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iClick Reactions of Square-Planar Palladium(II) and Platinum(II) Azido Complexes with Electron-Poor Alkynes: Metal-Dependent Preference for N1 vs N2 Triazolate Coordination and Kinetic Studies with ^{1}H and ^{19}F NMR Spectroscopy

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Supporting Information

ABSTRACT: Two square-planar palladium(II) and platinum(II) azido complexes $[M(N_3)(L)]$ with L = *N*-phenyl-2-[1-(2-pyridinyl)ethylidene]hydrazine carbothioamide reacted with four different electron-poor alkynes R−C≡C−R′ with R = R′ = $COOCH_3$, COOEt, $COOCH_2CH_2OCH_3$ or R = CF_3, R′′ = COOEt in a [3 + 2] cycloaddition "iClick" reaction. The resulting triazolate complexes $[M(triazolate^{R,R'})(L)]$ were isolated by simple precipitation and/or washing in high purity and good yield. Six out of the eight new compounds feature the triazolate ligand coordinated to the metal center via the N2 nitrogen atom, but fortuitous solubility properties allowed isolation of the N1 isomer in two cases from acetone. When the solvent was changed to DMSO, the N1 → N2 isomerization could be studied by NMR spectroscopy and took several days to complete. ^{19}F NMR studies of the iClick reaction with F_3C−C≡C−COOEt led to identification of a putative early linear intermediate in addition to the N1 and N2 isomers, however with the latter as the final product. Rate constants determined by ^{1}H or ^{19}F NMR spectroscopy increased in the order Pd > Pt and CF_3/COOEt > COOR/COOR with R = CH_3, Et, $CH_2CH_2OCH_3$. The second-order rate constant $k_2 > 3.7\ M^{-1}\ s^{-1}$ determined for the reaction of $[Pd(N_3)(L)]$ with F_3C−C≡C−COOEt is the fastest observed for an iClick reaction so far and compares favorably with that of the most evolved strained alkynes reported for the SPAAC (strain-promoted azide−alkyne cycloaddition) to date. Selected title compounds were evaluated for their anticancer activity on the GaMG human glioblastoma brain cancer cell line and gave EC_{50} values in the low micromolar range (2−16 μM). The potency of the Pd(II) complexes increased with the chain length of the substituents in the 4- and 5-positions of the triazolate ligand.

INTRODUCTION

Quick generation of molecular diversity is an important aspect in medicinal chemistry, as systematic modification of lead compounds is required to identify key structure−activity relationships (SAR). In the context of bioorganic chemistry, a wide range of "click" reactions and bioorthogonal coupling methods has been developed for the facile synthesis of both bioactive small molecules[1] as well as bio(macro)molecule conjugates.[2−5] Mild functionalization methods such as the copper-catalyzed (CuAAC) and strain-promoted azide−alkyne cycloaddition (SPAAC) as well as the oxime ligation have also been applied to the ligand periphery of transition-metal complexes.[6−9] In contrast to their huge success in bioorganic chemistry, inherently inorganic "click" reactions, directly taking place in the inner coordination sphere of a metal center and controlled by a judicious choice of metal and (co)ligands, are much more rare. The term "iClick" (for *inorganic click*) was introduced by Veige and co-workers in a report on the 1,3-dipolar cycloaddition of the linear gold(I) azido complex $[Au(N_3)(PPh_3)]$ with gold(I) acetylide compound $[Au(C{\equiv}C{-}C_6H_5)(PPh_3)]$, which leads to a homobimetallic 1,2,3-triazolate complex, with the two gold(I) phosphine moieties bound to the N1 and C5 atoms of the five-membered ring (Scheme 1A).[10] More recently, this approach was also extended to N-heterocyclic carbene complexes of the general structure $[Au(N_3)(NHC)]$.[11,12] However, as far back as the mid-1970s, there have been reports on the cycloaddition reaction of metal azido complexes with electron-poor organic alkynes and other dipolar molecules, as summarized by Frühauf and Beck.[13,14] Metal-based building blocks utilized include organometal half-sandwich complexes such as $[Fe(Cp)(N_3)(CO)_2]$[15] and $[Os(N_3)_2(\eta^6\text{-}C_6H_6)(PiPr_3)]$[16] as well as related ruthenium(II) arene complexes (Scheme 1B).[17−19] The aromatic arene ligand could also be replaced by tris(pyrazolyl)borate (tpz), as in $[Ru(N_3)(tpz)(PPh_3)_2]$.[20] In

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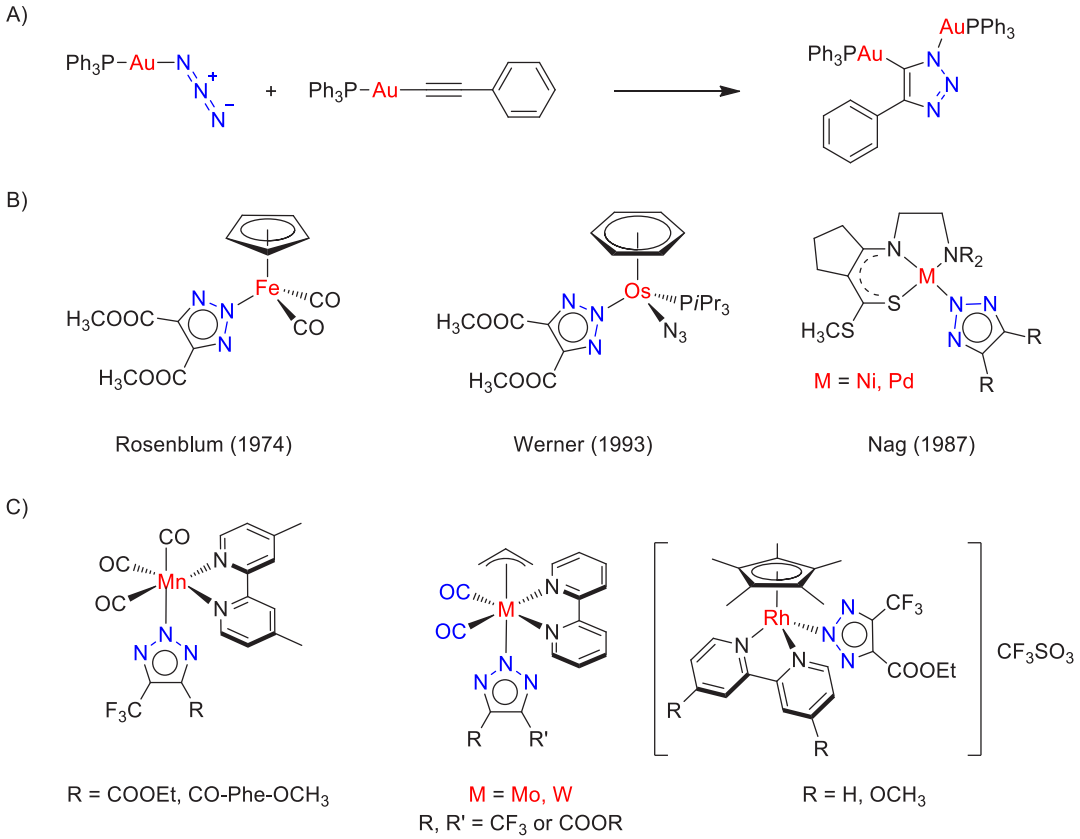
Scheme 1. (A) Prototypical "iClick" Reaction of a Linear Gold(I) Azido Complex with a Gold(I) Acetylide As Originally Reported by Veige et al.,[10] (B) Very Early Examples of Octahedral Triazolate Complexes Prepared by Cycloaddition Reaction with Electron-Poor Alkynes,[15,16] and (C) "iClick" Triazolate Complexes Prepared in Previous Work by This Group[26−28]



addition to group VIII metals such as iron(II), ruthenium(II), and osmium(II), Peng and co-workers extended the scope of the iClick reaction to molybdenum(II) allyl dicarbonyl complexes of the general formula $[Mo(\eta^3\text{-allyl})(N_3)(CO)_2(L\text{^}L)]$ with L^L as a chelating N,N or P,P ligand.[21,22]

We have recently used the iClick reaction to prepare a triazolate-linked phenylalanine bioconjugate attached to a $[Mn(bpy)(CO)_3]$ fragment, which also featured the first use of oxanorbornadiene as a "masked" alkyne equivalent[23−25] in such iClick reactions (Scheme 1C).[26] A study of the isoelectronic complexes $[M(\eta^3\text{-allyl})(N_3)(CO)_2(bpy)]$ with M = Mo, W allowed, for the first time, a systematic comparison of the efficiency of the iClick reaction for 4d vs 5d metals.[27] On the other hand, in $[Rh(Cp^*)(N_3)(bpy^{R,R})]^+$, the electronic influence of peripheral groups on the 2,2′-bipyridine (bpy) coligand was investigated and it was shown that the rate constant for the cycloaddition reaction increases with the electron-donating ability of the 4,4′-substituents.[28] In these two studies, rate constants of up to 7.3×10^{-2} M^{-1} s^{-1} were determined. In these pseudo-octahedral metal azido complexes, the cycloaddition reaction proceeds more quickly than in the gold(I) azido compound originally reported by Veige, who determined $k = 7.6 \times 10^{-3}$ M^{-1} s^{-1}.[29] In addition to terminal and internal alkynes, the utility of cycloalkynes, as originally employed in the catalyst-free SPAAC, was also explored in the iClick reaction, however with mixed success. While bicyclo[6.1.0]non-4-yne (BCN) and azadibenzocyclooctyne (ADIBO) reacted smoothly with $[Ru(N_3)(N\text{^}N)([9]aneS_3)]$, in which N^N is a bidentate chelator derived from staurosporine,[30] this was not the case in the attempted cycloaddition of BCN or dibenzocyclooctyne amine (DBCO) with $[Pt(N_3)_2(OH)_2(py)_2]$. This octahedral platinum(IV) bis-azido complex, on the other hand, underwent a smooth "iClick" reaction with dimethyl acetylenedicarboxylate (DMAD) and the corresponding diethyl ester (DEAD).[31] In contrast to the wealth of information available on the cycloaddition of the linear gold(I) as well as (pseudo)-octahedral group VI−X metal azido complexes with alkynes, very little information is available on the "iClick" reaction of square-planar late transition-metal complexes. About 30 years ago, Paul and Nag described the 1,3-dipolar cycloaddition reaction of a tridentate N^N^S chelating ligand coordinated to a nickel(II) or palladium(II) azido fragment with various dipolarophiles (Scheme 1B).[32,33] Kim et al. studied the reaction of $[Pd(N_3)(C_6H_5)(PR_3)_2]$ with DMAD using different phosphine coligands (R = CH_3, Et) and obtained a crystal structure of the triazolate product, which clearly showed the heterocyclic ligand in the symmetrical N2 coordination mode.[34] The related bis-azido complexes $[M(N_3)_2(PR_3)_2]$ with M = Pd, Pt also underwent cycloaddition reactions with a wide range of dipolarophiles, including nitriles, thiocyanates, and carbon disulfide, in addition to the commonly employed alkynes.[35,36] The latter work also reported the first determination of a rate constant for an iClick reaction, which increased with the σ-donor character of the phosphine coligand but generally was rather slow ($k \approx 10^{-4}$ s^{-1}).[36] Finally, a Pd(II) complex with a putative composition of $[Pd(\eta^3\text{-allyl})(N_3)]$ was proposed as an intermediate in palladium-catalyzed 1,3-dipolar cycloadditions.[37−39] Thus, in order to systematically evaluate the kinetics of the iClick reaction for an isoelectronic and

