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Strain-Promoted Azide–Alkyne Cycloaddition with Ruthenium(II)–Azido Complexes

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Abstract: The reactivity of an exemplary ruthenium(II)–azido complex towards non-activated, electron-deficient, and towards strain-activated alkynes at room temperature and low millimolar azide and alkyne concentrations has been investigated. Non-activated terminal and internal alkynes failed to react under such conditions, even under copper(I) catalysis conditions. In contrast, as expected, rapid cycloaddition was observed with electron-deficient dimethyl acetylenedicarboxylate (DMAD) as the dipolarophile. Since DMAD and related propargylic esters are excellent Michael acceptors and thus unsuitable for biological applications, we investigated the reactivity of the azido complex towards cycloaddition with derivatives of cyclooctyne (OCT), bicyclo[6.1.0]non-4-yne (BCN), and azadibenzocyclooctyne (ADIBO). While no reaction could be observed in the case of the less strained cyclooctyne OCT, the highly strained cyclooctynes BCN and ADIBO readily reacted with the azido complex, providing the corresponding stable triazolato complexes, which were amenable to purification by conventional silica gel column chromatography. An X-ray crystal structure of an ADIBO cycloadduct was obtained and verified that the formed 1,2,3-triazolato ligand coordinates the metal center through the central N2 atom. Importantly, the determined second-order rate constant for the ADIBO cycloaddition with the azido complex ($k_2 = 6.9 \times 10^{-2}\,M^{-1}s^{-1}$) is comparable to the rate determined for the ADIBO cycloaddition with organic benzyl azide ($k_2 = 4.0 \times 10^{-1}\,M^{-1}s^{-1}$). Our results demonstrate that it is possible to transfer the concept of strain-promoted azide–alkyne cycloaddition (SPAAC) from purely organic azides to metal-coordinated azido ligands. The favorable reaction kinetics for the ADIBO-azido-ligand cycloaddition and the well-proven bioorthogonality of strain-activated alkynes should pave the way for applications in living biological systems.

Keywords: azides · cycloaddition · cycloalkynes · ruthenium · triazolates

Introduction

In recent years, the copper(I)-catalyzed azide–alkyne cycloaddition[1] (CuAAC) to form 1,2,3-triazoles has emerged as a prime example of "click chemistry"[2] reactions.[3] Whereas the thermal azide–alkyne cycloaddition requires scope-limiting high temperatures when unactivated substrates are used, the presence of a copper(I) catalyst accelerates the reaction between organic azides and terminal alkynes to an extent, allowing the reaction to proceed rapidly at room temperature and low reactant concentrations.[1,3] However, the high cytotoxicity of copper salts renders CuAAC unsuitable for applications in living biological environments[4,5] and this has motivated the Bertozzi group[5–18] and others[19–25] to utilize the concept of strain-promoted azide–alkyne cycloaddition (SPAAC), which relies on the increased reactivity of strained cycloalkynes,[26–28] mostly cyclooctynes (Figure 1, left arrow).[29] Over the last several years, SPAAC has been extensively used to covalently label azido-modified synthetic molecules and biomolecules in a bioorthogonal fashion on and in living cells[6–13,19–22] as well as on and in multicellular organisms, including worms,[14,15] zebrafish,[16,17] and mice.[8,14,18]

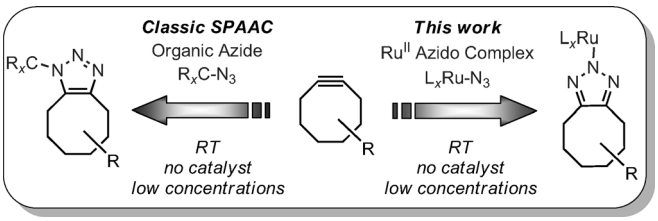

Figure 1. Comparison of SPAAC with organic azides (established) and ruthenium(II)–azido complexes (present work).

Recently, there has been a steadily growing interest for metal complexes in the life sciences.[30–43] The attractiveness of metal complexes for the modulation, sensing, and imaging

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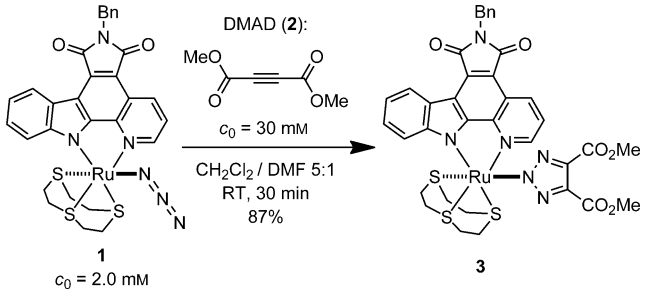
of biological processes calls for the development of bioorthogonal 1,3-dipolar cycloadditions involving metal-coordinated azido ligands. Although, numerous publications have appeared on the conversion of metal-coordinated azido ligands into metal-coordinated triazolato ligands,[44–68] the majority of these studies relied on alkynes as dipolarophiles that are activated by conjugation with electron-withdrawing groups, such as carboxylic esters and nitriles.[44–63] However, due to their high electrophilicity and susceptibility to conjugate addition, such activated dipolarophiles are incompatible with biological systems.[69–73] In contrast, reports on 1,3-dipolar cycloadditions between metal-coordinated azido ligands and non-activated alkynes are rare.[65–68] In a notable exception, Gray and co-workers reported rapid reactions between the electron-rich gold(I) azido complex [$Au^I(PPh_3)(N_3)$] and terminal alkynes at room temperature.[65] Interestingly, the resulting triazolato ligands are attached to the gold(I) center by a carbon–gold bond and not, as expected, by a nitrogen–gold bond.[65] Veige and co-workers carried out analogous reactions with [$Au^I(PPh_3)(N_3)$], but instead of terminal alkynes they used gold(I) acetylides as dipolarophiles. Consequently, they obtained binuclear gold(I)–triazolato complexes.[66]

Over the last several years, our group has introduced coordinatively inert metal complexes as sophisticated scaffolds for the design of highly potent and selective kinase inhibitors,[74–81] including complexes containing metal-coordinated azido ligands.[76,80] We envisioned that a biocompatible 1,3-dipolar cycloaddition with such metal-coordinated azido ligands would not only constitute an attractive imaging tool, but would also enable us to modulate the inhibition properties of such complexes in real time within a living biological system. We now demonstrate that it is possible to transfer the concept of strain-promoted azide–alkyne cycloaddition from purely organic azides to metal-coordinated azido ligands (Figure 1, right arrow) to obtain the corresponding robust triazolato complexes under ambient conditions with favorable reaction kinetics. To our knowledge, this is the first example of strain-promoted azide–alkyne cycloaddition applied to metal-coordinated azido ligands.

