JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

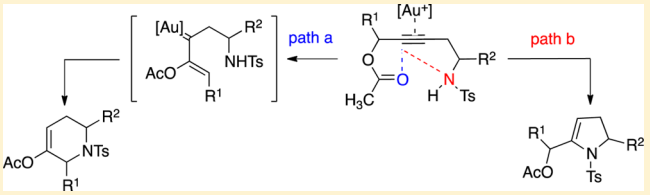
Gold(I)-Promoted Heterocyclization of Internal Alkynes: A Comparative Study of Direct Metallate *5-endo-dig* Cyclization versus a Stepwise Cyclization

Jonathan M. French and Steven T. Diver*

Department of Chemistry, University at Buffalo, the State University of New York, Buffalo, New York 14260, United States

Supporting Information

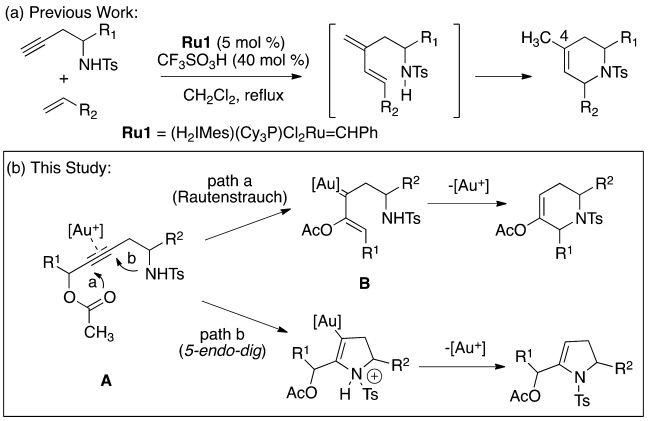
ABSTRACT: With cationic gold catalysts, internal alkynes bearing both propargylic acyloxy groups and tosylamide pronucleophiles were found to cyclize to give either five- or six-membered ring nitrogen heterocycles. A wide variety of gold catalysts, counterions, and solvents were examined to elucidate their effect on product distribution. In most cases, the direct 5-*endo*-dig cyclization was found to be the major pathway leading to good yields of dehydropyrrolidine products. Alkyne substrates bearing additional normal alkyl substituents at the propargylic position gave dehydropiperidines as the major product. This pathway is thought to proceed by way of a 1,2- Rautenstrauch rearrangement to produce a vinyl gold(I) carbene, which undergoes conjugate addition by the nitrogen pronucleophile. Structural and electronic factors were studied in the nitrogen pronucleophile and in the migrating acyloxy group. Each was found to have a minor effect on the product ratio.



INTRODUCTION

Nitrogen-containing heterocycles are commonly found in natural products and pharmaceutically relevant compounds; as such, methods for their synthesis continue to be of significant interest. Previously our group developed a method for the generation of dehydropiperidines through a tandem enyne metathesis/Brønsted acid-promoted 1,4-hydroamination reaction sequence (Scheme 1a).[1] This cyclization proved highly effective, giving high yields of substituted dehydropiperidines. However, a limitation of this methodology is the presence of a methyl group at the 4-position on the resulting dehydropiperidine's ring, arising from protonation of the methylene moiety.

Scheme 1. Previous Approach and Two Mechanistically Distinct Heterocyclizations



In this manuscript, we describe our efforts to expand the scope of this reaction via a gold(I) carbene intermediate **B**, which provides an alternative entry into this ring system (Scheme 1b). A systematic study of reaction conditions and structural effects provides a better understanding of the interplay between these two mechanistically distinct cyclization pathways, leading to either dehydropyrrolidines or dehydropiperidines.

In an effort to make six-membered heterocycles that were not limited to those possessing a methyl group at the 4-position, we sought late transition metals, which are known to activate alkynes toward heterocyclization.[2] Alkynophilic metal catalysts such as Pt(II) and Au(I) are by now well-known promoters of the Rautenstrauch rearrangement (1,2-acyloxy shift)[3] of propargylic acetates, which produces vinyl-substituted metal carbene intermediates such as **B** (path a, Scheme 1b).[4] However, most of the information on the 1,2-acyloxy rearrangement of propargylic acetates is restricted to terminal alkynes. In terminal alkynes, the success of the rearrangement is determined by the steric and electronic nature of the terminal alkyne substrate.[4a] Activation of internal alkynes by π-electrophiles is more difficult because of the added steric effect imposed by the other alkyne substituent, and is less studied. We were interested in bifunctional substrates such as **A** where either process could occur. How effectively would 5-*endo*-dig cyclization occur to make the 5-membered dehydropyrrolidine ring (path b, Scheme 1b)? Could the mechanistically distinct Rautenstrauch rearrangement compete with the direct cyclization in an internal alkyne where binding is presumed to be

Received: April 1, 2014
Published: May 28, 2014

   dx.doi.org/10.1021/jo500748e | J. Org. Chem. 2014, 79, 5569−5585

Scheme 2. Synthesis of the Key Substrate for Initial Optimization Studies

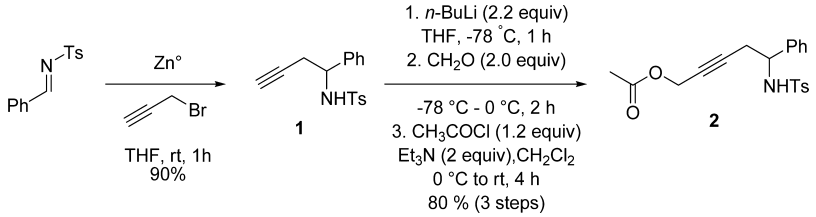
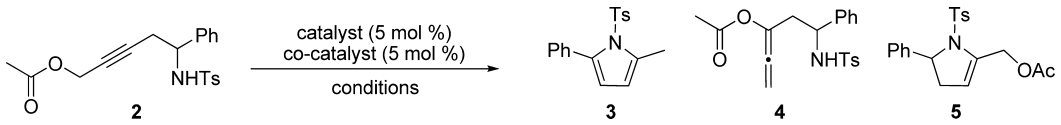


Table 1. Catalyst Optimization



entry	catalyst	solvent	temp (°C)	time (h)	conversion (%)	product (3:4:5)
1	$PtCl_2$[a]	$PhCH_3$	reflux	12	75	75:00:00
2	$AuCl_3$	CH_2Cl_2	reflux	12	54	00:00:54
3	$(PPh_3)AuOTf$	MeCN	rt	16	5	00:00:05
4	$(PPh_3)AuOTf$	MeCN	reflux	16	93	00:44:49
5	$(PPh_3)AuOTf$	CH_2Cl_2	rt	12	100	00:82:18
6	$(PPh_3)AuOTf$	THF	rt	16	100	00:19:81
7	$(PPh_3)AuSbF_6$	THF	rt	16	100	00:26:74
8	$(PPh_3)AuSbF_6$	$PhCH_3$	rt	4	100	00:12:88
9	$(PPh_3)AuSbF_6$	CH_2Cl_2	rt	12	100	00:20:80
10	(IPr)AuOTf	THF	rt	12	100	00:22:78
11	$(IPr)AuSbF_6$	THF	reflux	12	100	00:03:97
12	$(IPr)AuSbF_6$	THF	rt	4	100	00:05:95
13	$(IPr)AuSbF_6$	CH_2Cl_2	rt	4	100	00:05:95
14	$(PPh_3)AuCl$	THF	rt	16	0	–
15	$AgSbF_6$[a]	THF	rt	16	100	00:00:100
16	$AgSbF_6$[b]	THF	rt	4	11	00:00:11

[a]10 mol % catalyst loading. [b]5 mol % catalyst loading.

weaker? Since there was no clear direction from the literature, we designed internal alkyne **A** to contain two different pendant nucleophiles, a propargylic acetate and a homopropargylic sulfonamide. In terms of the Rautenstrauch pathway, alkyne **A** would undergo a 1,2-acetate migration leading to vinyl carbene **B**, which could then undergo cyclization. This pathway would lead to the six-membered ring heterocycle, the dehydropiperidine. Alternatively, direct 5-*endo*-dig cyclization would lead to the 5-membered dehydropyrrolidine. Each of these cycloisomerizations would proceed with atom economy making them efficient methods for heterocycle synthesis. Thus, we expected that this bifunctional internal alkyne substrate would potentially react through two different pathways, providing two nitrogen heterocycles of different size. We were interested in identifying reaction conditions so that either pathway would predominate, delivering either the 5- or 6-membered heterocyclic ring.

RESULTS AND DISCUSSION

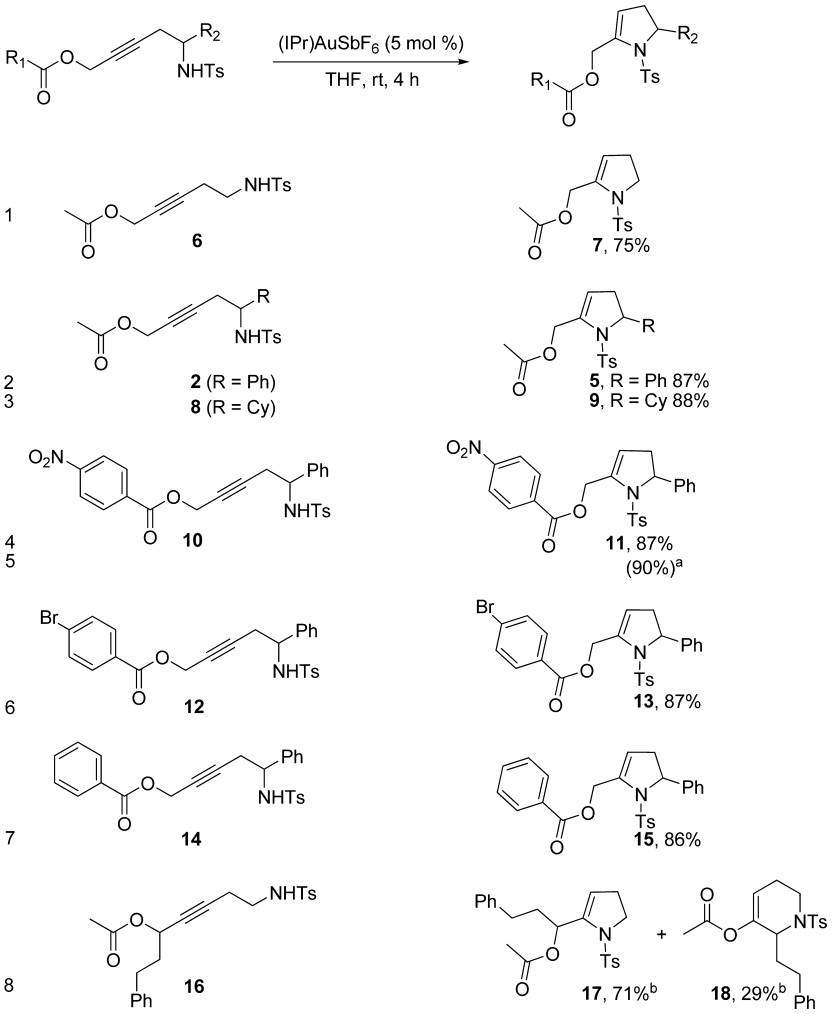
The required bifunctional internal alkyne was made through a four-step synthesis (Scheme 2). The Barbier reaction was used to introduce propargyl bromide into the imine[5] resulting in formation of the homopropargylic amine.[1] The alkyne was subsequently functionalized in a three step sequence. Treatment of the alkyne with 2 equiv of *n*-butyl lithium resulted in formation of the dianion. This deprotonation step was followed by the introduction of the aldehyde, which resulted in the formation of the propargyl alcohol upon work-up. The crude alcohol could then be taken directly into CH_2Cl_2 whereupon it was acylated with acetyl chloride in the presence of triethylamine. The bifunctional alkyne **2** was then purified by flash column chromatography. Additional homopropargylic alkynes were prepared similarly, and their preparation and characterization data can be found in the Experimental Section.

With the desired bifunctional substrate in hand, initial cyclization attempts led us to consider using lower temperatures and cationic gold(I) catalysts. Initial results with $PtCl_2$ resulted in formation of the pyrrole **3** (Table 1, entry 1). The high temperature needed to dissolve the $PtCl_2$ catalyst was also thought to facilitate the loss of the acetate, ultimately leading to formation of the pyrrole.[6] Since most cationic gold reactions are conducted at room temperature, a gold-based catalyst system was sought because of the milder reaction conditions possible. Lower temperatures were expected to result in less pyrrole formation. Gold(III) chloride was initially screened and found to deliver the dehydropyrrolidine. With this neutral catalyst, the reaction did not go to completion within a 12 h period (Table 1, entry 2). However, the major product of this reaction was not the expected 6-membered dehydropiperidine, but found to be the dehydropyrrolidine **5**. This product is derived from direct 5-*endo*-dig cyclization of the gold activated alkyne, and there are few reports of dehydropyrrolidine synthesis in the literature.[7]

The need for lower reaction temperatures led us to evaluate gold(I) catalyst systems. The cationic gold(I) catalysts were generated in standard fashion: prior to the reaction the gold

dx.doi.org/10.1021/jo500748e | J. Org. Chem. 2014, 79, 5569−5585

Table 2. Gold(I)-Catalyzed Synthesis of Dehydropyrrolidines from Propargylic Acetates[c]



[a]This reaction was conducted at 1 mol % catalyst loading for 8 h. [b]Percent of the product by ^{1}H NMR relative to mesitylene, isolated in 67 and 29% yield. [c]Isolated yields after column chromatography.

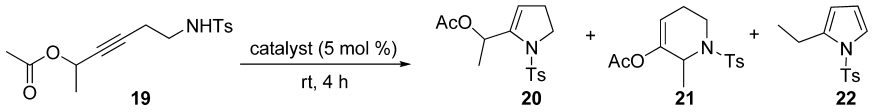
chloride was mixed with the silver salt of choice, which resulted in the precipitation of silver chloride. On the basis of the careful study of Shi et al.,[8] the resulting suspension was then filtered through a plug of Celite and added directly into the reaction vessel, eliminating potential side reactions that could be promoted by the cationic silver(I) cocatalyst. Gold(I) triflate in acetonitrile resulted in very poor conversions at room temperature, perhaps because of the ability of acetonitrile to act as a ligand for cationic gold (Table 1, entry 3). Increasing the temperature of the reaction improved the conversion, yet produced the allene as the major product (entry 4). Moving to dichloromethane solvent resulted in full conversion (entry 5), but allene **4** became the major product. The allene can be formed either by two successive 1,2-acetate migrations[4a] or a direct 3,3-acetate migration.[4f,9] Switching the solvent to THF still allowed full conversion, however there was a dramatic shift in the selectivity of the reaction (entry 6). Under these conditions, using THF as the reaction solvent resulted in the favored formation of the dehydropyrrolidine (entry 6). The counterion was also found to have a significant effect on the reaction. The SbF_6 counteranion resulted in a similar product distribution that favored the formation of the dehydropyrrolidine (entry 7). Two other solvents were screened (entry 8 and 9); however, no significant solvent effect was found in these cases.

Gold catalysts bearing a *N*-heterocyclic carbene (NHC) supported ligand also showed significant counterion and solvent effects. A combination of the 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene *N*-heterocyclic carbene (IPr) ligand with the triflate counterion delivered a similar product distribution as was observed with the $[Au(PPh_3)]^+$ catalyst (Table 1, entry 10). Replacing the triflate anion with the SbF_6 anion resulted in complete conversion and high selectivity for 5 within a 12 h reaction time (entry 11). As seen in entry 12, this selectivity could be maintained even after decreasing the temperature and the time of the reaction, and demonstrated little solvent effect upon moving to dichloromethane (entry 13).

Several control experiments were done to assign the relative contribution of Au(I) and Ag(I) in the heterocyclizations. First, were neutral gold(I) catalysts effective? As a control experiment, the gold source was screened without addition of the silver salt, and as expected for an internal alkyne, no reactivity was observed (Table 1, entry 14). Even though precautions were taken to eliminate the presence of silver in the reaction,[8] another control experiment was performed to evaluate the innate reactivity of the silver salt. Silver(I) is a powerful π-acid

dx.doi.org/10.1021/jo500748e | J. Org. Chem. 2014, 79, 5569−5585

Table 3. Effect of Reaction Conditions on 5- vs 6-Membered Ring Formation



19 20 21 22

entry	catalyst	solvent	product (**20**:**21**:**22**)
1	$(PPh_3)AuOTf$	CH_2CI_2	58:42:00
2	$(PPh_3)AuOTf$	THF	57:35:08
3	$(PPh_3)AuSbF_6$	CH_2CI_2	48:52:00
4	$(PPh_3)AuSbF_6$	THF	32:68:00
5	(IPr)AuOTf	CH_2CI_2	33:30:37
6	(IPr)AuOTf	THF	62:32:06
7	$(IPr)AuSbF_6$	CH_2CI_2	47:43:10
8	$(IPr)AuSbF_6$	THF	40:46:14

in its own right, and known to promote heterocyclizations and cycloisomerizations.[10] There are several examples of gold-catalyzed reactions that suffer from a lower conversion or fail all together without the presence of silver.[11] Surprisingly, full conversion was observed within 16 h with 10 mol % of Ag(I) catalyst (entry 15). Under the gold-catalyzed conditions, the reaction was complete in less than 4 h, yet the same conditions under silver catalysis only resulted in 11% conversion (entry 16). The Ag(I) catalyst gave exclusive cyclization to the dihydropyrrole **5** without any allene detected. This contrast clearly demonstrates that cationic gold catalyst is the more effective catalyst for heterocyclization leading to the dehydropyrrolidine.

On the basis of the optimization studies, $IPrAuSbF_6$ was chosen as the ideal catalyst system as it provided high selectivity and high turnover during the course of the reaction. Similar product distributions were observed in both CH_2Cl_2 and THF. THF was selected for the additional substrates as it is a more environmentally friendly choice than dichloromethane, despite the fact that under experimental conditions some solvent polymerization was occasionally observed.[12]

Several propargylic acetates were evaluated under the optimized reaction conditions (Table 2). Simple propargylic acetate (entry 1) resulted in clean formation of the corresponding dehydropyrrolidine, which was isolated in 75% yield. Substituents adjacent to the pendant nucleophile were also well tolerated in the reaction without any observed drop in yield (entry 2 and 3). The reaction also proceeded in high yield for propargylic benzoates, and the catalyst loading could be dropped to 1 mol % without diminishing the yield (entries 4 and 5). The product in entry 4 provided suitable crystals for an X-ray diffraction study, and the solid state structure determination confirmed our structural assignment based on NMR data (Figure S1, Supporting Information). Additional benzoates performed well in the cyclization giving excellent chemical yields of dehydropyrrolidines (entries 6 and 7).

