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Palladium-Catalyzed Regioselective Alkynylation of Pyrroles and Azoles under Mild Conditions: Application to the Synthesis of a Dopamine D-4 Receptor Agonist

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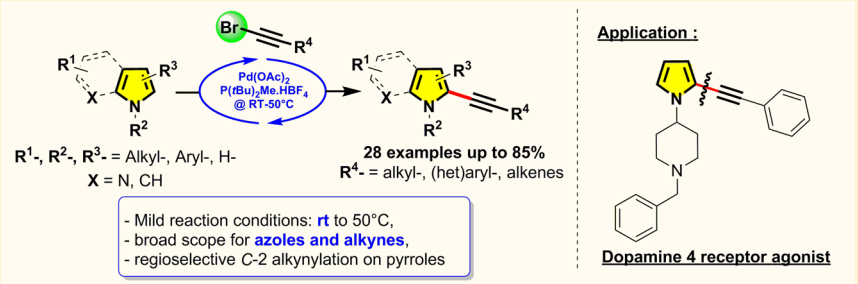
Supporting Information

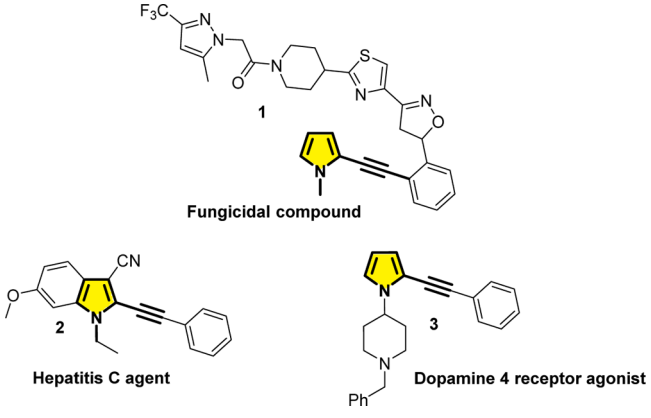


ABSTRACT: A mild and general method for the direct alkynylation of azoles such as pyrrole, indole, and 7-azaindole is described here. Using a simple catalytic system such as $Pd(OAc)_2$ (2.5 mol %), $P(tBu)_2Me{\cdot}HBF_4$ (5 mol %), and NaOAc (2 equiv) allowed the regioselective introduction of various alkynyl residues at the *C*-2 position of pyrroles. Interestingly, *C*-2 alkynylation was also observed on *C*-3-substituted indoles, whereas classical *C*-3 alkynylation was obtained on selected unsubstituted indoles and 7-azaindole. Our methodology has been illustrated by the efficient synthesis of a potential schizophrenia drug (dopamine D-4 inhibitor).

INTRODUCTION

Heterocycles are ubiquitous in nature and are constitutive of many essential compounds.[1] Nitrogen-contaning heterocycles are probably the most popular and useful family of heterocycles (e.g., pyrroles, indoles, purines),[2] with various properties in therapeutics, materials, and agrochemicals sciences.[3] As shown in Scheme 1, alkynylated pyrrole (or indole) patterns are found in many bioactive compounds: for instance, compound **1** exhibits fungicidal activity,[4] compound **2** is a hepatitis agent,[5] and compound **3** targets the dopamine 4 receptor.[6] With the aim of building these compounds, many strategies have been developed to ideally functionalize the pyrrole core. One of the most recent and powerful breakthroughs in the direct functionalization of azoles has been carried out by C−H activation. This method has already been reported for the introduction of many electrophiles, or pseudoelectrophiles, onto heteroarene compounds.[8]

Scheme 1. Bioactive Alkynylated Pyrrole-Containing Compounds



As part of our efforts to find and develop new methods to synthesize and functionalize heterocyclic structures,[7] we envisioned the functionalization of pyrroles, and particularly the introduction of alkynyl residues at their *C*-2 position, in order to obtain new building blocks. At first, we thought that the most convergent strategy would be the direct introduction of an alkynyl residue by an attractive C−H activation reaction. However, although C−H arylation or C−H alkenylation has been well described and reviewed in recent years for many heteroarenes, including indoles or pyrroles,[8] the C−H alkynylation version has been much less explored, especially for pyrroles.[9] In fact, tremendous efforts in C−H alkynylation

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Scheme 2. State of the Art of C−H Alkynylation of Pyrroles

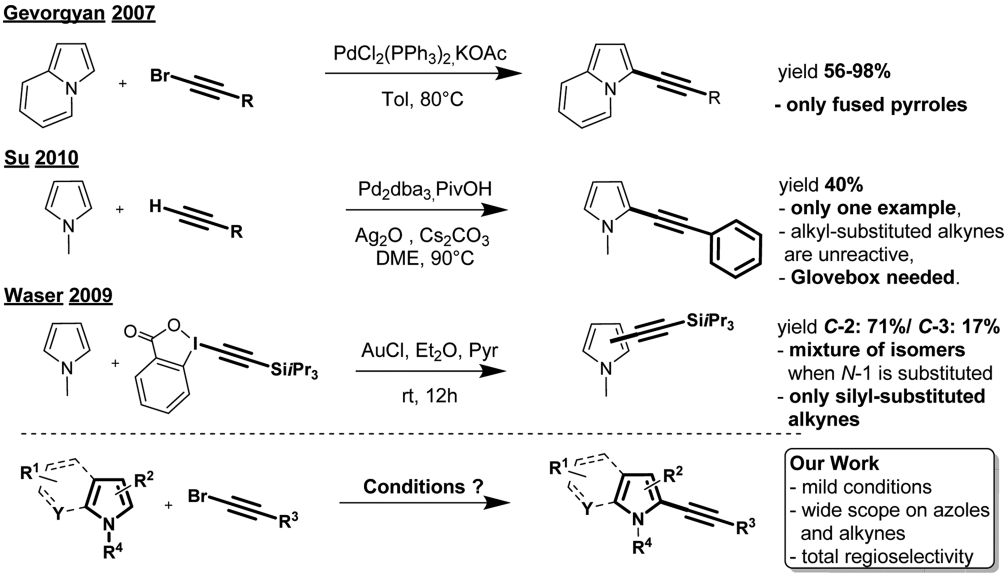
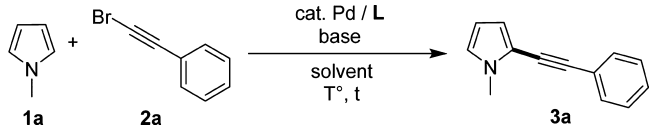


Table 1. Optimization Coupling Reaction of 1a with 2a under Various Conditions[a]



entry	Pd (5 mol %)	ligand (10 mol %)	base (2 equiv)	solvent (0.25 M)	conversn (%)[b]	yield of **3a** (%)[c]
1	**$PdCl_2(PPh_3)_2$**		KOAc	toluene	95	15
2	**$Pd(OAc)_2$**	**PPh_3**	KOAc	toluene	<5	
3	$Pd(OAc)_2$	**dppb**	KOAc	toluene	<5	
4	$Pd(OAc)_2$	**Xphos**	KOAc	toluene	<5	
5	$Pd(OAc)_2$	**$P(tBu)_2Me{\cdot}HBF_4$**	**KOAc**	toluene	100	71
6	**$Pd(OAc)_2$ (2.5 mol %)**	**$P(tBu)_2Me{\cdot}HBF_4$ (5 mol %)**	**NaOAc**	**toluene**	**100**	**85**
7	**$Pd(OAc)_2$ (2.5 mol %)**	**$P(tBu)_2Me{\cdot}HBF_4$ (5 mol %)**	**NaOAc**	**dioxane**	**100**	**85**
8	$Pd(OAc)_2$	$P(tBu)_2Me{\cdot}HBF_4$	NaOAc	**DMF**	<5	
9[d]	$Pd(OAc)_2$	$P(tBu)_2Me{\cdot}HBF_4$	NaOAc	toluene	100	24
10[e]	$Pd(OAc)_2$	$P(tBu)_2Me{\cdot}HBF_4$	NaOAc	toluene	100	78

[a]Reaction conditions unless specified otherwise: **1a** (0.50 mmol), **2a** (0.25 mmol), $Pd(OAc)_2$ (5 mol %), ligand (10 mol %), and base (0.50 mmol) in solvent (1.0 mL) were heated in a sealed Schlenk tube at 50 °C for 10 h. [b]Conversion was determined by ^1H NMR on the crude reaction mixture. [c]Yield of isolated product. [d]Reaction was run at 75 °C. [e]The reaction was run at room temperature. *Control experiments*: no conversion at all was observed in the absence of $Pd(OAc)_2$ or L and in the absence of $Pd(OAc)_2$ and L.

have been made by different research groups;[10] however, when we looked carefully for direct alkynylation of pyrroles in the literature, we were surprised to find no general methods for introducing a C(sp) moiety at the *C*-2 position of pyrroles, despite its wide utility. To the best of our knowledge, only three related examples of C−H alkynylation of pyrrole derivatives have been reported, but with a limited scope for the nature of pyrroles or alkynes used, which led us to examine this reaction further. Indeed, in a seminal paper Gevorgyan and co-workers were the first to report the efficient alkynylation of electron-rich *N*-fused azoles[10a] (Scheme 2). In their case, one pyrrole α-position was blocked, therefore avoiding potential dialkynylation reactions. Moreover, the use of unsubstituted pyrroles as starting materials led only to poor yields of the alkynylated products.[11] Indeed, electron-rich structures were clearly needed to carry out an efficient C−H alkynylation reaction.[10a] Furthermore, in the case of a pyrrolo dimer with two free α-positions (*C*-2 positions), Gevorgyan's team had obtained the *C*-2-disubstituted product, and the isolation of the mono-substituted compound was not reported. Therefore, inspired by Gevorgyan's work and observing that very little information on functionalized or unprotected pyrroles is known in the literature, we decided to launch our investigations. Hence, it may be important to find alternative and regioselective reactions compatible with pyrroles exhibiting unsubtituted α-positions. Indeed, another recent report based on C−H alkynylation was published by Su and co-workers on several heteroarenes (Scheme 2), but mostly concentrating on 2-substituted thiophenes, by an oxidative strategy.[12] In their reaction only one example was reported with pyrrole and had a low 40% yield due to concomitant dimerizations of both alkyne and heterocycle moieties in a significant amount. Finally, Waser's group[16] described the alkynylation of several heteroarenes, especially pyrroles, using a hypervalent iodine reagent under gold catalysis (Scheme 2). Despites the use of mild conditions, only silylethynyl groups were introduced on

