Tetrahedron 64 (2008) 6002–6014

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

The versatile role of norbornene in C–H functionalization processes: concise synthesis of tetracyclic fused pyrroles via a threefold domino reaction

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ARTICLE INFO

Article history:
Received 21 September 2007
Received in revised form 12 January 2008
Accepted 14 January 2008
Available online 16 April 2008

Keywords:
C–H activation
Domino reaction
Palladium
Catalysis
Norbornene
ortho-Functionalization
Fused pyrroles
Catellani reaction

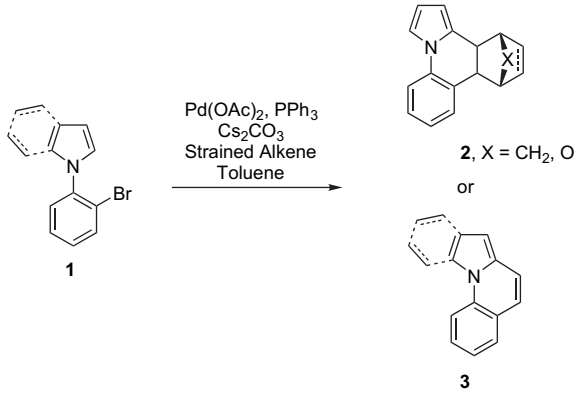
ABSTRACT

The synthesis of novel tetracyclic fused pyrroles from 1-(2-iodophenyl)-1*H*-pyrrole and various bromoalkyl-aryl alkynes via a palladium(0)-catalyzed and norbornene-mediated threefold domino reaction is reported. $PdCl_2$ and tri-2-furylphosphine (TFP) in the presence of norbornene and Cs_2CO_3 in CH_3CN at 90 °C gave a variety of tetracyclic fused pyrroles in usually high yields. In the described reaction sequence two of the three carbon–carbon bonds are formed by functionalization of an unactivated aryl C–H bond.

1. Introduction

The development of highly efficient synthetic procedures toward complex molecules is an important aim in modern preparative organic chemistry. One way to improve efficiency is the use of domino reactions, which allows for multiple bond forming steps in a single reaction.[1] In domino reactions, each new bond delivers a reactive species, which undergoes further steps without changing the reaction conditions. These reaction cascades ultimately lead to the formation of complex molecules usually starting from simple substrates. The carbon–hydrogen bond represents the apex of functional group simplicity, therefore, catalytic activation represents a powerful methodology for the construction of carbon–carbon bonds, and has recently garnered significant attention within the research community.[2] The main advantage of this strategy is that prefunctionalization of one or both coupling partners is not required; this simplifies the preparation of substrates, shortens the synthetic route, and therefore minimizes waste production.

The strained alkene norbornene occupies a special position within the field of C–H functionalization.[3] We have recently reported on an annulation reaction, which involves the intermolecular addition of an arylpalladium(II) halide across a strained alkene; subsequently an intramolecular C–H functionalization of a pendant heterocycle occurs (Scheme 1).[4] This reaction sequence can either lead to the formation of annulated products like **2**, or when norbornadiene is used as strained alkene, a retro-Diels–Alder reaction takes place after the annulation furnishing compounds of type **3**. In addition, it has been shown that aryl halides **4** react under palladium(0)-catalysis with norbornene **5**



1 3

Scheme 1. Palladium-catalyzed annulation of aryl heterocycles with strained alkenes.

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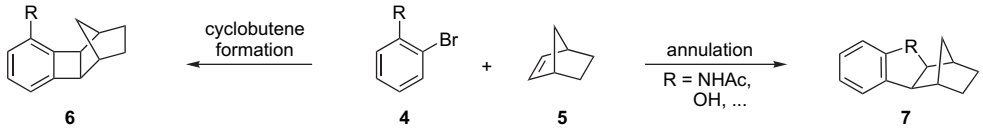
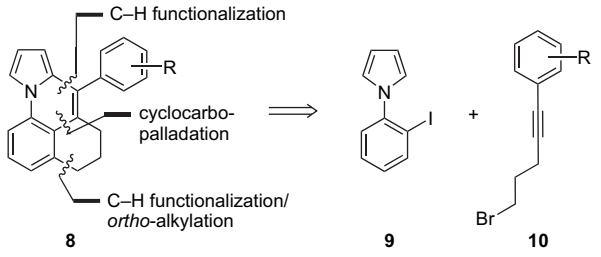
doi:10.1016/j.tet.2008.01.146



Scheme 2. Palladium-catalyzed reaction of aryl halides with norbornene.

delivering cyclobutene products **6** via an *ortho*-C–H functionalization (Scheme 2).[5] If the R group adjacent to the halide is nucleophilic, a different reaction mode occurs and annulation products of type **7** are formed.[6] If norbornene is used along with an alkyl halide, *ortho*-functionalization occurs prior to expulsion of norbornene producing an aryl palladium bond that can react with an acceptor, the Catellani reaction.[7] We have previously reported on the efficient synthesis of functionalized fused aromatic carbo- and heterocycles using primary and secondary alkyl halides.[8]

Herein we describe a powerful combination of these concepts, namely the use of domino reactions and C–H functionalization, for an efficient synthesis of tetracyclic fused pyrrole derivatives. The retrosynthetic analysis of compound **8** is outlined in Scheme 3. The first disconnection results from a carbon–carbon bond formation between a vinylpalladium(II) species and the pyrrole moiety via a C–H functionalization. The vinylpalladium(II) species should in turn result from a cyclocarbopalladation of an arylpalladium(II) species onto a tethered alkyne. Finally, the generation of the arylpalladium(II) species as well as the introduction of the alkyne tether could be achieved by a norbornene-mediated *ortho*-alkylation of aryl iodide **9** using various bromoalkyl-aryl alkynes **10** again via C–H functionalization.



Scheme 3. Retrosynthetic analysis of tetracyclic pyrrole **8**.

We report that this reaction proceeds to construct three carbon–carbon bonds in a single step without any change of the reaction conditions. Due to the employment of two C–H functionalization processes, only very simple and easily accessible substrates are required to synthesize the complex and unique tetracyclic pyrroles. These novel compounds should be of pharmaceutical interest since pyrroles in general and also the pyrrolo[1,2-*a*] motif are known to be present in a broad variety of biologically active natural products and drug molecules.[9] Moreover, structures of similar type are known to exhibit fluorescent properties and are useful for electroluminescent devices in the field of material science.[10]

2. Results and discussion

We began our investigation with the synthesis of bromoalkyl-aryl alkynes **10a**–**n** (Table 1). In order to investigate the influence of the adjacent aryl moiety, we decided to introduce different substituents at all possible positions. At this point we hypothesized that the electron density of the aryl group would affect the character of the alkyne and therefore influencing both the cyclocarbopalladation and the final C–H functionalization step. Furthermore, we also prepared the naphthalene-, indole-, and pyrazole-substituted alkynes.

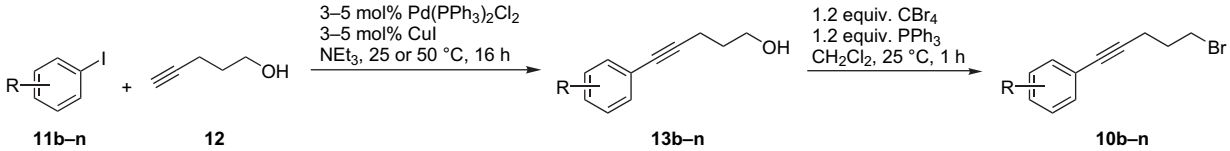
Except for the non-substituted compound **10a**, which was synthesized from lithiated phenylacetylene and 1,3-dibromopropane in 60% yield,[11] all other bromoalkyl-aryl alkynes were accessible utilizing the same straightforward strategy. Starting from various commercially available aryl iodides **11b**–**n**, a Sonogashira cross-coupling[12] with pent-4-yn-1-ol **12** led to the desired products **13b**–**n** in excellent yields. The subsequent Appel reaction[13] converted the alcohols smoothly, in very high yields, into the bromoalkyl-aryl alkynes **10b**–**n**.

We then turned our attention to the domino reaction of 1-(2-iodophenyl)-pyrrole **9**[14] and alkynes **10a**–**n**. Carrying out the reaction using alkyne **10g** (2 equiv) under our standard conditions for the *ortho*-alkylation of aryl iodides (10 mol % $Pd(OAc)_2$, 20 mol % TFP, 3 equiv Cs_2CO_3, CH_3CN, 90 °C, 24 h) led to the formation of the desired tetracycle **8g** in about 40% yield. Beside compound **8g** we could also isolate the corresponding acetoxyalkyl-aryl alkyne, which is formed via a substitution reaction of **10g** and the acetate released by the catalyst. Switching the stoichiometry to 2 equiv of **9** and 1 equiv of **10g** resulted in a much cleaner conversion, which, in turn, led to a much easier purification and therefore higher yields. Finally, we changed the catalyst to $PdCl_2$ to avoid the consumption of the limiting alkyne reagent **10g** from reaction with acetate as described before. Through these changes we could increase the yield of product **8g** up to 90% by using 5 mol % $PdCl_2$ and 10 mol % TFP (Table 2). Since the initiating *ortho*-alkylation is known to be very sensitive in terms of ligand, base, and solvent, we did not undertake further attempts to improve the reaction conditions.

Screening of the prepared alkynes **10a**–**n** indicated that the process is rather general concerning the substituent on the aryl moiety. Whereas the non-substituted alkyne **10a** furnished the tetracycle **8a** in 80% yield, the electron-rich systems like **10b**, **10g**, and **10k** gave even higher yields. In contrast, the rather electron-deficient systems like **10c**, **10d**, and **10e** delivered the desired products **8c**, **8d**, and **8e** in slightly lower yields. The fact that a chloro substituent is tolerated under the applied reaction conditions shows promise for further functionalization using modern cross-coupling technology. Furthermore, it has been shown that the reaction conditions are compatible with trifluoromethyl and ester groups delivering the compounds **8f** and **8i** in moderate to good yields. The rather low yield (47%) of the electron-rich 2,5-dimethoxy aryl product **8j** can be explained by steric effects whereas the low yield of **8h** is likely caused by an interaction between the vinylpalladium(II) species, which is formed after the cyclocarbopalladation and the nitrogen of the anilide. Interestingly, both the naphthyl- and the indole alkynes led to the tetracycles **8k** and **8m** in good yields, leading to the possibility for the introduction of a broader number of aromatic and heterocyclic moieties. In the case of the pyrazole-terminated alkyne we again propose that the low yield (15%) of product **8n** is primarily due to the interaction of the non-protected nitrogen of the heterocycle and the vinylpalladium intermediate. It is worth noting that all synthesized compounds exhibit strong fluorescence during irradiation with UV-light at 366 nm. Fortunately, we were able to obtain a single-crystal of tetracycles **8d** and **8n**, so that the structures could be unambiguously proven by X-ray analysis (Figs. 1 and 2).[15]

The proposed mechanism of the observed domino reaction is outlined in Scheme 4. We hypothesize that the reaction is initiated by an oxidative addition of a preformed Pd(0)-complex into aryl

Table 1
Synthesis of bromoalkyl-aryl alkynes **10b–n** via a Sonogashira/Appel sequence



