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28 April 2024

Synthesis of 1,2,3-substituted pyrroles from propargylamines via a one-pot tandem enyne cross metathesis – cyclization reaction.

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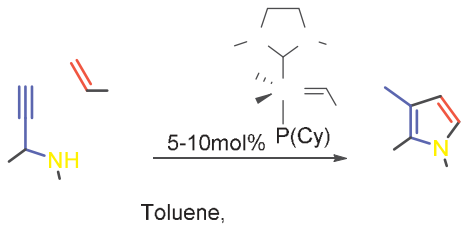
ABSTRACT:



Enyne cross metathesis of propargylamines with ethyl-vinyl ether enables the one-pot synthesis of substituted pyrroles. A series of substituted pyrroles, bearing alkyl, aryl and heteroaryl substituents, has been synthesised in good yields under microwave irradiation. The reactions are rapid and procedurally simple and also represent a facile entry to the synthetically challenging 1,2,3-substituted pyrroles. The value of the methodology is further corroborated by the conversion of pyrroles into 3-methyl-pyrrolines and the derivatization of the 3-methyl-substituent arising from the metathesis reaction.

The occurrence of the pyrrole nucleus in many natural and synthetic biologically active compounds represents an incentive toward the development of new synthetic methodologies towards this important heterocycle.[1] Metathesis reactions have been established as a powerful and effective method for the construction of many functionalized heterocycles from acyclic unsaturated precursors.[1b] Pioneering approaches to the synthesis of substituted pyrroles through ring closing metathesis (RCM) were reported by Donohoe[2] and Rutjes.[3] These works are based on the olefin RCM synthesis of 3-pyrrolines starting from appropriate allylamines, followed by an elimination step catalysed by acids. An evolution of this approach has been the development of one-pot RCM-aromatization sequences using $RuCl_3$,[4] Pd/C,[5a] $FeCl_3$[5b] or ^{t}BuOOH[6] to promote the dehydrogenative step. More recently, Donohoe[7] and Grela[8] described an olefin cross-metathesis (CM) approach for the synthesis of pyrroles. The alkyne-alkene (enyne) metathesis reaction offers advantages over the olefin version in terms of atom economy and it has found large application in the synthesis of heterocyclic compounds as well.[9-10] However, to the best of our knowledge only one paper by Stevens and coworkers[11] describes the synthesis of pyrroles via a ring-closing enyne metahesis-aromatization sequence, whilst no examples to access pyrroles via the enyne CM have been reported so far. Herein, we describe the first approach to substituted pyrroles through a one-pot tandem enyne CM cyclization reaction starting from appropriate propargylamines and the cheap ethyl vinyl ether (EVE) (Figure 1). In our early work, we demonstrated that EVE can be used as the olefin synthetic equivalent of the acetaldehyde in enyne CM reactions, leading to the formation of crotonaldehydes when reacted with terminal alkynes in the presence of the weak Lewis acid $CuSO_4$.[12] Herein, we demonstrate that an analogous strategy is applicable to the synthesis of pyrroles when propargylamines are used as substrates. Moreover, our CM-cyclization protocol offers an easy approach to the synthetically challenging pyrroles **3** unsubstituted at positions C4 and C5. Only few examples for the synthesis of 4,5-

unsubstituted pyrroles have been reported so far, most of them relying on multistep synthetic sequences.[13]

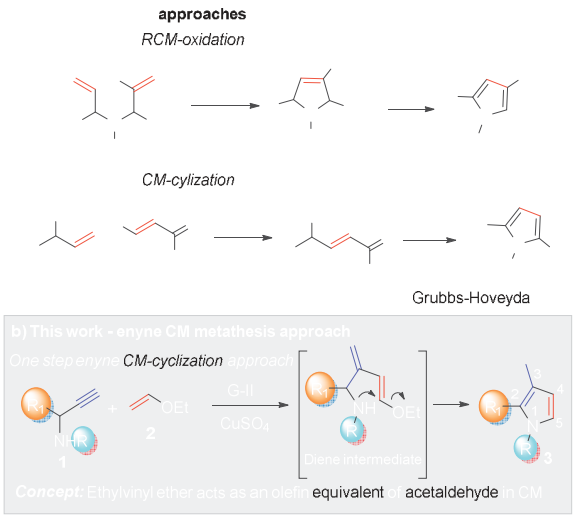
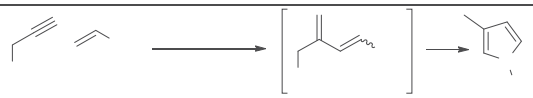


Figure 1. Examples of pyrrole syntheses and the one-pot tandem enyne cross metathesis-cyclization reaction

Our initial studies focused on the identification of the best reaction conditions (Table 1). The Boc-protected propargyl amine **4a** was first reacted with EVE in the presence of Grubbs'catalyst G-II under microwave irradiation according to our previous method.[12] When the reaction was carried out at 80 °C in an aqueous solution the desired pyrrole **6a** was obtained in 25-29% yield (*entries 1-2*), while a slightly higher amount (36%, *entry 3*) was isolated when the reaction was run in degassed toluene. The use of a higher catalysts loading (*entry 2*) did not lead to any improvement of the yield. Increasing the temperature to 120 °C and the reaction time to 30 min proved to be beneficial and the yield rose up to 56% (*entry 4*). When the reaction was performed under the same conditions and without $CuSO_4$ the pyrrole **6a** was not detected and the corresponding diene **5** was recovered in 41% yield (*entry 5*).On the other hand the use of a stoichiometric amount of $CuSO_4$ led to **6a** in only 18% yield

(*entry 6*). It is noteworthy that heating the diene intermediate **5** in refluxing toluene led to pyrrole **6a** in 24h, while in the presence of $CuSO_4$ the reaction was completed in 6h. We hypothesise that $CuSO_4$ plays a crucial role in increasing the rate of the cyclization reaction presumably by coordinating the ethoxy group.[14]

Table 1. Optimization of the reaction conditions



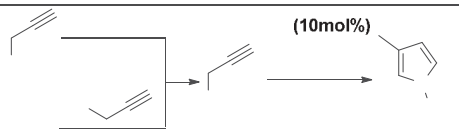
Entry	Solvent	G-II mol%	$CuSO_4$	T°C/ Time	Yield %[a]
1	H_2O/ ^tBuOH	5	2 eq.	80°C/ 20min	29%
2	H_2O/ ^tBuOH	10	2 eq.	80°C/ 20min	25%
3	Toluene	5	2 eq.	80°C/ 30min	36%
4	**Toluene**	**5**	**2 eq.**	**120°C/ 30min**	**56%**
5	Toluene	5	-	120°C/ 30min	0%[b]
6	Toluene	5	1 eq.	120°C/ 30min	18%
7	Toluene	10	2 eq.	120°C/ 30min	55%
8	**Toluene**	**5**	**-** [c]	**120°C/ 30min**	**56%**

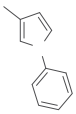
[a]Isolated yields. [b]41% diene **5** isolated. [c]2eq of $Cu(OTf)_2$ were used.

No significant differences were observed when the reaction was carried out with 5mol% or 10mol% catalysts loading (*entries 4 and 7*). Finally, the use of a different copper source, the

stronger Lewis acid $Cu(OTf)_2$, did not lead to any improvement in the yield of the reaction (*entry 8*). The influence of different amine group substituents on the outcome of the reaction was then explored. A set of propargylamines **4b-e** was synthesised according to Table 2.The treatment of the tosyl derivative **4b** with 10mol% of G-II led to desired **6b** in 53% yield, while a lower amount of **6b** (25%) was recovered when 5mol% of catalyst was used (*entry 1*). The benzoyl compound **4d** afforded the pyrrole **6d** in moderate yield (*entry 3*). On the other hand, the propargylaniline **4c** afforded the phenylpyrrole **6c** in good yield (*entry 2*), while the benzyl-derivative **4e** was recovered unreacted from the reaction mixture and no pyrrole **6e** was observed (*entry 4*).

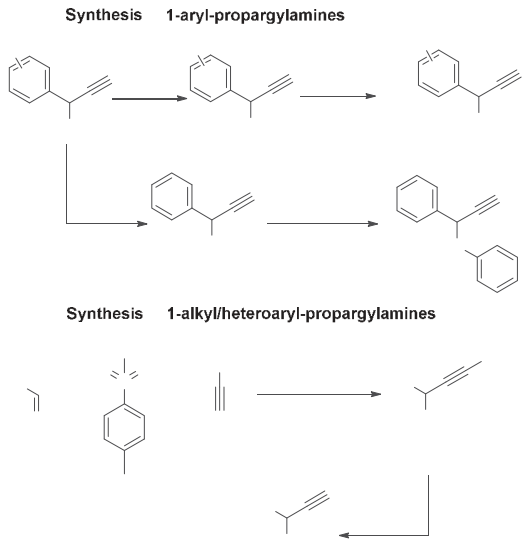
Table 2. Synthesis of pyrroles **6b-e**



Entry	Substrate	Pyrrole	Yield %[a]	Additive
1			53%	-
2			54%	-
3			39%	-
4			NO[b]	$TsOH{\cdot}H_2O$ (1.2 eq)

[a]Isolated yields were reported. [b] Product **6e** was not observed

It is reported that, contrary to the electron poorer anilines and tertiary hindered amines, the aliphatic primary and secondary amines poison the Ru-catalysts thus preventing the metathesis reactions.[15] The addition of a Brønsted acid to secondary amines makes the lone pair unable to bind the ruthenium, allowing the metathesis reaction to occur.[16] Amine **4e** was treated with a stoichiometric amount of *p*-toluensulphonic acid (PTSA) and then reacted with EVE under standard conditions. No pyrrole was observed and a mixture of side products was recovered. The possibility to synthesise 1,2,3-trisubstituted pyrroles starting from the appropriate 1-substituted propargylamines and using this tandem metathesis-cyclization protocol was explored. A first batch of aryl-propargylacetamides **8a-e** was synthesised in high yields from the appropriate propargylic alcohols (Scheme 1, Path a).[17]