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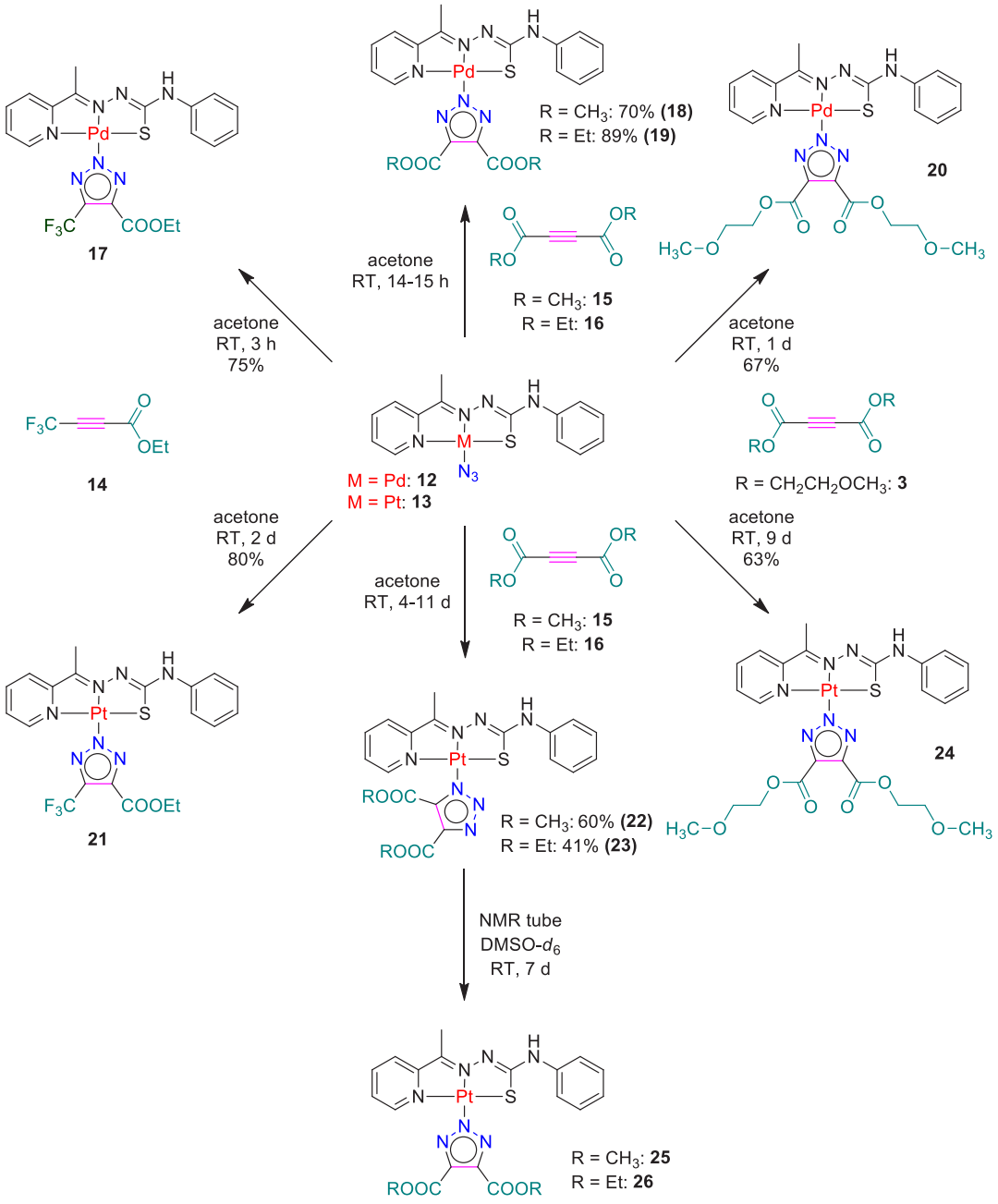
Scheme 2. Click Reaction of Palladium(II) and Platinum(II) Azido Complexes 12 and 13 with Electron-Poor Alkynes 3 and 14−16



isostructural series of square-planar late transition-metal complexes, we prepared palladium(II) and platinum(II) azido complexes with a N^N^S chelating coligand based on thiosemicarbazone, which also features a methyl group with a distinct chemical shift to serve as a NMR spectroscopic marker in kinetic studies, and studied their reaction with a variety of alkynes. The selection of the thiosemicarbazone coligand was also inspired by the well-established pharmacological activity of the purely organic compound[40] and its metal complexes.[41−46]

RESULTS AND DISCUSSION

Synthesis and Characterization. To expand the range of alkynes on hand for the iClick reaction, in addition to commercially available dimethyl acetylenedicarboxylate (DMAD) and diethyl acetylenedicarboxylate (DEAD) as well as 4,4,4-trifluoro-2-butynoic acid ethyl ester[47] already utilized in previous studies of azide−alkyne cycloaddition reactions of molybdenum(II) and tungsten(II) as well as Cp* rhodium(III) complexes,[27,28] an ethylene glycol-substituted alkyne was prepared by esterification of acetylenedicarboxylic acid **1** with 2-methoxyethanol **2** in benzene in the presence of *p*-toluene sulfonic acid as a catalyst (Scheme S1A), to give 2-butynedioic acid 1,4-bis(2-methoxyethyl) ester **3** in good yield (81%).[48]

The semithiocarbazone ligand **HL 7** was prepared in a two-step literature procedure via reaction of phenyl isothiocyanate **4** with hydrazine to give *N*-phenylhydrazine carbothioamide **5**, which was subsequently condensed with 2-acetylpyridine **6** in a mixture of ethanol and acetic acid. The desired product **7** was then isolated on a gram scale in an overall yield of 75% (Scheme S1B).[49]

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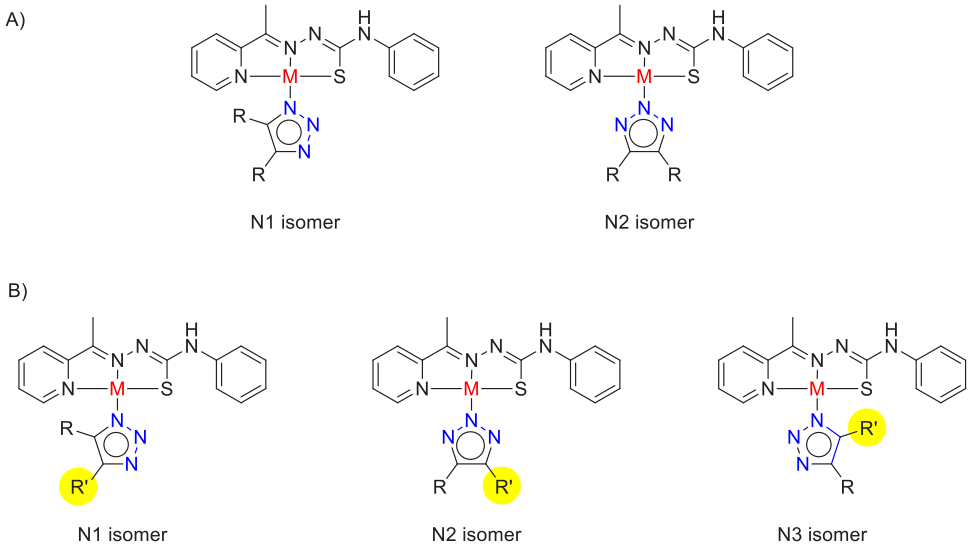
Chart 1. Linkage Isomerism in 4,5-Disubstituted 1,2,3-Triazolate Complexes: (A) Formation of Two Isomers in the Case of Identical Substituents and (B) Formation of Three Different Isomers in the Case of Nonidentical Substituents



Metal complex synthesis started with the reaction of palladium(II) chloride or potassium tetrachloroplatinate(II) with 1,5-cyclooctadiene (cod) to give $[MCl_2(cod)]$ complexes **8** and **9** with M = Pd, Pt in yields of 84 and 80%, respectively (Scheme S1C).[50,51] These compounds reacted in an acetone/water mixture with the semithiocarbazone ligand **HL 7** at elevated temperature. When it was cooled to room temperature, [MCl(L)] was obtained as a yellow (M = Pd, **10**) or red (M = Pt, **11**) precipitate in near-quantitative yield.[41] This was followed by a ligand exchange reaction with excess sodium azide in an acetone/water mixture at elevated temperature (Scheme S1C). After partial removal of the solvent, $[M(N_3)(L)]$ precipitated as a yellow (M = Pd, **12**) or red (M = Pt, **13**) solid. A washing step with water was important for removal of remaining traces of sodium azide. The desired products **12** and **13** were subsequently isolated in analytically pure form and very good yields of 87 and 88%, respectively. Characteristic spectral features include the prominent azide stretching vibrations at 2048 and 2061 cm^{-1} for the palladium(II) and platinum(II) complexes, respectively (see the Supporting Information). The ^{195}Pt NMR signal experiences a minor downfield shift from −3165 ppm in the chlorido complex **11** to −3101 ppm in the azido compound **13**.[52] All other spectroscopic data was as expected and is collected in the Supporting Information.

The iClick reaction generally involved suspending the azido complex **12** or **13** in acetone in a large glass vial followed by addition of an excess of alkyne (Scheme 2). The reaction mixture was then stirred at room temperature, the solvent completely removed under vacuum, and the resulting solid washed with *n*-hexane (or diethyl ether in the case of the ethylene glycol derivative **3**) to remove unreacted alkyne. Finally, the product was dried under vacuum for an extended period of time to get rid of the last traces of solvent. This simple procedure was generally sufficient to obtain analytically pure product in good to excellent isolated yield (63−89%). Only in the case of the reaction of the platinum(II) azido complex **13** with DMAD and DEAD were lower yields of 60 and 41% observed, but these were found to proceed different from the others in any event (vide infra). Reaction times were consistently shorter for the palladium complex **12**, with a range of several hours to about one day, while in the case of the platinum analogue **13**, several days to over one week was required for complete conversion.

Triazolate ligands are characterized by a notable linkage isomerism, as they can bind to a metal center via different nitrogen atoms.[14,16] In the case of identical functional groups on the C4 and C5 carbon atoms of the five-membered ring, two different binding modes are possible, via the N1 or the N2 nitrogen atom (Chart 1A). On the other hand, when the C4 and C5 substituents are not identical, as in the case of triazolates resulting from the iClick reaction with 4,4,4-trifluoro-2-butynoic acid ethyl ester, for example, three different isomers can form, with binding via the N1, N2, or N3 nitrogen donor atom (Chart 1B). In our previous studies on molybdenum(II) and tungsten(II),[27] manganese(I),[26] and rhodium(III)[28] triazolate complexes, products were consistently and exclusively isolated as the N2 isomer, although in the starting materials, the azido ligand is terminally coordinated via N1. This was a rather surprising result, as the available X-ray structures did not reveal any obvious intramolecular interactions which would stabilize the N2 relative to the N1 isomer.[26,27] Therefore, in the case of the triazolate iClick products **17**−**24**, the preference for a particular binding mode was carefully analyzed by ^{1}H and ^{13}C NMR spectroscopy and, where appropriate, by ^{19}F NMR spectroscopy.