11b–n **12** **13b–n** **10b–n**

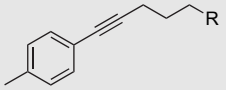
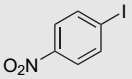
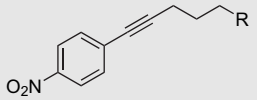
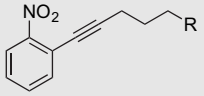
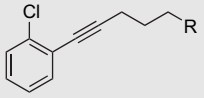
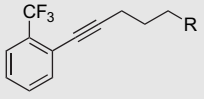
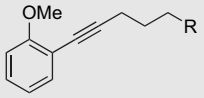
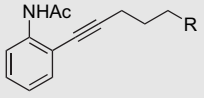
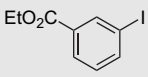
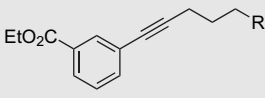
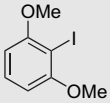
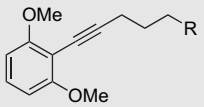
Entry	Aryl iodide	Product **13**/**10** (yield %)
1	 **11b**	 **13b**, R = OH (97%) **10b**, R = Br (98%)
2	 **11c**	 **13c**, R = OH (98%) **10c**, R = Br (91%)
3	 **11d**	 **13d**, R = OH (91%) **10d**, R = Br (97%)
4	 **11e**	 **13e**, R = OH (93%) **10e**, R = Br (92%)
5	 **11f**	 **13f**, R = OH (85%) **10f**, R = Br (92%)
6	 **11g**	 **13g**, R = OH (99%) **10g**, R = Br (92%)
7	 **11h**	 **13h**, R = OH (90%) **10h**, R = Br (94%)
8	 **11i**	 **13i**, R = OH (97%) **10i**, R = Br (98%)
9	 **11j**	 **13j**, R = OH (97%) **10j**, R = Br (98%)

Table 1 (*continued*)

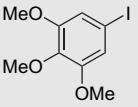
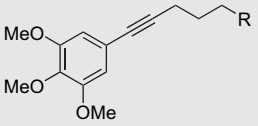
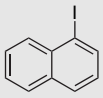
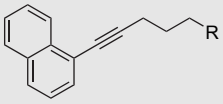
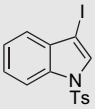
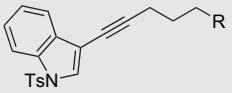
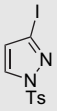
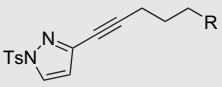
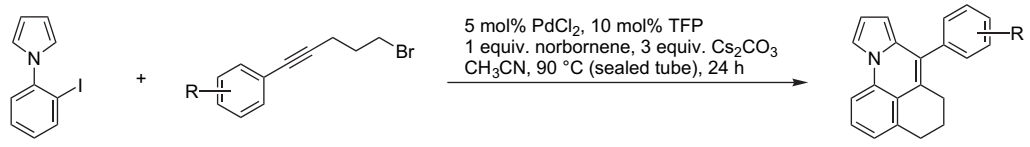
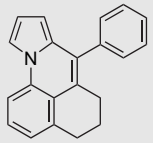
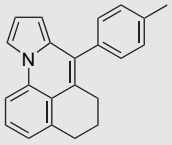
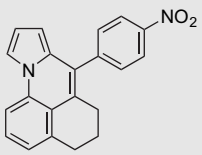
Entry	Aryl iodide	Product **13**/**10** (yield %)
10	 **11k**	 **13k**, R = OH (89%) **10k**, R = Br (94%)
11	 **11l**	 **13l**, R = OH (95%) **10l**, R = Br (93%)
12	 **11m**	 **13m**, R = OH (95%) **10m**, R = Br (92%)
13	 **11n**	 **13n**, R = OH (97%) **10n**, R = Br (93%)

Table 2
Threefold domino reaction for the construction of tetracyclic fused pyrroles **8a**–**n**



9 **10a–n** **8a–n**

Entry	Alkyne	Product **8** (yield %)
1	**10a**	 **8a** (80%)
2	**10b**	 **8b** (85%)
3	**10c**	 **8c** (72%)

(*continued on next page*)

Table 2 (*continued*)

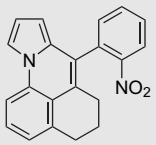
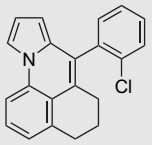
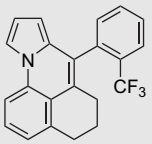
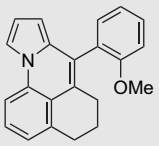
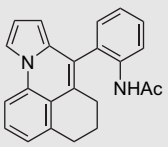
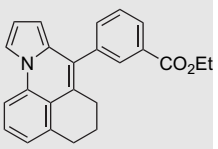
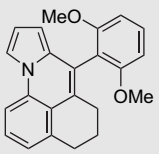
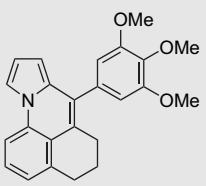
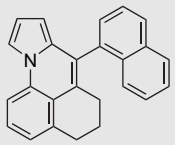
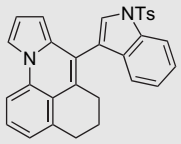
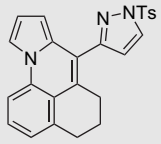
Entry	Alkyne	Product **8** (yield %)
4	**10d**	 **8d** (81%)
5	**10e**	 **8e** (72%)
6	**10f**	 **8f** (51%)
7	**10g**	 **8g** (90%)
8	**10h**	 **8h** (25%)
9	**10i**	 **8i** (60%)
10	**10j**	 **8j** (47%)
11	**10k**	 **8k** (87%)

Table 2 (*continued*)

Entry	Alkyne	Product **8** (yield %)
12	**10l**	 **8l** (67%)
13	**10m**	 **8m** (75%)
14	**10n**	 **8n** (15%)

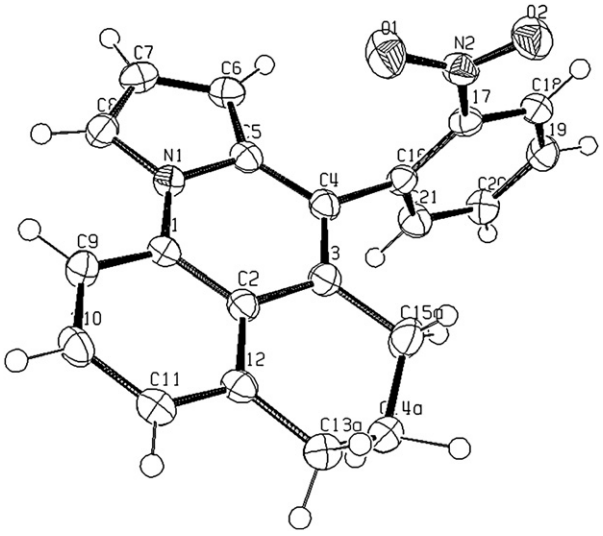


Figure 1. ORTEP diagram of compound **8d** (disorder at two positions at C14).

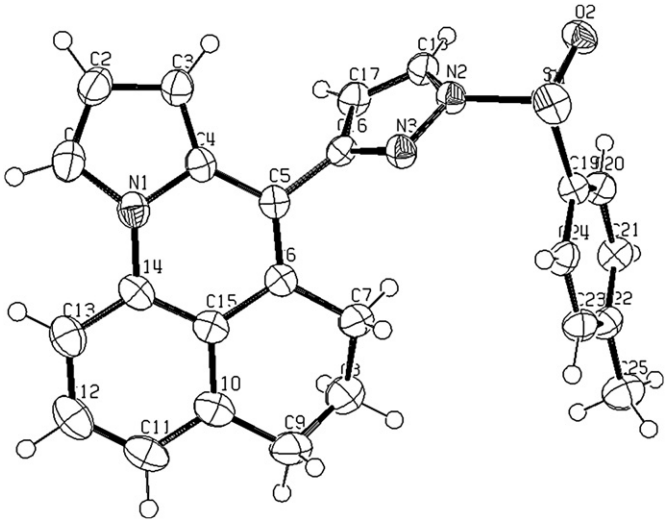
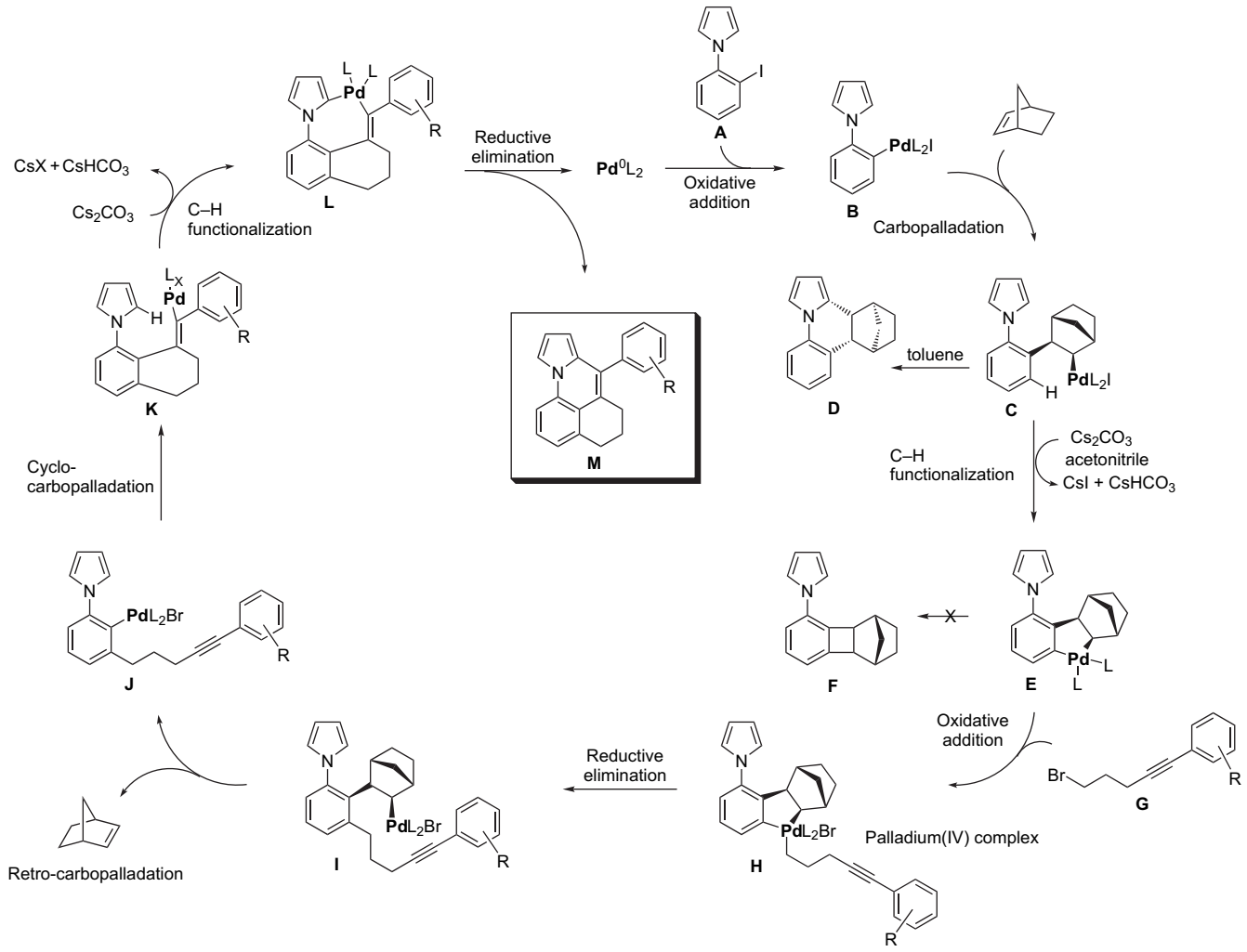


Figure 2. ORTEP diagram of compound **8n**.

iodide **A** generating the arylpalladium(II) species **B**. Subsequent *syn*-carbopalladation of the reactive olefin norbornene in an *exo*-fashion leads to complex **C**. Instead of undergoing the previously described formation of annulated pyrrole **D** via a seven-membered palladacycle, **C** forms the five-membered palladacycle **E**. Thus, under the reaction conditions the rate of the *ortho*-functionalization to give **E** is faster than the competitive annulation onto the pyrrole resulting in the formation of compound **D**. This dramatic alteration of the reaction mechanism is caused by change of the solvent from toluene to acetonitrile; as shown when reaction of **9** with **10g** in toluene gave only trace amounts of the desired tetracycle **8g**.