Results and Discussion

Cycloaddition of ruthenium(II)–azido complex 1 with an electron-deficient alkyne: In most of this study, we selected ruthenium(II)–azido complex **1** as a representative model complex. The ruthenium(II)–azido complex **1** is a readily available azido-ligand-bearing derivative of coordinatively inert pyridocarbazole-based ruthenium(II) complexes, previously introduced by our group. These complexes have been designed to act as reversible kinase inhibitors and have proven their stability in biological environments.[76,80] We first confirmed the capability of the azido ligand of **1** to participate in a rapid 1,3-dipolar cycloaddition by subjecting **1** to dimethyl acetylenedicarboxylate (DMAD, **2**) at room temperature. Within just 30 min, this experiment afforded



Scheme 1. Cycloaddition of ruthenium(II)–azido complex **1** with DMAD (**2**) providing triazolato complex **3** in 87% yield after chromatographic purification.

the expected 1,2,3-triazolato complex **3**, which was isolated in 87% yield (Scheme 1). An X-ray crystal structure of this complex is shown in Figure 2 (Table 3, see below) and reveals that the C_s-symmetric triazolato ligand is bound to the metal center by N2, which implies that an N1→N2 linkage isomerization occurs in the course of the cycloaddition reaction. This type of linkage isomerization has been reported numerous times for 1,3-dipolar cycloadditions with metal-coordinated azides.[44–62]

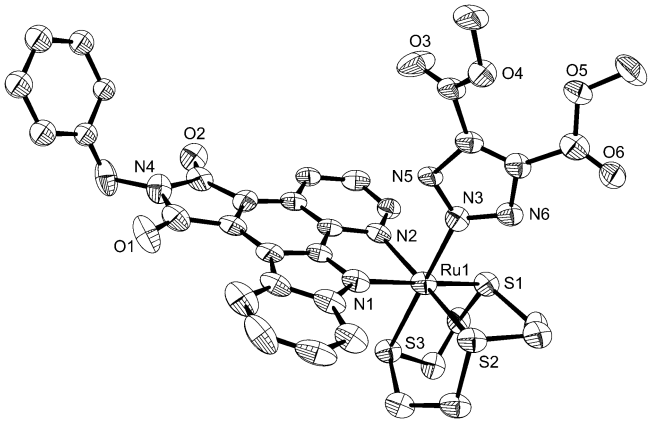


Figure 2. Molecular structure of ruthenium(II)–triazolato complex **3**. ORTEP drawing with 50% probability thermal ellipsoids. Hydrogen atoms and positional disorder of the benzyl group have been omitted for clarity. Selected bond lengths (Å): Ru1–N1 = 2.106(6), Ru1–N2 = 2.112(5), Ru1–N3 = 2.068(5), Ru1–S1 = 2.2824(19), Ru1–S2 = 2.2867(18), Ru1–S3 = 2.2941(17).

Attempted cycloadditions of ruthenium(II)–azido complex 1 with non-activated alkynes: Although the cycloaddition with DMAD proceeded rapidly, DMAD and related propargylic esters are excellent Michael acceptors and hence they react with cellular thiols, causing glutathione depletion and protein cross-linking. Accordingly, such compounds are cytotoxic and thus unsuitable for biological applications.[69–73] Therefore, we next turned our attention to non-activated alkynes, which are well-known for their biocompatibility. However, examination of a small library of terminal (**4**–**6** Figure 3) and internal alkynes (**7**–**9** Figure 3) in terms of their reactivi-

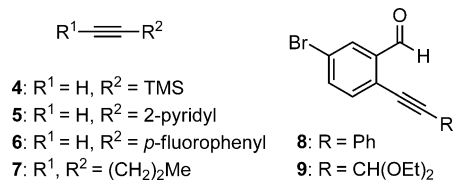


Figure 3. Terminal and internal alkynes tested for their ability to undergo cycloaddition with ruthenium(II)–azido complex **1**. None of these alkynes displayed any reactivity towards **1** at ambient temperature (2–10 mM **1**, 20–30 mM alkyne, CH_2Cl_2/DMF 5:1, RT, 5 d, sealed vial) or under copper(I) catalysis conditions (7 mM **1**, 20 mM terminal alkyne, DMF/H_2O 3:1 and DMSO/H_2O 3:1, 10 mol% $CuSO_4$, 20 mol% sodium ascorbate, RT, 1 d, sealed vial).

ty towards **1**, resulted in a complete recovery of the starting materials. It is worth noting that no products were formed when the same reactions were carried out under copper(I) catalysis conditions either.

Cycloadditions of ruthenium(II)–azido complexes with strained alkynes: The recent impressive reports on strain-promoted azide–alkyne cycloaddition[5–25] encouraged us to next examine the reactivity of azido complex **1** towards strain-activated alkynes. To our surprise, despite a careful literature search, we were not able to find any report dealing with a cycloaddition reaction between a metal-coordinated azido ligand and a strain-activated alkyne.

We selected the cyclooctynes OCT (**10**),[6,18] BCN (**11a**,**b**),[21] and ADIBO (**12a–c**)[24,25,82] for our study as they are synthetically easily accessible and are reported to display a range of reactivities towards organic azides (Figure 4; see legend for definition of the abbreviations OCT, BCN, and ADIBO). In fact, BCN and ADIBO have been reported to be significantly more reactive towards organic azides ($k_{2,BCN} = 1.4 \times 10^{-1}\,M^{-1}s^{-1}$;[21] $k_{2,ADIBO} = 3.1 \times 10^{-1}\,M^{-1}s^{-1}$[25]) than OCT ($k_2 = 2.4 \times 10^{-3}\,M^{-1}s^{-1}$[6]). The increased reactivity of BCN and ADIBO is attributed to additional ring strain caused by the fused cyclopropane ring in the case of BCN[21,83] and by the fused benzene rings in combination with the exocyclic amide moiety in the case of ADIBO.[27,28]

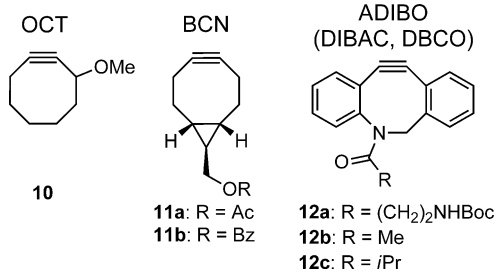
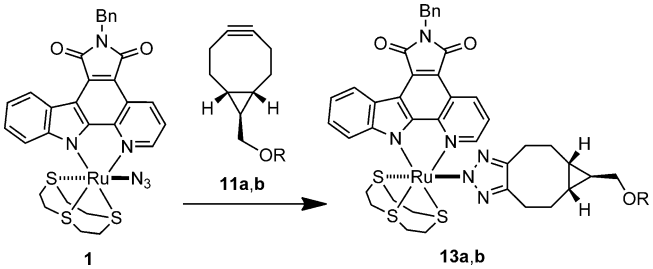


Figure 4. Investigated cyclooctynes for Ru^{II}–azido-ligand SPAAC. Abbreviations: OCT (**10**): Cyclooctyne (ref. [18]), BCN (**11a**,**b**): bicyclo-[6.1.0]non-4-yne (ref. [21]), ADIBO (**12a–c**): azadibenzocyclooctyne (ref. [24]). Common synonyms for ADIBO: DIBAC (dibenzoazacyclooctyne; ref. [25]), DBCO (azadibenzocyclooctyne; ref. [82]).

Indeed, while we did not observe any reaction between **1** and the less strained OCT, we were pleased to observe smooth cycloaddition reactions with BCN and ADIBO. Table 1 shows the reactions of the BCN derivatives **11a** and **11b** with azido complex **1** to provide the triazolato complexes **13a** and **13b** in 74% and 87% yield, respectively. NMR analysis revealed that in analogy to the DMAD-derived triazolato complex **3**, the C_s-symmetric BCN-derived triazolato ligands of **13a** and **13b** are attached to the ruthenium center through N2. Products **13a**,**b** displayed remarkable stability and were purified by standard silica flash chromatography without any indication of partial decomposition.[84] It is worth noting that **13a** and **13b** were found to be quite basic and the addition of Et_3N during flash chromatography was necessary to achieve elution.

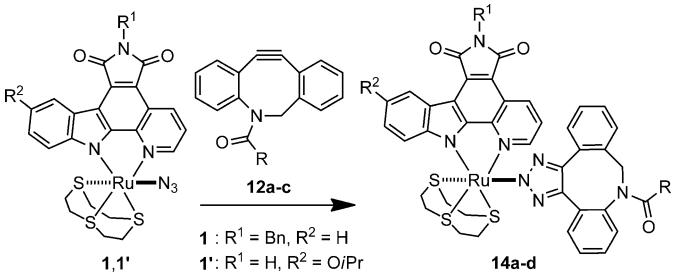
Table 1. Strain-promoted cycloadditions of **1** with BCN derivatives **11a** and **11b**.