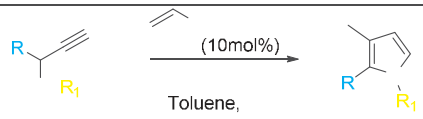


Scheme 1. Synthesis of propargylamine substrates

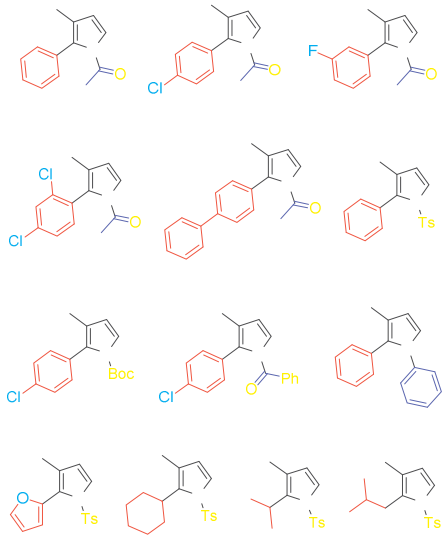
Hydrolysis of **8a-b** followed by Boc-, Bz and Ts-protections led to substrates **8f-h**. Propargyl alcohol **7** was acetylated to give **9** and in turn converted into the phenyl substrate **10** through a copper mediated amination reaction.[18] (Scheme 1, Path a). A multicomponent strategy[19] was used for the synthesis of aliphatic and heteroaryl derivatives **15a-d**. The appropriate aldehydes **11a-d** were refluxed in toluene in the presence of *p*-toluensulphonamide **12**, TIPS-acetylene **13** and $Cu(OTf)_2$ affording, after silyl-deprotection with TBAF, the terminal alkynes **15a-d**. (Scheme 1, path b). The alkynes **8**, **10** and **15** were then converted into pyrroles **6**. Results are reported in Table 3. Acetamides **8a-e** were first reacted with EVE and G-II leading to the desired pyrroles **6f-j** in high yields (59-76%). Only pyrrole **6i** bearing a di-chloro-phenyl group was obtained in lower yield (38%) probably due to a combination of steric and electronic factors. The pyrroles **6l** and **6m**, bearing the bulky groups Boc and Bz, were obtained in lower yields than the acetyl analogue **6g**. Similarly, the tosylpyrrole **6k** was isolated in lower yield than **6f**. Reactions were performed using both a 5mol% and 10mol% Grubbs' cat. loading. However, in the case of 1-susbtituted propargylamines a lower catalyst loading resulted into poorer yields. On the other hand, the aliphatic and the furyl *N*-tosyl-propargylamides **15a-d** were converted into pyrroles **6o-r** in excellent yields with the only exception of the bulky cyclohexyl derivative **6p**. Finally, the treatment of the substrate **10** with EVE and Grubbs' cat. did not lead to the desired pyrrole **6n** in significant amount. Traces of **6n** were detected only by GC-MS analysis of the crude reaction mixture. Attempts to react the propargylamines with 2-methoxypropene, a substituted EVE analogue, proved to be unsuccessful. Methoxypropene proved to be unreactive toward CM due to its steric hindrance and propargylamines were recovered unreacted from the reaction mixtures. The present methodology allows the synthesis in one synthetic step of pyrroles unsubstituted on C4-C5, which could be in turn further functionalised as described in Scheme 2. As an

example, pyrrole **6f** was hydrolysed affording the disubstituted **16** which was further functionalised at C5 by Vilsmeir-Haack reaction leading to aldehyde **17**.

Table 3. Synthesis of 1,2,3-substituted pyrroles



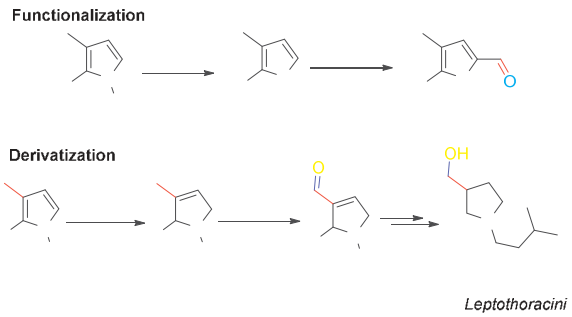
Alkyne	R	R_1	Pyrrole	Yield[a]
8a	C_6H_5	Ac	**6f**	70%
8b	4-Cl-C_6H_5	Ac	**6g**	72%
8c	3-F-C_6H_5	Ac	**6h**	76%
8d	2,4-Cl-C_6H_5	Ac	**6i**	38%
8e	4-Ph-C_6H_5	Ac	**6j**	59%
8f	C_6H_5	Ts	**6k**	38%
8g	4-Cl-C_6H_5	Boc	**6l**	50%
8h	4-Cl-C_6H_5	Bz	**6m**	64%
10	C_6H_5	C_6H_5	**6n**	Traces[b]
15a	2-Furyl	Ts	**6o**	76%
15b	CycHexyl	Ts	**6p**	43%
15c	iPr	Ts	**6q**	71%
15d	iBu	Ts	**6r**	69%



[a]Isolated yields were reported. [b]Observed by GC-MS

All the pyrroles **6** have a methyl group at C3 deriving from the diene intermediate **5** of the enyne metathesis reaction. Attempts to derivatize the methyl group through NBS-mediated bromination[20] or $KMnO_4$ oxidation[21] of **6** were unsuccessful due to the presence of the reactive CH at positions C4 and C5, leading to a complex mixture of polymeric derivatives. Nevertheless, pyrroles can be easily converted into 3-pyrrolines, compounds endowed with pharmaceutical properties and precursors in the synthesis of natural alkaloids.[22,23] The

pyrroles **6r** and **6b** were treated with $NaCNBH_3$ in TFA leading respectively to pyrrolines **18-20** which were in turn oxidized at the methyl group with SeO_2 affording the aldehydes **19** and **21** in 65-56% yield (over two-step) respectively (Scheme 2). The aldehyde **21** can be converted in a few steps into the alkaloid **22**.[22]



Scheme 2. Derivatization of pyrroles and synthesis of 3-methyl-pyrrolines

In conclusion, a new approach for the synthesis of pyrroles based on an enyne cross metathesis-cyclization cascade has been described. The present methodology represents the first example of one-pot synthesis of pyrroles via enyne cross-metathesis reaction and it constitutes a facile approach to the synthetically challenging 1,2,3-substituted pyrroles. Finally, the versatility of the method was shown through the synthesis of pyrroline analogues as well as the derivatization of the methyl substituent at C3.

EXPERIMENTAL SECTION

General Methods. Nuclear Magnetic Resonance (NMR) spectra were recorded on a 400 MHz spectrometer. ^{1}H and ^{13}C spectra were referenced relative to the solvent residual peaks

and chemical shifts (δ) reported in ppm downfield of trimethylsilane ($CDCl_3$ δ H: 7.26 ppm, δ C: 77.0 ppm). Coupling constants (J) are reported in Hertz and rounded to 0.5 Hz. Splitting patterns are abbreviated as follows: singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), broad (br) or some combination of these. Positive and negative electrospray ionisation spectrometry (ESI-MS) were conducted by direct injection. GC-MS analyses were performed using aliquots of the compound dissolved in DCM (5 µL) and injected onto a DB-5MS (30 m × 0.25 mm i.d. × 0.15 µm film thickness) column at 250 °C. The oven temperature was set at 40 °C for 4 min and raised at 15 °C/min to 135 °C, then at 5 °C/min to 250 °C and held at 250 °C for 5 minutes. The carrier gas flow was 1.0 mL/min. The mass spectrometer was operated in the full scan mode. The transfer line and ion source temperatures were 250 °C and 200 °C, respectively. A LTQ Orbitrap XL instrument was used for the HRMS measurements. Thin layer chromatography (TLC) was performed using commercially available pre-coated plates and visualized with UV light at 254 nm; K_2MnO_4 or Ninhydrin dips were used to reveal the products. Flash column chromatography was carried out using Fluorochem Davisil 40-63u 60Å. All reactions were conducted under a nitrogen atmosphere in oven-dried glassware unless stated otherwise. Tetrahydrofuran was distilled under nitrogen from sodium using a benzophenone indicator. Dichloromethane, toluene and diethyl ether were obtained by distillation over calcium hydride under a nitrogen atmosphere. Petrol refers to the fraction of light petroleum ether boiling between 40 and 65 °C. All other solvents and commercially available reagents were used as received. All chemicals and solvents were used as supplied, unless noted otherwise.

Microwave irradiation experiments. Microwave irradiations were conducted using a CEM Discover Synthesis Unit. The machine consists of a continuous focused microwave power delivery system with operator, selectable power output from 0 to 300 W. The temperature of the contents of the vessels was monitored using a calibrated infrared temperature control

mounted under the reaction vessel. All the experiments were performed using a stirring option whereby the contents of the vessel are stirred by means of rotating magnetic plate located below the floor of the microwave cavity and a Teflon, coated magnetic stirring bar in the vessel.

Synthesis of monosubstituted propargylic amines.

t-Butyl-prop-2-ynylcarbamate ***4a***. Lit[24] A solution of $(Boc)_2O$ (436 mg, 2.00 mmol, 1.1 equiv) in DCM (5 mL) was added dropwise to a solution of propargylamine (100 mg, 1.81 mmol, 1 equiv) in DCM (5 mL), at 0 °C. The reaction mixture was then allowed to stir at room temperature for 30 min. The solution was concentrated under reduced pressure. The product (275 mg, 1.77 mmol) was obtained as a yellow oil.

Yield: 98%. ^{1}H NMR (400 MHz $CDCl_3$) δ 4.78 (bs, 1H), 3.88 (s, 2H), 2.18 (t, *J* = 2.8 Hz, 1H), 1.42 (s, 9H) ppm. LRMS m/z (ES+) m/z: 156 $[M+H]^+$.

4-Methyl-N-2-propyn-1-yl-benzenesulfonamide ***4b***. Lit[25]. Propargyl amine (0.17 mL, 2.69 mmol, 1 equiv), and triethylamine (0.45 mL, 3.23 mmol, 1.2 equiv) were added to a solution of *p*-toluenesulfonyl chloride (564 mg, 2.96 mmol, 1.1 equiv) in anhydrous DCM at 0 °C, under N_2 atmosphere. The reaction mixture was allowed to stir at room temperature for 6h, and then it was quenched with a saturated NH_4Cl solution. The aqueous layer was extracted with DCM. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure, giving the pure product (539 mg, 2.57 mmol) as yellow oil.