The reaction of palladium(II) azido complex **12** with 4,4,4-trifluoro-2-butynoic acid ethyl ester **14** gave the triazolate product **17** in which the ^{19}F NMR spectrum shows only one major peak for the trifluoromethyl group at −58.58 ppm. In comparison to the alkyne starting material, which shows the CF_3 resonance at approximately −52 ppm,[26] this is an upfield shift by 6.6 ppm, which is indicative of triazolate formation.[26−28] The presence of only one main product is also corroborated by the ^{13}C NMR, which shows only one set of intense peaks at 60.74, 14.00, and 13.99 ppm, due to the ester methylene and methyl carbon atoms as well as the methyl group of the semithiocarbazone ligand backbone. Likewise, the ^{1}H NMR shows only two signals for the ethyl ester moiety at 4.31 and 1.30 ppm, while the signal of the ligand backbone

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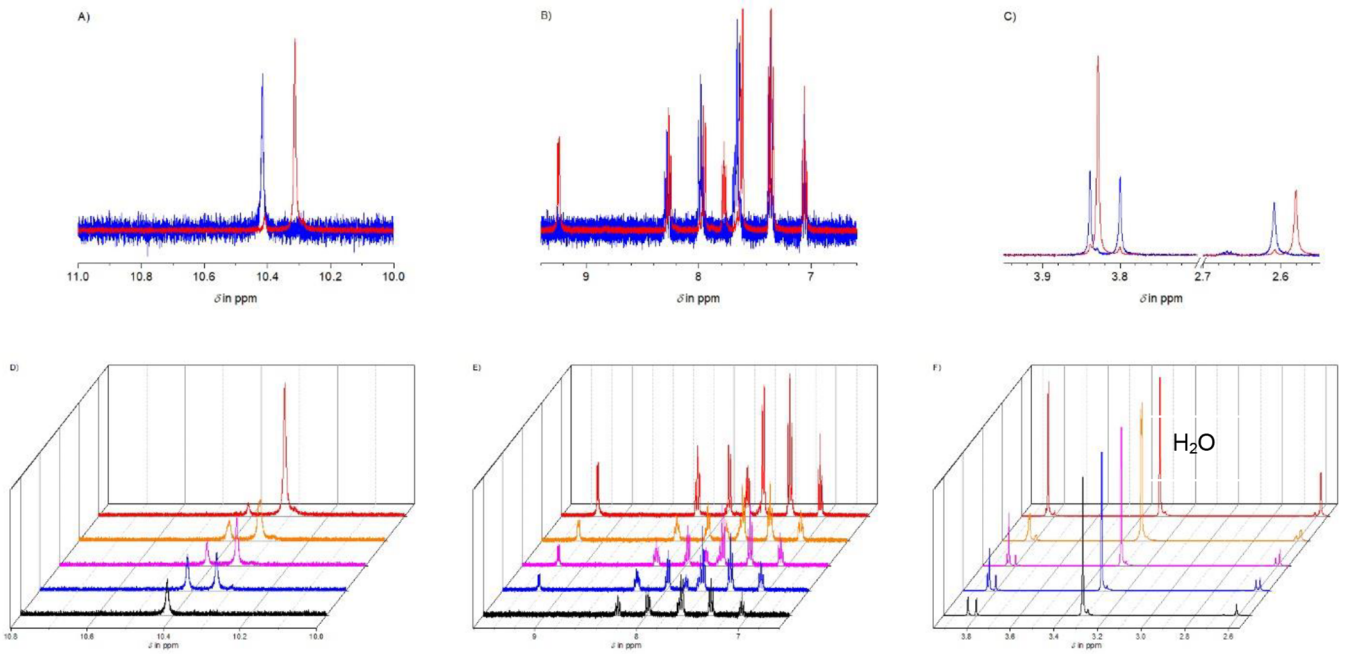

Figure 1. Changes in the 400 MHz ^{1}H NMR spectrum of **22** in DMSO-d_6 with increasing incubation time at room temperature: (A−C) different spectral regions recorded immediately after mixing (blue trace) and after 4 days (red trace); (D−F) different spectral regions recorded at different time intervals (from front to back: 0 days, black trace; 1 day, blue trace; 2 days, magenta trace; 3 days, orange trace; 4 days, red trace). Note that, due to the low solubility in DMSO-d_6, the signal intensity of the N1 species is significantly smaller than that of the N2 isomer and spectra were normalized accordingly. The intense peak observed at 3.32 ppm in (F) is due to residual water in the DMSO-d_6 solvent.

methyl group is difficult to analyze, as it appears at 2.53 ppm, partially overlapping with the DMSO solvent peak. Only upon very close inspection of the ^{19}F NMR does an additional low intensity signal become evident at −58.42 ppm, shifted by 0.16 ppm relative to the main peak, with an intensity ratio of 1:12.5. Thus, this minor species accounts for less than 10% of the total product and is assigned to the N1 or N3 isomer, while the major species is assumed to be the N2-coordinated complex **17**.

Reaction with the symmetrical alkynes dimethyl and diethyl acetylenedicarboxylates (DMAD, **15**, and DEAD, **16**, respectively) resulted in isolation of palladium triazolate complexes **18** and **19**. The symmetrical N2 coordination mode is clearly evident from only one major methyl group signal in the ^{1}H NMR at 3.81 ppm with a relative intensity of 6H and a single methyl ester carbon signal at 52.05 ppm in the case of **18**, while the iClick product obtained with DEAD shows a quartet with an intensity of 4H at 4.28 ppm and a triplet integrating to 6H at 1.28 ppm, also indicative of symmetry-equivalent ethyl ester groups. Likewise, in the ^{13}C NMR of **19**, there are only three major peaks in the aliphatic spectral region, at 60.65, 14.03, and 13.95 ppm, due to the symmetry-equivalent ester methylene and methyl carbon atoms as well as the ligand backbone methyl moiety.

This trend also extends to the triazolate complex **20**, which is obtained by an iClick reaction with the bis(ethylene glycol)-substituted alkyne **3**. Its ^{1}H NMR shows two signals of 4H each at 4.35 and 3.62 ppm, respectively, due to two equivalent methylene groups, and a single main peak with an integral close to 6H at 3.29 ppm for the two methoxy moieties, while the ^{13}C NMR features three signals for the triazolate substituents at 69.64, 63.81, and 58.12 ppm, which are of higher intensity than the peak of the single ligand backbone methyl carbon at 13.99 ppm.

Thus, the combined ^{1}H and ^{13}C NMR spectroscopic data clearly support a "symmetrical" N2 coordination mode for the palladium(II) triazolate complexes **18**−**20**, and the same is also assumed for the trifluoromethyl-substituted complex **17**, although the ^{19}F NMR does not allow a definitive assignment beyond the presence of a single species. Furthermore, from the consistent observation of only a single set of resonances for the C4 and C5 substituents of the triazolate, it can be corroborated that either the triazolate mean plane is perpendicular to that of the semithiocarbazone ligand or rotation around the Pd−N2 bond is fast on the NMR time scale, as a "locked-in" fully planar conformation would result in chemically nonequivalent C4/C5 substituents, with one of them pointing toward the pyridine ring and the other one in the direction of the thiolate donor group (Chart 1B).

Among the platinum(II) complexes, the ethylene glycol substituted triazolate compound **24** also exhibits the spectral signature of a symmetrical N2 coordination of the five-membered ring, with the ^{1}H and ^{13}C NMR signals only marginally shifted (<0.1 ppm) relative to those of the palladium(II) congener **20**. The ^{195}Pt NMR of this compound shows only one major peak at −3106 ppm, indicating that the triazolate ligand induces only a minor change in the chemical shift relative to the azido complex **13**, in which the signal appears at −3101 ppm. The trifluoromethyl-substituted triazolate complex **21** also exhibits a spectral pattern very similar to that of the palladium analogue **17**, with only one signal in the ^{19}F and ^{195}Pt NMR at −58.71 and −3108 ppm, respectively, and two signals for the ethyl group of the ester moiety in both the ^{1}H and ^{13}C NMR.

Interestingly, a different spectral signature was observed when platinum(II) azido complex **13** was reacted with DMAD (**15**) or DEAD (**16**). The ^{1}H NMR spectrum of the methyl ester compound **22** clearly shows three methyl group signals of

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equal intensity at 3.84, 3.80, and 2.61 ppm. Unfortunately, no ^{13}C NMR could be recorded due to poor solubility of the product in common NMR solvents, but the ethyl ester analogue **23** showed two overlapping quartets and triplets of 4H and 6H in the ^{1}H NMR at 4.32−4.24 and 1.28−1.23 ppm, respectively, and most importantly, two peaks for the methylene carbon atoms of the ethyl ester moiety at 61.51 and 60.31 ppm, further supporting a nonsymmetrical N1 coordination of the triazolate ligand in this case (see the Supporting Information).

Interestingly, when solid samples of complexes **22** and **23** were suspended in DMSO-d_6 and kept in an NMR tube for several days at room temperature, the solution became clear and the resulting spectra changed to that of a symmetrically N2 coordinated triazolate (Scheme 2, bottom), with only one methyl group signal observed for **25** at 3.83 ppm in the ^{1}H NMR and 52.07 ppm in the ^{13}C NMR. The ethyl ester compound **23** also underwent this slow N1 → N2 isomerization, as the spectrum of resulting **26** showed only one set of peaks for the ethyl ester group, manifested in the ^{1}H NMR as a quartet at 4.29 ppm and a triplet at 1.29 ppm with a 4:6 intensity ratio and ^{13}C NMR peaks for the ethyl and methyl group carbon atoms at 60.75, 14.02, and 13.76 ppm (see the Supporting Information).

The isomerization of **22** to **25** was monitored by ^{1}H NMR spectroscopy in DMSO-d_6 at room temperature (Figure 1). In particular, the methyl ester signal at about 3.8 ppm undergoes prominent changes with incubation time. Directly after dissolution of the sample, two peaks of equal intensity are observed at 3.84 and 3.80 ppm, indicative of a nonsymmetrical N1 coordination mode of the triazolate (Figure 1C, blue trace). A very small signal between these two peaks at 3.83 ppm gradually increases in intensity with time, and after 4 days, the conversion is almost complete (Figure 1C, red trace). This interconversion is also reflected in a shift of the signal of the methyl group in the periphery of the semithiocarbazone coligand. In the N1 isomer, it appears at 2.61 ppm, but over the course of the isomerization, a new peak at 2.58 ppm continuously gains in intensity (Figure 1F) and after 4 days an intensity ratio of 0.07 to 1.00 indicates that the conversion level has reached 93%.

Interestingly, the secondary amine proton signal of the semithiocarbazone coligand is also sensitive to the triazolate coordination mode. In the N1 isomer **22**, it is found at 10.42 ppm (Figure 1A, blue trace). However, on a time scale similar to that of changes in the methyl group peaks, a new signal appears at 10.30 ppm, which continuously gains in intensity over time until day 4, when only a very small N1 signal remains, with a relative intensity of 0.07 to 1.00, in comparison to the N2 signal (Figure 1D). The interconversion also leads to spectral changes in the aromatic region. Most notably, a new doublet of doublets appears at 9.24 ppm together with a triplet at 7.77 ppm while other changes are less obvious due to signal overlap (Figure 1B,E).

To rule out a potential replacement of the triazolate ligand by DMSO upon extended incubation in this coordinating solvent, [Pt(L)(dmso)]OTf (with OTf = trifluoromethanesulfonate) was prepared in situ by treatment of the chlorido complex **11** with silver triflate. The ^{195}Pt NMR recorded for this species after filtration from the silver chloride which had precipitated showed a single peak at −3650 ppm, significantly shifted relative to the approximately −3105 ppm observed for all platinum(II) triazolate compounds (**21**, **25**, **26**, and **24**) studied in this work. On the other hand, when the N1 isomer **22** was heated to 50 °C in DMSO-d_6 for 2 days, only one peak at −3105 ppm was observed, as expected for the coordinated N2 isomer, while there was no signal in the −3600 to −3700 ppm range (Figure S1). Furthermore, the color of [Pt(L)(dmso)]OTf is distinctly different from that of triazolate complexes **22** and **25** (Figure S2).

Additional evidence for the robust coordination of the triazolate ligand to the platinum center is provided by ESI mass spectrometry. In the case of palladium compound **18**, the most intense signal is due to $[M - \text{triazolate} + CH_3CN]^+$, together with the slightly less intense peaks of the adducts $[M + H]^+$ and $[M + Na]^+$ as well as those of the cluster ions $[2M - \text{triazolate}]^+$ and $[2M + Na]^+$, plus minor signals resulting from higher cluster ions $[3M - \text{triazolate}]^+$ and $[3M + Na]^+$. However, in the ESI mass spectrum of **22**/**25** (as it is not possible to distinguish the constitutional N1 and N2 isomers in the mass spectra), the $[M - \text{triazolate} + CH_3CN]^+$ species is absent, which is in line with the slower ligand exchange kinetics of Pt vs Pd and the dominant peaks are $[M + Na]^+$ and $[M + H]^+$, together with the weaker signals of the cluster ions $[2M - \text{triazolate}]^+$, $[2M + Na]^+$, $[2M + K]^+$, and $[3M + Na]^+$ (see the Supporting Information).