Once formed, **E** undergoes an oxidative addition of bromoalkylaryl alkyne **G** and formation of palladium(IV)-complex **H** takes place. Reductive elimination of the five-membered palladacycle **E** to yield cyclobutene **F**, a common byproduct in Catellani-type reactions, does not occur due to the relatively high strain.[16] The octahedral palladium(IV)-complex **H** can now undergo rapid reductive elimination furnishing the *ortho*-alkylated intermediate **I**. Due to increased steric demand and no possibility of *syn*-β-H elimination, a retro-carbopalladation of norbornene occurs providing arylpalladium(II) species **J**. The latter performs an intramolecular carbopalladation onto the tethered alkyne producing the second carbon–carbon bond. Following formation of the fused cyclohexane, vinylpalladium(II) intermediate **K** induces another C–H functionalization at the adjacent electron-rich pyrrole ring. This process could either proceed via a direct C–H insertion leading to palladacycle **L** or via an electrophilic aromatic substitution by attack of the pyrrole onto the palladium(II) species. Reductive elimination from the seven-membered palladacycle **L** leads finally to the construction of the third carbon–carbon bond delivering the desired tetracyclic structure **M**.



Scheme 4. Proposed mechanism of the threefold domino reaction.

3. Conclusion

In summary, we have developed a concise route toward the synthesis of interesting tetracyclic fused pyrrole derivatives, some of which show strong fluorescence under UV-irradiation. This methodology utilizes a novel palladium-catalyzed and norbornene-mediated threefold domino process, which constructs three challenging carbon–carbon bonds in a one-pot procedure; two of them from unactivated aryl C–H bonds. Moreover, this approach stands out for its efficiency, the use of easy accessible substrates, and a broad functional group tolerance. Further studies of the described methodology regarding the introduction of other heterocycles are in progress.

4. Experimental

4.1. General

The following includes general experimental procedures, specific details for representative reactions, and isolation and spectroscopic information for new compounds. Melting points were recorded using a Fisher–Johns melting point apparatus and are uncorrected. ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded at room temperature using a Varian Gemini-300, Unity-400 or Mercury 400 machine. ^{1}H spectra were referenced to tetramethylsilane (TMS, 0 ppm) and ^{13}C spectra were referenced to solvent carbons (77.23 ppm for $CDCl_3$ and 128.4 ppm for C_6D_6). No special notation is used for equivalent carbons. IR spectra were obtained using a Nicolet DX FT-IR spectrometer as thin films on NaCl plates. High-resolution mass spectra were obtained using a VG 70-250S (double focusing) mass spectrometer at 70 eV unless otherwise noted. Tetrahydrofuran (THF) was distilled under nitrogen from Na/benzophenone immediately prior to use. Dichloromethane and acetonitrile were distilled under nitrogen from CaH_2 immediately prior to use. Neutral silica (Silicycle, Quebec, Canada) for flash chromatography was used as received. Thin layer chromatography (TLC) was carried out on precoated SIL G/UV_{254} (0.2 mm) plates from EM Separations. All reagents and metal catalysts were purchased from Sigma–Aldrich, Lancaster, Alfa Aesar or Strem-Chemical Company and used without further purification unless otherwise noted. Tri-2-furylphosphine (TFP) was synthesized according to the procedure of Santelli-Rouvier and Santelli.[17] CuI was thoroughly washed for 16 h with hot THF using a Soxhlet extractor. All reactions were performed in dry glassware under an atmosphere of argon.

*4.1.1. (5-Bromo-pent-1-ynyl)-benzene (**10a**)*

To a solution of phenylacetylene (6.51 g, 63.7 mmol, 1.0 equiv) in THF (25 mL) was added dropwise *n*BuLi (39.8 mL, 63.7 mmol, 1.0 equiv, 1.6 M in hexane) at 0 °C. After addition the reaction mixture was allowed to warm up to 25 °C and stirring was continued for 1 h. Afterwards, 1,3-dibromopropane (7.3 mL, 70 mmol,

1.1 equiv) was added in one portion at −78 °C. After 2 h at this temperature the reaction mixture was stirred for another 12 h under reflux. The reaction was quenched by adding small pieces of ice at 0 °C, H_2O (200 mL) was added and the mixture was extracted with Et_2O (3×200 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was subjected to silica gel flash chromatography (hexane) and concentration of the appropriate fractions in vacuo afforded the alkyne **10a** (8.50 g, 60% yield) as colorless liquid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.43–7.34 (m, 2H), 7.32–7.24 (m, 3H), 3.57 (t, J=6.6 Hz, 2H), 2.60 (t, J=6.6 Hz, 2H), 2.12 (m_c, 2H) ppm; ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 131.8, 128.5, 128.0, 123.8, 88.15, 81.86, 32.66, 31.80, 18.29 ppm; IR (neat) 3056, 2959, 2841, 1597, 1489, 1441, 1430, 1351, 1271, 1247, 1070, 914, 850 cm^{-1}; HRMS-EI: [M$^+$] calcd for $C_{11}H_{11}Br$: 222.0044, found: 222.0044.

4.2. General procedure for the Sonogashira coupling of aryl iodides and 4-pentyn-1-ol

To the corresponding aryl iodides **11b–n** (1.0 equiv) in Et_3N (3–5 mL/mmol) were added subsequently $PdCl_2(PPh_3)_2$ (3–5 mol %), CuI (3–5 mol %) and 4-pentyn-1-ol (1.2 equiv) at 25 °C. Stirring was continued for 16 h at 25 °C (for very electron-rich or sterically hindered aryl iodides the temperature was raised to 50 °C). The reaction mixture was treated with satd NH_4Cl solution (200–300 mL) and the resulting mixture was extracted with CH_2Cl_2 (3×150 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography and concentration of the appropriate fractions in vacuo afforded the desired compounds **13b–n**.

4.2.1. 5-(4-Methylphenyl)pent-4-yn-1-ol (*13b*)

Following the general procedure for the Sonogashira coupling 4-iodo-toluene (**11b**, 5.00 g, 22.9 mmol, 1.0 equiv), 4-pentyn-1-ol (2.32 g, 2.56 mL, 27.5 mmol, 1.2 equiv), $PdCl_2(PPh_3)_2$ (526 mg, 0.75 mmol, 3.3 mol %), and CuI (143 mg, 0.75 mmol, 3.3 mol %) in Et_3N (80 mL) were stirred for 16 h at 25 °C. After silica gel flash chromatography using 10→25% EtOAc/hexanes as eluent the desired compound **13b** (3.86 g, 97%) was delivered as colorless solid. Mp 34–36 °C; IR ($CHCl_3$) 3623, 3432, 2952, 2400, 1510, 1432, 1052, 925, 819 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.28 (d, J=8.0 Hz, 2H), 7.09 (d, J=8.0 Hz, 2H), 3.82 (t, J=6.1 Hz, 2H), 2.53 (t, J=6.1 Hz, 2H), 2.33 (s, 3H), 1.85 (m_c, 2H), 1.69 (br s, 1H) ppm; ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 146.9, 137.9, 131.6, 129.2, 120.8, 88.7, 81.4, 62.1, 31.6, 21.6, 16.2 ppm; HRMS-EI: [M$^+$] calcd for $C_{12}H_{14}O$: 174.1045, found: 174.1044.

4.2.2. 5-(4-Nitrophenyl)pent-4-yn-1-ol (*13c*)

Following the general procedure for the Sonogashira coupling 4-iodo-nitrobenzene (**11c**, 4.98 g, 20.0 mmol, 1.0 equiv), 4-pentyn-1-ol (2.02 g, 2.23 mL, 24.0 mmol, 1.2 equiv), $PdCl_2(PPh_3)_2$ (421 mg, 0.60 mmol, 3 mol %), and CuI (114 mg, 0.60 mmol, 3 mol %) in Et_3N (70 mL) were stirred for 16 h at 25 °C. After silica gel flash chromatography using 25→50% EtOAc/hexanes as eluent the desired compound **13c** (4.02 g, 98%) was delivered as slightly orange solid. Mp 31–33 °C; IR ($CHCl_3$) 3371, 2952, 2447, 2227, 1593, 1516, 1341, 1174, 1108, 1060, 854, 689 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.16 (m_c, 2H), 7.52 (m_c, 2H), 3.83 (m_c, 2H), 2.60 (t, J=6.9 Hz, 2H), 1.89 (m_c, 2H), 1.41 (br t, J=4.9 Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 132.5, 131.1, 123.7, 95.9, 79.9, 61.7, 31.3, 16.3 ppm; HRMS-EI: [M$^+$] calcd for $C_{11}H_{11}NO_3$: 205.0739, found: 205.0736.

4.2.3. 5-(2-Nitrophenyl)pent-4-yn-1-ol (*13d*)

Following the general procedure for the Sonogashira coupling 2-iodo-nitrobenzene (**11d**, 6.00 g, 24.1 mmol, 1.0 equiv), 4-pentyn-1-ol (2.43 g, 2.69 mL, 28.9 mmol, 1.2 equiv), $PdCl_2(PPh_3)_2$ (592 mg, 0.84 mmol, 3.5 mol %), and CuI (161 mg, 0.84 mmol, 3.5 mol %) in Et_3N (120 mL) were stirred for 16 h at 25 °C. After silica gel flash chromatography using 20→40% EtOAc/hexanes as eluent the desired compound **13d** (4.50 g, 91%) was delivered as slightly yellow solid. Mp 29–31 °C; IR ($CHCl_3$) 3624, 3417, 2954, 2400, 2231, 1609, 1526, 1345, 1052, 853 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.98 (dd, J=7.9, 1.2 Hz, 1H), 7.58 (dd, J=7.9, 1.2 Hz, 1H), 7.53 (dt, J=6.8, 1.7 Hz, 1H), 7.41 (m_c, 1H), 3.86 (m_c, 2H), 2.63 (t, J=6.9 Hz, 2H), 1.90 (m_c, 2H), 1.60 (br s, 1H) ppm; ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 150.2, 135.0, 132.8, 128.2, 124.6, 119.3, 98.6, 76.6, 61.6, 31.1, 16.6 ppm; HRMS-EI: [M$^+$] calcd for $C_{11}H_{11}NO_3$: 205.0739, found: 205.0745.

4.2.4. 5-(2-Chlorophenyl)pent-4-yn-1-ol (*13e*)

Following the general procedure for the Sonogashira coupling 1-chloro-2-iodobenzene (**11e**, 3.00 g, 12.6 mmol, 1.0 equiv), 4-pentyn-1-ol (1.72 g, 1.41 mL, 15.1 mmol, 1.2 equiv), $PdCl_2(PPh_3)_2$ (265 mg, 0.38 mmol, 3.0 mol %), and CuI (72 mg, 0.38 mmol, 3.0 mol %) in Et_3N (80 mL) were stirred for 16 h at 25 °C. After silica gel flash chromatography using 10→25% EtOAc/hexanes as eluent the desired compound **13e** (2.28 g, 93%) was delivered as colorless oil. IR (neat) 3300, 2948, 2232, 1473, 1429, 1128, 1065, 1033, 962, 925, 755, 662 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.45–7.35 (m, 2H), 7.24–7.14 (m, 2H), 3.86 (t, J=6.9 Hz, 2H), 2.61 (t, J=6.9 Hz, 2H), 1.90 (m_c, 2H), 1.64 (br s, 1H) ppm; ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 135.9, 133.5, 129.3, 128.9, 126.6, 123.7, 95.3, 78.3, 61.9, 31.4, 16.4 ppm; HRMS-EI: [M$^+$] calcd for $C_{11}H_{11}ClO$: 194.0498, found: 194.0499.