BCN	Solvent	Conditions	Product	Yield
11a	DMF	45 °C, overnight	**13a**	74%
11b	DMF	RT, 4 d	**13b**	87%

We then subjected **1** to the ADIBO derivatives **12a–c** at ambient temperature and again we observed smooth reactions which, however, proceeded noticeably faster than the corresponding reactions with BCN. The resulting triazolato complexes **14a–c** were isolated in 82–86% yield after chromatographic purification (Table 2). In spite of numerous efforts, we did not obtain X-ray crystal structures of complexes **14a–c**. However, an X-ray crystal structure of complex **14d**, which was analogously obtained in 83% yield by the reaction of ruthenium(II)–azido complex **1′** with ADIBO derivative **12c** (Table 2), was obtained as shown in Figure 5 (Table 3). The X-ray crystal structure of **14d** reveals that the triazolato ligand again coordinates the ruthenium center through N2. As the NMR signals (^1H,^{13}C) of **14d** follow the same pattern as the signals of **14a–c**, the triazolato ligands of the latter are also attached through N2. As with the BCN-derived triazolato complexes, all of the ADIBO-derived triazolato complexes displayed remarkable stability and showed no sign of partial decomposition during chromatographic purification.[84] Again, the addition of Et_3N to the eluent during flash chromatography was necessary to achieve elution of **14a–d**. It is worth noting that we observed two separate sets of close NMR signals at a ratio of almost 1:1 for all isolated ADIBO-derived triazolato complexes (**14a–d**) (^1H,^{13}C NMR; 27 °C; [D_6]DMSO). Analysis of the NMR spectra of **14a–d** suggests that this is due to

Table 2. Strain-promoted cycloadditions of **1** with ADIBO derivatives **12a–c** and of **1′** with **12c**.



Azide	ADIBO	Solvent	Conditions	Product	Yield
1	**12a**	CH_2Cl_2/DMF 1:3	RT, overnight	**14a**	86%
1	**12b**	CH_2Cl_2/DMF 1:3	RT, overnight	**14b**	86%
1	**12c**	CH_2Cl_2/DMF 3:1	RT, overnight	**14c**	82%
1′	**12c**	CH_2Cl_2/DMF 3:1	RT, overnight	**14d**	83%

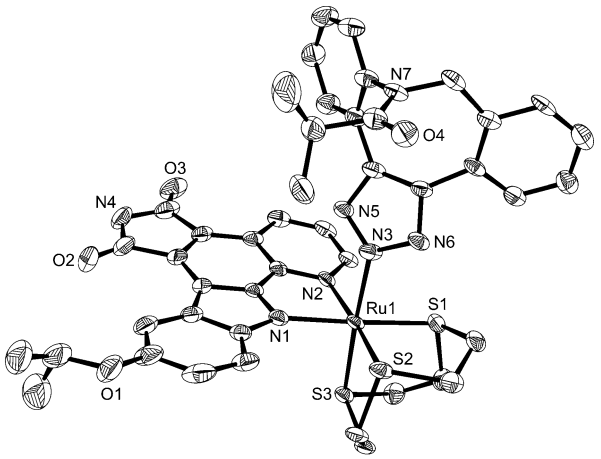


Figure 5. Molecular structure of ruthenium(II)–triazolato complex **14d**. ORTEP drawing with 50% probability thermal ellipsoids. Hydrogen atoms and positional disorder of the isopropoxy group have been omitted for clarity. Selected bond lengths (Å): Ru1–N1 = 2.108(3), Ru1–N2 = 2.140(3), Ru1–N3 = 2.092(3), Ru1–S1 = 2.2997(9), Ru1–S2 = 2.2877(9), Ru1–S3 = 2.3060(8).

a slow (with respect to the NMR timescale) interconversion of two conformers of the eight-membered rings of **14a–d**, a phenomenon that is well-known for rigid dibenzofused eight-membered rings (see Supporting Information for further details and discussion).[85–87]

Kinetics experiments: To gain more insight into the kinetics of the strain-promoted cycloadditions with azido complex **1**, we experimentally determined the second-order rate constants of the reactions of **1** with BCN derivative **11b** and ADIBO derivative **12c**. For comparison, we also determined the rate constants for the corresponding reactions with benzyl azide.[88] The obtained rate constants are summarized in Table 4 and confirm our observation that ruthenium(II)–azido complex **1** is significantly more reactive towards ADIBO cyclooctynes than towards BCN cyclooctynes. In fact, azido complex **1** reacted with ADIBO cyclooctyne **12c** approximately 250 times faster than with BCN cyclooctyne **11b** under almost identical reaction conditions. This difference in reactivity towards **1** is remarkable since benzyl azide only reacts roughly seven times faster with ADIBO cyclooctyne **12c** than with BCN cyclooctyne **11b**. Furthermore, a comparison of the reactivity of each cyclooctyne derivative towards both benzyl azide and coordinated azide **1** reveals that ADIBO cyclooctyne **12c** reacts approximately six times faster with benzyl azide than with azido complex **1** and that BCN cyclooctyne **11b** reacts about 200 times faster with organic benzyl azide than with coordinated azide **1**.

Table 3. Crystallographic data for ruthenium(II)–triazolato complexes **3** and **14d**.

	3	**14d**
formula	$[C_{36}H_{32}N_6O_6RuS_3]$ ·2(CH_2Cl_2)	$[C_{45}H_{43}N_7O_4RuS_3]$ ·2(C_3H_7NO)
ρ_{calcd} [g cm^{-3}]	1011.78	1089.3
crystal system	trigonal	triclinic
space group	$R\bar{3}$	$P\bar{1}$
a [Å]	33.716(3)	12.2748(16)
b [Å]	33.716(3)	14.0557(16)
c [Å]	20.5052(15)	16.9461(19)
α [°]	90	90.298(4)
β [°]	90	106.275(4)
γ [°]	120	115.510(4)
V [Å^3]	20187.(3)	2506.1(5)
Z	18	2
μ [mm^{-1}]	0.778	0.497
crystal size [mm]	0.030×0.070×0.150	0.180×0.090×0.040
T_{min} / T_{max}	0.6508 / 0.7453	0.92 / 0.98
measured reflns	45627	33799
independent reflns	8610	9315
obs. reflns [$I > 2\sigma(I)$]	3515	6862
R_{int}	0.2168	0.0729
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$[a]	0.0737, 0.1734	0.0433, 0.1113
S[b]	0.872	1.027
reflns, restraints, parameters	8610, 426, 442	9315, 36, 584
ρ_{max}, $\Delta\rho_{min}$ (eÅ^{-3})	0.975, −0.460	0.508, −0.366

[a] $R_1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$; $wR_2 = [w(F_o^2 - F_c^2)^2/\Sigma w(F_o^2)^2]^{1/2}$. [b] $S = \{\Sigma[w(F_o^2 - F_c^2)^2]/(n-p)\}^{1/2}$.

Table 4. Experimentally determined rate constants for the SPAACs of benzyl azide and Ru^{II}–azido complex **1** with BCN cyclooctyne **11b** and ADIBO cyclooctyne **12c**.[a]

Azide	Alkyne	Solvent	k_2 [L mol^{-1} s^{-1}]
complex **1**	BCN (**11b**)	DMF	2.7×10^{-4}
complex **1**	ADIBO (**12c**)	CH_2Cl_2/DMF 2:1	6.9×10^{-2}
BnN_3	BCN (**11b**)	CH_2Cl_2/DMF 2:1	5.7×10^{-2}
BnN_3	ADIBO (**12c**)	CH_2Cl_2/DMF 2:1	4.0×10^{-1}

[a] Each experiment was carried out in duplicate at 25 °C in a sealed flask in a temperature-controlled water bath. Rate constants were determined by means of HPLC. See Supporting Information for further details.