In the case of the reaction of platinum azido complex **13** with trifluoromethyl-substituted alkyne **14**, ^{19}F NMR offers an additional handle to follow the course of the iClick reaction. Therefore, spectra were recorded in 5 min intervals for 0.5 h and after overnight incubation. Interestingly, already in the first spectrum collected after about 5 min, which is the minimum time required for sample preparation and setting up the instrument, in addition to the signal of the alkyne precursor at −50.93 ppm, there are two additional prominent peaks at −54.85 and −58.46 ppm (Figure 2).

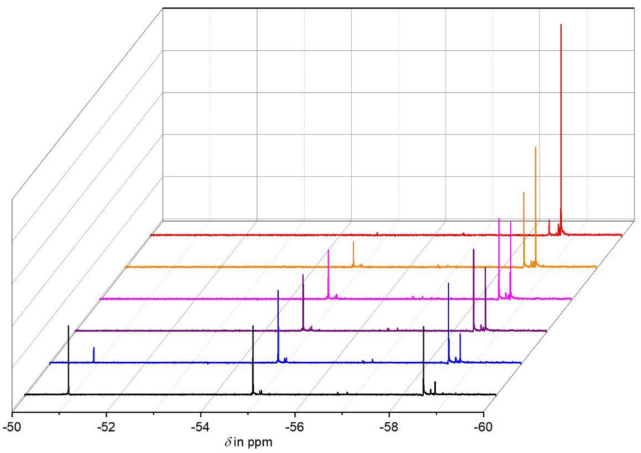

Figure 2. Changes in the 376 MHz ^{19}F NMR spectrum of an equimolar mixture of **13** and **14** in DMSO-d_6 with increasing incubation time at room temperature (from front to back: 5 min, black trace; 10 min, blue trace; 20 min, purple trace; 25 min, magenta trace; 30 min, orange trace; 14.6 h, red trace).

The alkyne signal fully disappeared within 20 min, while the intensity of the other two peaks decreased more slowly and it took about 15 h for them to go close to zero. During this time, a new signal at −58.71 ppm grew in and became by far the most prominent peak at the end of the incubation time (Figure 2).

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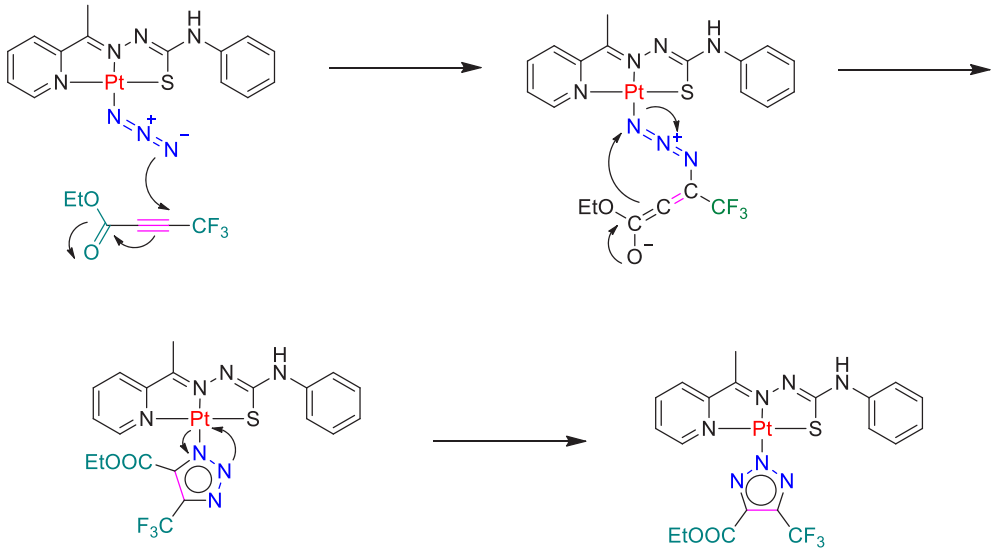
Scheme 3. Proposed Stepwise Mechanism of the iClick Reaction of Azido Complex 13 with Trifluoromethyl-Substituted Alkyne 14 To Account for Three Major Groups of Signals Observed in the ^{19}F NMR of the Reaction Mixture



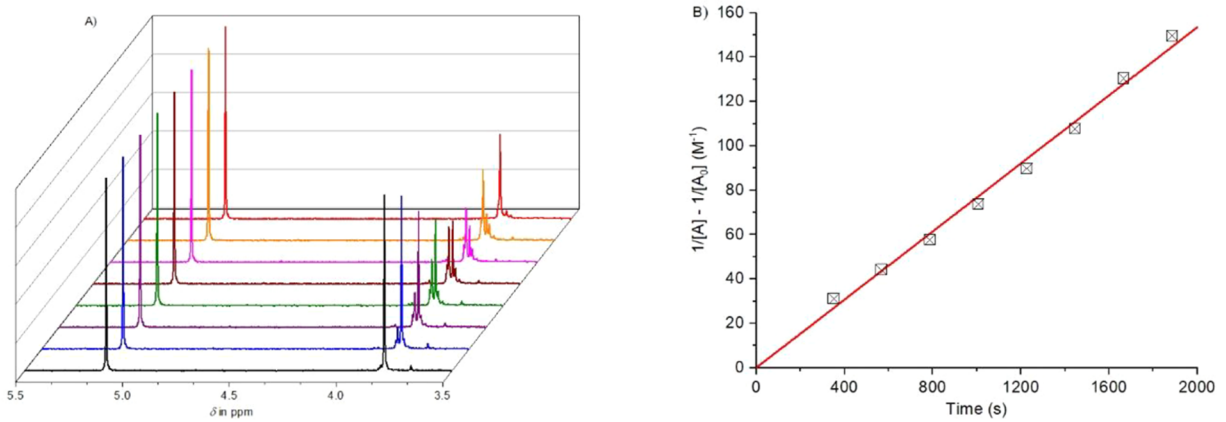


Figure 3. (A) Changes in the 200 MHz ^{1}H NMR spectra of a mixture of platinum(II) azido complex **13** (6 mM), dimethyl acetylenedicarboxylate **15** (DMAD, 6 mM), and 1,3,5-trioxane (6 mM) in DMSO-d_6 at room temperature for up to 20 h. (B) Linear fit of the change of the intensity of the DMAD methyl ester proton signal at 3.81 ppm to the second-order rate law (see main text for details). Due to a lag time between mixing of the reactants and recording of the first spectrum, no data was collected during the initial 5 min.

The chemical shift of this signal is similar to that of the as-isolated compound **21** and is thus assigned to the N2-coordinated triazolate (generalized structure shown in Chart 1B, center). In contrast, the peak at −58.46 ppm is assigned to the N1 (or N3) linkage isomer, as its chemical shift is very similar to that of the N2 species and it appears first, then gradually isomerizing to the more stable N2 form.[14,16] Rather unexpected is the additional prominent third signal at −54.85 ppm, with a chemical shift midway between the alkyne and triazolate peaks, which, on close inspection, is also accompanied by a much smaller peak at −55.02 ppm. The significantly shifted peak position relative to the other two product signals argues against this being the N3 isomer. Instead, we assign it to a linear intermediate, as shown in Scheme 3, top right, with the nucleophilic attack of the distal azido N3 atom preferentially taking place at the C3 carbon atom of the 2-butynoic acid ester due to the stronger electron-withdrawing character of the adjacent trifluoromethyl group. Some additional signals in the −60 to −80 ppm range are of very low intensity and therefore were not assigned. On the other hand, except for some very minor additional peaks in the ^{19}F NMR of complex **17**, no signs of the N1 isomer or any other species were found for the as-isolated palladium complexes **18**−**20**. Therefore, we carried out a detailed kinetic study of the iClick reaction of selected azido complex/alkyne combinations for both the palladium(II) and platinum(II) complexes using ^{1}H and ^{19}F NMR.

Kinetic Studies. The second-order rate constant for the iClick reaction of platinum(II) azido complex **13** with dimethyl acetylenedicarboxylate (DMAD, **15**) was determined by ^{1}H NMR using 1,3,5-trioxane as an internal standard. First, alkyne and standard were mixed in DMSO-d_6 and the ratio of the integrals of the 3.81 and 5.12 ppm peaks was determined, which are assigned to the DMAD methyl ester and standard methylene groups, respectively. Then, platinum(II) azido complex **13** dissolved in the same solvent was added to give a final concentration of all species of approximately 6 mM and ^{1}H NMR spectra were recorded over 20 h at regular intervals. The peak of the methyl ester protons of DMAD at 3.81 ppm gradually disappeared with increasing incubation time while a

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new signal grew in at 3.83 ppm, which is assigned to the symmetry-equivalent methyl ester groups in the 4- and 5-positions of the N2-coordinated triazolate iClick product **25** (Figure 3A). Since the DMSO solvent is different from the acetone used in the preparative-scale reaction, no N1 triazolate formation is evident. The change in the normalized intensity of the DMAD methyl ester peak with increasing incubation time t was then fit to the second-order rate law

$$\frac{1}{A} - \frac{1}{A_0} = k_2 t$$

to obtain the rate constant k_2 from the slope of the fit with a very high correlation coefficient of >99% (Figure 3B). Similar kinetic experiments were also carried out for the reaction of **13** with alkynes **3** and **16**, but the intensity of the semithiocarbazone methyl group peak was monitored instead, which shifts from 2.45 ppm in the azido complex **13** to 2.60 ppm in the triazolate products **24** and **26** (Figures S3 and S4). This is due to difficulties in the proper integration of the multiplet peaks of the ethyl ester and ethylene groups in alkynes **3** and **16**, respectively. The resulting second-order rate constants are collected in Table 1.

Table 1. Second-Order Rate Constants for the Cycloaddition Reaction of Electron-Poor Alkynes 3 and 14−16 with Palladium(II) and Platinum(II) Azide Complexes [M(N$_3$)(L)] 12 and 13

complex	metal	alkyne	substituent	k_2 (M^{-1} s^{-1})
12	Pd	**3**	$COOCH_2CH_2OCH_3$	>0.8
12	Pd	**14**	CF_3, COOEt	>3.7
12	Pd	**15**	$COOCH_3$	>0.8
12	Pd	**16**	COOEt	>0.8
13	Pt	**3**	$COOCH_2CH_2OCH_3$	$(3.0 \pm 0.2) \times 10^{-2}$
13	Pt	**14**	CF_3, COOEt	>0.6
13	Pt	**15**	$COOCH_3$	$(7.7 \pm 0.1) \times 10^{-2}$
13	Pt	**16**	COOEt	$(3.4 \pm 0.1) \times 10^{-2}$

The reaction of platinum(II) azido complex **13** with the trifluoromethyl-substituted alkyne **14** under addition of tetrabutylammonium hexafluorophosphate as an internal standard was investigated by ^{19}F NMR with all final concentrations adjusted to 5 mM. However, the signal of the starting material **14** had already fully disappeared after 10.5 min and, therefore, no meaningful fit was possible, as the cycle time of the NMR experiment is approximately 3−4 min. However, assuming a half-time of the reaction of less than 5.25 min, a lower limit for the rate constant can be estimated (Table 1).

In the case of the reaction of palladium(II) azido complex **12** with the trifluoromethyl-substituted alkyne **14**, the ^{19}F NMR spectrum measured immediately after mixing of the reactants showed no trace of the CF_3 signal at −50.94 ppm. With a lag time between mixing of the compounds and recording of the first spectrum of approximately 3 min, this reaction apparently is too fast to be monitored by NMR. However, with an estimated half-time of less than 1.5 min, again a lower limit for the rate constant can be calculated (Table 1). The same estimation was also applied to the iClick reaction of the palladium(II) azido complex **13** with alkynes **3**, **15**, and **16**, as all of them were too fast to be monitored by NMR spectroscopy.