4.2.5. 5-(2-(Trifluoromethyl)phenyl)pent-4-yn-1-ol (*13f*)

Following the general procedure for the Sonogashira coupling 1-iodo-2-(trifluoromethyl)benzene (**11f**, 5.00 g, 18.4 mmol, 1.0 equiv), 4-pentyn-1-ol (1.86 g, 2.06 mL, 22.1 mmol, 1.2 equiv), $PdCl_2(PPh_3)_2$ (387 mg, 0.55 mmol, 3.0 mol %), and CuI (105 mg, 0.55 mmol, 3.0 mol %) in Et_3N (70 mL) were stirred for 16 h at 25 °C. After silica gel flash chromatography using 20→33% EtOAc/hexanes as eluent the desired compound **13f** (3.57 g, 85%) was delivered as slightly yellow oil. IR (neat) 3314, 2948, 2234, 1604, 1574, 1490, 1451, 1319, 1266, 1130, 1063, 1033, 958, 922, 765, 751, 650 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.62 (d, J=7.6 Hz, 1H), 7.53 (d, J=7.2 Hz, 1H), 7.45 (t, J=7.2 Hz, 1H), 7.35 (t, J=7.6 Hz, 1H), 3.83 (m_c, 2H), 2.59 (t, J=6.9 Hz, 2H), 1.88 (m_c, 2H), 1.50 (br s, 1H) ppm; ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 134.1, 131.8, 131.4, 127.6, 126.0, 125.9, 125.8, 125.7, 122.3, 122.0, 95.8, 77.4, 61.6, 31.3, 16.2 ppm; ^{19}F NMR ($CDCl_3$, 282 MHz) δ −62.9 ppm; HRMS-EI: [M$^+$] calcd for $C_{12}H_{11}F_3O$: 228.0762, found: 228.0758.

4.2.6. 5-(2-Methoxyphenyl)pent-4-yn-1-ol (*13g*)

Following the general procedure for the Sonogashira coupling 1-iodo-2-methoxybenzene (**11g**, 5.00 g, 21.4 mmol, 1.0 equiv), 4-pentyn-1-ol (2.15 g, 2.38 mL, 25.6 mmol, 1.2 equiv), $PdCl_2(PPh_3)_2$ (526 mg, 0.75 mmol, 3.5 mol %), and CuI (143 mg, 0.75 mmol, 3.5 mol %) in Et_3N (70 mL) were stirred for 16 h at 25 °C. After silica gel flash chromatography using 20→50% EtOAc/hexanes as eluent the desired compound **13g** (3.73 g, 99%) was delivered as slightly yellow oil. IR (neat) 3373, 3074, 2946, 2836, 2229, 1595, 1576, 1491, 1464, 1435, 1261, 1180, 1162, 1117, 1049, 1025, 925, 754, 696 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.36 (dd, J=7.6, 1.6 Hz, 1H), 7.25 (m_c, 1H), 6.88 (dt, J=7.6, 1.2 Hz, 1H), 6.85 (d, J=8.1 Hz, 1H), 3.89–3.82 (m, 5H), 2.60 (t, J=6.8 Hz, 2H), 2.13 (br s, 1H), 1.89 (m_c, 2H) ppm; ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 160.1, 133.5, 129.3, 120.6, 112.9, 110.7, 94.0, 77.6, 62.4, 55.9, 31.5, 17.0 ppm; HRMS-EI: [M$^+$] calcd for $C_{12}H_{14}O_2$: 190.0994, found: 190.0988.

4.2.7. N-(2-(5-Hydroxypent-1-ynyl)phenyl)acetamide (*13h*)

Following the general procedure for the Sonogashira coupling *N*-(2-iodophenyl)acetamide (**11h**, 4.00 g, 15.3 mmol, 1.0 equiv),

4-pentyn-1-ol (1.54 g, 1.71 mL, 18.3 mmol, 1.2 equiv), $PdCl_2(PPh_3)_2$ (537 mg, 0.77 mmol, 5.0 mol %), and CuI (146 mg, 0.77 mmol, 5.0 mol %) in Et_3N (120 mL) and DMF (10 mL) were stirred for 16 h at 25 °C. After silica gel flash chromatography using 33→66% EtOAc/hexanes as eluent the desired compound **13h** (2.99 g, 90%) was delivered as slightly yellow oil. IR (neat) 3388, 2930, 2225, 1653, 1579, 1521, 1447, 1387, 1304, 1269, 1097, 1061, 760, 662 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.35 (d, J=8.3 Hz, 1H), 8.05 (br s, 1H), 7.32 (dd, J=9.3, 1.6 Hz, 1H), 7.26 (m_c, 1H), 7.00 (d, J=7.6 Hz, 1H), 3.85 (t, J=6.0 Hz, 2H), 2.65 (t, J=7.0 Hz, 2H), 2.22 (s, 3H), 1.95–1.84 (m, 3H) ppm; ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 168.8, 139.2, 131.7, 129.1, 123.5, 119.5, 112.8, 97.3, 76.6, 61.7, 31.5, 25.0, 16.6 ppm; HRMS-EI: [M^+] calcd for $C_{13}H_{15}NO_2$: 217.1103, found: 217.1100.

4.2.8. Ethyl 3-(5-hydroxypent-1-ynyl)benzoate (**13i**)

Following the general procedure for the Sonogashira coupling ethyl 3-iodobenzoate (**11i**, 5.52 g, 20.0 mmol, 1.0 equiv), 4-pentyn-1-ol (2.02 g, 2.23 mL, 24.0 mmol, 1.2 equiv), $PdCl_2(PPh_3)_2$ (421 mg, 0.60 mmol, 3.0 mol %), and CuI (114 mg, 0.60 mmol, 3.0 mol %) in Et_3N (80 mL) were stirred for 16 h at 25 °C. After silica gel flash chromatography using 20→40% EtOAc/hexanes as eluent the desired compound **13i** (4.51 g, 97%) was delivered as slightly yellow oil. IR (neat) 3362, 2947, 2234, 1716, 1604, 1574, 1490, 1451, 1318, 1266, 1170, 1134, 1111, 1063, 1033, 957, 765, 751, 650 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.06 (t, J=1.6 Hz, 1H), 7.94 (dt, J=7.8, 1.6 Hz, 1H), 7.36 (dt, J=7.8, 1.6 Hz, 1H), 4.38 (q, J=7.2 Hz, 2H), 3.83 (t, J=6.2 Hz, 2H), 2.56 (t, J=6.2 Hz, 2H), 1.88 (m_c, 2H), 1.64 (br s, 1H), 1.39 (t, J=7.2 Hz, 3H) ppm; ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 166.3, 135.8, 132.8, 130.8, 128.9, 128.5, 124.4, 90.6, 80.4, 61.8, 61.4, 31.5, 16.1, 14.5 ppm; HRMS-EI: [M^+] calcd for $C_{14}H_{16}O_3$: 232.1099, found: 232.1103.

4.2.9. 5-(2,6-Dimethoxyphenyl)pent-4-yn-1-ol (**13j**)

Following the general procedure for the Sonogashira coupling 2-iodo-1,3-dimethoxybenzene (3.00 g, 11.4 mmol, 1.0 equiv), 4-pentyn-1-ol (**11j**, 1.15 g, 1.27 mL, 9.09 mmol, 1.2 equiv), $PdCl_2(PPh_3)_2$ (399 mg, 0.57 mmol, 5.0 mol %), and CuI (108 mg, 0.57 mmol, 5.0 mol %) in Et_3N (100 mL) were stirred for 16 h at 50 °C. After silica gel flash chromatography using 20→50% EtOAc/hexanes as eluent the desired compound **13j** (2.23 g, 89%) was delivered as colorless oil. IR (neat) 3382, 3005, 2937, 2838, 1583, 1473, 1432, 1300, 1252, 1110, 1031, 958, 924, 777, 754, 727, 667 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.19 (t, J=8.5 Hz, 1H), 6.52 (d, J=8.5 Hz, 2H), 3.89–3.82 (m, 8H), 2.68 (t, J=6.7 Hz, 2H), 1.90 (m_c, 2H), 1.74 (br s, 1H) ppm; ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 161.5, 129.3, 103.6, 101.8, 98.5, 73.9, 62.8, 56.2, 31.3, 17.8 ppm; HRMS-EI: [M^+] calcd for $C_{13}H_{16}O_3$: 220.1099, found: 220.1097.

4.2.10. 5-(3,4,5-Trimethoxyphenyl)pent-4-yn-1-ol (**13k**)

Following the general procedure for the Sonogashira coupling 5-iodo-1,2,3-trimethoxybenzene (**11k**, 2.00 g, 6.80 mmol, 1.0 equiv), 4-pentyn-1-ol (686 mg, 0.76 mL, 27.5 mmol, 1.2 equiv), $PdCl_2(PPh_3)_2$ (239 mg, 0.34 mmol, 5.0 mol %), and CuI (65 mg, 0.34 mmol, 5.5 mol %) in Et_3N (80 mL) were stirred for 16 h at 50 °C. After silica gel flash chromatography using 20→40% EtOAc/hexanes as eluent the desired compound **13k** (1.62 g, 95%) was delivered as slightly yellow solid. Mp 44–46 °C; IR ($CHCl_3$) 2940, 1579, 1505, 1464, 1411, 1346, 1236, 1130, 999, 836 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.63 (s, 2H), 3.86–3.78 (m, 11H), 2.54 (t, J=7.0 Hz, 2H), 1.87 (m_c, 2H), 1.57 (br t, J=4.7 Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 153.2, 138.6, 119.0, 109.0, 88.7, 81.3, 62.0, 61.1, 56.3, 31.6, 16.2 ppm; MS-EI m/z: 250 (M^+, 100), 235 (36%); HRMS-EI: [M^+] calcd for $C_{14}H_{18}O_4$: 250.1205, found: 250.1206.

4.2.11. 5-(Naphthalen-1-yl)pent-4-yn-1-ol (**13l**)

Following the general procedure for the Sonogashira coupling 1-iodo-naphthalene (**11l**, 5.00 g, 19.7 mmol, 1.0 equiv), 4-pentyn-1-ol (2.02 g, 2.23 mL, 24.0 mmol, 1.2 equiv), $PdCl_2(PPh_3)_2$ (414 mg, 0.59 mmol, 3.0 mol %), and CuI (112 mg, 0.59 mmol, 3.0 mol %) in Et_3N (70 mL) were stirred for 16 h at 25 °C. After silica gel flash chromatography using 20→33% EtOAc/hexanes as eluent the desired compound **13l** (3.86 g, 97%) was delivered as slightly yellow oil. IR (neat) 3351, 3057, 2945, 2224, 1716, 1585, 1506, 1429, 1395, 1051, 799, 774 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.32 (m_c, 1H), 7.85–7.45 (m, 2H), 7.62 (dd, J=7.1, 1.2 Hz, 1H), 7.52 (m_c, 2H), 7.39 (dd, J=8.2, 7.4 Hz, 2H), 3.90 (t, J=6.1 Hz, 2H), 2.71 (t, J=6.8 Hz, 2H), 1.97 (m_c, 2H), 1.57 (br s, 1H) ppm; ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 133.7, 133.4, 130.3, 128.5, 128.3, 126.8, 126.5, 126.4, 125.4, 121.7, 94.6, 79.4, 62.1, 31.8, 16.5 ppm; HRMS-EI: [M^+] calcd for $C_{15}H_{14}O$: 210.1045, found: 210.1047.