Conclusion

In summary, we report that cycloadditions between an exemplary ruthenium(II)–azido complex and strained cyclooctynes readily occur under ambient conditions. These results

demonstrate that the concept of strain-promoted azide–alkyne cycloaddition (SPAAC) is not limited to organic azides, but also readily applicable to transition-metal-coordinated azides. The presented reactions were carried out in DMF and DMF/CH_2Cl_2 due to solubility restrictions, whereas living biological systems exhibit an aqueous environment. However, strain-promoted azide–alkyne cycloadditions and concerted 1,3-dipolar cycloadditions in general, are known to be less solvent-dependant and even drastic solvent alterations have been shown to cause the rate constants of SPAACs to vary within one or not much more than one orders of magnitude.[89,90] Moreover, highly polar protic solvents, such as methanol and water, have been found to promote the reaction rates of SPAACs.[89] Thus, we are confident that more soluble ruthenium(II)–azido complexes or other coordinatively inert azido complexes will be able to react with strain-activated alkynes in aqueous media under ambient conditions. The favorable reaction kinetics, in particular in the case of ADIBO, should allow applications in living biological systems, for which high rate constants are necessary to counterbalance cytotoxicity-limiting concentration restrictions. The scope and the limitations of SPAAC with coordinatively inert azido complexes within biological systems will be subject to future work. Moreover, apart from applications in living biological systems, this chemistry might be attractive for other areas of research. For instance, in consideration of the remarkable stability of **13a**,**b** and **14a–d**, this chemistry might be used to attach azido complexes to cyclooctyne-functionalized surfaces and macromolecules under ambient conditions.

Experimental Section

Remarks: Cyclooctyne **10** was synthesized according to published procedures.[91] General experimental remarks, NMR signal assignment remarks, the syntheses of the Ru^{II}–azido complexes **1** and **1′**, the syntheses of **11a**,**b** (BCN) and **12a–c** (ADIBO), detailed crystallographic data of **3** and **14d**, detailed information concerning the kinetics experiments and the related kinetic plots (Table 4), and additional information relating to the two sets of NMR signals observed for **14a–d** are provided in the Supporting Information. CCDC-943048 (**3**) and CCDC-943049 (**14d**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Ruthenium(II)–triazolato complex 3: Azido complex **1** (10.0 mg, 14.3 μmol, 1.00 equiv) was dissolved in a mixture of CH_2Cl_2 (6.0 mL) and DMF (1.2 mL). Dimethyl acetylenedicarboxylate (**2**, 26.5 μL, 216 μmol, 15.1 equiv) was added under stirring. After 30 min stirring at RT, full conversion was indicated by TLC analysis. All volatiles were removed in vacuo (45 °C) and the crude product was purified by flash chromatography (CH_2Cl_2/MeOH 10:1). After solvent removal and drying in vacuo, the desired triazolato complex **3** (10.5 mg, 12.5 μmol, 87 %) was obtained as a dark purple solid. TLC: R_f = 0.50 (CH_2Cl_2/MeOH 5:1); ^{1}H NMR (400 MHz, [D_6]DMSO): δ = 9.15–9.06 (m, 2H; H_{Pycarb}), 8.72 (d, J = 7.9 Hz, 1H; H_{Pycarb}), 7.79 (dd, J = 8.4 Hz, J = 5.1 Hz, 1H; H_{Pycarb}), 7.79 (d, J = 8.4 Hz, 1H; H_{Pycarb}), 7.49 (ddd, J = 8.3 Hz, J = 7.0 Hz, J = 1.5 Hz, 1H; H_{Pycarb}), 7.45–7.38 (m, 2H; $H_{arom,Benzyl}$), 7.38–7.32 (m, 2H; $H_{arom,Benzyl}$), 7.32–7.24 (m, 2H; 1×H_{Pycarb}, 1×$H_{arom,Benzyl}$), 4.90 (s, 2H; $CH_{2,Benzyl}$), 3.54 (s, 6H; (CO)OCH_3), 3.20–2.90 (m, 5H; $CH_{2,[9]aneS3}$), 2.88–2.65 (m, 3H; $CH_{2,[9]aneS3}$), 2.63–2.44 (m, 3H; $CH_{2,[9]aneS3}$), 2.27–2.14 ppm (m, 1H; $CH_{2,[9]aneS3}$); ^{13}C NMR (100 MHz, [D_6]DMSO): δ = 169.3 (C=O_{Imide}), 169.2 (C=O_{Imide}), 162.3 (2C, (*C*)OMe), 154.4 ($C_{q,Pycarb}$), 152.1 ($C_{q,Pycarb}$), 151.1 (CH_{Pycarb}), 143.5 ($C_{q,Pycarb}$), 138.7 (2C, C=N), 137.4 ($C_{q,Benzyl}$), 132.1 (CH_{Pycarb}), 129.2 ($C_{q,Pycarb}$), 128.6 (2C, CH_{Benzyl}), 127.2 (2C, CH_{Benzyl}), 127.2 (CH_{Benzyl}), 126.0 (CH_{Pycarb}), 124.0 (CH_{Pycarb}), 123.7 (CH_{Pycarb}), 123.7 ($C_{q,Pycarb}$), 121.1 ($C_{q,Pycarb}$), 118.9 (CH_{Pycarb}), 115.1 (CH_{Pycarb}), 114.9 ($C_{q,Pycarb}$), 110.4 ($C_{q,Pycarb}$), 51.4 (2C, (CO)O*C*H_3), 40.6 ($CH_{2,Benzyl}$), 35.0 ($CH_{2,[9]aneS3}$), 34.1 ($CH_{2,[9]aneS3}$), 33.9 ($CH_{2,[9]aneS3}$), 31.6 ($CH_{2,[9]aneS3}$), 31.5 ($CH_{2,[9]aneS3}$), 29.3 ppm ($CH_{2,[9]aneS3}$); IR (film): $\tilde{\nu}$ = 2944, 1718, 1688, 1383, 1225, 1080, 745, 700, 627, 502 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{36}H_{32}N_6O_6RuS_3Na$: 865.0489 [*M*+Na]$^+$; found: 865.0502; X-ray quality crystals of **3** were grown at RT by slow diffusion of hexanes into a concentrated CH_2Cl_2 solution of **3** (liquid-liquid diffusion technique).