However, from these studies, a number of clear trends emerged. First of all, the palladium(II) azido complex consistently reacted at least one order of magnitude faster than its platinum(II) congener, reflecting a higher reactivity of the 4d relative to the 5d complexes also observed in the comparison of molybdenum(II) vs tungsten(II) compounds.[27] Second, the mixed-substituent trifluoromethyl-functionalized $F_3C-C\equiv C-COOEt$ **14** showed a significantly higher rate constant in comparison to the related diesters $ROOC-C\equiv C-COOR$. Finally, a small but statistically significant decrease in the speed of the reaction was observed with increasing length of the ester substituents R in the order $COOCH_3$ > COOEt > $COOCH_2CH_2OCH_3$ (Table 1). Furthermore, the square-planar Pd(II) and Pt(II) azido complexes **12** and **13** consistently react more quickly than the linear gold(I) azido species originally reported by Veige, for which k was determined as 7.6×10^{-3} M^{-1} s^{-1}.[29]

Biological Activity. Glioblastomas are the most malignant, invasive, and difficult to treat primary brain tumors in adults with an unfavorable prognosis of only 14.6 months median survival.[53] Since chemotherapeutic options are limited in these devastating tumors and platinum-based compounds have already shown therapeutic efficacy in vivo,[54] we evaluated the anticancer activity of some of the title complexes on the human GaMG glioblastoma cell line using the standard MTT assay.[55] The study was restricted to palladium(II) triazolates **17**−**20** as well as platinum(II) complex **21**, as the other compounds were either expected to undergo slow N1 to N2 isomerization in solution (**22** and **23**) or were not available in sufficient amount for biological studies (**24**). All compounds tested were quite active and exhibited EC_{50} values in the low micromolar range, between 2 and 16 μM, although their potency was less than that of cisplatin used as a reference, which has an EC_{50} value of 0.9 μM under similar conditions (Table 2).

Table 2. EC_{50} values determined with the MTT Assay upon Exposure of GaMG Brain Cancer Cells to Selected Metal Complexes 17−21[a]

complex	metal	C4, C5 triazolate substituents	EC_{50} (μM)
17	Pd	CF_3, COOEt	16.2 ± 0.1
18	Pd	$COOCH_3$	5.2 ± 0.1
19	Pd	COOEt	4.8 ± 0.1
20	Pd	$COOCH_2CH_2OCH_3$	3.7 ± 0.1
21	Pt	CF_3, COOEt	2.4 ± 0.1
cisplatin			0.9 ± 0.1

[a]Shown is the mean ± standard deviation of three independent experiments.

Surprisingly, the palladium compounds were quite active,[56,57] although by a factor of about 7 lower than the corresponding platinum analogue (**17** vs **21**). Within the palladium series, a clear trend is evident, as the anticancer activity increases with the chain length of the substituents in the 4- and 5-positions of the triazolate in the order CF_3/COOEt < $COOCH_3$ < COOEt < $COOCH_2CH_2OCH_3$, but EC_{50} values varied only by a factor of 3−4.

CONCLUSION

Two square-planar palladium(II) and platinum(II) azido complexes with a N^N^S chelating semithiocarbazone coligand were prepared in good yield and evaluated as a coupling

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partner in the [3 + 2] cycloaddition "iClick" reaction with a variety of electron-poor alkynes of the general structure R−C≡C−R′ with R = R′ = $COOCH_3$, COOEt, $COOCH_2CH_2OCH_3$ or R = CF_3, R′ = COOEt. A total of eight triazolate cycloaddition products were easily isolated by simple precipitation and/or washing in high purity and good yield. In most of the complexes, the triazolate ligand is coordinated via the central N2 atom. However, the two platinum compounds resulting from the reaction with dimethyl or diethyl acetylenedicarboxylate (DMAD or DEAD, respectively) showed two sets of signals in the ^{1}H and ^{13}C NMR for the methyl or ethyl ester protons and thus are rare examples of a N1-coordinated triazolate resulting from an iClick reaction. The fortuitous isolation of the N1 isomer is due to the very low solubility of the $COOCH_3$- and COOEt-substituted triazolate complexes in the acetone solvent utilized in this reaction, while the more polar $COOCH_2CH_2OCH_3$- and CF_3/COOEt-functionalized compounds remain in solution, where they quickly isomerize to the more stable N2 isomer. However, isomerization of the N1-coordinated complexes could be studied in DMSO-d_6 solution due to the slow kinetics, in which conversion to the N2 species required several days to go to completion.

As far as we are aware, this is one of the very rare instances in which a N1-coordinated triazolate has been isolated as the product of an iClick reaction of a metal azido complex. Werner and co-workers reported on the formation of [$Os(N_3)$(triazolate$^{COOCH3,\ COOCH3}$-N^1)(arene)($PiPr_3$)] from the corresponding bis-azido complex upon reaction with DMAD and its isomerization to the more stable N2 product within 2.5 h but did not study the kinetics in detail.[16] On the other hand, the very slow N1 → N2 isomerization reported in this work, on a time scale of several days in DMSO solution, is without precedence in the field so far. The cycloaddition of the platinum(II) azido complex with F_3C−C≡C−COOEt was also studied by ^{19}F NMR. While the signal of the trifluoromethyl-substituted alkyne fully disappeared within 20 min at room temperature, three new signals grew in. However, two of them were only transient and gradually disappeared again at later stages, with only the signal of the N2-coordinated triazolate remaining at the end of the experiment. While one of the two intermittent peaks is the N1 isomer initially formed from the end-on coordinated azido ligand, the third signal is tentatively assigned to a linear intermediate not described so far.

The kinetics of the iClick reaction were studied for all eight combinations of the two azido complexes and four alkynes by ^{1}H or ^{19}F NMR spectroscopy. However, triazolate formation was very fast in the case of the palladium(II) azido complexes and thus only a lower limit of the rate constant could be estimated. The platinum(II) azido compounds, on the other hand, reacted more slowly and second-order rate constants were determined for all four reactions. Rate constants generally increased in the order Pd > Pt and CF_3/COOEt > COOR with R = CH_3, Et, $CH_2CH_2OCH_3$, both by a factor of approximately 5−10. With k_2 > 3.7 M^{-1} s^{-1} determined for the reaction of [$Pd(N_3)$(L)] with F_3C−C≡C−COOEt, this is the fastest rate constant determined for an iClick reaction so far, more than 2 orders of magnitude faster than the initial k_2 value reported by Veige et al. for the iClick reaction of a linear gold(I) azido complex with a gold(I) acetylide[29] and three orders of magnitude faster than that recently reported for the reaction of molybdenum(II) and tungsten(II) allyl as well as Cp* rhodium(III) azido complexes with the same alkynes as used in this study.[27,28] The speed of the iClick reaction reported herein compares favorably with that of the most evolved strained alkynes reported for the SPAAC (strain-promoted azide−alkyne cycloaddition) so far[3] and approaches that of the copper-catalyzed variant (CuAAC) as well as simple, nonoptimized tetrazine ligations.[5]

A selection of the new palladium(II) and platinum(II) triazolate complexes easily obtained in high purity by this facile method was then evaluated for their biological activity on a human glioblastoma brain cancer cell line. Using the standard MTT assay, EC_{50} values in the low micromolar range (2−16 μM) were determined. Although the potency of the title compounds was smaller than that of cisplatin used as a reference (EC_{50} = 0.9 μM under similar conditions), in particular the palladium(II) complexes turned out to be surprisingly active relative to related species,[41,56−58] and a clear trend emerged, with the anticancer activity increasing with the chain length of the substituents in the 4- and 5-positions of the triazolate. Current studies are under way to expand this series of compounds for further biological testing and also utilize the fast kinetics for the preparation of bioconjugates.

EXPERIMENTAL SECTION

Materials and Methods. Palladium(II) chloride and potassium tetrachloroplatinate(II) were obtained from Strem. All other chemicals were purchased from commercial sources and used as received. 4,4,4-Trifluoro-2-butynoic acid ethyl ester was prepared according to a published procedure.[47] *Caution! Azides and azido complexes are potentially explosive. Although no problems were encountered with the preparations mentioned below, synthesis should only be performed on a very small scale (<100 mg) and in particular heating of the solid compounds avoided.* NMR spectra were recorded at room temperature (298 K) on Bruker Avance 200, 400, and 500 spectrometers (^{1}H at 200.13, 400.40, and 500.13 MHz, respectively; ^{13}C at 100.68 and 125.76 MHz; ^{19}F at 376.76 and 470.59 MHz; ^{195}Pt at 107.51 MHz). Solution chemical shifts δ in ppm represent a downfield shift relative to tetramethylsilane (TMS) and were referenced relative to the signal of the solvent.[59] The ^{19}F and ^{195}Pt NMR shifts are reported relative to CCl_3F and 1.2 M $Na_2[PtCl_6]$ in D_2O, respectively.[60] Coupling constants J are given in Hertz. Peak multiplicities are marked as singlet (s), doublet (d), doublet of doublets (dd), doublet of doublets of doublets (ddd), doublet of triplets (dt), triplet (t), and multiplet (m), respectively. IR spectra of pure solid samples were recorded on a Nicolet 380 FT-IR spectrometer fitted with a smart iTR ATR accessory. ESI mass spectra were recorded for selected compounds dissolved in acetonitrile on a Thermo Fisher Exactive Plus Orbitrap mass spectrometer in positive ion mode at a solvent flow rate of 50 μL min^{-1}. The elemental composition of the compounds was determined with an Elementar Vario MICRO cube CHN analyzer. Addition of V_2O_5 was usually required to obtain proper results in the case of the metal complexes.

Synthesis of Metal Complexes. *[Pd(N$_3$)(L)] (12).* In a round-bottom flask, [PdCl(L)] (120 mg, 0.29 mmol) was dissolved in acetone (80 mL) with heating to 75 °C. To the clear orange solution was added sodium azide (325 mg, 5.00 mmol) in water (15 mL), and heating was continued for 6 h. The volume of the resulting solution was decreased to about 20 mL, upon which a yellow precipitate formed, which was collected, washed with water (3 × 10 mL), and dried under vacuum for 1 day. Yield: 87% (106 mg, 0.25 mmol). IR (ATR): 3271, 3085, 2048, 1599, 1550, 1502, 1457, 1435, 1317, 1254, 1156, 1073, 757, 735 cm^{-1}. ^{1}H NMR (500.13 MHz, DMSO-d_6): δ 10.20 (s, 1H, N*H*-phenyl), 8.23−8.21 (m, 1H, py-H6), 8.19 (dd, 1H, $^3J_{H4,H3/H5}$ = 7.9 Hz, $^4J_{H4,H6}$ = 1.7 Hz, py-H4), 7.93 (d, 1H, $^3J_{H3,H4}$ = 7.9 Hz, py-H3), 7.66 (ddd, 1H, $^3J_{H5,H4}$ = 7.7 Hz, $^3J_{H5,H6}$ = 5.3 Hz, $^4J_{H5,H3}$ = 1.2 Hz, py-H5), 7.61 (d, 2H, $^3J_{H3'/H5',H2'/H6'}$ = 7.7 Hz,

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phenyl-H3′/H5′), 7.33 (t, 2H, $^{3}J_{H2'/H6',H3'/H5'}$ = 8.0 Hz, phenyl-H2′/H6′), 7.04 (t, 1H, $^{3}J_{H4',H3'/H5'}$ = 7.4 Hz, phenyl-H4′), 2.45 (s, 3H, CH_3) ppm; ^{13}C NMR (125.76 MHz, DMSO-d_6): δ 172.68 (*C*-S), 159.30 (*C*═N), 157.57 (py-C2), 147.20 (py-C6), 141.09 (phenyl-C1′), 140.21 (py-C4), 128.72 (phenyl-C3′/C5′), 126.91 (py-C5), 125.57 (py-C3), 123.21 (phenyl-C4′), 119.89 (phenyl-C2″/C6′), 13.61 (CH_3) ppm; Anal. Calcd for $C_{14}H_{13}N_7PdS$ (417.79 g mol^{-1}): C, 40.25; H, 3.14; N, 23.47; S, 7.68. Found (%): C, 40.29; H, 3.33; N, 23.16; S, 7.63.