4.2.12. 5-(1-Tosyl-1H-indol-3-yl)pent-4-yn-1-ol (**13m**)

Following the general procedure for the Sonogashira coupling 3-iodo-1-tosyl-1*H*-indole[18] (**11m**, 3.00 g, 7.55 mmol, 1.0 equiv), 4-pentyn-1-ol (0.76 g, 0.84 mL, 9.06 mmol, 1.2 equiv), $PdCl_2(PPh_3)_2$ (265 mg, 0.38 mmol, 5.0 mol %), and CuI (72 mg, 0.38 mmol, 5.0 mol %) in Et_3N (80 mL) were stirred for 16 h at 25 °C. After silica gel flash chromatography using 40% EtOAc/hexanes as eluent the desired compound **13m** (2.51 g, 94%) was delivered as white solid. Mp 100–102 °C; IR ($CHCl_3$) 3615, 3017, 1952, 2399, 1597, 1447, 1374, 1277, 1188, 1176, 1129, 1104, 1089, 668 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.95 (m_c, 1H), 7.72 (m_c, 2H), 7.65 (s, 1H), 7.58 (m_c, 1H), 7.35–7.20 (m, 3H), 7.15 (d, J=8.1 Hz, 2H), 3.81 (t, J=6.3 Hz, 2H), 2.53 (t, J=7.1 Hz, 2H), 2.27 (s, 3H), 1.95–1.80 (m, 3H) ppm; ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 145.4, 135.1, 134.4, 131.3, 130.1, 128.5, 127.1, 125.5, 123.8, 120.7, 113.7, 106.0, 94.1, 72.0, 61.8, 31.7, 21.7, 16.4 ppm; HRMS-EI: [M^+] calcd for $C_{20}H_{19}NO_3S$: 353.1079, found: 353.1079.

4.2.13. 5-(1-Tosyl-1H-pyrazol-5-yl)pent-4-yn-1-ol (**13n**)

Following the general procedure for the Sonogashira coupling 5-iodo-1-tosyl-1*H*-pyrazole (**11n**, 2.00 g, 5.57 mmol, 1.0 equiv), 4-pentyn-1-ol (0.58 g, 0.64 mL, 6.89 mmol, 1.2 equiv), $PdCl_2(PPh_3)_2$ (201 mg, 0.29 mmol, 5.0 mol %), and CuI (55 mg, 0.29 mmol, 5.0 mol %) in Et_3N (50 mL) were stirred for 16 h at 25 °C. After silica gel flash chromatography using 40% EtOAc/hexanes as eluent the desired compound **13n** (1.69 g, 97%) was delivered as colorless wax. IR ($CHCl_3$) 3395, 3015, 2951, 2243, 1596, 1516, 1437, 1384, 1304, 1191, 1178, 1135, 1029, 909 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.04 (d, J=1.6 Hz, 1H), 7.90 (dt, J=8.4, 1.8 Hz, 2H), 7.34 (m_c, 2H), 6.39 (d, J=2.7 Hz, 1H), 3.77 (t, J=6.1 Hz, 2H), 2.51 (t, J=7.0 Hz, 2H), 2.43 (s, 3H), 1.83 (m_c, 2H), 1.65 (br s, 1H) ppm; ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 146.3, 141.3, 133.9, 131.6, 130.3, 128.5, 112.2, 93.5, 72.8, 61.6, 31.0, 21.9, 16.1 ppm; HRMS-EI: [M^+] calcd for $C_{15}H_{16}N_2O_3S$: 304.0882, found: 304.0880.

4.3. General procedure for the conversion of primary alcohols into bromides via Appel reaction

To the corresponding alcohols **13b–n** (1.0 equiv) and CBr_4 (1.2 equiv) in CH_2Cl_2 (3–5 mL/mmol) was added PPh_3 (1.2 equiv) in small portions at 0 °C. The reaction mixture was allowed to warm up to 25 °C and stirring was continued for 1 h. Afterwards, the solvent was removed in vacuo, the crude product was purified by silica gel flash chromatography, and concentration of the appropriate fractions in vacuo afforded the desired compounds **10b–n**.

4.3.1. 1-(5-Bromopent-1-ynyl)-4-methylbenzene (**10b**)

Following the general procedure for the Appel reaction alcohol **13b** (3.80 g, 21.8 mmol, 1.0 equiv), CBr_4 (8.69 g, 26.2 mmol, 1.2 equiv), and PPh_3 (6.87 g, 26.2 mmol, 1.2 equiv) furnished after silica gel flash chromatography using 5% EtOAc/hexanes as eluent the desired compound **10b** (5.07 g, 98%) as slightly yellow oil.

IR (neat) 3026, 2921, 2867, 1906, 1509, 1430, 1351, 1272, 1246, 1106, 817 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.29 (d, J=8.1 Hz, 2H), 7.09 (d, J=8.1 Hz, 2H), 3.58 (t, J=6.5 Hz, 2H), 2.59 (t, J=6.7 Hz, 2H), 2.33 (s, 3H), 2.12 (m_c, 2H) ppm; ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 138.0, 131.7, 129.2, 120.6, 87.3, 81.9, 32.8, 31.8, 21.7, 18.4 ppm; HRMS-EI: [M^+] calcd for $C_{12}H_{13}Br$: 236.0201, found: 236.0201.

*4.3.2. 1-(5-Bromopent-1-ynyl)-4-nitrobenzene (**10c**)*

Following the general procedure for the Appel reaction alcohol **13c** (2.20 g, 10.7 mmol, 1.0 equiv), CBr_4 (4.29 g, 12.9 mmol, 1.2 equiv), and PPh_3 (3.38 g, 12.9 mmol, 1.2 equiv) furnished after silica gel flash chromatography using 10% EtOAc/hexanes as eluent the desired compound **10c** (2.65 g, 91%) as light-brown solid. Mp 35–36 °C; IR ($CHCl_3$) 3017, 2226, 1594, 1521, 1345, 1108, 854 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.16 (d, J=8.8 Hz, 2H), 7.53 (d, J=8.8 Hz, 2H), 3.58 (t, J=6.6 Hz, 2H), 2.69 (t, J=6.6 Hz, 2H), 2.17 (m_c, 2H) ppm; ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 147.0, 132.5, 130.8, 123.7, 94.3, 80.4, 32.4, 31.4, 18.5 ppm; HRMS-EI: [M^+] calcd for $C_{11}H_{10}BrNO_2$: 266.9895, found: 266.9901.

*4.3.3. 1-(5-Bromopent-1-ynyl)-2-nitrobenzene (**10d**)*

Following the general procedure for the Appel reaction alcohol **13d** (4.50 g, 21.9 mmol, 1.0 equiv), CBr_4 (8.72 g, 26.3 mmol, 1.2 equiv), and PPh_3 (6.89 g, 26.3 mmol, 1.2 equiv) furnished after silica gel flash chromatography using 10% EtOAc/hexanes as eluent the desired compound **10d** (5.70 g, 97%) as slightly yellow oil. IR (neat) 2913, 2228, 1608, 1568, 1521, 1479, 1435, 1343, 1246, 1145, 853, 784, 746 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.00 (dd, J=8.1, 1.0 Hz, 1H), 7.59 (dd, J=8.1, 1.9 Hz, 1H), 7.54 (dt, J=7.4, 1.3 Hz, 1H), 7.42 (m_c, 1H), 3.64 (t, J=6.3 Hz, 2H), 2.70 (t, J=6.6 Hz, 2H), 2.17 (m_c, 2H) ppm; ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 150.2, 135.0, 132.9, 128.4, 124.7, 119.1, 97.0, 77.2, 32.6, 31.3, 18.7 ppm; HRMS-EI: [M^+] calcd for $C_{11}H_{10}BrNO_2$: 266.9895, found: 266.9887.

*4.3.4. 1-(5-Bromopent-1-ynyl)-2-chlorobenzene (**10e**)*

Following the general procedure for the Appel reaction alcohol **13e** (2.31 g, 11.9 mmol, 1.0 equiv), CBr_4 (4.72 g, 14.2 mmol, 1.2 equiv), and PPh_3 (3.74 g, 14.2 mmol, 1.2 equiv) furnished after silica gel flash chromatography using 5% EtOAc/hexanes as eluent the desired compound **10e** (5.70 g, 92%) as colorless oil. IR (neat) 3065, 2961, 2231, 1473, 1437, 1430, 1350, 1272, 1246, 1127, 1061, 1033, 754, 726, 668, 663 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.45–7.35 (m, 2H), 7.19 (m_c, 2H), 3.64 (t, J=6.5 Hz, 2H), 2.68 (t, J=6.8 Hz, 2H), 2.17 (m_c, 2H) ppm; ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 136.0, 133.5, 129.4, 129.0, 126.6, 123.6, 93.8, 78.8, 32.6, 31.6, 18.5 ppm; HRMS-EI: [M^+] calcd for $C_{11}H_{10}BrCl$: 255.9654, found: 255.9661.

*4.3.5. 1-(5-Bromopent-1-ynyl)-2-(trifluoromethyl)benzene (**10f**)*

Following the general procedure for the Appel reaction alcohol **13f** (3.40 g, 14.9 mmol, 1.0 equiv), CBr_4 (5.93 g, 17.9 mmol, 1.2 equiv), and PPh_3 (4.69 g, 17.9 mmol, 1.2 equiv) furnished after silica gel flash chromatography using 5% EtOAc/hexanes as eluent the desired compound **10f** (3.99 g, 92%) as colorless oil. IR (neat) 3402, 3071, 2957, 2924, 2868, 2232, 1603, 1574, 1490, 1450, 1319, 1266, 1247, 1171, 1134, 1111, 1061, 1033, 765, 751 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.62 (d, J=8.0 Hz, 1H), 7.53 (d, J=7.6 Hz, 1H), 7.45 (t, J=7.6 Hz, 1H), 7.36 (t, J=8.0 Hz, 1H), 3.63 (t, J=6.4 Hz, 2H), 2.66 (t, J=6.8 Hz, 2H), 2.15 (m_c, 2H) ppm; ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 134.1, 131.9, 131.6, 127.7, 125.9 (q), 125.6, 122.1, 122.0, 94.4, 78.0, 32.4, 31.5, 18.5 ppm; ^{19}F NMR ($CDCl_3$, 282 MHz) δ −62.9 ppm; HRMS-EI: [M^+] calcd for $C_{12}H_{10}BrF_3$: 289.9918, found: 289.9934.

*4.3.6. 1-(5-Bromopent-1-ynyl)-2-methoxybenzene (**10g**)*

Following the general procedure for the Appel reaction alcohol **13g** (3.50 g, 19.9 mmol, 1.0 equiv), CBr_4 (7.89 g, 23.8 mmol, 1.2 equiv), and PPh_3 (6.24 g, 23.8 mmol, 1.2 equiv) furnished after silica gel flash chromatography using 10% EtOAc/hexanes as eluent the desired compound **10g** (4.63 g, 92%) as colorless oil. IR (neat) 3003, 2959, 2834, 1595, 1575, 1493, 1464, 1434, 1350, 1292, 1260, 1180, 1162, 1117, 1048, 1025, 850, 795, 754 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.37 (dd, J=7.2, 1.6 Hz, 1H), 7.25 (dt, J=8.1, 1.8 Hz, 1H), 6.88 (dt, J=7.5, 1.2 Hz, 1H), 6.85 (d, J=8.2 Hz, 1H), 3.87 (s, 3H), 2.66 (t, J=6.8 Hz, 2H), 2.16 (m_c, 2H) ppm; ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 160.2, 133.7, 129.4, 120.6, 112.9, 110.8, 92.4, 78.1, 56.0, 32.8, 31.9, 18.8 ppm; HRMS-EI: [M^+] calcd for $C_{12}H_{13}BrO$: 252.0150, found: 252.0153.

*4.3.7. N-(2-(5-Bromopent-1-ynyl)phenyl)acetamide (**10h**)*

Following the general procedure for the Appel reaction alcohol **13h** (2.80 g, 12.9 mmol, 1.0 equiv), CBr_4 (5.13 g, 15.5 mmol, 1.2 equiv), and PPh_3 (4.07 g, 15.5 mmol, 1.2 equiv) furnished after silica gel flash chromatography using 10% EtOAc/hexanes as eluent the desired compound **10h** (3.32 g, 92%) as white solid. Mp 63–65 °C; IR ($CHCl_3$) 3397, 3017, 2398, 1696, 1580, 1520, 1447, 1369, 1306, 1267, 668 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.37 (d, J=8.3 Hz, 1H), 7.89 (br s, 1H), 7.36 (dd, J=7.5, 1.4 Hz, 1H), 7.30 (m_c, 1H), 7.01 (dt, J=7.0, 0.8 Hz, 1H), 3.62 (t, J=6.4 Hz, 2H), 2.74 (t, J=6.7 Hz, 2H), 2.23 (s, 3H), 2.17 (m_c, 2H) ppm; ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 168.4, 139.2, 131.9, 129.4, 123.5, 119.4, 112.3, 95.3, 77.3, 32.6, 31.1, 25.2, 18.4 ppm; HRMS-EI: [M^+] calcd for $C_{13}H_{14}BrNO$: 279.0259, found: 279.0251.