Ruthenium(II)–triazolato complex 13a: A vial with a stir bar was charged with azido complex **1** (27.0 mg, 38.6 μmol, 1.00 equiv). A solution of BCN cyclooctyne **11a** (33.2 mg, 173 μmol, 4.47 equiv) in DMF (400 μL) was added and the vial sealed with a screw cap. The mixture was allowed to stir overnight at 45 °C. The next morning, TLC analysis indicated full conversion. All volatiles were removed in vacuo (45 °C) and the crude product was purified by flash chromatography (CH_2Cl_2/MeOH/Et_3N 600:30:15→600:60:15). The combined product fractions were diluted with toluene (to avoid excessive Et_3N enrichment) and all volatiles were removed in vacuo. The residue was dissolved in CH_2Cl_2 and washed successively with sat. NH_4Cl, sat. $NaHCO_3$, and sat. NaCl. The separated organic layer was dried over Na_2SO_4. After solvent removal and drying in vacuo, the desired triazolato complex **13a** (25.4 mg, 28.5 μmol, 74 %) was obtained as a dark purple solid. TLC: R_f = 0.23 (CH_2Cl_2/MeOH 5:1 + Et_3N); ^{1}H NMR (500 MHz, [D_6]DMSO): δ = 9.07 (dd, J = 8.3 Hz, J = 1.3 Hz, 1H; H_{Pycarb}), 9.02 (dd, J = 5.1 Hz, J = 1.3 Hz, 1H; H_{Pycarb}), 8.72 (d, J = 7.9 Hz, 1H; H_{Pycarb}), 7.76 (d, J = 8.3 Hz, 1H; H_{Pycarb}), 7.72 (dd, J = 8.3 Hz, J = 5.0 Hz, 1H; H_{Pycarb}), 7.47 (ddd, J = 8.3 Hz, J = 7.0 Hz, J = 1.4 Hz, 1H; H_{Pycarb}), 7.44–7.39 (m, 2H; $H_{arom,Benzyl}$), 7.38–7.32 (m, 2H; $H_{arom,Benzyl}$), 7.30–7.23 (m, 2H; 1×H_{Pycarb}, 1×$H_{arom,Benzyl}$), 4.90 (s, 2H; $CH_{2,Benzyl}$), 3.75 (d, J = 7.2 Hz, 2H; C*H*$_2$OAc), 3.25–3.15 (m, 1H; $CH_{2,[9]aneS3}$), 3.10–3.00 (m, 2H; $CH_{2,[9]aneS3}$), 2.95–2.55 (m, 5H; $CH_{2,[9]aneS3}$), 2.52–2.35 (m, 5H; 3×$CH_{2,[9]aneS3}$, 2×CH_2C*H*$_2$-(C=N)), 2.20–1.85 (m, 5H; 2×CH_2C*H*$_2$-(C=N), 2×C*H*$_2$$CH_2$-(C=N), 1×$CH_{2,[9]aneS3}$), 1.93 (s, 3H; (CO)C*H*$_3$), 0.90–0.74 (m, 2H; C*H*$_2$$CH_2$-(C=N)), 0.74–0.65 (m, 2H; $CH_{bridgehead}$), 0.45 ppm (m$_s$, 1H; *CH*CH_2OAc); ^{13}C NMR (125 MHz, [D_6]DMSO): δ = 170.4 ((*C*=O)Me), 169.4 (C=O_{Imide}), 169.3 (C=O_{Imide}), 154.7 ($C_{q,Pycarb}$), 152.3 ($C_{q,Pycarb}$), 150.6 (CH_{Pycarb}), 143.8 ($C_{q,Pycarb}$), 142.1 (2C, C=N), 137.5 ($C_{q,Benzyl}$), 131.5 (CH_{Pycarb}), 129.0 ($C_{q,Pycarb}$), 128.6 (2C, CH_{Benzyl}), 127.3 (2C, CH_{Benzyl}), 127.2 (CH_{Benzyl}), 125.7 (CH_{Pycarb}), 123.9 (CH_{Pycarb}), 123.8 ($C_{q,Pycarb}$), 123.3 (CH_{Pycarb}), 121.1 ($C_{q,Pycarb}$), 118.7 (CH_{Pycarb}), 115.3 (CH_{Pycarb}), 114.7 ($C_{q,Pycarb}$), 109.9 ($C_{q,Pycarb}$), 67.6 (*C*H_2OAc), 40.6 ($CH_{2,Benzyl}$), 35.0 ($CH_{2,[9]aneS3}$), 34.3 ($CH_{2,[9]aneS3}$), 33.8 ($CH_{2,[9]aneS3}$), 31.4 ($CH_{2,[9]aneS3}$), 31.4 ($CH_{2,[9]aneS3}$), 29.1 ($CH_{2,[9]aneS3}$), 28.0 (2C, 2×$CH_2$$CH_2$-(C=N)), 25.5 (2C, 2×$CH_2$C*H*$_2$-(C=N)), 23.6 (2C, 2×$CH_{bridgehead}$), 22.8 (*C*H$CH_2$OAc), 20.7 ppm ((CO)*C*$H_3$); IR (film): $\tilde{\nu}$ = 2929, 1737, 1690, 1385, 1348, 1335, 1227, 820, 746, 704, 628, 444, 424 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{42}H_{43}N_6O_4RuS_3$: 893.1555 [*M*+H]$^+$; found: 893.1550.

Ruthenium(II)–triazolato complex 13b: A vial with a stir bar was charged with azido complex **1** (31.7 mg, 45.2 μmol, 1.00 equiv). A solution of BCN cyclooctyne **11b** (16.7 mg, 65.7 μmol, 1.45 equiv) in DMF (900 μL) was added and the vial sealed with a screw cap. After 4 d stirring at RT, full conversion was indicated by TLC analysis (first TLC analysis). The product was isolated as described for **13a** and purified by flash chromatography (CH_2Cl_2/MeOH/Et_3N 40:2:1→20:2:1). The desired triazolato complex **13b** (37.7 mg, 39.5 μmol, 87 %) was obtained as a dark purple solid. TLC: R_f = 0.32 (CH_2Cl_2/MeOH 5:1 + Et_3N); ^{1}H NMR (500 MHz, [D_6]DMSO): δ = 9.06 (d, J = 8.4 Hz, 1H; H_{Pycarb}), 9.02 (d, J = 5.0 Hz, 1H; H_{Pycarb}), 8.71 (d, J = 7.8 Hz, 1H; H_{Pycarb}), 7.90 (d, J = 7.5 Hz, 2H; $H_{arom,Benzyl}$), 7.76 (d, J = 8.4 Hz, 1H; H_{Pycarb}), 7.72 (dd, J = 8.2 Hz, J = 5.2 Hz, 1H; H_{Pycarb}), 7.65–7.57 (m, 1H; $H_{arom,Benzyl}$), 7.53–7.44 (m, 3H; 2×$H_{arom,Benzyl}$, 1×H_{Pycarb}), 7.44–7.38 (m, 2H; $H_{arom,Benzyl}$), 7.35 (dd, J = 7.6 Hz, J = 7.6 Hz, 2H; $H_{arom,Benzyl}$), 7.30–7.21 (m, 2H; 1×$H_{arom,Benzyl}$, 1×H_{Pycarb}), 4.90 (s, 2H; $CH_{2,Benzyl}$), 4.04 (d, J = 7.2 Hz, 2H; C*H*$_2$OBz), 3.25–3.15 (m, 1H; $CH_{2,[9]aneS3}$), 3.13–2.97 (m, 2H; $CH_{2,[9]aneS3}$), 2.96–2.57 (m, 5H;