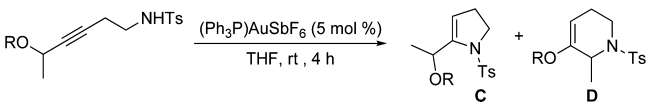
Additional substitution on the acyloxy bearing propargylic carbon resulted in formation of a six-membered ring heterocycle. After analyzing the propensity of 5-*endo*-dig cyclization with substrates containing a variety of acetate and benzoate protecting groups, substrates with propargylic substitution were explored. The initial substrate **16** resulted in a mixture of products (Table 2, entry 8), which proved separable by column chromatography. The major product could be assigned as the dehydropyrrolidine by analogy to the previous entries in Table 2. The second product was new. The distinguishing feature of the new product, as observed by proton NMR, was a dramatic shift of the proton next to the acetate. With dehydropyrrolidine **17**, the chemical shift of this methine proton is affected by the electron-withdrawing nature of the acetate, appearing downfield at δ 6.09 ppm. In the dehydropiperidine **18**, this proton is now alpha to the nitrogen of the sulfonamide, and more shielded than in the starting material. As a result of these changes, this proton appears upfield at δ 4.52 ppm. The same dramatic electron-withdrawing effect is observed in the carbon spectrum as well. In the dehydropyrrolidine **17**, the carbon bonded to the acetate oxygen is downfield at δ 71.2 ppm, whereas the same carbon of dehydropiperidine **18** is upfield at δ 52.8 ppm. The new six-membered ring product most likely resulted from a 1,2-acetate migration preceding cyclization onto the vinyl carbene intermediate (above, Scheme 1b). On the basis of previous results during optimization studies with unsubstituted propargylic acetates under Ag(I) conditions (Table 1, entry 15), we attempted a selective silver-catalyzed 5-*endo* dig cyclization with substituted propargylic acetate **16**. However, these same conditions with catalytic $AgSbF_6$ (5 mol %) were found ineffective with **16** presumably because of the bulk imposed by the additional propargylic substituent.

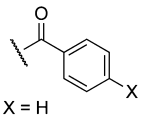
To better study the interplay of the two cyclization pathways, a simpler substrate was studied in greater detail. Internal alkyne **19** also afforded a mixture and 5- and 6-membered heterocycles as the major products (entry 1, Table 3). For this reoptimization study, we continued to take precautions to ensure that silver was not present in the reaction.[8] Introduction of the triflate anion into the system resulted in the generation of a significant amount of pyrrole side product (entries 2 and 5). Regardless of solvent choice or gold source (entries 1, 2, 5 and 6), the triflate counterion did not favor the formation of the 6-membered heterocycle **21** (entry 2). Formation of the pyrrole side product was also significant when using the IPr-gold catalyst (entries 5−8). In each of these cases, the solvent was found to have a minor effect on product distribution. The $(Ph_3P)AuSbF_6$ catalyst provided the highest selectivity for **21** (entries 3 and 4), with THF providing the highest ratio in favor of the 6-membered ring (entry 4). Further changes in the solvent, gold catalyst or the counterion did not exceed the maximum 2:1 product selectivity observed in entry 4. As a result, other factors that might influence product selectivity were subsequently explored.

In an effort to further change the observed product distribution, a variety of acetate and benzoates were investigated (Table 4). A more sterically hindered pivalate group was found to give an almost 1:1 mixture of heterocycles (entry 2). To the best of our knowledge, the effect of electronic

dx.doi.org/10.1021/jo500748e | J. Org. Chem. 2014, 79, 5569−5585

Table 4. Effect of the Migrating Group on Product Distribution



Entry	Alkyne	R =	Products	Ratio (C:D)[a]
1	19		20, 21	32 : 68
2	23		24, 25	47 : 53
3	26	 X = H		74 : 26
4	27	X = Br		56 : 44
5	28	X = NO_2	29, -	72 : 28
6	30	X = OMe	- , 31	29 : 71

[a]Ratio established by ^{1}H NMR relative to mesitylene

variation of the migrating group in a 1,2-acetate migration has not been systematically studied under these conditions.[13] We thought that the propensity of 1,2-acyloxy group migration might be increased with more electron-rich acyloxy groups. Conversely, rearrangement of less electron-rich acyloxy groups would be less favorable and increase the likelihood of the direct 5-*endo*-dig cyclization. The electronically neutral benzoate, as well as the electron-deficient *p*-nitrobenzoate, were both found to favor the dehydropyrrolidine (entries 3 and 5). The product mixture obtained in entry 3 proved inseparable. In entry 5, the only product that could be isolated was the dehydropyrrolidine **29**. The *p*-bromobenzoate **27** demonstrated a slight preference for the dehydropyrrolidine as well, and the product mixture in this case also proved inseparable (entry 4). Finally the *p*-methoxybenzoate **30**, which was expected to be the most electron-rich benzoate, provided selectivity similar to that observed with acetate (entry 6 vs entry 1). Similar to entry 5, only the major product, in this case the dehydropiperidine, was only isolated from entry 6. Overall, the electronic nature of the acyloxy group could not be sufficiently enhanced in internal alkyne substrates to override the direct metalate 5-*endo*-dig cyclization pathway.

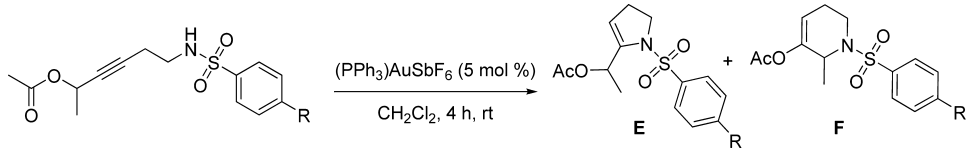
The nucleophilicity of the pendant nitrogen nucleophile was found to have little effect on the ratio of heterocycles. For this study, we returned to dichloromethane as the solvent since an almost 1:1 distribution of products is obtained (Table 5, entry 1) and perturbations would be easily detected. The sulfonamide group is already rather electron-deficient; however, further electronic deactivation of this nucleophile might retard 5-*endo*-dig cyclization. The (*p*-trifluoromethylbenzene)sulfonamide gave a slight increase in formation of the dehydropiperidine (entry 2). The (*p*-nitrobenzene)sulfonamide further favored the formation of the dehydropiperidine (entry 3), but was not able to completely shut down the 5-*endo*-dig cyclization pathway. Electronic effects in the nitrogen protecting group have a minor influence on product distribution.

Propargylic substitution affects heterocycle product distribution. Prior to cyclization, the cationic gold coordinates to the internal alkyne. Substitution at the propargylic position could sterically and electronically influence binding by the gold catalyst, altering selectivity. Alkyne **38** (Table 6, entry 1) was a 1:1 mixture of diastereomers prior to the reaction, after cyclization both products **39** and **40** could be isolated as 1:1 mixture of diastereomers. Substitution adjacent to the nitrogen nucleophile had modest effect on the product ratio (Table 6, entries 1 and 2). However, substitution at the propargylic position affected product distribution. The isopropyl substituent gave an erosion in the selectivity of the formation of the 6-membered heterocycle (entry 3), and *t*-butyl substitution (entry 4) resulted in only the dehydropyrrolidine **45**. Placing a phenyl substituent at the propargylic position resulted in product decomposition, and nothing could be isolated from this reaction (entry 5). Groups such as phenyl are highly stabilizing to an incipient carbocation; decomposition is assumed to proceed through this solvolytic pathway. It was discovered that steric factors could be used to eliminate one reaction pathway; however, none of the changes further increased the selective formation of 6-membered heterocycle.

Fortunately in all but two cases, the product mixtures were separable by chromatography. The benzoate and the *p*-bromobenzoate-containing heterocycles **26** and **27** (Table 4, entries 3 and 4) were inseparable mixtures. However, saponification of the mixture with aqueous sodium hydroxide in methanol gave products that were separable, permitting isolation and characterization.[14] The dehydropyrrolidine benzoate gave rise to secondary alcohol **47**, and the dehydropiperidine gave rise to ketone **48**. Because of the significant polarity difference of the saponification products, they were readily separable.

The saponification both helped corroborate the previously established structural assignments for both products and verified the ratios for the mixtures, which were determined by ^{1}H NMR spectroscopy. Upon hydrolysis, there is a dramatic effect on the chemical shift of the adjacent methine proton in the dehydropyrrolidine (Scheme 3). In the benzoate, this methine proton was found just over δ 6.0 ppm. Removal of the

Table 5. Evaluation of a Variety of Sulfonamides on Product Distribution

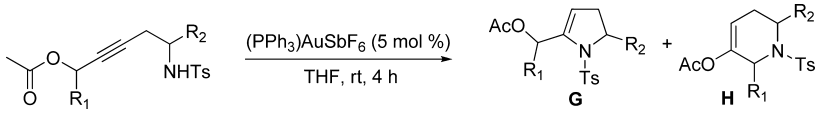


entry	alkyne	R	conversion (%)	product	ratio (E:F)[a]
1	**19**	CH_3	100	**20**/**21**	48:52
2	**32**	CF_3	100	**33**/**34**	44:56
3	**35**	NO_2	100	**36**/**37**	38:62

[a]Ratio established by ^{1}H NMR relative to mesitylene

dx.doi.org/10.1021/jo500748e | J. Org. Chem. 2014, 79, 5569−5585

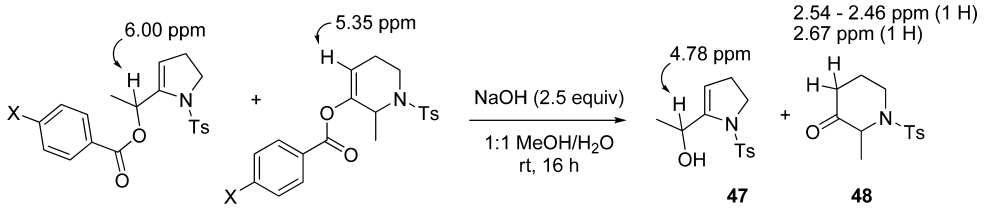
Table 6. Influence of Propargylic Substitution on the Reaction



entry	alkyne	R	product	ratio (G:H)[a]
1	**38**	R_1 = CH_3, R_2 = Ph	**39**/**40**	34:66
2	**19**	R_1 = CH_3, R_2 = H	**20**/**21**	32:68
3	**41**	R_1 = *i*-Pr, R_2 = H	**42**/**43**	43:57
4	**44**	R_1 = *t*-Bu, R_2 = H	**45**	100:0
5	**46**	R_1 = Ph, R_2 = Ph		decomp

[a]Ratio established by ^{1}H NMR relative to mesitylene

Scheme 3. Benzoate Hydrolysis



electron-withdrawing benzoate ester moves the proton upfield by over 1 ppm, to a value of δ 4.78 ppm. The broad singlet between δ 3.70 to 3.55 ppm was also indicative of the newly formed hydroxyl group.

Hydrolysis of the vinyl benzoate in the dehydropiperidine gave the expected ketone **48**. The vinyl proton at δ 5.35 ppm of the starting material was replaced by two protons, a doublet of doublets at δ 2.67 ppm and a multiplet between δ 2.53 and 2.46 ppm. This is consistent with endocyclic axial and equatorial protons adjacent to a ketone. That the hydrolysis of the benzoate gave **48** was also confirmed on the basis of ^{13}C analysis; both the vinyl carbon at δ 116.2 ppm and the benzoate carbonyl near δ 160 ppm were no longer present. Instead, a new signal at δ 206.5 ppm appeared in product **48**, indicative of a carbonyl carbon of a cyclic ketone.

■ CONCLUSIONS

The factors influencing two mechanistically distinct heterocyclization pathways were studied under gold(I) catalysis. With unsubstituted propargylic acetates, direct 5-*endo*-dig cyclization was found to occur in preference to the Rautenstrauch rearrangement/cyclization providing an effective synthetic route to dehydropyrrolidines. Propargylic acetates with substitution at the propargylic center, however, do allow for a competition between the 1,2-acetate migration and direct cyclization. The 1,2-acyloxy shift leads to a dehydropiperidine product by cyclization onto a putative Au(I) vinyl carbene intermediate. Greater bulk at the promigratory acyloxy group tended to favor direct cyclization to give the five-membered ring. Further studies toward the selective synthesis of dehydropiperidines using these methods are currently underway and will be reported in due course.

■ EXPERIMENTAL SECTION

General Information. Unless otherwise stated, reactions were performed using oven-dried glassware under an atmosphere of nitrogen. Solvents were dried by passage through alumina (dichloromethane, THF) and stored under nitrogen. Commercially available reagents were used without further purification, unless otherwise noted. Gold catalysts and silver cocatalysts were stored in a nitrogen-filled glovebox and transferred out of the box in one dram vials. Flash column chromatography was carried out on untreated silica gel 60 (230−400 mesh) under air pressure. Thin layer chromatography was performed on glass-backed silica plates (F254, 250 μm thickness), visualized with UV light or stained with $KMnO_4$ stain. ^{1}H NMR spectra were recorded at 500 MHz, and ^{13}C NMR spectra were recorded at 75 MHz. FT-IR spectra were recorded as thin films and reported in wavenumbers.

Preparation of Alkyne Starting Materials. *General Procedure for the Synthesis of Homopropargylic Amines.* This procedure was adapted from a literature report.[15] To a dry 500 mL round-bottom flask was added imine (120.0 mmol, 1 equiv) and 120 mL of THF (1.0 M). To this solution was added activated zinc[16] (9.42 g, 144.0 mmol), and the solution was allowed to stir at room temperature. To this solution was introduced, slowly via syringe, propargyl bromide (17.5 mL, 180.0 mmol) so as to not allow temperature to go over 25 °C. After stirring for 30 min the reaction was judged complete by TLC and quenched with NH_4Cl (sat.) and extracted with 3 × 100 mL portions of dichloromethane. The organic layers were collected, combined and washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The crude yellow solid was recrystallized from absolute ethanol, resulting in pure alkynyl amine as a white solid.

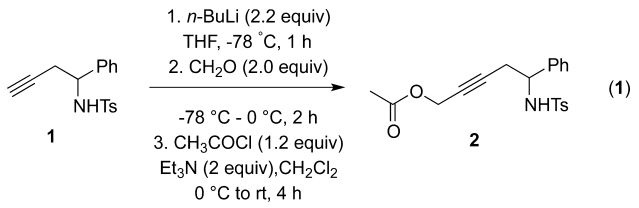
General Procedure for the Synthesis of Propargyl Alcohols. In an oven-dried 100 mL round-bottom flask kept under nitrogen, the alkynyl sulfonamide (3 mmol, 1 equiv) was dissolved in 12 mL of THF and cooled down to −78 °C. To this solution was added dropwise *n*-butyl lithium (3.6 mmol, 1.2 equiv for Boc protected homopropargyl amines and 6.6 mmol, 2.2 equiv for non-Boc protected homopropamines), and stirring was continued at the same temperature for 1 h. At this time, the requisite aldehyde was added as a solution in 5 mL of THF (6.0 mmol, 2 equiv), and stirring was continued at −78 °C for 1 h, and then the mixture was warmed to 0 °C in an ice water bath for 1 h. The reaction was quenched with saturated aqueous NH_4Cl (5 mL). The mixture was diluted with ether (30 mL) and separated. The combined extract containing the crude amino alcohol was dried over sodium sulfate and concentrated in vacuo (rotary evaporator). The propargyl alcohol was then column purified via column chromatography using a gradient of 5−40% ethyl acetate in hexanes.

dx.doi.org/10.1021/jo500748e | J. Org. Chem. 2014, 79, 5569−5585

General Procedure for the Synthesis of Propargyl Acetates. Procedure A. To a 50 mL round-bottom flask containing CH_2Cl_2 was added the propargyl alcohol (1.0 equiv), and triethylamine (2.0 equiv). The solution was cooled to 0 °C with an ice bath for 30 min, at which point the corresponding acyl chloride (1.2 equiv) was added dropwise. The reaction was left to warm to room temperature over 4 h and then quenched with the addition of water. The organic layer was diluted with CH_2Cl_2 and then washed with 1 N HCl and then washed with brine. The organic layer was dried over sodium sulfate, and concentrated in vacuo (rotary evaporator). The crude propargylic ester was purified via flash column chromatography using a gradient elution of 0−30% ethyl acetate in hexanes.

Procedure B. In an oven-dried 100 mL round-bottom flask kept under nitrogen, the alkynyl sulfonamide (3 mmol, 1.0 equiv) was dissolved in 12 mL of THF and cooled down to −78 °C. To this solution was added dropwise *n*-butyl lithium (3.6 mmol, 1.2 equiv for Boc protected homopropargyl amines and 6.6 mmol, 2.2 equiv for non-Boc protected homopropamines), and stirring was continued at the same temperature for 1 h. At this time, the requisite aldehyde was added as a solution in 5 mL of THF (6.0 mmol, 2.0 equiv), and stirring was continued at −78 °C for 1 h, and then the mixture was warmed to 0 °C in an ice water bath for 1 h. The reaction was quenched with saturated aqueous NH_4Cl (5 mL). The mixture was diluted with ether (30 mL), and the organic layer was separated and washed with water and brine. The combined extract containing the crude propargyl alcohol was dried over sodium sulfate and concentrated in vacuo (rotary evaporator). The propargyl alcohol was then dissolved in 10 mL of CH_2Cl_2, along with triethylamine (6 mmol, 2.0 equiv). The solution was placed in an ice bath for 30 min, at which time to the reaction was added the requisite acid chloride (3.6 mmol, 1.2 equiv), and resulting solution was allowed to warm to room temperature for 4 h before being quenched with the addition of water. The reaction was diluted with another 20 mL of CH_2Cl_2, the organic layer was separated, washed with 10 mL of 1 M HCl, dried over sodium sulfate, concentrated under a vacuum, and then column purified via flash column chromatography using a gradient of 5−30% ethyl acetate in hexanes to afford the propargyl acetates.

General Procedure for Boc Deprotection. The Boc protected sulfonamide was dissolved in 10 mL of CH_2Cl_2, and to the solution was added 3 mL of TFA. The solution was left to stir for 4 h at room temperature or until judged complete by TLC. The reaction was then diluted with 30 mL of CH_2Cl_2 and then neutralized with the addition of a saturated solution of sodium bicarbonate. The organic layer was removed and dried over magnesium sulfate. The organic fraction was then concentrated (rotary evaporator) and then purified via flash column chromatography using a gradient elution of 0−30% ethyl acetate in hexanes to afford the pure sulfonamide.



4-Methyl-*N*-(1-phenylbut-3-ynyl)benzenesulfonamide (1). According to the general procedure, alkynyl amine **1** was obtained as a white solid in 90% yield (10.4 g). Compound **1** is a known, fully characterized compound and spectral data matched those previously reported:[17] ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 7.63 (d, J = 8.5 Hz, 2 H), 7.20−7.14 (m, 7 H), 5.37 (br s, 1 H), 4.52 (dt, J = 6.5, 6.0 Hz, 1 H), 2.64−2.62 (m, 2 H), 2.37 (s, 3 H), 2.41−2.37 (m, 2 H), 1.96 (s, 1 H).

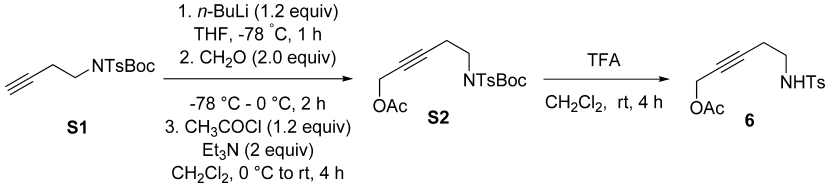
5-(4-Methylphenylsulfonamido)-5-phenylpent-2-ynyl acetate (2). According to the general procedure **B** of the synthesis of propargylic acetates, **2** was obtained as a white solid in 80% yield (980 mg): mp 78−80 °C; Analytical TLC R_f = 0.22 (1:5 ethyl acetate:petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 7.62 (d, J = 8.3 Hz, 2 H), 7.16−6.94 (m, 7 H), 5.29 (d, J = 7.3 Hz, 1 H), 4.54 (s, 2 H), 4.55−4.49 (m, 1 H), 2.70−2.65 (m, 2 H), 2.38 (s, 3 H), 2.08 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 170.3, 143.3, 139.2, 137.3, 129.4, 128.4, 127.1, 126.5, 82.1, 77.9, 55.8, 52.3, 27.7, 21.4, 20.7; FT-IR (thin film, cm^{-1}) 3273, 3232, 3036, 2921, 2251, 1740, 1596, 1426, 1332, 1234, 1164, 1091, 1062, 1021, 956, 915, 809; High-resolution MS (ESI$^+$, m/z) molecular ion [M + Na]$^+$ calculated for $C_{20}H_{21}O_4N_1S_1$ 394.1084, found 394.1074, error 2.4 ppm.