*4.3.8. Ethyl 3-(5-bromopent-1-ynyl)benzoate (**10i**)*

Following the general procedure for the Appel reaction alcohol **13i** (4.50 g, 19.4 mmol, 1.0 equiv), CBr_4 (7.73 g, 23.3 mmol, 1.2 equiv), and PPh_3 (6.11 g, 23.3 mmol, 1.2 equiv) furnished after silica gel flash chromatography using 5% EtOAc/hexanes as eluent the desired compound **10i** (5.62 g, 98%) as colorless oil. IR (neat) 2978, 2232, 1718, 1576, 1430, 1367, 1296, 1227, 1167, 1105, 1081, 1026, 754, 684 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.06 (t, J=1.5 Hz, 1H), 7.95 (dt, J=8.0, 1.2 Hz, 1H), 7.56 (d, J=7.7 Hz, 1H), 7.36 (t, J=8.0 Hz, 1H), 4.38 (q, J=7.1 Hz, 2H), 3.59 (t, J=6.5 Hz, 2H), 2.63 (t, J=6.9 Hz, 2H), 2.15 (m_c, 2H), 1.40 (t, J=7.1 Hz, 3H) ppm; ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 166.1, 135.8, 132.8, 130.9, 129.0, 128.5, 124.1, 89.2, 80.9, 61.3, 32.6, 31.7, 18.3, 14.5 ppm; HRMS-EI: [M^+] calcd for $C_{14}H_{15}BrO_2$: 294.0255, found: 294.0260.

*4.3.9. 2-(5-Bromopent-1-ynyl)-1,3-dimethoxybenzene (**10j**)*

Following the general procedure for the Appel reaction alcohol **13j** (2.10 g, 9.53 mmol, 1.0 equiv), CBr_4 (3.78 g, 11.4 mmol, 1.2 equiv), and PPh_3 (2.99 g, 11.4 mmol, 1.2 equiv) furnished after silica gel flash chromatography using 10% EtOAc/hexanes as eluent the desired compound **10j** (2.64 g, 98%) as colorless oil. IR (neat) 3001, 1936, 1837, 1583, 1473, 1432, 1301, 1253, 1111, 1034, 776, 725, 658 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.19 (t, J=8.5 Hz, 1H), 6.52 (d, J=8.5 Hz, 2H), 3.87 (s, 6H), 3.69 (t, J=6.7 Hz, 2H), 2.72 (t, J=6.7 Hz, 2H), 2.17 (m_c, 2H) ppm; ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 161.6, 129.3, 103.7, 101.9, 96.9, 74.2, 56.3, 32.8, 32.0, 19.1 ppm; HRMS-EI: [M^+] calcd for $C_{13}H_{15}BrO_2$: 222.0255, found: 282.0258.

*4.3.10. 5-(5-Bromopent-1-ynyl)-1,2,3-trimethoxybenzene (**10k**)*

Following the general procedure for the Appel reaction alcohol **13k** (1.50 g, 5.99 mmol, 1.0 equiv), CBr_4 (2.38 g, 7.19 mmol, 1.2 equiv), and PPh_3 (1.89 g, 7.19 mmol, 1.2 equiv) furnished after silica gel flash chromatography using 10% EtOAc/hexanes as eluent the desired compound **10k** (1.76 g, 94%) as colorless oil. IR (neat) 2938, 2837, 1734, 1576, 1505, 1464, 1431, 1410, 1344, 1322, 1236, 1166, 1130, 1004, 832, 757, 733, 631 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.63 (s, 2H), 3.85 (s, 6H), 3.64 (m, 3H), 3.58 (t, J=6.6 Hz, 2H), 2.60 (t, J=6.8 Hz, 2H), 2.14 (m_c, 2H) ppm; ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 153.2, 138.7, 119.0, 109.0, 88.2, 81.7, 61.1, 56.3, 32.7, 31.8,

18.3 ppm; MS-EI *m/z*: 250 (M^+, 100), 235 (36%); HRMS-EI: [M^+] calcd for $C_{14}H_{17}BrO_3$: 312.0361, found: 312.0358.

*4.3.11. 1-(5-Bromopent-1-ynyl)naphthalene (**10l**)*

Following the general procedure for the Appel reaction alcohol **13l** (3.93 g, 18.7 mmol, 1.0 equiv), CBr_4 (7.44 g, 22.4 mmol, 1.2 equiv), and PPh_3 (5.89 g, 22.4 mmol, 1.2 equiv) furnished after silica gel flash chromatography using 2.5% EtOAc/hexanes as eluent the desired compound **10l** (4.75 g, 93%) as colorless oil. IR (neat) 3056, 2960, 2227, 1942, 1585, 1430, 1395, 1270, 1246, 799, 774 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.30 (m_c, 1H), 7.79 (dd, J=8.7, 8.1 Hz), 7.62 (d, J=7.1 Hz, 1H), 7.59–7.45 (m, 2H), 7.38 (t, J=7.2 Hz, 2H), 3.64 (t, J=6.4, 0.5 Hz, 2H), 2.76 (t, J=6.7 Hz, 2H), 2.21 (m_c, 2H) ppm; ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 133.7, 133.4, 130.5, 128.5, 126.9, 126.6, 126.4, 125.5, 121.5, 93.2, 80.0, 32.8, 31.9, 18.7 ppm; HRMS-EI: [M^+] calcd for $C_{15}H_{13}Br$: 272.0201, found: 272.0199.

*4.3.12. 3-(5-Bromopent-1-ynyl)-1-tosyl-1H-indole (**10m**)*

Following the general procedure for the Appel reaction alcohol **13m** (2.05 g, 5.80 mmol, 1.0 equiv), CBr_4 (2.31 g, 6.96 mmol, 1.2 equiv), and PPh_3 (1.83 g, 6.96 mmol, 1.2 equiv) furnished after silica gel flash chromatography using 10% EtOAc/hexanes as eluent the desired compound **10m** (2.31 g, 92%) as pale yellow solid. Mp 80–82 °C; IR ($CHCl_3$) 1448, 1374, 1277, 1188, 1176, 1129, 1103, 1089, 1019 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.99 (d, J=8.3 Hz, 1H), 7.77 (d, J=8.3 Hz, 2H), 7.68 (s, 1H), 7.60 (d, J=8.5 Hz, 1H), 7.39–7.25 (m, 2H), 7.20 (d, J=8.5 Hz, 2H), 3.61 (t, J=6.4 Hz, 2H), 2.68 (t, J=6.8 Hz, 2H), 2.32 (s, 3H), 2.16 (m_c, 2H) ppm; ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 145.5, 135.2, 134.4, 131.2, 130.2, 128.6, 127.1, 125.6, 123.9, 120.6, 113.8, 105.7, 92.6, 72.6, 32.6, 31.7, 21.8, 18.6 ppm; HRMS-EI: [M^+] calcd for $C_{20}H_{18}BrNO_2S$: 415.0241, found: 415.0253.

*4.3.13. 3-(5-Bromopent-1-ynyl)-1-tosyl-1H-pyrazole (**10n**)*

Following the general procedure for the Appel reaction alcohol **13n** (1.50 g, 4.93 mmol, 1.0 equiv), CBr_4 (1.96 g, 5.91 mmol, 1.2 equiv), and PPh_3 (1.55 g, 5.91 mmol, 1.2 equiv) furnished after silica gel flash chromatography using 10% EtOAc/hexanes as eluent the desired compound **10n** (1.68 g, 93%) as pale yellow solid. Mp 95–97 °C; IR ($CHCl_3$) 3017, 2245, 1596, 1517, 1437, 1387, 1305, 1191, 1178, 1136, 1028 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.04 (d, J=2.5 Hz, 1H), 7.90 (dt, J=7.7, 2.0 Hz, 2H), 7.33 (d, J=8.1 Hz, 2H), 6.39 (d, J=3.0 Hz, 1H), 3.52 (t, J=6.4 Hz, 2H), 2.58 (t, J=6.9 Hz, 2H), 2.42 (s, 3H), 2.10 (m_c, 2H) ppm; ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 146.3, 141.1, 133.9, 131.7, 130.3, 128.5, 112.2, 92.0, 73.4, 32.4, 22.0, 18.3 ppm; HRMS-EI: [M^+] $C_{15}H_{15}BrN_2O_2S$: 366.0038, found: 366.0035.

4.4. General procedure for the domino reaction of 1-(2-iodophenyl)-1-*H*-pyrrole 9 and bromoalkyl-aryl alkynes 10a–n

A 10 mL sealable tube was charged with 1-(2-iodophenyl)-1*H*-pyrrole **9** (215 mg, 0.80 mmol, 2.0 equiv), bromoalkyl-aryl alkynes **10a–n** (0.40 mmol, 1.0 equiv), norbornene (37.7 mg, 0.40 mmol, 1.0 equiv), Cs_2CO_3 (391 mg, 1.20 mmol, 3.0 equiv), $PdCl_2$ (3.5 mg, 0.020 mmol, 5 mol%), tri-2-furylphosphine (9.3 mg, 0.040 mmol, 10 mol%), and CH_3CN (4 mL). The mixture was stirred at 25 °C for 10 min while being purged with argon. Afterwards, the tube was sealed and submitted to a pre-heated oil bath (90 °C) for 24 h. The reaction mixture was treated with H_2O (50 mL) and the resulting mixture was extracted with CH_2Cl_2 (3×30 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography and concentration of the appropriate fractions in vacuo afforded the desired compounds **8a–n**.

*4.4.1. 7-Phenyl-5,6-dihydro-4H-benzo[de]pyrrolo[1,2-a]-quinoline (**8a**)*

Following the general procedure for the domino reaction 1-(2-iodophenyl)-1*H*-pyrrole **9** (215 mg, 0.80 mmol, 2.0 equiv) and bromoalkyl-aryl alkyne **10a** (113 mg, 0.40 mmol) furnished after silica gel flash chromatography using 5% NEt_3/hexanes the desired tetracycle **8a** (102 mg, 80%) as yellow oil. IR ($CHCl_3$) 3051, 2928, 2860, 2826, 1589, 1494, 1467, 1439, 1358, 1334, 1310, 1252, 1167, 1072, 1049, 1028, 814, 787, 756, 702 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 7.18 (dd, J=2.8, 1.6 Hz, 1H), 6.97 (dd, J=8.4, 0.8 Hz, 1H), 6.93 (dd, J=8.4, 1.6 Hz, 2H), 6.87–6.68 (m, 4H), 6.46 (dq, J=7.6, 0.8 Hz, 1H), 6.30 (dd, J=3.6, 2.8 Hz, 1H), 5.86 (dd, J=4.0, 1.6 Hz, 1H), 2.24 (t, J=6.4 Hz, 2H), 2.09 (t, J=6.0 Hz, 2H), 1.13 (m_c, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.5, 138.4, 133.4, 130.0, 128.5, 128.4, 128.3, 128.0, 127.8, 127.5, 127.0, 123.1, 122.7, 121.6, 113.0, 112.9, 111.9, 103.0, 31.3, 28.2, 23.2 ppm; HRMS-EI: [M^+] calcd for $C_{21}H_{17}N$: 283.1361, found: 283.1358.