Yield: 96%. ^{1}H NMR (400 MHz $CDCl_3$) δ 7.69 (d, *J* = 8.2 Hz, 2H), 7.19 (d, *J* = 8.4 Hz, 2H), 3.69 (d, *J* = 2.8 Hz, 2H), 2.31 (s, 3H), 2.03 (t, *J* = 2.2 Hz, H) ppm.

N-2-Propyn-1-yl-benzenamine ***4c***. Lit.[26] Aniline (0.46 mL, 5 mmol, 5 equiv) was added to a solution of propargyl bromide (0.11 mL, 1 mmol, 1 equiv) in ethanol. The reaction mixture

was stirred at room temperature for 2 days, and then concentrated under reduced pressure. The crude product was purified by chromatography on silica gel, using hexane/EtOAc (9:1) as eluent. The pure product (84 mg, 0.64 mmol) was obtained as a yellow oil.

Yield: 64%. ^{1}H NMR (400 MHz $CDCl_3$) δ 7.21 (t, *J* = 7.6 Hz, 2H), 6.78 (t, *J* = 7.2 Hz, 1H), 6.68 (d, *J* = 7.6 Hz, 2H), 3.93 (s, 2H), 3.96 (bs, 1H), 2.20 (t, *J* = 2.4 Hz, 1H) ppm.

N-Prop-2-ynylbenzamide ***4d***.Lit.[27] Benzoyl chloride (257 mg, 1.83 mmol, 1.01 equiv) and triethylamine (0.30 mL, 2.21 mmol, 1.2 equiv) were added to a solution of propargylamine (100 mg, 1.82 mmol, 1 equiv) in DCM (20 mL) at 0 °C. The reaction mixture was allowed to stir at room temperature for 1 h, then it was quenched with 20 mL of 1M HCl solution, and extracted with DCM. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude mixture was purified by chromatography on silica gel, using hexane/EtOAc (4:1) as eluent, affording 254 mg (1.60 mmol) of **4d**.

Yield: 88%. ^{1}H NMR (400 MHz $CDCl_3$) δ 7.77 (d, *J* = 7.6 Hz, 2H), 7.48 (t, *J* = 7.2 Hz, 2H), 7.39 (t, *J* = 7.6 Hz, 2H), 6.64 (bs, 1H), 4.22 (dd, *J* = 2.8, 5.6 Hz, 2H), 2.25 (t, *J* = 2.8Hz, 1H) ppm.

N-benzyl-propargylamine ***4e***. Lit.[28] Benzylamine (1.1 mL, 10.08 mmol, 6 equiv) was added to a solution of propargyl bromide (100 mg, 1.68 mmol, 1 equiv) in 1 mL of DCM. The reaction mixture was stirred at room temperature for 2 days, and then concentrated under reduced pressure. The crude product was purified by chromatography on silica gel, using hexane/EtOAc (9:1) as eluent. Compound **4e** (136 mg, 0.94 mmol) was obtained as a tan oil.

Yield: 56%. ^{1}H NMR (400 MHz $CDCl_3$) δ 7.35-7.25 (m, 5H), 3.85 (s, 2H), 3.40 (d, 2H), 2.25 (s, 1H) ppm.

*Synthesis of propargylamides **8a-e**.General procedure.* A solution of 96% H_2SO_4 (490 mg, 5 mmol) in dry acetonitrile (2 mL) was added to a stirred mixture of the appropriate propargylalcohol[17a] (1 mmol) and anhydrous Na_2SO_4 (142 mg, 1 mmol) in dry acetonitrile (3.1 mL) at 20 °C. The mixture was allowed to reach room temperature, and stirring was continued for the required time. The mixture was concentrated, poured on ice, and extracted with ether and dichloromethane. The combined organic layers were dried over Na_2SO_4, filtered and concentrated. Flash chromatography, using ethyl acetate/ petroleum ether (1:1) as eluent, afforded pure propargylamides **8a-e**.

*Propragylamide **8d***. Yield: 76% (183 mg, 0.76 mmol). ^{1}H NMR (400 MHz $CDCl_3$) δ 7.57-7.55 (d, 1H, *J* = 8.2 Hz), 7.40 (s, 1H), 7.22-7.24 (m, 1H), 6.09 (br s, 1H), 6.08 (s, 1H), 2.46 (d, 1H, *J* = 1.8 Hz), 1.99 (s, 3H) ppm. ^{13}C NMR (100 MHz $CDCl_3$) δ 168.7, 135.0, 134.2, 134.1, 130.1, 127.5, 80.5, 73.3, 42.8, 23.0 ppm. IR ν max (film)/cm^{-1} 1676, 1497. LRMS m/z (ES+) m/z: 242 $[M+H]^+$, 264 $[M+Na]^+$. HRMS (ESI): calcd for $C_{11}H_{10}Cl_2NO$ (M + H^+) 242.0139, found 242.0137.

*Propragylamide **8e***.Yield: 75% (186 mg, 0.74 mmol). ^{1}H NMR (400 MHz $CDCl_3$) δ 7.57-7.55 (m, 6H), 7.45-7.41 (m, 2H), 7.36-7.33 (m, 1H), 6.06-6.04 (d, 1H), 6.00 (br d, 1H), 2.51 (s, 1H), 2.03 (s, 3H) ppm. ^{13}C NMR (100 MHz $CDCl_3$) δ 168.8, 141.4, 140.5, 137.3, 128.9, 127.6, 127.2, 81.7, 73.2, 44.3, 23.3 ppm. IR ν max (film)/cm^{-1} 1674, 1486. LRMS m/z (ES+) m/z: 250 $[M+H]^+$, 272 $[M+Na]^+$. HRMS (ESI): calcd for $C_{17}H_{16}NO$ (M + H^+) 250.1232, found 250.1227.

Spectroscopy data of propargylamides **8a-c** were identical to those previously reported.[16a]

*Synthesis of propargylacetate **9**.*[32] Acetic anhydride (0.19 mL, 1.96 mmol, 1.3 equiv), triethylamine (0.42 mL, 3.02 mmol, 2 equiv), and a catalytic amount of DMAP were added to a solution of 1-phenyl-2-propynol (200 mg, 1.51 mmol, 1 equiv) in DCM. The reaction

mixture was stirred at room temperature for the indicated time, and then concentrated under reduced pressure. The crude product was purified by chromatography on silica gel, using hexane/EtOAc (9:1) as eluent.

Yield: 77% (201 mg, 1.15 mmol). ^{1}H NMR (400 MHz $CDCl_3$) δ 7.53 (d, *J* = 6.8 Hz, 2H), 7.39 (m, 3H), 6.45 (d, *J* = 2.4 Hz, 1H), 2.66 (d, *J* = 2.4 Hz, 1H), 2.10 (s, 3H) ppm. LRMS m/z (ES+) m/z: 197 $[M+Na]^+$.

Synthesis of 1-Phenyl-2-propynylamine ***S8***.[17a] A suspension of *N*-(1-phenyl-2-propynyl)acetamide (0,76 mmol, 1 equiv) and 1.2M HCl (5 mL) was heated to 90 °C for 18h. The reaction mixture was then cooled at room temperature, quenched with 20 mL of saturated $NaHCO_3$ solution, and diluted with Et_2O (10 mL). The aqueous layer was extracted twice with Et_2O (20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude 1-phenyl-2-propynylamine was purified by flash column chromatography (SiO_2) using 1:1 EtOAc/hexanes as the eluent to yield the desired 1-phenyl-2-propynylamine as an oil.

Yield: 72 % (71 mg, 0.54 mmol). ^{1}H NMR (400 MHz $CDCl_3$) δ 7.75 (d, *J* = 8.4 Hz, 2H), 7.43 (d, *J* = 8.4 Hz, 2H), 7.32-7.22 (m,5H), 5.30 (d, *J* = 4.0 Hz, 1H), 5.06 (d, *J* = 4.0 Hz, 1H), 2.41 (s, 3H), 2.29 (d, *J* = 2.4 Hz, 1H) ppm. LRMS m/z (ES+) m/z: 132 $[M+H]^+$.

Synthesis of 4-methyl-N-(1-phenylprop-2-yn-1-yl)benzenesulfonamide ***8f***.[33] 1-Phenyl-2-propynylamine **S8** (0.35 mmol, 1 equiv) was added to a round bottom flask containing pyridine (5 mL). Then *p*-toluenesulphonic chloride (0.62 mmol, 1.77 equiv) was added at 0 °C to the solution previously obtained. The solution was allowed to stir at 100 °C for 18h. The reaction mixture was then quenched with 10 mL of 1M HCl solution and washed with 10 mL of DCM. Then, 20 mL of saturated $NaHCO_3$ solution was added to the aqueous layer and this was extracted twice with DCM. The combined organic layers were washed with brine,

dried over Na_2SO_4 and concentrated under reduced pressure. The crude compound was purified by flash column chromatography (SiO_2) using 1:4 EtOAc/hexanes as the eluent to yield the desired **8f** as an oil.

Yield: 62 % (62 mg, 0.21 mmol). ^{1}H NMR (400 MHz $CDCl_3$) δ 7.65 (d, *J* = 8.4 Hz, 2H), 7.25 (d, *J* = 8.4 Hz, 2H), 4.78 (s,1H), 4.32 (d, *J* = 1.6 Hz, 2H), 2.38 (s, 3H), 1.92-1.85 (m, 1H), 1,56 (s, 3H), 1.48 (d, *J* = 1.8 Hz, 2H), 1.01 (d, *J* = 6.8 Hz, 3H), 0.88 (d, *J* = 6.8 Hz, 3H) ppm. ^{13}C NMR (100 MHz $CDCl_3$) δ 143.7, 137.3, 137.0, 129.6, 128.8, 128.6, 127.5, 127.2, 80.5, 74.8, 49.0, 21.6 ppm. LRMS m/z (ES+) m/z: 308 $[M+Na]^+$.

N-[1-(4-chlorophenyl)-2-propyn-1-yl]- 1,1-dimethylethyl ester carbamic acid ***8g***. A solution of $(Boc)_2O$ (183 mg, 0.84 mmol, 1 equiv) in DCM (5 mL) was added dropwise to a solution of propargyl amine **S8** (150 mg, 0.84 mmol, 1 equiv) in DCM (5 mL) and saturated $NaHCO_3$ solution (5 mL), at 0 °C. The reaction mixture was then allowed to stir at room temperature for 2h. The solution was quenched with DCM. The aqueous layer was extracted with DCM and EtOAc. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The obtained product was purified by silica gel chromatography, using hexane/EtOAc (4:1) as eluent.