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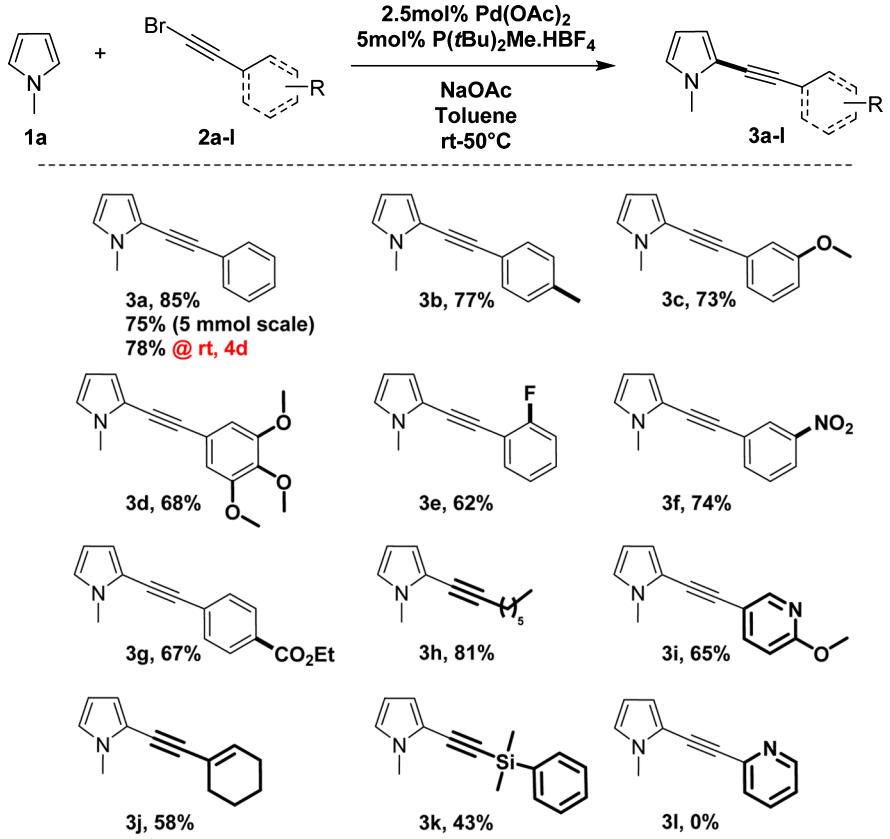
Table 2. Scope of Bromoalkynes with *N*-Methylpyrrole[a]



[a]Reaction conditions: **1a** (0.50 mmol), **2a** (0.25 mmol), $Pd(OAc)_2$ (2.5 mol %), $P(tBu)_2Me.HBF_4$ (5 mol %), and NaOAc (0.50 mmol) in toluene (1.0 mL) were heated in a sealed Schlenk tube at 50 °C for 10 h.

pyrroles, and troubles with regioselectivity were observed on *N*-substituted heterocycles.

Because of the reported regioselectivity and reactivity limitations in obtaining *C*-2 alkynylated pyrroles, we were motivated to develop an efficient method. Herein, we report a mild and general method for a selective and efficient access to *C*-2 regioselective alkynylation of pyrroles, using various bromoalkynes as starting materials. The reactivity of related heteroarenes will also be reported and discussed. An application to the synthesis of a bioactive compound, a dopamine D-4 inhibitor, has also been investigated.

RESULTS AND DISCUSSION

To find the best reaction conditions, we chose in a model reaction to use *N*-methylpyrrole **1a** as the heteroarene moiety and tested its reactivity toward 1-bromophenylacetylene (**2a**) (Table 1). Bromoacetylene derivatives are readily available from the corresponding terminal alkynes using $AgNO_3$ as the catalyst and *N*-bromosuccinimide as the brominating agent at room temperature.[13] Thus, we tried to find the best conditions to get the desired alkynylated product at position 2 of pyrrole and to avoid the formation of side products such as alkynylation in position 3[9] or dialkynylation of positions *C*-2 and *C*-5. The coupling was initially run following conditions reported previously by Gevorgyan, $PdCl_2(PPh_3)_2$ and KOAc in toluene, setting our reactions at 50 °C.[10a] However, as expected we got only a 15% yield of the desired product and traces of the *C*-3-alkynylated product (Table 1, entry 1). Then, we started to optimize the reaction conditions by changing first the palladium source to $Pd(OAc)_2$ (5 mol %) and to evaluate the impact of palladium ligands on this reaction. Importantly, the results in entries 2−5 (Table 1) demonstrated that the nature of the ligand was crucial for the C−H alkynylation reaction. Indeed, trialkylphosphines, especially Fu's $P(tBu)_2Me.HBF_4$,[14] proved to be the best ligands for this reaction, giving the desired product in a good 71% yield (Table 1, entry 5). Other type of ligands such as mono- or bidentate species were less efficient in this reaction and led to poor conversion of the starting materials (Table 1, entries 2−4). Switching the base from potassium acetate to sodium acetate (Table 1, entry 6) allowed us to reach a better 85% yield. Other types of bases such as *tert*-butylates, carbonates, and organic bases gave lower yields, which is in accordance with a concerted mechanism deprotonation route due to the acetate moiety.[15] The catalytic load could also be reduced from 5 to 2.5 mol % of Pd (Pd/L 1/2) to afford a similar yield of 85% after 10 h (Table 1, entry 6). Trying different solvents failed to improve the yields of the reaction; interestingly, the reaction run in dioxane gave a yield similar to that in toluene (Table 1, entries 6 and 7), and in DMF no conversion was observed (Table 1, entry 8). The amount of bromoalkyne and pyrrole derivatives was also crucial to obtain good yields; indeed 2 equiv of *N*-methylpyrrole (**1a**) for 1 equiv of 1-bromophenylacetylene (**2a**) gave the best yield (85%). By diminishing the amount of *N*-methylpyrrole to 1.5 equiv, the yield of the C−H alkynylation reaction dropped to 74%, but still no dialkynylation product was observed; for this reason we kept the ratio 2/1 between pyrroles and bromoalkynes for our studies. We also investigated the effect on temperature: increasing the temperature to 75 °C gave a very low yield (24%, Table 1, entry 9), certainly due to the

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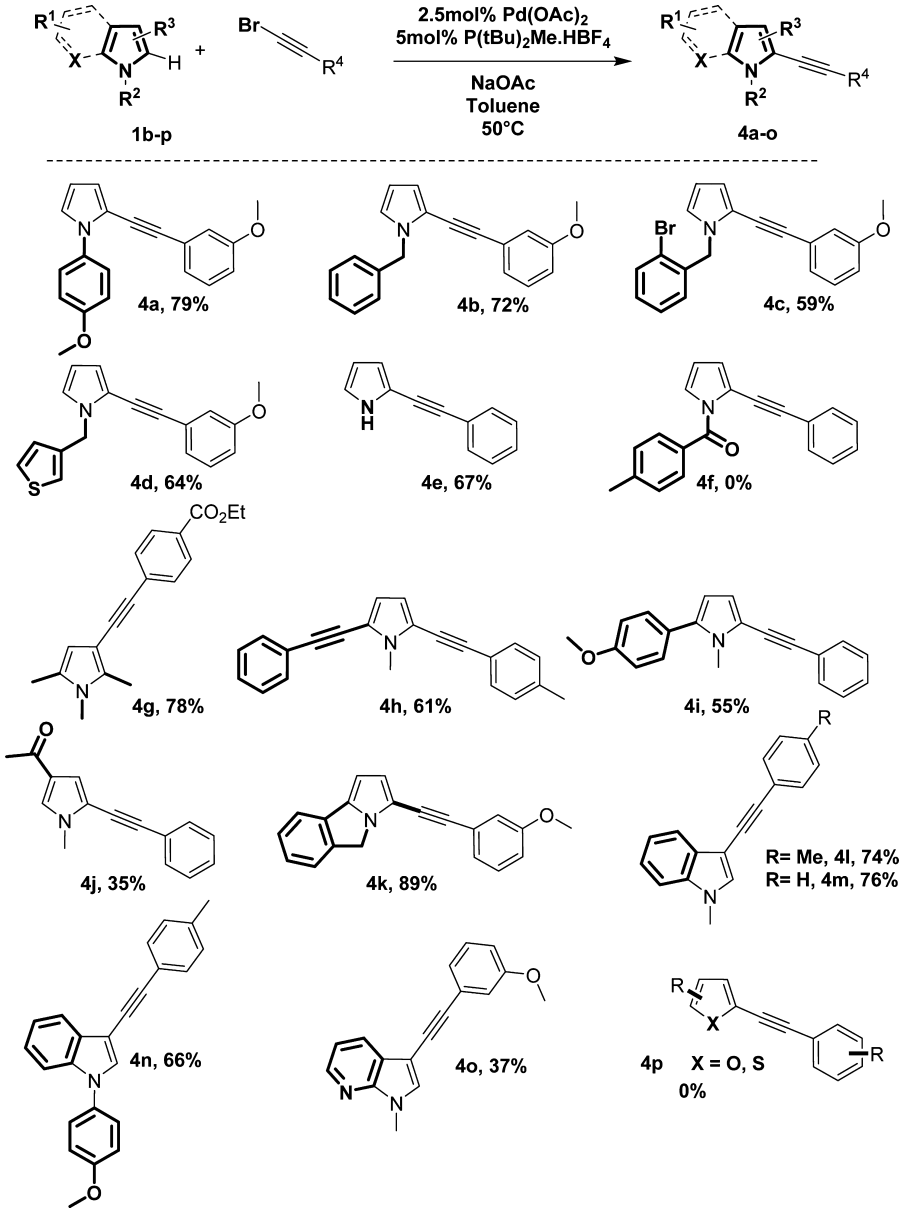
Table 3. Scope of Pyrrole-Containing Derivatives[a]



[a]Reaction conditions: **1b−p** (0.50 mmol), **2** (0.25 mmol), $Pd(OAc)_2$ (2.5 mol %), $P(tBu)_2Me{\cdot}HBF_4$ (5 mol %), and NaOAc (0.50 mmol) in toluene (1.0 mL) were heated in a sealed Schlenk tube at 50 °C for 10 h.

instability of the bromoalkyne derivatives, and when we lowered the temperature to room temperature, we were pleased to find that the reaction was still effective, giving rise to the desired product in a good 78% yield; however, the reaction took 4 days (Table 1, entry 10). These mild conditions could be particularly interesting in total synthesis, for a late-stage functionalization of a complex molecule. Not surprisingly,[10a] chloro- and iodoalkynes were not efficient under these reaction conditions, leading only to traces of products or formation of diyne products (data not shown).