***N*-(But-3-ynyl)-4-methylbenzenesulfonamide (S1).** See Scheme 4. TsNHBoc (5.37 g, 19.8 mmol) was dissolved in THF (25 mL) in a dry 250 mL round-bottom flask. Homopropargyl alcohol (1.98 mL, 26.0 mmol) was added to the solution, followed by PPh_3 (10.0 g, 40 mmol) and diethyl azodicarboxylate (5.22 g, 4.66 mL, 30 mmol) and let stir for 16 h. The reaction was concentrated to a yellow oil, which was triturated with copious amounts of hexanes and filtered to remove the triphenylphosphine oxide. The combined hexanes washings could be concentrated to afford a light yellow solid. The crude solid was then purified via flash column chromatography over SiO_2 using 10% ethyl acetate in hexanes as the mobile phase to afford the alkyne in 62% yield (3.60 g) of **S1** as a white solid. Compound **S1** is a known, fully characterized compound and spectral data matched those reported:[18] ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 7.81 (d, J = 7.0 Hz, 2 H), 7.31 (d, J = 8.5 Hz, 2 H), 4.00 (t, J = 7.0 Hz, 2 H), 2.68−2.64 (m, 2 H), 2.44 (s, 3 H), 2.02 (s, 1 H), 1.35 (s, 9 H).

5-(*N*-(*tert*-Butoxycarbonyl)-4-methylphenylsulfonamido)-pent-2-ynyl acetate (S2). According to the general procedure **B** of the synthesis of propargylic acetates, compound **S2** was obtained as a white solid in 88% yield (550 mg): mp 72−74 °C; Analytical TLC R_f = 0.27 (1:4 ethyl acetate:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 7.80 (d, J = 8.0 Hz, 2 H), 7.32 (d, J = 8.0 Hz, 2 H), 4.65 (s, 2 H), 3.98 (t, J = 7.5 Hz, 2 H), 2.72−2.68 (m, 2 H), 2.44 (s, 3 H), 2.09 (s, 3 H), 1.35 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 170.2, 150.6, 144.2, 137.2, 129.2, 127.8, 84.5, 83.4, 76.1, 52.5, 45.1, 27.8, 21.6, 20.7, 20.2; FT-IR (thin film, cm^{-1}) 2980, 2936, 1731, 1597, 1439, 1358, 1292, 1225, 1157, 1091, 1026, 969, 914, 846, 815, 771, 741, 719, 675; High-resolution MS (ESI$^+$, m/z) molecular ion [M + Na]$^+$ calculated for $C_{19}H_{25}O_6N_1S_1$ 418.1295, found 418.1294, error 0.1 ppm.

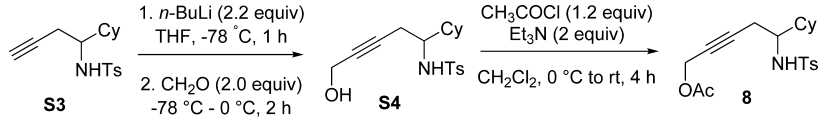
5-(4-Methylphenylsulfonamido)pent-2-ynyl acetate (6). According to the general procedure for TFA deprotection, propargylic acetate **6** was obtained as a white solid in 94% yield (385 mg): mp 62−64 °C; Analytical TLC R_f = 0.14 (1:4 ethyl acetate:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 7.77 (d, J = 8.5 Hz, 2 H), 7.32 (d, J = 8.0 Hz, 2 H), 5.24 (t, J = 6.0 Hz, 1 H), 4.60 (s, 2 H), 3.10 (dt, J = 6.5, 6.5 Hz, 2 H), 2.43 (s, 3 H), 2.41−2.37 (m, 2 H), 2.08 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ170.3, 143.5, 136.9, 129.7, 126.9, 83.2, 52.4, 41.5, 21.4, 20.7, 20.1; FT-IR (thin film, cm^{-1}) 3273, 2950, 1732, 1597, 1434, 1323, 1230, 1156, 1095, 1021, 817, 662; High-resolution MS (EI$^+$, m/z) molecular ion [M]$^+$ calculated for $C_{14}H_{17}O_4N_1S_1$ 295.0873, found 295.0875, error 0.9 ppm.

Scheme 4. Synthesis of Alkyne 6

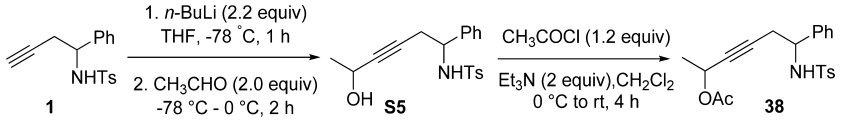


dx.doi.org/10.1021/jo500748e | J. Org. Chem. 2014, 79, 5569−5585

Scheme 5. Synthesis of Alkyne 8



Scheme 6. Synthesis of Alkyne 38



***N*-(1-Cyclohexylbut-3-ynyl)-4-methylbenzenesulfonamide (S3).** See Scheme 5. According to the general procedure, homopropargyl amine S3 was obtained white solid in 59% yield (1.45 g): mp 92−95 °C; Analytical TLC R_f = 0.55 (1:3 ethyl acetate:petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.75 (d, J = 9.5 Hz, 2 H), 7.29 (d, J = 10.5 Hz, 2 H), 4.67 (d, J = 11.5 Hz, 1 H), 3.10 (m, 1 H), 2.42 (s, 3 H), 2.34−2.28 (m, 1 H) 2.19−2.13 (m, 1 H), 1.94−1.92 (m, 1 H), 1.84−1.49 (m, 6 H), 1.21−1.05 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 143.3, 138.1, 129.6, 127.3, 79.6, 71.3, 56.4, 40.2, 29.5, 28.7, 26.1, 26.0, 25.9, 25.8, 22.2, 21.5; IR (thin film, cm^{-1}) 3282, 2928, 2853, 1598, 1448, 1329, 1160, 1093, 961, 909, 814; High-resolution MS (ESI$^+$, m/z) molecular ion [M + Na]$^+$ calculated for $C_{17}H_{23}O_2N_1S_1$ 328.1346, found 328.1344, error 0.9 ppm.

***N*-(1-Cyclohexyl-5-hydroxypent-3-ynyl)-4-methylbenzenesulfonamide (S4).** Following the general procedure for propargylic alcohols, alkyne **S4** was isolated as clear oil in 58% yield (928 mg): Analytical TLC R_f = 0.09 (1:4 ethyl acetate:petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 7.81 (d, J = 8.5 Hz, 2 H), 7.32 (d, J = 8.0 Hz, 2 H), 5.54 (d, J = 9.5 Hz, 1 H), 4.18 (s, 2 H), 3.16−3.08 (m, 1 H), 2.74 (br s, 1 H), 2.43 (s, 3 H), 2.36−2. Thirty (m, 1 H), 2.24−2.18 (m, 1 H), 1.82 (d, J = 13.0 Hz, 1 H), 1.70−1.47 (m, 5 H), 1.22−1.02 (m, 3 H), 093−0.76 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 143.3, 138.2, 129.6, 126.9, 81.5, 81.1, 56.9, 51.0, 40.3, 29.3, 28.9, 25.8, 22.3, 21.5; FT-IR (thin film, cm^{-1}) 3520, 3284, 2930, 2853, 1598, 1447, 1330, 1160, 1093, 1065, 965, 915, 815; High-resolution MS (ESI$^+$, m/z) molecular ion [M + Na]$^+$ calculated for $C_{18}H_{25}O_3N_1S_1$ 358.1447, found 358.1452, error 1.4 ppm.

5-Cyclohexyl-5-(4-methylphenylsulfonamido)pent-2-ynyl acetate (8). According to the general procedure **B** of the synthesis of propargylic acetates, **8** was obtained as a clear oil in 73% yield (758 mg): Analytical TLC R_f = 0.60 (1:3 ethyl acetate:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 7.78 (d, J = 8.5 Hz, 2 H), 7.30 (d, J = 8.0 Hz, 2 H), 5.14 (d, J = 9.5 Hz, 1 H), 4.56 (s, 2 H), 3.16−3.11 (m, 1 H), 2.42 (s, 3 H), 2.37−2.23 (m, 2 H), 2.08 (s, 3 H), 1.78 (d, J = 13.0 Hz, 1 H), 1.67−1.48 (m, 5 H), 1.21−0.76 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 170.1, 143.0, 138.0, 129.4, 126.8, 82.7, 56.5, 52.4, 40.2, 29.2, 28.2, 25.9, 25.8, 25.7, 22.4, 21.3, 20.6; FT-IR (thin film, cm^{-1}) 3283, 2927, 2853, 1745, 1598, 1494, 1447, 1378, 1329, 1226, 1160, 1093, 1065, 1026, 965, 915, 815, 732, 667; High-resolution MS (EI$^+$, m/z) molecular ion [M]$^+$ calculated for $C_{20}H_{27}O_4N_1S_1$ 377.1655, found 377.1657, error 0.6 ppm.

5-(4-Methylphenylsulfonamido)-5-phenylpent-2-ynyl 4-nitrobenzoate (10). According to the general procedure **B** of the synthesis of propargylic acetates, **10** was obtained as an off-white solid in 85% yield (1100 mg): mp 118−120 °C; Analytical TLC R_f = 0.35 (1:3 ethyl acetate:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 8.31 (d, J = 8.5 Hz, 2 H), 8.22 (d, J = 8.5 Hz, 2 H), 7.61 (d, J = 8.5 Hz, 2 H), 7.16−7.10 (m, 7 H), 5.28 (br s, 1 H), 4.86 (s, 2 H), 4.56 (dt, J = 7.5, 6.0 Hz, 1 H), 2.79−2.68 (m, 2 H), 2.39 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 163.9, 143.2, 139.0, 137.2, 134.7, 130.8, 129.3, 128.3, 127.7, 127.0, 126.4, 123.5, 83.2, 77.3, 55.8, 53.8, 27.8, 21.5; FT-IR (thin film, cm^{-1}) 3289, 2921, 1728, 1597, 1524, 1434, 1348, 1270, 1160, 1099, 948, 813, 723; High-resolution MS (EI$^+$, m/z) molecular ion [M]$^+$ calculated for $C_{25}H_{22}O_6N_2S_1$ 478.1199, found 478.1193, error 2.3 ppm.

5-(4-Methylphenylsulfonamido)-5-phenylpent-2-ynyl 4-bromobenzoate (12). According to the general procedure **B** of the synthesis of propargylic acetates, **12** was obtained as a white solid in 82% yield (1204 mg): mp 108−110 °C; Analytical TLC R_f = 0.43 (1:4 ethyl acetate:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 7.91 (d, J = 8.5 Hz, 2 H), 7.62−7.60 (m, 4 H), 7.17−7.12 (m, 7 H), 5.24 (d, J = 7.5 Hz, 1 H), 4.78 (t, J = 2.0 Hz, 2 H), 4.55 (dt, J = 6.0, 6.0 Hz, 1 H), 2.71−2.66 (m, 2 H), 2.36 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 165.3, 143.3, 139.2, 137.4, 131.8, 131.3, 129.4, 128.4, 127.8, 127.1, 126.5, 82.6, 77.9, 55.7, 53.1, 27.8, 21.5; IR (thin film, cm^{-1}) 1725, 1590, 1268, 1160, 1097; High-resolution MS (ESI$^+$, m/z) molecular ion [M + Na]$^+$ calculated for $C_{25}H_{22}O_4N_1Br_1S_1$ 534.0345, found 534.0346, error 0.1 ppm.

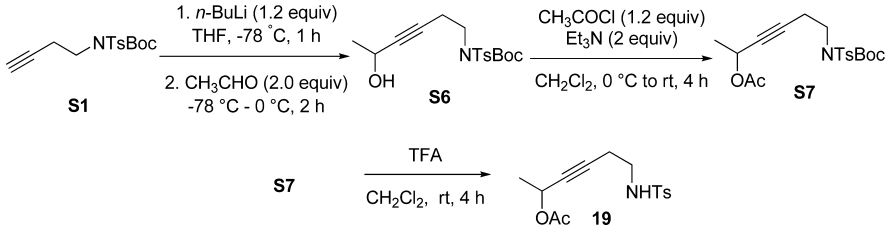
5-(4-Methylphenylsulfonamido)-5-phenylpent-2-ynyl benzoate (14). According to the general procedure **B** of the synthesis of propargylic acetates, compound **14** was isolated as a clear oil in 87% yield (1010 mg): Analytical TLC R_f = 0.29 (1:4 ethyl acetate:petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 8.02 (d, J = 7.5 Hz, 2 H), 7.63 (d, J = 8.0 Hz, 2 H), 7.56 (t, J = 7.0 Hz, 1 H), 7.43 (t, J = 7.5 Hz, 2 H), 7.15−7.07 (m, 7 H), 5.84 (d, J = 8.0 Hz, 1 H), 4.74 (s, 2 H), 4.55 (dt, J = 7.0, 6.5, Hz, 1 H), 2.67 (m, 2 H), 2.30 (s, 3 H);^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 165.8, 143.0, 139.2, 137.3, 133.1, 129.6, 129.2, 128.3, 128.2, 127.5, 126.9, 126.4, 82.4, 77.7, 55.8, 52.8, 27.6, 21.2; FT-IR (thin film, cm^{-1}) 3264, 3064, 2929, 2251, 1712, 1597, 1495, 1446, 1434, 1323, 1266, 1156, 1099, 1066, 960, 907, 817. High-resolution MS (EI$^+$, m/z) molecular ion [M]$^+$ calculated for $C_{25}H_{23}O_4N_1S_1$ 433.1342, found 433.1340, error 0.5 ppm.

***N*-(5-Hydroxy-1-phenylhex-3-ynyl)-4-methylbenzenesulfonamide (S5).** See Scheme 6. Following the general procedure for propargylic alcohols, isolated as a clear oil in 54% yield (625 mg): Analytical TLC R_f = 0.05 (1:4 ethyl acetate:petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 7.65 (d, J = 8.0 Hz, 2 H), 7.17−7.13 (m, 7 H), 6.16 (d, J = 7.5, 1 H), 4.50 (q, J = 7.5 Hz, 1 H), 4.42−4.37 (m, 1 H), 2.88 (t, J = 6.0 Hz, 1 H), 2.64−2.55 (m, 2 H), 2.34 (s, 3 H), 1.33 (d, J = 6.0 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 143.2, 139.5, 137.2, 129.4, 129.3, 128.2, 127.5, 127.0, 126.5, 86.1, 78.9, 58.1, 56.1, 27.7, 24.1, 21.4; FT-IR (thin film, cm^{-1}) 3277, 3064, 3032, 2981, 2929, 2250, 1592, 1434, 1346, 1228, 1168, 1089, 1062, 1032, 952, 814; High-resolution MS (ESI$^+$, m/z) molecular ion [M + Na]$^+$ calculated for $C_{19}H_{21}O_3N_1S_1$ 366.1134, found 366.1135, error 0.5 ppm.

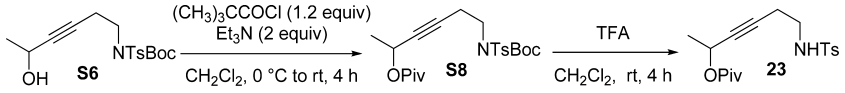
6-(4-Methylphenylsulfonamido)-6-phenylhex-3-yn-2-yl acetate (38). According to the general procedure **A** of the synthesis of propargylic acetates, compound **38** was isolated as a 1:1 mixture of diastereomers as a clear oil in 48% yield (338 mg): Analytical TLC R_f = 0.21 (1:4 ethyl acetate:petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 7.63−7.60 (m, 4 H), 7.18−7.12 (m, 14 H), 5.62 (d, J = 7.5 Hz, 1 H), 5.58 (d, J = 7.5 Hz, 1 H), 5.28−5.24 (m, 2 H), 4.50−4.47 (m, 2 H), 2.65−2.61 (m, 4 H), 2.36 (s, 6 H), 2.04 (s, 3 H), 2.02 (s, 3 H), 1.35 (d, J = 7.0 Hz, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ170.1, 169.9, 143.1, 139.2, 137.3, 129.3, 128.2, 127.6, 127.5, 127.0, 126.9, 126.5, 82.3, 80.2, 60.5, 60.4, 55.9, 55.8, 27.7, 27.6, 21.3, 21.1, 21.0, 20.94, 20.9; FT-IR (thin film, cm^{-1}) 3314, 3260, 3023, 2995, 2933, 1736, 1593, 1495, 1446, 1364, 1332, 1242, 1160, 1058, 1025,

dx.doi.org/10.1021/jo500748e | J. Org. Chem. 2014, 79, 5569−5585

Scheme 7. Synthesis of Alkyne 19



Scheme 8. Synthesis of Alkyne 23



948, 915, 821, 731, 694; High-resolution MS (ESI$^+$, m/z) molecular ion [M + Na]$^+$ calculated for $C_{21}H_{23}O_4N_1S_1$ 408.1240, found 408.1249, error 2.4 ppm.

5-(4-Methylphenylsulfonamido)-1,5-diphenylpent-2-ynyl acetate (46). According to the general procedure **B** of the synthesis of propargylic acetates, compound **46** was isolated as a clear oil in 63% yield (558 mg): Analytical TLC R_f = 0.38 (1:4 ethyl acetate:petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 7.60−7.57 (m, 2 H), 7.32 (s, 5 H), 7.19−7.07 (m, 7 H), 6.30−6.27 (m, 1 H), 5.44 (t, J = 8.5 Hz, 1 H), 4.53 (dt, J = 7.0, 6.5 Hz, 1 H), 2.73−2.70 (m, 2 H), 2.35−2.34 (m, 3 H), 2.07−2.05 (m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 170.0, 169.8, 143.2, 139.1, 137.2, 136.6, 129.4, 128.8, 128.7, 128.5, 128.3, 127.7, 127.6, 127.5, 127.0, 126.6, 83.0, 82.9, 80.4, 65.8, 65.7, 55.9, 55.8, 27.7, 27.6, 21.4, 21.0; FT-IR (thin film, cm^{-1}) 3292, 3272, 3024, 2923, 1733, 1598, 1495, 1454, 1331, 1232, 1157, 1092, 1022, 965, 912, 816, 701, 664; High-resolution MS (ESI$^+$, m/z) molecular ion [M + Na]$^+$ calculated for $C_{26}H_{25}O_4N_1S_1$ 470.1397, found 470.1409, error 2.9 ppm.