Yield: 60 % (132 mg, 0.5 mmol). ^{1}H NMR (400 MHz $CDCl_3$) δ 7.45 (d, *J* = 8.8 Hz, 2H), 7.33 (d, *J* = 8.8 Hz, 2H), 5.64 (d, *J* = 7.4 Hz, 1H), 5.06 (bs, 1H), 2.51 (d, *J* = 2.2 Hz, 1H), 1.46 (s, 6H) ppm. ^{13}C NMR (100 MHz $CDCl_3$) δ 154.7, 137.4, 134.0, 128.8, 128.3, 81.6, 80.6, 73.4, 45.6, 28.3 ppm. LRMS m/z (ES+) m/z: 288 $[M+Na]^+$. HRMS (ESI): calcd for $C_{14}H_{16}ClNNaO_2$ ($M + Na^+$) 288.0767, found 288.0765.

N-[1-(4-chlorophenyl)-2-propyn-1-yl]-benzamide ***8h***.Benzoyl chloride (0.07 mL, 0.57 mmol, 1.01 equiv) and triethylamine (0.09 mL, 0.67 mmol, 1.2 equiv) were added to a solution of propargylic amine **5** (100 mg, 0.56 mmol, 1 equiv) in DCM (20 mL) at 0 °C. The reaction

mixture was allowed to stir at room temperature for 1 h, and then quenched with 20 mL of 1M HCl solution, and extracted with DCM and EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The obtained product was purified by chromatography on silica gel, using hexane/EtOAc (4:1) as eluent.

Yield: 65 % (98 mg, 0.36 mmol). ^{1}H NMR (400 MHz $CDCl_3$) δ 7.79 (d, *J* = 7.2 Hz, 2H), 7.51 (d, *J* = 6.4 Hz, 3H), 7.43 (t, *J* = 7.8 Hz, 2H), 7.33 (d, *J* = 8.2 Hz, 2H), 6.72 (d, *J* = 8.2 Hz, 1H), 6.21 (dd, *J* = 2.2, 8.4 Hz, 1H), 2.55 (d, *J* = 2.4 Hz, 1H) ppm. ^{13}C NMR (100 MHz $CDCl_3$) δ 166.4, 136.9, 134.2, 133.4, 132.1, 128.9, 128.7, 128.6, 127.2, 81.2, 73.8, 44.4 ppm. LRMS m/z (ES+) m/z: 270 $[M+H]^+$. HRMS (ESI): calcd for $C_{16}H_{13}ClNO$ (M + H^+) 270.0686, found 270.0683.

*Synthesis of N-phenyl-propargylamine **10**.* Lit.[29] Copper iodide (25 mg, 0.13 mg, 0.5 equiv) was added to a solution of propargylic acetate **9** (45 mg, 0.26 mmol, 1 equiv) in MeOH at 0 °C, under N_2 atmosphere. The reaction mixture was allowed to stir for 10 min before the addition of aniline (0.05 mL, 0.52 mmol, 2 equiv) and triethylamine (0.15 mL, 1.04 mmol, 4 equiv). The mixture was then stirred at 0 °C, and allowed to reach room temperature overnight. The reaction mixture was quenched with EtOAc and ammonia solution. The aqueous layer extracted with EtOAc. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by chromatography on silica gel, using hexane as eluent. The pure product was obtained as a tan oil (32 mg, 0.15 mmol).

Yield: 59%. ^{1}H NMR (400 MHz $CDCl_3$) δ 7.61 (d, *J* = 7.2 Hz, 2H), 7.43-7.35 (m, 3H), 7.21 (t, *J* = 7.2 Hz, 2H), 6.79 (t, *J* = 7.6 Hz, 1H), 6.74 (d, *J* = 7.8 Hz, 2H), 5.29 (s, 1H), 4.06 (bs, 1H), 2.47 (d, *J* = 2.4 Hz, 1H) ppm. LRMS m/z (ES+) m/z: 230 $[M+Na]^+$.

Synthesis of silylpropargylamines ***14a-d****.General procedure.* The appropriate aldehyde (1.1 equiv) and triisopropylsilyl acetylene (1.5 equiv) were added to a solution of *p*-toluenesulfonamide (200 mg, 1.17 mmol, 1 equiv), sodium sulphate (1 equiv), cesium carbonate (0.1 equiv) and copper triflate (0.1 equiv) in anhydrous toluene under N_2 atmosphere. The reaction mixture was allowed to stir at 120 °C for 48 h. The reaction mixture was then quenched with EtOAc and washed with a saturated $NaHCO_3$ solution. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by chromatography on silica gel, using hexane/EtOAc (4:1) as eluent.

N-[1-(2-furanyl)-3-(triisopropylsilyl)-2-propyn-1-yl]-4-methyl-benzenesulfonamide ***14a****.*Yield: 48% (242 mg, 0.56 mmol). ^{1}H NMR (400 MHz $CDCl_3$) δ 7.77 (d, *J* = 8.4 Hz, 2H), 7.31 (s, 1H), 7.25 (d, *J* = 8.4 Hz, 2H), 6.35 (d, *J* = 3.2 Hz, 1H), 6.27 (t, *J* = 2.2 Hz, 1H), 5.41 (d, *J* = 9.2 Hz, 1H), 5.21 (d, *J* = 8.4 Hz, 1H), 2.39 (s, 3H), 0.96 (m, 18H), 0.93-0.82 (m, 3H) ppm. ^{13}C NMR (100 MHz $CDCl_3$) δ 150.1, 143.5, 143.2, 137.5, 129.7, 127.2, 110.4, 108.4, 101.4, 87.0, 44.1, 21.6, 18.5, 11.0 ppm. LRMS m/z (ES+) m/z: 432 $[M+H]^+$. HRMS (ESI): calcd for $C_{23}H_{37}SSiN_2O_3$ ($M+NH_4^+$) 449.2294, found 449.2284.

N-[1-cyclohexyl-3-[tris(1-methylethyl)silyl]-2-propyn-1-yl]-4-methyl-benzenesulfonamide ***14b****.*[19] Yield: 45% (235 mg, 0.52 mmol). ^{1}H NMR (400 MHz $CDCl_3$) δ 7.74 (d, *J* = 8.4 Hz, 2H), 7.25 (d, *J* =8.4 Hz, 2H), 4.55 (d, *J* = 9.6Hz, 1H), 3.92 (dd, *J* = 5.6, 9.8Hz, 1H), 2.38 (s, 3H), 1.84-1.68 (m, 5H), 1.68-1.50 (m, 4H), 1.30-0.97 (m, 2H), 0.91 (d, *J* = 5.0 Hz, 18H), 0.88-0.81 (m, 3H) ppm. LRMS m/z (ES+) m/z: 448 $[M+H]^+$.

N-[1-isobutyl-3-[tris(1-methylethyl)silyl]-2-propyn-1-yl]-4-methyl-benzenesulfonamide ***14c****.* Yield: 22% (105 mg, 0.25 mmol). ^{1}H NMR (400 MHz $CDCl_3$) δ 7.77 (d, *J* = 8.8 Hz, 2H), 7.28 (d, *J* = 8.8 Hz, 2H), 4.63 (d, *J* = 9.2 Hz, 1H), 3.95 (dd, *J* = 5.6, 9.6 Hz, 1H), 2.40 (s, 3H),

2.00-1.88 (m, 1H), 1.00 (d, J = 6.8Hz, 6H), 0.92 (d, J = 5.0 Hz, 18H), 0.95-0.84 (m, 3H) ppm. ^{13}C NMR (100 MHz $CDCl_3$) δ 143.4, 137.5, 129.7, 127.2, 104.0, 86.0, 52.3, 34.3, 21.5, 18.7, 18.5, 17.4, 11.0 ppm. LRMS m/z (ES+) m/z: 408 $[M+H]^+$. HRMS (ESI): calcd for $C_{22}H_{41}SSiN_2O_2$ ($M+NH_4^+$) 425.2658, found 425.2645.

N-[1-(3-methylbutyl)-3-[tris(1-methylethyl)silyl]-2-propyn-1-yl]-4-methyl-benzenesulfonamide ***14d***. Yield: 56% (276 mg, 0.65 mmol). ^{1}H NMR (400 MHz $CDCl_3$) δ 7.77 (d, J = 8.4 Hz, 2H), 7.27 (d, J = 8.4 Hz, 2H), 4.49 (d, J = 9.6 Hz, 1H), 4.13 (q, J = 7.8 Hz, 1H), 2.40 (s, 3H), 1.96-1.83 (m, 1H), 1.60-1.44 (m, 2H), 0.93-0.79 (m, 27H) ppm. ^{13}C NMR (100 MHz $CDCl_3$) δ 143.4, 137.6, 129.7, 127.2, 85.0, 46.6, 45.0, 24.8, 22.3, 22.0, 21.5, 18.5, 11.0 ppm. LRMS m/z (ES+) m/z: 422 $[M+H]^+$.HRMS (ESI): calcd for $C_{23}H_{43}SSiN_2O_2$ ($M + NH_4^+$) 439.2815, found 439.2804.

General procedure for the synthesis of propargylamides ***15a-d***. A TBAF solution 1M in THF (1.1equiv) was added to a solution of compound **14** (0.25 mmol, 1 equiv) in THF at 0 °C. The reaction mixture was stirred at room temperature for 1h30, then quenched with a saturated $NaHCO_3$ solution and extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by chromatography on silica gel, using hexane/EtOAc (4:1) as eluent.

N-[1-(2-furanyl)-2-propyn-1-yl]-4-methyl-benzenesulfonamide ***15a***.[34] Yield: 82% (56 mg, 0.20 mmol). ^{1}H NMR (400 MHz $CDCl_3$) δ 7.75 (d, J = 8.2 Hz, 2H), 7.30 (d, J = 1.2 Hz, 1H), 7.28 (d, J = 8.0 Hz, 2H), 6.33 (d, J = 3.2 Hz, 1H), 6.27 (t, J = 2.4 Hz, 1H), 5.37 (d, J = 2.4 Hz, 1H), 2.42 (s, 3H), 2.30 (d, J = 2.4 Hz, 1H) ppm. ^{13}C NMR (100 MHz $CDCl_3$) δ 149.0, 143.6, 143.1, 137.1, 129.4, 127.3, 110.4, 108.4, 78.3, 73.6, 43.1, 21.5 ppm. LRMS m/z (ES+) m/z: 298 $[M+Na]^+$.

