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Microwave-Enhanced Rhodium-Catalyzed [2+2+2] Cycloaddition Reactions To Afford Highly Functionalized Pyridines and Bipyridines

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Rhodium(I)-catalyzed [2+2+2] cycloaddition reactions of *N*-tosyl-, carbon-, and oxygen-tethered cyanodiynes in a completely intramolecular fashion have been optimized to afford highly functionalized pyridines by conventional and/or microwave heating. Microwaves have been shown to enhance the process by allowing the reaction to be conducted effectively in short reaction times. The methodology has been extended for the synthesis of bipyridines, either by treating a cyanodiyne with an appended pyridine or by conducting a double [2+2+2] cycloaddition reaction on a dicyanotetrayne scaffold. The choice of the solvent in the microwave heating reaction has been shown to be crucial for the success of the process.

Introduction

Transition-metal-catalyzed [2+2+2] cycloadditions are essential strategic reactions in increasing the complexity of target molecules, as they enable bond connections to be made in one single step.[1] This reaction is remarkable in terms of its ability to generate carbocyclic systems by the involvement of various unsaturated substrates such as alkynes and alkenes and heterocyclic systems when involving heterounsaturated derivatives such as nitriles, isocyanates, isothiocyanates, CO_2, SO_2, and carbonyl groups.[1b,1e,1g,1h,1j] Of these, cycloaddition between two alkynes and a nitrile is one of the most powerful methods for creating large numbers of differentially substituted pyridines.[1b,1h,1j] The preparation of complex polycyclic pyridine derivatives is a major goal, because these compounds have taken on an important role in various scientific branches such as the chemistry of biological systems, the pharmaceutical and agrochemical industries, preparative organic chemistry, as well as coordination chemistry and polymers.[2]

The synthesis of pyridines by this methodology has been discussed in detail in recent reviews.[1b,1h,1j] The most common cases described are either intermolecular or partially intramolecular reactions between two alkynes and a nitrile.[3] However, the completely intramolecular version, namely, the [2+2+2] cycloaddition of cyanodiynes, opens the door to the one-step preparation of new polycyclic-fused pyridines displaying frameworks that can be found in compounds of biological interest. To the best of our knowledge, there are only a few reported cases of completely intramolecular reactions for the synthesis of pyridine derivatives. The first cases, described in 2006 by Yamamoto et al.,[4] were of three different cyanodiynes bearing a 1,6-diyne moiety and a pendant nitrile, which were efficiently converted into tricyclic pyridines under ruthenium catalysis. Later, Snyder et al.[5] described a Co-catalyzed [2+2+2] cycloaddition of cyanodiynes to give tetrahydro-1,6-naphthyridines promoted by microwave heating, and Cheng et al.[6] reported the synthesis of tetra- and pentacyclic pyridine derivatives by cycloaddition of cyanodiynes with a bulky substitution at the terminal carbon atom of the alkyne and catalyzed by a CoI_2(dppe)/Zn system. More recently, Aubert, Malacria et al.[7] described an efficient preparation of tricyclic-fused 3-aminopyridines through intramolecular Co^I-catalyzed [2+2+2] cycloaddition reactions. In the case of rhodium complexes, there has only been one report by Tanaka et al.[8] in which a cationic rhodium(I) complex and chiral bidentate phosphanes promoted a double [2+2+2] cycloaddition of bis-diynenitriles to afford spirobipyridine ligands in excellent yields and moderate enantiomeric excesses.

In this study, we present Rh^I-catalyzed [2+2+2] cycloaddition reactions of *N*-tosyl-, carbon-, and oxygen-tethered cyanodiynes to afford highly functionalized tricyclic-fused pyridines by conventional and/or microwave heating. The use of microwave heating was found to favor cycloaddition and only short reaction times were required. Furthermore, it was even successful in cases where conventional heating failed. This methodology was also applied to the synthesis of bipyridines.

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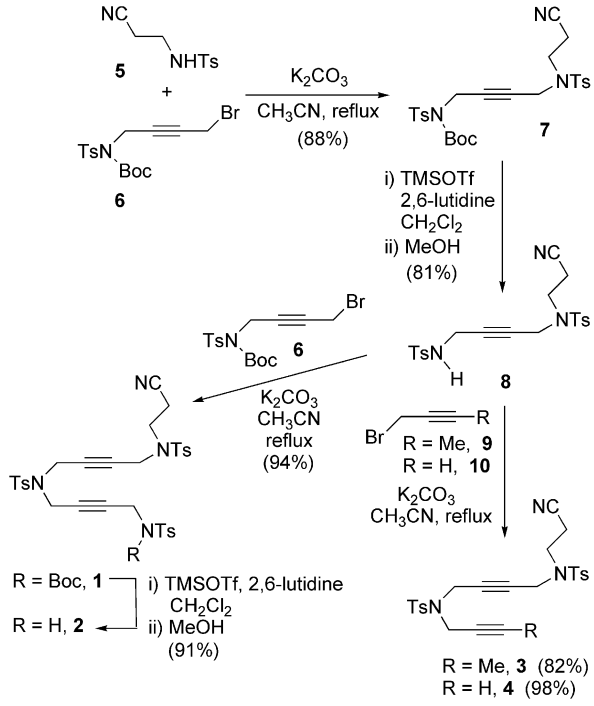
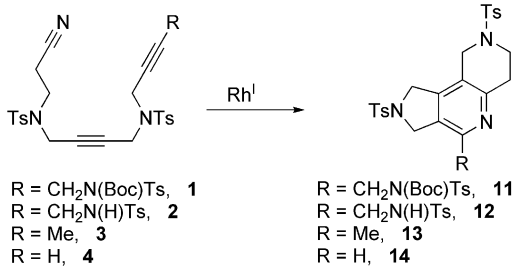
Results and Discussion

In a first step we chose 1,6-diynes tethered to an *N*-tosyl group and a pendant nitrile. Substituents with different steric demand were introduced into the terminal alkyne moiety. We have fine-tuned the synthetic pathways as shown in Scheme 1 to achieve the preparation of cyanodiyne derivatives **1**–**4**. The synthesis started when *N*-(2-cyanoethyl)(4-methylphenyl)sulfonamide **5**[9] was treated with bromide **6**[10] to give derivative **7** in 88% yield. The removal of the Boc group was first attempted by employing trifluoroacetic acid in dichloromethane but this resulted in the partial hydrolysis of the cyano group. In order to eliminate this secondary reaction, we avoided strongly acidic elimination conditions. Trimethylsilyl triflate (TMSOTf) in the presence of 2,6-lutidine and the later treatment with MeOH was used by Ohfune[11] to remove the Boc group from compounds that have other functional groups that are sensitive in acidic conditions. Hence, unprotected derivative **8** was obtained in 81% yield under these conditions. Compound **8** was a common intermediate in the synthesis of the four cyanodiynes. Treatment of **8** with bromide **6** (1 equiv.) using K_2CO_3 as a base in refluxing CH_3CN afforded **1** in 94% yield. The same conditions as described previously were employed to eliminate the Boc group of **1**. Cyanodiyne **2** was obtained in 91% yield. The reaction of **8** with 1-bromobut-2-yne (**9**) and propargyl bromide (**10**) also with the use of K_2CO_3 in CH_3CN gave derivatives **3** and **4** in 82 and 98% yield, respectively.



Scheme 1. Synthesis of cyanodiynes **1**–**4**.

Once the corresponding unsaturated substrates were obtained, we studied their [2+2+2] cycloaddition reactions. Our aim was to use the Wilkinson complex, as it is simple, relatively inexpensive, and commercially available (Scheme 2 and Table 1).



Scheme 2. [2+2+2] Cycloaddition reactions of cyanodiynes **1**–**4**.

The cycloaddition reactions of cyanodiynes **1**–**4** were carried out with $RhCl(PPh_3)_3$ (10 mol-%) in toluene at 90 °C. Derivative **1** gave an excellent yield of cycloaddition product **11** in only 3 h (Table 1, Entry 1). However, cyanodiynes **2** and **3** gave only moderate yields whilst affording large quantities of decomposition products (Table 1, Entries 2 and 3). Derivative **4** with a terminal alkyne gave a benzene dimer[12] as a product (Figure 1), whereas the nitriles did not participate in the [2+2+2] cycloaddition reaction (Table 1, Entry 4). In order to minimize temperature-associated decomposition processes, we tested the reaction at 60 °C (Table 1, Entries 5–8). The reaction time was longer

Table 1. Rh^I-catalyzed [2+2+2] cycloadditions of cyanodiynes **1**–**4** with conventional heating.