7-(4-Methylphenylsulfonamido)-1-phenylhept-4-yn-3-yl acetate (16). To an oven-dried three neck-round-bottom flask 4.3 g (13.4 mmol, 1 equiv) of alkyne **S1** was dissolved in 35 mL of THF. The solution was cooled to −78 °C, and 15 mL (29.4 mmol, 2.2 equiv) of 2 M *n*-butyl lithium was added to the reaction in a dropwise fashion. After 1 h, the requisite aldehyde (16.1 mmol, 1.2 equiv) was added to the reaction, and it was allowed to warm to 0 °C over the period of 1 h. The reaction was quenched by the addition of 0.95 mL (13.4 mmol, 1.0 equiv) of acetyl chloride and allowed to warm to room temperature for another hour. The reaction was then quenched with the addition of ammonium chloride and extracted with diethyl ether. The organic extracts were combined, washed with brine and dried over magnesium sulfate. The crude oil was directly concentrated and then dissolved in a minimum volume of dichloromethane and 3 mL of TFA. The reaction was allowed to stir for 3 h at room temperature. The reaction was then quenched with the addition of sodium carbonate until neutral pH was obtained (pH paper). The reaction was diluted with more dichloromethane and washed with brine. The organic layer was dried over magnesium sulfate and concentrate to afford a yellow oil. The crude oil was then purified by flash column chromatography on silica gel using a gradient elution of 10−40% ethyl acetate in hexanes to afford compound **16** as a yellow oil in 56% yield (2.59 g): Analytical TLC R_f = 0.14 (1:4 ethyl acetate:petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 7.76 (d, J = 8.0 Hz, 2 H), 7.29−7.26 (m, 4 H), 7.20−7.16 (m, 3 H), 5.25 (t, J = 6.5 Hz, 1 H), 5.10 (t, J = 6.0 Hz, 1 H), 3.09 (dt, J = 7.0, 7.0 Hz, 2 H), 2.73 (t, J = 8.0 Hz, 2 H), 2.41−2.36 (m, 5 H), 2.06−2.01 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 170.0, 145.0, 143.4, 140.7, 140.5, 136.9, 136.4, 129.9, 126.6, 128.4, 128.3, 127.4, 126.9, 126.0, 82.3, 79.9, 63.7, 41.6, 36.1, 31.2, 21.4, 20.9, 20.0; FT-IR (thin film, cm^{-1}) 3292, 3024, 2923, 1733, 1598, 1495, 1454, 1331, 1232, 1157, 1092, 1022, 912, 815, 701; High-resolution MS (ESI$^+$, m/z) molecular ion [M + Na]$^+$ calculated for $C_{22}H_{25}O_4N_1S_1$ 422.1397, found 422.1395, error 0.3 ppm.

***tert*-Butyl 5-hydroxyhex-3-ynyl(tosyl)carbamate (S6).** See Scheme 7. Following the general procedure for propargylic alcohols, isolated as a white solid in 78% yield (4.4 g): mp 102−104 °C; Analytical TLC R_f = 0.11 (1:4 ethyl acetate:petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 7.80 (d, J = 8.0 Hz, 2 H), 7.32 (d, J = 9.0, 2 H), 4.51−4.48 (m, 1 H), 4.00 (t, J = 7.0 Hz, 2 H), 2.68 (t, J = 7.5 Hz, 2 H), 2.59−2.53 (br s, 1 H), 2.44 (s, 3 H), 1.42 (d, J = 6.5 Hz, 3 H), 1.34 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 150.6, 144.2, 137.1, 129.2, 127.6, 84.6, 84.4, 80.3, 58.1, 45.2, 27.7, 24.3, 21.4, 19.9; FT-IR (thin film, cm^{-1}) 3517, 2972, 2930, 2238, 1731, 1595, 1448, 1364, 1275, 1155, 1086, 971, 913, 845, 809, 767, 730, 672; High-resolution MS (ESI$^+$, m/z) molecular ion [M + Na]$^+$ calculated for $C_{18}H_{25}O_5N_1S_1$ 390.1346, found 390.1340, error 1.4 ppm.

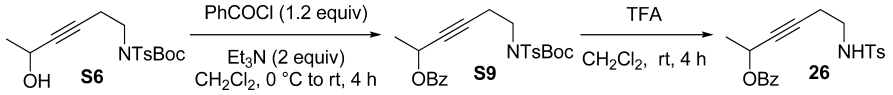
6-(*N*-(*tert*-Butoxycarbonyl)-4-methylphenylsulfonamido)-hex-3-yn-2-yl acetate (S7). Following the general procedure **A** of the synthesis of propargylic acetates, isolated as a clear oil in 90% yield (530 mg): Analytical TLC R_f = 0.21 (1:4 ethyl acetate:petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 7.80 (d, J = 8.0 Hz, 2 H), 7.32 (d, J = 8.0, 2 H), 5.45 (q, J = 7.0 Hz, 1 H), 3.97 (t, J = 7.5 Hz, 2 H), 2.68 (t, J = 6.5 Hz, 2 H), 2.44 (s, 3 H), 2.06 (s, 3 H), 1.45 (d, J = 6.5 Hz, 3 H), 1.34 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 169.9, 150.7, 144.2, 137.3, 129.2, 127.8, 84.5, 81.3, 80.6, 60.5, 45.2, 27.8, 21.6, 21.6, 21.1, 20.2; FT-IR (thin film, cm^{-1}) 2976, 2931, 1734, 1597, 1443, 1369, 1292, 1237, 1157, 1090, 1059, 1018, 970, 913, 846, 814, 769, 742, 674; High-resolution MS (ESI$^+$, m/z) molecular ion [M + Na]$^+$ calculated for $C_{20}H_{27}O_6N_1S_1$ 432.1451, found 432.1461, error 2.4 ppm.

6-(4-Methylphenylsulfonamido)hex-3-yn-2-yl acetate (19). Following the general procedure for TFA deprotection, compound **19** was isolated as a clear oil in 77% yield (410 mg): Analytical TLC R_f = 0.14 (1:4 ethyl acetate:petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 7.78 (d, J = 8.0 Hz, 2 H), 7.32 (d, J = 8.0, 2 H), 5.38−5.32 (m, 1 H), 5.18−5.15 (m, 1 H), 3.09 (dt, J = 7.0, 6.5 Hz, 2 H), 2.43 (s, 3 H), 2.38 (t, J = 6.5 Hz, 2 H), 2.06 (s, 3 H), 1.43 (d, J = 7.0 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 170.0, 143.4, 136.9, 129.6, 126.9, 81.2, 81.0, 60.4, 41.6, 21.4, 21.3, 21.0, 20.0; FT-IR (thin film, cm^{-1}) 3293, 2938, 1740, 1593, 1434, 1373, 1328, 1242, 1156, 1095, 1062, 1021, 952, 817, 662; High-resolution MS (ESI$^+$, m/z) molecular ion [M + Na]$^+$ calculated for $C_{15}H_{19}O_4N_1S_1$ 332.0927, found 332.0921, error 1.5 ppm.

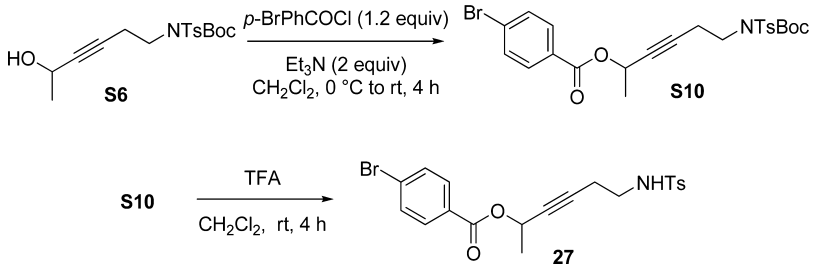
6-(*N*-(*tert*-Butoxycarbonyl)-4-methylphenylsulfonamido)-hex-3-yn-2-yl pivalate (S8). See Scheme 8. According to the general procedure **A** of the synthesis of propargylic acetates, compound **S8** was isolated as a clear oil in 94% yield (345 mg): Analytical TLC R_f = 0.53 (1:4 ethyl acetate:petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 7.80 (d, J = 8.0 Hz, 2 H), 7.32 (d, J = 8.5 Hz, 2 H), 5.42 (q, J = 6.5 Hz, 1 H), 3.97 (t, J = 8.0 Hz, 2 H), 2.67 (t, J = 6.5 Hz, 2 H), 2.44 (s, 3 H), 1.44 (d, J = 7.0 Hz, 2 H), 1.34 (s, 9 H), 1.20 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 177.4, 150.7, 144.2, 137.2, 129.3, 127.8, 84.5, 80.9, 80.8, 60.5, 45.2, 38.6, 27.8, 27.0, 21.6, 21.4, 20.2; FT-IR (thin film, cm^{-1}) 2979, 2935, 1728, 1598, 1480, 1442, 1367, 1279, 1155, 1091, 1058, 971, 848, 813, 770, 717, 675; High-resolution MS

dx.doi.org/10.1021/jo500748e | J. Org. Chem. 2014, 79, 5569−5585

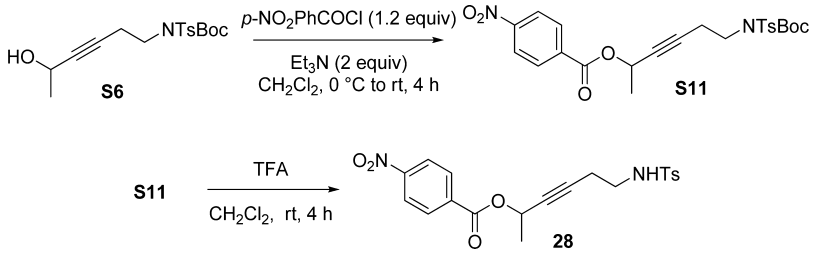
Scheme 9. Synthesis of Alkyne 26



Scheme 10. Synthesis of Alkyne 27



Scheme 11. Synthesis of Alkyne 28



(ESI$^+$, m/z) molecular ion $[M + Na]^+$ calculated for $C_{23}H_{33}O_6N_1S_1$ 474.1921, found 474.1929, error 1.8 ppm.

6-(4-Methylphenylsulfonamido)hex-3-yn-2-yl pivalate (23). Following the general procedure for TFA deprotection, compound **23** was isolated as an oil in 79% yield (110 mg): Analytical TLC R_f = 0.25 (1:4 ethyl acetate:petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 7.77 (d, J = 8.5 Hz, 2 H), 7.32(d, J = 7.5 Hz, 2 H), 5.32−5.28 (m, 1 H), 5.02 (t, J = 6.0 Hz, 1 H), 3.08 (q, J = 7.0 Hz, 2 H), 2.42 (s, 3H), 2.36 (dt, J = 6.5, 1.5 Hz, 2 H), 1.42 (d, J = 7.0 Hz, 3 H), 1.20 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 177.5, 143.4, 137.0, 129.7, 127.0, 81.4, 80.9, 60.3, 41.7, 38.6, 26.9, 21.5, 21.1, 19.9; FT-IR (thin film, cm^{-1}) 3285, 2975, 2936, 2873, 1727, 1598, 1480, 1331, 1280, 1159, 1094, 1059, 861, 815, 663; High-resolution MS (EI$^+$, m/z) molecular ion $[M]^+$ calculated for $C_{18}H_{25}O_4N_1S_1$ 351.1499, found 351.1503, error 1.4 ppm.

6-(*N*-(*tert*-Butoxycarbonyl)-4-methylphenylsulfonamido)-hex-3-yn-2-yl benzoate (S9). See Scheme 9. According to the general procedure **A** of the synthesis of propargylic acetates, compound **S9** was isolated as a clear oil in 72% yield (930 mg): Analytical TLC R_f = 0.43 (1:4 ethyl acetate:petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 8.07 (d, J = 8.5 Hz, 2 H), 7.80 (d, J = 7.0 Hz, 2 H), 7.58 (t, J = 6.5 Hz, 1 H), 7.45 (t, J = 7.0 Hz, 2 H), 7.29 (d, J = 8.0, 2 H), 5.71 (q, J = 6.5 Hz, 1 H), 4.01 (t, J = 7.0 Hz, 2 H), 2.72 (t, J = 7.5 Hz, 2 H), 2.40 (s, 3 H), 1.59 (d, J = 7.0 Hz, 3 H), 1.33 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 165.3, 150.6, 144.1, 137.1, 132.9, 129.9, 129.6, 129.2, 128.2, 127.7, 84.4, 81.5, 80.6, 61.1, 45.0, 27.7, 21.6, 21.4, 20.1; FT-IR (thin film, cm^{-1}) 2982, 2940, 2259, 1726, 1600, 1453, 1348, 1259, 1160, 1086, 1055, 1024, 971, 913, 845, 814, 709, 672; High-resolution MS (ESI$^+$, m/z) molecular ion $[M + Na]^+$ calculated for $C_{25}H_{29}O_6N_1S_1$ 494.1608, found 494.1611, error 0.8 ppm.

6-(4-Methylphenylsulfonamido)hex-3-yn-2-yl benzoate (26). Following the general procedure for TFA deprotection, compound **26** was isolated as a clear oil in 97% yield (710 mg): Analytical TLC R_f = 0.21 (1:4 ethyl acetate:petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 8.06 (d, J = 7.5 Hz, 2 H), 7.76 (d, J = 8.0 Hz, 2 H), 7.56 (t, J = 7.0 Hz, 1 H), 7.46 (t, J = 8.0 Hz, 2 H), 7.25 (d, J = 8.5, 2 H), 5.59−5.55 (m, 1 H), 5.15 (t, J = 6.5 Hz, 1 H), 3.10 (q, J = 6.5 Hz, 2 H), 2.39 (s, 3 H), 2.36−2.35 (m, 2 H), 1.57 (d, J = 7.0 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 165.6, 143.4, 136.9, 133.1, 129.8, 129.6, 128.3, 127.0, 81.5, 81.2, 61.1, 41.6, 21.4, 21.3, 19.9; FT-IR (thin film, cm^{-1}) 3284, 2988, 2938, 2251, 1721, 1599, 1451, 1318, 1267, 1161, 1095, 1059, 1026, 912, 862, 815, 713, 665; High-resolution MS (ESI$^+$, m/z) molecular ion $[M]^+$ calculated for $C_{20}H_{21}O_4N_1S_1$ 371.1186, found 371.1197, error 3.1 ppm.

6-(*N*-(*tert*-Butoxylcarbonyl)-4-methylphenylsulfonamido)-hex-3-yn-2-yl 4-bromobenzoate (S10). See Scheme 10. According to the general procedure **A** of the synthesis of propargylic acetates, compound **S10** was isolated as a white tacky oil in 91% yield (1370 mg): Analytical TLC R_f = 0.48 (1:4 ethyl acetate:petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 7.94−7.91 (m, 2 H), 7.82−7.78 (m, 2 H), 7.60−7.56 (m, 2 H), 7.31−7.28 (m, 2 H), 5.69−5.66 (m, 1 H), 4.01 (t, J = 8.0 Hz, 2 H), 2.71 (t, J = 7.0 Hz, 2 H), 2.41 (s, 3 H), 1.59 (d, J = 6.5 Hz, 3 H), 1.35 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 164.6, 150.6, 144.1, 137.2, 131.5, 131.2, 129.2, 128.9, 128.1, 127.7, 84.4, 81.7, 80.4, 61.4, 45.0, 27.7, 21.6, 21.5, 20.1; FT-IR (thin film, cm^{-1}) 2982, 2930, 2248, 1731, 1589, 1485, 1448, 1359, 1270, 1160, 1092, 1055, 1008, 971, 908, 845, 814, 756, 735, 672; High-resolution MS (ESI$^+$, m/z) molecular ion $[M + Na]^+$ calculated for $C_{25}H_{28}O_6N_1Br_1S_1$ 572.0719, found 572.0721, error 0.3 ppm.

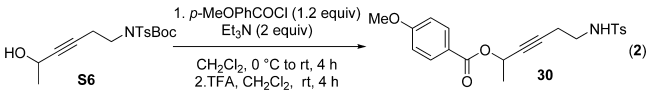
6-(4-Methylphenylsulfonamido)hex-3-yn-2-yl 4-bromobenzoate (27). Following the general procedure for TFA deprotection, compound **27** was isolated as a clear oil in 88% yield (980 mg): Analytical TLC R_f = 0.26 (1:4 ethyl acetate:petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 7.91 (d, J = 8.5 Hz, 2 H), 7.76 (d, J = 8.0 Hz, 2 H), 7.57 (d, J = 8.5 Hz, 2 H), 7.27 (d, J = 8.5, 2 H), 5.58 (q, J = 6.5 Hz, 1 H), 5.40 (t, J = 6.5 Hz, 1 H), 3.11 (q, J = 6.5 Hz, 2 H), 2.39−2.37 (m, 5 H), 1.56 (d, J = 6.5 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 164.7, 143.3, 136.8, 131.5, 131.1,129.5, 128.6, 128.1, 126.8, 81.7, 80.7, 61.4, 41.5, 21.3, 21.2, 19.8; FT-IR (thin film, cm^{-1}) 3287, 2989, 2938, 2254, 1722, 1590, 1484, 1398, 1328, 1265, 1159, 1096, 1058, 1011, 911, 849, 814, 758, 734, 665; High-resolution MS (EI$^+$, m/z) molecular ion $[M]^+$ calculated for $C_{20}H_{20}O_4N_1Br_1S_1$ 449.0291, found 449.0262, error 6.5 ppm.

6-(*N*-(*tert*-Butoxylcarbonyl)-4-methylphenylsulfonamido)-hex-3-yn-2-yl 4-nitrobenzoate (S11). See Scheme 11. According

dx.doi.org/10.1021/jo500748e | J. Org. Chem. 2014, 79, 5569−5585

to the general procedure **A** of the synthesis of propargylic acetates, compound **S11** was isolated as an oil in 94% yield (1320 mg): Analytical TLC R_f = 0.32 (1:4 ethyl acetate:petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 8.30 (d, J = 9.0 Hz, 2 H), 8.25 (d, J = 9.5 Hz, 2 H), 7.79 (d, J = 8.5 Hz, 2 H), 7.31(d, J = 8.5 Hz, 2 H), 5.72 (q, J = 7.0 Hz, 1 H), 4.02 (t, J = 7.0 Hz, 2 H), 2.73 (t, J = 7.5 Hz, 2 H), 2.43 (s, 3 H), 1.64 (d, J = 7.0 Hz, 3 H), 1.33 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 163.6, 150.7, 150.5, 144.2, 137.2, 135.5, 130.9, 129.2, 127.7, 123.4, 84.5, 82.3, 80.1, 62.3, 45.1, 27.8, 21.6, 20.2; FT-IR (thin film, cm^{-1}) 2983, 2253, 1728, 1607, 1529, 1354, 1269, 1157, 1118, 1092, 1056, 971, 913, 874, 842, 720, 673; High-resolution MS (ESI$^+$, m/z) molecular ion $[M + Na]^+$ calculated for $C_{25}H_{28}O_8N_2S_1$ 539.1459, found 539.1475, error 3.1 ppm.

6-(4-Methylphenylsulfonamido)hex-3-yn-2-yl 4-nitrobenzoate (28). Following the general procedure for TFA deprotection, compound **28** was isolated as a white solid in 91% yield (950 mg): mp 117−119 °C; Analytical TLC R_f = 0.12 (1:4 ethyl acetate:petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 8.31 (d, J = 8.5 Hz, 2 H), 8.25 (d, J = 9.0 Hz, 2 H), 7.77 (d, J = 7.5 Hz, 2 H), 7.30 (d, J = 7.5 Hz, 2 H), 5.62 (q, J = 6.5 Hz, 1 H), 4.88 (br s, 1 H), 3.12 (q, J = 7.0 Hz, 2 H), 2.42−2.39 (m, 5 H), 1.62 (d, J = 7.0 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 163.8, 150.7, 143.6, 137.0, 135.2, 130.9, 129.7, 127.0, 123.5, 82.3, 80.7, 62.3, 41.5, 21.5, 21.4, 20.1; FT-IR (thin film, cm^{-1}) 3291, 2989, 2938, 2872, 2250, 1725, 1607, 1528, 1411, 1340, 1269, 1160, 1098, 1057, 873, 841, 815, 720, 550; High-resolution MS (ESI$^+$, m/z) molecular ion $[M + Na]^+$ calculated for $C_{20}H_{20}O_6N_2S_1$ 439.0934, found 439.0913, error 4.8 ppm.



