) 296.2 ([M + H]$^+$, 100); HR-MS (ESI) calcd. for $C_{19}H_{22}NO_2$ [M + H]$^+$ 296.1651, found 296.1659.

*(E)-4-(1-(3-Phenylprop-2-yn-1-yl)pyrrolidin-2-yl)but-3-en-2-ol (**12**).* (0.47 g, 1.86 mmol, 53%). Compound **12** was obtained as a mixture of diastereomers. A yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46−7.41 (m, 2H + 2H′), 7.32− Jonsnow57.27 (m, 3H + 3H′), 5.79 (dd, *J* = 6.2, 0.8 Hz, 1H′), 5.75 (dd, *J* = 6.2, 0.8 Hz, 1H), 5.55 (dd, *J* = 8.5, 1.0 Hz, 1H), 5.51 (dd, *J* = 8.5, 1.0 Hz, 1H′), 4.38−4.29 (m, 1H + 1H′), 3.74 (d, *J* = 5.0 Hz, 1H′), 3.70 (d, *J* = 5.0 Hz, 1H), 3.50 (d, *J* = 9.7 Hz, 1H), 3.46 (d, *J* = 9.7 Hz, 1H′), 3.18−3.11 (m, 1H + 1H′), 3.02 (q, *J* = 8.2 Hz, 1H + 1H′), 2.64 (q, *J* = 8.9 Hz, 1H + 1H′), 2.04−1.93 (m, 2H + 2H′), 1.92−1.83 (m, 1H + 1H′), 1.83−1.74 (m, 1H + 1H′), 1.71−1.60 (m, 1H + 1H′), 1.30 (d, *J* = 2.8 Hz, 3H), 1.28 (d, *J* = 2.7 Hz, 3H′); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 137.3, 137.3, 131.7 (2C), 131.3, 131.3, 128.2 (2C), 128.0, 123.3 84.9, 84.8, 84.8, 68.3, 64.4, 64.3, 52.3, 52.3, 41.2, 41.1, 31.7, 31.7, 23.4, 23.3, 22.1; IR (CH_2Cl_2) 3050, 2855, 2450,1221, 990, 887 cm^{-1}; MS (ESI) *m/e* (%) 256.2 ([M + H]$^+$, 100), 238.4 (3), 144.1 (4), 115.1 (11); HRMS (ESI) calcd. for $C_{17}H_{22}NO$ [M + H]$^+$ 256.1701, found 256.1700.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02025.

NMR spectra for compounds **1a−s**, **3−6**, **7a−d**, **7f**, **7h−n**, **7r−s**, **8a−c**, **8e−g**, **8m−o**, **8r**, **9a**, **11**, and **12**. (PDF)

DOI: 10.1021/acs.joc.5b02025
J. Org. Chem. XXXX, XXX, XXX−XXX

AUTHOR INFORMATION

Corresponding Author

*E-mail: cheyeh@ntnu.edu.tw.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

This work has been supported by the Ministry of Science and Technology (MOST 104-2113-M-003-003) and National Taiwan Normal University.

REFERENCES

(1) (a) Robertson, J.; Stevens, K. *Nat. Prod. Rep.* **2014**, *31*, 1721. (b) Robins, D. J. *Nat. Prod. Rep.* **1989**, *6*, 221. (c) Hartmann, T.; Biller, A.; Witte, L.; Ernst, L.; Boppré, M. *Biochem. Syst. Ecol.* **1990**, *18*, 549. (d) Liddell, J. R. *Nat. Prod. Rep.* **2002**, *19*, 773. (e) Hartmann, T.; Witte. L. *Chemistry, Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Pergamon: Oxford, 1995; pp 155−233. (f) Becker, D. P.; Flynn, D. L.; Moormann, A. E.; Nosal, R.; Villamil, C. I.; Loeffler, R.; Gullikson, G. W.; Moummi, C.; Yang, D. C. *J. Med. Chem.* **2006**, *49*, 1125. (g) Morriello, G. J.; DeVita, R. J.; Mills, S. G.; Young, J. R.; Lin, P.; Doss, G.; Chicchi, G. G.; DeMartino, J.; Kurtz, M. M.; Tsao, K.-L. C.; Carlson, E.; Townson, K.; Wheeldon, A.; Boyce, S.; Collinson, N.; Rupniak, N.; Moore, S. *Bioorg. Med. Chem.* **2008**, *16*, 2156. (h) Brinner, K. M.; Ellman, J. A. *Org. Biomol. Chem.* **2005**, *3*, 2109.

