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Ring-closing enyne metathesis of allylic and propargylic cyanamides

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Dedicated to Prof. Samir Z. Zard, a pioneer in radical chemistry and a passionate chemist

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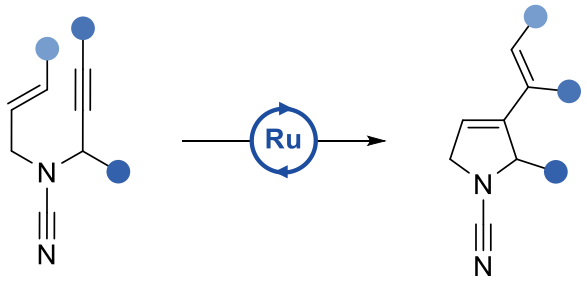
Abstract

A straightforward entry to 5-membered cyclic cyanamides from readily available allylic and propargylic cyanamides is reported. These starting materials are easily obtained by a multicomponent A^3 coupling followed by a von Braun reaction and they were shown to be readily cyclized by a ring-closing enyne metathesis, upon simple reaction with Grubbs II catalyst, to the corresponding highly functionalized cyclic cyanamides.



Keywords: Cyanamides, pyrrolidines, enyne metathesis, ruthenium catalysis, Grubbs catalyst

Introduction

Due to their unique N-C≡N connectivity and their unique reactivity, cyanamides represent an important class of synthetic intermediates which have been utilized in a vast array of transformations.[1,2,3] The cyanamide moiety can be moreover found in some natural products, such as the antibacterial agent 11-*N*-cyano-11-*N*-methylmoloka'iamine **1**[4] or fradcarbazole C **2**,[5] a cytotoxic molecule and kinase inhibitor, as well as in a range of molecules displaying various biological activities including drugs such as pinacidil **3**,[6] an antihypertensive, cimetidine **4**,[7] a cyanamide drug used for the treatment of heartburns and peptic ulcers, or the Janus kinase inhibitor **5**[8] developed by Pfizer. Cyanamides are also commonly utilized in agrochemicals and a variety of insecticides contain a cyanamide moiety, sulfoxalor **6**,[9] thiacloprid **7**,[10] and acetamiprid **8**[11] being representative examples.

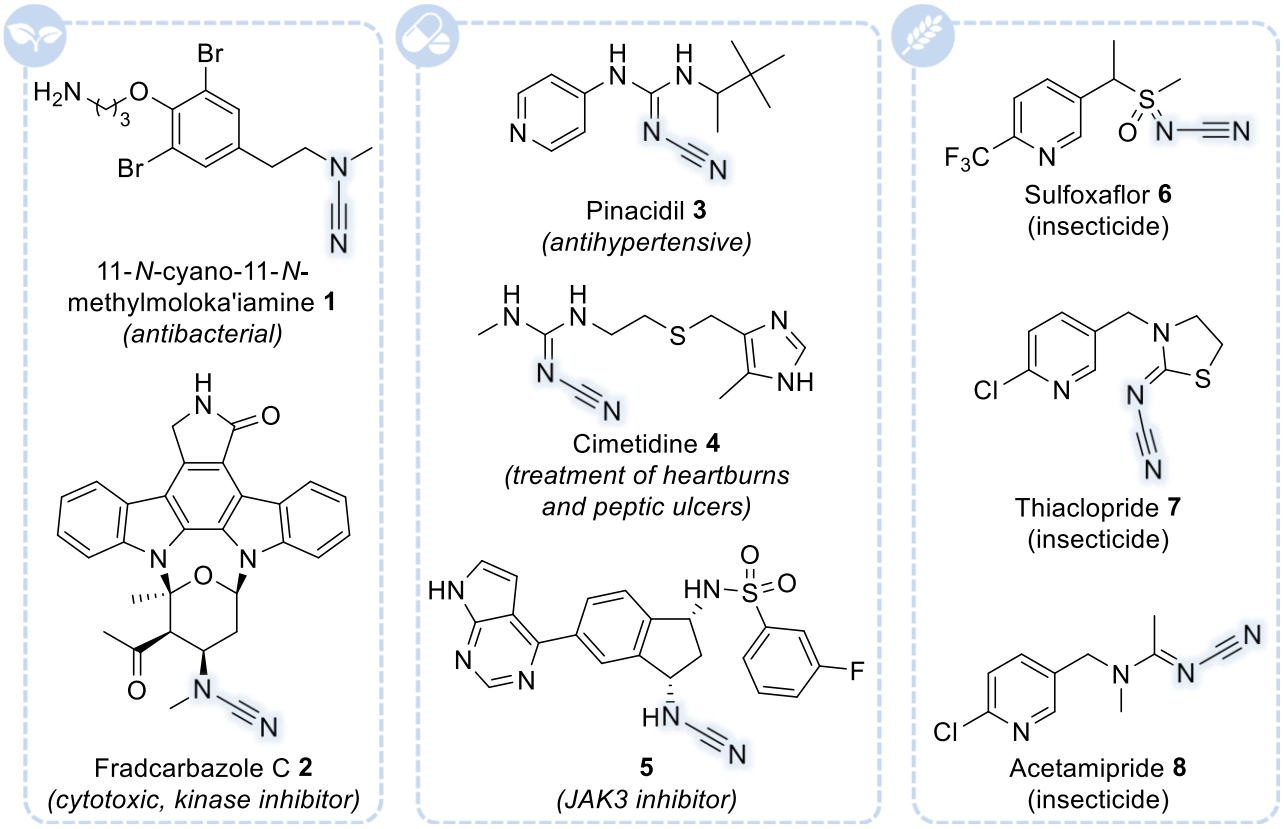
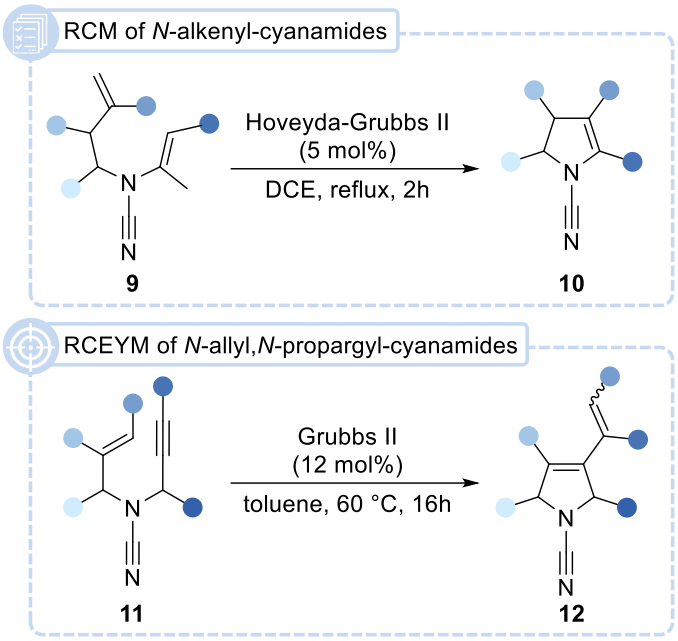


Figure 1. Representative naturally occurring and/or biologically active cyanamides.

Due to the importance of cyanamides, notably in medicinal chemistry where nitrogen-containing heterocycles are among the most significant structural components of pharmaceuticals,[12] and based on our recent interest in the chemistry of cyanamides,[13,14,15,16] we report in this manuscript an efficient and rapid entry to 5-membered cyclic cyanamides from readily available allylic and propargylic cyanamides. The ring-closing metathesis reaction of *N*-alkenyl-cyanamides **9** to cyclic unsaturated cyanamides **10** we reported in 2021[15] (Scheme 1, top) indeed prompted us to investigate the related cyclization of *N*-allyl,*N*-propargyl-cyanamides **11**, compounds that are readily available through a A^3 coupling[17] followed by a von Braun reaction, to the corresponding highly functionalized cyclic cyanamides **12** that would result from a ring-closing enyne metathesis[18] (Scheme 1, bottom). Results from this study are reported in this manuscript.



Scheme 1. Previously reported ring-closing metathesis reaction of *N*-alkenyl-cyanamides (top) and ring-closing enyne metathesis of allylic and propargylic cyanamides (this work, bottom).

Results and Discussion

We first focused our efforts on the optimization of this ring-closing enyne metathesis starting from model allylic and propargylic cyanamide **11a**. A variety of catalysts, additives and conditions was evaluated and results from this study are shown in Figure 2.

An initial screening of representative ruthenium-based catalysts typically used for ring-closing enyne metathesis, including Grubbs I and II catalysts as well as Hoveyda-Grubbs II catalyst revealed the superiority of Grubbs II catalyst (not shown), which was therefore selected for the next steps of the optimization. Screening the catalyst loading showed that the reaction was best performed using 12 mol% of this catalyst. A range of additives were next evaluated, including 3-bromopyridine, phenol and titanium isopropoxide, the first two ones being known additives facilitating the activation of Grubbs catalysts[19,20,21,22] while the third one was evaluated to avoid a potential deactivation of the catalyst by the coordinating cyanamide moiety.[23,24] None of these additives however had a significant effect on the reaction. Screening different solvents compatible with both the substrate and the catalyst showed that 1,2-dichloroethane could be suitably replaced by more sustainable toluene. Increasing the concentration resulted in a significant drop in yield, which is not surprising for a ring-closing metathesis reaction. Finally, the influence of the temperature on the reaction was briefly evaluated and we noted that performing the reaction at 60 °C for 16 h was as effective as conducting it at higher temperatures. As a note, the reaction was still efficient at room temperature but required 65 hours to go to completion. The optimal conditions were therefore set with 12 mol% of the Grubbs II catalyst in toluene at 0.025 M under argon at 60 °C for 16 h. Using these conditions, the desired cyclic cyanamide **12a** could be formed in 64% ^{1}H NMR yield and 60% isolated yield.

With these optimized conditions in hands, we next focused our efforts on the study of the scope and limitations of this ring-closing enyne metathesis of allylic and propargylic cyanamides, which first involved the synthesis of a library of these starting materials with representative electronic and steric properties.