6-(4-Methylphenylsulfonamido)hex-3-yn-2-yl 4-methoxybenzoate (30). Following the general procedure for the synthesis of propargyl acetates except the Boc deprotection was carried out directly after the acylation without purifying or isolating the intermediate structure. The resulting alkyne was isolated as a clear oil in 54% yield (1.4 g) over two steps: Analytical TLC R_f = 0.05 (1:4 ethyl acetate:petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 8.03−7.99 (m, 2 H), 7.76 (d, J = 12.5 Hz, 2 H), 7.24 (d, J = 10 Hz, 2 H), 6.94−6.90 (m, 2 H), 5.56 (q, J = 10.5 Hz, 1 H), 5.07 (br s, 1 H), 3.86 (s, 3 H), 3.10 (q, J = 11.0 Hz, 2 H), 2.40−2.34 (m, 5 H), 1.62 (d, J = 7.0 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 165.4, 163.5, 143.4, 137.0, 131.8, 129.7, 127.0, 122.2, 113.6, 81.6, 81.3, 60.8, 55.4, 41.6, 21.5, 21.4, 19.9 ; FT-IR (thin film, cm^{-1}) 3583, 3281, 2987, 2937, 2841, 2253, 1918, 1714, 1606, 1581, 1512, 1455, 1422, 1318, 1258, 1163, 1095, 1059, 1028, 912, 848, 815, 772, 732, 665; High-resolution MS (ESI$^+$, m/z) molecular ion $[M + H]^+$ calculated for $C_{21}H_{23}O_5N_1S_1$ 402.1370, found 402.1371, error 0.4 ppm.

***tert*-Butyl 5-hydroxy-6-methylhept-3-ynyl(tosyl)carbamate (S12).** See Scheme 12. Following the general procedure for propargylic alcohols, isolated as an oil in 97% yield (1.2 g): Analytical TLC R_f = 0.27 (1:4 ethyl acetate:petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 7.80 (d, J = 8.0 Hz, 2 H), 7.32 (d, J = 8.5, 2 H), 4.14−4.11 (m, 1 H), 4.00 (t, J = 7.0 Hz, 2 H), 2.69 (t, J = 6.5 Hz, 2 H), 2.44 (s, 3 H), 2.20 (s, 1 H), 1.85 (d, J = 6.5 Hz, 1 H), 1.33 (s, 9 H), 0.99 (d, J = 6.5 Hz, 3 H), 0.98 (d, J = 7.0 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 150.7, 144.2, 137.2, 129.2, 127.7, 84.5, 82.3, 81.9, 67.9, 45.3, 34.4, 27.7, 21.5, 20.0, 18.0, 17.5; FT-IR (thin film, cm^{-1}) 3533, 2968, 2931, 2873, 1726, 1598, 1435, 1352, 1292, 1258, 1156, 1091, 1020, 971, 914, 843, 813, 734, 674; High-resolution MS (ESI$^+$, m/z) molecular ion $[M + Na]^+$ calculated for $C_{20}H_{29}O_5N_1S_1$ 418.1659, found 418.1659, error 0.0 ppm.

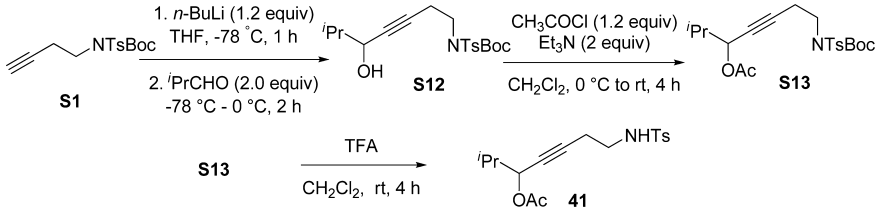
7-(*N*-(*tert*-Butoxycarbonyl)-4-methylphenylsulfonamido)-2-methylhept-4-yn-3-yl acetate (S13). According to the general procedure **A** of the synthesis of propargylic acetates, compound **S13** was isolated as a clear oil in 69% yield (380 mg): Analytical TLC R_f = 0.34 (1:4 ethyl acetate:petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 7.80 (d, J = 8.5 Hz, 2 H), 7.32 (d, J = 8.0 Hz, 2 H), 5.21−5.20 (m, 1 H), 3.98 (t, J = 7.5 Hz, 2 H), 2.70 (t, J = 7.5 Hz, 2 H), 2.44 (s, 3 H), 2.08 (s, 3 H), 1.96 (sextet, J = 6.5 Hz, 1 H), 1.34 (s, 9 H), 1.00 (d, J = 6.0 Hz, 3 H), 0.97 (d, J = 7.0 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 170.0, 150.6, 144.2, 137.2, 129.2, 127.7, 84.5, 82.3, 78.2, 69.1, 45.2, 32.3, 27.8, 21.5, 21.0, 20.2, 18.1, 17.5; FT-IR (thin film, cm^{-1}) 2973, 2933, 2876, 1726, 1598, 1433, 1357, 1291, 1234, 1156, 1091, 1019, 971, 908, 845, 814, 770, 721, 675; High-resolution MS (ESI$^+$, m/z) molecular ion $[M + Na]^+$ calculated for $C_{22}H_{31}O_6N_1S_1$ 460.1764, found 460.1763, error 0.2 ppm.

2-Methyl-7-(4-methylphenylsulfonamido)hept-4-yn-3-yl acetate (41). Following the general procedure for TFA deprotection, compound **41** was isolated as an oil in 76% yield (220 mg): Analytical TLC R_f = 0.18 (1:4 ethyl acetate:petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 7.73 (d, J = 8.5 Hz, 2 H), 7.27 (d, J = 8.0 Hz, 2 H), 5.24 (t, J = 6.5 Hz, 1 H), 5.07−5.05 (m, 1 H), 3.04 (q, J = 7.0 Hz, 2 H), 2.38 (s, 3 H), 2.34 (dt, J = 7.0, 2.5 2 H), 2.03 (s, 3 H), 1.90 (sextet, J = 7.0 Hz, 1 H), 0.93 (d, J = 7.0 Hz, 3 H), 0.91 (d, J = 6.5, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 170.1, 143.3, 136.8, 129.5, 126.8, 82.4, 78.5, 69.0, 41.6, 32.0, 21.3, 20.8, 19.8, 17.9, 17.4; FT-IR (thin film, cm^{-1}) 3285, 2967, 2932, 2875, 1738, 1727, 1598, 1427, 1371, 1331, 1236, 1160, 1094, 1020, 982, 911, 815, 733; High-resolution MS (EI$^+$, m/z) molecular ion $[M]^+$ calculated for $C_{17}H_{23}O_4N_1S_1$ 337.1342, found 337.1342, error 0.1 ppm.

***tert*-Butyl 5-hydroxy-6,6-dimethylhept-3-ynyl(tosyl)-carbamate (S14).** See Scheme 13. Following the general procedure for the synthesis of propargylic alcohols, compound **S14** was isolated in 77% yield (1.93 g) as a clear oil which crystallized upon standing: mp 91−93 °C; Analytical TLC R_f = 0.37 (1:4 ethyl acetate:petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 7.79 (d, J = 8.5 Hz, 2 H), 7.31 (d, J = 8.5 Hz, 2 H), 4.02−3.97 (m, 3 H), 2.69 (t, J = 7.0 Hz, 2 H), 2.44 (s, 3 H), 1.96 (t, J = 5.0 Hz, 1 H), 1.33 (s, 9 H), 0.97 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 150.7, 144.2, 137.3, 129.3, 127.8, 84.6, 82.2, 77.2, 71.5, 45.4, 35.7, 27.8, 25.3, 21.6, 20.1; FT-IR (thin film, cm^{-1}) 3545, 2971, 2869, 1732, 1361, 1291, 1156, 1090, 1042, 1007, 971, 813, 675; High-resolution MS (ESI$^+$, m/z) molecular ion $[M + Na]^+$ calculated for $C_{21}H_{31}O_5N_1S_1$ 432.1815, found 432.1823, error 0.8 ppm.

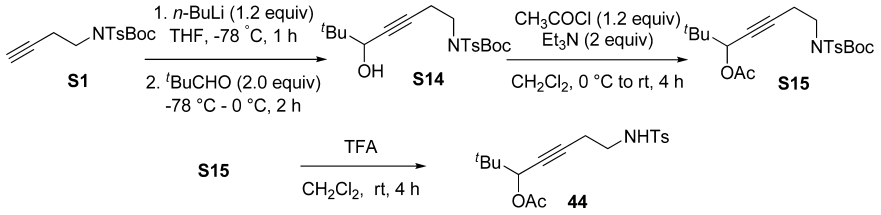
7-(*N*-(*tert*-Butoxycarbonyl)-4-methylphenylsulfonamide)-2,2-dimethylhept-4-yn-3-yl acetate (S15). According to the general procedure **A** of the synthesis of propargylic acetates, compound **S15** was isolated as an oil in 63% yield (520 mg): Analytical TLC R_f = 0.43 (1:4 ethyl acetate:petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 7.79 (d, J = 8.5 Hz, 2 H), 7.32 (d, J = 9.0 Hz, 2 H), 5.11 (t, J = 1.5 Hz, 1 H), 3.97 (t, J = 7.5 Hz, 2 H), 2.70 (dt, J = 7.5, 1.5 Hz, 2 H), 2.44 (s, 3 H), 2.08 (s, 3 H), 1.34 (s, 9 H), 0.98 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 170.0, 150.6, 144.1, 137.1, 129.2, 127.7, 84.4, 82.0, 78.3, 71.9, 45.2, 34.9, 27.7, 25.4, 21.5, 20.8, 20.1; FT-IR (thin film, cm^{-1}) 2973, 2871, 1732, 1598, 1479,

Scheme 12. Synthesis of Alkyne 41

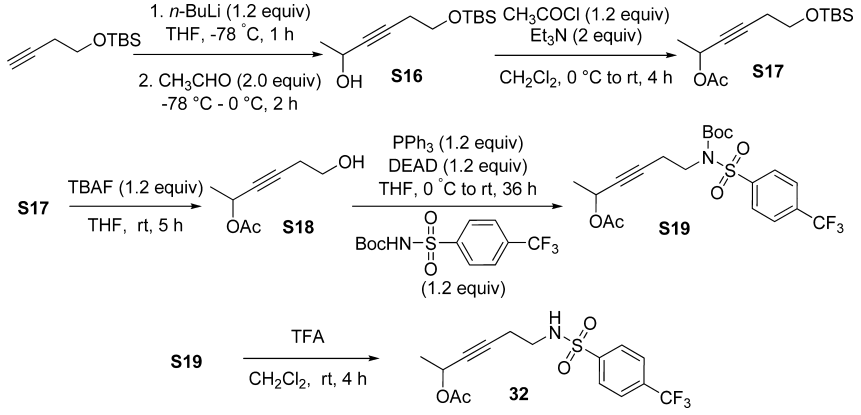


dx.doi.org/10.1021/jo500748e | J. Org. Chem. 2014, 79, 5569−5585

Scheme 13. Synthesis of Alkyne 44



Scheme 14. Synthesis of Alkyne 32



1456, 1395, 1371, 1291, 1238, 1156, 1090, 1018, 972, 913, 844, 813, 771, 734, 675; High-resolution MS (ESI$^+$, m/z) molecular ion [M + Na]$^+$ calculated for $C_{23}H_{33}O_6N_1S_1$ 474.1921, found 474.1912, error 1.7 ppm.

2,2-Dimethyl-7-(4-methylphenylsulfonamido)hept-4-yn-3-yl acetate (44). Following the general procedure for TFA deprotection, compound **44** was isolated as an oil in 56% yield (254 mg): Analytical TLC R_f = 0.17 (1:4 ethyl acetate:petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 7.77 (d, J = 8.0 Hz, 2 H), 7.32 (d, J = 8.5 Hz, 2 H), 5.15 (t, J = 6.5 Hz, 1 H), 4.98 (t, J = 2.0 Hz, 1 H), 3.08 (q, J = 7.0 Hz, 2 H), 2.43 (s, 3 H), 2.40 (dt, J = 7.0, 2.0 Hz, 2 H), 2.09 (s, 3 H), 0.96 (d, J = 7.0 Hz, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 170.3, 143.3, 136.9, 129.6, 126.9, 82.3, 78.8, 72.1, 41.6, 34.7, 25.4, 21.4, 20.8, 19.9; FT-IR (thin film, cm^{-1}) 3287, 2968, 1734, 1558, 1540, 1456, 1436, 1370, 1333, 1239, 1161, 1093, 1018, 977, 815, 662; High-resolution MS (ESI$^+$, m/z) molecular ion [M + Na]$^+$ calculated for $C_{18}H_{25}O_4N_1S_1$ 374.1397, found 374.1389, error 2.0 ppm.

6-(*tert*-Butyldimethylsilyloxy)hex-3-yn-2-ol (S16). See Scheme 14. To an oven-dried 3-neck flask under nitrogen was added 60 mL of freshly distilled THF and 6 g (32.5 mmol, 1 equiv) of the TBS protected homopropargylic alcohol. The solution was cooled to −78 °C in an acetone/dry ice bath for 30 min, at which point 19.5 mL (39 mmol, 1.2 equiv) of 2 M *n*-butyl lithium was added to the reaction. After 1 h, 3.6 mL (65 mmol, 2.0 equiv) of acetaldehyde was added, and the reaction was left to warm to 0 °C in an ice bath over 2 h. The reaction was then quenched with the addition of aqueous ammonium chloride, diluted with diethyl ether and washed with water and brine. The organic extract was then dried over magnesium sulfate and then concentrated in vacuo (rotary evaporator). The crude oil was column purified over SiO_2 using a gradient of 0−30% diethyl ether in hexanes to afford the desired product as a clear oil in 97% yield (5.7 g): Analytical TLC R_f = 0.38 (1:4 ethyl acetate:petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 4.78−4.45 (m, 1 H), 3.67 (t, J = 7.5 Hz, 2 H), 2.39 (dt, J = 7.0, 2.0 Hz, 2 H), 1.92 (d, J = 5.0 Hz, 1 H), 1.40 (d, J = 7.0 Hz, 3 H), 0.87 (s, 9 H), 0.04 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 83.3, 81.5, 61.8, 58.5, 25.9, 24.6, 23.0, 18.3, −5.3 ; FT-IR (thin film, cm^{-1}) 3361, 2955, 2930, 2858, 1472, 1387, 1362, 1333, 1255, 1155, 1108, 1005, 938, 913, 837, 777, 723, 663; High-resolution MS (ESI$^+$, m/z) molecular ion [M + Na]$^+$ calculated for $C_{12}H_{24}O_2Si_1$ 251.1438, found 251.1435, error 1.1 ppm.

6-(*tert*-Butyldimethylsilyloxy)hex-3-yn-2-yl acetate (S17). To a 100 mL oven-dried round-bottom flask was added 50 mL of freshly distilled CH_2Cl_2 and 5.7 g (25.1 mmol, 1.0 equiv) of propargyl alcohol **S16** and 7.0 mL (50 mmol, 2.0 equiv) of triethyl amine. The reaction was cooled to 0 °C in an ice/water bath for 30 min, at which point 2.15 mL (30 mmol, 1.2 equiv) of acetyl chloride was added to the reaction. The reaction was then left to warm to room temperature over the course of 4 h, at which point it was quenched with the addition of water. The reaction was washed with 1 M HCl, water, and brine. The organic fraction was then dried over sodium sulfate, concentrated in vacuo (rotary evaporator) and purified over SiO_2 using a gradient elution of 0−20% diethyl ether in hexanes to afford the desired product as a clear oil in 70% yield (4.7 g): Analytical TLC R_f = 0.62 (1:4 ethyl acetate:petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 5.45−5.37 (m, 1 H), 3.67 (t, J = 7.5 Hz, 2 H), 2.38 (dt, J = 7.0, 2.0 Hz, 2 H), 2.02 (s, 3 H), 1.42 (d, J = 6.5 Hz, 3 H), 0.86 (s, 9 H), 0.03 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 169.8, 82.4, 79.6, 61.6, 60.6, 25.8, 23.0, 21.6, 21.0, 18.2, −5.4; FT-IR (thin film, cm^{-1}) 2955, 2930, 2857, 1746, 1472, 1371, 1340, 1236, 1168, 1110, 1058, 1018, 950, 914, 838, 777; High-resolution MS (ESI$^+$, m/z) molecular ion [M + Na]$^+$ calculated for $C_{14}H_{26}O_3Si_1$ 293.1543, found 293.1543, error 0.2 ppm.

6-Hydroxylhex-3-yn-2-yl acetate (S18). To an oven-dried 100 mL round-bottom flask was added 40 mL of freshly distilled THF, 6 g (22.3 mmol, 1 equiv) of the propargylic acetate **S17**, and 26 mL (26.6 mmol, 1.2 equiv) of 1 M solution of TBAF in THF. The reaction was left to stir at room temperature until judged compete by TLC (5 h), at which point the reaction was quenched with the addition of aqueous ammonium chloride, extracted with diethyl ether, dried over sodium sulfate, concentrated in vacuo (rotary evaporator) and column purified over SiO_2 using a gradient of 20−100% diethyl ether in hexanes to afford the desired alcohol as a clear oil in 79% yield (2.77 g): Analytical TLC R_f = 0.08 (1:4 ethyl acetate:petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 5.42−4.40 (m, 1 H), 3.71 (t, J = 7.5 Hz, 2 H), 2.56 (br s, 1 H), 2.48 (dt, J = 7.0, 2.0 Hz, 2 H), 2.07 (s, 3 H), 1.48 (d, J = 7.0 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 170.1, 82.0, 80.3, 60.7, 22.9, 21.5, 21.0; FT-IR (thin film, cm^{-1}) 3420, 2989, 2939, 2884, 1733, 1435, 1373, 1340, 1239, 1168, 1058, 1021, 949, 847; High-resolution MS (ESI$^+$, m/z) molecular ion [M + Na]$^+$ calculated for $C_8H_{12}O_3$ 179.0679, found 179.0679, error 0.7 ppm.

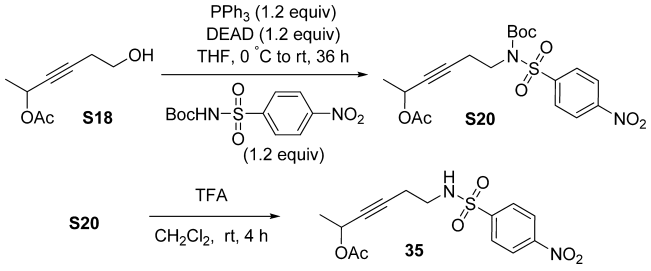
dx.doi.org/10.1021/jo500748e | J. Org. Chem. 2014, 79, 5569−5585

6-(*N*-(*tert*-Butoxycarbonyl)-4-(trifluoromethyl)phenylsulfonamido)hex-3-yn-2-yl acetate (S19). To an oven-dried 100 mL 3-neck round-bottom flask was added 25 mL of freshly distilled THF, 0.83 g (5.3 mml, 1.1 equiv) of homopropargyl alcohol **S18**, 1.6 g (4.8 mmol, 1.0 equiv) of *t*-butyl 4-trifluoromethylphenysulfonylcarbamate, and 1.5 g (5.8 mmol, 1.2 equiv) of triphenyl phosphine. The solution was then cooled to 0 °C in an ice water bath. To the cooled solution was then added 1.0 g (5.8 mmol, 1.2 equiv) of DEAD as a solution in 5 mL of THF. The solution was then left to warm to room temperature and left to react for 36 h. The reaction was then concentrated and purified via flash column chromatography using a gradient elution of 0−30% diethyl ether in hexanes to afford the desired propargylic acetate as a clear oil in 27% yield (520 mg): Analytical TLC R_f = 0.42 (1:4 ethyl acetate:petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 8.02 (d, J = 8.0 Hz, 2 H), 7.74 (d, J = 8.0 Hz, 2 H), 5.35 (q, J = 7.0 Hz, 1 H) 3.92 (t, J = 7.0 Hz, 2 H), 2.62 (t, J = 7.0 Hz, 2 H), 1.97 (s, 3 H), 1.36 (d, J = 7.0, 2 H), 1.27 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 169.6, 150.2, 143.6, 134.9 (q, $J_{C,F}$ = 33 Hz), 128.3, 125.7, 124.8 (q, $J_{C,F}$= 271 Hz), 85.0, 80.9, 80.8, 60.3, 45.0, 27.6, 21.3, 20.8, 19.9; FT-IR (thin film, cm^{-1}) 2985, 2939, 1748, 1608, 1564, 1443, 1405, 1368, 1323, 1295, 1247, 1134, 1092, 1063, 1017, 970, 946, 916, 845, 769, 715; High-resolution MS (ESI$^+$, m/z) molecular ion [M + Na]$^+$ calculated for $C_{20}H_{24}O_6N_1F_3S_1$ 486.1169, found 486.1186, error 3.6 ppm.