$CH_{2,[9]aneS3}$), 2.55–2.33 (m, 5H; 3×$CH_{2,[9]aneS3}$, 2×CH_2CH_2-(C=N)), 2.21–2.06 (m, 3H; 1×$CH_{2,[9]aneS3}$, 2×CH_2CH_2-(C=N)), 2.06–1.90 (m, 2H; CH_2CH_2-(C=N)), 0.95–0.72 (m, 4H; 2×CH_2CH_2-(C=N), 2×$CH_{bridgehead}$), 0.65–0.55 ppm (m, 1H; $CHCH_2OBz$); ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ=169.4 ($C{=}O_{Imide}$), 169.2 ($C{=}O_{Imide}$), 165.7 ((*C*=O)Ph), 154.7 ($C_{q,Pycarb}$), 152.3 ($C_{q,Pycarb}$), 150.6 (CH_{Pycarb}), 143.8 ($C_{q,Pycarb}$), 142.0 (2C, C=N), 137.5 ($C_{q,Benzyl}$), 133.1 (CH_{Benzyl}), 131.4 (CH_{Pycarb}), 129.9 ($C_{q,Benzyl}$), 129.0 (3C, 2×CH_{Benzyl}, 1×$C_{q,Pycarb}$), 128.7 (2C, CH_{Benzyl}), 128.6 (2C, CH_{Benzyl}), 127.3 (2C, CH_{Benzyl}), 127.2 (CH_{Benzyl}), 125.7 (CH_{Pycarb}), 123.9 (CH_{Pycarb}), 123.8 ($C_{q,Pycarb}$), 123.4 (CH_{Pycarb}), 121.1 ($C_{q,Pycarb}$), 118.7 (CH_{Pycarb}), 115.3 (CH_{Pycarb}), 114.7 ($C_{q,Pycarb}$), 109.9 ($C_{q,Pycarb}$), 68.4 (CH_2OBz), 40.6 ($CH_{2,Benzyl}$), 35.0 ($CH_{2,[9]aneS3}$), 34.3 ($CH_{2,[9]aneS3}$), 33.8 ($CH_{2,[9]aneS3}$), 31.4 ($CH_{2,[9]aneS3}$), 31.4 ($CH_{2,[9]aneS3}$), 29.1 ($CH_{2,[9]aneS3}$), 28.0 (2C, 2×CH_2CH_2-(C=N)), 25.5 (2C, 2×CH_2CH_2-(C=N)), 23.7 (2C, 2×$CH_{bridgehead}$), 22.8 ppm ($CHCH_2OBz$); IR (film): $\tilde{\nu}$=2930, 1692, 1383, 1335, 1268, 1227, 1108, 1098, 745, 709, 626, 503 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{47}H_{45}N_6O_4RuS_3$: 955.1713 $[M+H]^+$; found: 955.1700.

Ruthenium(II)–triazolato complex 14a: ADIBO cyclooctyne **12a** (24.0 mg, 63.8 μmol, 1.10 equiv) was dissolved in a mixture of CH_2Cl_2 (4.0 mL) and DMF (4.0 mL). A solution of azido complex **1** (40.4 mg, 57.7 μmol, 1.00 equiv) in DMF (8.0 mL) was added under stirring and the mixture was stirred for 17 h at RT. Full conversion was indicated by TLC analysis. All volatiles were removed in vacuo (45 °C) and the crude product was purified by flash chromatography (CH_2Cl_2/MeOH/Et_3N 400:10:5). The combined product fractions were diluted with toluene (to avoid excessive Et_3N enrichment) and all volatiles were removed in vacuo. The residue was dissolved in CH_2Cl_2 and washed successively with sat. NH_4Cl, sat. $NaHCO_3$, and sat. NaCl. The separated organic layer was dried over Na_2SO_4. After solvent removal and drying in vacuo, the desired triazolato complex **14a** (53.2 mg, 49.4 μmol, 86%) was obtained as a dark purple solid. TLC: R_f=0.30 (CH_2Cl_2/MeOH 20:1 + Et_3N); ^{1}H NMR (600 MHz, [D$_6$]DMSO): δ=9.19–9.06 (m, 2H; H_{Pycarb}), 8.75 (d, J=8.5 Hz) + 8.73 (d, J=8.5 Hz, 1H; H_{Pycarb}), 7.88 (d, J=8.4 Hz) + 7.85 (d, J=8.3 Hz, 1H; H_{Pycarb}), 7.81–7.72 (m, 1H; H_{Pycarb}), 7.51 (dd, J=7.7 Hz, J=7.7 Hz, 1H; H_{Pycarb}), 7.45–7.39 (m, 2H; $H_{arom,Benzyl}$), 7.34 (dd, J=7.6 Hz, J=7.6 Hz, 2H; $H_{arom,Benzyl}$), 7.31–6.72 (m, 10H; 1×$H_{arom,Benzyl}$, 1×H_{Pycarb}, 8×H_{ADIBO}), 6.32 (m_s, 1H; NH), 5.39 (d, J=16.3 Hz) + 5.34 (d, J=16.0 Hz, 1H; $CH_{2,8\text{-}Ring}$), 4.91 (s, 2H; $CH_{2,Benzyl}$), 4.02 (d, J=16.5 Hz) + 3.98 (d, J=16.3 Hz, 1H; $CH_{2,8\text{-}Ring}$), 3.25–2.22 (m, 14H; 12×$CH_{2,[9]aneS3}$, 2×CH_2CH_2N), 1.94–1.81 (m, 1H; N(CO)CH_2), 1.35 (s) + 1.33 (s, 9H; C-(CH_3)$_3$), 1.35–1.27 ppm (m, 1H; N(CO)CH_2); ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ=169.5 + 169.3 (1C; $C{=}O_{Amide}$), 169.4 ($C{=}O_{Imide}$), 169.2 ($C{=}O_{Imide}$), 155.2 + 155.1 (1C; $C{=}O_{Carbamate}$), 154.9 + 154.8 (1C; $C_{q,Pycarb}$), 152.3 + 152.3 (1C; $C_{q,Pycarb}$), 150.9 + 150.8 (1C; CH_{Pycarb}), 144.1 + 144.0 (1C; $C_{q,Pycarb}$), 141.1 + 140.9 (1C; $C_{q,ADIBO}$), 139.9 ($C_{q,ADIBO}$), 139.0 + 139.0 (1C; $C_{q,ADIBO}$), 137.5 ($C_{q,Benzyl}$), 133.4–133.0 (2C; $C_{q,ADIBO}$), 131.8 (CH_{Pycarb}), 131.0 + 131.0 (1C; $C_{q,ADIBO}$), 130.9 + 130.6 (1C; CH_{ADIBO}), 129.1 + 129.1 (1C; $C_{q,Pycarb}$), 129.7–129.0 (2C; CH_{ADIBO}), 128.6 (2C; CH_{Benzyl}), 127.8–127.1 (3C; CH_{ADIBO}), 127.3 (2C; CH_{Benzyl}), 127.2 (CH_{Benzyl}), 125.9–125.6 (2C; CH_{Pycarb} + CH_{ADIBO}), 125.5 + 125.3 (1C; CH_{ADIBO}), 123.9 (CH_{Pycarb}), 123.8 ($C_{q,Pycarb}$), 123.3 + 123.2 (1C; CH_{Pycarb}), 121.1 ($C_{q,Pycarb}$), 118.8 + 118.8 (1C; CH_{Pycarb}), 115.2 + 115.2 (1C; CH_{Pycarb}), 114.9 ($C_{q,Pycarb}$), 110.1 ($C_{q,Pycarb}$), 77.4 (3C; C(CH_3)$_3$), 53.4 + 53.1 (1C; $CH_{2,8\text{-}Ring}$), 40.6 ($CH_{2,Benzyl}$), 36.1 + 36.0 (1C; CH_2CH_2N), 35.1–34.1 (2C; $CH_{2,[9]aneS3}$), 33.8 + 33.7 (1C; $CH_{2,[9]aneS3}$), 33.4 + 33.3 (1C; N(C=O)CH_2), 31.9–31.3 (2C; $CH_{2,[9]aneS3}$), 29.4 + 29.2 (1C; $CH_{2,[9]aneS3}$), 28.2 ppm (C(CH_3)$_3$); IR (film): $\tilde{\nu}$=2923, 1690, 1493, 1383, 1335, 1227, 1163, 1137, 745, 697, 627, 499 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{53}H_{51}N_8O_5RuS_3$: 1077.2195 $[M+H]^+$; found: 1077.2199.