Entry	Cyanodiyne	Catalyst (mol-%)	Solvent	*T* [°C]	Time [h]	Product, % Yield
1	**1**	$RhCl(PPh_3)_3$ (10)	toluene	90	3	**11**, 84
2	**2**	$RhCl(PPh_3)_3$ (10)	toluene	90	3	**12**, 39
3	**3**	$RhCl(PPh_3)_3$ (10)	toluene	90	5.5	**13**, 53
4	**4**	$RhCl(PPh_3)_3$ (10)	toluene	90	24	**14**, 0
5	**1**	$RhCl(PPh_3)_3$ (10)	toluene	60	5	**11**, 93
6	**2**	$RhCl(PPh_3)_3$ (10)	toluene	60	6	**12**, 67
7	**3**	$RhCl(PPh_3)_3$ (10)	toluene	60	8	**13**, 42
8	**4**	$RhCl(PPh_3)_3$ (10)	toluene	60	7	**14**, 0
9[a]	**1**	$[Rh(cod)_2]BF_4$ / binap (5)	CH_2Cl_2	reflux	24	**11**, 68
10[a]	**3**	$[Rh(cod)_2]BF_4$ / binap (5)	CH_2Cl_2	reflux	24	**13**, 37
11[a]	**4**	$[Rh(cod)_2]BF_4$ / binap (5)	CH_2Cl_2	reflux	24	**14**, 0
12[a]	**1**	$[Rh(cod)_2]BF_4$ / binap (5)	DCE	reflux	5.5	**11**, 72
13[a]	**3**	$[Rh(cod)_2]BF_4$ / binap (5)	DCE	reflux	8.5	**13**, 41
14[a]	**4**	$[Rh(cod)_2]BF_4$ / binap (5)	DCE	reflux	7	**14**, 0

[a] H_2 was bubbled into the mixture of the rhodium complex and the ligand for 30 min prior to the addition of the cyanodiyne.

but yields were generally improved with the exception of terminal cyanodiyne **4** (Table 1, Entry 8), which gave the same benzene derivative depicted in Figure 1. Other Rh^I catalytic systems were also tested. By changing to a mixture of the cationic complex $[Rh(cod)_2]BF_4$ and the bidentate phosphane binap in CH_2Cl_2, conditions typically used with excellent results by Tanaka et al.,[1g,8] our reaction times were extended to 24 h and the yields of **11** and **13** were worse than those obtained when using the Wilkinson complex (Table 1, Entries 9 and 10 vs. Entries 5 and 7). Cyanodiyne **4** behaved in the same way as before (Table 1, Entry 11). When the reaction temperature was increased to reflux in dichloroethane (DCE) with the cationic rhodium catalyst, almost the same results were obtained as those in Entries 9–11 (Table 1). Shorter reaction times were required for cyanodiynes **1** and **3** (Table 1, Entries 12 and 13) to obtain similar yields of **11** and **13**. Again, pyridine derivative **14** was not obtained under these reaction conditions (Table 1, Entry 14).

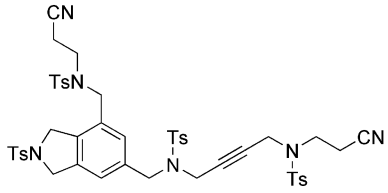
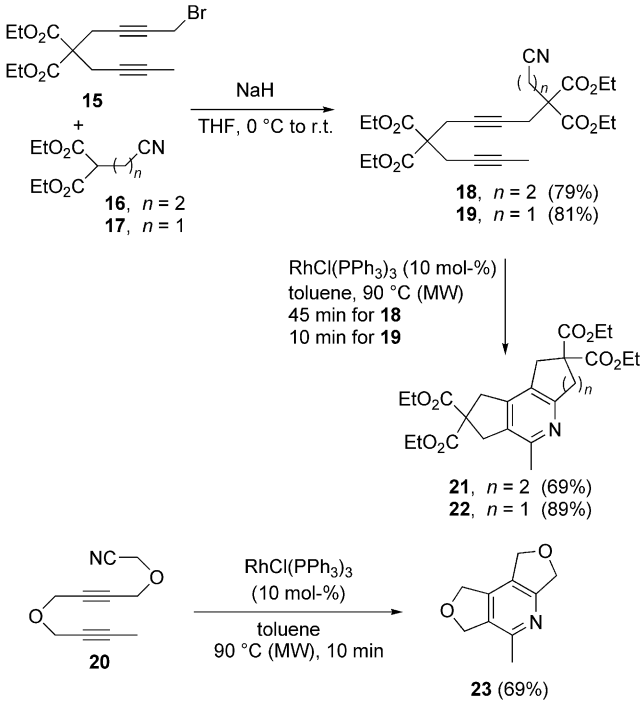


Figure 1. Benzene derivative obtained in the conventional heating cycloaddition of **4**.

In order to avoid the decomposition products caused by prolonged heating of the reactants and to attempt to increase the yields of the desired reaction, especially the reaction of cyanodiyne **4**, which until then had always failed, we decided to carry out the cycloaddition under microwave irradiation. The synthetic utility of microwave irradiation in organic synthesis has increased considerably in recent years. Dramatic rate enhancements between reactions performed at room temperature or heating under reflux and high-temperature microwave-heated processes have frequently been observed.[13] The results obtained by using microwave irradiation are shown in Table 2.

We began to test cyanodiynes **2**–**4**, as **1** had already given good results under conventional heating conditions. Initially, toluene was used as the solvent at 90 °C with $RhCl(PPh_3)_3$ (10 mol-%) under microwave irradiation. We were pleased to find that good yields of pyridine derivatives **12** and **13** were obtained with short reaction times (Table 2, Entries 1 and 2). Even cyanodiyne **4**, which had not successfully given derivative **14** under conventional heating, could be cycloisomerized under microwave heating with a 73% yield when reacted in a toluene/chlorobenzene (3:1) mixture (Table 2, Entry 3). The addition of the higher microwave absorbing solvent chlorobenzene was selected, as the reaction in toluene alone did not reach completion. For the cycloaddition of **4** we also tested the $[Rh(cod)_2]BF_4$/binap catalytic system in dichloromethane at 75 °C under microwave heating for 30 min. Derivative **14** was obtained in 67% yield (Table 2, Entry 4).[14]

After optimizing the microwave reaction conditions for the synthesis of tricyclic pyridines **12**–**14**, we investigated the scope of the cyanodiyne substrates. We extended the methodology to malonate-linked 1-cyano-6,11-diyne **18** and 1-cyano-5,10-diyne **19** and ether-linked cyanodiyne **20**[4] (Scheme 3). Compounds **18** and **19** were prepared by alkylation of the corresponding cyanomalonates **16**[15] and **17**[7] with bromo derivative **15**.[16] The cycloaddition of derivatives **18**–**20** furnished good yields of pyridine derivatives **21**–**23** when they were treated with Wilkinson's catalyst (10 mol-%) in toluene at 90 °C under microwave irradiation.



Scheme 3. [2+2+2] Cycloaddition reactions of cyanodiynes **18**, **19**, and **20**.

Table 2. Rh^I-catalyzed [2+2+2] cycloadditions of cyanodiynes **2**–**4** with microwave irradiation.[a]

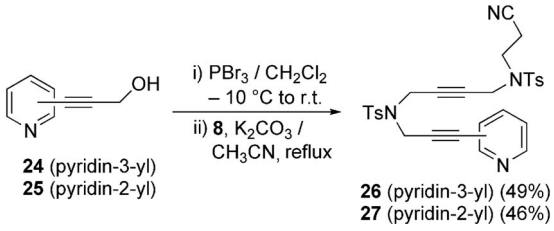
Entry	Cyanodiyne	Solvent	*T* [°C]	Time [min]	Product, % Yield
1	**2**	toluene	90	30	**12**, 75
2	**3**	toluene	90	10	**13**, 81
3	**4**	toluene/chlorobenzene, 3:1	90	30	**14**, 73
4[b]	**4**	dichloroethane	75	30	**14**, 67

[a] Reactions were carried out in the presence of $RhCl(PPh_3)_3$ (10 mol-%) unless otherwise noted. [b] $[Rh(cod)_2]BF_4$/binap (5 mol-%) was used as the catalytic system. H_2 was bubbled into the mixture of the rhodium complex and the ligand for 30 min prior to the addition of the cyanodiyne.

Interestingly the formation of **22** and **23** showed that this protocol allowed us not only to obtain five–six–six-fused ring compounds but also five–six–five-fused derivatives. The results are shown in Scheme 3.

We then extended the methodology to bipyridines, which are useful ligands for metal coordination.[17] We tested two different ways of constructing such compounds. The first was to start with a cyanodiyne containing a pyridine ring in its structure and perform the [2+2+2] cycloaddition, and the second was to start with a dicyanotetrayne and construct the two pyridine rings in one step by two simultaneous [2+2+2] cycloaddition reactions.

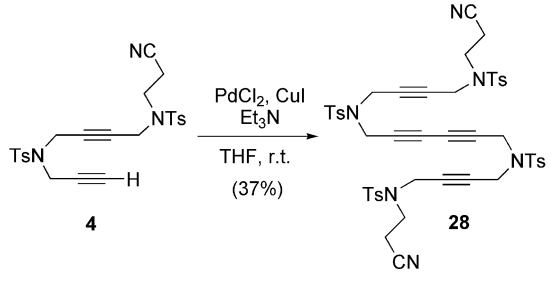
From cyanoyne intermediate **8**, pyridine derivatives **26** and **27** were prepared by treating **8** with 3-(pyridin-3-yl)-2-propyn-1-ol (**24**) and 3-(pyridin-2-yl)-2-propyn-1-ol (**25**), respectively (Scheme 4).