6-(4-(Trifluoromethyl)phenylsulfonamido)hex-3-yn-2-yl acetate (32). Following the general procedure for TFA deprotection, the following alkyne was isolated in quantitative yield (314 mg) as clear oil: Analytical TLC R_f = 0.14 (1:4 ethyl acetate:petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 7.96 (d, J = 8.5 Hz, 2 H), 7.71 (d, J = 8.5 Hz, 2 H), 5.66 (br s, 1 H) 5.25−5.21 (m, 1 H), 3.06 (dd, J = 6.5, 6.0 Hz, 2 H), 2.33 (dt, J = 7.0, 2.0 Hz, 2 H), 1.96 (s, 3 H), 1.33 (d, J = 7.0, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 170.1, 143.6, 134.7 (q, $J_{C,F}$ = 33 Hz), 128.5 (q, $J_{C,F}$= 271 Hz), 127.4, 126.1, 80.9, 60.4, 41.6, 21.0, 20.8, 19.9; FT-IR (thin film, cm^{-1}) 3288, 2991, 2941, 2877, 1726, 1609, 1432, 1405, 1373, 1324, 1246, 1169, 1132, 1097, 1063, 1018, 950, 845, 711; High-resolution MS (ESI$^+$, m/z) molecular ion [M + Na]$^+$ calculated for $C_{15}H_{16}O_4N_1F_3S_1$ 386.0644, found 386.0638, error 1.6 ppm.

6-(*N*-(*tert*-Butoxycarbonyl)-4-nitrophenylsulfonamide)hex-3-yn-2-yl acetate (S20). See Scheme 15. To an oven-dried 250 mL 3-neck round-bottom flask was added 75 mL of freshly distilled THF, 2.8 g (17.9 mml, 1.2 equiv) of homopropargyl alcohol **S18**, 4.5 g (15.0 mmol, 1.0 equiv) of *t*-butyl 4-nitrophenysulfonylcarbamate, and 4.7 g (17.9 mmol, 1.2 equiv) of triphenyl phosphine. The solution was then cooled to 0 °C in an ice water bath. To the cooled solution was then added 3.1 g (17.9 mmol, 1.2 equiv) of DEAD as a solution in 7 mL of THF. The solution was then left to warm to room temperature and left to react for 36 h. The reaction was then concentrated and purified via flash column chromatography using a gradient elution of 0−30% diethyl ether in hexanes to afford the desired propargylic acetate as a clear oil in 85% yield (5.6 g): Analytical TLC R_f = 0.28 (1:4 ethyl acetate:petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 8.39 (d, J = 8.5 Hz, 2 H), 8.16 (d, J = 8.5 Hz, 2 H), 5.43 (q, J = 6.5 Hz, 1 H), 4.00 (t, J = 7.0 Hz, 2 H), 2.70 (t, J = 6.5 Hz, 2 H), 2.06 (s, 3 H), 1.46 (d, J = 6.0 Hz, 3 H), 1.37 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 169.8, 150.3, 150.2, 145.6, 129.2, 123.9, 85.6, 81.2, 80.8, 60.4, 45.2, 27.8, 21.5, 21.0, 20.1; FT-IR (thin film, cm^{-1}) 3108, 2984, 2938, 1733, 1534, 1370, 1351, 1292, 1238, 1172, 1154, 1090, 1059, 1014, 970, 855, 742, 683; High-resolution MS (ESI$^+$, m/z) molecular ion [M + Na]$^+$ calculated for $C_{19}H_{24}O_8N_2S_1$ 463.1146, found 463.1142, error 0.6 ppm.

Scheme 15. Synthesis of Alkyne 35



6-(4-Nitrophenylsulfonamido)hex-3-yn-2-yl acetate (35). Following the standard procedure for TFA deprotection, the desired compound was isolated as clear oil in 88% yield (1.57 g): Analytical TLC R_f = 0.11 (1:4 ethyl acetate:petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 8.39 (d, J = 9.0 Hz, 2 H), 8.11 (d, J = 9.0 Hz, 2 H), 5.30−5.20 (m, 2 H), 3.17 (dt, J = 6.5, 6.0 Hz, 2 H), 2.42 (t, J = 6.5 Hz, 2 H), 2.09 (s, 3 H), 1.45 (d, J = 7.5 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 170.4, 150.1, 146.0, 128.3, 124.4, 81.9, 80.9, 60.6, 41.7, 21.1, 20.1; FT-IR (thin film, cm^{-1}) 3287, 306, 2987, 2938, 1732, 1531, 1429, 1372, 1350, 1310, 1239, 1164, 1094, 1060, 1019, 949, 855, 736, 685, 665; High-resolution MS (ESI$^+$, m/z) molecular ion [M + Na]$^+$ calculated for $C_{14}H_{16}O_6N_2S_1$ 363.0621, found 363.0614, error 2.0 ppm.

Optimization Procedure (Table 1). Unless otherwise noted, the catalyst was introduced from an oven-dried one dram vial that contained 5 mol % of the gold source and 5 mol % silver source; the metal salts were dissolved in 1 mL of the reaction solvent. The solution was allowed to stir at room temperature for 5 min and then filtered through a 1 cm plug of oven-dried Celite and eluted directly into a 50 mL Schlenk tube with another 1 mL of the reaction solvent. To the Schlenk tube was then added the propargylic acetate (0.11 mmol, 1.0 equiv) in 1.5 mL of the reaction solvent, bringing the reaction volume to 3.5 mL. The reaction was then left at room temperature until judged complete as determined by TLC analysis. The resulting mixture was quenched with two to three drops of triethylamine and concentrated in vacuo. Mesitylene was added as an internal standard, and the ratio of products was determined by ^{1}H NMR relative to the internal standard. Conversion was determined by integrating the doublet of triplets at 4.50 ppm (1 H) of the starting material, to the doublet of triplets at 4.28 ppm (1 H) in the allene, and to the doublet of doublet at 5.03 ppm (1 H), all relative to mesitylene. When the reaction reached full conversion, the ratio of products was determined by using the same two signals from the allene and the dehydropyrrolidine.

2-Methyl-5-phenyl-1-tosyl-1*H*-pyrrole (3). The pyrrole was isolated from entry 1 (Table 1) by flash column chromatography using silica gel (gradient elution 0−10% ethyl acetate in petroleum ether) as an oil in 70% yield (27 mg): Analytical TLC R_f = 0.50 (1:4 ethyl acetate:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 7.33−7.29 (m, 7 H), 7.16 (d, J = 8.0 Hz, 2 H), 6.04 (d, J = 3.0 Hz, 1 H), 6.00−5.98 (m, 1 H), 2.51 (s, 3 H), 2.36 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 144.3, 137.7, 136.4, 134.3, 133.2, 130.6, 129.4, 127.7, 127.2, 126.4, 115.2, 113.5, 21.5, 16.0; FT-IR (thin film, cm^{-1}) 2928, 1596, 1530, 1483, 1443, 1369, 1306, 1247, 1188, 1173, 1118, 1015, 979, 913, 811, 761, 693, 657; High-resolution MS (EI$^+$, m/z) molecular ion [M]$^+$ calculated for $C_{18}H_{17}O_2N_1S_1$ 311.0975, found 311.0983, error 2.6 ppm.

5-(4-Methylphenylsulfonamido)-5-phenylpenta-1,2-dien-3-yl acetate (4). The allene was isolated, for characterization purposes, by combining several experiments from the initial optimization studies, the compound was purified by flash column chromatography using silica gel (gradient elution 0−40% ethyl acetate in petroleum ether) affording 95 mg of **4** as clear oil: Analytical TLC R_f = 0.08 (1:4 ethyl acetate:pentane); ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 7.52 (d, J = 8.5 Hz, 2 H), 7.15−7.09 (m, 5 H), 6.96−6.94 (m, 2 H), 5.21 (d, J = 8.5 Hz, 1 H), 4.62 −(d, J = 6.5 Hz, 2 H), 4.28 (dt, J = 9.0, 9.0 Hz, 1 H), 2.57−2.46 (m, 2 H), 2.35 (s, 3 H), 2.16 (s, 3 H), 2.05−2.00 (m, 2 H), ^{13}C (75 MHz, $CDCl_3$, ppm) δ 203.5, 170.2, 143.0, 140.3, 137.4, 129.3, 128.5, 127.4, 126.9, 126.1, 68.9, 57.4, 35.0, 30.5, 21.3, 20.4; FT-IR (thin film, cm^{-1}) 3285, 3060, 3023, 2925, 2251, 1748, 1728, 1597, 1495, 1454, 1417, 1377, 1328, 1230, 1156, 1066, 911, 817, 735, 702; High-resolution MS (EI$^+$, m/z) molecular ion [M]$^+$ calculated for $C_{20}H_{21}O_4N_1S_1$ 371.1186, found 371.1196, error 2.7 ppm.

General Procedure for the Synthesis of Dehydropyrrolidines (Table 2). To an oven-dried one dram vial was added 5 mol %

dx.doi.org/10.1021/jo500748e | J. Org. Chem. 2014, 79, 5569−5585

IPrAuCl and 5 mol % $AgSbF_6$; the metal salts were dissolved in 1 mL of THF. The solution was allowed to stir at room temperature for 5 min and then filtered through a 1 cm plug of oven-dried Celite and eluted directly into a 50 mL Schlenk tube with another 1 mL of THF. To the Schlenk tube was then added the propargylic acetate (0.3 mmol, 1.0 equiv) in 7 mL of THF, bringing the reaction volume to 9 mL. The reaction was then left at room temperature until judged complete as determined by TLC analysis. The resulting mixture was quenched with two to three drops of triethylamine and concentrated in vacuo. Purification by chromatography on flash grade silica gel (230−400 mesh) using gradient elution (0−40% ethyl acetate in petroleum ether) afforded the analytically pure dehydropyrrolidines or dehydropiperidines.

(5-Phenyl-1-tosyl-4,5-dihydro-1*H*-pyrrol-2-yl)methyl acetate (5). According to the general procedure, dehydropyrrolidine **5** was obtained from alkyne **2** as a clear oil in 89% yield (89 mg): Analytical TLC R_f = 0.33 (1:4 ethyl acetate:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 7.76 (d, J = 8.5 Hz, 2 H), 7.37−7.29 (m, 7 H), 5.28 (d, J = 1.0 Hz, 1 H), 5.23 (dd, J = 14.5, 1.0 Hz, 1 H), 5.14 (dd, J = 7.0, 2.5 Hz, 1 H), 5.03 (dd, J = 14.0, 1.5 Hz, 1 H), 2.66 (m, 1 H), 2.47 (s, 3 H), 2.30 (m, 1 H), 2.14 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 170.3, 143.9, 142.7, 138.8, 134.8, 129.7, 128.8, 127.5, 127.5, 125.7, 114.4, 64.8, 60.4, 37.2, 21.6, 20.8; FT-IR (thin film, cm^{-1}) 2938, 1744, 1597, 1495, 1450, 1348, 1225, 1164, 1119, 1086, 670; High-resolution MS (ESI$^+$, m/z) molecular ion $[M + Na]^+$ calculated for $C_{20}H_{21}O_4N_1S_1$ 394.1084, found 394.1081, error 0.7 ppm.

(1-Tosyl-4,5-dihydro-1*H*-pyrrol-2-yl)methyl acetate (7). According to the general procedure, dehydropyrrolidine **7** was obtained from alkyne **6** as a white solid in 75% yield (75 mg): mp 78−80 °C; Analytical TLC R_f = 0.19 (1:4 ethyl acetate:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 7.75 (d, J = 8.5 Hz, 2 H), 7.34 (d, J = 8.0 Hz, 2 H), 5.25 (s, 1 H), 4.99 (s, 2 H), 3.82 (t, J = 8.5, 2 H), 2.43 (s, 3 H) 2.23−2.20 (m, 2 H), 2.10 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 170.3, 143.9, 138.9, 134.2, 129.7, 127.6, 114.7, 60.0, 50.4, 27.4, 21.5, 20.8; IR (thin film, cm^{-1}) 2938, 1744, 1659, 1601, 1450, 1348, 1238, 1160, 1091, 1054, 813; High-resolution MS (ESI$^+$, m/z) molecular ion $[M + Na]^+$ calculated for $C_{14}H_{17}O_4N_1S_1$ 318.0771, found 318.0767, error 0.9 ppm.

(5-Cyclohexyl-1-tosyl-4,5-dihydro-1*H*-pyrrol-2-yl)methyl acetate (9). According to the general procedure, dehydropyrrolidine **9** was obtained from alkyne **8** as a white solid in 88% yield (100 mg): mp 135−137 °C; analytical TLC R_f = 0.36 (1:4 ethyl acetate:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 7.71 (d, J = 8.5 Hz, 2 H), 7.30 (d, J = 8.0 Hz, 2 H), 5.22 (s, 1 H), 5.15 (d, J = 14.5 Hz, 1 H), 4.85 (d, J = 14.5 Hz, 1 H), 3.86−3.83 (m, 1 H), 2.42 (s, 3 H), 2.10 (s, 3 H), 1.99−1.92 (m, 2 H), 1.77−1.56 (m, 7 H), 1.26−0.97 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 170.3, 143.7, 138.7, 134.4, 129.5, 127.5, 125.6, 117.0, 67.5, 60.6, 42.9, 30.1, 28.3, 27.2, 26.5, 26.1, 26.0, 21.5, 20.8; FT-IR (thin film, cm^{-1}) 3199, 2929, 1748, 1446, 1344, 1221, 1168, 1054; High-resolution MS (EI$^+$, m/z) molecular ion $[M]^+$ calculated for $C_{20}H_{27}O_4N_1S_1$ 377.1655, found 377.1662, error 1.8 ppm.

(5-Phenyl-1-tosyl-4,5-dihydro-1*H*-pyrrol-2-yl)methyl 4-nitrobenzoate (11). According to the general procedure, dehydropyrrolidine **11** was obtained from alkyne **10** as a white solid in 89% yield (125 mg): mp 147−149 °C; Analytical TLC R_f = 0.21 (1:4 ethyl acetate:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 8.29 (d, J = 9.5 Hz, 2 H), 8.20 (d, J = 9.0 Hz, 2 H), 7.74 (d, 8.5 Hz, 2 H), 7.38 (d, J = 8 Hz, 2 H) 7.30−7.27 (m, 5 H), 5.42−5.33 (m, 3 H), 5.17 (dd, J = 9.5, 2.5 Hz, 1 H), 2.71−2.65 (m, 1 H), 2.41 (s, 3 H), 2.33−2.29 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 163.8, 150.4, 143.9, 142.4, 138.0, 135.0, 134.7, 130.7, 129.7, 128.5, 127.6, 127.3, 125.6, 123.4, 115.9, 64.8, 61.5, 37.1 21.6; FT-IR (thin film, cm^{-1}) 1724, 1654, 1597, 1528, 1491, 1446, 1348, 1279, 1168, 1103, 1013, 952, 845, 723 ; High-resolution MS (ESI$^+$, m/z) molecular ion $[M + Na]^+$ calculated for $C_{25}H_{22}O_6N_2S_1$ 501.1091, found 501.1089, error 0.3 ppm.

(5-Phenyl-1-tosyl-4,5-dihydro-1*H*-pyrrol-2-yl)methyl 4-bromobenzoate (13). According to the general procedure, dehydropyrrolidine **13** was obtained from alkyne **12** as a white solid in 89% yield (134 mg): mp 122−125 °C; Analytical TLC R_f = 0.29 (1:5 ethyl acetate:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 7.88 (d, J = 9.0 Hz, 2 H), 7.71 (d, J = 8.5 Hz, 2 H), 7.58 (d, J = 9.0 Hz, 2 H), 7.35−7.24 (m, 7 H), 5.36 (m, 2 H), 5.32 (s, 1 H), 5.17 (dd, J = 9.5, 2.0 Hz, 1 H), 2.66 (m, 1 H), 2.39 (s, 3 H), 2.28 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 165.1, 143.9, 142.6, 138.6, 134.9, 131.7, 131.2, 129.7, 128.7, 128.6, 128.3, 127.6, 127.4, 125.7, 115.2, 64.8, 60.9, 37.2, 21.5; FT-IR (thin film, cm^{-1}) 1723, 1591, 1353, 1269, 1165, 1102, 1012; High-resolution MS (ESI$^+$, m/z) molecular ion $[M + Na]^+$ calculated for $C_{25}H_{22}O_4N_1Br_1S_1$ 534.0345, found 534.0349, error 0.7 ppm.

(5-Phenyl-1-tosyl-4,5-dihydro-1*H*-pyrrol-2-yl)methyl benzoate (15). According to the general procedure, dehydropyrrolidine **15** was obtained from alkyne **14** as a an oil in 86% yield (112 mg): Analytical TLC R_f = 0.4 (1:4 ethyl acetate:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 8.08 (t, J = 8.0 Hz, 2 H), 7.77 (t, J = 8.5 Hz, 2 H), 7.60 (t, J = 7.0 Hz, 1 H), 7.47−7.43 (m, 2 H), 7.38−7.25 (m, 7 H), 5.47 (d, J = 14 Hz, 1 H), 5.35 (s, 1 H), 5.26 (d, J = 15 Hz, 1 H), 5.19−5.16 (m, 1 H), 2.72−2.65 (m, 1 H), 2.40 (s, 3 H), 2.29−2.26 (m, 1 H), ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 165.8, 143.9, 142.7, 138.8, 134.9, 133.1, 129.7, 128.5, 128.4, 127.5, 127.4, 125.7, 114.8, 64.8, 60.7, 37.2, 21.5; FT-IR (thin film, cm^{-1}) 3060, 2950, 1724, 1593, 1491, 1446, 1352, 1270, 1164, 1111, 1082, 1025, 911, 809, 711, 618; High-resolution MS (EI$^+$, m/z) molecular ion $[M]^+$ calculated for $C_{25}H_{23}O_4N_1S_1$ 433.1342, found 433.1334, error 1.8 ppm.