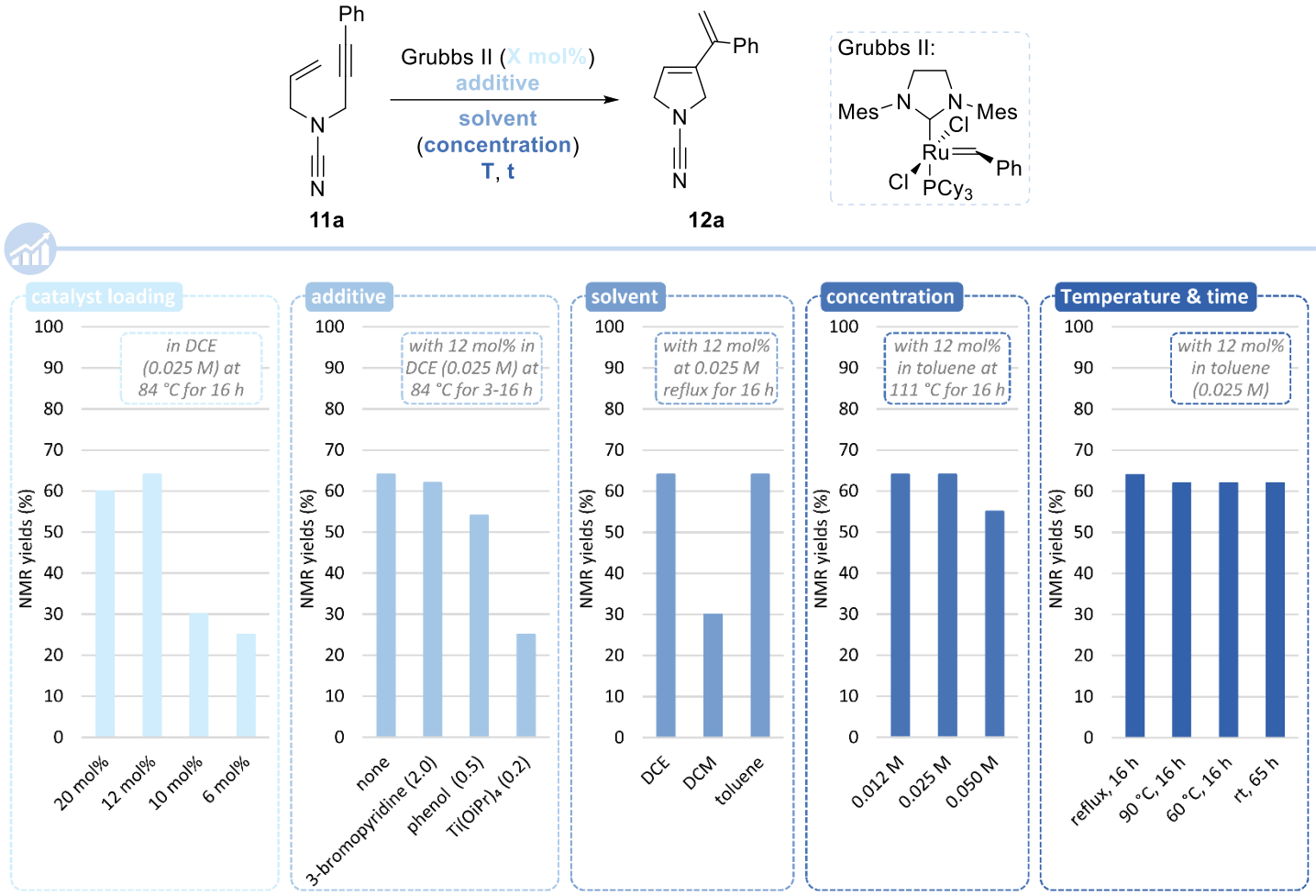


Figure 2. Optimization of the ring-closing enyne metathesis of allylic and propargylic cyanamides. *^{1}H NMR yields determined using 1,1,2,2-tetrachloroethane as an internal standard.*

The starting allylic and propargylic cyanamides **11** were indeed readily prepared using a two-step sequence based on an A^3 coupling followed by a von Braun reaction as shown in Figure 3. PMB-protected allylic amines **13** were thus reacted with an excess of an aldehyde **14** and a slight excess of an alkyne **15** in the presence of catalytic amounts of copper(I) bromide in acetonitrile at room temperature for 16 hours,[25] providing the corresponding PMB-protected allylic and propargylic amines **16** in fair to excellent yields. These conditions were found to be more efficient with formaldehyde compared to other aldehydes (**11j** and **11k**), which required additional 4Å molecular sieves and heating in toluene, and a diminished reactivity was also noted in the case of a less nucleophilic α-substituted amine (**11n**). These PMB-protected amines **16** were then subjected to a von Braun reaction by simple treatment with cyanogen bromide in the presence of potassium carbonate in dioxane at room temperature for 16 hours. To our delight, the more labile PMB group was systematically cleaved, and the allylic and propargylic groups were left untouched. This deprotection proceeded smoothly in most cases, with a slight decrease in efficiency in the presence of substituents at the propargylic or allylic positions (**11j** and **11n**).

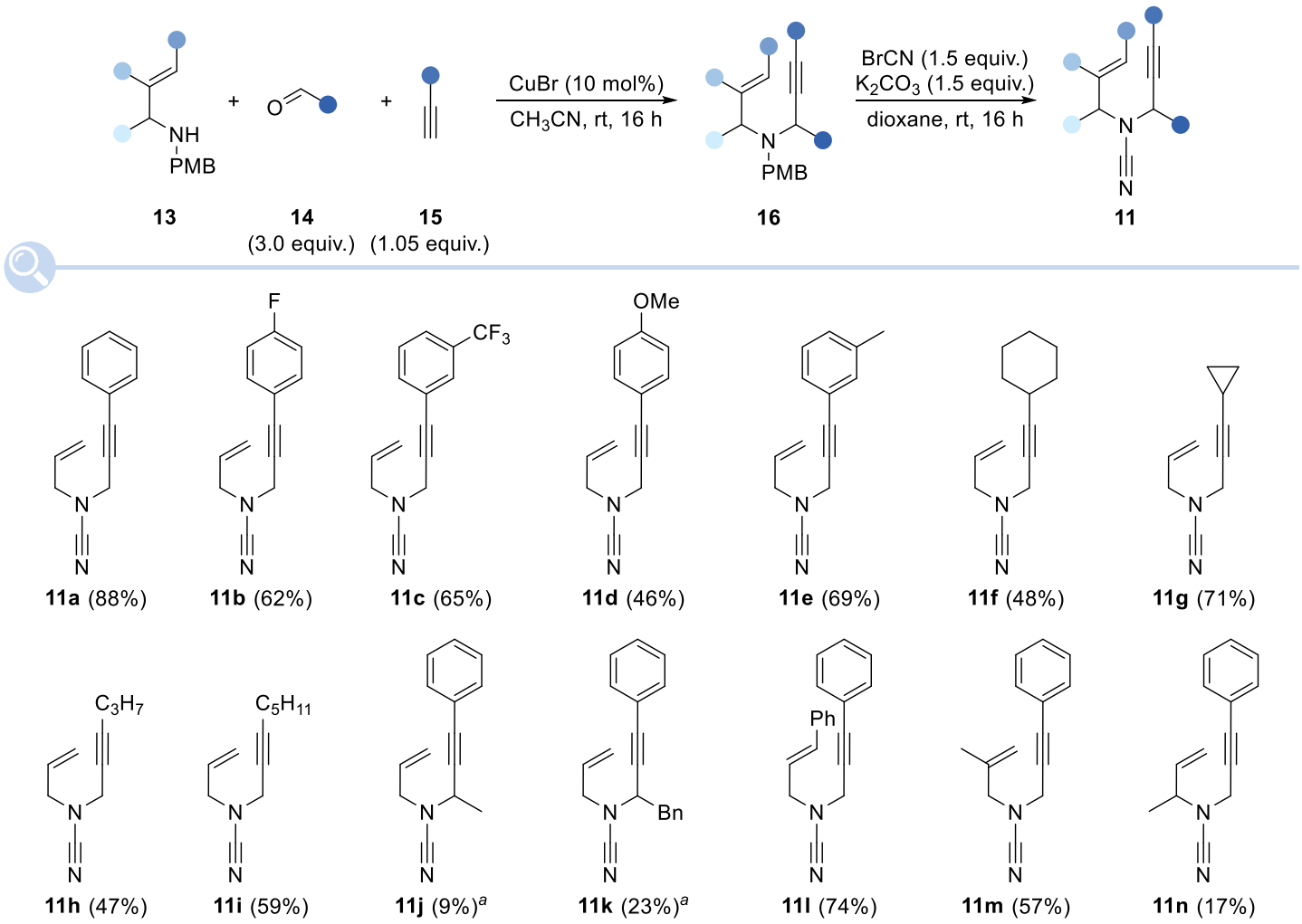


Figure 3. Synthesis of the starting allylic and propargylic cyanamides by an A^3 coupling followed by a von Braun reaction. *[a] A^3 coupling performed with 1.1 equiv. of aldehyde, 1.5 equiv. of alkyne, 4 Å molecular sieves, in toluene at 80-100 °C for 16-24 h.*

With this collection of allylic and propargylic cyanamides **11** at our disposal, they were next all engaged in the key ring-closing enyne metathesis under our optimized conditions. The metathesis reaction of all substrates was carried out using 12 mol% of Grubbs II catalyst at 60 °C in toluene, at a concentration of 0.025 M. As shown in Figure 4, the corresponding cyclic dienyl cyanamides **12** could be obtained in fair yields in most cases.
The electronic properties of the aryl group on the alkyne had a little effect on the yields, electron-poor (**11b** and **11c**) and electron-donating (**11d** and **11e**) having a similar influence. In terms of reactivity, it is worth noting however that in the presence of the anisole moiety in **11d**, the electron-rich alkyne resulted in an increased reactivity since a full conversion could be reached within 6 hours in this case. Alkyl substituents on the alkyne were also well tolerated and also required shorter reaction times, cyclic ones (**11f** and **11g**) giving lower yields compared to linear acyclic ones (**11h** and **11i**).

The first limitation was met starting from substrates substituted at their propargylic position such as **11j** and **11k**. The steric hindrance brought by these substituents is clearly detrimental for the alkyne to react with the ruthenium catalyst, which resulted in lower yields, even with protracted reaction times.

A longer reaction time was also required in the presence of a substituent at the terminal position of the alkene as in **11l**. The corresponding cyclic cyanamide **12l** was however isolated in 56% yield and as a single isomer, the most stable *E* one.

Finally, internal substitution of the alkene (**11m**) precluded its reaction with the catalyst, resulting in a total lack of reactivity, but the presence of a substituent at the allylic position (**11n**) was tolerated, an isomerization of the diene being observed in this case, **12n** and **12n'** being isolated in a 9:91 ratio and with an overall yield of 56%.