*4.4.2. 7-(4-Methylphenyl)-5,6-dihydro-4H-benzo[de]pyrrolo-[1,2-a]quinoline (**8b**)*

Following the general procedure for the domino reaction 1-(2-iodophenyl)-1*H*-pyrrole **9** (215 mg, 0.80 mmol, 2.0 equiv) and bromoalkyl-aryl alkyne **10b** (95 mg, 0.40 mmol) furnished after silica gel flash chromatography using 1% EtOAc/hexanes the desired tetracycle **8b** (101 mg, 85%) as slightly yellow foam. IR ($CHCl_3$) 3018, 2940, 1399, 1728, 1591, 1512, 1473, 1359, 1313, 1052, 928 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 7.63 (dd, J=2.9, 1.4 Hz, 1H), 7.43 (d, J=7.8 Hz, 1H), 7.30 (dt, J=8.4, 0.8 Hz, 2H), 7.12 (dd, J=7.8, 6.5 Hz, 3H), 6.91 (dd, J=7.4, 0.8 Hz, 1H), 6.75 (dd, J=3.8, 2.9 Hz, 1H), 6.37 (dd, J=3.8, 1.4 Hz, 1H), 2.70 (t, J=6.0 Hz, 2H), 2.59 (t, J=6.0 Hz, 2H), 2.21 (s, 3H), 1.60 (m_c, 2H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 138.4, 136.9, 135.5, 133.3, 132.7, 129.9, 129.2, 126.8, 123.1, 122.7, 121.7, 112.9, 112.1, 111.9, 109.7, 103.1, 31.3, 28.2, 23.2, 21.1 ppm; HRMS-EI: [M^+] calcd for $C_{22}H_{19}N$: 297.1518, found: 297.1515.

*4.4.3. 7-(4-Nitrophenyl)-5,6-dihydro-4H-benzo[de]pyrrolo-[1,2-a]quinoline (**8c**)*

Following the general procedure for the domino reaction 1-(2-iodophenyl)-1*H*-pyrrole **9** (215 mg, 0.80 mmol, 2.0 equiv) and bromoalkyl-aryl alkyne **10c** (107 mg, 0.40 mmol) furnished after silica gel flash chromatography using 2% EtOAc/hexanes the desired tetracycle **8c** (95 mg, 72%) as orange foam. IR ($CHCl_3$) 3018, 1945, 2399, 1599, 1520, 1466, 1430, 1348, 1107, 1067, 1016, 928, 853 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 8.35 (dt, J=8.5, 2.1 Hz, 2H), 7.85 (dd, J=3.6, 1.6 Hz, 1H), 7.76 (d, J=8.2 Hz, 1H), 7.60 (dt, J=8.9, 2.1 Hz, 2H), 7.45 (t, J=8.1 Hz, 1H), 7.15 (dd, J=7.1, 1.0 Hz, 1H), 6.70 (dd, J=3.8, 1.4 Hz, 1H), 5.94 (dd, J=3.8, 1.3 Hz, 2H), 3.64 (t, J=6.0 Hz, 2H), 2.68 (t, J=6.0 Hz, 2H), 1.93 (m_c, 2H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 147.5, 145.3, 139.0, 133.4, 131.3, 131.1, 127.9, 126.1, 124.0, 123.8, 121.0, 113.0, 112.4, 112.3, 102.3, 31.3, 28.3, 23.2 ppm; HRMS-EI: [M^+] calcd for $C_{21}H_{16}N_2O_2$: 328.1212, found: 328.1197.

*4.4.4. 7-(2-Nitrophenyl)-5,6-dihydro-4H-benzo[de]pyrrolo-[1,2-a]quinoline (**8d**)*

Following the general procedure for the domino reaction 1-(2-iodophenyl)-1*H*-pyrrole **9** (215 mg, 0.80 mmol, 2.0 equiv) and bromoalkyl-aryl alkyne **10d** (107 mg, 0.40 mmol) furnished after silica gel flash chromatography using 2% EtOAc/hexanes the desired tetracycle **8d** (106 mg, 71%) as orange solid. Mp 185–187 °C; IR ($CHCl_3$) 3018, 2399, 1608, 1528, 1426, 1353, 1045, 929 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 8.10 (dd, J=8.2, 1.4 Hz, 1H), 7.81 (dd, J=2.8, 1.6 Hz, 1H), 7.78–7.67 (m, 2H), 7.59 (m_c, 1H), 7.50–7.38 (m, 2H), 7.13 (m_c, 1H), 6.65 (dd, J=3.7, 3.0 Hz, 1H), 5.80 (dd, J=3.5, 1.4 Hz, 1H), 3.02 (t, J=6.1 Hz, 2H), 2.58 (t, J=6.1 Hz, 2H), 1.93 (m_c, 2H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 149.5, 138.5, 133.1, 133.1, 132.7, 132.6, 130.9, 128.8, 127.4, 124.4, 124.0, 123.6, 123.3, 120.8, 112.6, 112.1,

112.0, 101.2, 31.0, 27.8, 22.8 ppm; HRMS-EI: [M^+] calcd for $C_{21}H_{16}N_2O_2$: 328.1212, found: 328.1205.

4.4.5. 7-(2-Chlorophenyl)-5,6-dihydro-4H-benzo[de]pyrrolo-[1,2-a]quinoline (**8e**)

Following the general procedure for the domino reaction 1-(2-iodophenyl)-1*H*-pyrrole **9** (215 mg, 0.80 mmol, 2.0 equiv) and bromoalkyl-aryl alkyne **10e** (103 mg, 0.40 mmol) furnished after silica gel flash chromatography using 5% NEt_3/hexanes the desired tetracycle **8e** (92 mg, 72%) as yellow foam. IR ($CHCl_3$) 2935, 2860, 1650, 1589, 1551, 1538, 1483, 1433, 1354, 1310, 1252, 1215, 1174, 1123, 1066, 1028, 790, 767, 750, 685 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 7.53 (dd, J=2.8, 1.2 Hz, 1H), 7.33 (d, J=8.0 Hz, 1H), 7.29 (dd, J=7.6, 0.8 Hz, 1H), 7.13–7.05 (m, 2H), 6.82–6.96 (m, 3H), 6.65 (dd, J=3.6, 2.8 Hz, 1H), 6.06 (dd, J=4.0, 1.6 Hz, 1H), 2.62 (t, J=6.4 Hz, 2H), 2.56 (ddd, J=16.0, 7.6, 4.4 Hz, 1H), 2.36 (ddd, J=16.0, 7.6, 4.4 Hz, 1H), 1.58 (m_c, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.5, 131.7, 129.8, 129.0, 128.0, 127.7, 127.2, 126.9, 125.7, 124.0, 123.2, 121.2, 113.0, 112.2, 112.1, 102.4, 31.1, 27.8, 23.0 ppm; HRMS-EI: [M^+] calcd for $C_{21}H_{16}ClN$: 317.0971, found: 317.0975.

4.4.6. 7-(2-(Trifluoromethyl)phenyl)-5,6-dihydro-4H-benzo[de]pyrrolo[1,2-a]quinoline (**8f**)

Following the general procedure for the domino reaction 1-(2-iodophenyl)-1*H*-pyrrole **9** (215 mg, 0.80 mmol, 2.0 equiv) and bromoalkyl-aryl alkyne **10f** (116 mg, 0.40 mmol) furnished after silica gel flash chromatography using 5% NEt_3/hexanes the desired tetracycle **8f** (72 mg, 51%) as white solid. Mp 172–174 °C; IR ($CHCl_3$) 3413, 2928, 1650, 1463, 1422, 1258, 1314, 1263, 1212, 1174, 1161, 1120, 1103, 1066, 1032, 780, 770, 746, 682 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 7.18 (d, J=8.0 Hz, 1H), 7.14 (dd, J=2.9, 1.4 Hz, 1H), 6.95 (d, J=8.2 Hz, 1H), 6.72–6.55 (m, 4H), 6.47 (dd, J=7.2, 1.2 Hz, 1H), 6.27 (dd, J=3.7, 2.9 Hz, 1H), 5.54 (dd, J=3.7, 1.4 Hz, 1H), 2.25 (t, J=6.0 Hz, 2H), 2.09 (ddd, J=16.0, 7.8, 4.1 Hz, 1H), 2.86 (ddd, J=16.0, 7.6, 4.1 Hz, 1H), 1.26–1.12 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.5, 133.6, 132.2, 132.0, 128.1, 128.0, 127.8, 127.34, 127.32, 125.7, 124.0, 123.3, 121.1, 113.0, 112.9, 112.2, 111.9, 111.8, 102.9, 102.8, 31.1, 28.2, 22.9 ppm; HRMS-EI: [M^+] calcd for $C_{22}H_{16}F_3O_3$: 351.1235, found: 351.1237.

4.4.7. 7-(2-Methoxyphenyl)-5,6-dihydro-4H-benzo[de]pyrrolo-[1,2-a]quinoline (**8g**)

Following the general procedure for the domino reaction 1-(2-iodophenyl)-1*H*-pyrrole **9** (215 mg, 0.80 mmol, 2.0 equiv) and bromoalkyl-aryl alkyne **10g** (101 mg, 0.40 mmol) furnished after silica gel flash chromatography using 5% NEt_3/hexanes the desired tetracycle **8g** (113 mg, 90%) as slightly yellow foam. IR ($CHCl_3$) 3018, 2940, 2836, 2400, 1591, 1494, 1467, 1435, 1361, 1244, 1114, 1048, 1026 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 7.60 (dd, J=2.8, 1.5 Hz, 1H), 7.40 (d, J=8.3 Hz, 1H), 7.24 (m_c, 1H), 7.12 (d, J=7.6 Hz, 1H), 6.98 (dt, J=7.6, 1.2 Hz, 1H), 7.36 (dd, J=7.83, 1.7 Hz, 1H), 7.24 (m_c, 1H), 6.89 (m_c, 1H), 6.76–6.64 (m, 2H), 6.28 (dd, J=3.5, 1.2 Hz, 1H), 3.18 (s, 3H), 2.77–2.54 (m, 4H), 1.77–1.58 (m, 2H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 157.8, 138.3, 133.5, 132.6, 131.6, 129.2, 127.3, 126.9, 125.2, 140.0, 123.1, 121.7, 120.9, 112.9, 112.2, 111.8, 111.5, 102.5, 55.1, 31.4, 28.1, 23.2 ppm; HRMS-EI: [M^+] calcd for $C_{22}H_{19}NO$: 313.1467, found: 313.1467.

4.4.8. N-(2-(5,6-Dihydro-4H-benzo[de]pyrrolo[1,2-a]quinolin-7-yl)phenyl)acetamide (**8h**)

Following the general procedure for the domino reaction 1-(2-iodophenyl)-1*H*-pyrrole **9** (215 mg, 0.80 mmol, 2.0 equiv) and bromoalkyl-aryl alkyne **10h** (112 mg, 0.40 mmol) furnished after silica gel flash chromatography using 10% EtOAc+5% NEt_3/hexanes the desired tetracycle **8h** (34 mg, 25%) as yellow foam. IR ($CHCl_3$) 3399, 3311, 2997, 2935, 2867, 1677, 1575, 1514, 1477, 1463, 1443, 1358, 1300, 1242, 1212, 1171, 1038, 1008, 957, 777, 746, 695 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 7.52 (dd, J=2.9, 1.4 Hz, 1H), 7.32 (d, J=8.4 Hz, 1H), 7.24 (t, J=7.8 Hz, 1H), 7.15–7.05 (m, 2H), 7.00–6.94 (m, 2H), 6.82 (dd, J=7.6, 0.4 Hz, 1H), 6.62 (t, J=2.8 Hz, 1H), 6.12 (dd, J=4.0, 1.2 Hz, 1H), 2.58 (t, J=5.6 Hz, 2H), 2.36 (t, J=6.4 Hz, 2H), 1.48 (m_c, 2H), 1.14 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.7, 138.7, 136.9, 130.3, 129.1, 127.8, 127.7, 126.8, 125.1, 124.7, 123.9, 123.6, 123.5, 121.4, 121.2, 121.0, 113.4, 112.6, 112.2, 103.0, 31.1, 27.8, 23.1 ppm; HRMS-EI: [M^+] calcd for $C_{23}H_{20}O_2N$: 340.1576, found: 340.1584.