3-Phenyl-1-(1-tosyl-4,5-dihydro-1*H*-pyrrol-2-yl)propyl acetate (17). According to the general procedure, dehydropyrrolidine **17** was obtained from alkyne **16** as a white solid in 67% yield (140 mg): mp 140−142 °C; Analytical TLC R_f = 0.22 (1:4 ethyl acetate:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 7.87 (dd, J = 8.5, 2.5 Hz, 2 H), 7.32−7.25 (m, 4 H), 7.23 (d, J = 8.0 Hz, 2 H), 7.18 (t, J = 8.0 Hz, 1 H), 6.10−6.08 (m, 1 H), 5.15 (s, 1 H), 3.78−3.71 (m, 2 H), 2.78−2.67 (m, 2 H), 2.46−2.41 (m, 4 H), 2.14−2.07 (m, 5 H), 1.94−1.87 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 170.1, 143.8, 143.1, 141.4, 133.4, 129.6, 128.4, 128.3, 128.0, 125.8, 112.9, 71.2, 51.2, 34.8, 31.6, 27.2, 21.5, 20.9; IR (thin film, cm^{-1}) 3026, 2859, 1743, 1597, 1495, 1451, 1349, 1294, 1232, 1163, 1090, 1044, 979, 933, 815, 751, 694, 665; High-resolution MS (ESI$^+$, m/z) molecular ion $[M + Na]^+$ calculated for $C_{22}H_{25}O_4N_1S_1$ 422.1397, found 422.1413, error 4.0 ppm.

2-Phenethyl-1-tosyl-1,2,5,6-tetrahydropyridin-3-yl acetate (18). According to the general procedure, dehydropiperidine **18** was obtained from alkyne **16** as an oil in 29% yield (64 mg): Analytical TLC R_f = 0.16 (1:4 ethyl acetate:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 7.71 (d, J = 7.5 Hz, 2 H), 7.29−7.25 (m, 4 H), 7.20−7.17 (m, 3 H), 5.40−5.38 (m, 1 H), 4.52 (d, J = 4.0 Hz, 1 H), 3.98 (dd, J = 14.5, 6.0 Hz, 1 H), 3.34−3.27 (m, 1 H), 2.81−2.68 (m, 2 H), 2.41 (s, 3 H), 2.05 (s, 3 H), 2.01−1.90 (m, 3 H), 1.83 (dd, J = 16.5, 3.5 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 168.5, 146.3, 143.4, 141.4, 137.9, 129.7, 128.3, 128.3, 126.9, 125.9, 114.6, 52.8, 38.4, 36.8, 32.3, 25.2, 21.5, 20.9; IR (thin film, cm^{-1}) 3026, 2943, 2861, 1759, 1692, 1598, 1564, 1495, 1453, 1366, 1339, 1223, 1203, 1160, 1133, 1096, 1044, 1018, 953, 920, 814, 709, 690, 656; High-resolution MS (ESI$^+$, m/z) molecular ion $[M + Na]^+$ calculated for $C_{22}H_{25}N_1O_4S_1$ 422.1397, found 422.1398, error 0.4 ppm.

Optimization of Heterocycle Synthesis (Table 3). To an oven-dried one dram vial was added 5 mol % of the gold catalyst and 5 mol % of the silver cocatalyst; the metal salts were dissolved in 1 mL of the reaction solvent. The solution was allowed to stir at room temperature for 5 min and then filtered through a 1 cm plug of oven-dried Celite and eluted directly into a 50 mL Schlenk tube with another 1 mL of the reaction solvent. To the Schlenk tube was then added the propargylic acetate (0.3 mmol, 1.0 equiv) in 7 mL of the reaction solvent, bringing the total reaction volume to 9 mL. After 4 h, the reaction was quenched by the addition of two to three drops of triethylamine and concentrated in vacuo. 0.1 mmol of mesitylene was added to the crude reaction mixture, and the ratio of the three products was determined by ^{1}H NMR analysis. The product ratio was established by integrating the singlet at 5.99 ppm (1 H) of the pyrrole, the singlet at 5.19 ppm (1 H) of the dehydropyrrolidine, and the singlet at 4.58 ppm (1 H) of the dehydropiperidine. All three products

dx.doi.org/10.1021/jo500748e | J. Org. Chem. 2014, 79, 5569−5585

could be separated by standard column chromatography and were characterized as such.

1-(1-Tosyl-4,5-dihydro-1*H*-pyrrol-2-yl)ethyl acetate (20). According to the general procedure, dehydropyrrolidine **20** was obtained from alkyne **19** as an oil in 26% yield (25 mg): Analytical TLC R_f = 0.31 (1:4 ethyl acetate:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 7.84 (d, J = 8.0 Hz, 2 H), 7.33 (d, J = 8.5 Hz, 2 H), 6.07−6.02 (m, 1 H), 5.19 (s, 1 H), 3.86−3.73 (m, 2 H), 2.42 (s, 3 H), 2.16−2.10 (m, 4 H), 2.00−1.94 (m, 1 H), 1.55 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 170.0, 144.7, 143.8, 133.7, 129.6, 127.9, 112.5, 67.5, 51.2, 27.3, 21.5, 21.1, 20.0; IR (thin film, cm^{-1}) 3292, 2986, 2933, 1740, 1593, 1373, 1348, 1238, 1164, 1078, 1013, 817, 662; High-resolution MS (ESI$^+$, m/z) molecular ion [M + Na]$^+$ calculated for $C_{15}H_{19}O_4N_1S_1$ 332.0927, found 332.0934, error 2.2 ppm.

2-Methyl-1-tosyl-1,2,5,6-tetrahydropyridin-3-yl acetate (21). According to the general procedure, dehydropiperidine **21** was obtained from alkyne **19** as an oil in 64% yield (60 mg): Analytical TLC R_f = 0.25 (1:4 ethyl acetate:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 7.71 (d, J = 8.0 Hz, 2 H), 7.29 (d, J = 8.0 Hz, 2 H), 5.35−5.33 (m, 1 H), 4.58 (s, 1 H), 3.92 (dd, J = 14.5, 6.0 Hz, 1 H), 3.30−3.24 (m, 1 H), 2.42 (s, 3 H), 2.16−2.11 (m, 1 H), 2.07 (s, 3 H), 1.91 (dd, J = 17.5, 4.0 Hz, 1 H), 1.29 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 168.7, 146.0, 143.2, 138.0, 129.7, 126.8, 116.2, 48.8, 37.8, 26.0, 21.5, 20.9, 20.7 ; IR (thin film, cm^{-1}) 2974, 2933, 1753, 1687, 1589, 1454, 1360, 1336, 1221, 1201, 1156, 1136, 1082, 997, 915, 817, 715; High-resolution MS (EI$^+$, m/z) molecular ion [M]$^+$ calculated for $C_{15}H_{19}O_4N_1S_1$ 309.1029, found 309.1026, error 1.2 ppm.

2-Ethyl-1-tosyl-1*H*-pyrrole (22). The pyrrole **22** was isolated, for characterization purposes, by combining several experiments from the optimization studies (Table 3), the compound was purified by flash column chromatography using silica gel (gradient elution 0−10% ethyl acetate in petroleum ether): Analytical TLC R_f = 0.55 (1:4 ethyl acetate:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 7.65 (d, J = 8.5 Hz, 2 H), 7.29−7.27 (m, 3 H), 6.20 (t, J = 3.0 Hz, 1 H), 5.99 (s, 1 H), 2.69 (q, J = 8.0 Hz, 2 H), 2.40 (s, 3 H), 1.16 (t, J = 7.5 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 144.7, 137.3, 136.4, 129.9, 126.7, 122.2, 111.1, 110.9, 21.6, 20.4, 12.6; FT-IR (thin film, cm^{-1}) 2974, 2919, 1596, 1484, 1441, 1365, 1177, 155, 1126, 1092, 1051, 872, 813, 685; High-resolution MS (ESI$^+$, m/z) molecular ion [M + H]$^+$ calculated for $C_{13}H_{15}O_2N_1S_1$ 250.0896, found 250.0895, error 0.2 ppm.

Effect of the Acyl Group on Product Ratio (Table 4). To an oven-dried one dram vial was added 5 mol % of the PPh_3AuCl and 5 mol % of $AgSbF_6$; the metal salts were dissolved in 1 mL of THF. The solution was allowed to stir at room temperature for 5 min and then filtered through a 1 cm plug of oven-dried Celite and eluted directly into a 50 mL Schlenk tube with another 1 mL of THF. To the Schlenk tube was then added the propargylic acetate (0.3 mmol, 1.0 equiv) in 7 mL of THF, bringing the reaction volume to 9 mL. After 4 h, the reaction was quenched with the addition of two to three drops of triethylamine and concentrated in vacuo. 0.1 mmol of mesitylene was added to the crude reaction mixture, and the ratio of the three products was determined by ^{1}H NMR analysis. The product ratio between the dehydropyrrolidine and the dehydropiperidine was established by integrating the singlet at 5.19 ppm (1 H) of the dehydropyrrolidine, and the singlet at 4.58 ppm (1 H) of the dehydropiperidine. All products could be separated by standard column chromatography except for the benzoate (alkyne **26**) and the *p*-bromo benzoate (alkyne **27**). The ratio of these products was established by ^{1}H NMR by analogy to the previously isolated compounds. These two compounds were separated by hydrolysis of the benzoate and separation of the resulting alcohol and ketone products. These two products were characterized after hydrolysis, and yield reported is of the material isolated after hydrolysis.

1-(1-Tosyl-4,5-dihydro-1*H*-pyrrol-2-yl)ethyl pivalate (24). According to the general procedure, dehydropyrrolidine **24** was obtained from alkyne **23** as an oil in 26% yield (25 mg): Analytical TLC R_f = 0.41 (1:4 ethyl acetate:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 7.84 (d, J = 8.0 Hz, 2 H), 7.33 (d, J = 8.0 Hz, 2 H), 6.05−6.01 (m, 1 H), 5.16 (s, 1 H), 3.84−3.71 (m, 2 H), 2.42 (s, 3 H), 2.13−2.07 (m, 1 H), 1.97−1.92 (m, 1 H), 1.54 (d, J = 6.0 Hz, 3 H), 1.25 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 177.1, 145.1, 143.7, 133.6, 129.6, 127.9, 112.1, 67.3, 51.2, 38.7, 27.3, 27.2, 21.5, 20.1; IR (thin film, cm^{-1}) 2976, 2913, 2858, 1727, 1650, 1596, 1480, 146, 1349, 1281, 1163, 1083, 982, 911, 815, 732, 714, 665; High-resolution MS (ESI$^+$, m/z) molecular ion [M + Na]$^+$ calculated for $C_{18}H_{25}O_4N_1S_1$ 374.1397, found 374.1391, error 1.3 ppm.

2-Methyl-1-tosyl-1,2,5,6-tetrahydropyridin-3-yl pivalate (25). According to the general procedure, dehydropiperidine **25** was obtained from alkyne **23** as an oil in 32% yield (30 mg): Analytical TLC R_f = 0.32 (1:4 ethyl acetate:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 7.72 (d, J = 7.5 Hz, 2 H), 7.29 (d, J = 8.0 Hz, 2 H), 5.32 (s, 1 H), 4.58 (s, 1 H), 3.90 (dd, J = 14.0, 5.0 Hz, 1 H), 3.30−3.24 (m, 1 H), 2.41 (s, 3 H), 1.88 (dd, J = 16.5, 3.5 Hz, 1 H), 1.29 (d, J = 6.5 Hz, 3 H), 1.20 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 176.5, 146.3, 143.2, 138.0, 129.7, 126.8, 115.9, 48.8, 38.8, 37.8, 26.9, 26.0, 21.5, 20.7; IR (thin film, cm^{-1}) 2976, 2922, 2858, 1727, 1455, 1347, 1283, 1157, 1084, 984, 912, 812, 731, 667; High-resolution MS (ESI$^+$, m/z) molecular ion [M]$^+$ calculated for $C_{18}H_{25}O_4N_1S_1$ 374.1397, found 374.1388, error 2.0 ppm.

1-(1-Tosyl-4,5-dihydro-1*H*-pyrrol-2-yl)ethyl 4-nitrobenzoate (29). According to the general procedure, dehydropyrrolidine **29** was obtained from alkyne **28** as a white solid in 70% yield (87 mg): mp 135 °C (decomposition); Analytical TLC R_f = 0.28 (1:4 ethyl acetate:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 8.31 (d, J = 8.0 Hz, 2 H), 8.28 (d, J = 8.0 Hz, 2 H), 7.86 (d, J = 8.5 Hz, 2 H), 7.34 (d, J = 8.0 Hz, 2 H), 6.34−6.33 (m, 1 H), 5.29 (s, 1 H), 3.90−3.79 (m, 2 H), 2.42 (s, 3 H), 2.18−2.12 (m, 1 H), 2.05−2.00 (m, 1 H), 1.71 (d, J = 6.0 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 163.6, 150.5, 144.0, 143.9, 135.5, 133.7, 130.8, 129.6, 129.2, 127.7, 123.5, 113.4, 69.0, 51.2, 27.3, 21.5, 19.9; IR (thin film, cm^{-1}) 3111, 2938, 2860, 1727, 1651, 1598, 1528, 1448, 1347, 1273, 1163, 1102, 1014, 982, 912, 874, 841, 815, 720, 586; High-resolution MS (ESI$^+$, m/z) molecular ion [M + Na]$^+$ calculated for $C_{20}H_{20}O_6N_2S_1$ 439.0934, found 439.0926, error 1.7 ppm.

2-Methyl-1-tosyl-1,2,5,6-tetrahydropyridin-3-yl 4-methoxybenzoate (31). According to the general procedure, dehydropiperidine **31** was obtained from alkyne **30** as an oil in 58% yield (72 mg): Analytical TLC R_f = 0.29 (1:4 ethyl acetate:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 7.96 (d, J = 9.0 Hz, 2 H), 7.75 (d, J = 8.5 Hz, 2 H), 7.31 (d, J = 8.0 Hz, 2 H), 6.92 (d, J = 9.0 Hz, 2 H), 5.47−5.46 (m, 1 H), 4.64 (br s, 1 H), 3.96 (dd, J = 14.5, 6.0 Hz, 1 H), 3.86 (s, 3 H), 3.37−3.31 (m, 1 H), 2.43 (s, 3 H), 2.31−2.24 (m, 1 H), 2.04 (dd, J = 16.5, 2.5, 1 H), 1.33 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 164.2, 163.8, 146.4, 143.2, 138.1, 131.9, 129.7, 126.8, 121.6, 116.4, 113.7, 55.5, 48.9, 37.9, 26.3, 21.5, 20.7; IR (thin film, cm^{-1}) 3078, 2980, 2933, 2842, 1731, 1605, 1511, 1458, 1444, 1365, 1338, 1258, 1167, 1141, 1095, 1028, 995, 903, 848, 815, 765, 687, 613; High-resolution MS (ESI$^+$, m/z) molecular ion [M + Na]$^+$ calculated for $C_{21}H_{23}O_5N_1S_1$ 424.1189, found 424.1181, error 1.8 ppm.

Study of Role of Sulfonamide on Product Ratio (Table 5). To an oven-dried one dram vial was added 5 mol % of the PPh_3AuCl and 5 mol % of $AgSbF_6$; the metal salts were dissolved in 1 mL of dichloromethane. The solution was allowed to stir at room temperature for 5 min and then filtered through a 1 cm plug of oven-dried Celite and eluted directly into a 50 mL Schlenk tube with another 1 mL of dichloromethane. To the Schlenk tube was then added the propargylic acetate (0.3 mmol, 1.0 equiv) in 7 mL of dichloromethane, bringing the total reaction volume to 9 mL. After 4 h, the reaction was quenched with the addition of two to three drops of triethylamine and concentrated in vacuo. 0.1 mmol of mesitylene was added to the crude reaction mixture, and the ratio of the two products was determined by ^{1}H NMR analysis. The product ratio between the dehydropyrrolidine and the dehydropiperidine was established by integrating the singlet at 5.24 ppm (1 H) of the dehydropyrrolidine, and the singlet at 4.62 ppm (1 H) of the dehydropiperidine.

1-(1-(4-(Trifluoromethyl)phenylsulfonyl)-4,5-dihydro-1*H*-pyrrol-2-yl)ethyl acetate (33). According to the general procedure,

dx.doi.org/10.1021/jo500748e | J. Org. Chem. 2014, 79, 5569−5585

dehydropyrrolidine **33** was obtained from alkyne **32** as an oil in 33% yield (100 mg): Analytical TLC R_f = 0.34 (1:4 ethyl acetate:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 8.14 (d, J = 8.0 Hz, 2 H), 7.82 (d, J = 9.0 Hz, 2 H), 6.06−6.01 (m, 1 H), 5.24−5.22 (m, 1 H), 3.91−3.84 (m, 1 H), 3.78−3.72 (m, 1 H), 2.22−2.14 (m, 1 H), 2.12 (s, 3 H), 2.02−1.94 (m, 1 H), 1.56 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 170.0, 144.4, 140.2, 134.8 (q, $J_{C,F}$ = 33.2 Hz), 128.5, 126.2, 125.0 (q, $J_{C,F}$ = 271.4 Hz), 112.9, 67.3, 51.3, 27.2, 21.0, 20.0; IR (thin film, cm^{-1}) 3103, 2992, 2940, 2862, 1742, 1653, 1607, 1449, 1404, 1355, 1324, 1241, 1169, 1134, 1110, 1084, 1063, 1016, 984, 930, 845, 786, 739, 719; High-resolution MS (ESI$^+$, m/z) molecular ion [M + Na]$^+$ calculated for $C_{15}H_{16}O_4N_1F_3S_1$ 386.0644, found 386.0651, error 1.8 ppm.

2-Methyl-1-(4-(trifluoromethyl)phenylsulfonyl)-1,2,5,6-tetrahydropyridin-3-yl acetate (34). According to the general procedure, dehydropiperidine **34** was obtained from alkyne **32** as an oil in 53% yield (160 mg): Analytical TLC R_f = 0.26 (1:4 ethyl acetate:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 7.97 (d, J = 8.0 Hz, 2 H), 7.77 (d, J = 8.5 Hz, 2 H), 5.37−5.36 (m, 1 H), 4.63 (t, J = 7.0 Hz, 1 H), 3.98 (dd, J = 14.0, 6.0 Hz, 1 H), 3.35−3.29 (m, 1 H), 2.20−2.12 (m, 1 H), 2.07 (s, 3 H), 1.95 (dd, J = 17.0, 4.5 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 168.6, 146.0, 144.6, 134.8 (q, $J_{C,F}$ = 33.1 Hz), 127.2, 126.4, 125.0 (q, JC,F = 270.2 Hz), 116.1, 49.1, 37.9, 26.0, 20.8, 20.7; IR (thin film, cm^{-1}) 2978, 2935, 1761, 1695, 1608, 1460, 1432, 1404, 1365, 1324, 1274, 1225, 1206, 1164, 1137, 1108, 1090, 1062, 1015, 995, 969, 909, 844, 786, 737, 717, 682, 625; High-resolution MS (ESI$^+$, m/z) molecular ion [M + Na]$^+$ calculated for $C_{15}H_{16}O_4$ $N_1F_3S_1$ 386.0644, found 386.0645, error 0.4 ppm.

1-(1-(4-Nitrophenylsulfonyl)-4,5-dihydro-1*H*-pyrrol-2-yl)-ethyl acetate (36). According to the general procedure, dehydropyrrolidine **36** was obtained from alkyne **35** as an oil in 31% yield (63 mg): Analytical TLC R_f = 0.20 (1:4 ethyl acetate:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 8.39 (d, J = 8.0 Hz, 2 H), 8.21 (d, J = 9.0 Hz, 2 H), 6.02−6.00 (m, 1 H), 5.24 (s, 1 H), 3.93−3.87 (m, 1 H), 3.79 (dt, J = 10.0, 5.0 Hz, 1 H), 2.24−2.17 (m, 1 H), 2.11 (s, 3 H), 2.03−1.95 (m, 1 H), 1.56 (d, J = 7.0 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 170.1, 150.3, 144.3, 142.4, 129.2, 124.2, 113.0, 67.3, 51.4, 27.2, 21.0, 20.0; IR (thin film, cm^{-1}) 3106, 2989, 2938, 2866, 1740, 1606, 1531, 1351, 1309, 1240, 1168, 1085, 1042, 1014, 985, 856, 740, 686; High-resolution MS (ESI$^+$, m/z) molecular ion [M + Na]$^+$ calculated for $C_{14}H_{16}O_6N_2S_1$ 363.0621, found 363.0627, error 1.6 ppm.