Scheme 4. Synthesis of cyanodiynepyridine derivatives **26** and **27**.

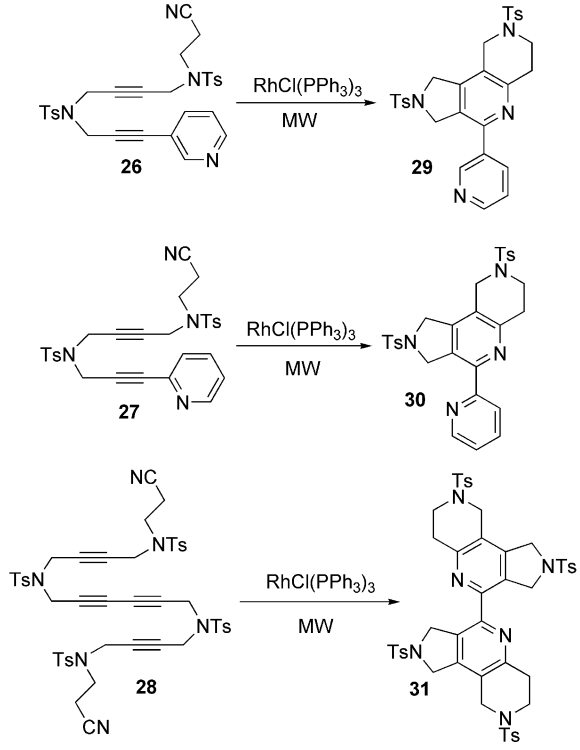
Propargylic alcohols **24** and **25** were prepared by palladium-catalyzed coupling of propargyl alcohol with the appropriate pyridine halide under Sonogashira conditions.[18] These alcohols were then converted into the corresponding bromides by treatment with PBr_3. Without isolation, the halo derivatives were coupled with derivative **8** in the presence of potassium carbonate as a base. Pyridine derivatives **26** and **27** were obtained in 49 and 46% yield, respectively, in a two-step procedure.

In order to prepare dicyanotetrayne **28**, a palladium-catalyzed acetylenic oxidative homocoupling reaction between the two sp-carbon terminal alkyne atoms of **4** (Glaser-type process)[19] was run (Scheme 5).



Scheme 5. Synthesis of dicyanotetrayne derivative **28**.

Substrates **26**–**28** were tested for a [2+2+2] cycloaddition process by using Wilkinson's catalyst under microwave heating. The results are shown in Scheme 6 and Table 3. In a first step, we began by testing the optimized conditions of earlier cases. The use of toluene as a solvent led to decomposition products in the cases of derivatives **26** and **27**, whereas in the case of derivative **28** only the starting product was recovered. We then decided to change to DMSO, as this is a higher microwave absorbing solvent.[13] Derivative **26** was tested at 90 °C, and the reaction, which was complete after 30 min, gave bipyridine **29** in 92% yield (Table 3, Entry 1). Derivative **28** also underwent complete cycloaddition in DMSO at 90 °C after a reaction time of just 10 min to afford bipyridine **31** in 88% yield (Table 3, Entry 4). Surprisingly, 2-pyridine derivative **27** did not react in DMSO at 90 °C nor at 150 °C when the temperature was increased (Table 3, Entry 2). Other solvents would be required. In a mixture of DMF/H_2O (1:1), derivative **30** was obtained in 89% yield (Table 3, Entry 3).



Scheme 6. [2+2+2] Cycloaddition reactions of derivatives **26**–**28**.

Table 3. Rh^I-catalyzed [2+2+2] cycloadditions of derivatives **26**–**28** under microwave irradiation.[a]

Entry	Substrate	Solvent	*T* [°C]	Time [min]	Product, % Yield
1	**26**	DMSO	90	30	**29**, 92
2	**27**	DMSO	90 or 150	30	**30**, 0
3	**27**	DMF/H_2O (1:1)	90	60	**30**, 89
4	**28**	DMSO	90	10	**31**, 88

[a] Reactions were carried out in the presence of $RhCl(PPh_3)_3$ (10 mol-%).

Conclusions

In summary, we have synthesized a series of highly functionalized fused-tricyclic pyridines and bipyridines by [2+2+2] cycloaddition reactions under rhodium(I) catalysis. We have also demonstrated that microwave irradiation con-

siderably improves the yields and reactions times achieved with conventional heating and is even effective in cases where conventional heating fails. This study has shown the importance of fine-tuning the reaction conditions. This is especially seen in the case of the solvent, as even when the substrates are very similar, the choice of solvent dramatically affects the outcome of the reaction.

Experimental Section

General: Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. *N*-(4-Bromo-2-butynyl)-*N*-(*tert*-butyloxycarbonyl)(4-methylphenyl)sulfonamide (**6**) was prepared as described previously by our group.[10] 5,5-Bis(carbethoxy)-1-bromonona-2,7-diyne (**15**),[16] cyanomalonates **16**[15] and **17**,[7] and 1-cyano-2,7-dioxaundeca-4,9-diyne (**20**)[4] were prepared following the method described previously in the literature. Spectroscopic data for pyridine derivative **23** are as described in the literature for this compound.[4] Propargylic alcohols **24** and **25** were prepared with a modification of the reported method[18] by using $PdCl_2(PPh_3)_2$ as the palladium source. All reactions requiring anhydrous conditions were conducted in oven-dried glassware under a dry nitrogen atmosphere. Dichloromethane and THF were degassed and dried under a nitrogen atmosphere by passing through solvent purification columns (MBraun, SPS-800). Toluene was distilled under a nitrogen atmosphere over sodium as the drying agent. Solvents were removed under reduced pressure with a rotary evaporator. When necessary, reaction mixtures were chromatographed on a silica gel column (230–400 mesh) by using a gradient solvent system as the eluent. ^1H and ^{13}C NMR spectra were recorded with 600, 400, 250, and 200 MHz NMR spectrometers. Chemical shifts (δ) for ^1H and ^{13}C NMR are referenced to internal solvent resonances and reported relative to $SiMe_4$. Electrospray mass spectrometry analyses were recorded with an Esquire 6000 Ion Trap Mass Spectrometer (Bruker) equipped with an electrospray ion source. The instrument was operated in the positive ESI(+) ion mode. Microwave heated reactions were performed in septum-containing, screw-capped sealed vials in an Ethos SEL Lab station (Milestone Inc.), a multimode microwave with a dual magnetron (1600 W). During the experiments, the time, temperature, and the power were measured with an "EasyControl" software package. The temperature was monitored and controlled throughout the reaction by an ATC-400FO Automatic Fiber Optic Temperature Control system. The wattage was automatically adjusted to maintain the desired temperature for the desired period of time.

***N*-(2-Cyanoethyl)-(4-methylphenyl)sulfonamide (5):** A mixture of (4-methylphenyl)sulfonamide (2.07 g, 12.11 mmol), acrylonitrile (1.6 mL, 24.30 mmol), cesium carbonate (7.89 g, 24.21 mmol), and toluene (80 mL) was heated at 110 °C and stirred in a sealed tube for 5.5 h (TLC monitoring). The liquid was distilled off under vacuum, and the residue was dissolved in dichloromethane (10 mL). The organic layer was subsequently washed with water (3 × 10 mL), dried (Na_2SO_4), and filtered. The solvent was removed under reduced pressure to afford **5** (2.22 g, 82%) as a colorless solid. M.p. 80–81 °C (ref.[9] 83–83.5 °C). IR (ATR): $\tilde{\nu}$ = 3257, 2250, 1303, 1155 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 2.43 (s, 3 H, C*H*$_3$-Ts), 2.59 (t, $^3J_{H,H}$ = 6.6 Hz, 2 H, CH$_2$-C*H*$_2$-CN), 3.22 (q, $^3J_{H,H}$ = 6.6 Hz, 2 H, C*H*$_2$-CH$_2$-CN), 5.60 (t, $^3J_{H,H}$ = 6.6 Hz, 1 H, N*H*), 7.33 (AA′ part, AA′BB′ system, $^3J_{H,H}$ = 8.3 Hz, 2 H, *Ar*), 7.76 (BB′ part, AA′BB′ system, $^3J_{H,H}$ = 8.3 Hz, 2 H, *Ar*) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): δ = 19.8, 22.1, 39.5, 118.3, 127.6, 130.5, 137.0, 144.6 ppm. MS (ESI+): *m*/*z* = 247 [M + Na]$^+$, 263 [M + K]$^+$. HRMS (ESI+): calcd. for [$C_{10}H_{12}N_2SO_2$ + Na]$^+$ 247.0512; found 247.0523.