4.4.9. Ethyl 3-(5,6-dihydro-4H-benzo[de]pyrrolo[1,2-a]quinolin-7-yl)benzoate (**8i**)

Following the general procedure for the domino reaction 1-(2-iodophenyl)-1*H*-pyrrole **9** (215 mg, 0.80 mmol, 2.0 equiv) and bromoalkyl-aryl alkyne **10i** (118 mg, 0.40 mmol) furnished after silica gel flash chromatography using 5% NEt_3/hexanes the desired tetracycle **8i** (85 mg, 60%) as white foam. IR ($CHCl_3$) 3420, 2976, 2928, 1721, 1602, 1589, 1480, 1463, 1436, 1365, 2190, 1256, 1212, 1164, 1106, 1076, 783, 746, 692 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 8.35 (t, J=1.2 Hz, 1H), 8.21 (dt, J=8.0, 1.2 Hz, 1H), 7.56 (dd, J=2.8, 1.6 Hz, 1H), 7.36 (m_c, 2H), 7.18–7.08 (m, 2H), 6.85 (dd, J=7.6, 0.8 Hz, 1H), 6.67 (dd, J=3.6, 2.8 Hz, 1H), 6.15 (dd, J=4.0, 1.6 Hz, 1H), 4.10 (q, J=7.2 Hz, 2H), 2.60 (t, J=5.2 Hz, 2H), 2.39 (t, J=5.2 Hz, 2H), 1.47 (m_c, 2H), 0.96 (t, J=4.0 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1, 138.8, 138.5, 134.2, 131.5, 131.2, 128.9, 128.7, 128.0, 127.8, 127.4, 127.1, 123.2, 123.1, 121.4, 113.1, 112.1, 102.9, 60.8, 31.2, 28.1, 23.1, 14.1 ppm; HRMS-EI: [M^+] $C_{24}H_{21}O_2N$: 355.1572, found: 355.156733.

4.4.10. 7-(2,6-Dimethoxyphenyl)-5,6-dihydro-4H-benzo[de]pyrrolo[1,2-a]quinoline (**8j**)

Following the general procedure for the domino reaction 1-(2-iodophenyl)-1*H*-pyrrole **9** (215 mg, 0.80 mmol, 2.0 equiv) and bromoalkyl-aryl alkyne **10j** (113 mg, 0.40 mmol) furnished after silica gel flash chromatography using 5% EtOAc/hexanes the desired tetracycle **8j** (65 mg, 47%) as slightly yellow foam. IR ($CHCl_3$) 3018, 2340, 1588, 1523, 1471, 1432, 1112, 1045, 929 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 7.57 (m_c, 1H), 7.37 (d, J=8.4 Hz, 1H), 7.24 (t, J=8.4 Hz, 1H), 7.08 (t, J=7.9 Hz, 1H), 6.86 (d, J=7.4 Hz, 1H), 6.74 (t, J=3.0 Hz, 1H), 6.48 (d, J=8.2 Hz, 2H), 6.29 (m_c, 1H), 3.24 (s, 6H), 2.77 (t, J=6.2 Hz, 2H), 2.71 (t, J=6.2 Hz, 2H), 1.74 (m_c, 1H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 158.9, 138.0, 133.5, 132.3, 129.3, 128.2, 127.9, 127.6, 126.6, 124.5, 122.8, 121.9, 121.8, 115.6, 112.7, 112.1, 111.3, 104.4, 101.5, 55.3, 31.3, 28.0, 23.2 ppm; HRMS-ESI: [M^+] calcd for $C_{23}H_{21}NO_2+H^+$: 344.1645, found: 344.1659.

4.4.11. 7-(3,4,5-Trimethoxyphenyl)-5,6-dihydro-4H-benzo[de]pyrrolo[1,2-a]quinoline (**8k**)

Following the general procedure for the domino reaction 1-(2-iodophenyl)-1*H*-pyrrole **9** (215 mg, 0.80 mmol, 2.0 equiv) and bromoalkyl-aryl alkyne **10k** (125 mg, 0.40 mmol) furnished after silica gel flash chromatography using 5% EtOAc/hexanes the desired tetracycle **8k** (130 mg, 87%) as slightly yellow foam. IR ($CHCl_3$) 3684, 3017, 2940, 2399, 1727, 1583, 1505, 1475, 1464, 1411, 1345, 1128, 1001, 928 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 7.68 (dd, J=3.0, 1.5 Hz, 1H), 7.48 (dd, J=7.4, 1.5 Hz, 1H), 7.21–7.14 (m, 1H), 6.95 (m_c, 1H), 6.82–6.78 (m, 1H), 6.60 (s, 2H), 7.37 (d, J=8.4 Hz, 1H), 7.24 (t, J=8.4 Hz, 1H), 7.08 (t, J=7.9 Hz, 1H), 6.86 (d, J=7.4 Hz, 1H), 6.74 (dd, J=3.8, 1.5 Hz, 1H), 2.76 (t, J=6.3 Hz, 2H), 2.65 (t, J=6.3 Hz, 2H), 1.72–1.62 (m, 2H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 154.1, 138.6, 138.5, 133.6, 133.3, 132.5, 128.7, 127.0, 123.3, 122.7, 121.6, 113.0, 112.2, 112.0, 107.4, 103.2, 60.5, 55.7, 31.3, 28.4, 23.3 ppm; HRMS-ESI: [M^+] calcd for $C_{24}H_{23}NO_3+H^+$: 374.1750, found: 374.1767.

4.4.12. 7-(Naphthalen-1-yl)-5,6-dihydro-4H-benzo[de]pyrrolo-[1,2-a]quinoline (**8l**)

Following the general procedure for the domino reaction 1-(2-iodophenyl)-1*H*-pyrrole **9** (215 mg, 0.80 mmol, 2.0 equiv) and

bromoalkyl-aryl alkyne **10l** (109 mg, 0.40 mmol) furnished after silica gel flash chromatography using 1% EtOAc/hexanes the desired tetracycle **8l** (89 mg, 67%) as slightly yellow foam. IR ($CHCl_3$) 3018, 2399, 1594, 1519, 1476, 1427, 1360, 1046, 929 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 7.52 (dd, J=2.9, 1.4 Hz, 1H), 7.32 (d, J=8.4 Hz, 1H), 7.24 (t, J=7.8 Hz, 1H), 7.15–7.05 (m, 2H), 7.00–6.94 (m, 2H), 6.82 (dd, J=7.6, 0.4 Hz, 1H), 6.62 (t, J=2.8 Hz, 1H), 6.12 (dd, J=4.0, 1.2 Hz, 1H), 2.58 (t, J=5.6 Hz, 2H), 2.36 (t, J=6.4 Hz, 2H), 1.48 (m_c, 2H), 1.14 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.5, 136.1, 134.3, 133.6, 132.7, 132.4, 128.5, 128.1, 127.1, 126.6, 126.4, 126.2, 126.1, 125.8, 124.3, 123.2, 121.5, 113.1, 112.2, 111.8, 103.2, 31.2, 28.0, 23.0 ppm; HRMS-EI: [M^+] calcd for $C_{25}H_{19}N$: 333.1518, found: 333.1519.

4.4.13. *7-(1-Tosyl-1H-indol-3-yl)-5,6-dihydro-4H-benzo[de]pyrrolo[1,2-a]quinoline (**8m**)*

Following the general procedure for the domino reaction 1-(2-iodophenyl)-1*H*-pyrrole **9** (215 mg, 0.80 mmol, 2.0 equiv) and bromoalkyl-aryl alkyne **10m** (167 mg, 0.40 mmol) furnished after silica gel flash chromatography using 5% EtOAc/hexanes the desired tetracycle **8m** (134 mg, 75%) as slightly yellow foam. IR ($CHCl_3$) 3685, 3018, 2940, 2400, 1728, 1597, 1475, 1446, 1428, 1372, 1256, 1174, 1128, 987, 931 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 8.24 (d, J=7.2 Hz, 1H), 7.68 (t, J=4.0 Hz, 3H), 7.58 (dd, J=3.0, 1.4 Hz, 1H), 7.40 (d, J=7.5 Hz, 1H), 7.18–7.08 (m, 3H), 6.96–6.85 (m, 2H), 6.64 (dd, J=3.6, 3.0 Hz, 1H), 6.51 (dd, J=8.8, 0.6 Hz, 2H), 6.05 (dd, J=3.8, 1.4 Hz, 1H), 2.65 (t, J=6.3 Hz, 2H), 2.48–2.22 (m, 2H), 1.65 (s, 3H), 1.58–1.37 (m, 2H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 144.5, 141.3, 138.6, 135.8, 133.5, 131.9, 131.1, 129.7, 127.4, 126.8, 126.0, 125.3, 125.0, 123.7, 123.3, 121.3, 120.0, 118.9, 114.3, 112.9, 112.2, 112.0, 102.8, 31.2, 28.2, 23.1, 20.9 ppm; HRMS-ESI: [M^+] calcd for $C_{30}H_{24}N_2O_2S$: 476.1559, found: 476.1578.

4.4.14. *7-(1-Tosyl-1H-pyrazol-3-yl)-5,6-dihydro-4H-benzo[de]pyrrolo[1,2-a]quinoline (**8n**)*

Following the general procedure for the domino reaction 1-(2-iodophenyl)-1*H*-pyrrole **9** (215 mg, 0.80 mmol, 2.0 equiv) and bromoalkyl-aryl alkyne **10n** (147 mg, 0.40 mmol) furnished after silica gel flash chromatography using 5% EtOAc/hexanes the desired tetracycle **8n** (26 mg, 15%) as slightly yellow solid. IR ($CHCl_3$) 2399, 1718, 1559, 1506, 1473, 1379, 1176, 1032, 928 cm^{-1}; ^1H NMR (300 MHz, CD_2Cl_2) δ 8.22 (d, J=2.4 Hz, 1H), 7.92 (dt, J=8.5, 1.9 Hz, 2H), 7.79 (dd, J=3.0, 1.4 Hz, 2H), 7.72 (d, J=8.0 Hz, 1H), 7.45–7.34 (m, 3H), 7.12 (m_c, 1H), 6.66–6.61 (m, 2H), 6.05 (dd, J=3.8, 1.3 Hz, 1H), 2.99 (t, J=6.2 Hz, 1H), 2.73 (t, J=6.2 Hz, 2H), 2.43 (s, 3H), 1.84 (m_c, 2H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 154.1, 146.3, 139.3, 134.3, 133.3, 131.9, 130.1, 128.2, 128.0, 126.2, 125.5, 123.5, 123.5, 120.7, 118.5, 112.6, 112.1, 112.0, 110.9, 102.0, 31.1, 28.2, 23.1, 21.6 ppm; HRMS-ESI: [M^+] calcd for $C_{25}H_{21}N_3O_2S$: 427.1354, found: 427.1341.

Acknowledgements

We gratefully acknowledge the financial support of the Natural Sciences and Engineering Research Council (NSERC) of Canada, the Merck Frosst Centre for Therapeutic Research for an Industrial Research Chair, and the University of Toronto. K.M.G. thanks the Deutsche Forschungsgemeinschaft (DFG) for a postdoctoral scholarship. We thank Brian Mariampillai, Frederic Menard, and Dr. David Hulcoop for helpful discussions, and Dr. A. Lough for X-ray analysis.

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15. CCDC-672235 **8d** and CCDC-672236 **8n** contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
16. The existence of cyclobutene **F** as intermediate, which re-enters the catalytic cycle via C–C bond activation is possible but unlikely. Cyclobutenes are often observed as byproducts within Catellani-type reactions, which means that they are stable under the applied reaction conditions.
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