2-Methyl-1-(4-nitrophenylsulfonyl)-1,2,5,6-tetrahydropyridin-3-yl acetate (37). According to the general procedure, dehydropiperidine **37** was obtained from alkyne **35** as an oil in 39% yield (79 mg): Analytical TLC R_f = 0.12 (1:4 ethyl acetate:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 8.35 (d, J = 8.5 Hz, 2 H), 8.03 (d, J = 9.0 Hz, 2 H), 5.37−5.36 (m, 1 H), 4.62 (t, J = 6.5 Hz, 1 H), 4.01 (dd, J = 14.5, 6.5 Hz, 1 H), 3.38−3.32 (m, 1 H), 2.18−2.10 (m, 1 H), 2.05 (s, 3 H), 1.94−1.86 (m, 1 H), 1.34 (d, J = 7.0 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 168.5, 149.9, 146.8, 146.0, 127.9, 124.5, 116.0, 49.3, 37.9, 25.9, 20.7; IR (thin film, cm^{-1}) 3106, 2978, 2934, 1759, 1693, 1606, 1530, 1461, 1431, 1350, 1311, 1274, 1225, 1205, 1163, 1138, 1109, 1087, 1012, 996, 969, 910, 855, 740, 692, 624; High-resolution MS (ESI$^+$, m/z) molecular ion [M + Na]$^+$ calculated for $C_{14}H_{16}O_6N_2S_1$ 363.0621, found 363.0618, error 0.9 ppm.

Influence of Propargylic Substitution on the Product Ratio (Table 6). To an oven-dried one dram vial was added 5 mol % of the PPh_3AuCl and 5 mol % of $AgSbF_6$; the metal salts were dissolved in 1 mL of THF. The solution was allowed to stir at room temperature for 5 min and then filtered through a 1 cm plug of oven-dried Celite and eluted directly into a 50 mL Schlenk tube with another 1 mL of THF. To the Schlenk tube was then added the propargylic acetate (0.3 mmol, 1.0 equiv) in 7 mL of THF, bringing the total reaction volume to 9 mL. After 4 h, the reaction was quenched by the addition of two to three drops of triethylamine and concentrated in vacuo. 0.1 mmol of mesitylene was added to the crude reaction mixture, and the ratio of the two products was determined by ^{1}H NMR analysis. The product ratio between the dehydropyrrolidine and the dehydropiperidine was established by integrating the singlet at 5.24 ppm (1 H) of the dehydropyrrolidine, and the singlet at 4.62 ppm (1 H) of the dehydropiperidine.

1-(5-Phenyl-1-tosyl-4,5-dihydro-1*H*-pyrrol-2-yl)ethyl acetate (39). According to the general procedure, dehydropyrrolidine **39** was obtained from alkyne **38** as a 1:1 mixture of diastereomers, and white solid in 32% yield (37 mg): mp 132−135 °C (decomposition); Analytical TLC R_f = 0.30 (1:4 ethyl acetate:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 7.68 (d, J = 8.0 Hz, 2 H), 7.40 (d, J = 7.5 Hz, 2 H), 7.32 (t, J = 7.0 Hz, 2 H), 7.28−7.24 (m, 3 H), 6.00 (q, J = 6.5 Hz, 1 H), 5.35 (s, 1 H), 5.29 (dd, J = 9.5, 2.0 Hz, 1 H), 2.72−2.65 (m, 1 H), 2.42 (s, 3 H), 2.25−2.21 (m, 1 H), 2.07 (s, 3 H), 1.51 (d, J = 7.0 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 170.1, 143.9, 143.7, 142.8, 135.6, 129.6, 128.5, 127.4, 127.3, 125.7, 114.7, 65.8, 64.7, 37.2, 21.5, 21.1, 18.2; IR (thin film, cm^{-1}) 3029, 2938, 1739, 1598, 1450, 1350, 1240, 1165, 1090, 996, 814, 736, 670; High-resolution MS (ESI$^+$, m/z) molecular ion [M + Na]$^+$ calculated for $C_{21}H_{23}O_4N_1S_1$ 408.1240, found 408.1238, error 0.4 ppm.

2-Methyl-6-phenyl-1-tosyl-1,2,5,6-tetrahydropyridin-3-yl acetate (40). According to the general procedure, dehydropyrrolidine **40** was obtained from alkyne **38** as a 1:1mixture of diastereomers, as a clear oil in 60% yield (69 mg): Analytical TLC R_f = 0.24 (1:4 ethyl acetate:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 7.92 (d, J = 8.5 Hz, 2 H), 7.76 (d, J = 8.0 Hz, 2 H), 7.62 (d, J = 7.5 Hz, 2 H), 7.37−7.31 (m, 10 H), 7.29−7.25 (m, 2 H), 6.20−6.18 (m, 1 H), 5.41 (d, J = 7.0 Hz, 1 H), 5.31−5.30 (m, 1 H), 5.12−5.10 (m, 1 H), 5.04 (d, J = 9.5 Hz, 1 H), 4.62−4.60 (m, 1 H), 2.47−2.41 (m, 7 H), 2.36−2.31 (m, 1 H), 2.22−2.18 (m, 1 H), 2.13−2.11 (m, 6 H), 1.63 (d, J = 6.5 Hz, 3 H), 0.78 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 169.9, 168.8, 144.3, 144.0, 143.9, 143.4, 142.8, 140.0, 137.8, 133.8, 129.9, 129.7, 128.6, 128.2, 128.1, 127.9, 127.6, 127.5, 126.7, 125.7, 115.7, 111.1, 68.2, 65.2, 52.1, 49.6, 36.5, 26.6, 22.0, 21.6, 21.1, 21.0, 20.; IR (thin film, cm^{-1}) 2962, 1744, 1597, 1499, 1446, 1368, 1348, 1242, 1217, 1164, 1136, 1091, 993, 915, 817, 735, 715; High-resolution MS (ESI$^+$, m/z) molecular ion [M + Na]$^+$ calculated for $C_{21}H_{23}O_4N_1S_1$, 408.1240 found 408.1241, error 0.4 ppm.

2-Methyl-1-(1-tosyl-4,5-dihydro-1*H*-pyrrol-2-yl)propyl acetate (42). According to the general procedure, dehydropyrrolidine **42** was obtained from alkyne **41** as an oil in 15% yield (15 mg): Analytical TLC R_f = 0.43 (1:4 ethyl acetate:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 7.89 (d, J = 7.5 Hz, 2 H), 7.33 (d, J = 8.5 Hz, 2 H), 5.99 (s, 1 H), 5.12 (s, 1 H), 3.82−3.74 (m, 2 H), 2.54−2.48 (m, 1 H), 2.42 (s, 3 H), 2.13 (s, 3 H), 2.11−2.05 (m, 1 H), 1.89−1.81 (m, 1 H), 1.03 (d, J = 7.0 Hz, 3 H), 0.87 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 170.4, 143.8, 142.4, 133.4, 129.5, 128.1, 113.8, 75.1, 51.3, 29.5, 27.2, 21.5, 20.8, 19.2, 15.3; IR (thin film, cm^{-1}) 2966, 2932, 2874, 1741, 1597, 1467, 1350, 1239, 1163, 1091, 1026, 986, 905, 816, 773, 708, 691, 670; High-resolution MS (ESI$^+$, m/z) molecular ion [M + Na]$^+$ calculated for $C_{17}H_{23}O_4N_1S_1$ 360.1240, found 360.1245, error 1.4 ppm.

2-Isopropyl-1-tosyl-1,2,5,6-tetrahydropyridin-3-yl acetate (43). According to the general procedure, dehydropiperidine **43** was obtained from alkyne **41** as an oil in 34% yield (35 mg): Analytical TLC R_f = 0.33 (1:4 ethyl acetate:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 7.71 (d, J = 8.0 Hz, 2 H), 7.27 (d, J = 8.5 Hz, 2 H), 5.48−5.47 (m, 1 H), 4.16 (t, J = 3.5 Hz, 1 H), 3.93−3.87 (dd, J = 15.0, 6.5 Hz, 1 H), 3.30−3.24 (m, 1 H), 2.41 (s, 3 H), 2.04 (s, 3 H), 1.95−1.82 (m, 2 H), 1.77 (dd, J = 16.5, 4.5 Hz, 1 H), 1.03 (d, J = 6.5 Hz, 3 H), 0.99 (d, J = 6.0 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 168.6, 146.2, 143.2, 138.1, 129.6, 126.9, 133.4, 58.6, 39.1, 33.8, 24.7, 21.5, 20.8, 20.1, 19.1; IR (thin film, cm^{-1}) 2963, 2928, 2873, 1756, 1692, 1598, 1452, 1367, 1338, 1221, 1204, 1159, 1134, 1092, 1045, 1010, 952, 918, 815, 714, 660; High-resolution MS (ESI$^+$, m/z) molecular ion [M + Na]$^+$ calculated for $C_{17}H_{23}O_4N_1S_1$ 360.1240, found 360.1237, error 0.8 ppm.

2,2,-Dimethyl-1-(1-tosyl-4,5-dihydro-1*H*-pyrrol-2-yl)propyl acetate (45). According to the general procedure, dehydropyrrolidine **45** was obtained from alkyne **44** as an oil in 86% yield (172 mg): Analytical TLC R_f = 0.42 (1:4 ethyl acetate:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 7.90 (d, J = 8.5 Hz, 2 H), 7.27 (d, J = 9.0 Hz, 2 H), 6.07 (s, 1 H), 5.24 (s, 1 H), 3.90−3.85 (m, 1 H), 3.74−3.67 (m, 1

dx.doi.org/10.1021/jo500748e | J. Org. Chem. 2014, 79, 5569−5585

H), 2.39 (s, 3 H), 2.10 (s, 3 H), 2.00−1.93 (m, 1 H), 1.73−1.66 (m, 1 H), 1.02 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 169.6, 143.5, 142.6, 134.0, 129.4, 128.1, 116.7, 76.7, 51.4, 35.2, 27.0, 26.2, 21.5, 20.9; IR (thin film, cm^{-1})2968, 2869, 1738, 1370, 1346, 1244, 1162, 1090, 1048, 1023, 991, 916, 817, 688; High-resolution MS (ESI$^+$, m/z) molecular ion $[M + Na]^+$ calculated for $C_{18}H_{25}O_4N_1S_1$ 374.1397, found 374.1388, error 2.0 ppm.

Procedure for the Hydrolysis of the Benzoate Esters. This procedure was used if the mixture of five- and six-membered heterocycles was inseparable. The benzoate ester was dissolved in 10 mL of a 1/1 v/v mixture of MeOH and water that contained 2.5 equiv of powdered sodium hydroxide,[14] and the mixture was allowed to stir at room temperature for 16 h. The reaction was then concentrated under a vacuum and dissolved in ether and washed with water. The aqueous layer was separated and further extracted with ether. The organic extracts were combined and washed with brine, dried over magnesium sulfate, and concentrated under a vacuum. The crude oil was then purified by flash chromatography to afford the respective alcohol and ketone products.

1-(1-Tosyl-4,5-dihydro-1*H*-pyrrol-2-yl)ethanol (47). According to the general procedure, dehydropyrrolidine **47** was obtained as an oil in 49% yield (30 mg): Analytical TLC R_f = 0.11 (1:4 ethyl acetate:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 7.75 (d, J = 8.5 Hz, 2 H), 7.33 (d, J = 8.0 Hz, 2 H), 5.30−5.29 (m, 1 H), 4.79 (q, J = 6.0 Hz, 1 H), 3.86−3.75 (m, 2 H), 3.62 (br s, 1 H), 2.44 (s, 3 H), 2.16−2.10 (m, 2 H), 1.46 (d, J = 6.0 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 147.5, 144.0, 134.1, 129.8, 127.4, 127.0, 113.4, 63.5, 50.9, 27.3, 21.5, 20.8; FT-IR (thin film, cm^{-1}) 3523, 2978, 2927, 1716, 1597, 1448, 1340, 1161, 1091, 982, 815, 715, 665; High-resolution MS (EI$^+$, m/z) molecular ion $[M]^+$ calculated for $C_{13}H_{17}O_3N_1S_1$ 267.0924, found 267.0928, error 1.8 ppm.

2-Methyl-1-tosylpiperidin-3-one (48). According to the general procedure, piperidinone **48** was obtained as an oil in 20% yield (12 mg): Analytical TLC R_f = 0.20 (1:4 ethyl acetate:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 7.76 (t, J = 8.0 Hz, 2 H), 7.33 (d, J = 8.5 Hz, 2 H), 4.60 (quintet, J = 6.5 Hz, 1 H), 4.14−4.10 (m, 1 H), 3.35−3.30 (m, 1 H), 2.67 (dd, J = 15.0, 7.0 Hz, 1 H), 2.53−2.46 (m, 1 H), 2.44 (s, 3 H), 2.33−2.29 (m, 1 H), 2.21 (dt, J = 16.5, 2.0 Hz, 1 H), 1.06 (d, J = 7.5 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 206.5, 143.8, 137.2, 129.9, 127.0, 50.3, 47.1, 40.6, 39.9, 21.5, 18.0; FT-IR (thin film, cm^{-1}) 2973, 2922, 1720, 1597, 1358, 1339, 1228, 1160, 1115, 1090, 1019, 977, 926, 816, 712; High-resolution MS (ESI$^+$, m/z) molecular ion $[M + H]^+$ calculated for $C_{13}H_{17}O_3N_1S_1$ 268.1002, found 268.1009, error 3.0 ppm.

■ ASSOCIATED CONTENT

Supporting Information

Complete proton and carbon-13 NMR spectra and the X-ray structure of compound **11** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: diver@buffalo.edu.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors thank the NSF (CHE-0848560 and CHE-1012839) and the Kapoor Graduate Fellowship awarded to J.M.F. for financial support of this work. We also thank Dr. Bill Brennesel (U. of Rochester) for the crystal structure determination of **11**.

■ REFERENCES

(1) Kalbarczyk, K. P.; Diver, S. T. *J. Org. Chem.* **2009**, *74*, 2193−2196.

(2) (a) Fürstner, A.; Davies, P. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 3410−3449. (b) Fürstner, A. *Chem. Soc. Rev.* **2009**, *38*, 3208−3221. (c) Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Commun.* **2007**, 333−346. (d) Jiménez-Núñez, E. S.; Echavarren, A. M. *Chem. Rev.* **2008**, *108*, 3326−3350. (e) Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180−3211. (f) Corma, A.; Leyva-Pérez, A.; Sabater, M. J. *Chem. Rev.* **2011**, *111*, 1657−1712. (g) Gorin, D. J.; Sherry, B. D.; Toste, F. D. *Chem. Rev.* **2008**, *108*, 3351−3378. (h) Shapiro, N. D.; Toste, F. D. *Synlett* **2010**, *2010*, 675−691. (i) Rudolph, M.; Hashmi, A. S. K. *Chem. Soc. Rev.* **2012**, *41*, 2448−2462. (j) Zhang, L.; Sun, J.; Kozmin, S. A. *Adv. Synth. Catal.* **2006**, *348*, 2271−2296.

(3) Rautenstrauch, V. *J. Org. Chem.* **1984**, *49*, 950−952.

(4) (a) Correa, A.; Marion, N.; Fensterbank, L.; Malacria, M.; Nolan, S. P.; Cavallo, L. *Angew. Chem., Int. Ed.* **2008**, *47*, 718−721. (b) Marion, N.; Lemière, G.; Correa, A.; Costabile, C.; Ramón, R. S.; Moreau, X.; de Frémont, P.; Dahmane, R.; Hours, A.; Lesage, D.; Tabet, J.-C.; Goddard, J.-P.; Gandon, V.; Cavallo, L.; Fensterbank, L.; Malacria, M.; Nolan, S. P. *Chem.—Eur. J.* **2009**, *15*, 3243−3260. (c) Shi, X.; Gorin, D. J.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 5802−5803. (d) Zhang, L. *J. Am. Chem. Soc.* **2005**, *127*, 16804−16805. (e) Hashmi, A. S. K. *Angew. Chem., Int. Ed.* **2010**, *49*, 5232−5241. (f) Mauleón, P.; Krinsky, J. L.; Toste, F. D. *J. Am. Chem. Soc.* **2009**, *131*, 4513−4520.

(5) Chemla, F.; Hebbe, V.; Normant, J.-F. *Synthesis* **2000**, *2000*, 75−77.

(6) (a) Aponick, A.; Li, C.-Y.; Malinge, J.; Marques, E. F. *Org. Lett.* **2009**, *11*, 4624−4627. (b) Egi, M.; Azechi, K.; Akai, S. *Org. Lett.* **2009**, *11*, 5002−5005. (c) Gorin, D. J.; Davis, N. R.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 11260−11261.

(7) Knight, D. W.; Redfern, A. L.; Gilmore, J. *J. Chem. Soc., Perkin Trans. 1* **2002**, 622−628.

(8) Wang, D.; Cai, R.; Sharma, S.; Jirak, J.; Thummanapelli, S. K.; Akhmedov, N. G.; Zhang, H.; Liu, X.; Petersen, J. L.; Shi, X. *J. Am. Chem. Soc.* **2012**, *134*, 9012−9019.

(9) Wang, S.; Zhang, G.; Zhang, L. *Synlett* **2010**, *2010*, 692−706.

(10) (a) Álvarez-Corral, M. R.; Muñoz-Dorado, M.; Rodríguez-García, I. *Chem. Rev.* **2008**, *108*, 3174−3198. (b) Agarwal, S.; Knölker, H.-J. *Org. Biomol. Chem.* **2004**, *2*, 3060−3062. (c) Knölker, H.-J.; Agarwal, S. *Tetrahedron Lett.* **2005**, *46*, 1173−1175.

(11) (a) Patrick, S. R.; Boogaerts, I. I. F.; Gaillard, S.; Slawin, A. M. Z.; Nolan, S. P. *Beilstein J. Org. Chem.* **2011**, *7*, 892−896. (b) Wang, L.-J.; Zhu, H.-T.; Wang, A.-Q.; Qiu, Y.-F.; Liu, X.-Y.; Liang, Y.-M. *J. Org. Chem.* **2013**, *79*, 204−212. (c) Zhang, Z.; Bender, C. F.; Widenhoefer, R. A. *Org. Lett.* **2007**, *9*, 2887−2889.

(12) Kobayashi, S.; Morikawa, K.; Saegusa, T. *Macromolecules* **1975**, *8*, 386−390.

(13) (a) Schienebeck, C. M.; Robichaux, P. J.; Li, X.; Chen, L.; Tang, W. *Chem. Commun.* **2013**, *49*, 2616−2618. (b) Hardin, A. R.; Sarpong, R. *Org. Lett.* **2007**, *9*, 4547−4550.

(14) Martin, S. F.; Dodge, J. A.; Burgess, L. E.; Limberakis, C.; Hartmann, M. *Tetrahedron* **1996**, *52*, 3229−3246.

(15) Short, K. M.; Ziegler, C. B., Jr. *Tetrahedron Lett.* **1995**, *36*, 355−356.

(16) Wang, J.-X.; Jia, X.; Meng, T.; Xin, L. *Synthesis* **2005**, *17*, 2838−2844.

(17) Ding, C. H.; Dai, L. X.; Hou, X. L. *Tetrahedron* **2005**, *61*, 9586−9593.

(18) Teichert, J. F.; Zhang, S.; van Zijl, A. W.; Slaa, J. W.; Minnaard, A. J.; Feringa, B. L. *Org. Lett.* **2010**, *12*, 4658−4660.