***N*,*N*′-Bis(4-methylphenyl)sulfonyl-*N*-(*tert*-butyloxycarbonyl)-*N*′-(2-cyanoethyl)-2-butyn-1,4-diamine (7):** A stirred mixture of **5** (0.81 g, 3.61 mmol), **6** (1.45 g, 3.59 mmol), potassium carbonate (2.00 g, 14.45 mmol), and acetonitrile (50 mL) was heated at reflux for 4 h (TLC monitoring). The salts were filtered off, and the filtrate was evaporated. The residue was purified by column chromatography on silica gel (hexanes/ethyl acetate, 9:1 to 7:3) to afford **7** (1.73 g, 88%) as a colorless oil. IR (ATR): $\tilde{\nu}$ = 2982, 1729, 1349, 1154 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 1.32 (s, 9 H, Boc), 2.43 (s, 3 H, C*H*$_3$-Ar), 2.45 (s, 3 H, C*H*$_3$-Ar), 2.71 (t, $^3J_{H,H}$ = 7.1 Hz, 2 H, CH$_2$-C*H*$_2$-CN), 3.45 (t, $^3J_{H,H}$ = 7.1 Hz, 2 H, C*H*$_2$-CH$_2$-CN), 4.21 (s, 2 H, N-C*H*$_2$-C), 4.46 (s, 2 H, N-C*H*$_2$-C), 7.33 (d, $^3J_{H,H}$ = 8.4 Hz, 2 H, *Ar*), 7.34 (d, $^3J_{H,H}$ = 8.4 Hz, 2 H, *Ar*), 7.74 (d, $^3J_{H,H}$ = 8.4 Hz, 2 H, *Ar*), 7.80 (d, $^3J_{H,H}$ = 8.4 Hz, 2 H, *Ar*) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): δ = 18.9, 22.2, 22.3, 28.4, 36.2, 39.1, 43.9, 77.1, 82.4, 85.8, 118.0, 128.2, 128.6, 130.0, 130.6, 135.6, 137.3, 145.0, 145.3, 150.8 ppm. HRMS (ESI+): calcd. for [$C_{26}H_{31}N_3S_2O_6$ + Na]$^+$ 568.1546; found 568.1540.

***N*,*N*′-Bis(4-methylphenyl)sulfonyl-*N*′-(2-cyanoethyl)-2-butyn-1,4-diamine (8):** A mixture of **7** (2.40 g, 4.39 mmol), trimethylsilyl triflate (2.40 mL, 13.26 mmol), 2,6-lutidine (2.10 mL, 18.03 mmol), and dichloromethane (50 mL) was stirred in a sealed tube at room temperature for 7 h (TLC monitoring). The reaction mixture was subsequently washed with saturated aqueous ammonium chloride solution (2 × 10 mL) and water (3 × 10 mL). The organic phase was dried (Na_2SO_4) and concentrated in vacuo to give an oil that was dissolved in MeOH (20 mL) and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (dichloromethane/ethyl acetate, 9:1) to afford **8** (1.58 g, 81%) as a colorless solid. M.p. 83–85 °C. IR (KBr): $\tilde{\nu}$ = 3348, 2971, 2253, 1364, 1162 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 2.44 (s, 6 H, C*H*$_3$-Ar), 2.66 (t, $^3J_{H,H}$ = 6.8 Hz, 2 H, CH$_2$-C*H*$_2$-CN), 3.30 (t, $^3J_{H,H}$ = 6.8 Hz, 2 H, C*H*$_2$-CH$_2$CN), 3.61 (dt, $^3J_{H,H}$ = 6.0 Hz, $^5J_{H,H}$ = 2.0 Hz, 2 H, HN-C*H*$_2$-C), 3.95 (t, $^5J_{H,H}$ = 2.0 Hz, 2 H, N-C*H*$_2$-C), 4.81 (t, $^3J_{H,H}$ = 6.0 Hz, 1 H, N*H*), 7.32 (d, $^3J_{H,H}$ = 8.2 Hz, 2 H, *Ar*), 7.33 (d, $^3J_{H,H}$ = 8.2 Hz, 2 H, *Ar*), 7.66 (AA′ part, AA′BB′ system, $^3J_{H,H}$ = 8.4 Hz, 2 H, *Ar*), 7.72 (BB′ part, AA′BB′ system, $^3J_{H,H}$ = 8.4 Hz, 2 H, *Ar*) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): δ = 19.3, 22.2, 33.5, 39.2, 43.9, 78.1, 81.3, 118.3, 128.0, 128.4, 130.4, 130.5, 135.5, 137.2, 144.7, 145.3 ppm. MS (ESI+): *m*/*z* = 446 [M + H]$^+$, 468 [M + Na]$^+$, 484 [M + K]$^+$. HRMS (ESI+): calcd. for [$C_{21}H_{23}N_3S_2O_4$ + Na]$^+$ 468.1022; found 468.1014.

1-(*tert*-Butyloxycarbonyl)-11-(2-cyanoethyl)-1,6,11-tris[(4-methylphenyl)sulfonyl]-1,6,11-triazaundeca-3,8-diyne (1): A stirred mixture of **8** (0.16 g, 0.36 mmol), **6** (0.12 g, 0.31 mmol), potassium carbonate (0.19 g, 1.37 mmol), and acetonitrile (15 mL) was heated at reflux for 8 h (TLC monitoring). The salts were filtered off, and the filtrate was evaporated. The residue was purified by column chromatography on silica gel (dichloromethane/ethyl acetate/hexanes, 1:1:9 to 1:2:8) to afford **1** (0.22 g, 94%) as a colorless solid. M.p. 61–63 °C. IR (ATR): $\tilde{\nu}$ = 2980, 1729, 1347, 1154 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 1.32 (s, 9 H, Boc), 2.44 (s, 3 H, C*H*$_3$-Ar), 2.45 (s, 6 H, C*H*$_3$-Ar), 2.66 (t, $^3J_{H,H}$ = 6.8 Hz, 2 H, CH$_2$-C*H*$_2$-CN), 3.37 (t, $^3J_{H,H}$ = 6.8 Hz, 2 H, C*H*$_2$-CH$_2$-CN), 3.93 (t, $^5J_{H,H}$ = 1.8 Hz, 2 H, N-C*H*$_2$-C), 3.95 (t, $^5J_{H,H}$ = 1.8 Hz, 2 H, N-C*H*$_2$-C), 4.05 (t, $^5J_{H,H}$ = 1.8 Hz, 2 H, N-C*H*$_2$-C), 4.46 (t, $^5J_{H,H}$ = 1.8 Hz, 2 H, N-C*H*$_2$-C), 7.28–7.37 (m, 6 H, *Ar*), 7.66 (BB′ part, AA′BB′ system, $^3J_{H,H}$ = 8.4 Hz, 2 H, *Ar*), 7.67 (BB′ part, AA′BB′ system, $^3J_{H,H}$ = 8.4 Hz, 2 H, *Ar*), 7.81 (BB′ part, AA′BB′ system, $^3J_{H,H}$ = 8.4 Hz, 2 H, *Ar*) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C):

δ = 19.0, 22.2, 22.3, 28.5, 36.3, 36.9, 37.2, 38.8, 43.6, 76.9, 78.9, 79.6, 82.1, 85.8, 118.1, 128.2, 128.4, 128.6, 130.0, 130.4, 130.6, 135.7, 135.8, 137.3, 144.9, 145.1, 145.3, 150.8 ppm. MS (ESI+): *m*/*z* = 789 [M + Na]$^+$. HRMS (ESI+): calcd. for [$C_{37}H_{42}N_4S_3O_8$ + Na]$^+$ 789.2057; found 789.2018. $C_{37}H_{42}N_4O_8S_3$ (766.95): calcd. C 57.94, H 5.52, N 7.31, S 12.54; found C 57.62, H 6.00, N 6.91, S 12.49.

1-(2-Cyanoethyl)-1,6,11-tris[(4-methylphenyl)sulfonyl]-1,6,11-triazaundeca-3,8-diyne (2): A mixture of **1** (0.10 g, 0.13 mmol), trimethylsilyl triflate (0.21 mL, 1.16 mmol), 2,6-lutidine (0.18 mL, 1.54 mmol), and dichloromethane (2 mL) was stirred in a sealed tube at room temperature for 48 h (TLC monitoring). The crude was subsequently washed with saturated aqueous ammonium chloride solution (1 × 10 mL) and water (1 × 10 mL). The organic layer was dried (Na_2SO_4) and concentrated in vacuo to give an oil that was dissolved in MeOH (1 mL) and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (dichloromethane/ethyl acetate/hexanes, 10:1:6 to 10:1:4) to afford **2** (0.08 g, 91%) as a colorless solid. M.p. 50–53 °C. IR (ATR): $\tilde{\nu}$ = 3286, 2923, 1328, 1154 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 2.44 (s, 9 H, C*H*$_3$-Ar), 2.67 (t, $^3J_{H,H}$ = 6.8 Hz, 2 H, CH$_2$-C*H*$_2$-CN), 3.36 (t, $^3J_{H,H}$ = 6.8 Hz, 2 H, C*H*$_2$-CH$_2$-CN), 3.55–3.63 (m, 2 H, HN-C*H*$_2$-C), 3.78–3.87 (m, 4 H, N-C*H*$_2$-C), 4.03 (br. s, 2 H, N-C*H*$_2$-C), 4.80 (t, $^3J_{H,H}$ = 6.0 Hz, 1 H, N*H*), 7.27–7.37 (m, 6 H, *Ar*), 7.61 (BB′ part, AA′BB′ system, $^3J_{H,H}$ = 8.2 Hz, 2 H, *Ar*), 7.68 (BB′ part, AA′BB′ system, $^3J_{H,H}$ = 8.4 Hz, 2 H, *Ar*), 7.70 (BB′ part, AA′BB′ system, $^3J_{H,H}$ = 8.2 Hz, 2 H, *Ar*) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): δ = 18.9, 22.2, 33.4, 37.0, 37.1, 38.9, 43.8, 77.5, 79.1, 79.6, 81.1, 118.2, 127.8, 128.2, 128.5, 130.3, 130.4, 130.6, 135.5, 135.7, 137.1, 144.6, 145.0, 145.2 ppm. MS (ESI+): *m*/*z* = 689 [M + Na]$^+$. HRMS (ESI+): calcd. for [$C_{32}H_{34}N_4S_3O_6$ + Na]$^+$ 689.1533; found 689.1566.