[Pt(N$_3$)(L)] ***(13)***. In a round-bottom flask, [PtCl(L)] (80 mg, 0.16 mmol) was dissolved in acetone (40 mL) with heating to 75 °C. To the clear dark red solution was then added sodium azide (259 mg, 3.98 mmol) in water (10 mL), and heating was continued for 6 h. The volume of resulting solution was decreased to about 15 mL, upon which a red precipitate formed, which was collected, washed with water (3 × 10 mL), and dried under vacuum for 1 day. Yield: 88% (72 mg, 0.14 mmol). IR (ATR): = 3279, 3137, 3086, 2061, 1600, 1550, 1493, 1458, 1434, 1317, 1252, 1154, 1073, 755, 735 cm^{-1}. ^{1}H NMR (500.13 MHz, DMSO-d_6): δ 10.30 (s, 1H, N*H*-phenyl), 8.44 (ddd, 1H, $^{3}J_{H6,H5}$= 5.4 Hz, $^{4}J_{H6,H4}$ = 1.5 Hz, $^{5}J_{H6,H3}$= 0.7 Hz, py-H6), 8.21 (dt, 1H, $^{3}J_{H4,H3/H5}$ = 7.9 Hz, $^{4}J_{H4,H6}$ = 1.6 Hz, py-H4), 7.87 (d, 1H, $^{3}J_{H3,H4}$ = 8.0 Hz, py-H3), 7.69 (ddd, 1H, $^{3}J_{H5,H4}$ = 7.7 Hz, $^{3}J_{H5,H6}$ = 5.5 Hz, $^{4}J_{H5,H3}$ = 1.3 Hz, py-H5), 7.62 (d, 2H, $^{3}J_{H3'/H5',H2'/H6'}$ = 7.7 Hz, phenyl-H3′/H5′), 7.35 (t, 2H, $^{3}J_{H2'/H6',H3'/H5'}$ = 8.0 Hz, phenyl-H2′/H6′), 7.05 (t, 1H, $^{3}J_{H4',H3'/H5'}$ = 7.4 Hz, phenyl-H4′), 2.45 (s, 3H, CH_3) ppm. ^{13}C NMR (125.76 MHz, DMSO-d_6): δ 175.42 (*C*-S), 159.57 (*C*═N), 158.72 (py-C2), 146.02 (py-C6), 140.72 (phenyl-C1′), 140.24 (py-C4), 128.68 (phenyl-C3′/C5′), 127.65 (py-C5), 126.24 (py-C3), 123.39 (phenyl-C4′), 120.14 (phenyl-C2′/C6′), 13.64 (CH_3) ppm. ^{195}Pt NMR (107.51 MHz, DMSO-d_6): δ −3101 ppm. Anal. Calcd for $C_{14}H_{13}N_7PtS$ (506.45 g mol^{-1}): C, 33.20; H, 2.59; N, 19.36; S, 6.33. Found: C, 33.38; H, 2.84; N, 19.34; S, 6.29.

[Pd(triazolate^{CF3,COOEt}-N^2)(L)] ***(17)***. In a large glass vial, [Pd(N$_3$)(L)] (35 mg, 0.08 mmol) was suspended in acetone (20 mL) at room temperature. Then, 4,4,4-trifluoro-2-butynoic acid ethyl ester (30 μL, 38.1 mg, 0.23 mmol) was added to the orange suspension and stirring was continued at room temperature until the solution became clear, which took about 3 h. The resulting clear dark orange solution was then evaporated to dryness. The orange solid obtained was washed with *n*-hexane (5 × 5 mL) and dried under vacuum for 1 day. Yield: 75% (37 mg, 0.06 mmol). IR (ATR): 3333, 1709, 1601, 1544, 1510, 1466, 1438, 1310, 1191, 1134, 1060, 763, 746 cm^{-1}. ^{1}H NMR (500.13 MHz, DMSO-d_6): δ 10.22 (s, 1H, N*H*-phenyl), 8.91 (dd, 1H, $^{3}J_{H6,H5}$= 5.4 Hz, $^{4}J_{H6,H4}$= 1.1 Hz, py-H6), 8.24 (dt, 1H, $^{3}J_{H4,H3/H5}$ = 7.9 Hz, $^{4}J_{H4,H6}$ = 1.6 Hz, py-H4), 8.00 (d, 1H, $^{3}J_{H3,H4}$ = 8.0 Hz, py-H3), 7.72 (ddd, 1H, $^{3}J_{H5,H4}$ = 7.7 Hz, $^{3}J_{H5,H6}$ = 5.5 Hz, $^{4}J_{H5,H3}$ = 1.3 Hz, py-H5), 7.60 (d, 2H, $^{3}J_{H3'/H5',H2'/H6'}$ = 7.8 Hz, phenyl-H3′/H5′), 7.33 (t, 2H, $^{3}J_{H2'/H6',H3'/H5'}$ = 7.7 Hz, phenyl-H2′/H6′), 7.05 (t, 1H, $^{3}J_{H4',H3'/H5'}$ = 7.4 Hz, phenyl-H4′), 4.31 (q, 2H, ^{3}J = 7.1 Hz, CH_2CH_3), 2.53 (s, 3H, CH_3), 1.30 (t, 3H, ^{3}J = 7.1 Hz, CH_2CH_3) ppm. ^{13}C NMR (125.76 MHz, DMSO-d_6): δ 172.89 (*C*-S), 160.69 (*C*═N), 159.70 (COOEt), 157.76 (py-C2), 149.36 (py-C6), 141.30 (phenyl-C1′), 140.13 (py-C4), 137.88 (triazolate-C4), 136.64 (triazolate-C5), 128.77 (phenyl-C3′/C5′), 126.91 (py-C5), 125.98 (py-C3), 123.26 (phenyl-C4′), 121.41 (q, $^{1}J_{C,F}$= 268.1 Hz, CF_3), 119.88 (phenyl-C2′/C6′), 60.74 (CH_2CH_3), 14.00 (CH_3), 13.99 (CH_2CH_3) ppm. ^{19}F NMR (470.59 MHz, DMSO-d_6): δ −58.58 (CF_3) ppm. Anal. Calcd for $C_{20}H_{18}F_3N_7O_2PdS$ (583.89 g mol^{-1}): C, 41.14; H, 3.11; N, 16.79 S, 5.49. Found: C, 41.23; H, 3.09; N, 16.21; S, 5.43.

[Pt(triazolate^{CF3,COOEt}-N^2)(L)] ***(21)***. In a large glass vial, [Pt(N$_3$)(L)] (25 mg, 0.05 mmol) was suspended in acetone (20 mL) at room temperature. Then, 4,4,4-trifluoro-2-butynoic acid ethyl ester (10 μL, 12.7 mg, 0.07 mmol) was added to the red suspension and stirring was continued at room temperature for 2 d. The resulting clear red solution was evaporated to dryness. The red solid obtained was washed with *n*-hexane (5 × 5 mL) and dried under vacuum for 1 day. Yield: 80% (25 mg, 0.04 mmol). IR (ATR): 3336, 1710, 1546, 1499, 1467, 1437, 1311, 1192, 1135, 1061, 760, 747 cm^{-1}. ^{1}H NMR (500.13 MHz, DMSO-d_6): δ 10.30 (s, 1H, N*H*-phenyl), 9.21 (ddd, 1H, $^{3}J_{H6,H5}$= 5.5 Hz, $^{4}J_{H6,H4}$ = 1.5 Hz, $^{5}J_{H6,H3}$= 0.6 Hz, py-H6), 8.23 (dt, 1H, $^{3}J_{H4,H3/H5}$ = 7.9 Hz, $^{4}J_{H4,H6}$ = 1.6 Hz, py-H4), 7.92 (d, 1H, $^{3}J_{H3,H4}$ = 7.4 Hz, py-H3), 7.72 (ddd, 1H, $^{3}J_{H5,H4}$ = 7.7 Hz, $^{3}J_{H5,H6}$ = 5.6 Hz, $^{4}J_{H5,H3}$ = 1.3 Hz, py-H5), 7.60 (d, 2H, $^{3}J_{H3'/H5',H2'/H6'}$ = 7.7 Hz, phenyl-H3′/H5′), 7.34 (t, 2H, $^{3}J_{H2'/H6',H3'/H5'}$ = 8.0 Hz, phenyl-H2′/H6′), 7.05 (t, 1H, $^{3}J_{H4',H3'/H5'}$ = 7.4 Hz, phenyl-H4′), 4.32 (q, 2H, ^{3}J = 7.1 Hz, CH_2CH_3), 2.56 (s, 3H, CH_3), 1.31 (t, 3H, ^{3}J = 7.1 Hz, CH_2CH_3) ppm. ^{13}C NMR (125.76 MHz, DMSO-d_6): δ 175.24 (*C*-S), 161.21 (*C*═N), 159.42 (COOEt), 158.72 (py-C2), 148.70 (py-C6), 140.85 (phenyl-C1′), 140.14 (py-C4), 138.17 (q, $^{2}J_{C,F}$= 37.8 Hz, triazolate-C4), 136.74 (q, $^{3}J_{C,F}$= 0.9 Hz, triazolate-C5), 128.67 (phenyl-C3′/C5′), 127.51 (py-C5), 126.53 (py-C3), 123.34 (phenyl-C4′), 121.14 (q, $^{1}J_{C,F}$= 268.2 Hz, CF_3), 120.07 (phenyl-C2′/C6′), 61.80 (CH_2CH_3), 13.95 (CH_3), 13.76 (CH_2CH_3) ppm. ^{19}F NMR (470.59 MHz, DMSO-d_6): δ −58.71 (CF_3) ppm. ^{195}Pt NMR (107.51 MHz, DMSO-d_6): δ −3108 ppm. Anal. Calcd for $C_{20}H_{18}F_3N_7O_2PtS$ (672.55 g mol^{-1}): C, 35.72; H, 2.70; N, 14.58; S, 4.77. Found: C, 35.78; H, 2.55; N, 14.24; S, 4.60.

[Pd(triazolate^{COOCH3,COOCH3}-N^2)(L)] ***(18)***. In a large glass vial, [Pd(N$_3$)(L)] (40 mg, 0.10 mmol) was suspended in acetone (16 mL) at room temperature. Then, dimethyl acetylenedicarboxylate (20 μL, 23.1 mg, 0.16 mmol) was added to the orange suspension and stirring was continued at room temperature for 15 h. The resulting orange precipitate was filtered off, washed with *n*-hexane (5 × 5 mL), and dried under vacuum for 1 day. Yield: 70% (39 mg, 0.07 mmol). IR (ATR): 3308, 3092, 1730, 1709, 1602, 1553, 1502, 1460, 1437, 1396, 1294, 1159, 1090, 828, 800, 770, 756 cm^{-1}; ^{1}H NMR (500.13 MHz, DMSO-d_6): δ 10.18 (s, 1H, N*H*-phenyl), 8.91 (ddd, 1H, $^{3}J_{H6,H5}$= 5.4 Hz, $^{4}J_{H6,H4}$ = 1.6 Hz, $^{5}J_{H6,H3}$= 0.5 Hz, py-H6), 8.24 (dt, 1H, $^{3}J_{H4,H3/H5}$ = 7.9 Hz, $^{4}J_{H4,H6}$ = 1.6 Hz, py-H4), 7.97 (d, 1H, $^{3}J_{H3,H4}$ = 7.5 Hz, py-H3), 7.69 (ddd, 1H, $^{3}J_{H5,H4}$ = 7.7 Hz, $^{3}J_{H5,H6}$ = 5.4 Hz, $^{4}J_{H5,H3}$ = 1.3 Hz, py-H5), 7.58 (d, 2H, $^{3}J_{H3'/H5',H2'/H6'}$ = 7.7 Hz, phenyl-H3′/H5′), 7.32 (t, 2H, $^{3}J_{H2'/H6',H3'/H5'}$ = 8.0 Hz, phenyl-H2′/H6′), 7.04 (t, 1H, $^{3}J_{H4',H3'/H5'}$ = 7.4 Hz, phenyl-H4′), 3.81 (s, 6H, $COOCH_3$), 2.52 (s, 3H, CH_3) ppm. ^{13}C NMR (125.76 MHz, DMSO-d_6): δ 173.21 (*C*-S), 161.99 ($COOCH_3$), 160.47 (*C*═N), 157.78 (py-C2), 149.47 (py-C6), 141.24 (phenyl-C1′), 140.17 (py-C4), 139.40 (triazolate-C4/C5), 128.80 (phenyl-C3′/C5′), 12.89 (py-C5), 125.92 (py-C3), 123.31 (phenyl-C4′), 120.04 (phenyl-C2′/C6′), 52.05 ($COOCH_3$), 14.01 (CH_3) ppm. MS (ESI$^+$, CH_3CN): 416.0149 [M − triazolate + CH_3CN]$^+$, 560.0325 [M + H]$^+$, 582.0143 [M + Na]$^+$, 936.0145 [2M − triazolate]$^+$, 1143.0409 [2M + Na]$^+$. Anal. Calcd for $C_{20}H_{19}N_7O_4PdS$ (559.90 g mol^{-1}): C, 42.90; H, 3.42; N, 17.51; S, 5.73. Found: C, 42.85; H, 3.79; N, 17.58; S, 5.62.