(2) Célérier, J. P.; Haddad, M.; Saliou, C.; Lhommet, G.; Dhimane, H.; Pommelet, J. C.; Chuche, J. *Tetrahedron* **1989**, *45*, 6161.

(3) Roche, C.; Delair, P.; Greene, A. E. *Org. Lett.* **2003**, *5*, 1741.

(4) Takahata, H.; Banba, Y.; Momose, T. *Tetrahedron* **1991**, *47*, 7635.

(5) Keck, G. E.; Cressman, E. N. K.; Enholm, E. J. *J. Org. Chem.* **1989**, *54*, 4345.

(6) (a) Jolly, R. S.; Livinghouse, T. *J. Am. Chem. Soc.* **1988**, *110*, 7536. (b) Hart, D. J.; Tsai, Y.-M. *J. Am. Chem. Soc.* **1984**, *106*, 8209.

(7) Aoyagi, Y.; Manabe, T.; Ohta, A.; Kurihara, T.; Pang, G. L.; Yuhara, T. *Tetrahedron* **1996**, *52*, 869.

(8) Xing, D.; Yang, D. *Org. Lett.* **2013**, *15*, 4370.

(9) Lim, A. D.; Codelli, J. A.; Reisman, S. E. *Chem. Sci.* **2013**, *4*, 650.

(10) (a) Tufariello, J. J.; Lee, G. E. *J. Am. Chem. Soc.* **1980**, *102*, 373. (b) Brandi, A.; Cardona, F.; Cicchi, S.; Cordero, F. M.; Goti, A. *Chem. - Eur. J.* **2009**, *15*, 7808.

(11) Sugimoto, K.; Yamamoto, N.; Tominaga, D.; Matsuya, Y. *Org. Lett.* **2015**, *17*, 1320.

(12) (a) Yeh, M. C. P.; Fang, C. W.; Lin, H. H. *Org. Lett.* **2012**, *14*, 1830. (b) Yeh, M. C. P.; Liang, C. J.; Huang, T. L.; Hsu, H. J.; Tsau, Y. S. *J. Org. Chem.* **2013**, *78*, 5521.

(13) Sonogashira, K. *J. Organomet. Chem.* **2002**, *653*, 46.

(14) Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651.

(15) (a) Dischmann, M.; Frassetto, T.; Breuning, M. A.; Koert, U. *Chem. - Eur. J.* **2014**, *20*, 11300. (b) Wittig, G.; Haag, W. *Chem. Ber.* **1955**, *88*, 1654.

(16) (a) Barry, C. S.; Bushby, N.; Harding, J. R.; Hughes, R. A.; Parker, G. D.; Roe, R.; Willis, C. L. *Chem. Commun.* **2005**, 3727. (b) Kumar, H. M. S.; Qazi, N. A.; Shafi, S.; Kumar, V. N.; Krishna, A. D.; Yadav, J. S. *Tetrahedron Lett.* **2005**, *46*, 7205. (c) Kataoka, K.; Ode, Y.; Matsumoto, M.; Nokami, J. *Tetrahedron* **2006**, *62*, 2471. (d) Olier, C.; Gastaldi, S.; Gil, G.; Bertrand, M. P. *Tetrahedron Lett.* **2007**, *48*, 7801. (e) Bahnck, K. B.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2008**, *130*, 13177. (f) Crosby, S. R.; Harding, J. R.; King, C. D.; Parker, G. D.; Willis, C. L. *Org. Lett.* **2002**, *4*, 577.

(17) (a) Mukaiyama, T.; Kobayashi, S.; Murakami, M. *Chem. Lett.* **1984**, 1759. (b) Mukaiyama, T.; Kobayashi, S.; Murakami, M. *Chem. Lett.* **1985**, 447. (c) Kobayashi, S.; Murakami, M.; Mukaiyama, T. *Chem. Lett.* **1985**, 1535. (d) Ohshima, M.; Murakami, M.; Mukaiyama, T. *Chem. Lett.* **1985**, 1871.