To conclude, we found our optimal conditions: 2.5 mol % of $Pd(OAc)_2$ with 5.0 mol % of $P(tBu)_2Me.HBF_4$ and NaOAc (2 equiv) in toluene at 50 °C over 10 h. With these conditions in hand, we then explored the scope and limitations of this process toward the different bromoalkynes **2a−l** (Table 2) and thereafter on the different heteroarene substrates **1b−o** (Table 3).

First of all, bromoalkynes were obtained easily from a well-described bromination reaction of the corresponding terminal alkynes under $AgNO_3$ catalysis using *N*-bromosuccinimide as the brominating agent.[13] Then, they were engaged in the C−H alkynylation procedure with *N*-methylpyrrole (**1a**) (Table 2). Gratifyingly, almost all of the bromoalkynes used in this study were efficiently coupled under our optimized conditions. Indeed, bromoalkynes possessing electron-withdrawing or electron-donating groups in ortho, meta, or para positions were efficiently introduced on the *C*-2 position of *N*-methylpyrrole (**1a**). The model compound **3a** was obtained in a satisfactory 85% yield at the 0.25 mmol scale, and when we increased the scale to 5 mmol, we still observed a good 75% yield for this transformation. As described previously in the optimization condition step, compound **3a** was also obtained in a good 78% yield at room temperature but after a longer reaction time (4 days).

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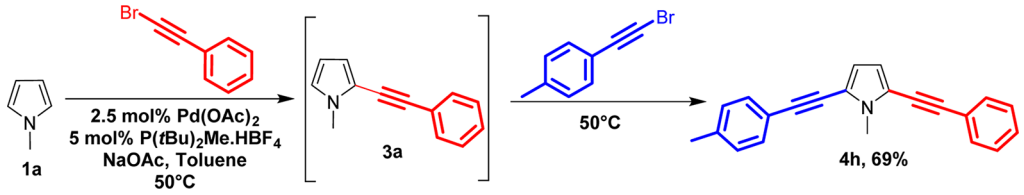
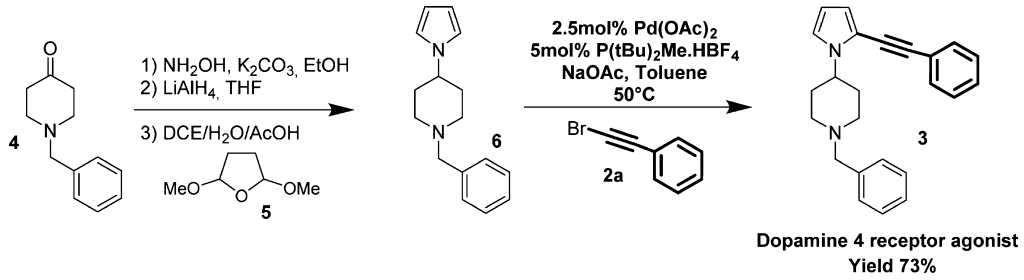
Scheme 3. One-Pot Tandem Dialkynylation Reaction



Scheme 4. Synthesis of a Dopamine D-4 Agonist



Bromoalkynes substituted with electron-donating groups were introduced efficienly to produce **3b–d** in good yields ranging from 68% to 77%. Phenylacetylene units possessing fluoro (**3e**), nitro (**3f**), or ethyl ester substituents (**3g**) were also successfully introduced (62–74% yield), especially the sensitive ester function in an encouraging 67% yield. Interestingly, it was also possible to introduce on *N*-methylpyrrole (**1a**) an alkyl-substituted alkyne (octynyl chain) in a good 81% yield (compound **3h**). Furthermore, 1-(bromoethynyl)cyclohex-1-ene, as an ene-yne substituent, was introduced, giving rise to the product **3j** in a reasonable 58% yield, and silylethynyl-substituted pyrrole could also be formed (compound **3k**, 43%).

Moreover, 5-(bromoethynyl)-2-methoxypyridine was also a good partner as a heteroarene substituent, yielding product **3i** (65% yield). However, when using simple 2-(bromoethynyl)-pyridine we could not observe the formation of the desired product **3l**, and the reaction led only to the slow degradation of the starting material.

After exploring the scope of the reaction with various alkynyl derivatives on *N*-methylpyrrole (**1a**), we turned our attention to the heteroarene counterparts (Table 3). Thus, we examined not only differently substituted pyrroles but also other heteroarenes. We were pleased to find that substituted pyrroles were quite well tolerated under our reaction conditions. In fact, the pyrrole *N*-position could be substituted by aryl, benzyl, or heterobenzyl substituents (**4a–d**), giving the desired products in satisfactory yields up to 79%. We observed that a bromine atom on the C(sp) carbon is much more reactive than that on a C(sp^2) carbon, allowing access to product **4c** in a satisfiying 59% yield. Compound **4c** might be further functionnalized in cross-coupling reactions to bring structural diversity. Interestingly, the reaction conditions are very selective for the pyrrole *C*-2 position, since the reaction of two different heteroarenes linked together, in our case a pyrrole and a thiophene, led only to the alkynylation at the pyrrole unit (**4d**, 64% yield). This is particularly interesting, because thiophene is known to be reactive in related C–H activation reactions.[12,16] This observation could be particularly useful in a late-stage functionalization of a complex molecule possessing both heteroarenes. However, the pyrrole *N*-substituted by an acyl group (compound **4f**) was unreactive under these conditions, leading only to the degradation of the alkynyl bromide unit. This result seems to indicate that electron-rich pyrroles are necessary in order to perform the C–H alkynylation reaction under our reaction conditions. Nevertheless, we were pleased to observe that unprotected pyrroles, known to be very sensitive[17] and thus hard to engage in classical Sonogashira reactions, were here good partners, giving the *C*-2-alkynylated compound in a satisfiying 67% yield (**4e**). Differently alkyl substituted pyrroles were also good partners in this reaction, leading to compound **4g** in 78% yield. Thanks to compound **4g**, we were able to observe that when position 2 is blocked, the alkynyl derivative can still be introduced, but now at position 3, with a good 78% yield.

We observed previously that electron-deficient substituents were not well tolerated in this reaction (**4f**), and indeed the use of 3-acetylpyrrole led to the alkynylated compound **4j** with a low 35% yield. An alkynyl- or aryl-substituted pyrrole (compounds **4h,i**) could also be engaged in this reaction, giving the desired products in fair yields (61 and 55%, respectively). Then we turned our attention on other heterocycles. Thus, pyrroloisoindoline was a good partner, giving the desired product **4k** in an excellent 89% yield. Indoles, *N*-protected by an aryl or alkyl substituent, were also good partners for this reaction, giving compounds **4l–n** regioselectively alkynylated at their electron-rich *C*-3 position. 1-(Bromoethynyl)-3-methoxybenzene was also reactive on the 7-azaindole moiety, at the *C*-3 position, but with a low 37% yield (**4o**). Moreover, as observed with compound **4d**, other heteroarenes (furane and thiophene) were strictly unreactive under our reaction conditions (compound **4p**), whatever the nature of the bromoalkyne used.

Inspired by the synthesis of product **4h**, we wondered if two successive alkynylation reactions could be done in a one-pot, two-step reaction using our protocol (Scheme 3). We thus chose to work in the first step with equimolar quantities of pyrrole **1a** and 1-bromophenylacetylene, in order to avoid competition in the second step between nonalkynylated *N*-methylpyrrole (**1a**) with compound **3a** toward 1-(bromoethynyl)-4-methylbenzene. After checking the completion of the first reaction (formation of compound **3a**), we then added the 1-(bromoethynyl)-4-methylbenzene derivative and kept on heating for 10 h more. We were pleased to isolate compound

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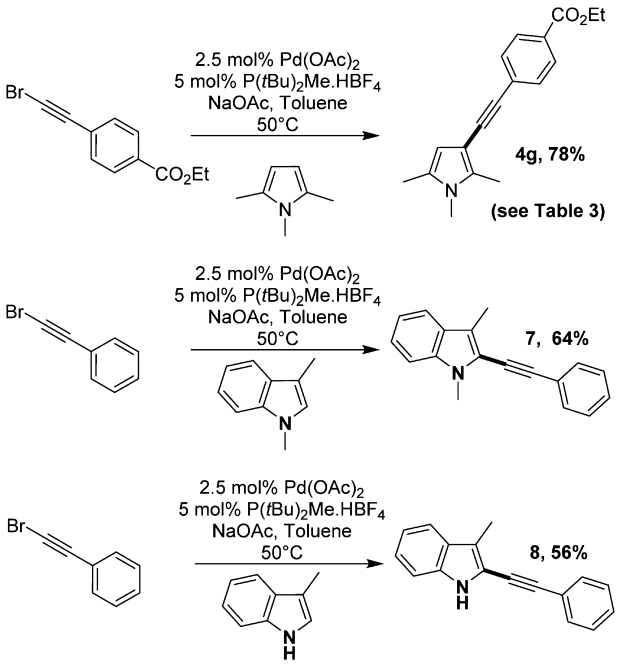
4h in a good 69% yield on a one-pot, two-step procedure. To the best of our knowledge, this is the first example of a sequential C−H alkynylation reaction on pyrrole.

Finally, we applied our methodology to the synthesis of the dopamine D-4 agonist **3**, of particular interest in the treatment of schizophrenia (Scheme 4).[6] Starting from the commercially available 4-benzylpiperidone (**4**), we obtained the oxime derivative, which was directly reduced by $LiAlH_4$ to give the 4-aminobenzylpiperidine.[6] Using a reported procedure,[6] the reaction of 4-aminobenzylpiperidine with 2,5-dimethoxytetrahydrofuran (**5**) gave pyrrole derivative **6**,[6] which successfully underwent our C−H alkynylation protocol using (bromoethynyl)benzene **2a** to synthesize the desired dopamine D-4 agonist **3**, in a satisfiying 73% yield. The reported strategy[6] required the selective pyrrole *C*-2 iodination of compound **6**, which was challenging. In our case bromination of the alkyne is efficient and high-yielding; moreover, our alkynylation step is totally regioselective for the pyrrole *C*-2 position.[18]

From a mechanistic point of view, the alkynylation reaction seems to proceed most likely though an electrophilic mechanism, as previously reported by Gevorgyan and co-workers.[10a] Indeed, our methodology furnished exclusively 2-alkynylpyrroles or 3-alkynylindoles, which support this kind of mechanism.[10a,c] However, when both α-positions were blocked (e.g., for the 2,5-dimethylpyrrole derivative), *C*-3-alkynylated pyrrole **4g** was obtained in a good 78% yield (Table 3 and Scheme 5). In the same manner, when position 3 of indoles was

Scheme 5. Further Reactivities on Methylated Azoles



substituted, we observed the alkynylation reaction at position 2 of compounds **7** and **8** (64% and 56% yields, respectively; Scheme 5), which is in stark contrast in comparison to the reported work.[10c] Indeed, Wang and co-workers did not observe an alkynylation product on 3-substituted indole. Furthermore, the formation following our method of the known[19] 2-alkynylated indole **7** confirmed the regioselectivity of the reaction.