1-(2-Cyanoethyl)-1,6-bis[(4-methylphenyl)sulfonyl]-1,6-diazadeca-3,8-diyne (3): A stirred mixture of **8** (0.28 g, 0.63 mmol), **9** (0.06 mL, 0.36 mmol), potassium carbonate (0.44 g, 3.16 mmol), and acetonitrile (20 mL) was heated at reflux for 6 h (TLC monitoring). The salts were filtered off, and the filtrate was evaporated. The residue was purified by column chromatography on silica gel (dichloromethane/ethyl acetate/hexanes, 1:1.5:8.5 to 1:3:7) to afford **3** (0.26 g, 82%) as a colorless solid. M.p. 114–115 °C. IR (KBr): $\tilde{\nu}$ = 2927, 2254, 1345, 1163 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 1.62 (s, 3 H, C*H*$_3$-C$_{alkyne}$), 2.42 (s, 3 H, C*H*$_3$-Ar), 2.45 (s, 3 H, C*H*$_3$-Ar), 2.68 (t, $^3J_{H,H}$ = 7.0 Hz, 2 H, CH$_2$-C*H*$_2$-CN), 3.37 (t, $^3J_{H,H}$ = 7.0 Hz, 2 H, C*H*$_2$-CH$_2$-CN), 3.85 (br. s, 2 H, N-C*H*$_2$-C), 3.92 (br. s, 2 H, N-C*H*$_2$-C), 4.08 (br. s, 2 H, N-C*H*$_2$-C), 7.32 (AA′ part, AA′BB′ system, $^3J_{H,H}$ = 8.1 Hz, 4 H, *Ar*), 7.67 (BB′ part, AA′BB′ system, $^3J_{H,H}$ = 8.1 Hz, 4 H, *Ar*) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): δ = 3.9, 18.9, 22.1, 22.2, 36.8, 37.4, 38.8, 43.6, 71.7, 78.5, 80.0, 82.8, 118.0, 128.2, 128.5, 130.1, 130.5, 135.6, 135.9, 144.5, 145.1 ppm. MS (ESI+): *m*/*z* = 520 [M + Na]$^+$. HRMS (ESI+): calcd. for [$C_{25}H_{27}N_3O_4S_2$ + Na]$^+$ 520.1335; found 520.1330. $C_{25}H_{27}N_3O_4S_2$ (497.63): calcd. C 60.34, H 5.47, N 8.44, S 12.89; found C 59.98, H 5.40, N 8.16, S 12.69.

1-(2-Cyanoethyl)-1,6-bis[(4-methylphenyl)sulfonyl]-1,6-diazanona-3,8-diyne (4): A stirred mixture of **8** (0.45 g, 1.02 mmol), **10** (0.12 mL, 1.08 mmol), potassium carbonate (0.70 g, 5.05 mmol), and acetonitrile (40 mL) was heated at reflux for 1 h (TLC monitoring). The salts were filtered off, and the filtrate was evaporated. The residue was purified by column chromatography on silica gel (hexanes/ethyl acetate, 7:3 to 6:4) to afford **4** (0.48 g, 98%) as a colorless solid. M.p. 146–147 °C. IR (ATR): $\tilde{\nu}$ = 3277, 2925, 1346, 1156 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C): δ = 2.11 (t, $^4J_{H,H}$ = 2.1 Hz, 1 H, *H*-C$_{alkyne}$), 2.43 (s, 3 H, C*H*$_3$-Ar), 2.45 (s, 3 H, C*H*$_3$-Ar), 2.67 (t, $^3J_{H,H}$ = 6.9 Hz, 2 H, CH$_2$-C*H*$_2$-CN), 3.36 (t, $^3J_{H,H}$ = 6.9 Hz, 2 H, C*H*$_2$-CH$_2$-CN), 3.95 (d, $^4J_{H,H}$ = 2.1 Hz, 2 H, N-C*H*$_2$-C$_{alkyne}$H), 3.98 (s, 2 H, N-C*H*$_2$-C), 4.08 (s, 2 H, N-C*H*$_2$-C), 7.30 (AA′ part, AA′BB′ system, $^3J_{H,H}$ = 7.8 Hz, 2 H, *Ar*), 7.34 (AA′ part, AA′BB′ system, $^3J_{H,H}$ = 7.8 Hz, 2 H, *Ar*), 7.65 (BB′ part, AA′BB′ system, $^3J_{H,H}$ = 7.8 Hz, 2 H, *Ar*), 7.68 (BB′ part, AA′BB′ system, $^3J_{H,H}$ = 7.8 Hz, 2 H, *Ar*) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): δ = 19.0, 22.1, 22.2, 36.8, 36.9, 38.8, 43.6, 74.8, 76.6, 78.8, 79.6, 118.0, 128.2, 128.4, 130.3, 130.5, 135.6, 135.7, 144.8, 145.1 ppm. MS (ESI+): *m*/*z* = 506 [M + Na]$^+$. HRMS (ESI+): calcd. for [$C_{24}H_{25}N_3O_4S_2$ + Na]$^+$ 506.1179; found 506.1166.

1-Cyano-3,3,8,8-tetra(carbethoxy)dodeca-5,10-diyne (18): Diethyl 2-cyanoethylmalonate (**16**) (0.096 g, 0.45 mmol) in anhydrous THF (2 mL) was added to a suspension of NaH (60% dispersion in mineral oil, 0.021 g, 0.52 mmol) in anhydrous THF (2 mL) at 0 °C under an atmosphere of N_2. A solution of **15** (0.17 g, 0.49 mmol) in anhydrous THF (2 mL) was then added to the first solution, and the resulting mixture was stirred at room temperature for 16 h (TLC monitoring). Water was added to quench the reaction, and the reaction mixture was extracted with EtOAc. The organic solution was washed with water (2 × 10 mL), dried (Na_2SO_4), filtered, and concentrated. The residue was purified by column chromatography on silica gel (hexanes/ethyl acetate, 20:1 to 10:1) to afford **18** (0.170 g, 79%) as a pale-yellow oil. IR (ATR): $\tilde{\nu}$ = 2921, 1727, 1187 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.24 (t, $^3J_{H,H}$ = 7.2 Hz, 6 H, C*H*$_3$-CH$_2$-OCO), 1.27 (t, $^3J_{H,H}$ = 7.2 Hz, 6 H, C*H*$_3$-CH$_2$-OCO), 1.74 (t, $^5J_{H,H}$ = 2.4 Hz, 3 H, C*H*$_3$-C$_{alkyne}$), 2.32–2.40 (m, 2 H, CH$_2$-C*H*$_2$-CN), 2.41–2.48 (m, 2 H, C*H*$_2$-CH$_2$-CN), 2.78 (t, $^5J_{H,H}$ = 2.2 Hz, 2 H, C-C*H*$_2$-C), 2.84 (q, $^5J_{H,H}$ = 2.4 Hz, 2 H, C-C*H*$_2$-C$_{alkyne}$CH$_3$), 2.90 (t, $^5J_{H,H}$ = 2.2 Hz, 2 H, C-C*H*$_2$-C), 4.18–4.30 (m, 8 H, CH$_3$-C*H*$_2$-OCO) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 3.4, 12.8, 13.8, 13.9, 22.7, 22.8, 23.6, 28.4, 55.7, 56.5, 61.7, 62.1, 72.9, 78.7, 78.9, 118.8, 168.9, 169.1 ppm. HRMS (ESI+): calcd. for [$C_{25}H_{33}NO_8$ + Na]$^+$ 498.2098; found 498.2121.