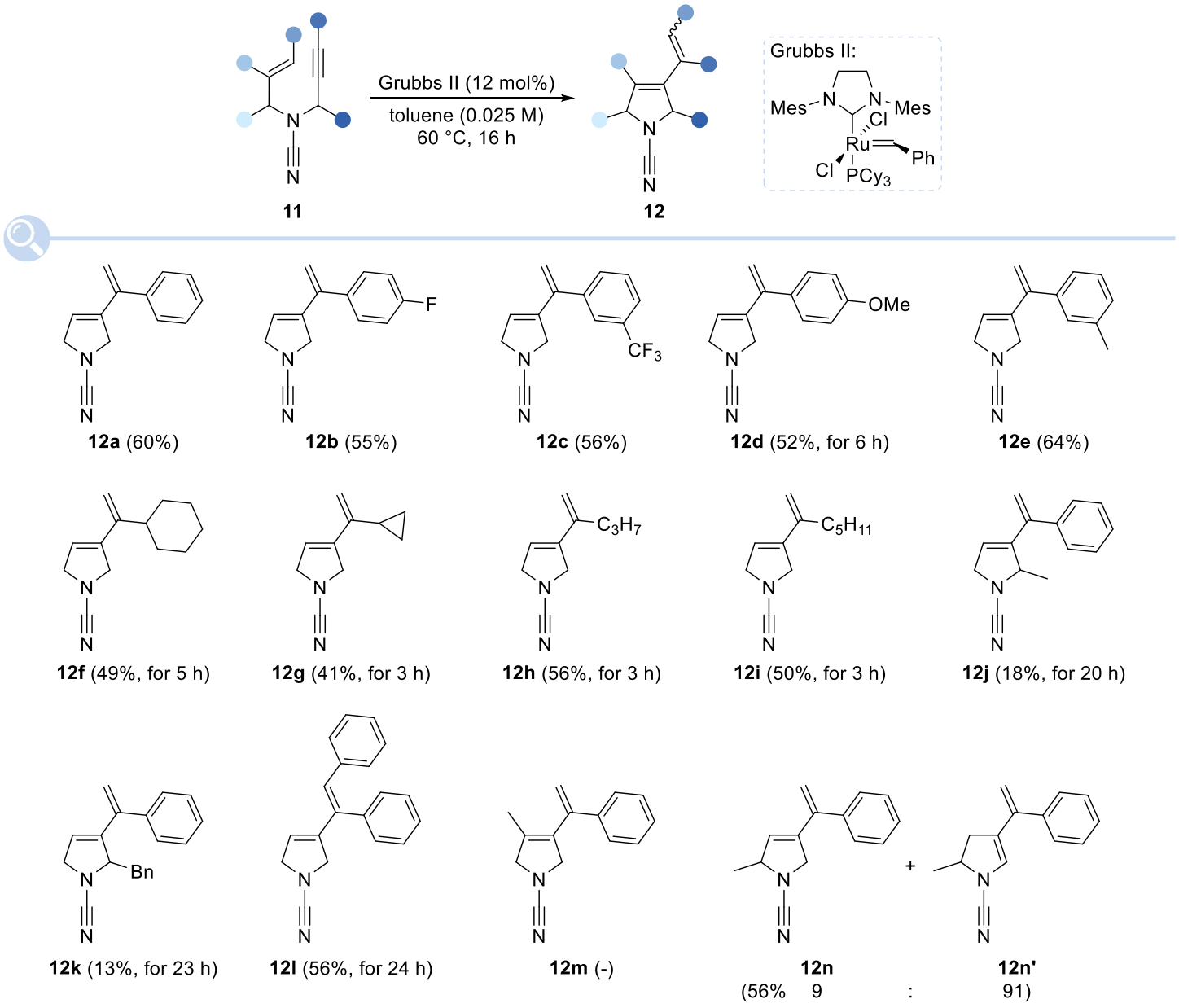


Figure 4. Scope and limitations of the ring-closing enyne metathesis of allylic and propargylic cyanamides.

Conclusions

In conclusion, we have developed a straightforward synthesis of 5-membered cyclic cyanamides from readily available allylic and propargylic cyanamides. These starting materials are easily obtained by a multicomponent A^3 coupling followed by a von Braun reaction and they were shown to be readily cyclized by a ring-closing enyne metathesis, upon simple reaction with Grubbs II catalyst, to the corresponding unreported, highly functionalized cyclic cyanamides. In addition to the potential of these heterocyclic scaffolds, this work brings additional insights into the chemistry of cyanamides and ring-closing enyne metathesis.

Experimental Section

General. All reactions were carried out in oven-dried glassware under an argon atmosphere employing standard techniques in handling air-sensitive materials. Dichloromethane and 1,2-dichloroethane were freshly distilled from calcium hydride under argon. Anhydrous 1,4-dioxane and toluene were used from commercially available argon-filled sealed bottles with molecular sieves. Copper bromide (99% purity) was purchased from Sigma-Aldrich and used as supplied.

Reactions were magnetically stirred and monitored by thin layer chromatography using Merck-Kiesegel $60F_{254}$ plates. Flash chromatography was performed with silica gel 60 (particle size 35-70 µm) supplied by Merck. Yields refer to chromatographically and spectroscopically pure compounds unless otherwise stated.

Proton NMR spectra were recorded using an internal deuterium lock at ambient temperature on Bruker 300 MHz or Jeol 400 MHz spectrometers. Internal reference of δ_H 7.26 was used for $CDCl_3$. Data are presented as follows: chemical shift (in ppm on the δ scale relative to δ_{TMS} 0), multiplicity (*s singlet, d doublet, t triplet, q quartet, quint. quintuplet, sept. septuplet, m multiplet, br. broad, app. apparent*), coupling constant (*J*/Hz) and integration. Resonances that are either partially or fully obscured are denoted obscured (obs.). Carbon-13 NMR spectra were recorded at 100 MHz using $CDCl_3$ (δ_C 77.16) as internal reference. Fluorine-19 NMR spectra were recorded at 376 MHz using 2,2,2-trifluoroethanol (δ_F -77.51) as internal reference.

Melting points were recorded on a Stuart Scientific Analogue SMP11. Infrared spectra were recorded on a Bruker Alpha (ATR). High-resolution mass-spectra in positive mode were recorded using a 6520 series quadrupole time-of-flight (Q-TOF) mass spectrometer (Agilent) fitted with a multimode ion source and on a on an Impact II quadrupole time-of-flight (Q-TOF) mass spectrometer (Bruker Daltonics GmbH) fitted with an electrospray Apollo II ESI source.

General Procedure I: A^3 coupling. To a solution of the *N*-(4-methoxybenzyl)-protected amine **13** (1.0 equiv.) in acetonitrile (0.2 M) were successively added CuBr (10 mol%), the terminal alkyne **15** (1.05 equiv.) and the aldehyde **14** (3.0 equiv.; formaldehyde was used as a 37% wt. solution in water). The resulting mixture was stirred at rt for 16 h before being concentrated under reduced pressure. The crude residue was finally purified by flash column chromatography over silica gel to afford the PMB-protected allylic and propargylic amines **16**.

***N*-[3-(Phenyl)prop-2-yn-1-yl]-*N*-(4-methoxybenzyl)-allylamine (16a)**. Prepared according to general procedure I (starting from 574 mg (3.24 mmol) of *N*-(4-methoxybenzyl)allylamine). Solvent system for flash column chromatography: petroleum ether/EtOAc: 10/1. Yield: 76% (717 mg, 2.46 mmol); Light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50-7.46 (m, 2H), 7.34-7.30 (m, 5H), 6.88 (dd, *J* 6.6 and 2.1 Hz, 2H), 5.93 (ddt, *J* 16.8, 10.1 and 6.5 Hz, 1H), 5.31 (app. dq, *J* 17.2 and 1.6 Hz, 1H), 5.20 (ddt, *J* 10.1, 2.2 and 1.2 Hz, 1H), 3.81 (s, 3H), 3.66 (s, 2H), 3.52 (s, 2H), 3.25 (dt, *J* 6.5 and 1.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.9, 135.9, 131.9, 130.8, 130.5, 128.4,

128.1, 123.6, 118.1, 113.8, 85.8, 84.6, 56.92, 56.89, 55.4, 42.1; IR (ATR): ν_{max} 2923, 2834, 1605, 1512, 1295, 1246, 1041, 931, 825 cm^{-1}; ESIHRMS *m/z* calcd for $C_{20}H_{22}NO$ $[M+H]^+$ 262.1696, found 292.1707. This compound was previously reported.[25]

***N*-[3-(4-Fluorophenyl)prop-2-yn-1-yl]-*N*-(4-methoxybenzyl)-allylamine (16b)**. Prepared according to general procedure I (starting from 200 mg (1.13 mmol) of *N*-(4-methoxybenzyl)allylamine). Solvent system for flash column chromatography: petroleum ether/EtOAc: 10/1. Yield: 78% (274 mg, 886 µmol); Light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.44 (dd, *J* 8.9 and 5.4 Hz, 2H), 7.30 (d, *J* 8.6 Hz, 2H), 7.01 (app. t, *J* 8.7 Hz, 2H), 6.87 (d, *J* 8.7 Hz, 2H), 5.91 (ddt, *J* 16.7, 10.2 and 6.5 Hz, 1H), 5.28 (app. dq, *J* 17.2 and 1.4 Hz, 1H), 5.19 (ddt, *J* 10.2, 2.1 and 1.1 Hz, 1H), 3.79 (s, 3H), 3.63 (s, 2H), 3.48 (s, 2H), 3.22 (dt, *J* 6.5 and 1.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 162.5 (d, *J* 247.5 Hz), 159.0, 135.8, 133.7 (d, *J* 8.2 Hz), 130.7, 130.5, 119.6 (d, *J* 3.6 Hz), 118.1, 115.6 (d, *J* 87.5 Hz), 113.9, 84.6, 84.3, 57.0, 56.9, 55.4, 42.1; ^{19}F NMR (376 MHz, $CDCl_3$): *δ* -111.9 (app. ddd, *J* 13.9, 8.7 and 5.4 Hz); IR (ATR): ν_{max} 2920, 2835, 1611, 1506, 1441, 1301, 1246, 1037, 835, 814 cm^{-1}.