On the basis of all these observations along with the literature reports,[10,20] we propose two competitive mechanistic pathways (Scheme 6), with the prevalence of the electrophilic alkynylation mechanism being justified by the regioselectivity observed on the pyrrole ring (note that although the mechanism is described here for pyrroles, the same mechanistic pathway may occur with indoles, for which the more nucleophilic center is in this case the *C*-3 position). Thus, upon formation of the alkynylpalladium(II) intermediate **A**, the nucleophilic attack of the pyrroles produces the iminium intermediates **B** and **B′**. In the case of pyrroles unsubstituted at their α-positions (or at the *C*-3 position for indoles), deprotonation by the base would lead to rearomatization of the pyrrole ring (**C**), leading after reductive elimination to the *C*-2-alkynylated pyrrole. Alternatively, when pyrroles are substituted at their α-positions (or at the *C*-3 position for indoles), the iminium intermediate **B′** may undergo a *C*-2/*C*-3 shift (*C*-3/*C*-2 shift for indoles),[21] leading to the carbocation **C′**, which upon rearomatization to the pyrrole ring (**D′**) and reductive elimination produces the *C*-3-alkynylated pyrrole (or the *C*-2-alkynylated indole).

CONCLUSION

In summary, we have developed a C−H alkynylation method on pyrroles and related azoles, allowing the introduction of a variety of substituted alkynes. Combination of $Pd(OAc)_2$ with $PMe(tBu)_2{\cdot}HBF_4$ as the catalytic system demonstrates a good activity under mild conditions (50 °C) down to room temperature; these conditions are still rare in palladium-catalyzed C−H activation reactions. Reported methods in the literature are known to proceed efficiently on furans, thiophenes, and related heterocycles but are more reluctant on pyrroles; therefore, our methodology is a gap-filling alternative, since it offers a wide substitution pattern on pyrrole and alkyne substrates, the only limitations occurring with electron-deficient pyrroles. We proposed an electrophilic alkynylation mechanism for this transformation, since pyrroles and indoles react at their more nucleophilic position (*C*-2 pyrroles, *C*-3 indoles). Interestingly, when these positions are masked, the reaction can still occur but on a different site (*C*-3 pyrroles, *C*-2 indoles). Moreover, this protocol has been successfully applied to the synthesis of a bioactive ligand of the dopamine D-4 receptor. Application of this method in constructing new bioactive compounds is currently underway in our laboratory and will be reported in due course.

EXPERIMENTAL SECTION

General Considerations. All glassware was oven-dried at 140 °C, and all reactions were conducted under an argon atmosphere. For chromatography, technical grade Et_2O, cyclohexane, and ethyl acetate solvents (EtOAc) were used. All new compounds were characterized by ^1H NMR, ^{13}C NMR, and HR-MS analysis. ^1H and ^{13}C NMR spectra were measured in $CDCl_3$ at 300 or 400 MHz. ^1H chemical shifts are reported in ppm from the internal standard TMS or from residual chloroform (7.27 ppm). The following abbreviations are used: m (multiplet), s (singlet), br s (broad singlet), d (doublet), t (triplet), dd (doublet of doublets), dt (doublet of triplets). ^{13}C chemical shifts are reported in ppm from the central peak of deuterochloroform (77.14). Analytical TLC was performed on precoated silica gel 60 F-254 plates. Silica gel 60 (230−400 mesh) was used for column chromatography. The TLC plates were visualized either by UV light (254 nm) or by a solution of phosphomolybdic acid in ethanol. Melting points (mp) were recorded uncorrected. Low- and high-resolution mass spectra (MS and HRMS) were analyzed by TOF-Q.

General Procedure for the Bromation of Terminal Alkynes. To a solution of terminal alkyne (1.0 equiv, 30 mmol) in acetone (1 mL/1

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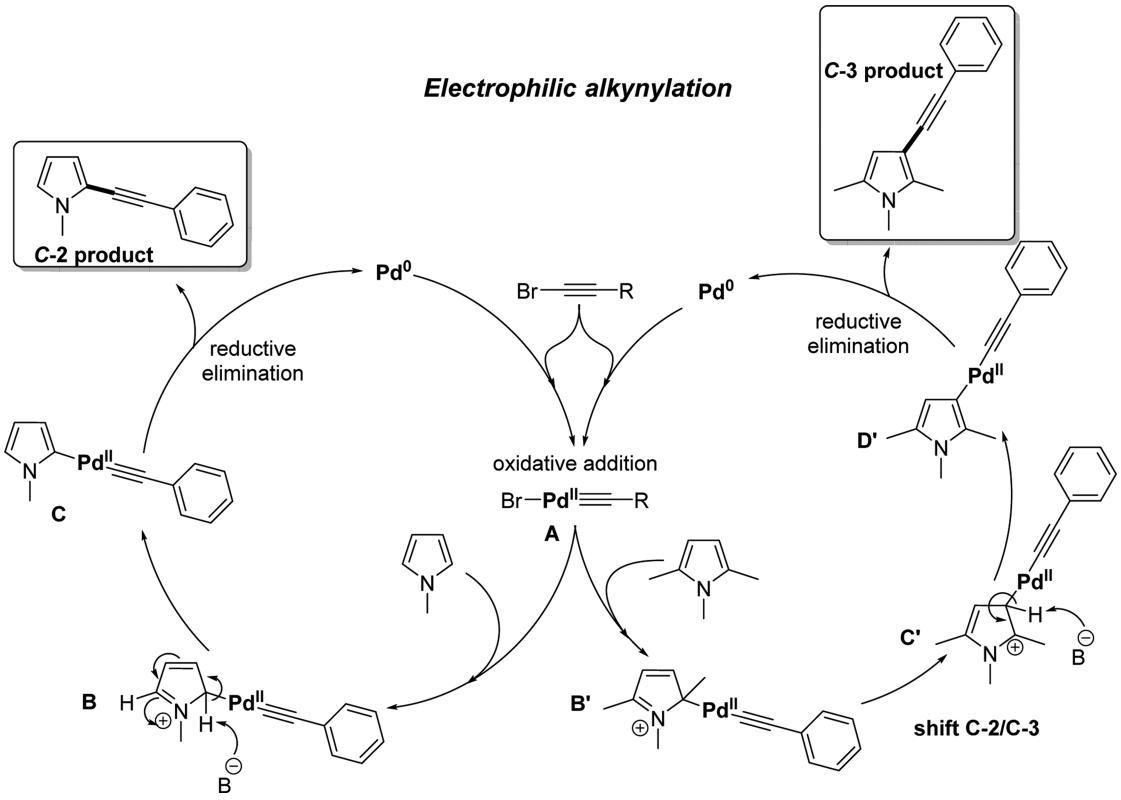
Scheme 6. Proposed Mechanism



mmol) were successively added *N*-bromosuccinimide (1.1 equiv, 33 mmol) and $AgNO_3$ (0.1 equiv, 3 mmol). The reaction mixture was stirred in the dark for 3 h at room temperature. Upon completion the reaction mixture was concentrated under reduced pressure, filtered through a silica plug, and then eluted with cyclohexane. The solvent was then concentrated, giving the desired product. The analytical data obtained for bromoalkynes were similar to those reported in the literature.[13]

General Procedure for the C–H Alkynylation Reaction. A flame-dried resealable tube was charged with $Pd(OAc)_2$ (0.00625 mmol, 2.5 mol %), $PMe(tBu)_2{\cdot}HBF_4$ (0.0125 mmol, 5 mol %), and NaOAc (0.5 mmol, 2 equiv). The tube was capped with a rubber septum, evacuated, and back-filled with argon; this evacuation/back-fill sequence was repeated one additional time. Toluene (1 mL per 0.25 mmol of bromoalkynes) was added through the septum. Liquid reactants were then added: substituted pyrrole (0.5 mmol, 2 equiv) and bromoalkynes (0.25 mmol, 1 equiv). The septum was replaced with a Teflon screw cap. The Schlenk tube was sealed, and the mixture was stirred at 50 °C (or room temperature in the case of product **3a**). Completion of the reaction was checked by TLC; the resulting suspension was cooled to room temperature and filtered through a pad of Celite with ethyl acetate as eluent, and the inorganic salts were removed. The filtrate was concentrated, and purification of the residue by silica gel column chromatography gave the desired product.

Procedure for the One-Pot Tandem Dialkynylation Reaction. A flame-dried resealable tube was charged with $Pd(OAc)_2$ (0.00625 mmol, 2.5 mol %), $PMe(tBu)_2{\cdot}HBF_4$ (0.0125 mmol, 5 mol %), and NaOAc (1 mmol, 4 equiv). The tube was capped with a rubber septum, evacuated, and back-filled with argon; this evacuation/back-fill sequence was repeated one additional time. Toluene (1 mL per 0.25 mmol of bromoalkynes) was added through the septum. Liquid reactants were then added: pyrrole (0.25 mmol, 1 equiv) and (bromoethynyl)benzene (0.25 mmol, 1 equiv). The septum was replaced with a Teflon screw cap. The Schlenk tube was sealed, and the mixture was stirred at 50 °C. Completion of the reaction was checked by TLC; the resulting suspension was cooled to room temperature. 1-(Bromoethynyl)-4-methylbenzene (0.25 mmol, 1 equiv) was then added, and the reaction mixture was stirred for 10 h at 50 °C. Completion of the reaction was checked by TLC; the resulting suspension was cooled to room temperature and filtered through a pad of Celite with ethyl acetate as eluent, and the inorganic salts were removed. The filtrate was concentrated, and purification of the residue by silica gel column chromatography gave the desired product.