N-(1-cyclohexyl-2-propyn-1-yl)-4-methyl-benzenesulfonamide ***15b***.[34] Yield: 99% (72 mg, 0.24 mmol). ^{1}H NMR (400 MHz $CDCl_3$) δ 7.75 (d, *J* = 6.8 Hz, 2H), 7.27 (d, *J* = 7.2 Hz, 2H), 4.69 (d, *J* = 7.4 Hz, 1H), 3.86 (m, 1H), 2.40 (s, 3H), 2.01 (s, 1H), 1.84-1.67 (m, 5H), 1.66-146 (m, 4H), 1.33-0.99 (m, 2H). ^{13}C NMR (100 MHz $CDCl_3$) δ 143.4,132.2, 129.4, 127.3, 80.7, 73.1, 50.6, 42.8, 28.8, 25.7, 25.6, 21.5, 14.1 ppm. LRMS m/z (ES+) m/z: 314 $[M+Na]^+$.

*N-(1-isobutyl-2-propyn-1-yl)-4-methyl-benzenesulfonamide****15c***.[35] Yield: 95% (60 mg, 0.24 mmol). ^{1}H NMR (400 MHz $CDCl_3$) δ 7.78 (d, *J* = 8.2 Hz, 2H), 7.30 (d, *J* = 7.8 Hz, 2H), 4.71 (d, *J* = 9.6 Hz, 1H), 3.90 (ddd, *J* = 2.2, 5.4, 10.0 Hz, 1H), 2.43 (s, 3H), 2.04 (d, *J* = 2.8 Hz, 1H), 1.91 (sex, *J* = 6.8 Hz, 1H), 0.98 (d, *J* = 6.8 Hz, 6H) ppm. ^{13}C NMR (100 MHz $CDCl_3$) δ 143.5, 137.2, 129.5, 127.3, 80.4, 73.1, 51.3, 33.5, 21.5, 18.5, 17.3 ppm. LRMS m/z (ES+) m/z: 274 $[M+Na]^+$.

N-(1-methylbutyl -2-propyn-1-yl)-4-methyl-benzenesulfonamide ***15d***. Yield: 93% (66 mg, 0.23 mmol). ^{1}H NMR (400 MHz $CDCl_3$) δ 7.79 (d, *J* = 8.4 Hz, 2H), 7.30 (d, *J* = 8.6Hz, 2H), 4.71 (d, *J* = 9.2Hz, 1H), 4.15-4.04 (m, 1H), 2.43 (s, 3H), 2.03 (d, *J* = 2.2 Hz, 1H), 1.89-1.77 (m, 1H), 1.53 (td, *J* = 7.6, 3.2 Hz, 2H), 0.89 (dd, *J* = 6.4, 3.0 Hz, 6H) ppm. ^{13}C NMR (100 MHz $CDCl_3$) δ 143.6, 137.3, 129.5, 127.5, 82.2, 72.4, 45.6, 44.0, 24.6, 22.2, 22.0, 21.6 ppm. LRMS m/z (ES+) m/z: 288 $[M+Na]^+$. HRMS (ESI): calcd for $C_{14}H_{19}NNaO_2S$ (M + H^+) 288.1034, found 288.1008.

General procedure for the synthesis of 3-methyl-pyrroles ***6***.Ethyl vinyl ether (9 equiv), $CuSO_4$ (2 equiv) and Grubbs' catalyst 2nd generation (5-10mol%) were added to a microwave vial containing a solution of the appropriate propargylamine derivative (50 mg, 1 equiv) in 3 mL of degassed toluene. The reaction mixture was heated at 120 °C under microwaves irradiation (300W) for 2x10min. The maximum internal pressure observed during the reaction was 44 psi. The reaction mixture was then quenched with 10 mL of saturated NH_4Cl

solution, 0.5 mL of NH_4OH solution and 10 mL of Et_2O. The aqueous layer was extracted twice with Et_2O. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. All the crude products were purified by flash column chromatography (SiO_2) using 1:4 Et_2O/hexanes as the eluent to yield the desired pyrroles **6** as tan oils.

t-Butyl 3-methyl-1H-pyrrole-1-carboxylate ***6a***. Yield: 56% (33 mg, 0.18 mmol). ^{1}H NMR (400 MHz $CDCl_3$) δ 7.12 (s, 1H), 6.95 (s, 1H), 6.04 (s, 1H), 2.04 (s, 3H), 1.56 (s, 9H) ppm. ^{13}C NMR (100 MHz $CDCl_3$) δ 149.0, 122.6, 120.0, 117.2, 114.1, 83.2, 28.1, 12.0 ppm. IR ν max (film)/cm^{-1} 2924, 1730. GC-MS m/z (ES+) m/z: 181 $[M]^+$, HRMS (ESI): calcd for $C_{10}H_{16}NO_2$ (M + H^+) 182.1181, found 182.1173.

(E/Z)-tert-butyl-(4-ethoxy-2-methylenebut-3-en-1-yl)carbamate **5**. Yield: 41% (30 mg, 0.13 mmol). Obtained as a 2:1 mixture of *E/Z* isomers as revealed by GC-MS. ^{1}H NMR (400 MHz $CDCl_3$) major isomer *E* δ 6.63 (d, 1H, *J* = 12.8 Hz), 5.53 (d, 1H, *J* = 12.8 Hz), 4.85 (s, 1H), 4.80 (s, 1H), 4.59 (br s, 1H), 3.84-3.76 (m, 4H), 1.43 (s, 9H), 1.27 (t, 3H, *J* = 4.0 Hz) ppm; peaks from minor isomer *Z* δ 5.96 (d, 1H, *J* = 6.9 Hz), 5.09 (s, 1H), 4.96 (s, 1H) ppm. ^{13}C NMR (100 MHz $CDCl_3$) δ 155.8, 148.2, 140.9, 111.0, 106.2, 79.4, 65.8, 42.8, 28.4, 14.9 ppm; peaks from minor isomer δ 146.0, 113.6, 105.2, 69.0, 45.5, 27.4, 15.3 ppm. GC-MS m/z (ES+) m/z: 227 $[M]^+$, 171 $[M–tBu]^+$, 154 $[M\text{-}tBuOH]^+$. HRMS (ESI): calcd for $C_{12}H_{21}NO_3$ (M^+) 227.1516, found 227.1553.

3-Methyl-1-[(4-methylphenyl)sulfonyl]-1H-pyrrole ***6b***.Yield: 53% (30 mg, 0.13 mmol). ^{1}H NMR (400 MHz $CDCl_3$) δ 7.70 (d, 2H, *J* = 7.6 Hz), 7.25 (d, 2H, *J* = 7.6 Hz), 7.03 (s, 1H), 6.86 (s, 1H), 6.10 (s, 1H), 2.38 (s, 3H), 2.00 (s, 3H) ppm. ^{13}C NMR (100 MHz $CDCl_3$) δ 144.6, 136.2, 129.8, 126.7, 124.5, 120.8, 117.7, 115.7, 21.6, 11.8 ppm. IR ν max (film)/cm^{-1}

1364, 1179. GC-MS m/z (ES+) m/z: 235 $[M]^+$, HRMS (ESI): calcd for $C_{12}H_{14}NO_2S$ (M + H^+) 236.0745, found 236.0738.

3-Methyl-1-phenyl-1H-pyrrole ***6c***. *Lit.*[30] Yield: 54% (32 mg, 0.2 mmol). ^{1}H NMR (400 MHz $CDCl_3$) δ 7.40-7.35 (m, 4H), 7.19-7.18 (m, 1H), 6.98 (s, 1H), 6.86 (m, 1H), 6.16 (m, 1H), 2.16 (s, 3H) ppm. ^{13}C NMR (100 MHz $CDCl_3$) δ 140.8, 129.5, 125.1, 121.2, 120.0, 119.0, 117.2, 112.0, 12.0 ppm. GC-MS m/z (ES+) m/z: 157 $[M]^+$, HRMS (ESI): calcd for $C_{11}H_{12}N$ (M + H^+) 158.0970, found 158.0960.

3-Methyl-1-benzoyl-1H-pyrrole ***6d***. Yield: 39% (23 mg, 0.12 mmol). ^{1}H NMR (400 MHz $CDCl_3$) δ 7.71-7.70 (d, 2H, *J* = 7.3 Hz), 7.57-7.55 (m, 1H), 7.50-7.46 (m, 2H), 7.16 (s, 1H), 7.03 (s, 1H), 6.18 (s, 1H), 2.08 (s, 3H) ppm. ^{13}C NMR (100 MHz $CDCl_3$) δ 165.5, 132.0, 129.4, 128.4, 124.1, 121.4, 118.5, 115.6, 12.1 ppm. IR ν max (film)/cm^{-1} 1682, 1394, 1335. GC-MS m/z (ES+) m/z: 185 $[M]^+$, HRMS (ESI): calcd for $C_{12}H_{12}NO$ (M + H^+) 186.0919, found 186.0906.

3-Methyl-2-phenyl-1-acetyl-1H-pyrrole ***6f***. Lit.[31] Compound **6f** was synthesised starting from 200 mg (1.15 mmol) of **8a**. Yield: 70% (160 mg). ^{1}H NMR (400 MHz $CDCl_3$) δ 7.42-7.30 (m, 3H,), 7.28(d, 1H, *J* = 3.6Hz), 7.27-7.23 (m, 2H), 6.16 (d, 1H, *J* = 3.6 Hz,), 1.90 (s, 3H), 1.55 (s, 3H) ppm. ^{13}C NMR (100 MHz $CDCl_3$) δ 169.1, 133.7, 130.5, 130.2, 128.1, 126.8, 124.5, 120.2, 113.9, 25.0, 11.4 ppm. GC-MS m/z (ES+) m/z: 199 $[M+H]^+$.