***N*-(4-Methoxybenzyl)-*N*-{3-[3-(trifluoromethyl)phenyl]prop-2-yn-1-yl}allylamine (16c)**. Prepared according to general procedure I (starting from 200 mg (1.13 mmol) of *N*-(4-methoxybenzyl)allylamine). Solvent system for flash column chromatography: petroleum ether/EtOAc: 10/1. Yield: 81% (330 mg, 918 µmol); Light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.71 (s, 1H), 7.63 (d, *J* 7.7 Hz, 1H), 7.56 (d, *J* 7.9 Hz, 1H), 7.45 (app. t, *J* 7.8 Hz, 1H), 7.30 (d, *J* 8.7 Hz, 2H), 6.87 (d, *J* 8.7 Hz, 2H), 5.92 (ddt, *J* 16.7, 10.2 and 6.5 Hz, 1H), 5.31 (app. dq, *J* 17.2 and 1.5 Hz, 1H), 5.19 (ddt, *J* 10.2, 2.0 and 1.0 Hz, 1H), 3.81 (s, 3H), 3.65 (s, 2H), 3.52 (s, 2H), 3.24 (dt, *J* 6.5 and 1.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 159.0, 135.7, 135.0, 131.1 (q, *J* 32.3 Hz), 130.6, 130.4, 128.9, 128.5 (q, *J* 3.8 Hz), 124.7 (q, *J* 3.7 Hz), 124.5, 123.9 (q, *J* 270.8 Hz), 118.2, 113.8, 86.5, 84.3, 57.0, 56.9, 55.3, 41.9; ^{19}F NMR (376 MHz, $CDCl_3$): *δ* -63.3; IR (ATR): ν_{max} 2931, 2835, 2358, 1612, 1333, 1246, 1167, 1128, 800, 695 cm^{-1}.

***N*-(4-Methoxybenzyl)-*N*-[3-(4-methoxyphenyl)prop-2-yn-1-yl]allylamine (16d)**. Prepared according to general procedure I (starting from 200 mg (1.13 mmol) of *N*-(4-methoxybenzyl)allylamine). Solvent system for flash column chromatography: petroleum ether/EtOAc: 10/1. Yield: 84% (306 mg, 952 µmol); Light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.41 (d, *J* 8.9 Hz, 2H), 7.30 (d, *J* 8.8 Hz, 2H), 6.86 (d, *J* 8.6 Hz, 2H), 6.84 (d, *J* 8.8 Hz, 2H), 5.91 (ddt, *J* 16.7, 10.2 and 6.5 Hz, 1H), 5.28 (app. dq, *J* 17.1 and 1.4 Hz, 1H), 5.17 (ddt, *J* 10.1, 2.1 and 1.2 Hz, 1H), 3.82 (s, 3H), 3.81 (s, 3H),3.65 (s, 2H), 3.49 (s, 2H), 3.24 (dt, *J* 6.5 and 1.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 159.5, 158.9, 135.9, 133.2, 130.8, 130.5, 118.0, 115.6, 114.0, 113.8, 85.5, 83.0, 56.8 (2C), 55.4, 55.3, 42.1; IR (ATR): ν_{max} 2925, 2834, 1607, 1508, 1290, 1245, 1172, 1034, 921, 831 cm^{-1}.

***N*-(4-Methoxybenzyl)-*N*-[3-(*m*-tolyl)prop-2-yn-1-yl]allylamine (16e)**. Prepared according to general procedure I (starting from 200 mg (1.13 mmol) of *N*-(4-methoxybenzyl)allylamine). Solvent system for flash column chromatography: petroleum ether/EtOAc: 10/1. Yield: 90% (276 mg, 904 µmol); Light yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.36 (d, *J* 8.2 Hz, 2H), 7.30 (d, *J* 8.7 Hz, 2H), 7.14 (br. s, 1H), 7.12 (br. s, 1H), 6.86 (d, *J* 8.6 Hz, 2H), 5.92 (ddt, *J* 16.8, 10.2 and 6.5 Hz, 1H), 5.30 (app. dq, *J* 17.2 and 1.6 Hz, 1H), 5.18 (ddt, *J* 10.0, 2.1 and 1.1 Hz, 1H), 3.80 (s, 3H), 3.65 (s, 2H),3.50 (s, 2H), 3.23 (dt, *J* 6.5 and 1.3 Hz, 2H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 158.9, 138.2, 135.9, 131.8 (2C), 130.8, 130.6, 129.2 (2C), 120.5, 118.1, 113.8, 85.9, 83.8, 56.9 (2C), 55.4, 42.1, 21.6; IR (ATR): ν_{max} 2923, 2834, 1611, 1509, 1455, 1246, 1171, 1036, 923, 815 cm^{-1}.

***N*-(3-Cyclohexylprop-2-yn-1-yl)-*N*-(4-methoxybenzyl)allylamine (16f)**. Prepared according to general procedure I (starting from 200 mg (1.13 mmol) of *N*-(4-methoxybenzyl)allylamine). Solvent system for flash column chromatography: petroleum ether/EtOAc: 10/1. Yield: 89% (300 mg, 1.01 mmol); Light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.27 (d, *J* 8.6 Hz, 2H), 6.85 (d, *J* 8.8 Hz, 2H), 5.88 (ddt, *J* 16.7, 10.2 and 6.5 Hz, 1H), 5.25 (app. dq, *J* 17.1 and 1.4 Hz, 1H), 5.15 (ddt, *J* 10.2, 2.1 and 1.1 Hz, 1H), 3.80 (s, 3H), 3.56 (s, 2H), 3.27 (d, *J* 2.0 Hz, 2H), 3.14 (dt, *J* 6.5 and 1.3 Hz, 2H), 2.49-2.40 (m, 1H), 1.87-1.79 (m, 2H), 1.78-1.70 (m, 2H), 1.54-1.43 (m, 3H),

1.40-1.30 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.8, 136.1, 131.0, 130.5, 117.8, 113.8, 90.3, 74.3, 56.7, 56.6, 55.4, 41.7, 33.3, 29.3, 26.1, 25.0; IR (ATR): ν_{max} 2929, 2853, 1511, 1448, 1326, 1246, 1038, 921, 848, 814 cm^{-1}.

***N*-(3-Cyclopropylprop-2-yn-1-yl)-*N*-(4-methoxybenzyl)allylamine (16g)**. Prepared according to general procedure (starting from 200 mg (1.13 mmol) of *N*-(4-methoxybenzyl)allylamine). Solvent system for flash column chromatography: petroleum ether/EtOAc: 10/1. Yield: 90% (260 mg, 1.02 mmol); Light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25 (d, *J* 8.5 Hz, 2H), 6.85 (d, *J* 8.9 Hz, 2H), 5.86 (ddt, *J* 16.7, 10.1 and 6.2 Hz, 1H), 5.24 (app. dq, *J* 17.2 and 1.5 Hz, 1H), 5.14 (ddt, *J* 10.1, 2.3 and 1.2 Hz, 1H), 3.80 (s, 3H), 3.54 (s, 2H), 3.22 (d, *J* 1.9 Hz, 2H), 3.12 (dt, *J* 6.5 and 1.2 Hz, 2H), 1.32-1.24 (m,1H), 0.80-0.75 (m, 2H), 0.70-0.65 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.8, 136.0, 130.9, 130.5, 117.8, 113.8, 89.0, 70.0, 56.7, 55.4, 41.8, 8.5 (2C), -0.3; IR (ATR): ν_{max} 3085, 2917, 2833, 2239, 1611, 1511, 1246, 1037, 922, 810 cm^{-1}.

***N*-(Hex-2-yn-1-yl)-*N*-(4-methoxybenzyl)allylamine (16h)**. Prepared according to general procedure I (starting from 200 mg (1.13 mmol) of *N*-(4-methoxybenzyl)allylamine). Solvent system for flash column chromatography: petroleum ether/EtOAc: 20/1. Yield: 55% (160 mg, 621 µmol); Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27 (d, *J* 8.4 Hz, 2H), 6.85 (d, *J* 8.7 Hz, 2H), 5.88 (ddt, *J* 16.7, 10.2 and 6.5 Hz, 1H), 5.25 (app. dq, *J* 17.0 and 1.6 Hz, 1H), 5.15 (ddt, *J* 10.0, 2.1 and 1.2 Hz, 1H), 3.80 (s, 3H), 3.56 (s, 2H), 3.26 (t, *J* 2.3 Hz, 2H), 3.14 (dt, *J* 6.5 and 1.2 Hz, 2H), 2.22 (tt, *J* 7.0 and 2.2 Hz, 2H), 1.57 (app. sext., *J* 7.2 Hz, 2H), 1.03 (t, *J* 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.9, 136.1, 131.0, 130.5, 117.8, 113.8, 85.7, 74.8, 56.7 (2C), 55.4, 41.7, 22.7, 20.9, 13.7; IR (ATR): ν_{max} 2960, 2933, 2834, 1612, 1571, 1325, 1246, 1037, 920, 807 cm^{-1}.

***N*-(Oct-2-yn-1-yl)-*N*-(4-methoxybenzyl)allylamine (16i)**. Prepared according to general procedure I (starting from 200 mg (1.13 mmol) of *N*-(4-methoxybenzyl)allylamine). Solvent system for flash column chromatography: petroleum ether/EtOAc: 20/1. Yield: 59% (190 mg, 666 µmol); Colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.26 (d, *J* 8.4 Hz, 2H), 6.85 (d, *J* 8.5 Hz, 2H), 5.88 (ddt, *J* 16.8, 10.0 and 6.5 Hz, 1H), 5.25 (app. dq, *J* 17.0 and 1.2 Hz, 1H), 5.15 (ddt, *J* 10.1, 3.0 and 1.0 Hz, 1H), 3.80 (s, 3H), 3.56 (s, 2H), 3.25 (t, *J* 2.4 Hz, 2H), 3.14 (d, *J* 6.6 Hz, 2H), 2.24 (tt, *J* 7.1 and 2.1 Hz, 2H), 1.55 (app. quint., *J* 7.6 Hz, 2H), 1.46-1.39 (m, 2H), 1.35 (app. sext., *J* 7.6 Hz, 2H), 0.92 (t, *J* 7.4 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 158.9, 136.1, 131.0, 130.5 (2C), 117.8, 113.8 (2C), 85.9, 74.6, 56.7 (2C), 55.4, 41.7, 31.3, 28.9, 22.4, 18.9, 14.2; IR (ATR): ν_{max} 2914, 2835, 1612, 1511, 1246, 1171, 1038, 920, 850, 807 cm^{-1}.