1-Methyl-2-(phenylethynyl)-1*H*-pyrrole (3a).[12] Following the general procedure, a mixture of pyrrole (0.5 mmol, 41 mg) and (bromoethynyl)benzene was heated at 50 °C for 10 h. The residue was purified by flash chromatography over silica gel (cyclohexane/EtOAc 99/1) to afford the desired product **3a** as a yellow oil: yield 85% (0.21 mmol, 39 mg); R_f = 0.66 (cyclohexane/EtOAc 95/5); ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.55–7.45 (m, 2H), 7.39–7.29 (m, 3H), 6.69 (br s, 1H), 6.50 (br s, 1H), 6.13 (br s, 1H), 3.75 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 131.2 (2CH), 128.5 (2CH), 128.0, 123.9, 123.6, 115.8, 114.9, 108.3, 93.2, 81.4, 34.7; HR-MS (ESI+) *m*/*z* calculated for $C_{13}H_{12}N$ 182.0964, obtained 182.0959. These spectral data are in agreement with the literature.[12]

1-Methyl-2-(*p*-tolylethynyl)-1*H*-pyrrole (3b). Following the general procedure, a mixture of pyrrole (0.5 mmol, 41 mg) and 1-(bromoethynyl)-4-methylbenzene was heated at 50 °C for 10 h. The residue was purified by flash chromatography over silica gel (cyclohexane/EtOAc: 97/3) to afford the desired product **3b** as a yellow oil: yield 77% (0.18 mmol, 40 mg); R_f = 0.30 (cyclohexane/EtOAc 95/5); ^{1}H NMR (300 MHz, chloroform-*d*) δ 7.34–7.28 (m, 1H), 7.13 (dd, *J* = 7.6, 1.3 Hz, 1H), 7.06 (dd, *J* = 2.5, 1.4 Hz, 1H), 6.95–6.86 (m, 1H), 6.78–6.67 (m, 1H), 6.53 (dd, *J* = 3.8, 1.7 Hz, 1H), 6.16 (dd, *J* = 3.8, 2.6 Hz, 1H), 3.86 (s, 3H), 3.78 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.5, 129.5, 124.6, 124.0, 123.8, 116.0, 115.7, 115.0, 114.6, 108.3, 93.1, 81.3, 55.4, 34.8; HR-MS (ESI+) *m*/*z* calculated for $C_{14}H_{14}N$ 196.1121 obtained 196.1118.

2-((3-Methoxyphenyl)ethynyl)-1-methyl-1*H*-pyrrole (3c). Following the general procedure, a mixture of pyrrole (0.5 mmol, 41 mg) and 1-(bromoethynyl)-3-methoxybenzene was heated at 50 °C for 10 h. The residue was purified by flash chromatography over silica gel (cyclohexane/EtOAc 95/5) to afford the desired product **3c** as a

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yellow oil: yield 73% (0.18 mmol, 39 mg); R_f = 0.30 (cyclohexane/EtOAc 95/5); ^{1}H NMR (300 MHz, chloroform-*d*) δ 7.34−7.28 (m, 1H), 7.13 (dd, *J* = 7.6, 1.3 Hz, 1H), 7.06 (dd, *J* = 2.5, 1.4 Hz, 1H), 6.95−6.86 (m, 1H), 6.78−6.67 (m, 1H), 6.53 (dd, *J* = 3.8, 1.7 Hz, 1H), 6.16 (dd, *J* = 3.8, 2.6 Hz, 1H), 3.86 (s, 3H), 3.78 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.5, 129.5, 124.6, 124.0, 123.8, 116.0, 115.7, 115.0, 114.6, 108.3, 93.1, 81.3, 55.4, 34.8; HR-MS (ESI+) *m*/*z* calculated for $C_{14}H_{14}NO$ 212.1070, obtained 212.1066.

1-Methyl-2-((3,4,5-trimethoxyphenyl)ethynyl)-1*H*-pyrrole (3d). Following the general procedure, a mixture of pyrrole (0.5 mmol, 41 mg) and 5-(bromoethynyl)-1,2,3-trimethoxybenzene was heated at 50 °C for 10 h. The residue was purified by flash chromatography over silica gel (cyclohexane/EtOAc 95/5) to afford the desired product **3d** as a yellow oil: yield 68% (0.18 mmol, 46 mg); R_f = 0.34 (cyclohexane/EtOAc 9/1); viscous oil; ^{1}H NMR (400 MHz, chloroform-*d*) δ 6.73 (s, 2H), 6.68 (br s, 1H), 6.48 (dd, *J* = 3.9, 1.8 Hz, 1H), 6.19−6.07 (m, 1H), 3.87 (s, 6H), 3.87 (s, 3H), 3.74 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.3 (2C), 138.8, 123.9, 118.6, 115.7, 115.0, 108.6 (2CH), 108.3, 93.1, 80.5, 61.1, 56.3 ($2CH_3$), 34.8; HR-MS (ESI+) *m*/*z* calculated for $C_{16}H_{17}NNaO_3$ 294.1106, obtained 294.1103.

2-((2-Fluorophenyl)ethynyl)-1-methyl-1*H*-pyrrole (3e). Following the general procedure, a mixture of pyrrole (0.5 mmol, 41 mg) and 1-(bromoethynyl)-2-fluorobenzene was heated at 50 °C for 10 h. The residue was purified by flash chromatography over silica gel (cyclohexane/EtOAc 95/5) to afford the desired product **3e** as a yellow oil: yield 62% (0.155 mmol, 31 mg); R_f = 0.31 (cyclohexane/EtOAc 98/2); viscous oil; ^{1}H NMR (400 MHz, acetone-d_6) δ 7.61−7.50 (m, 1H), 7.41 (dtd, *J* = 9.8, 5.4, 2.7 Hz, 1H), 7.23 (td, *J* = 7.9, 1.6 Hz, 2H), 6.86 (d, *J* = 2.3 Hz, 1H), 6.46 (dd, *J* = 3.8, 1.8 Hz, 1H), 6.08 (dd, *J* = 3.9, 2.3 Hz, 1H), 3.76 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.0, 160.7, 132.8, 132.8, 129.6, 129.5, 124.3, 124.1, 124.1, 115.7, 115.5, 115.4, 115.3, 115.0, 112.4, 112.2, 108.4, 86.7, 77.4, 34.7; HR-MS (ESI+) *m*/*z* calculated for $C_{13}H_{11}FN$ 200.0870, obtained 200.0866.

1-Methyl-2-((3-nitrophenyl)ethynyl)-1*H*-pyrrole (3f). Following the general procedure, a mixture of pyrrole (0.5 mmol, 41 mg) and 1-(bromoethynyl)-3-nitrobenzene was heated at 50 °C for 10 h. The residue was purified by flash chromatography over silica gel (cyclohexane/EtOAc 95/5) to afford the desired product **3f** as a yellow oil: yield 74% (0.19 mmol, 43 mg); R_f = 0.35 (cyclohexane/EtOAc 95/5); viscous oil; ^{1}H NMR (400 MHz, acetone-d_6) δ 8.30 (t, *J* = 1.9 Hz, 1H), 8.20 (ddd, *J* = 8.3, 2.3, 1.1 Hz, 1H), 7.92 (dt, *J* = 7.8, 1.3 Hz, 1H), 7.71 (t, *J* = 8.1 Hz, 1H), 6.89 (dd, *J* = 2.7, 1.7 Hz, 1H), 6.51 (dd, *J* = 3.8, 1.7 Hz, 1H), 6.09 (dd, *J* = 3.8, 2.6 Hz, 1H), 3.80 (s, 3H); ^{13}C NMR (101 MHz, acetone) δ 149.3, 137.4, 135.5, 130.9, 126.0, 125.8, 123.3, 116.8, 115.2, 109.1, 91.8, 85.0, 34.8; HR-MS (ESI+) *m*/*z* calculated for $C_{13}H_{11}N_2O_2$ 227.0815, obtained 227.0814.

Ethyl 4-((1-Methyl-1*H*-pyrrol-2-yl)ethynyl)benzoate (3g). Following the general procedure, a mixture of pyrrole (0.5 mmol, 41 mg) and ethyl 4-(bromoethynyl)benzoate was heated at 50 °C for 10 h. The residue was purified by flash chromatography over silica gel (cyclohexane/EtOAc 9/1) to afford the desired product **3g** as a yellow oil: yield 67% (0.17 mmol, 43 mg); R_f = 0.35 (cyclohexane/EtOAc 9/1); viscous oil; ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.01 (d, *J* = 8.1 Hz, 2H), 7.52 (d, *J* = 8.1 Hz, 2H), 6.71 (s, 1H), 6.59−6.42 (m, 1H), 6.13 (d, *J* = 1.8 Hz, 1H), 4.38 (q, *J* = 7.0 Hz, 2H), 3.75 (s, 3H), 1.40 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, acetone) δ 166.2, 131.5 (2CH), 130.4, 130.3 (2CH), 129.0, 125.9, 116.5, 115.6, 109.1, 93.4, 85.6, 61.6, 34.8, 14.6; HR-MS (ESI+) *m*/*z* calculated for $C_{32}H_{31}N_2O_4$ ($2M + H^+$) 507.2284, obtained 507.2288.

1-Methyl-2-(oct-1-yn-1-yl)-1*H*-pyrrole (3h). Following the general procedure, a mixture of pyrrole (0.5 mmol, 41 mg) and 1-bromooct-1-yne was heated at 50 °C for 10 h. The residue was purified by flash chromatography over silica gel (cyclohexane/EtOAc 9/1) to afford the desired product **3h** as a yellow oil: yield 81% (0.20 mmol, 39 mg); R_f = 0.38 (cyclohexane); viscous oil; ^{1}H NMR (300 MHz, chloroform-*d*) δ 6.58 (t, *J* = 2.1 Hz, 1H), 6.30 (dd, *J* = 3.7, 1.6 Hz, 1H), 6.04 (t, *J* = 3.2 Hz, 1H), 3.64 (s, 3H), 2.43 (t, *J* = 7.0 Hz, 2H), 1.58 (d, *J* = 8.7 Hz, 3H), 1.44 (p, *J* = 6.7 Hz, 2H), 1.31 (q, *J* = 3.7 Hz, 3H), 0.90 (t, *J* = 6.5 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 122.7, 116.6, 113.4, 107.7, 93.9, 72.3, 34.5, 31.5, 29.0, 28.7, 22.7, 19.8, 14.2; HR-MS (ESI+) *m*/*z* calculated for $C_{13}H_{20}N$ 190.1590, obtained 190.1582.

2-Methoxy-5-((1-methyl-1*H*-pyrrol-2-yl)ethynyl)pyridine (3i). Following the general procedure, a mixture of pyrrole (0.5 mmol, 41 mg) and 5-(bromoethynyl)-2-methoxypyridine was heated at 50 °C for 10 h. The residue was purified by flash chromatography over silica gel (cyclohexane/EtOAc 9/1) to afford the desired product **3i** as a yellow oil: yield 65% (0.17 mmol, 35 mg), R_f = 0.33 (cyclohexane/EtOAc 9/1); viscous oil; ^{1}H NMR (400 MHz, acetone-d_6) δ 8.32 (t, *J* = 1.9 Hz, 1H), 7.78 (dd, *J* = 8.6, 2.2 Hz, 1H), 6.99−6.58 (m, 2H), 6.48−6.21 (m, 1H), 6.05 (dd, *J* = 3.9, 2.3 Hz, 1H), 3.92 (s, 3H), 3.74 (s, 3H); ^{13}C NMR (101 MHz, acetone) δ 164.2, 150.2, 141.7, 125.1, 116.0, 115.5, 114.3, 111.5, 108.8, 90.3, 83.5, 53.9, 34.7; HR-MS (ESI+) *m*/*z* calculated for $C_{13}H_{13}N_2O$ 213.1022, obtained 213.1020.