3-Methyl-2-(4-chlorophenyl)-1-acetyl-1H-pyrrole ***6g***. Yield: 72% (40 mg, 0.17 mmol). ^{1}H NMR (400 MHz $CDCl_3$) δ 7.35 (d, 2H, *J* = 8.4 Hz), 7.21 (d, 1H, *J* = 3.2 Hz), 7.17 (d, 2H, *J* = 8.4 Hz), 6.16 (d, 1H, *J* = 3.2 Hz), 2.29 (s, 3H), 1.89 (s, 3H) ppm. ^{13}C NMR (100 MHz $CDCl_3$) δ 168.4, 133.5, 132.1, 131.5, 129.4, 128.3, 123.9, 120.7, 114.3, 24.6, 11.4 ppm. IR ν max (film)/cm^{-1} 2925, 1721, 1305. GC-MS m/z (ES+) m/z: 233 $[M]^+$, HRMS (ESI): calcd for $C_{13}H_{13}ClNO$ (M + H^+) 234.0686, found 234.0677.

3-Methyl-2-(3-fluorophenyl)-1-acetyl-1H-pyrrole ***6h***. Yield: 76% (43 mg, 0.2 mmol). ^{1}H NMR (400 MHz $CDCl_3$) δ 7.36-7.29 (m, 1H), 7.21 (d, 1H, *J* = 3.2 Hz), 7.06-6.91 (m, 3H), 6.15 (d, *J* = 3.2 Hz), 2.27 (s, 3H), 1.90 (s, 3H) ppm. ^{13}C NMR (100 MHz $CDCl_3$) δ 168.4, 163.7, 161.2, 135.8, 135.7, 129.5, 129.4, 126.0, 124.1, 120.7, 117.2, 117.0, 114.6, 114.4, 114.3, 22.7, 14.2 ppm. IR ν max (film)/cm^{-1} 2924, 1730, 1367. GC-MS m/z (ES+) m/z: 217 $[M]^+$, HRMS (ESI): calcd for $C_{13}H_{13}FNO$ (M + H^+) 218.0981, found 218.0975.

3-Methyl-2-(2,4-dichlorophenyl)-1-acetyl-1H-pyrrole ***6i***. Yield: 38% (21 mg, 0.08 mmol). ^{1}H NMR (400 MHz $CDCl_3$) δ 7.47-7.40 (m, 1H), 7.30-7.25 (m, 1H), 7.20 (d, 1H, *J* = 3.6 Hz), 6.20 (d, 1H, *J* = 3.6 Hz), 2.35 (s, 3H) 1.85 (s, 3H) ppm. ^{13}C NMR (100 MHz $CDCl_3$) δ 168.6, 136.0, 134.4, 132.6, 131.9, 129.3, 127.0, 126.4, 124.3, 102.6, 114.3, 23.6, 11.1 ppm. IR ν max (film)/cm^{-1}2926, 1725, 1474. GC-MS m/z (ES+) m/z: 267 $[M]^+$, HRMS (ESI): calcd for $C_{13}H_{12}Cl_2NO$ (M + H^+) 268.0296, found 268.0285.

3-Methyl-2-(4-phenyl-phenyl)-1-acetyl-1H-pyrrole ***6j***. Yield: 59% (32 mg, 0.11 mmol). ^{1}H NMR (400 MHz $CDCl_3$) δ 7.67-7.59 (m, 4H), 7.48-7.40 (m, 2H), 7.37-7.30 (m, 3H), 7.28 (d, 1H, *J* = 3.2 Hz), 6.18 (d, 1H, *J* = 3.2 Hz), 2.26 (s, 3H), 1.96 (s, 3H) ppm. ^{13}C NMR (100 MHz $CDCl_3$) δ 168.9, 140.7, 140.2, 132.6, 130.6, 130.2, 128.8, 127.4, 127.1, 126.8, 123.8, 120.5, 114.2, 25.0, 11.6 ppm. IR ν max (film)/cm^{-1}2925, 1726, 1305. GC-MS m/z (ES+) m/z: 275 $[M]^+$, HRMS (ESI): calcd for $C_{19}H_{18}NO$ (M + H^+) 276.1388, found 276.1380.

3-Methyl-2-phenyl-1-[(4-methylphenyl)sulfonyl]-1H-pyrrole ***6k***. Yield: 38 % (21 mg, 0.07 mmol). ^{1}H NMR (400 MHz $CDCl_3$) δ 7.38-7.18 (m, 7H), 7.08-7.05 (m, 3H), 6.18 (d, 1H, *J* = 3.2 Hz), 2.34 (s, 3H), 1.80 (s, 1H) ppm. ^{13}C NMR (100 MHz $CDCl_3$) δ 144.4, 135.9, 131.9, 131.2, 130.7, 129.3, 128.1, 127.4, 127.2, 123.8, 122.4, 114.2, 21.6, 11,6 ppm. IR ν max (film)/cm^{-1} 1344, 1160. GC-MS m/z (ES+) m/z: 311 $[M]^+$, HRMS (ESI): calcd for $C_{18}H_{18}NO_2S$ (M + H^+) 312.1058, found 312.1047.

tert-Butyl 2-(4-chlorophenyl)-3-methyl-1H-pyrrole-1-carboxylate ***6l***. Yield: 50% (27 mg, 0.093 mmol). ^{1}H NMR (400 MHz $CDCl_3$) δ 7.34 (t, *J* = 2.3 Hz, 1H), 7.32 (t, *J* = 2.3 Hz, 1H), 7.27 (d, *J* = 3.2 Hz, 1H), 7.17 (t, *J* = 1.6 Hz, 1H), 7.15 (t, *J* = 2.3 Hz, 1H), 6.10 (d, *J* = 3.7 Hz, 1H), 1.89 (s, 3H), 1.30 (s, 9H) ppm. ^{13}C NMR (100 MHz $CDCl_3$) δ 149.2, 133.0, 132.5, 131.6, 129.1, 127.2, 122.6, 121.3, 113.0, 83.3, 27.6, 11.6 ppm. IR ν max (film)/cm^{-1} 2922, 2357, 1739, 1458. GC-MS m/z (ES+) m/z: 291 $[M]^+$, HRMS (ESI): calcd for $C_{16}H_{19}ClNO_2$ (M + H^+) 292.1104, found 292.1098.

3-Methyl-2-(4-chlorophenyl) -1-benzoyl-1H-pyrrole ***6m***. Yield: 64% (35 mg, 0.19 mmol). ^{1}H NMR (400 MHz $CDCl_3$) δ 7.74 (d, *J* = 6.8 Hz, 2H), 7.56 (t, *J* = 7.2 Hz, 1H), 7.43 (t, *J* = 7.8 Hz, 2H), 7.29 (d, *J* = 8.4 Hz, 2H), 7.18 (d, *J* = 8.8 Hz), 6.96 (d, *J* = 3.2 Hz, 1H), 6.18 (d, *J* = 3.2 Hz, 1H), 2.08 (s, 3H) ppm. ^{13}C NMR (100 MHz $CDCl_3$) δ 168.2, 133.6, 132.7, 131.4, 130.7, 130.2, 128.8, 128.4, 128.2, 128.0, 123.9, 123.7, 113.9, 11.6 ppm. IR ν max (film)/cm^{-1} 1681, 1330. GC-MS m/z (ES+) m/z: 295 $[M]^+$, HRMS (ESI): calcd for $C_{18}H_{15}ClNO$ (M + H^+) 296.0842, found 296.0836.

2-(Furan-2-yl)-3-methyl-1-[(4-methylphenyl)sulfonyl]-1H-pyrrole ***6o***. Yield: 76% (41 mg, 0.13 mmol). ^{1}H NMR (400 MHz $CDCl_3$) δ 7.49 (d, *J* = 8.3 Hz, 2H), 7.46 (dd, *J* = 1.8, 0.9 Hz, 1H), 7.39 (d, *J* = 3.1 Hz, 1H), 7.22 (d, *J* = 8.2 Hz, 2H), 6.47 (dd, *J* = 3.1, 1.8 Hz, 1H), 6.38 (d, *J* = 3.2 Hz, 1H), 6.19 (d, *J* = 3.2 Hz, 1H), 2.39 (s, 3H), 1.93 (s, 3H) ppm. ^{13}C NMR (100 MHz $CDCl_3$) δ 144.6, 143.1, 142.9, 136.0, 129.5, 127.7, 127.3, 123.5, 120.9, 113.9, 113.1, 110.7, 21.7, 11.8 ppm. IR ν max (film)/cm^{-1} 2917, 1368, 1172. GC-MS m/z (ES+) m/z: 301 $[M]^+$, HRMS (ESI): calcd for $C_{16}H_{16}NO_3S$ (M + H^+) 302.0851, found 302.0846.

2-Cyclohexyl-3-methyl-1-[(4-methylphenyl)sulfonyl]-1H-pyrrole ***6p***. Yield: 43% (23 mg, 0.07 mmol). ^{1}H NMR (400 MHz $CDCl_3$) δ 7.64 (d, *J* = 8.4 Hz, 2H), 7.29 (d, *J* = 8.1 Hz, 2H), 7.23 (d, *J* = 3.3 Hz, 1H), 6.03 (d, *J* = 3.0 Hz, 1H), 3.10 (dt, *J* = 11.9, 3.3 Hz, 1H), 2.42 (s, 3H),

2.06 (s, 3H), 1.69-1.58 (m, 4H), 1.51-1.44 (m,4H), 1.34-1.27 (m, 2H) ppm. ^{13}C NMR (100 MHz $CDCl_3$) δ 144.5, 137.1, 134.4, 129.8, 126.8, 120.6, 120.3, 114.7, 36.0, 31.1, 29.7, 27.0, 26.0, 21.7, 13.2 ppm. IR ν max (film)/cm^{-1} 2222, 1368, 1145. GC-MS m/z (ES+) m/z: 317 $[M]^+$, HRMS (ESI): calcd for $C_{18}H_{24}NO_2S$ (M + H^+) 318.1528, found 318.1516.

3-Methyl-1-[(4-methylphenyl)sulfonyl]-2-(propan-2-yl)-1H-pyrrole ***6q***. Yield: 71% (31 mg, 0.11 mmol). ^{1}H NMR (400 MHz $CDCl_3$) δ 7.60 (d, *J* = 8.3 Hz, 2H), 7.28 (d, *J* = 8.3 Hz, 2H), 7.21 (d, *J* = 3.3 Hz, 1H), 6.03 (d, *J* =2.9 Hz, 1H), 3.49 (s, *J* = 7.2 Hz, 1H), 2.41 (s, 3H), 2.04 (s, 3H), 1.04 (d, *J* = 6.7 Hz, 6H) ppm. ^{13}C NMR (100 MHz $CDCl_3$) δ 144.5, 137.1, 135.3, 129.9, 126.7, 120.6, 120.5, 114.9, 29.7, 25.4, 21.6, 21.2, 12.9 ppm. IR ν max (film)/cm^{-1} 2359, 1362, 1166. GC-MS m/z (ES+) m/z: 277 $[M]^+$, HRMS (ESI): calcd for $C_{15}H_{20}NO_2S$ (M + H^+) 278.1215, found 278.1207.