[Pt(triazolate^{COOCH3,COOCH3}-N^1)(L)] ***(22)***. In a large glass vial, [Pt(N$_3$)(L)] (30 mg, 0.06 mmol) was suspended in acetone (15 mL) at room temperature. Then, dimethyl acetylenedicarboxylate (30 μL, 34.7 mg, 0.24 mmol) was added to the red suspension and stirring was continued at room temperature for 11 days. Then the volume of solution was decreased to about 7 mL and the resulting orange precipitate was filtered off, washed with *n*-hexane (3 × 5 mL), and dried under vacuum for 1 day. Yield: 60% (23 mg, 0.04 mmol). IR (ATR): 3013, 1730, 1728, 1560, 1512, 1461, 1440, 1322, 1259, 1202, 1154, 1108, 1037, 758 cm^{-1}. ^{1}H NMR (400.40 MHz, DMSO-d_6): δ 10.42 (s, 1H, N*H*-C_6H_5), 8.28 (t, 1H, $^{3}J_{H4,H3/H5}$= 8.4 Hz, py-H4), 8.00−7.96 (m, 2H, py-H3, py-H6), 7.69−7.64 (m, 3H, py-H5, phenyl-H3′/H5′), 7.36 (t, 2H, $^{3}J_{H2'/H6',H3'/H5'}$ = 7.7 Hz, phenyl-H2′/H6′), 7.06 (t, 1H, $^{3}J_{H4',H3'/H5'}$ = 7.6 Hz, phenyl-H4′), 3.84 (s, 3H, triazolate-C5-$COOCH_3$), 3.80 (s, 3H, triazolate-C4-$COOCH_3$), 2.61 (s, 3H, CH_3) ppm. No ^{13}C and ^{195}Pt NMR spectra could be recorded due to the low solubility of the compound in common solvents. Anal. Calcd for $C_{20}H_{19}N_7O_4PtS$ (648.56 g mol^{-1}): C, 37.04; H, 2.95; N, 15.12; S, 4.94. Found (%): C, 36.95; H, 3.03; N, 15.22; S, 4.94.

[Pt(triazolate^{COOCH3,COOCH3}-N^2)(L)] ***(25)***. A suspension of [Pt(triazolate^{COOCH3,COOCH3}-N^1)(L)] (approximately 10 mg) in DMSO-d_6 was kept in an NMR tube at room temperature for 7 days, during which time the light orange suspension turned to a clear dark red solution. ^{1}H NMR (500.13 MHz, DMSO-d_6): δ 10.30 (s, 1H, N*H*-C_6H_5), 9.24 (ddd, 1H, $^{3}J_{H6,H5}$= 5.6 Hz, $^{4}J_{H6,H4}$ = 1.5 Hz, $^{5}J_{H6,H3}$= 0.6 Hz, py-H6), 8.25 (dt, 1H, $^{3}J_{H3,H4}$ = 7.9 Hz, $^{4}J_{H3,H5}$ = 1.6

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Hz, py-H3), 7.93 (d, 1H, $^3J_{H4,H3/H5}$ = 7.4 Hz, py-H4), 7.75 (ddd, 1H, $^3J_{H5,H4}$ = 7.7 Hz, $^3J_{H5,H6}$ = 5.6 Hz, $^4J_{H5,H3}$ = 1.4 Hz, py-H5), 7.61 (d, 2H, $^3J_{H3'/H5',H2'/H6'}$ = 7.7 Hz, phenyl-H3′/H-5′), 7.35 (t, 2H, $^3J_{H2'/H6',H3'/H5'}$ = 8.0 Hz, phenyl-H2′/H-6′), 7.06 (t, 1H, $^3J_{H4',H3'/H5'}$ = 7.4 Hz, phenyl-H4′), 3.83 (s, 6H, $COOCH_3$), 2.57 (s, 3H, CH_3) ppm. ^{13}C NMR (125.76 MHz, DMSO-d_6): δ 175.59 (*C*-S), 161.64 ($COOCH_3$), 161.03 (*C*═N), 158.76 (py-C2), 148.76 (py-C6), 140.87 (phenyl-C1′), 140.15 (py-C4), 139.54 (triazolate-C4/C5), 128.71 (phenyl-C3′/C5′), 127.61 (py-C5), 126.52 (py-C3), 123.43 (phenyl-C4′), 120.25 (phenyl-C2′/C6′), 52.07 ($COOCH_3$), 13.76 (CH_3) ppm. ^{195}Pt NMR (107.51 MHz, DMSO-d_6): δ −3105 ppm; MS (ESI$^+$, CH_3CN): 649.0937 [M + H]$^+$, 671.0758 [M + Na]$^+$, 1112.1356 [2M − triazolate]$^+$, 1319.1622 [2M + Na]$^+$, 1335.1353 [2M + K]$^+$.

[Pd(triazolate^{COOEt,COOEt}-N^2)(L)] ***(19)***. In a large glass vial, [Pd(N_3)(L)] (12 mg, 28.7 μmol) was suspended in acetone (9 mL) at room temperature. Then, diethyl acetylenedicarboxylate (24 μL, 25.5 mg, 150 μmol) was added to the orange suspension and stirring was continued at room temperature for 14 h. The resulting yellow precipitate was filtered off, washed with *n*-hexane (5 × 5 mL), and dried under vacuum for 1 day. Yield: 89% (15 mg, 25.5 μmol). IR (ATR): 3303, 1727, 1602, 1498, 1461, 1437, 1293, 1194, 1155, 1090, 762, 742 cm^{-1}. ^1H NMR (500.13 MHz, DMSO-d_6): δ 10.23 (s, 1H, N*H*-phenyl), 8.92 (ddd, 1H, $^3J_{H6,H5}$= 5.4 Hz, $^4J_{H6,H4}$ = 1.6 Hz, $^5J_{H6,H3}$= 0.6 Hz, py-H6), 8.25 (dt, 1H, $^3J_{H4,H3/H5}$ = 7.9 Hz, $^4J_{H4,H6}$ = 1.6 Hz, py-H4), 8.02 (d, 1H, $^3J_{H3,H4}$ = 7.4 Hz, py-H3), 7.75 (ddd, 1H, $^3J_{H5,H4}$ = 7.7 Hz, $^3J_{H5,H6}$ = 5.4 Hz, $^4J_{H5,H3}$ = 1.3 Hz, py-H5), 7.62 (d, 2H, $^3J_{H3'/H5',H2'/H6'}$ = 7.7 Hz, phenyl-H3′/H5′), 7.35 (t, 2H, $^3J_{H2'/H6',H3'/H5'}$ = 8.0 Hz, phenyl-H2′/H-6′), 7.06 (t, 1H, $^3J_{H4',H3'/H5'}$ = 7.4 Hz, phenyl-H4′), 4.28 (q, 4H, ^3J = 7.1 Hz, $COOCH_2CH_3$), 2.54 (s, 3H, CH_3), 1.28 (t, 6H, ^3J = 7.1 Hz, $COOCH_2CH_3$) ppm. ^{13}C NMR (100.68 MHz, DMSO-d_6): δ 173.18 (*C*-S), 161.58 ($COOCH_2CH_3$), 160.40 (*C*═N), 157.75 (py-C2), 149.39 (py-C6), 141.21 (phenyl-C1′), 140.14 (py-C4), 139.53 (triazolate-C4/C5), 128.73 (phenyl-C3′/C5′), 126.84 (py-C5), 125.88 (py-C3), 123.24 (phenyl-C4′), 119.96 (phenyl-C2′/C6′), 60.65 (CH_2CH_3), 14.03 (CH_2CH_3), 13.95 (CH_3) ppm. Anal. Calcd for $C_{22}H_{23}N_7O_4PdS$: C, 44.94; H, 3.94; N, 16.68; S, 5.45. Found: C, 44.80; H, 4.01; N, 16.57; S, 5.37.

[Pt(triazolate^{COOEt,COOEt}-N^1)(L)] ***(23)***. In a large glass vial, [Pt(N_3)(L)] (20 mg, 39.5 μmol) was suspended in acetone (10 mL) at room temperature. Then, diethyl acetylenedicarboxylate (40 μL, 42.5 mg, 250 μmol) was added to the red suspension and stirring was continued at room temperature for 4 days. The resulting light red precipitate was filtered off, washed with *n*-hexane (5 × 5 mL), and dried under vacuum for 1 day. Yield: 41% (11 mg, 16.3 μmol). IR (ATR): 3252, 2987, 1721, 1605, 1559, 1503, 1462, 1440, 1337, 1259, 1191, 1156, 1105, 758 cm^{-1}. ^1H NMR (400.40 MHz, DMSO-d_6): δ 10.39 (s, 1H, N*H*-phenyl), 8.27 (t, 1H, $^3J_{H4,H3/H5}$= 7.6 Hz, py-H4), 7.98 (d, 1H, $^3J_{H3,H4}$= 7.7 Hz, py-H3), 7.88 (d, 1H, $^3J_{H6,H5}$= 5.4 Hz py-H6), 7.68−7.64 (m, 3H, py-H5, phenyl-H3′/H5′), 7.36 (t, 2H, $^3J_{H2'/H6',H3'/H5'}$ = 7.9 Hz, phenyl-H2′/H6′), 7.06 (t, 1H, $^3J_{H4',H3'/H5'}$ = 7.2 Hz, phenyl-H4′), 4.32−4.24 (m, 4H, triazolate-C4-$COOCH_2CH_3$/triazolate-C5-$COOCH_2CH_3$), 2.61 (s, 3H, CH_3), 1.28−1.23 (m, 6H, triazolate-C4-$COOCH_3$/triazolate-C5-$COOCH_2CH_3$) ppm. ^{13}C NMR (100.68 MHz, DMSO-d_6): δ 162.30 (triazolate-C5-$COOCH_2CH_3$), 160.79 (triazolate-C4-$COOCH_2CH_3$), 158.48 (py-C2), 147.81 (py-C6), 141.00 (phenyl-C1′), 140.82 (py-C4), 128.71 (phenyl-C3′/C5′), 128.14 (py-C5), 126.70 (py-C3), 123.53 (phenyl-C4′), 120.22 (phenyl-C2′/C6′), 61.51 (triazolate-C5-$COOCH_2CH_3$), 60.31 (triazolate-C4-$COOCH_2CH_3$), 14.08 (triazolate-C5-$COOCH_2CH_3$), 13.90 (CH_3), 13.86 (triazolate-C4-$COOCH_2CH_3$) ppm. The C−S and C═N, as well as triazolate C4 and C5 carbon atoms, all expected to have low signal intensity, were not observed due to low solubility of the compound. Furthermore, no ^{195}Pt NMR could be obtained for this compound for the same reason. Anal. Calcd for $C_{22}H_{23}N_7O_4PtS$ (676.61 g mol^{-1}): C, 39.05; H, 3.43; N, 14.49; S, 4.74. Found: C, 39.03; H, 3.51; N, 14.63; S, 4.63.