***N*-Allyl-*N*-(4-methoxybenzyl)-4-phenylbut-3-yn-2-amine (16j)**. A pressure tube was charged with *N*-(4-methoxybenzyl)allylamine (100 mg, 564 µmol), CuBr (10 mg, 73 µmol) and 4Å molecular sieves (300 mg). The tube was fitted with a rubber septum, evacuated under high vacuum and backfilled with argon three times. Dry toluene (2 mL), phenylacetylene (68 µL, 846 µmol) and acetaldehyde (47 µL, 620 µmol) were then added. The rubber septum was replaced by a Teflon-coated screw cap and the reaction mixture was stirred at 100 °C for 16 h. The reaction mixture was then cooled to room temperature, filtered through a plug of Celite® and concentrated under reduced pressure. The crude residue was finally purified by flash column chromatography (petroleum ether/EtOAc: 100/1) to afford the desired product **16j** as a light yellow oil (30 mg, 98 µmol, 17%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49-7.47 (m, 1H), 7.46 (d, *J* 1.8 Hz, 1H), 7.35-7.28 (m, 5H), 6.87 (d, *J* 8.6 Hz, 2H), 5.89 (dddd, *J* 17.3, 10.1, 7.7 and 4.8 Hz, 1H), 5.28 (app. dq, *J* 17.1 and 1.7 Hz, 1H), 5.14 (br. app. d, *J* 10.1 Hz, 1H), 3.89-3.82 (m, 2H), 3.81 (s, 3H), 3.42 (app. d, *J* 13.7 Hz, 1H), 3.33 (ddt, *J* 14.1, 4.5 and 1.8 Hz, 1H), 3.04 (dd, *J* 14.3 and 7.8 Hz, 1H), 1.41 (d, *J* 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.7, 137.0, 132.0, 131.9, 130.0, 128.3, 127.9, 123.6, 117.1, 113.7, 89.0, 84.7, 55.3, 54.3, 53.8, 47.6, 20.2; IR (ATR): ν_{max} 2977, 2932, 2833, 1511, 1302, 1248, 1037, 829, 755, 691 cm^{-1}.

***N*-Allyl-*N*-(4-methoxybenzyl)-1,4-diphenylbut-3-yn-2-amine (16k)**. A pressure tube charged with *N*-(4-methoxybenzyl)allylamine (100 mg, 564 µmol), CuBr (8 mg, 56 µmol), 4Å molecular sieves (600 mg). The tube was fitted with a rubber septum, evacuated under high vacuum and backfilled with argon three times. Dry

toluene (2 mL), phenylacetylene (68 µL, 864 µmol) and phenylacetaldehyde (73 µL, 620 µmol) were then added. The rubber septum was replaced by a Teflon-coated screw cap and the reaction mixture was stirred at 80 °C for 24h. The reaction mixture was then cooled to room temperature, filtered through a plug of Celite® and concentrated under reduced pressure. The crude residue was finally purified by flash column chromatography (petroleum ether/EtOAc: 100/1) to afford the desired product **16k** as a light yellow oil (60 mg, 157 µmol, 28%). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.47-7.43 (m, 2H), 7.33-7.31 (m, 3H), 7.30-7.27 (m, 2H), 7.25-7.20 (m, 3H), 7.15 (d, *J* 8.5 Hz, 2H), 6.80 (d, *J* 8.9 Hz, 2H), 5.84 (dddd, *J* 17.7, 10.0, 7.6 and 4.3 Hz, 1H), 5.24 (app. d, *J* 17.1 Hz, 1H), 5.12 (app. d, *J* 10.0 Hz, 1H), 3.96-3.87 (m, 2H), 3.80 (s, 3H), 3.46 (d, *J* 13.5 Hz, 1H), 3.40 (ddt, *J* 14.3, 4.5 and 2.0 Hz, 1H), 3.11-3.06 (m, 1H), 3.03 (dd, *J* 7.7 and 2.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 158.7, 138.9, 136.7, 131.9, 131.7, 129.9, 129.7, 128.4, 128.2, 128.0, 126.4, 123.6, 117.2, 113.7, 87.7, 86.1, 55.4, 54.7, 54.5, 53.9, 40.6; IR (ATR): ν_{max} 3027, 2933, 2822, 1611, 1511, 1247, 1036, 911, 828, 696 cm^{-1}.

(*E*)-*N*-(4-Methoxybenzyl)-3-phenyl-*N*-(3-phenylprop-2-yn-1-yl)allylamine (16l). Prepared according to general procedure I (starting from 400 mg (1.57 mmol) of (*E*)-*N*-(4-methoxybenzyl)-3-phenylprop-2-en-1-amine). Solvent system for flash column chromatography: petroleum ether/EtOAc: 10/0, then 10/1. Yield: 98% (570 mg, 1.55 mmol); Light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.50-7.49 (m, 1H), 7.48 (d, *J* 2.0 Hz, 1H), 7.41-7.37 (m, 2H), 7.35-7.28 (m, 7H), 7.24 (app. tt, *J* 7.3 and 1.3 Hz, 1H), 6.89 (d, *J* 8.7 Hz, 2H), 6.64 (d, *J* 15.9 Hz, 1H), 6.34 (dt, *J* 15.9 and 6.5 Hz, 1H), 3.81 (s, 3H), 3.72 (s, 2H), 3.57 (s, 2H), 3.41 (d, *J* 6.9 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 159.0, 137.2, 133.1, 131.9, 130.7, 130.6, 128.7, 128.4, 128.2, 127.6, 127.5, 126.5, 123.6, 113.9, 85.9, 84.7, 57.2, 56.3, 55.4, 42.2; IR (ATR): ν_{max} 2910, 2828, 1611, 1511, 1247, 1036, 968, 830, 736, 691 cm^{-1}.

***N*-(4-Methoxybenzyl)-2-methyl-*N*-(3-phenylprop-2-yn-1-yl)prop-2-en-1-amine (16m)**. Prepared according to general procedure I (starting from 956 mg (5.00 mmol) of *N*-(4-methoxybenzyl)-2-methylprop-2-en-1-amine). Solvent system for flash column chromatography: petroleum ether/EtOAc: 10/1. Yield: 92% (1.4 g, 4.62 mmol); Light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.48 (m, 2H), 7.32 (m, 5H), 6.87 (m, 2H), 5.03 (dq, *J* 2.2 and 1.1 Hz, 1H), 4.91 (dd, *J* 2.4 and 1.4 Hz, 1H), 3.81 (s, 3H), 3.63 (s, 2H),3.48 (s, 2H), 3.13 (s, 2H), 1.81 (t, *J* 1.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 158.8, 143.4, 131.9, 131.3, 130.3, 128.4, 128.0, 123.7, 113.8, 113.4, 85.7, 84.8, 60.5, 56.8, 55.4, 42.1, 20.9; IR (ATR): ν_{max} 2969, 2833, 1612, 1511, 1301, 1248, 1172, 1037, 907, 850, 756 cm^{-1}.

***N*-(4-Methoxybenzyl)-*N*-(3-phenylprop-2-yn-1-yl)but-3-en-2-amine (16n)**. Prepared according to general procedure I (starting from 669 mg (3.50 mmol) of *N*-(4-methoxybenzyl)but-3-en-2-amine). Solvent system for flash column chromatography: petroleum ether/EtOAc: 10/1. Yield: 75% (800 mg, 2.62 mmol); Light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.46 (m, 2H), 7.31 (m, 5H), 6.87 (m, 2H), 5.94 (ddd, *J* 17.5, 10.3 and 7.6 Hz, 1H), 5.23 (ddd, *J* 17.3, 1.8 and 1.0 Hz, 1H), 5.14 (ddd, *J* 10.3, 1.8 and 0.9 Hz, 1H), 3.81 (s, 3H), 3.77 (A of AB syst., *J* 13.1 Hz, 1H), 3.64 (B of AB syst., *J* 13.1 Hz, 1H), 3.51 (d, *J* 5.8 Hz, 2H), 3.43 (app. p, *J* 6.5 Hz, 1H), 1.30 (d, *J* 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 158.8, 141.8, 131.8, 131.6, 130.3, 128.4, 128.0, 123.7, 115.6, 113.8, 86.0, 85.2, 59.5, 55.4, 53.6, 39.3, 18.3; IR (ATR): ν_{max} 2974, 2834, 1612, 1511, 1301, 1248, 1172, 1037, 920, 822, 756 cm^{-1}.

General Procedure II: von Braun reaction. To a solution of the *N*-(4-methoxybenzyl)-protected allylic and propargylic amine **16** (1.0 equiv.) in dry dioxane (0.17 M) were successively added potassium carbonate (1.5 equiv.) and cyanogen bromide (1.2 equiv.). The resulting mixture was stirred at rt for 16 h, quenched with a saturated aqueous solution of sodium bicarbonate and extracted with EtOAc. The combined organic layers were then dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was finally purified by flash column chromatography over silica gel to afford the desired allylic and propargylic cyanamide **11**.

***N*-Allyl-*N*-[3-(4-phenyl)prop-2-yn-1-yl]cyanamide (11a)**. Prepared according to general procedure II (starting from 583 mg (2.00 mmol) of **16a**). Solvent system for flash column chromatography: petroleum ether/EtOAc: 10/1. Yield: 65% (256 mg, 1.30 mmol); Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.45 (dd, *J* 7.5 and 1.5 Hz, 2H), 7.36-7.32 (m, 3H), 5.89 (ddt, *J* 16.6, 10.1 and 6.5 Hz, 1H), 5.41 (obs. dq, *J* 16.5 and 1.3 Hz, 1H), 5.38 (obs. dq, *J*

10.0 and 1.1 Hz, 1H), 4.04 (s, 2H), 3.78 (dt, *J* 6.5 and 1.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 162.1, 132.0, 130.5, 129.0, 128.5, 122.0, 121.4, 117.0, 87.1, 81.3, 53.6, 41.5; IR (ATR): ν_{max} 2928, 2858, 2214, 1711, 15010, 1355, 1169, 1100, 937, 827 cm^{-1}; ESIHRMS *m/z* calcd for $C_{13}H_{12}N_2Na$ $[M+Na]^+$ 219.0893 found 219.0890. This compound was previously reported.[25]

***N*-Allyl-*N*-[3-(4-fluorophenyl)prop-2-yn-1-yl]cyanamide (11b)**. Prepared according to general procedure II (starting from 274 mg (885 µmol) of **16b**). Solvent system for flash column chromatography: petroleum ether/EtOAc: 10/1. Yield: 79% (150 mg, 700 µmol); Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.44 (dd, *J* 8.9 and 5.4 Hz, 2H), 7.02 (app. t, *J* 8.7 Hz, 2H), 5.89 (ddt, *J* 16.7, 10.2 and 6.4 Hz, 1H), 5.41 (app. dq, *J* 17.1 and 1.3 Hz, 1H), 5.19 (app. dq, *J* 10.0 and 1.1 Hz, 1H), 4.02 (s, 2H), 3.77 (dt, *J* 6.5 and 1.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 163.0 (d, *J* 250.6 Hz), 134.0 (d, *J* 8.5 Hz), 130.5, 121.5, 118.1 (d, *J* 3.6 Hz), 117.0, 115.9 (d, *J* 3.6 Hz), 86.1, 81.1, 53.7, 41.4; ^{19}F NMR (376 MHz, $CDCl_3$): *δ* -110.1 (app. tt, *J* 8.6 and 5.3 Hz); IR (ATR): ν_{max} 2923, 2853, 2214, 1601, 1506, 1222, 1156, 1094, 938, 837 cm^{-1}.