1-Cyano-2,2,7,7-tetra(carbethoxy)undeca-4,9-diyne (19): Diethyl cyanomethylmalonate (**17**) (0.090 g, 0.45 mmol) in anhydrous THF (2 mL) was added to a suspension of NaH (60% dispersion in mineral oil, 0.021 g, 0.52 mmol) in anhydrous THF (2 mL) at 0 °C under an atmosphere of N_2. A solution of **15** (0.170 g, 0.49 mmol) in anhydrous THF (2 mL) was then added to the reaction, and the resulting mixture was stirred at room temperature for 16 h (TLC monitoring). Water was added to quench the reaction, and the reaction mixture was extracted with EtOAc. The organic solution was washed with water (2 × 10 mL), dried (Na_2SO_4), filtered, and concentrated. The residue was purified by column chromatography on silica gel (hexanes/ethyl acetate, 20:1 to 10:1) to afford **19** (0.169 g, 81%) as a pale-yellow oil. IR (ATR): $\tilde{\nu}$ = 2982, 1732, 1192 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.25 (t, $^3J_{H,H}$ = 7.2 Hz, 6 H, C*H*$_3$-CH$_2$-OCO), 1.29 (t, $^3J_{H,H}$ = 7.2 Hz, 6 H, C*H*$_3$-CH$_2$-OCO), 1.74 (t, $^5J_{H,H}$ = 2.4 Hz, 3 H, C*H*$_3$-C$_{alkyne}$), 2.83 (q, $^5J_{H,H}$ = 2.4 Hz, 2 H, C-C*H*$_2$C$_{alkyne}$CH$_3$), 2.91 (t, $^5J_{H,H}$ = 2.2 Hz, 2 H, C-C*H*$_2$-C), 2.96 (t, $^5J_{H,H}$ = 2.2 Hz, 2 H, C-C*H*$_2$-C), 3.12 (s, 2 H, C*H*$_2$-CN), 4.21 (q, $^3J_{H,H}$ = 7.2 Hz, 4 H, CH$_3$-C*H*$_2$-OCO), 4.26 (q, $^3J_{H,H}$ = 7.2 Hz, 4 H, CH$_3$-C*H*$_2$-OCO) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 3.4, 13.8, 13.9, 21.5, 22.7, 22.8, 23.6, 54.9, 56.5, 61.8, 62.7, 72.9, 76.1, 78.9, 79.4, 116.1, 167.3, 168.9 ppm. HRMS (ESI+): calcd. for [$C_{24}H_{31}NO_8$ + Na]$^+$ 484.1972; found 484.1960.

1-(2-Cyanoethyl)-9-(3-pyridyl)-1,6-bis[(4-methylphenyl)sulfonyl]-1,6-diazanona-3,8-diyne (26): PBr_3 (1 M in dichloromethane, 0.43 mL, 0.43 mmol) was added to a cold (–10 °C) stirred solution of 3-(pyridin-3-yl)-2-propyn-1-ol (**24**) (0.05 g, 0.39 mmol) in anhydrous

dichloromethane (5 mL) under a N_2 atmosphere. The reaction mixture was stirred at –10 to 0 °C for 1.5 h and warmed to room temperature over 2 h until completion (TLC monitoring). The dichloromethane solution was washed with water (3 × 10 mL), and the organic layer was dried (Na_2SO_4) and added directly over a solution of **8** (0.19 g, 0.44 mmol), K_2CO_3 (0.28 g, 2.00 mmol), and acetonitrile (20 mL). The reaction mixture was heated at reflux for 7 h until completion (TLC monitoring). The salts were filtered off, and the filtrate was evaporated. The residue was purified by column chromatography on silica gel (dichloromethane/ethyl acetate, 20:1 to 9:1) to afford **26** (0.11 g, 49%) as a pale-yellow oil. IR (ATR): $\tilde{\nu}$ = 2923, 1347, 1157 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 2.37 (s, 3 H, CH_3-Ar), 2.44 (s, 3 H, CH_3-Ar), 2.68 (t, $^3J_{H,H}$ = 6.8 Hz, 2 H, CH_2-CH_2-CN), 3.39 (t, $^3J_{H,H}$ = 6.8 Hz, 2 H, CH_2-CH_2-CN), 4.00 (br. s, 2 H, N-CH_2-C), 4.13 (br. s, 2 H, N-CH_2-C), 4.20 (s, 2 H, N-CH_2-C), 7.19–7.25 (m, 1 H, pyr-H), 7.28 (AA′ part, AA′BB′ system, $^3J_{H,H}$ = 8.0 Hz, 2 H, *Ar*), 7.34 (AA′ part, AA′BB′ system, $^3J_{H,H}$ = 8.0 Hz, 2 H, *Ar*), 7.46 (dt, $^3J_{H,H}$ = 7.6 Hz, $^4J_{H,H}$ = 1.6 Hz, 1 H, pyr-H), 7.67–7.72 (m, 4 H, *Ar*), 8.32 (br. abs, 1 H, pyr-H), 8.53 (br. abs, 1 H, pyr-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 18.4, 21.4, 21.6, 36.6, 37.0, 38.3, 43.0, 78.3, 79.0, 82.6, 84.6, 117.3, 119.3, 123.0, 127.6, 127.8, 129.7, 129.9, 134.9, 135.0, 138.5, 144.3, 144.5, 148.9, 152.1 ppm. MS (ESI+): *m*/*z* = 561 [M + H]$^+$. HRMS (ESI+): calcd. for $[C_{29}H_{28}N_4S_2O_4 + H]^+$ 561.1626; found 561.1618.

1-(2-Cyanoethyl)-9-(2-pyridyl)-1,6-bis[(4-methylphenyl)sulfonyl]-1,6-diazanona-3,8-diyne (27): Prepared by following the general method described above. Column chromatography: dichloromethane/ethyl acetate (10:1); pale-yellow oil. IR (ATR): $\tilde{\nu}$ = 2922, 1346, 1157 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 2.35 (s, 3 H, CH_3-Ar), 2.43 (s, 3 H, CH_3-Ar), 2.68 (t, $^3J_{H,H}$ = 6.8 Hz, 2 H, CH_2-CH_2-CN), 3.39 (t, $^3J_{H,H}$ = 6.8 Hz, 2 H, CH_2-CH_2-CN), 4.00 (br. s, 2 H, N-CH_2-C), 4.10 (br. s, 2 H, N-CH_2-C), 4.16 (s, 2 H, N-CH_2-C), 7.10–7.15 (m, 1 H, pyr-H), 7.22–7.26 (m, 1 H, pyr-H), 7.27 (part AA′, AA′BB′ system, $^3J_{H,H}$ = 8.0 Hz, 2 H, *Ar*), 7.34 (part AA′, AA′BB′ system, $^3J_{H,H}$ = 8.0 Hz, 2 H, *Ar*), 7.62 (dt, $^3J_{H,H}$ = 7.6 and $^4J_{H,H}$ = 1.6 Hz, 1 H, pyr-H), 7.65–7.73 (m, 4 H, *Ar*), 8.54 (br. abs, 1 H, pyr-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 18.4, 21.4, 21.5, 36.7, 37.0, 38.2, 43.0, 78.4, 79.0, 81.3, 85.2, 117.4, 123.3, 127.1, 127.6, 127.8, 129.6, 129.9, 134.9, 135.0, 136.1, 142.1, 144.1, 144.5, 150.0 ppm. MS (ESI+): *m*/*z* = 561 [M + H]$^+$. HRMS (ESI+): calcd. for $[C_{29}H_{28}N_4S_2O_4 + Na]^+$ 583.1444; found 583.1454.

1,18-Bis(2-cyanoethyl)-1,6,13,18-tetrakis[(4-methylphenyl)sulfonyl]-1,6,13,18-tetraazaoctadeca-3,8,10,15-tetrayne (28): A mixture of **4** (0.108 g, 0.22 mmol), $PdCl_2$ (0.0004 g, 0.0022 mmol), CuI (0.0022 g, 0.011 mmol), triethylamine (0.28 mL, 2.01 mmol), and anhydrous THF (5 mL) was stirred at room temperature for 2 h (TLC monitoring). The salts were filtered off, and the filtrate was evaporated. The residue was purified by column chromatography on silica gel (hexanes/ethyl acetate, 1:1) to afford **28** (0.402 g, 37%) as a colorless solid. M.p. 172–173 °C (decomp.). IR (ATR): $\tilde{\nu}$ = 1353, 1334, 1159 cm^{-1}. ^1H NMR (400 MHz, [D_6]DMSO, 25 °C): δ = 2.38 (s, 6 H, CH_3-Ar), 2.40 (s, 6 H, CH_3-Ar), 2.76 (t, $^3J_{H,H}$ = 6.4 Hz, 4 H, CH_2-CH_2-CN), 3.23 (t, $^3J_{H,H}$ = 6.4 Hz, 4 H, CH_2-CH_2-CN), 3.81 (br. s, 4 H, N-CH_2-C), 3.98 (br. s, 4 H, N-CH_2-C), 4.10 (br. s, 4 H, N-CH_2-C), 7.36–7.43 (m, 8 H, *Ar*), 7.63 (BB′ part, AA′BB′ system, $^3J_{H,H}$ = 8.0 Hz, 4 H, *Ar*), 7.68 (BB′ part, AA′BB′ system, $^3J_{H,H}$ = 8.0 Hz, 4 H, *Ar*) ppm. ^{13}C NMR (100 MHz, [D_6]-DMSO, 25 °C): δ = 17.0, 21.0, 36.7, 36.8, 36.9, 42.6, 68.4, 72.6, 78.1, 78.8, 118.5, 127.4, 127.5, 129.8, 134.4, 134.9, 143.9, 144.2 ppm. MS (ESI+): *m*/*z* = 965 [M + H]$^+$, 987 [M + Na]$^+$. HRMS (ESI+): calcd. for $[C_{48}H_{48}N_6S_4O_8 + Na]^+$ 987.2309; found 987.2270.