Ruthenium(II)–triazolato complex 14b: A flask was charged with azido complex **1** (63.0 mg, 90.0 μmol, 1.00 equiv) and DMF (19 mL). A solution of ADIBO cyclooctyne **12b** (33.0 mg, 134 μmol, 1.48 equiv) in CH_2Cl_2 (6.5 mL) was added under stirring and the mixture was stirred overnight at RT. The next morning, full conversion was indicated by TLC analysis. The product was isolated as described for **14a** and purified by flash chromatography (CH_2Cl_2/MeOH/Et_3N 200:10:5). The desired triazolato complex **14b** (73.2 mg, 77.3 μmol, 86%) was obtained as a dark purple solid. TLC: R_f=0.07 (CH_2Cl_2/MeOH 20:1 + Et_3N); ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ=9.20–9.05 (m, 2H; H_{Pycarb}), 8.78–8.67 (m, 1H; H_{Pycarb}), 7.90–7.79 (m, 1H; H_{Pycarb}), 7.79–7.71 (m, 1H; H_{Pycarb}), 7.49 (dd, J=7.7 Hz, J=7.7 Hz, 1H; H_{Pycarb}), 7.45–7.39 (m, 2H; $H_{arom,Benzyl}$), 7.38–7.32 (m, 2H; $H_{arom,Benzyl}$), 7.31–6.73 (m, 10H; 1×$H_{arom,Benzyl}$, 1×H_{Pycarb}, 8×H_{ADIBO}), 5.33 (d, J=16.0 Hz) + 5.28 (d, J=16.1 Hz, 1H; $CH_{2,8\text{-}Ring}$), 4.91 (s, 2H; $CH_{2,Benzyl}$), 3.97 (d, J=16.1 Hz) + 3.92 (d, J=16.3 Hz, 1H; $CH_{2,8\text{-}Ring}$), 3.30–2.20 (m, 12H; $CH_{2,[9]aneS3}$), 1.16 (s) + 1.10 ppm (s, 3H; N(CO)CH_3); ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ=169.4 ($C{=}O_{Imide}$), 169.3 ($C{=}O_{Imide}$), 168.3 ($C{=}O_{Amide}$), 155.0 ($C_{q,Pycarb}$), 152.3 ($C_{q,Pycarb}$), 150.9 + 150.8 (1C; CH_{Pycarb}), 144.1 + 144.1 (1C; $C_{q,Pycarb}$), 141.1 + 140.8 (1C; $C_{q,ADIBO}$), 140.6 ($C_{q,ADIBO}$), 139.0 ($C_{q,ADIBO}$), 137.5 ($C_{q,Benzyl}$), 133.4 ($C_{q,ADIBO}$), 133.1–132.7 (1C; $C_{q,ADIBO}$), 131.8 (CH_{Pycarb}), 131.2 ($C_{q,ADIBO}$), 130.8 + 130.5 (1C; CH_{ADIBO}), 129.7–128.7 (3C; 1×$C_{q,Pycarb}$, 2×CH_{ADIBO}), 128.6 (2C; CH_{Benzyl}), 127.7–127.0 (3C; CH_{ADIBO}), 127.3 (2C; CH_{Benzyl}), 127.2 (CH_{Benzyl}), 125.9–125.6 (2C; 1×CH_{Pycarb}, 1×CH_{ADIBO}), 125.5–125.2 (1C; CH_{ADIBO}), 124.0–123.8 (1C; CH_{Pycarb}), 123.8 ($C_{q,Pycarb}$), 123.3 (CH_{Pycarb}), 121.2 ($C_{q,Pycarb}$), 118.8 (CH_{Pycarb}), 115.2 (CH_{Pycarb}), 114.9 ($C_{q,Pycarb}$), 110.0 ($C_{q,Pycarb}$), 53.3 + 53.1 (1C; $CH_{2,8\text{-}Ring}$), 40.6 ($CH_{2,Benzyl}$), 35.2–33.4 (3C; $CH_{2,[9]aneS3}$), 32.3–31.1 (2C; $CH_{2,[9]aneS3}$), 29.6 + 29.1 (1C; $CH_{2,[9]aneS3}$), 21.8–21.5 ppm (1C; N(C=O)CH_3); IR (film): $\tilde{\nu}$=2923, 1693, 1661, 1386, 1339, 1309, 1228, 745, 700, 628, 502 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{47}H_{40}N_7O_3RuS_3$: 948.1403 $[M+H]^+$; found: 948.1382.

Ruthenium(II)–triazolato complex 14c: A flask was charged with azido complex **1** (45.4 mg, 64.9 μmol, 1.00 equiv), DMF (3.0 mL), and CH_2Cl_2 (3.0 mL). A solution of ADIBO cyclooctyne **12c** (25.0 mg, 90.8 μmol, 1.40 equiv) in CH_2Cl_2 (6.0 mL) was added under stirring and the mixture was stirred overnight at RT. The next morning, full conversion was indicated by TLC analysis. The product was isolated as described for **14a** and purified by flash chromatography (CH_2Cl_2/MeOH/Et_3N 400:10:5). The desired triazolato complex **14c** (52.1 mg, 53.4 μmol, 82%) was obtained as a dark purple solid. TLC: R_f=0.21 (CH_2Cl_2/MeOH 20:1 + Et_3N); ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ=9.15–9.06 (m, 2H; H_{Pycarb}), 8.72 (d, J=7.9 Hz, 1H; H_{Pycarb}), 7.85–7.70 (m, 2H; H_{Pycarb}), 7.51–7.43 (m, 1H; H_{Pycarb}), 7.43–7.38 (m, 2H; $H_{arom,Benzyl}$), 7.37–7.30 (m, 2H; $H_{arom,Benzyl}$), 7.30–7.08 (m, 6H; 1×$H_{arom,Benzyl}$, 1×H_{Pycarb}, 4×H_{ADIBO}), 7.00–6.73 (m, 4H; H_{ADIBO}), 5.49 (d, J=17.0 Hz) + 5.46 (d, J=17.0 Hz, 1H; $CH_{2,8\text{-}Ring}$), 4.89 (s, 2H; $CH_{2,Benzyl}$), 4.12 (d, J=17.1 Hz) + 4.09 (d, J=17.2 Hz, 1H; $CH_{2,8\text{-}Ring}$), 3.39–2.20 (m, 12H; $CH_{2,[9]aneS3}$), 1.72 (sept, J=6.7 Hz) + 1.66 (sept, J=6.8 Hz, 1H; $CH(CH_3)_2$), 0.59 (d, J=6.8 Hz) + 0.56 (d, J=6.8 Hz, 3H; $CH(CH_3)_2$), −0.20 (d, J=6.6 Hz) + −0.32 ppm (d, J=6.6 Hz, 3H; $CH(CH_3)_2$); ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ=175.0 ($C{=}O_{Amide}$), 169.4 + 169.4 (1C; $C{=}O_{Imide}$), 169.3 + 169.2 (1C; $C{=}O_{Imide}$), 154.9 + 154.8 (1C; $C_{q,Pycarb}$), 152.4 + 152.3 (1C; $C_{q,Pycarb}$), 150.7 + 150.7 (1C; CH_{Pycarb}), 144.0 ($C_{q,Pycarb}$), 141.1 + 141.0 (1C; $C_{q,ADIBO}$), 140.5 + 140.4 (1C; $C_{q,ADIBO}$), 139.2 ($C_{q,ADIBO}$), 137.5 ($C_{q,Benzyl}$), 133.8 + 133.7 (1C; $C_{q,ADIBO}$), 133.2 ($C_{q,ADIBO}$), 131.8–131.4 (2C; 1×CH_{Pycarb}, 1×CH_{ADIBO}), 130.4 + 130.4 (1C; $C_{q,ADIBO}$), 129.2 + 129.0 (1C; $C_{q,Pycarb}$), 128.6 + 128.6 (1C; CH_{ADIBO}), 128.5 (2C; $CH_{arom,Benzyl}$), 128.2–127.7 (3C; CH_{ADIBO}), 127.3 (CH_{ADIBO}), 127.2 (2C; $CH_{arom,Benzyl}$), 127.2 ($CH_{arom,Benzyl}$), 125.7–125.3 (3C; 1×CH_{Pycarb}, 2×CH_{ADIBO}), 124.0–123.6 (2C; 1×CH_{Pycarb}, 1×$C_{q,Pycarb}$), 123.2 + 123.2 (1C; CH_{Pycarb}), 121.1 ($C_{q,Pycarb}$), 118.7 (CH_{Pycarb}), 115.2 (CH_{Pycarb}), 114.9 + 114.9 (1C; $C_{q,Pycarb}$), 109.9 + 109.9 (1C; $C_{q,Pycarb}$), 53.2 + 52.9 (1C; $CH_{2,8\text{-}Ring}$), 40.5 ($CH_{2,Benzyl}$), 35.2–33.4 (3C; $CH_{2,[9]aneS3}$), 32.0–31.3 (2C; $CH_{2,[9]aneS3}$), 29.7 ($CH(CH_3)_2$), 29.6 + 29.3 (1C; $CH_{2,[9]aneS3}$), 19.3 + 19.2 (1C; $CH(CH_3)_2$), 18.0 + 17.7 ppm (1C; $CH(CH_3)_2$); IR (film): $\tilde{\nu}$=2919, 2850, 1689, 1644, 1580, 1493, 1382, 1335, 1265, 1226, 1136, 1078, 744, 697, 626, 497 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{49}H_{44}N_7O_3RuS_3$: 976.1717 $[M+H]^+$; found: 976.1704.