2-(Cyclohex-1-en-1-ylethynyl)-1-methyl-1*H*-pyrrole (3j). Following the general procedure, a mixture of pyrrole (0.5 mmol, 41 mg) and 1-(bromoethynyl)cyclohex-1-ene was heated at 50 °C for 10 h. The residue was purified by flash chromatography over silica gel (cyclohexane/EtOAc 9/1) to afford the desired product **3j** as a yellow oil: yield 58% (0.15 mmol, 28 mg); R_f = 0.53 (cyclohexane); viscous oil; ^{1}H NMR (400 MHz, chloroform-*d*) δ 6.62 (q, *J* = 1.9 Hz, 1H), 6.38−6.29 (m, 1H), 6.17−6.10 (m, 1H), 6.09−6.01 (m, 1H), 3.65 (s, 3H), 2.22 (s, 2H), 2.17−2.11 (m, 2H), 1.73−1.59 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 134.2, 123.3, 120.9, 116.3, 114.2, 108.1, 94.9, 78.6, 34.6, 29.4, 25.9, 22.5, 21.7; HR-MS (ESI+) *m*/*z* calculated for $C_{13}H_{16}N$ 186.1277, obtained 186.1273.

2-((Dimethyl(phenyl)silyl)ethynyl)-1-methyl-1*H*-pyrrole (3k). Following the general procedure, a mixture of pyrrole (0.5 mmol, 41 mg) and (bromoethynyl)dimethyl(phenyl)silane was heated at 50 °C for 10 h. The residue was purified by flash chromatography over silica gel (cyclohexane/EtOAc 99/1) to afford the desired product **3k** as a yellow oil: yield 35% (0.10 mmol, 24 mg); R_f = 0.40 (cyclohexane/EtOAc 95/5); viscous oil; ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.76−7.65 (m, 2H), 7.41 (dd, *J* = 4.6, 2.5 Hz, 3H), 6.65 (d, *J* = 2.4 Hz, 1H), 6.52−6.46 (m, 1H), 6.09 (d, *J* = 3.4 Hz, 1H), 3.70 (s, 3H), 0.51 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.4, 133.9, 129.5, 128.1, 128.0, 124.0, 115.8, 108.1, 98.6, 96.4, 34.7, −0.6; HR-MS (ESI+) *m*/*z* calculated for $C_{15}H_{18}NSi$ 240.1203, obtained 240.1202.

1-(4-Methoxyphenyl)-2-((3-methoxyphenyl)ethynyl)-1*H*-pyrrole (4a). Following the general procedure, a mixture of 1-(4-methoxyphenyl)-1*H*-pyrrole (0.5 mmol, 87 mg) and 1-(bromoethynyl)-3-methoxybenzene was heated at 50 °C for 10 h. The residue was purified by flash chromatography over silica gel (cyclohexane/EtOAc 97/3) to afford the desired product **4a** as a yellow oil: yield 79% (0.20 mmol, 60 mg); R_f = 0.37 (cyclohexane/EtOAc 95/5); viscous oil; ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.46 (d, *J* = 7.9 Hz, 2H), 7.18 (t, *J* = 7.7 Hz, 1H), 6.98 (d, *J* = 8.0 Hz, 2H), 6.92 (d, *J* = 7.2 Hz, 2H), 6.87−6.74 (m, 2H), 6.70−6.59 (m, 1H), 6.27 (br s, 1H), 3.86 (s, 3H), 3.78 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.4, 158.7, 133.2, 129.5, 126.2 (2CH), 124.6, 123.9, 123.5, 116.7, 115.8, 115.5, 114.4, 114.1 (2CH), 109.4, 92.97, 82.2, 55.7, 55.4; HR-MS (ESI+) *m*/*z* calculated for $C_{20}H_{18}NO_2$ 304.1332, obtained 304.1327.

1-Benzyl-2-((3-methoxyphenyl)ethynyl)-1*H*-pyrrole (4b). Following the general procedure, a mixture of 1-benzyl-1*H*-pyrrole (0.5 mmol, 79 mg) and 1-(bromoethynyl)-3-methoxybenzene was heated at 50 °C for 10 h. The residue was purified by flash chromatography over silica gel (cyclohexane/EtOAc 95/5) to afford the desired product **4b** as a yellow oil: yield 72% (0.18 mmol, 52 mg); R_f = 0.61 (cyclohexane/EtOAc 95/5); viscous oil; ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.39−7.31 (m, 2H), 7.30−7.27 (m, 1H), 7.24−7.18 (m, 3H), 7.01 (dd, *J* = 7.7, 1.5 Hz, 1H), 6.94−6.90 (m, 1H), 6.85 (dd, *J* = 8.3, 2.6 Hz, 1H), 6.74 (dd, *J* = 2.9, 1.6 Hz, 1H), 6.54 (dt, *J* = 2.8, 1.4 Hz, 1H), 6.17 (t, *J* = 3.3 Hz, 1H), 5.24 (s, 2H), 3.80 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.4, 138.1, 129.5, 128.8, 127.7, 127.4, 124.5, 123.8, 123.3, 115.9, 115.5, 115.4, 114.6, 108.9, 93.5, 81.4, 55.4, 51.6; HR-MS (ESI+) *m*/*z* calculated for $C_{20}H_{18}NO$ 288.1383, obtained 288.1376.

1-(2-Bromobenzyl)-2-((3-methoxyphenyl)ethynyl)-1*H*-pyrrole (4c). Following the general procedure, a mixture of 1-(2-

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bromobenzyl)-1*H*-pyrrole (0.5 mmol, 118 mg) and 1-(bromoethynyl)-3-methoxybenzene was heated at 50 °C for 10 h. The residue was purified by flash chromatography over silica gel (cyclohexane/EtOAc 99/1) to afford the desired product **4c** as a yellow oil: yield 59% (0.15 mmol, 43 mg); R_f = 0.50 (cyclohexane/EtOAc 95/5); viscous oil; ^{1}H NMR (400 MHz, acetone-d_6) δ 7.65 (dd, J = 8.1, 1.7 Hz, 1H), 7.33 (t, J = 7.6 Hz, 1H), 7.24 (ddd, J = 9.8, 4.9, 1.8 Hz, 2H), 7.02 (dt, J = 3.3, 1.6 Hz, 1H), 6.97−6.92 (m, 1H), 6.88 (d, J = 9.2 Hz, 2H), 6.71 (d, J = 7.7 Hz, 1H), 6.53 (dt, J = 3.5, 1.7 Hz, 1H), 6.21 (dd, J = 4.0, 2.3 Hz, 1H), 5.40 (s, 2H), 3.79 (s, 3H);^{13}C NMR (101 MHz, acetone) δ 160.5, 138.7, 133.4, 130.5, 130.1, 129.2, 128.9, 125.2, 125.1, 123.9, 122.5, 116.3, 116.2, 116.1, 115.4, 109.6, 94.2, 81.8, 55.6, 52.0; HR-MS (ESI+) m/z calculated for $C_{20}H_{17}BrNO$ 366.0488, obtained 366.0471.

2-((3-Methoxyphenyl)ethynyl)-1-(thiophen-3-ylmethyl)-1*H*-pyrrole (4d). Following the general procedure, a mixture of 1-(thiophen-3-ylmethyl)-1*H*-pyrrole (0.5 mmol, 82 mg) and 1-(bromoethynyl)-3-methoxybenzene was heated at 50 °C for 10 h. The residue was purified by flash chromatography over silica gel (cyclohexane/EtOAc 99/1) to afford the desired product **4d** as a yellow oil: yield 64% (0.16 mmol, 47 mg); R_f = 0.32 (cyclohexane/EtOAc 98/2); viscous oil; ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.28−7.22 (m, 2H), 7.09 (dt, J = 7.6, 1.3 Hz, 1H), 7.04−7.00 (m, 2H), 6.95 (dd, J = 5.1, 3.5 Hz, 1H), 6.88 (ddd, J = 8.3, 2.7, 1.0 Hz, 1H), 6.78 (dd, J = 2.8, 1.6 Hz, 1H), 6.52 (dd, J = 3.8, 1.7 Hz, 1H), 6.16 (dd, J = 3.8, 2.7 Hz, 1H), 5.38 (s, 2H), 3.82 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.4, 140.2, 129.4, 126.9, 126.3, 125.6, 124.3, 123.7, 122.7, 116.0, 115.4, 115.0, 114.6, 109.0, 93.8, 81.0, 55.3, 46.1; HR-MS (ESI+) m/z calculated for $C_{18}H_{16}NOS$ 294.0947, obtained 294.0946.

2-(Phenylethynyl)-1*H*-pyrrole (4e). Following the general procedure, a mixture of 1*H*-pyrrole (0.5 mmol, 34 mg) and 1-(bromoethynyl)benzene was heated at 50 °C for 10 h. The residue was purified by flash chromatography over silica gel (cyclohexane/EtOAc 98/2) to afford the desired product **4e** as a yellow oil: yield 67% (0.16 mmol, 28 mg); R_f = 0.32 (cyclohexane/EtOAc 95/5); viscous oil; ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.79−8.16 (br s, 1H), 7.49 (dd, J = 7.1, 2.3 Hz, 2H), 7.33 (d, J = 6.6 Hz, 3H), 6.81 (d, J = 3.3 Hz, 1H), 6.56 (t, J = 2.9 Hz, 1H), 6.24 (d, J = 3.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 131.3, 128.5, 128.1, 123.3, 119.8, 115.0, 113.0, 109.6, 90.5, 82.0; HR-MS (ESI−) m/z calculated for $C_{12}H_8N$ 166.0657, obtained 166.0655.

Ethyl 4-((1,2,5-Trimethyl-1*H*-pyrrol-3-yl)ethynyl)benzoate (4g). Following the general procedure, a mixture of 1,2,5-trimethyl-1*H*-pyrrole (0.5 mmol, 55 mg) and ethyl 4-(bromoethynyl)benzoate was heated at 50 °C for 10 h. The residue was purified by flash chromatography over silica gel (cyclohexane/EtOAc 98/2) to afford the desired product **4g** as a yellow oil: yield 78% (0.17 mmol, 28 mg); R_f = 0.32 (cyclohexane/EtOAc 95/5); viscous oil; ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.56−8.19 (m, 1H), 7.49 (dd, J = 7.1, 2.3 Hz, 2H), 7.33 (d, J = 6.6 Hz, 3H), 6.81 (d, J = 3.3 Hz, 1H), 6.56 (t, J = 2.9 Hz, 1H), 6.24 (d, J = 3.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 131.3, 128.5, 128.1, 123.3, 119.8, 115.0, 113.0, 109.6 (2C), 90.5; HR-MS (ESI+) m/z calculated for $C_{18}H_{19}NNaO_2$ 304.1313, obtained 304.1327.