***N*-Allyl-*N*-{3-[3-(trifluoromethyl)phenyl]prop-2-yn-1-yl}cyanamide (11c)**. Prepared according to general procedure II (starting from 330 mg (916 µmol) of **16c**). Solvent system for flash column chromatography: petroleum ether/EtOAc: 10/1. Yield: 80% (195 mg, 738 µmol); Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.71 (s, 1H), 7.62 (app. t, *J* 8.3 Hz, 2H), 7.47 (app. t, *J* 7.8 Hz, 1H), 5.89 (ddt, *J* 16.6, 10.2 and 6.6 Hz, 1H), 5.42 (app. dq, *J* 17.1 and 1.3 Hz, 1H), 5.40 (app. dq, *J* 10.1 and 1.1 Hz, 1H), 4.05 (s, 2H), 3.78 (dt, *J* 6.5 and 1.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 135.2, 131.2 (q, *J* 32.8 Hz), 130.4, 129.1, 128.8 (q, *J* 3.8 Hz), 125.7 (q, *J* 3.8 Hz), 123.7 (q, *J* 272.3 Hz), 122.9, 121.6, 116.8, 85.5, 83.0, 53.8, 41.3; ^{19}F NMR (376 MHz, $CDCl_3$): *δ* -63.4; IR (ATR): ν_{max} 2216, 1434, 1332, 1239, 1167, 1126, 1074, 802, 695, 657 cm^{-1}.

***N*-Allyl-*N*-[3-(4-methoxyphenyl)prop-2-yn-1-yl]cyanamide (11d)**. Prepared according to general procedure II (starting from 306 mg (952) µmol of **16d**). Solvent system for flash column chromatography: petroleum ether/EtOAc: 10/1. Yield: 55% (120 mg, 530 µmol); Light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.39 (d, *J* 8.9 Hz, 2H), 6.85 (d, *J* 8.9 Hz, 2H), 5.89 (ddt, *J* 16.8, 10.1 and 6.4 Hz, 1H), 5.41 (app. dq, *J* 17.1 and 1.2 Hz, 1H), 5.38 (obs. dq, *J* 10.1 and 1.1 Hz, 1H), 4.03 (s, 2H), 3.82(s, 3H), 3.77 (dt, *J* 6.4 and 1.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 160.2, 133.5, 130.6, 121.4, 117.2, 114.2, 114.1, 87.1, 79.9, 55.5, 53.5, 41.6; IR (ATR): ν_{max} 2935, 2838, 2213, 1605, 1509, 1248, 1173, 1030, 937, 833 cm^{-1}.

***N*-Allyl-*N*-[3-(*m*-tolyl)prop-2-yn-1-yl]cyanamide (11e)**. Prepared according to general procedure II (starting from 276 mg (903 µmol) of **16e**). Solvent system for flash column chromatography: petroleum ether/EtOAc: 10/1. Yield: 77% (148 mg, 703 µmol); Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.35 (app. d, *J* 8.2 Hz, 2H), 7.13 (app. d, *J* 8.0 Hz, 2H), 5.89 (ddt, *J* 16.6, 10.1 and 6.5 Hz, 1H), 5.42 (app. dq, *J* 17.2 and 1.2 Hz, 1H), 5.38 (obs. dq, *J* 10.0 and 1.0 Hz, 1H), 4.04 (s, 2H), 3.78 (dt, *J* 6.5 and 1.2 Hz, 2H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 139.3, 131.9, 130.6, 129.3, 121.4, 118.9, 117.1, 87.3, 80.6, 53.5, 41.6, 21.7; IR (ATR): ν_{max} 2929, 2868, 2214, 1703, 1509, 1342, 1177, 1106, 936, 817 cm^{-1}.

***N*-Allyl-*N*-(3-cyclohexylprop-2-yn-1-yl)cyanamide (11f)**. Prepared according to general procedure II (starting from 255 mg (1.00 mmol) of **16f**). Solvent system for flash column chromatography: petroleum ether/EtOAc: 10/1. Yield: 54% (110 mg, 543 µmol); Light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 5.84 (ddt, *J* 16.7, 10.1 and 6.4 Hz, 1H), 5.35 (app. dq, *J* 17.1 and 1.3 Hz, 1H), 5.34 (app. dq, *J* 10.0 and 1.1 Hz, 1H), 3.79 (d, *J* 2.1 Hz, 2H), 3.69 (dt, *J* 6.5 and 1.2 Hz, 2H), 2.45-2.36 (m, 1H), 1.83-1.75 (m, 2H), 1.73-1.64 (m, 2H), 1.60-1.39 (m, 3H), 1.36-1.26 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 130.7, 121.1, 117.2, 92.2, 72.2, 53.3, 41.2, 32.6, 29.1, 25.9, 24.9; IR (ATR): ν_{max} 2930, 2854, 2215, 1698, 1449, 1260, 1160, 990, 934, 809 cm^{-1}.

***N*-Allyl-*N*-(3-cyclopropylprop-2-yn-1-yl)cyanamide (11g)**. Prepared according to general procedure II (starting from 260 mg (1.02 mmol) of **16g**). Solvent system for flash column chromatography: petroleum ether/EtOAc: 10/1. Yield: 79% (130 mg, 811 µmol); Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 5.82 (ddt, *J* 16.5, 10.1 and 6.4

Hz, 1H), 5.35 (app. dq, *J* 17.1 and 1.3 Hz, 1H), 5.32 (app. dq, *J* 10.1 and 1.1 Hz, 1H), 3.74 (d, *J* 2.0 Hz, 2H), 3.66 (dt, *J* 6.5 and 1.2 Hz, 2H), 1.29-1.20 (m, 1H), 0.81-0.76 (m, 2H), 0.71-0.66 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 130.6, 121.1, 117.1, 91.2, 67.5, 53.3, 41.2, 8.4 (2C), -0.5; IR (ATR): ν_{max} 3096, 3019, 2216, 1695, 1422, 1263, 1182, 939, 815, 723 cm^{-1}.

***N*-Allyl-*N*-(hex-2-yn-1-yl)cyanamide (11h)**. Prepared according to general procedure II (starting from 160 mg (621 µmol) of **16h**, reaction run for 72h). Solvent system for flash column chromatography: petroleum ether/EtOAc: 30/1. Yield: 85% (85 mg, 524 µmol); Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 5.84 (ddt, *J* 16.8, 10.2 and 6.6 Hz, 1H), 5.37 (app. dq, *J* 17.1 and 1.3 Hz, 1H), 5.34 (app. dq, *J* 10.1 and 1.1 Hz, 1H), 3.78 (t, *J* 2.2 Hz, 2H), 3.69 (dt, *J* 6.4 and 1.3 Hz, 2H), 2.20 (tt, *J* 7.0 and 2.3 Hz, 2H), 1.54 (app. sext., *J* 7.2 Hz, 2H), 0.99 (t, *J* 7.4, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 130.7, 121.2, 117.2, 88.0, 72.4, 53.3, 41.2, 22.0, 20.8, 13.6; IR (ATR): ν_{max} 2964, 2873, 2214, 1717, 1435, 1338, 1093, 937, 810, 734 cm^{-1}.

***N*-Allyl-*N*-(oct-2-yn-1-yl)cyanamide (11i)**. Prepared according to general procedure II (starting from 190 mg (665 µmol) of **16i**, reaction run for 72h). Solvent system for flash column chromatography: petroleum ether/EtOAc: 30/1. Yield: 100% (126 mg, 662 µmol); Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 5.84 (ddt, *J* 16.8, 10.1 and 6.5 Hz, 1H), 5.37 (app. dq, *J* 17.1 and 1.3 Hz, 1H), 5.34 (app. dq, *J* 10.1 and 1.1 Hz, 1H), 3.78 (t, *J* 2.2 Hz, 2H), 3.69 (dt, *J* 6.4 and 1.1 Hz, 2H), 2.21 (tt, *J* 7.2 and 2.2 Hz, 2H), 1.52 (app. quint., *J* 7.2 Hz, 2H), 1.41-1.26 (m, 4H), 0.90 (t, *J* 7.1, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 130.7, 121.2, 117.2, 88.2, 72.2, 53.3, 41.2, 31.1, 28.3, 22.3, 18.8, 14.1; IR (ATR): ν_{max} 2931, 2871, 2215, 1699, 1457, 1339, 1259, 1155, 934, 802 cm^{-1}.

***N*-Allyl-*N*-(4-phenylbut-3-yn-2-yl)cyanamide (11j)**. Prepared according to general procedure II (starting from 160 mg (523 µmol) of **16j**, reaction performed in DCM). Solvent system for flash column chromatography: petroleum ether/EtOAc: 100/1. Yield: 55% (60 mg, 285 µmol); Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.46-7.42 (m, 2H), 7.36-7.30 (m, 3H), 5.91 (dddd, *J* 17.1, 10.1, 6.9 and 6.0 Hz, 1H), 5.41 (app. dq, *J* 17.1 and 1.3 Hz, 1H), 5.35 (app. dq, *J* 10.1 and 1.1 Hz, 1H), 4.11 (q, *J* 6.9 Hz, 1H), 3.81 (dddt, *J* 23.1, 14.3, 6.0 and 1.3 Hz, 2H), 1.64 (d, *J* 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 132.0, 131.2, 128.9, 128.5, 122.1, 121.0, 115.7, 85.8 (2C), 53.3, 48.1, 20.5; IR (ATR): ν_{max} 2983, 2934, 2212, 1598, 1490, 1315,1192, 937, 757, 691 cm^{-1}.