General Method for [2+2+2] Cycloaddition Reactions of 1–4 using Conventional Heating: A degassed solution of cyanodiyne (0.08 mmol) and chlorotris(triphenylphosphane)rhodium(I) (0.008 mmol, 10 mol-%) in anhydrous toluene (5 mL) was heated (temperature and reaction time specified in Table 1) until completion (TLC monitoring). The solvent was then evaporated, and the residue was purified by column chromatography on silica gel.

General Method for [2+2+2] Cycloaddition Reactions of 2–4, 18–20, and 26–28 using Microwave Heating: In a sealed 20-mL, septum-containing, screw-capped vial a degassed solution of chlorotris(triphenylphosphane)rhodium(I) (0.008 mmol, 10 mol-%) and cyanodiyne (0.08 mmol) in the stated solvent (5 mL) (Table 2, Scheme 3, and Table 3) was heated for the time indicated (Table 2, Scheme 3, and Table 3) at 90 °C under microwave irradiation (TLC monitoring). Upon completion, the solvent was evaporated and the residue was purified.

Pyridine Derivative 11: Column chromatography: dichloromethane/ethyl acetate/hexanes (10:1:10 to 10:1:7); colorless solid; m.p. 175–177 °C (decomp.). IR (ATR): $\tilde{\nu}$ = 2982, 1728, 1361, 1341, 1160 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 1.27 (s, 9 H, Boc), 2.40 (s, 3 H, CH_3-Ar), 2.42 (s, 3 H, CH_3-Ar), 2.44 (s, 3 H, CH_3-Ar), 2.88 (t, $^3J_{H,H}$ = 5.7 Hz, 2 H, N-CH_2-CH_2-pyr), 3.36 (t, $^3J_{H,H}$ = 5.7 Hz, 2 H, N-CH_2-CH_2-pyr), 4.02 (br. s, 2 H, CH_2-N), 4.45 (br. s, 2 H, CH_2-N), 4.66 (br. s, 2 H, CH_2-N), 4.95 (s, 2 H, CH_2-N), 7.22 (d, $^3J_{H,H}$ = 8.2 Hz, 2 H, *Ar*), 7.34 (d, $^3J_{H,H}$ = 8.2 Hz, 2 H, *Ar*), 7.36 (d, $^3J_{H,H}$ = 8.2 Hz, 2 H, *Ar*), 7.72 (d, $^3J_{H,H}$ = 8.2 Hz, 2 H, *Ar*), 7.78 (d, $^3J_{H,H}$ = 8.2 Hz, 2 H, *Ar*), 7.82 (d, $^3J_{H,H}$ = 8.2 Hz, 2 H, *Ar*) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): δ = 22.1, 22.2, 22.3, 28.5, 32.4, 44.3, 45.3, 49.2, 52.1, 52.4, 85.3, 121.5, 128.2, 128.3, 128.4, 129.3, 129.5, 130.7, 130.8, 133.4, 134.0, 137.6, 144.1, 144.8, 144.9, 149.6, 151.6, 152.8 ppm. MS (ESI+): *m*/*z* = 767 [M + H]$^+$. HRMS (ESI+): calcd. for $[C_{37}H_{42}N_4S_3O_8 + H]^+$ 767.2238; found 767.2232. $C_{37}H_{42}N_4O_8S_3 \cdot H_2O$: calcd. C 56.61, H 5.65, N 7.14, S 12.25; found C 56.85, H 5.78, N 6.93, S 11.78.

Pyridine Derivative 12: Column chromatography: dichloromethane/ethyl acetate (20:1); colorless solid; m.p. 228–230 °C (decomp.). IR (ATR): $\tilde{\nu}$ = 2924, 1332, 1158 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 2.35 (s, 3 H, CH_3-Ar), 2.43 (s, 3 H, CH_3-Ar), 2.44 (s, 3 H, CH_3-Ar), 2.95 (t, $^3J_{H,H}$ = 5.7 Hz, 2 H, N-CH_2-CH_2-pyr), 3.36 (t, $^3J_{H,H}$ = 5.7 Hz, 2 H, N-CH_2-CH_2-pyr), 3.97–4.04 (m, 4 H, CH_2-N), 4.40 (br. s, 2 H, CH_2-N), 4.47 (br. s, 2 H, CH_2-N), 5.81 (t, $^3J_{H,H}$ = 5.2 Hz, 1 H, N*H*), 7.17 (d, $^3J_{H,H}$ = 8.2 Hz, 2 H, *Ar*), 7.34–7.38 (m, 4 H, *Ar*), 7.64 (d, $^3J_{H,H}$ = 8.2 Hz, 2 H, *Ar*), 7.71 (d, $^3J_{H,H}$ = 8.2 Hz, 2 H, *Ar*), 7.77 (d, $^3J_{H,H}$ = 8.2 Hz, 2 H, *Ar*) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): δ = 22.1, 22.2, 32.4, 44.2, 45.2, 45.6, 51.8, 52.5, 122.1, 127.8, 128.3, 128.4, 128.7, 130.2, 130.7, 130.9, 133.3, 133.9, 137.0, 144.3, 145.0, 145.1, 147.8, 152.9 ppm. MS (ESI+): *m*/*z* = 667 [M + H]$^+$. HRMS (ESI+): calcd. for $[C_{32}H_{34}N_4S_3O_6 + H]^+$ 667.1713; found 667.1685.

Pyridine Derivative 13: Column chromatography: dichloromethane/ethyl acetate/hexanes (9:1:4); colorless solid; m.p. 217–218 °C. IR (ATR): $\tilde{\nu}$ = 2918, 1339, 1154 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 2.35 (s, 3 H, CH_3-pyr), 2.43 (s, 3 H, CH_3-Ar), 2.44 (s, 3 H, CH_3-Ar), 3.02 (t, $^3J_{H,H}$ = 5.8 Hz, 2 H, N-CH_2-CH_2-pyr), 3.40 (t, $^3J_{H,H}$ = 5.8 Hz, 2 H, N-CH_2-CH_2-pyr), 4.02 (s, 2 H, CH_2-N), 4.47 (s, 2 H, CH_2-N), 4.54 (s, 2 H, CH_2-N), 7.36 (d, $^3J_{H,H}$ = 7.8 Hz, 4 H, *Ar*), 7.72 (d, $^3J_{H,H}$ = 7.8 Hz, 2 H, *Ar*), 7.78 (d, $^3J_{H,H}$ = 7.8 Hz, 2 H, *Ar*) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): δ = 22.2, 22.4, 32.5, 44.4, 45.2, 52.8, 120.3, 128.2, 128.4, 129.4, 130.6, 130.7, 133.5,

134.2, 143.2, 144.8, 151.6, 152.8 ppm. HRMS (ESI+): calcd. for $[C_{25}H_{27}N_3S_2O_4 + H]^+$ 498.1516; found 498.1518.

Pyridine Derivative 14: Column chromatography: dichloromethane/hexanes (8:2); colorless solid; m.p. 216–217 °C (decomp.). IR (ATR): $\tilde{\nu}$ = 2920, 1334, 1157 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 2.42 (s, 3 H, C*H*$_3$-Ar), 2.44 (s, 3 H, C*H*$_3$-Ar), 3.06 (t, $^3J_{H,H}$ = 5.8 Hz, 2 H, N-CH$_2$-C*H*$_2$-pyr), 3.41 (t, $^3J_{H,H}$ = 5.8 Hz, 2 H, N-C*H*$_2$-CH$_2$-pyr), 4.06 (s, 2 H, C*H*$_2$-N), 4.47 (s, 2 H, C*H*$_2$-N), 4.61 (s, 2 H, C*H*$_2$-N), 7.35 (d, $^3J_{H,H}$ = 8.4 Hz, 2 H, *Ar*), 7.36 (d, $^3J_{H,H}$ = 8.4 Hz, 2 H, *Ar*), 7.72 (d, $^3J_{H,H}$ = 8.4 Hz, 2 H, *Ar*), 7.77 (d, $^3J_{H,H}$ = 8.4 Hz, 2 H, *Ar*), 8.26 (s, 1 H, pyr-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 21.5, 31.7, 43.6, 44.5, 51.7, 122.2, 127.5, 127.6, 129.9, 130.0, 130.5, 132.5, 133.2, 142.1, 142.7, 144.2, 152.3 ppm. HRMS (ESI+): calcd. for $[C_{24}H_{25}N_3S_2O_4 + H]^+$ 484.1359; found 484.1364.