1-Methyl-2-(phenylethynyl)-5-(*p*-tolylethynyl)-1*H*-pyrrole (4h). Following the general procedure, a mixture of 1-methyl-2-(phenylethynyl)-1*H*-pyrrole (0.5 mmol, 91 mg) and 1-(bromoethynyl)benzene was heated at 50 °C for 10 h. The residue was purified by flash chromatography over silica gel (cyclohexane) to afford the desired product **4h** as a yellow oil: yield 61% (0.15 mmol, 45 mg); R_f = 0.75 (cyclohexane/EtOAc 98/2); viscous oil; ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.51 (dd, J = 6.1, 2.1 Hz, 2H), 7.41 (dd, J = 8.1, 1.7 Hz, 2H), 7.35 (d, J = 6.6 Hz, 3H), 7.16 (d, J = 7.7 Hz, 2H), 6.46 (dd, J = 3.5, 1.6 Hz, 2H), 3.81 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.6, 131.34, 131.29, 129.3, 128.5, 128.3, 123.2, 120.1, 117.8, 117.4, 114.7, 114.5, 94.0, 93.8, 81.3, 80.5, 32.9, 21.7; HR-MS (ESI+) m/z calculated for $C_{22}H_{18}N$ 296.1434, obtained 296.1424.

2-(4-Methoxyphenyl)-1-methyl-5-(phenylethynyl)-1*H*-pyrrole (4i). Following the general procedure, a mixture of 2-(4-methoxyphenyl)-1-methyl-1*H*-pyrrole (0.5 mmol, 62 mg) and 1-(bromoethynyl)benzene was heated at 50 °C for 10 h. The residue was purified by flash chromatography over silica gel (cyclohexane/EtOAc 99/1) to afford the desired product **4i** as a yellow oil: yield 55% (0.14 mmol, 40 mg); R_f = 0.62 (cyclohexane/EtOAc 95/5); viscous oil; ^{1}H NMR (300 MHz, chloroform-*d*) δ 7.55−7.47 (m, 2H), 7.34 (dd, J = 8.4, 2.2 Hz, 5H), 6.97 (d, J = 8.8 Hz, 2H), 6.57 (d, J = 3.8 Hz, 1H), 6.16 (d, J = 3.8 Hz, 1H), 3.86 (s, 3H), 3.72 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.0, 136.5, 131.1, 130.1, 128.4, 127.9, 125.5, 123.6, 116.5, 114.7, 114.0, 108.4, 93.7, 82.0, 55.4, 33.1; HR-MS (ESI+) m/z calculated for $C_{20}H_{18}NO$ 288.1383, obtained 288.1377.

1-(1-Methyl-5-(phenylethynyl)-1*H*-pyrrol-3-yl)ethan-1-one (4j). Following the general procedure, a mixture of 1-(1-methyl-1*H*-pyrrol-3-yl)ethan-1-one (0.5 mmol, 62 mg) and 1-(bromoethynyl)-benzene was heated at 50 °C for 10 h. The residue was purified by flash chromatography over silica gel (cyclohexane/EtOAc 98/2) to afford the desired product **4j** as a yellow oil: yield 35% (0.09 mmol, 21 mg); R_f = 0.34 (cyclohexane/EtOAc 7/3); viscous oil; ^{1}H NMR (300 MHz, chloroform-*d*) δ 7.50 (dd, J = 6.5, 2.8 Hz, 2H), 7.36 (q, J = 2.8 Hz, 3H), 7.30 (d, J = 1.8 Hz, 1H), 6.87 (d, J = 1.8 Hz, 1H), 3.76 (s, 3H), 2.40 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.9, 131.3, 128.6, 128.5, 127.8, 125.3, 122.6, 117.6, 115.0, 93.9, 79.7, 35.2, 27.2; HR-MS (ESI+) m/z calculated for $C_{15}H_{13}NONa$ 246.0895, obtained 246.0899.

3-((3-Methoxyphenyl)ethynyl)-5*H*-pyrrolo[2,1-*a*]isoindole (4k). Following the general procedure, a mixture of 5*H*-pyrrolo[2,1-*a*]isoindole (0.5 mmol, 78 mg) and 1-(bromoethynyl)-3-methoxybenzene was heated at 50 °C for 10 h. The residue was purified by flash chromatography over silica gel (cyclohexane) to afford the desired product **4k** as a yellow oil: yield 89% (0.23 mmol, 63 mg); R_f = 0.40 (cyclohexane); viscous oil; ^{1}H NMR (300 MHz, chloroform-*d*) δ 7.52 (d, J = 7.6 Hz, 1H), 7.42 (d, J = 7.5 Hz, 1H), 7.35 (t, J = 7.5 Hz, 1H), 7.30−7.17 (m, 2H), 7.13 (dd, J = 7.6, 1.3 Hz, 1H), 7.05 (dd, J = 2.6, 1.4 Hz, 1H), 6.89 (ddd, J = 8.3, 2.6, 1.0 Hz, 1H), 6.65 (d, J = 3.7 Hz, 1H), 6.32 (d, J = 3.7 Hz, 1H), 5.01 (s, 2H), 3.84 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.5, 140.8, 139.8, 133.6, 129.6, 128.2, 125.6, 124.5, 123.9, 123.4, 119.3, 119.1, 116.0, 114.7, 111.5, 99.5, 93.7, 81.3, 55.5, 50.0; HR-MS (ESI+) m/z calculated for $C_{20}H_{16}NO$ 286.1226, obtained 286.1215.

1-Methyl-3-(*p*-tolylethynyl)-1*H*-indole (4l). Following the general procedure, a mixture of 1-methyl-1*H*-indole (0.5 mmol, 62 mg) and 1-(bromoethynyl)-4-methylbenzene was heated at 50 °C for 10 h. The residue was purified by flash chromatography over silica gel (cyclohexane) to afford the desired product **4l** as a yellow oil: yield 74% (0.18 mmol, 45.5 mg); R_f = 0.20 (cyclohexane); viscous oil; ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.82 (d, J = 7.9 Hz, 1H), 7.46 (d, J = 8.1 Hz, 2H), 7.37−7.27 (m, 3H), 7.22 (ddd, J = 8.0, 6.8, 1.3 Hz, 1H), 7.16 (d, J = 7.9 Hz, 2H), 3.81 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.6, 136.4, 132.1, 131.3, 129.3, 129.2, 122.8, 121.4, 120.4, 120.4, 109.7, 97.4, 91.2, 82.4, 33.2, 21.6; HR-MS (ESI+) m/z calculated for $C_{18}H_{16}N$ 246.1277, obtained 246.1277.

1-Methyl-3-(phenylethynyl)-1*H*-indole (4m). Following the general procedure, a mixture of 1-methyl-1*H*-indole (0.5 mmol, 62 mg) and 1-(bromoethynyl)benzene was heated at 50 °C for 10 h. The residue was purified by flash chromatography over silica gel (cyclohexane) to afford the desired product **4m** as a yellow oil: yield 76% (0.185 mmol, 43 mg); R_f = 0.40 (cyclohexane); viscous oil; ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.82 (d, J = 7.9 Hz, 1H), 7.66−7.45 (m, 2H), 7.44−7.04 (m, 7H), 3.82 (s, 3H). The analytical data were identical with those reported.[19]

1-(4-Methoxyphenyl)-3-(*p*-tolylethynyl)-1*H*-indole (4n). Following the general procedure, a mixture of 1-(4-methoxyphenyl)-1*H*-indole (0.5 mmol, 111 mg) and 1-(bromoethynyl)-4-methylbenzene was heated at 50 °C for 10 h. The residue was purified by flash chromatography over silica gel (cyclohexane) to afford the desired product **4n** as a yellow oil: yield 66% (0.17 mmol, 55 mg); R_f = 0.15 (cyclohexane); viscous oil; ^{1}H NMR (300 MHz, chloroform-*d*) δ 7.91−7.83 (m, 1H), 7.54 (s, 1H), 7.48 (d, J = 8.1 Hz, 2H), 7.41 (d, J = 8.9 Hz, 2H), 7.27 (dd, J = 6.1, 3.2 Hz, 2H), 7.18 (d, J = 7.8 Hz, 2H), 7.05 (d, J = 8.9 Hz, 2H), 3.89 (s, 3H), 2.39 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.7, 137.8, 136.1, 132.1, 131.4, 131.4, 129.6, 129.2, 126.2, 123.4, 121.2, 121.1, 120.5, 115.0, 110.8, 99.3, 91.9, 82.0, 55.8,

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21.7; HR-MS (ESI+) m/z calculated for $C_{24}H_{20}NO$ 338.1544, obtained 338.1539.

3-((3-Methoxyphenyl)ethynyl)-1-methyl-1*H*-pyrrolo[2,3-*b*]-pyridine (4o). Following the general procedure, a mixture of 1-methyl-1*H*-pyrrolo[2,3-*b*]pyridine (0.5 mmol, 66 mg) and 1-(bromoethynyl)-3-methoxybenzene was heated at 50 °C for 10 h. The residue was purified by flash chromatography over silica gel (cyclohexane) to afford the desired product **4o** as a yellow oil: yield 37% (0.09 mmol, 25 mg); R_f = 0.50 (cyclohexane/EtOAc 98/2); viscous oil; ^{1}H NMR (300 MHz, acetone-d_6) δ 7.40 (dd, J = 9.1, 7.5 Hz, 1H), 7.30−7.24 (m, 3H), 7.01 (ddd, J = 12.9, 7.8, 2.6 Hz, 2H), 6.90 (d, J = 7.7 Hz, 1H), 6.83 (dd, J = 2.7, 1.4 Hz, 1H), 3.84 (s, 3H), 3.79 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.5, 160.22, 140.5, 134.8, 130.8, 130.2, 124.4, 123.2, 122.5, 117.1, 116.5, 115.5, 104.4, 96.7, 87.0, 55.7, 32.6; HR-MS (ESI+) m/z calculated for $C_{17}H_{15}N_2O$ 263.1184, obtained 263.1180.