3-Methyl-1-[(4-methylphenyl)sulfonyl]-2-(2-methylpropyl)-1H-pyrrole ***6r***. Yield: 69 % (36 mg, 0.12 mmol). ^{1}H NMR (400 MHz $CDCl_3$) δ 7.58 (d, *J* = 8.2 Hz, 2H), 7.26 (d, *J* = 8.8 Hz, 2H), 7.20 (d, *J* = 3.2 Hz, 1H), 6.09 (d, *J* = 3.2 Hz, 1H), 2.46 (d, *J* = 7.3 Hz, 2H), 2.40 (s, 3H), 2.03-1.93 (m, 1H), 1.92 (s, 3H), 0.86 (d, *J* = 6.4 Hz, 6H) ppm. ^{13}C NMR (100 MHz $CDCl_3$) δ 144.4, 137.0, 130.9, 129.8, 126.4, 122,5, 121.8, 114.5, 34.1, 29.9, 22.7, 22.3, 21.6, 12.0 ppm. IR ν max (film)/cm^{-1} 2170, 1371, 1170. GC-MS m/z (ES+) m/z: 291 $[M]^+$, HRMS (ESI): calcd for $C_{16}H_{22}NO_2S$ (M + H^+) 292.1371, found 292.1364.

Synthesis of 3-methyl-2-phenyl-1H-pyrrole ***16***. The pyrrole **6f** (90 mg, 0.452 mmol) was added to a round bottom flask containing 2.5M NaOH solution (2 mL). The reaction mixture was allowed to stir at r.t. for 3h. The reaction mixture was then diluted with 10 mL of water, and 10 mL of DCM were added. The aqueous layer was extracted twice with DCM. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under

reduced pressure. The crude pyrrole**16** was purified by flash column chromatography (SiO_2) using 2:3 EtOAc/hexanes as the eluent.

Yield: 90 % (64 mg, 0.4 mmol). ^{1}H NMR (400 MHz $CDCl_3$) δ 8.13 (brs, 1H), 7.45-7.37 (m, 4H), 7.25-7.21 (m, 1H), 6.76 (t, *J* = 2.7 Hz, 1H), 6.14 (t, *J* = 2.7 Hz, 1H), 2.27 (s, 3H) ppm. ^{13}C NMR (100 MHz $CDCl_3$) δ 133.7, 128.7, 128.6, 128.3, 128.0, 126.4, 126.0, 117.3, 116.1, 112.2, 14.2 ppm. GC-MS m/z (ES+) m/z: 157 $[M]^+$.

*Synthesis of pyrrole **17**.* DMF (0.11 mmol) and phosphorus oxychloride (0.10 mmol) were added to a round bottom flask containing DCM (2 mL). The solution was allowed to stir for 15 minutes at room temperature. Then the solution was cooled down at 0 °C and 3-methyl-2-phenyl-1H-pyrrole **16** (16 mg, 0.10 mmol) in 1 mL of DCM was added to the solution previously obtained. The solution was allowed to stir at room temperature for 1 h. The reaction mixture was then quenched with 10 mL of 1M Na_2CO_3 solution. The aqueous layer was extracted twice with DCM. The combined organic layers were washed with a $NaHCO_3$ saturated solution, brine and dried over Na_2SO_4 and concentrated under reduced pressure. The crude pyrrole was purified by flash column chromatography (SiO_2) using 1:4 EtOAc/hexanes as the eluent to yield the **17** as an oil.

Yield: 86 % (16 mg, 0.08 mmol). ^{1}H NMR (400 MHz $CDCl_3$) δ 9.44 (s, 1H), 9.22 (bs, 1H), 7.51-7.43 (m, 4H), 7.38-7.34 (m, 1H), 6.84 (d, *J* = 2.29 Hz 1H), 2.27 (s, 3H) ppm. ^{13}C NMR (100 MHz $CDCl_3$) δ 178.6, 136.9, 131.6, 131.4, 129.0, 128.3, 127.2, 123.7, 119.5, 12.5 ppm. IR ν max (film)/cm^{-1} 1634, 1418, 1261. GC-MS m/z (ES+) m/z: 185 $[M]^+$, HRMS (ESI): calcd for $C_{12}H_{12}NO$ $(M + H^+)$ 186.0919, found 186.0912.

*General procedure for the synthesis of pyrroles **18** and **20**.* Sodium cyanoborohydride (0.38 mmol, 3 equiv) was added to a round bottom flask containing trifluoroacetic acid (2 mL). The solution was allowed to stir for 20 minutes at room temperature. Then the appropriate pyrrole

6b or **6r** (0.127 mmol, 1 equiv), was added to the solution previously obtained. The solution was allowed to stir at room temperature for 1 h. The reaction mixture was then quenched with 10 mL of water, and 10 mL of DCM. The aqueous layer was extracted twice with DCM. The combined organic layers were washed with a $NaHCO_3$ saturated solution, brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude pyrrolines **18** and **20** proved to be pure enough to be used in the next synthetic step without any further purification.

2-isobutyl-3-methyl-1-[(4-methylphenyl)sulfonyl]-2,5-dihydro-1H-pyrrole ***18***. ^{1}H NMR (400 MHz $CDCl_3$) δ 7.65 (d, *J* = 8.4 Hz, 2H), 7.25 (d, *J* = 8.4 Hz, 2H), 4.78 (s,1H), 4.32 (d, *J* = 1.6 Hz, 2H), 2.38 (s, 3H), 1.92-1.85 (m, 1H), 1,56 (s, 3H), 1.48 (d, *J* = 1.8 Hz, 2H), 1.01 (d, *J* = 6.8 Hz, 3H), 0.88 (d, *J* = 6.8 Hz, 3H) ppm. ^{13}C NMR (100 MHz $CDCl_3$) δ 149.4, 138.6, 137.5, 129.6, 127.5, 118.9, 68.4, 42.4, 33.9, 24.3, 23.8, 23.2, 14.1 ppm. LRMS m/z (ES+) m/z: 294.

3-methyl-1-[(4-methylphenyl)sulfonyl]-2,5-dihydro-1H-pyrrole ***20***. ^{1}H NMR (400 MHz $CDCl_3$) δ 7.69 (d, *J* = 8.4 Hz, 2H), 7.30 (d, *J* = 8.4 Hz, 2H), 5.22 (s, 1H), 4.04 (d, *J* = 4.0 Hz, 2H), 3.94 (s,2H), 2.40 (s, 3H), 1.63 (s, 3H) ppm. ^{13}C NMR (100 MHz $CDCl_3$) δ 143.4, 135.1, 134.2, 129.8, 127.5, 119.1, 57.7, 55.2, 21.5, 14.1 ppm. LRMS m/z (ES+) m/z: 238.

General procedure for the synthesis of aldehydes ***19*** *and* ***21***.The appropriate pyrroline **18** or **20** (0.076 mmol, 1 equiv) was added to a round bottom flask containing anhydrous dioxane (2 mL). Then SeO_2 (0.076 mmol, 1 equiv) was added to the solution previously obtained. The solution was allowed to stir at reflux for 1 h under N_2 atmosphere. The reaction mixture was then cooled at room temperature, quenched with 10 mL of water, and 10 mL of DCM were added. The aqueous layer was extracted twice with DCM. The combined organic layers were washed with a $NaHCO_3$ saturated solution and brine, dried over Na_2SO_4 and concentrated

under reduced pressure. The crude aldehydes were purified by flash column chromatography (SiO_2) using 2:3 EtOAc/hexanes as the eluent to yield the desired **19** and **21** as an oils.

1-(2-isobutyl-1-[(4-methylphenyl)sulfonyl]-2,5-dihydro-1H-pyrrol-3-yl)ethanone ***19***. Yield: 65 % (25 mg, 0.08 mmol). ^{1}H NMR (400 MHz $CDCl_3$) δ 9.53 (s, 1H), 7.65 (d, *J* = 8.4 Hz, 2H), 7.25 (d, *J* = 8.2 Hz, 2H), 6.53 (s, 1H), 4.78 (d, *J* = 1.3 Hz, 1H), 4.34-4.32 (m, 2H), 2.41 (s, 3H), 1.92-1.85 (m, 1H) 1.48(d, *J* = 2.0 Hz, 2H), 1.01(d, *J* = 6.8 Hz, 3H), 0.88(d, *J* = 6.8 Hz, 3H) ppm. ^{13}C NMR (100 MHz $CDCl_3$) δ 186.5, 146.1, 143.9, 143.4, 134.3, 129.5, 127.5, 63.7, 54.9, 43.1, 28.3, 28.1, 24.4, 23.8, 22.4, 21.6 ppm. IR ν max (film)/cm^{-1} 1682, 1165. LRMS m/z (ES+) m/z: 308 $[M+H]^+$, HRMS (ESI): calcd for $C_{16}H_{22}NO_3S$ (M + H^+) 308.1320, found 308.1308.

1-[(4-methylphenyl)sulfonyl]-2,5-dihydro-1H-pyrrole-3-carbaldehyde ***21***. Yield: 56 % (18 mg, 0.07 mmol). ^{1}H NMR (400 MHz $CDCl_3$) δ 9.53 (s, 1H), 7.65 (d, *J* = 8.4 Hz, 2H), 7.25 (d, *J* = 8.4 Hz, 2H), 4.78 (s,1H), 4.32 (d, *J* = 1.6 Hz, 2H), 2.38 (s, 3H), 1.92-1.85 (m, 1H), 1.48 (d, *J* = 1.8 Hz, 2H), 1.01 (d, *J* = 6.8 Hz, 3H), 0.88 (d, *J* = 6.8 Hz, 3H), ppm. ^{13}C NMR (100 MHz $CDCl_3$) δ 186.5, 144.1, 142.4, 141.7, 130.0, 127.5, 55.5, 51.9, 21.6 ppm. IR ν max (film)/cm^{-1} 1681, 1344, 1163. LRMS m/z (ES+) m/z: 252 $[M+H]^+$, HRMS (ESI): calcd for $C_{12}H_{14}NO_3S$ (M + H^+) 252.0694, found 252.0686.