Pyridine Derivative 21: Column chromatography: dichloromethane/ethyl acetate (10:1 to 9:1); pale-yellow oil. IR (ATR): $\tilde{\nu}$ = 2979, 1727, 1243, 1183 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.24 (t, $^3J_{H,H}$ = 7.2 Hz, 6 H, C*H*$_3$-CH$_2$-OCO), 1.27 (t, $^3J_{H,H}$ = 7.2 Hz, 6 H, C*H*$_3$-CH$_2$-OCO), 2.39 (s, 3 H, C*H*$_3$-pyr), 2.40 (t, $^3J_{H,H}$ = 6.6 Hz, 2 H, C-CH$_2$-CH$_2$-pyr), 2.90 (t, $^3J_{H,H}$ = 6.6 Hz, 2 H, C-CH$_2$-CH$_2$-pyr), 3.13 (s, 2 H, C*H*$_2$-C), 3.53 (s, 4 H, C*H*$_2$-C), 4.15–4.30 (m, 8 H, CH$_3$C*H*$_2$-OCO) ppm. ^{13}C NMR (100 MHz, CD_2Cl_2, 25 °C): δ = 13.9, 21.7, 27.9, 28.6, 31.3, 38.7, 38.9, 53.1, 59.5, 61.6, 61.9, 122.6, 132.9, 148.2, 150.8, 152.4, 170.9, 171.3 ppm. HRMS (ESI+): calcd. for $[C_{25}H_{33}NO_8 + H]^+$ 476.2279; found 476.2277.

Pyridine Derivative 22: Column chromatography: dichloromethane/ethyl acetate (10:1 to 8:2); pale-yellow oil. IR (ATR): $\tilde{\nu}$ = 2981, 1727, 1248, 1182, 1064 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.26 (t, $^3J_{H,H}$ = 7.2 Hz, 6 H, C*H*$_3$-CH$_2$-OCO), 1.27 (t, $^3J_{H,H}$ = 7.2 Hz, 6 H, C*H*$_3$-CH$_2$-OCO), 2.43 (s, 3 H, C*H*$_3$-pyr), 3.49 (s, 2 H, C*H*$_2$-C), 3.52 (s, 4 H, C*H*$_2$-C), 3.62 (s, 2 H, C*H*$_2$-C), 4.21 (q, $^3J_{H,H}$ = 7.2 Hz, 4 H, CH$_3$-C*H*$_2$-OCO), 4.22 (q, $^3J_{H,H}$ = 7.2 Hz, 4 H, CH$_3$-C*H*$_2$-OCO) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 13.9, 21.7, 36.6, 38.6, 38.9, 41.5, 58.0, 59.6, 61.8, 61.9, 126.6, 132.5, 145.2, 152.5, 159.0, 171.1, 171.3 ppm. HRMS (ESI+): calcd. for $[C_{24}H_{31}NO_8 + Na]^+$ 484.1942; found 484.1931.

Bipyridine Derivative 29: Column chromatography: dichloromethane/ethyl acetate (10:1 to 0:10); colorless solid; m.p. 247–248 °C (decomp.). IR (ATR): $\tilde{\nu}$ = 2922, 1339, 1157 cm^{-1}. ^1H NMR (400 MHz, CD_2Cl_2, 25 °C): δ = 2.41 (s, 3 H, C*H*$_3$-Ar), 2.44 (s, 3 H, C*H*$_3$-Ar), 3.10 (t, $^3J_{H,H}$ = 5.8 Hz, 2 H, N-CH$_2$-C*H*$_2$-pyr), 3.43 (t, $^3J_{H,H}$ = 5.8 Hz, 2 H, N-C*H*$_2$-CH$_2$-pyr), 4.11 (s, 2 H, C*H*$_2$-N), 4.52 (s, 2 H, C*H*$_2$-N), 4.76 (s, 2 H, C*H*$_2$-N), 7.32–7.42 (m, 4 H + 1 H, *Ar* + pyr-H), 7.73 (BB′ part, AA′BB′ system, $^3J_{H,H}$ = 8.4 Hz, 2 H, *Ar*), 7.76 (BB′ part, AA′BB′ system, $^3J_{H,H}$ = 8.4 Hz, 2 H, *Ar*), 8.00 (dt, $^3J_{H,H}$ = 8.0 Hz, $^4J_{H,H}$ = 1.8 Hz, 1 H, pyr-H), 8.63 (br. abs, 1 H, *pyr*-H), 8.85 (br. abs, 1 H, *pyr*-H) ppm. ^{13}C NMR (100 MHz, CD_2Cl_2, 25 °C): δ = 21.6, 32.4, 44.2, 45.1, 52.1, 121.9, 123.9, 127.9, 128.1, 128.6, 129.9, 130.3, 130.4, 133.1, 133.4, 134.3, 134.4, 135.5, 144.7, 148.6, 149.1, 150.2, 153.5 ppm. HRMS (ESI+): calcd. for $[C_{29}H_{28}N_4S_2O_4 + H]^+$ 561.1625; found 561.1617.

Bipyridine Derivative 30: Column chromatography: dichloromethane/ethyl acetate (10:1); colorless oil. IR (ATR): $\tilde{\nu}$ = 2922, 1338, 1156 cm^{-1}. ^1H NMR (300 MHz, CD_2Cl_2, 25 °C): δ = 2.37 (s, 3 H, C*H*$_3$-Ar), 2.41 (s, 3 H, C*H*$_3$-Ar), 3.11 (t, $^3J_{H,H}$ = 5.7 Hz, 2 H, N-CH$_2$-C*H*$_2$-pyr), 3.41 (t, $^3J_{H,H}$ = 5.7 Hz, 2 H, N-C*H*$_2$-CH$_2$-pyr), 4.07 (s, 2 H, C*H*$_2$-N), 4.47 (s, 2 H, C*H*$_2$-N), 5.09 (s, 2 H, C*H*$_2$-N), 7.24–7.32 (m, 1 H, pyr-H), 7.30 (AA′ part, AA′BB′ system, $^3J_{H,H}$ = 8.1 Hz, 2 H, *Ar*), 7.36 (AA′ part, AA′BB′ system, $^3J_{H,H}$ = 8.1 Hz, 2 H, *Ar*), 7.71 (BB′ part, AA′BB′ system, $^3J_{H,H}$ = 8.1 Hz, 2 H, *Ar*), 7.80 (BB′ part, AA′BB′ system, $^3J_{H,H}$ = 8.1 Hz, 2 H, *Ar*), 7.79–7.88 (m, 1 H, pyr-H), 8.36 (d, $^3J_{H,H}$ = 7.8 Hz, 1 H, pyr-H), 8.66 (d, $J_{H,H}$ = 4.8 Hz, 1 H, pyr-H) ppm. ^{13}C NMR (75 MHz, CD_2Cl_2, 25 °C): δ = 21.5, 21.6, 32.3, 44.2, 45.2, 51.7, 55.3, 122.2, 123.9, 125.3, 127.8, 128.0, 130.3, 132.9, 133.8, 135.5, 137.1, 144.4, 144.7, 145.3, 149.1, 152.3 ppm. HRMS (ESI+): calcd. for $[C_{29}H_{28}N_4S_2O_4 + H]^+$ 561.1625; found 561.1614.

Bipyridine Derivative 31: Filtered off and washed with diethyl ether; colorless solid; m.p. 293–294 °C (decomp.). IR (ATR): $\tilde{\nu}$ = 1346, 1160 cm^{-1}. ^1H NMR (400 MHz, [D$_5$]pyridine, 25 °C): δ = 2.10 (s, 6 H, C*H*$_3$-Ar), 2.21 (s, 6 H, C*H*$_3$-Ar), 2.98 (br. abs, 4 H, N-C*H*$_2$-CH$_2$-pyr), 3.46 (br. abs, 4 H, N-C*H*$_2$-CH$_2$-pyr), 4.32 (s, 4 H, C*H*$_2$-N), 4.77 (s, 4 H, C*H*$_2$-N), 5.35 (s, 4 H, C*H*$_2$-N), 7.22–7.30 (m, 8 H, *Ar*), 7.93 (BB′ part, AA′BB′ system, $^3J_{H,H}$ = 8.0 Hz, 4 H, *Ar*), 8.09 (BB′ part, AA′BB′ system, $^3J_{H,H}$ = 7.6 Hz, 4 H, *Ar*) ppm. ^{13}C NMR (100 MHz, [D$_5$]pyridine, 25 °C): δ = 21.9, 22.0, 32.1, 44.5, 45.4, 51.9, 55.3, 122.7, 128.4, 130.2, 130.3, 130.8, 133.6, 134.3, 144.4, 144.5, 145.1, 152.1 ppm. MS (ESI+): *m/z* = 987 $[M + Na]^+$. HRMS (ESI+): calcd. for $[C_{48}H_{48}N_6S_4O_8 + H]^+$ 965.2489; found 965.2434.

Supporting Information (see footnote on the first page of this article): ^1H and ^{13}C NMR spectra of intermediates **5**, **7**, and **8**; cyanodiynes **1**–**4**, **18**–**19**, and **26**–**27**; dicyanotetrayne **28**; pyridine derivatives **11**–**14** and **21**–**22**; and bipyridines **29**–**31**.

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