1-Benzyl-4-(2-(phenylethynyl)-1*H*-pyrrol-1-yl)piperidine (3). Following the general procedure, a mixture of 1-benzyl-4-(1*H*-pyrrol-1-yl)piperidine (0.5 mmol, 120 mg) and 1-(bromoethynyl)benzene was heated at 50 °C for 10 h. The residue was purified by flash chromatography over silica gel (cyclohexane/EtOAc 6/4) to afford the desired product **3** as a yellow oil: yield 73% (0.18 mmol, 61 mg); R_f = 0.30 (cyclohexane/EtOAc 5/5); viscous oil; ^{1}H NMR (300 MHz, chloroform-*d*) δ 7.59−7.44 (m, 2H), 7.35 (m, 8H), 6.83 (t, J = 2.2 Hz, 1H), 6.50 (dd, J = 3.7, 1.6 Hz, 1H), 6.16 (t, J = 3.3 Hz, 1H), 4.29 (dq, J = 15.9, 7.9, 7.3 Hz, 1H), 3.60 (s, 2H), 3.09 (d, J = 11.2 Hz, 3H), 2.29−2.15 (m, 2H), 2.09 (dd, J = 8.3, 3.0 Hz, 2H), 1.49 (dd, J = 14.7, 7.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 131.0, 129.3, 128.4, 127.9, 127.3, 123.6, 119.4, 115.0, 114.9, 114.5, 108.4, 93.6, 81.5, 62.9, 55.2, 53.1, 33.0; HR-MS (ESI+) m/z calculated for $C_{24}H_{25}N_2$ 341.2012, obtained 341.2000.

1,3-Dimethyl-2-(phenylethynyl)-1*H*-indole (7). Following the general procedure, a mixture of 1,3-dimethyl-1*H*-indole (0.5 mmol, 72.6 mg) and 1-(bromoethynyl)benzene was heated at 50 °C for 10 h. The residue was purified by flash chromatography over silica gel (cyclohexane) to afford the desired product **7** as a yellow oil: yield 64% (0.16 mmol, 39 mg); R_f = 0.70 (cyclohexane); viscous oil; ^{1}H NMR (300 MHz, chloroform-*d*) δ 7.64−7.52 (m, 3H), 7.45−7.32 (m, 3H), 7.32−7.22 (m, 2H), 7.13 (ddd, J = 8.0, 4.8, 3.2 Hz, 1H), 3.84 (s, 3H), 2.48 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.3, 131.4, 128.5, 128.5, 127.5, 123.2, 123.2, 120.3, 119.4, 119.3, 117.1, 109.2, 97.8, 80.8, 30.7, 10.0. The analytical data were identical with those reported.[10g]

3-Methyl-2-(phenylethynyl)-1*H*-indole (8). Following the general procedure, a mixture of 3-methyl-1*H*-indole (0.5 mmol, 72.6 mg) and 1-(bromoethynyl)benzene was heated at 50 °C for 10 h. The residue was purified by flash chromatography over silica gel (cyclohexane/EtOAc 95/5) to afford the desired product **8** as a yellow oil: yield 56% (0.14 mmol, 33 mg); R_f = 0.30 (cyclohexane); viscous oil; ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.07 (br s, 1H), 7.64−7.54 (m, 3H), 7.40 (d, J = 6.0 Hz, 3H), 7.29 (dt, J = 13.7, 7.9 Hz, 2H), 7.17 (t, J = 7.4 Hz, 1H), 2.49 (s, 1H).^{13}C NMR (75 MHz, $CDCl_3$) δ 136.0, 131.3, 128.4, 128.4, 128.0, 123.6, 122.9, 119.8, 119.2, 118.4, 116.6, 110.7, 95.1, 81.3, 9.6, HR-MS (ESI−) m/z calculated for $C_{17}H_{12}N$ 230.0970, obtained 230.0965.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Figures giving spectroscopic data of new compounds. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01093.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) *Heterocycles in Natural Product Synthesis*; Majumdar, K. C., ChattopadhyaySS. K., Eds; Wiley: Hoboken, NJ, 2012. (b) Katritzky, A. R.; Pozharskii, A. F. *Handbook of Heterocyclic Chemistry*, 2nd ed.; Pergamon: Oxford, U.K., 2000.
(2) (a) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893. (b) Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199.
(3) (a) de Sá Alves, F. R.; Barreiro, E. J.; Fraga, C. A. *Mini-Rev. Med. Chem.* **2009**, *9*, 782. (b) Brancale, A.; Silvestri, R. *Med. Res. Rev.* **2007**, *27*, 209. (c) Zeni, G.; Larock, R. *Chem. Rev.* **2004**, *104*, 2285. (d) Bandini, M.; Eichholzer, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 9608. (e) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2011**, *111*, PR215.
(4) Hanagan, M. A.; Pasteris, R. J. PCT Int. Appl. WO 2009094407 A2 20090730, 2009.
(5) Gu, Z. PCT Int. Appl. WO 2010118009 A1 20101014, 2010.
(6) Haubmann, C.; Hubner, H.; Gmeiner, P. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 3143.
(7) (a) Mariaule, G.; Newsome, G.; Toullec, P. Y.; Belmont, P.; Michelet, V. *Org. Lett.* **2014**, *16*, 4570. (b) Mariaule, G.; Belmont, P. *Molecules* **2014**, *19*, 14366. (c) Belmont, P.; Dorange, I. *Expert Opin. Ther. Pat.* **2008**, *18*, 1211. (d) Godet, T.; Belmont, P. *Synlett* **2008**, *2008*, 2513. (e) Tiano, M.; Belmont, P. *J. Org. Chem.* **2008**, *73*, 4101. (f) Belmont, P.; Belhadj, T. *Org. Lett.* **2005**, *7*, 1793.
(8) (a) Dudnik, A. S.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2010**, *49*, 2096. (b) Messaoudi, S.; Brion, J.-D.; Alami, M. *Eur. J. Org. Chem.* **2010**, *2010*, 6495. (c) Wencel-Delord, J.; Dröge, T.; Liu, F.; Glorius, F. *Chem. Soc. Rev.* **2011**, *40*, 4740. (d) Arockiam, P. B.; Bruneau, C.; Dixneuf, P. H. *Chem. Rev.* **2012**, *112*, 5879. (e) Ackermann, L. *Acc. Chem. Res.* **2014**, *47*, 281.
(9) (a) Brand, J. P.; Charpentier, J.; Waser, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 9346. (b) Brand, J. P.; Chevalley, C.; Scopelliti, R.; Waser, J. *Chem. - Eur. J.* **2012**, *18*, 5655.
(10) (a) Seregin, I. V.; Ryabova, V.; Gevorgyan, V. *J. Am. Chem. Soc.* **2007**, *129*, 7742. (b) Matsuyama, N.; Hirano, K.; Satoh, K.; Miura, T. M. *Org. Lett.* **2009**, *11*, 4156. (c) Gu, Y.; Wang, X.-M. *Tetrahedron Lett.* **2009**, *50*, 763. (d) Besselievre, F.; Piguel, S. *Angew. Chem., Int. Ed.* **2009**, *48*, 9553. (e) de Haro, T.; Nevado, C. *J. Am. Chem. Soc.* **2010**, *132*, 1512. (f) Kim, S. H.; Chang, S. *Org. Lett.* **2010**, *12*, 1868. (g) Yang, L.; Zhao, L.; Li, C.-J. *Chem. Commun.* **2010**, *46*, 4184. (h) Brand, J. P.; Waser, J. *Angew. Chem., Int. Ed.* **2010**, *49*, 7304. (i) Matsuyama, N.; Kitahara, M.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2010**, *12*, 2358. (j) Pacheco Berciano, B. P.; Lebrequier, S.; Besselievre, F.; Piguel, S. *Org. Lett.* **2010**, *12*, 4038. (k) Kim, S. H.; Yoon, J.; Chang, S. *Org. Lett.* **2011**, *13*, 1474. (l) Brand, J. P.; Waser, J. *Synthesis* **2012**, *44*, 1155. (m) Ackermann, L.; Kornhaass, C.; Zhu, Y. *Org. Lett.* **2012**, *14*, 1824. (n) Shibahara, F.; Dohke, Y.; Murai, T. *J. Org. Chem.* **2012**, *77*, 5381. (o) Tolnai, G. L.; Ganss, S.; Brand, J. P.; Waser, J. *Org. Lett.* **2013**, *15*, 112. (p) Ohmura, T.; Kijima, A.; Komori, Y.; Suginome, M. *Org. Lett.* **2013**, *15*, 3510.
(11) From the Gevorgyan paper:[10a] "...attempts with non-fused heterocycles, such as pyrroles, under these reaction conditions, afforded low yields of the corresponding alkynylation products".
(12) Jie, X.; Shang, Y.; Hu, P.; Su, W. *Angew. Chem., Int. Ed.* **2013**, *52*, 3630.
(13) (a) Nie, X.; Wang, G. *J. Org. Chem.* **2006**, *71*, 4734. (b) Li, L.-S.; Wu, Y.-L. *Tetrahedron Lett.* **2002**, *43*, 2427. (c) Zatolochnaya, O. V.; Gevorgyan, V. *Org. Lett.* **2013**, *15*, 2562.

DOI: 10.1021/acs.joc.5b01093
J. Org. Chem. 2015, 80, 7519−7529

(14) Lee, J.-Y.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 5616.
(15) (a) Gorelsky, S. I.; Lapointe, D.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 10848. (b) Rousseaux, S.; Gorelsky, S. I.; Chung, B. K. W.; Fagnou, K. *J. Am. Chem. Soc.* **2010**, *132*, 10692. (c) Chaumontet, M.; Piccardi, R.; Audic, N.; Hitce, J.; Peglion, J.-L.; Clot, E.; Baudoin, O. *J. Am. Chem. Soc.* **2008**, *130*, 15157.
(16) Brand, J. P.; Waser, J. *Angew. Chem., Int. Ed.* **2010**, *49*, 7304.
(17) Jolicoeur, B.; Chapman, E. E.; Thompson, A.; Lubell, W. D. *Tetrahedron* **2006**, *62*, 11531.
(18) In our case, 2 equiv of compound **6** is needed to reach a good 73% yield. However compound **6** could be recovered in the reaction mixture, since about 90% of the remaining equivalent is recovered. Decreasing the amount of compound **6** to 1.5 equiv led to a lower 61% yield.
(19) Moulton, B. E.; Whitwood, A. C.; Duhme-Klair, A. K.; Lynam, J. M.; Fairlamb, I. J. S. *J. Org. Chem.* **2011**, *76*, 5320.
(20) Tang, D.-T.; Collins, K. D.; Glorius, F. *J. Am. Chem. Soc.* **2013**, *135*, 7450.
(21) Lane, B. S.; Brown, M. A.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 8050.

DOI: 10.1021/acs.joc.5b01093
J. Org. Chem. 2015, 80, 7519−7529