(18) (a) Bah, J.; Franzén, J. *Chem. - Eur. J.* **2014**, *20*, 1066. (b) Bah, J.; Naidu, V. R.; Teske, J.; Franzén, J. *Adv. Synth. Catal.* **2015**, *375*, 148.

(19) (a) Kobayashi, S.; Murakami, M.; Mukaiyama, T. *Chem. Lett.* **1985**, 953. (b) Hashimoto, Y.; Mukaiyama, T. *Chem. Lett.* **1986**, 755. (c) Hashimoto, Y.; Sugumi, H.; Okauchi, T.; Mukaiyama, T. *Chem. Lett.* **1987**, 1691.

(20) (a) Pearson, A. J. *Acc. Chem. Res.* **1980**, *13*, 463. (b) Yeh, M. C. P.; Shieh, B. A.; Fu, H. W.; Tau, S. I.; Chuang, L. W. *J. Am. Chem. Soc.* **1993**, *115*, 5941.

(21) (a) Ichikawa, J.; Yokota, M.; Kudo, T.; Umezaki, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 4870. (b) Lartia, R.; Bertrand, H.; Teulade-Fichou, M. P. *Synlett* **2006**, 610.

(22) Varin, M.; Barré, E.; Iorga, B.; Guillou, C. *Chem. - Eur. J.* **2008**, *14*, 6606.

(23) (a) Cresswell, A. J.; Davies, S. G.; Roberts, P. M.; Thomson, J. E. *Chem. Rev.* **2015**, *115*, 566. (b) Cui, J.; Jia, Q.; Feng, R. Z.; Liu, S. S.; He, T.; Zhang, C. *Org. Lett.* **2014**, *16*, 1442. (c) Kindt, S.; Heinrich, M. R. *Chem. - Eur. J.* **2014**, *20*, 15344. (d) Yuan, W.; Szabó, K. J. *Angew. Chem., Int. Ed.* **2015**, *54*, 8533.

(24) (a) Alloatti, D.; Giannini, G.; Cabri, W.; Lustrati, I.; Marzi, M.; Ciacci, A.; Gallo, G.; Tinti, M. O.; Marcellini, M.; Riccioni, T.; Guglielmi, M. B.; Carminati, P.; Pisano, C. *J. Med. Chem.* **2008**, *51*, 2708. (b) Niida, A.; Tomita, K.; Mizumoto, M.; Tanigaki, H.; Terada, T.; Oishi, S.; Otaka, A.; Inui, K.-i.; Fujii, N. *Org. Lett.* **2006**, *8*, 613. (c) Dutheuil, G.; Couve-Bonnaire, S.; Pannecoucke, X. *Angew. Chem., Int. Ed.* **2007**, *46*, 1290. (d) Hulin, B.; Cabral, S.; Lopaze, M. G.; Van Volkenburg, M. A.; Andrews, K. M.; Parker, J. C. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4770. (e) Van der Veken, P.; Senten, K.; Kertèsz, I.; De Meester, I.; Lambeir, A. M.; Maes, M. B.; Scharpé, S.; Haemers, A.; Augustyns, K. *J. Med. Chem.* **2005**, *48*, 1768. (f) Sciotti, R. J.; Pliushchev, M.; Wiedeman, P. E.; Balli, D.; Flamm, R.; Nilius, A. M.; Marsh, K.; Stolarik, D.; Jolly, R.; Ulrich, R.; Djuric, S. W. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2121.

(25) (a) Jung, M. E.; Brown, R. W. *Tetrahedron Lett.* **1978**, *19*, 2771. (b) Jung, M. E.; Speltz, L. M. *J. Am. Chem. Soc.* **1976**, *98*, 7882.

(26) Jin, T.; Himuro, M.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2009**, *48*, 5893.

DOI: 10.1021/acs.joc.5b02025
J. Org. Chem. XXXX, XXX, XXX−XXX