ASSOCIATED CONTENT

Supporting Information: Copies of ^{1}H- and ^{13}C-NMR spectra. Conversion of **5** into **6a**.This material is available free of charge via the Internet at http://pubs.acs.org/.

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REFERENCES

1. a) Bergman, J.; Janosik, T. "Five-Membered Heterocycles: Pyrrole and Related Systems", Chapter 4, Modern Heterocyclic Chemistry, Ed. Alvarez-Builla, J., Wiley-VCH, Weinheim; b) Estévez , V.; Villacampa, M.; Menéndez, J. C. *Chem. Soc. Rev.* **2010**, *39*, 4402-4421; c) Estévez , V.; Villacampa, M.; Menéndez, J. C. *Chem. Soc. Rev.* **2014**, *43*, 4633-4657.

2. a) Donohoe, T. J.; Orr, A. J.; Gosby, K.; Bingham, M. *Eur. J. Org. Chem.* **2005**, 1969–1971. b) Donohoe, T. J.; Kershaw, N. M.; Orr, A. J.; Wheelhouse, K. M. P.; Fishlock, L. P.; Lacy, A. R.; Bingham, M.; Procopiou, P. A. *Tetrahedron*, **2008**, *64*, 809.

3. De Matteis, V.; Dufay, O.; Waalboer, D. C. J.; van Delft, F. L.; Tiebes, J.; Rutjes, F. P. J. T. *Eur. J. Org. Chem.* **2007**, 2667–2675.

4. a) Dieltiens, N.; Stevens, C. V.; De Vos, D.; Allaert, B.; Drozdzak, R.; Verpoort, F. *Tetrahedron Lett.* **2004**, *45* , 8995 –8998; b) Dieltiens, N.; Stevens, C. V.; Allaert, B.; Verpoort, F. *ARKIVOC* **2005**, *i* ,92–97; c) Moonen, K.; Dieltiens, N.; Stevens, C. V. *J. Org. Chem.* **2006**, *71*,4006–4009.

5. a) Sánchez, I.; Pujol, M. D. *Synthesis* **2006**, 1823–1828; b) Chen, W.; Wang, *J. Organometallics* **2013**, *32*, 1958–1963.

6. Schmidt, B.; Khrel, S.; Jablowski, E. *Org. Biomol. Chem.* **2012**, *10*, 5119.

7. Donohoe, T. J.; Race, N. J.; Bower, J. F.; Callens, C. K. A. *Org. Lett.* **2010**, *12*, 4094-4097.

8. Shafi, S.; Kędziorek, M.; Grela, K. *Synlett* **2011**, 124-128.

9. For reviews on enyne metathesis see: a) Diver, S. T.; Giessert, A. J. *Chem. Rev.* **2004**, *104*, 1317−1382. b) Villar, H.; Frings, M.; Bolm, C. *Chem. Soc. Rev.* **2007**, *36*, 55-66. c) Mori, M. *Materials* **2010**, *3*, 2087-2140. d) Fischmeister, C.; Bruneau, C. *Beilstein J. Org.Chem.***2011**, *7*, 156-166.

10. For recent examples see: a) Boeda, F.; Clavier, H.; Jor-daan, M.; Meyer, W. H.; Nolan, S. P. *J. Org. Chem.* **2008**, *73*, 259-263; b) Yang, Q.; Alper, H.; Xiao, W.-J. *Org. Lett.* **2007**, *9*, 769-771; c) Kotha, S.; Meshram, M.; Tiwari, A. *Chem. Soc. Rev.* **2009**, *38*, 2065-2092; d) Castagnolo, D.; Botta, L.; Botta, M. *Tetrahedron Lett.* **2009**, *14*, 1526-1528.

11. Dieltiens, N.; Moonen, K.; Stevens C. V. *Chem. Eur. J.* **2007**, *13*, 203–221.

12. Castagnolo, D.; Botta, L.; Botta, M. *J. Org. Chem.***2009**, *74*, 3172-3174.

13. a) Taguchi, K.; Sakaguchi, S.; Ishii, Y. *Tetrahedron Lett.* **2005** , *46*, 4539 – 4542; b) Yagi, T.; Aoyama, T.; Shioiri, T. *Synlett* **1997**, *9*, 1063 – 1064; c) Aelterman, W.; De Kimpe, N.; Tyvorskii, V.; Kulinkovich, O. *J. Org. Chem.* **2001**, *66*, 53 – 58; d) Chandrasekhar, S.; Patroa, V.; Chavana, L. N.; Chegondia, R.; Gréeb, R. *Tetrahedron Lett.* **2014**, *55*, 5932-5935; e) Thies, N.; Gerlach, M.; Haak, E. *Eur. J. Org. Chem.* **2013**, 7354 - 7365; f) Martín, R.; Larsen, C. H.; Cuenca, A.; Buchwald, S. L. *Org. Lett.* **2007**, *9*, 3379–3382; g) Zhang, M.; Fang, X.; Neumann, H.; Beller, M. *J. Am. Chem. Soc.* **2013**, *135*, 11384–11388.

14. It is possible that both [Ru] and Cu^{2+} contribute to the cyclization of the diene intermediate. See Supporting Information for additional details.

15. a) Slugovc, C.; Demel, S.; Riegler, S.; Hobisch, J.; Stelzer, F. *J. Mol. Catal. A: Chemical* **2004**, *213 (1)*, 107–113; b) P. Compain *Adv. Synth. Catalysis* **2007**, 349, 1829.

16. Woodward, C. P.; Spiccia, N. D.; Jackson, W. R.; Robin-son, A. J. *Chem. Commun.***2011**, *47*, 779-781.

17. a) Castagnolo, D.; Armaroli, S.; Corelli, F.; Botta, M. *Tetrahedron: Asymmetry* **2004**, *15*, 941-949; b) Castagnolo, D.; Renzulli, M.L.; Galletti, E.; Corelli, F.; Botta, M. *Tetrahedron: Asymmetry* **2005**, *16*, 2893-2896; c) Castagnolo, D.; Dessì, F.; Radi, M.; Botta, M. *Tetrahedron: Asymmetry* **2007**, *11*, 1345-1350.

18. Detz, R. J.; Abiri, Z.; Le Griel, R.; Hiemstra, H.; Van Maarseveen, J. H. *Chem. Eur. J.* **2011**, *17*, 5921 – 5930.

19. Meyet, C. E.; Pierce, C. J.; Larsen, C. H. *Org. Lett.* **2012**, *14*, 964-967.

20. Lee, S. H.; Seo, H. J.; Kim, M. J.; Kang, S. Y.; Song, K.-S.; Lee, S.-H.; Jung, M. E.; Kim, J.; Lee, J. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 1899 – 1902.

21. Wang, J.-G.; Yang, Y.; Huang , Z.-H.; Kang, F. *J. Mater. Chem.* **2012**, *22*, 16943-16949.

22. a) Carballo, R. M.; Purino, M.; Ramírez, M. A.; Martín, V. S.; Padrón, J. *Org. Lett.* **2010**, *12*, 5334–5337. ; b) Aramini, A.; Brinchi, L.; Germani, R.; Savelli, G. *Eur. J. Org. Chem.* **2000**, *9*, 1793-1797. c) The aldehyde **21** was converted into the corresponding [1-(toluene-4-sulfonyl)-pyrrolidin-3-yl]-methanol described in Ref. 22a by treatment with

$NaBH_4$-$CoCl_2$ following the procedure described in Ref 22b. Details on the reduction step are reported in the Supporting Information.

23. Anderson, W. K.; Milowsky, A. S. *J. Med. Chem.* **1987**, *30*, 2144.

24. Molander,G. A.; Cadoret, F. *Tetrahedron Lett.***2011**, *52*, 2199 – 2202.

25. Campolo, D.; Arif, T.; Borie, C.; Mouysset, D.; Vanthuyne, N.; Naubron, J.-V.; Bertrand,M. P.; Nechab,M. *Angew. Chem. Int. Ed.* **2014**, *53*, 3227 – 3231.

26. Dinges, J.; Albert, D. H.; Arnold, L. D.; Ashworth, K. L.;Akritopoulou-Zanze, I.;Bousquet, P. F.; Bouska, J. J.; Cunha, G. A.; Davidsen, S. K.; Diaz, G. J.; Djuric, S. W.; Gasiecki, A. F.; Gintant, G. A.; Gracias, V. J.; Harris, C. M.; Houseman, K. A.; Hutchins, C. W.; Johnson, E. F.; Li, H.;Marcotte, P. A.; Martin, R. L.; Michaelides, M. R.; Nyein, M.; Sowin, T. J.; Su, Z.; Tapang, P. H.; Xia,Z.; ZhangH. Q. *J. Med. Chem.* **2007**, *50*, 2011 – 2029.

27. Wipf, P.; Aoyama,Y.; Benedum,T. E. *Org. Lett.***2004**, *6*, 3593 – 3595.

28. Iafe, R. G.; Kuo, J. L.; Hochstatter, D. G.; Saga, T.; Turner, J. W.; Merlic, C. A. *Org. Lett.* **2013**, *15*, 582 – 585.

29. Hattori, G.; Matsuzawa, H.; Miyake,Y.; Nishibayashi,Y. *Angew. Chem. Int. Ed.* **2008**, *47*, 3781 – 3783.

30. Chen, W.; Wang, J. *Organometallics* **2013**, *32*, 1958–1963.

31. Castagnolo, D.; Giorgi, G.; Spinosa, R.; Corelli,F.; Botta,M. *Eur. J. Org. Chem.* **2007**, *22*, 3676-3686.

32. Detz, R.J.; Delville, M.M. E.; Hiemstra, H.; Van Maarseveen, J.H. *Angew. Chem. Int. Ed.* **2008**, *47*, 3777-3780.

33. Nishibayashi, Y.; Milton, M.D.; Inada, Y.; Yoshikawa, M.; Wakiji, I.; Hidai, M.; Uemura, S. *Chem. Eur. J.* **2005**, *11*, 1433-1451.

34. Labonne, A.; Zani, L.; Hintermann, L.; Bolm, C. *J. Org. Chem.* **2007**, *72*, 5704-5708.

35. Shin, Y. H.; Maheswara, M.; Hwang, J. Y.; Kang, E. J. *Eur. J. Org. Chem.* **2014**, *11*, 2305-2311.