***N*-Allyl-*N*-(1,4-diphenylbut-3-yn-2-yl)cyanamide (11k)**. Prepared according to general procedure II (starting from 238 mg (623 µmol) of **16k**, reaction performed in DCM for 72h). Solvent system for flash column chromatography: petroleum ether/EtOAc: 100/1. Yield: 85% (152 mg, 530 µmol); Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.44-7.41 (m, 2H), 7.36-7.28 (m, 8H), 5.75 (ddt, *J* 16.3, 9.9 and 6.4 Hz, 1H), 5.30 (app. dq, *J* 17.2 and 1.3 Hz, 1H), 5.27 (app. dq, *J* 10.2 and 1.3 Hz, 1H), 4.12 (t, *J* 7.5 Hz, 1H), 3.71 (dt, *J* 6.3 and 1.3 Hz, 2H), 3.22 (dd, *J* 7.6 and 5.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 136.2, 132.0, 131.0, 129.6, 129.0, 128.7, 128.5, 127.4, 122.0, 121.0, 115.7, 87.4, 84.7, 54.6, 54.0, 40.7; IR (ATR): ν_{max} 3030, 2931, 2210, 1598, 1422, 1264, 1098, 937, 757, 691 cm^{-1}.

***N*-Cinnamyl-*N*-(3-phenylprop-2-yn-1-yl)cyanamide (11l)**. Prepared according to general procedure II (starting from 570 mg (1.55 mmol) of **16l**, reaction performed in DCM). Solvent system for flash column chromatography: petroleum ether/EtOAc:10/1. Yield: 76% (322 mg, 1.18 mmol); Yellow oi. ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.47-7.43 (m, 2H), 7.42-7.38 (m, 2H), 7.36-724 (m, 6H), 6.69 (d, *J* 15.8 Hz, 1H), 6.23 (dt, *J* 15.9 and 6.9 Hz, 1H), 4.07 (s, 2H), 3.94 (d, *J* 6.9 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 136.4, 135.8, 132.0, 129.0, 128.8, 128.5, 128.4, 126.9, 122.0, 121.3, 117.1, 87.1, 81.4, 53.3, 41.4; IR (ATR): ν_{max} 2941, 2328, 2214, 1490, 1377, 1263, 1165, 973, 757, 690 cm^{-1}.

***N*-(2-methylallyl)-*N*-(3-phenylprop-2-yn-1-yl)cyanamide (11m)**. Prepared according to general procedure II (starting from 611 mg (2.00 mmol) of **16m**). Solvent system for flash column chromatography: petroleum ether/EtOAc: 10/1. Yield: 52% (216 mg, 1.0 mmol); Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.45 (app. dd, *J* 7.6 and 2.0 Hz, 2H), 7.36-7.30 (m, 3H), 5.07 (q, *J* 1.1 Hz, 2H), 4.01 (s, 2H), 3.72 (s, 2H), 1.84 (t, *J* 1.1 Hz, 3H); ^{13}C NMR

δ 138.3, 132.0, 129.0, 128.5, 122.0, 117.3, 116.8, 87.0, 81.3, 57.4, 41.2, 20.0; IR (ATR): ν_{max} 2919, 2216, 1490, 1377, 914, 758, 692 cm^{-1}.

***N*-(1-Methylallyl)-*N*-(3-phenylprop-2-yn-1-yl)cyanamide (11n)**. Prepared according to general procedure II (starting from 611 mg (2.0 mmol) of **16n**). Solvent system for flash column chromatography: petroleum ether/EtOAc: 10/1. Yield: 51% (213 mg, 1.0 mmol); Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.45 (app. dd, *J* 7.5 and 2.1 Hz, 2H), 7.36-7.30 (m, 3H), 5.78 (ddd, *J* 17.2, 10.2 and 7.6 Hz, 1H), 5.33 (app. dt, *J* 17.2 and 1.1 Hz, 1H), 5.29 (app. dt, *J* 10.2 and 1.0 Hz, 1H), 4.08 (A of AB syst., *J* 17.3 Hz, 1H), 4.00 (B of AB syst., *J* 17.3 Hz, 1H), 3.79 (m, 1H), 1.46 (d, *J* 6.8 Hz, 3H); ^{13}C NMR *δ* 136.3, 132.0, 129.0, 128.5, 122.1, 118.7, 115.7, 86.8, 81.8, 57.8, 40.9, 18.9; IR (ATR): ν_{max} 2981, 2210, 1490, 1377, 933, 758, 692 cm^{-1}.

General Procedure III: ring-closing enyne metathesis. To a solution of allylic and propargylic cyanamide **11** (254 µmol, 1.0 equiv.) in dry toluene (0.025 M) was added Grubbs second generation catalyst (35 mg, 30 µmol, 12 mol %) under argon. The reaction mixture was stirred at 60 °C for 3 to 24 h before being concentrated under reduced pressure. The crude residue was finally purified by flash column chromatography over silica gel to afford the desired cyclic cyanamide **12**.

1-Cyano-3-(1-phenylvinyl)-2,5-dihydro-1*H*-pyrrole (12a). Prepared according to general procedure III (starting from 50 mg (254 µmol) of **11a** for 16 h). Solvent system for flash column chromatography: petroleum ether/EtOAc: 20/1. Yield: 60% (30 mg, 153 µmol); Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.42-7.35 (m, 3H), 7.35-7.29 (m, 2H), 5.58 (app. quint., *J* 2.0 Hz, 1H), 5.28 (s, 1H), 5.12 (s, 1H), 4.53 (td, *J* 4.2 and 1.9 Hz, 2H), 4.41-4.34 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 142.8, 140.1, 138.4, 128.5, 128.4, 128.1, 123.6, 117.1, 116.6, 58.7, 57.6; IR (ATR): ν_{max} 2213, 1494, 1472, 1354, 1253, 1170, 904, 815, 776, 705 cm^{-1}; ESIHRMS *m/z* calcd for $C_{13}H_{12}N_2Na$ $[M+Na]^+$ 219.0893 found 219.0890.

1-Cyano-3-[1-(4-fluorophenyl)vinyl]-2,5-dihydro-1*H*-pyrrole (12b). Prepared according to general procedure III (starting from 54 mg (254 µmol) of **11b** for 16 h). Solvent system for flash column chromatography: petroleum ether/EtOAc: 10/1. Yield: 55% (30 mg, 140 µmol); Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.25 (dd, *J* 8.8 and 5.4 Hz, 2H), 7.04 (app. t, *J* 8.8 Hz, 2H), 5.52 (app. quint., *J* 2.1 Hz, 1H), 5.22 (s, 1H), 5.09 (s, 1H), 4.49 (td, *J* 6.2 and 2.0 Hz, 2H), 4.38-4.33 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 162.6 (d, *J* 247.1 Hz), 141.8, 138.5, 136.1 (d, *J* 3.4 Hz), 130.0 (d, *J* 8.1 Hz), 123.7, 117.0, 116.9, 115.4 (d, *J* 21.4 Hz), 58.6, 57.5; ^{19}F NMR (376 MHz, $CDCl_3$): *δ* -114.4 (app. tt, *J* 8.6 and 5.4 Hz); IR (ATR): ν_{max} 2863, 2362, 2214, 1507, 1351, 1217, 1158, 924, 842, 818 cm^{-1}.

1-Cyano-3-{1-[3-(trifluoromethyl)phenyl]vinyl]-2,5-dihydro-1*H*-pyrrole (12c). Prepared according to general procedure III (starting from 67 mg (254 µmol) of **11c** for 16 h). Solvent system for flash column chromatography: petroleum ether/EtOAc: 10/1. Yield: 56% (38 mg, 143 µmol); Light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.62-7.59 (m, 1H), 7.55-7.53 (m, 1H), 7.50-7.47 (m, 2H), 5.50 (app. quint., *J* 2.0 Hz, 1H), 5.29 (s, 1H), 5.17 (s, 1H), 4.52 (td, *J* 4.3 and 1.9 Hz, 2H), 4.39-4.35 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 141.6, 140.8, 138.0, 131.7, 131.0 (q, *J* 32.3 Hz), 129.0, 125.2 (q, *J* 3.7 Hz), 124.9 (q, *J* 3.8 Hz), 124.1 (q, *J* 272.2 Hz), 124.0, 117.8, 116.9, 58.7, 57.5; ^{19}F NMR (376 MHz, $CDCl_3$): *δ* -63.0; IR (ATR): ν_{max} 2956, 2216, 1435, 1265, 1164, 1122, 1073, 906, 808, 703 cm^{-1}.

1-Cyano-3-[1-(4-methoxyphenyl)vinyl]-2,5-dihydro-1*H*-pyrrole (12d). Prepared according to general procedure III (starting from 57 mg (254 µmol) of **11d** for 6 h). Solvent system for flash column chromatography: petroleum ether/EtOAc: 10/1. Yield: 52% (30 mg, 132 µmol); Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.22 (d, *J* 8.6 Hz, 2H), 6.89 (d, *J* 8.7 Hz, 2H), 5.57 (app. quint., *J* 2.1 Hz, 1H), 5.21 (s, 1H), 5.04 (s, 1H), 4.49 (td, *J* 4.3 and 1.9 Hz, 2H), 4.38-4.33 (m, 2H), 3.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 159.6, 142.2, 138.7, 132.5, 129.5, 123.4, 117.2, 115.9, 113.8, 58.7, 57.6, 55.5; IR (ATR): ν_{max} 2960, 2213, 1607, 1511, 1442, 1248, 1176, 1029, 835, 802 cm^{-1}.

1-Cyano-3-[1-(*m*-tolyl)vinyl]-2,5-dihydro-1*H*-pyrrole (12e). Prepared according to general procedure III (starting from 53 mg (254 µmol) of **11e** for 16 h). Solvent system for flash column chromatography: petroleum ether/EtOAc: 10/1. Yield: 64% (34 mg, 161 µmol); Light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.19-7.15 (m,

4H), 5.56 (app. quint., *J* 2.1 Hz, 1H), 5.22 (s, 1H), 5.06 (s, 1H), 4.49 (td, *J* 4.3 and 1.9 Hz, 2H), 4.37-4.33 (m, 2H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 142.6, 138.5, 137.9, 137.2, 129.1 (2C), 128.2 (2C), 123.4, 117.2, 116.2, 58.6, 57.6, 21.3; IR (ATR): ν_{max} 2913, 2210, 1739, 1506, 1353, 1255, 1175, 921, 820, 734 cm^{-1}.