Ruthenium(II)–triazolato complex 14d: A flask was charged with azido complex **1′** (22.7 mg, 34.0 μmol, 1.00 equiv), CH_2Cl_2 (3.0 mL), and DMF (1.7 mL). A solution of ADIBO cyclooctyne **12c** (12.0 mg, 43.6 μmol, 1.28 equiv) in CH_2Cl_2 (2.0 mL) was added under stirring and the mixture stirred at RT. After 2 h 15 min, full conversion was indicated by TLC analysis. The mixture was left stirring overnight and the reaction was worked up the following morning. The product was isolated as described for **14a** and purified by flash chromatography (CH_2Cl_2/MeOH/Et_3N 400:20:5). The desired triazolato complex **14d** (26.6 mg, 28.2 μmol, 83%) was obtained as a dark green solid. TLC: R_f=0.16 (CH_2Cl_2/MeOH 15:1 + Et_3N); ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ=10.90 (s) + 10.89 (s, 1H; NH), 9.13–9.01 (m, 2H; H_{Pycarb}), 8.25 (m_s, 1H; H_{Pycarb}), 7.72 (dd, J=

8.2 Hz, $J=5.0$ Hz) + 7.69 (dd, $J=8.4$ Hz, $J=5.1$ Hz, 1H; H_{Pycarb}), 7.72–7.63 (m, 1H; H_{Pycarb}), 7.29–7.06 (m, 5H; $1\times CH_{Pycarb}$, $4\times CH_{ADIBO}$), 7.02–6.80 (m, 4H; CH_{ADIBO}), 5.51 (d, $J=17.2$ Hz) + 5.48 (d, $J=16.9$ Hz, 1H; $CH_{2,8\text{-}Ring}$), 4.62 (sept, $J=6.1$ Hz) + 4.62 (sept, $J=6.1$ Hz, 1H; $C_{arom}OCH(CH_3)_2$), 4.13 (d, $J=17.2$ Hz) + 4.11 (d, $J=16.9$ Hz, 1H; $CH_{2,8\text{-}Ring}$), 3.40–2.20 (m, 12H; $CH_{2,[9]aneS3}$), 1.73 (sept, $J=6.7$ Hz) + 1.65 (sept, $J=6.7$ Hz, 1H; $(C{=}O)CH(CH_3)_2$), 1.33 (d, $J=6.0$ Hz, 6H; $C_{arom}OCH(CH_3)_2$), 0.59 (d, $J=6.6$ Hz) + 0.56 (d, $J=6.9$ Hz, 3H; $(C{=}O)CH(CH_3)_2$), −0.20 (d, $J=6.6$ Hz) + −0.34 ppm (d, $J=6.6$ Hz, 3H; $(C{=}O)CH(CH_3)_2$); ^{13}C NMR (125 MHz, [D$_6$]DMSO): $\delta=175.0$ ($C{=}O_{Amide}$), 171.1 ($C{=}O_{Imide}$), 171.0 ($C{=}O_{Imide}$), 154.7 + 154.6 (1C; $C_{q,Pycarb}$), 150.8 ($C_{q,Pycarb}$), 150.4 + 150.3 (1C; CH_{Pycarb}), 147.4 + 147.2 (1C; $C_{q,Pycarb}$), 144.5 + 144.4 (1C; $C_{q,Pycarb}$), 141.1 + 141.0 (1C; $C_{q,ADIBO}$), 140.5 + 140.4 (1C; $C_{q,ADIBO}$), 139.3 ($C_{q,ADIBO}$), 133.9 + 133.7 (1C; $C_{q,ADIBO}$), 133.2 ($C_{q,ADIBO}$), 131.8–131.4 (2C; $1\times CH_{Pycarb}$, $1\times CH_{ADIBO}$), 130.6–130.3 (2C; $1\times C_{q,ADIBO}$, $1\times C_{q,Pycarb}$), 128.6 + 128.6 (1C; CH_{ADIBO}), 128.2–127.7 (3C; CH_{ADIBO}), 127.2 (CH_{ADIBO}), 125.6–125.3 (2C; CH_{ADIBO}), 124.1 + 124.1 (1C; $C_{q,Pycarb}$), 122.8 + 122.7 (1C; CH_{Pycarb}), 121.0 ($C_{q,Pycarb}$), 117.1 + 117.0 (1C; CH_{Pycarb}), 115.6 (CH_{Pycarb}), 114.5 ($C_{q,Pycarb}$), 110.7–110.3 (1C; $C_{q,Pycarb}$), 109.9 + 109.7 (1C; CH_{Pycarb}), 70.5 + 70.5 (1C; $C_{arom}OCH(CH_3)_2$), 53.1 + 52.9 (1C; $CH_{2,8\text{-}Ring}$), 35.2–33.3 (3C; $CH_{2,[9]aneS3}$), 32.1–31.3 (2C; $CH_{2,[9]aneS3}$), 29.7 ($(C{=}O)CH(CH_3)_2$), 29.7 + 29.3 (1C; $CH_{2,[9]aneS3}$), 22.2–21.9 (2C; $C_{arom}OCH(CH_3)_2$), 19.3 + 19.2 (1C; $(C{=}O)CH(CH_3)_2$), 18.0 + 17.7 ppm (1C; $(C{=}O)CH(CH_3)_2$); IR (film): $\tilde{\nu}=2968$, 1712, 1697, 1639, 1601, 1492, 1458, 1420, 1337, 1276, 1233, 1213, 1113, 979, 757, 735, 696, 634, 496 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{45}H_{44}N_7O_4RuS_3$: 944.1676 $[M+H]^+$; found: 944.1665; X-ray quality crystals of **14d** were grown at RT by slow diffusion of Et_2O into a concentrated CH_2Cl_2/DMF (1:1) solution of **14d** (liquid-liquid diffusion technique).

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[89] a) Influence of the solvent system on SPAAC with respect to cyclooctynes used in the present work: OCT: ref. [6]; BCN: ref. [21] and present work (Table 4); ADIBO: ref. [25] and present work (Table 4); b) Influence of the solvent system on SPAAC with respect to cyclooctynes not used in the present work: ref. [19]; C. D. McNitt, V. V. Popik, *Org. Biomol. Chem.* **2012**, *10*, 8200–8202.
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