1-Cyano-3-(1-cyclohexylvinyl)-2,5-dihydro-1*H*-pyrrole (12f). Prepared according to general procedure III (starting from 51 mg (254 µmol) of **11f** for 5 h). Solvent system for flash column chromatography: petroleum ether/EtOAc: 25/1. Yield: 49% (25 mg, 123 µmol); off-white solid; mp: 67 ℃. ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 5.70 (app. s, 1H), 5.04 (s, 1H), 4.79 (s, 1H), 4.35 (app. s, 4H), 2.23-2.14 (m, 1H), 1.83-1.75 (m, 4H), 1.38-1.11 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 146.5, 138.4, 118.6, 117.3, 112.1, 58.6, 57.7, 41.0, 33.2, 27.0, 26.5; IR (ATR): ν_{max} 2923, 2850, 2214, 1698, 1447, 1353, 1259, 1032, 883, 797 cm^{-1}.

1-Cyano-3-(1-cyclopropylvinyl)-2,5-dihydro-1*H*-pyrrole (12g). Prepared according to general procedure III (starting from 41 mg (254 µmol) of **11g** for 3 h). Solvent system for flash column chromatography: petroleum ether/EtOAc: 30/1. Yield: 41% (17 mg, 106 µmol); colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 5.97 (app. s, 1H), 4.95 (s, 1H), 4.73 (s, 1H), 4.37 (app. s, 4H), 1.54-1.44 (m, 1H), 0.75-0.70 (m, 2H), 1.38-1.11 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 141.9, 139.2, 120.2, 117.3, 112.1, 58.6, 57.4, 13.9, 5.6; IR (ATR): ν_{max} 2922, 2214, 1738, 1463, 1356, 1260, 1144, 1025, 884, 820 cm^{-1}.

1-Cyano-3-(pent-1-en-2-yl)-2,5-dihydro-1*H*-pyrrole (12h). Prepared according to general procedure III (starting from 41 mg (254 µmol) of **11h** for 3 h). Solvent system for flash column chromatography: petroleum ether/EtOAc: 25/1. Yield: 56% (23 mg, 142 µmol); Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 5.69-5.67 (m, 1H), 5.03 (s, 1H), 4.80 (s, 1H), 4.38-4.32 (m, 4H), 1.54-1.44 (app. td, *J* 7.5 and 1.0 Hz, 2H), 1.50 (app. sext., *J* 7.5 Hz, 2H), 0.92 (t, *J* 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 140.6, 138.5, 119.4, 117.2, 114.3, 58.6, 57.5, 35.7, 21.5, 14.0; IR (ATR): ν_{max} 2959, 2871, 2215, 1740, 1466, 1353, 1259, 1062, 994, 892 cm^{-1}.

1-Cyano-3-(hept-1-en-2-yl)-2,5-dihydro-1*H*-pyrrole (12i). Prepared according to general procedure III (starting from 48 mg (254 µmol) of **11i** for 3 h). Solvent system for flash column chromatography: petroleum ether/EtOAc: 30/1. Yield: 50% (24 mg, 126 µmol); Brown oil. ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 5.68 (br. s, 1H), 5.04 (s, 1H), 4.80 (s, 1H), 4.39-4.33 (m, 4H), 2.23 (t, *J* 7.6 Hz, 2H), 1.48 (app. quint., *J* 7.4 Hz, 2H), 1.35- 1.26 (m, 4H), 0.89 (t, *J* 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 140.9, 138.6, 119.4, 117.3, 114.2, 58.6, 57.5, 33.7, 31.8, 28.2, 22.6, 14.2; IR (ATR): ν_{max} 2931, 2868, 2216, 1742, 1602, 1456, 1353, 1258,993, 821 cm^{-1}.

1-Cyano-2-methyl-3-(1-phenylvinyl)-2,5-dihydro-1*H*-pyrrole (12j). Prepared according to general procedure III (starting from 53 mg (254 µmol) of **237j** for 20 h). Solvent system for flash column chromatography: petroleum ether/EtOAc: 30/1. Yield: 18% (10 mg, 47 µmol); Pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.36-7.32 (m, 3H), 7.30-7.27 (m, 2H), 5.53 (br. app. q, *J* 2.0 Hz, 1H), 5.32 (s, 1H), 5.20 (s, 1H), 4.80 (dddd, *J* 6.5, 5.0 2.4 and 1.5 Hz, 1H), 4.35 (ddd, *J* 14.2, 5.1 and 2.0 Hz,1H), 4.27 (app. dt, *J* 14.4 and 2.4 Hz,1H), 1.47 (d, *J* 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 140.9, 138.6, 119.4, 117.3, 114.2, 58.6, 57.5, 33.7, 31.8, 28.2, 22.6, 14.2; IR (ATR): ν_{max} 2972, 2863, 2354, 2209, 1742, 1446, 1347, 1056, 905, 710 cm^{-1}.

2-Benzyl-1-cyano-3-(1-phenylvinyl)-2,5-dihydro-1*H*-pyrrole (12k). Prepared according to general procedure III (starting from 73 mg (254 µmol) of **11k** for 23 h). Solvent system for flash column chromatography: petroleum ether/EtOAc: 15/1. Yield: 13% (10 mg, 35 µmol); Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.34-7.31 (m, 4H), 7.30-7.28 (m, 4H), 7.18-7.15 (m, 2H), 5.42 (s, 1H), 5.36 (br. s, 1H), 5.32 (s, 1H), 5.13-5.07 (m, 1H), 4.08 (app. dt, *J* 14.4 and 1.9 Hz, 1H), 3.82 (ddd, *J* 14.5, 5.3 and 1.3 Hz, 1H), 3.25 (dd, *J* 14.4 and 3.9 Hz, 1H), 3.12 (dd, *J* 14.4 and 3.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 143.0, 140.4, 140.2, 135.7, 130.4, 128.4, 128.3 (2C), 128.2, 127.1, 125.2, 116.6, 116.4, 68.7, 57.2, 37.8; IR (ATR): ν_{max} 3032, 2854, 2209, 1602, 1494, 1354, 1078, 908, 778, 701 cm^{-1}.

(*E*)-1-Cyano-3-(1,2-diphenylvinyl)-2,5-dihydro-1*H*-pyrrole (12l). Prepared according to general procedure III (starting from 69 mg (254 µmol) of **11l** for 24 h). Solvent system for flash column chromatography: petroleum ether/EtOAc: 30/1. Yield: 56% (39 mg, 143 µmol); Light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.40-7.24 (m,

8H), 7.11 (app. d, *J* 7.2 Hz, 2H), 6.49 (s, 1H), 5.74 (app. td, *J* 3.6 and 0.6 Hz, 1H), 4.28 (app. d, *J* 1.4 Hz, 2H), 4.04 (app. dd, *J* 3.6 and 0.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 140.3, 139.6, 135.9, 131.3, 130.3, 129.3, 129.1, 128.6, 128.5, 128.0, 127.8, 122.7, 118.0, 48.8, 48.1; IR (ATR): ν_{max} 2926, 2850, 2216, 1696, 1446, 1262, 1156, 911, 758, 700 cm^{-1}.

(*E*)-1-Cyano-2-methyl-4-(1-phenylvinyl)-2,5-dihydro-1*H*-pyrrole 12n and 1-cyano-2-methyl-4-(1-phenylvinyl)-2,3-dihydro-1*H*-pyrrole (12n'). Prepared according to general procedure III (starting from 105 mg (500 µmol) of **11n**) and obtained as an unseparable mixture of regioisomers. Solvent system for flash column chromatography: petroleum ether/EtOAc: 10/1. Yield (**12n**+**12n'**): 56% (59 mg, 280 µmol). Ratio before purification: **12n**/**12n'**: 20/80; ratio after purification: **12n**/**12n'**: 9:91. Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.38-7.33 (m, 3H, major and minor regioisomers), 7.30-7.26 (m, 2H, major and minor regioisomers), 5.62 (app. dd, *J* 2.9 and 1.8 Hz, 0.09H, minor regioisomer), 5.49 (app. q, *J* 2.0 Hz, 0.91H, major regioisomer), 5.24 (s, 0.91H, major regioisomer), 5.14 (s, 0.09H, minor regioisomer), 5.10 (s, 0.91H, major regioisomer), 5.01 (s, 0.09H, minor regioisomer), 4.61 (dddd, *J* 11.6, 8.5, 4.5 and 2.2 Hz, 0.91H, major regioisomer), 4.54 (ddd, *J* 12.3, 5.0 and 1.8 Hz, 0.91H, major regioisomer), 4.47 (ddd, *J* 12.3, 3.0 and 2.0 Hz, 0.91H, major regioisomer), 4.11 (qd, *J* 6.9 and 3.1 Hz, 0.09H, minor regioisomer), 4.05 (app. d, *J* 14.1 Hz, 0.09H, minor regioisomer), 3.96 (dt, *J* 14.1 and 1.3 Hz, 0.09H, minor regioisomer), 1.47 (d, J 6.9 Hz, 0.27H, minor regioisomer), 1.37 (d, *J* 6.5 Hz, 2.73H, major regioisomer); ^{13}C NMR *δ* 142.8 (major regioisomer), 140.1 (major regioisomer), 138.8 (minor regioisomer), 138.5 (minor regioisomer), 137.1 (major regioisomer), 136.4 (minor regioisomer), 129.2 (major regioisomer), 129.0 (minor regioisomer), 128.4 (major and minor regioisomers), 128.4 (major and minor regioisomers), 128.1 (major regioisomer), 128.0 (minor regioisomer), 116.7 (major regioisomer), 116.3 (major and minor regioisomers), 115.3 (minor regioisomer), 65.2 (major regioisomer), 57.0 (major regioisomer), 53.3 (minor regioisomer), 51.5 (minor regioisomer), 20.2 (major regioisomer), 19.1 (minor regioisomer); IR (ATR): ν_{max} 2975, 2210, 1494, 1342, 904, 776, 736, 701 cm^{-1}.

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Supplementary Material

Copies of ^{1}H, ^{13}C and ^{19}F NMR spectra.

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