[Pt(triazolate^{COOEt,COOEt}-N^2)(L)] ***(26)***. A suspension of [Pt(triazolate^{COOEt,COOEt}-N^1)(L)] (approximately 10 mg) in DMSO-d_6 was kept in a NMR tube at room temperature for 7 days, during which time the light orange suspension changed to a clear dark red solution. ^1H NMR (500.13 MHz, DMSO-d_6): δ 10.30 (s, 1H, N*H*-phenyl), 9.24 (ddd, 1H, $^3J_{H6,H5}$= 5.5 Hz, $^4J_{H6,H4}$ = 1.5 Hz, $^5J_{H6,H3}$= 0.6 Hz, py-H6), 8.24 (dt, 1H, $^3J_{H4,H3/H5}$ = 7.9 Hz, $^4J_{H4,H6}$ = 1.6 Hz, py-H4), 7.93 (d, 1H, $^3J_{H3,H4}$ = 7.4 Hz, py-H3), 7.74 (ddd, 1H, $^3J_{H5,H4}$ = 7.7 Hz, $^3J_{H5,H6}$ = 5.6 Hz, $^4J_{H5,H3}$ = 1.4 Hz, py-H5), 7.61 (d, 2H, $^3J_{H3'/H5',H2'/H6'}$ = 7.7 Hz, phenyl-H3′/H5′), 7.35 (t, 2H, $^3J_{H2'/H6',H3'/H5'}$ = 8.0 Hz, phenyl-H2′/H6′), 7.05 (t, 1H, $^3J_{H4',H3'/H5'}$ = 7.4 Hz, phenyl-H4′), 4.29 (q, 4H, ^3J = 7.1 Hz, $COOCH_2CH_3$), 2.58 (s, 3H, CH_3), 1.29 (t, 6H, ^3J = 7.1 Hz, $COOCH_2CH_3$) ppm. ^{13}C NMR (125.76 MHz, DMSO-d_6): δ 175.55 (*C*-S) 161.29 ($COOCH_3$), 161.01 (*C*═N), 158.76 (py-C2), 148.72 (py-C6), 140.85 (phenyl-C1′), 140.16 (py-C4), 139.68 (triazolate-C4/C5), 128.68 (phenyl-C3′/C5′), 127.54 (py-C5), 126.51 (py-C3), 123.39 (phenyl-C4′), 120.22 (phenyl-C2′/C6′), 60.75 (CH_2CH_3), 14.02 (CH_2CH_3), 13.76 (CH_3) ppm. ^{195}Pt NMR (107.51 MHz, DMSO-d_6): δ −3104 ppm.

[Pd(triazolate^{COOCH2CH2OCH3,COOCH2CH2OCH3}-N^2)(L)] ***(20)***. In a large glass vial, [Pd(N_3)(L)] (21 mg, 50.4 μmol) was suspended in acetone (10 mL) at room temperature. Then, 2-butynedioic acid 1,4-bis(2-methoxyethyl) ester (11.0 μL, 12.9 mg, 56.0 μmol) was added to the orange suspension and stirring was continued at room temperature for 1 day. The resulting clear orange solution was evaporated to dryness, and the orange solid product washed with diethyl ether (5 × 5 mL) and dried under vacuum for 1 day. Yield: 67% (22 mg, 34.0 μmol). IR (ATR): 3340, 2939, 1727, 1600, 1502, 1458, 1435, 1292, 1188, 1077, 753 cm^{-1}. ^1H NMR (500.13 MHz, DMSO-d_6): δ 10.19 (s, 1H, N*H*-phenyl), 8.90 (dd, 1H, $^3J_{H6,H5}$= 5.4 Hz, $^4J_{H6,H4}$ = 1.2 Hz, py-H6), 8.21 (dt, 1H, $^3J_{H4,H3/H5}$ = 7.9 Hz, $^4J_{H4,H6}$ = 1.6 Hz, py-H4), 7.98 (d, 1H, $^3J_{H3,H4}$ = 7.7 Hz, py-H3), 7.67 (ddd, 1H, $^3J_{H5,H4}$ = 7.7 Hz, $^3J_{H5,H6}$ = 5.5 Hz, $^4J_{H5,H3}$ = 1.3 Hz, py-H5), 7.59 (d, 2H, $^3J_{H3'/H5',H2'/H6'}$ = 7.7 Hz, phenyl-H3′/H5′), 7.32 (t, 2H, $^3J_{H2'/H6',H3'/H5'}$ = 8.0 Hz, phenyl-H2′/H6′), 7.04 (t, 1H, $^3J_{H4',H3'/H5'}$ = 7.4 Hz, phenyl-H4′), 4.35 (t, 4H, ^3J = 4.7 Hz, $OCH_2CH_2OCH_3$), 3.62 (t, 4H, ^3J = 4.8 Hz, $OCH_2CH_2OCH_3$), 3.29 (s, 6H, OCH_3) 2.53 (s, 3H, CH_3) ppm. ^{13}C NMR (125.76 MHz, DMSO-d_6): δ 173.12 (*C*-S), 161.48 ($COOCH_3$), 160.43 (*C*═N), 157.77 (py-C2), 149.36 (py-C6), 141.22 (phenyl-C1′), 140.14 (py-C4), 139.41 (triazolate-C4/C5), 128.73 (phenyl-C3′/C5′), 126.75 (py-C5), 125.90 (py-C3), 123.23 (phenyl-C4′), 119.97 (phenyl-C2′/C6′), 69.64 ($OCH_2CH_2OCH_3$), 63.81 ($OCH_2CH_2OCH_3$), 58.12 (OCH_3) 13.99 (CH_3) ppm. Anal. Calcd for $C_{24}H_{27}N_7O_6PdS$ (648.01 g mol^{-1}): C, 44.48; H, 4.20; N, 15.13; S, 4.95. Found: C, 44.20; H, 4.35; N, 14.69; S, 4.92.

[Pt(triazolate^{COOCH2CH2OCH3,COOCH2CH2OCH3}-N^2)(L)] ***(24)***. In a large glass vial, [Pt(N_3)(L)] (10 mg, 19.3 μmol) was suspended in acetone (8 mL) at room temperature. Then, 2-butynedioic acid 1,4-bis(2-methoxyethyl) ester (4.4 μL, 5.1 mg, 22.3 μmol) was added to the red suspension. Stirring was continued at room temperature for 9 days, during which the reaction mixture slowly cleared up. The resulting red solution was evaporated to dryness, and the solid red product was washed with diethyl ether (5 × 5 mL), and dried under vacuum for 1 day. Yield: 63% (9 mg, 12.2 μmol). IR (ATR): 3341, 2947, 1738, 1599, 1502, 1463, 1435, 1294, 1250, 1191, 1190, 1078, 1028, 867, 753; ^1H NMR (500.13 MHz, DMSO-d_6): δ 10.30 (s, 1H, N*H*-phenyl), 9.22 (ddd, 1H, $^3J_{H6,H5}$= 5.6 Hz, $^4J_{H6,H4}$ = 1.5 Hz, $^5J_{H6,H3}$= 0.6 Hz, py-H6), 8.23 (dt, 1H, $^3J_{H4,H3/H5}$ = 7.9 Hz, $^4J_{H4,H6}$ = 1.6 Hz, py-H4), 7.92 (d, 1H, $^3J_{H3,H4}$ = 7.4 Hz, py-H3), 7.70 (ddd, 1H, $^3J_{H5,H4}$ = 7.6 Hz, $^3J_{H5,H6}$ = 5.6 Hz, $^4J_{H5,H3}$ = 1.4 Hz, py-H5), 7.61 (d, 2H, $^3J_{H3'/H5',H2'/H6'}$ = 7.7 Hz, phenyl-H3′/H5′), 7.34 (t, 2H, $^3J_{H2'/H6',H3'/H5'}$ = 8.0 Hz, phenyl-H2′/H6′), 7.05 (t, 1H, $^3J_{H4',H3'/H5'}$ = 7.4 Hz, phenyl-H4′), 4.36 (t, 4H, ^3J = 4.7 Hz, O−CH_2−CH_2−O−CH_3), 3.62 (t, 4H, ^3J = 4.7 Hz, O−CH_2−CH_2−O−CH_3), 3.30 (s, 6H, O−CH_3) 2.58 (s, 3H, CH_3) ppm. ^{13}C NMR (125.76 MHz, DMSO-d_6): δ 175.52 (*C*-S) 161.20 ($COOCH_3$), 161.06 (*C*═N), 158.79 (py-C2), 148.70 (py-C6), 140.88 (phenyl-C1′), 140.17 (py-C4), 139.58 (triazolate-C4/C5), 128.70 (phenyl-C3′/C5′), 127.48 (py-C5), 126.53 (py-C3), 123.42 (phenyl-C4′), 120.26 (phenyl-C2′/C6′),

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69.62 ($O-CH_2-CH_2-O-CH_3$), 63.91 ($O-CH_2-CH_2-O-CH_3$), 58.13 ($O-CH_3$) 13.79 (CH_3) ppm. ^{195}Pt NMR (107.51 MHz, DMSO-d_6): δ −3106 ppm. Anal. Calcd for $C_{24}H_{27}N_7O_6PtS$ (736.67 g mol^{-1}): C, 39.13; H, 3.69; N, 13.31; S, 4.35. Found: C, 38.94; H, 3.66; N, 12.93; S, 4.24.

Kinetic Studies. The second-order rate constants were determined by monitoring changes in the intensities of representative alkyne and azido complex signals relative to 1,3,5-trioxane or *tert*-butylammonium hexafluorophosphate serving as an internal standard with ^1H or ^{19}F NMR at room temperature (298 K) on Bruker Avance 200 and 400 spectrometers (^1H at 199.93 and 400.40 MHz; ^{19}F at 188.12 and 376.76 MHz). For sample preparation, in a small glass vial, 1,3,5-trioxane (approximately 15 mg) or *tert*-butyl ammonium hexafluorophosphate (approximately 5 mg) and alkyne (2 μL) were dissolved in DMSO-d_6. Then, a ^1H or ^{19}F NMR spectrum was recorded and the precise molar amount of standard calculated from comparison of the alkyne methyl ester proton or CF_3 signal intensities relative to the 1,3,5-trioxane or hexafluorophosphate peak integrals. In a second vial, a precisely weighed amount of an azido complex was dissolved in DMSO-d_6. Then, the NMR measurement was set up and, right next to the spectrometer, a stock solution of the alkyne/standard mixture was added to that of the metal azido complex directly in a NMR tube. The amount of both solutions was adjusted to give a final alkyne to azido complex ratio of 1:1 (approximately 6 mM each). Then, the tube was immediately inserted into the spectrometer and an initial NMR spectrum recorded. Further measurements were done at regular intervals of approximately 6−30 min, depending on the rate of the reaction. The time lag between mixing of the reaction partners and recording of the first NMR spectrum was estimated to be approximately 1.5 min, which was considered in the determination of the rate constants.

Biological Assays. The human glioblastoma cell line GaMG (DSMZ) was cultured in 75 cm^2 cell culture flasks (Corning) in Dulbecco Modified Eagle Medium (DMEM) supplemented with 10% fetal bovine serum, 2% nonessential amino acids, and 0.4% penicillin/streptomycin (all from Gibco) in a cell culture incubator at 37 °C and 5% CO_2. For the MTT assay (Cell Proliferation KIT I (MTT) from Roche), 3000 cells resuspended in 100 μL of medium were plated into the wells of a 96-well plate (Sarstedt) each and incubated overnight so that the cells could adhere. Metal complexes **17**−**21** were dissolved in dimethyl sulfoxide (Roth) and diluted in medium. The medium in the 96-well plates was replaced by 100 μL of medium containing the metal complexes in different concentrations ranging from 0.25 to 50 μM. After an incubation period of 72 h, the MTT assay was performed according to the manufacturer's manual and measured with an ELISA Reader (Tecan). EC_{50} values were calculated with Graph Pad Prism 6.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.inorgchem.9b01304.

Synthetic procedures and analytical data for ligand and metal complex precursors, detailed information on ^1H, ^{13}C, ^{19}F, and ^{195}Pt NMR as well as IR spectra for all azido and triazolato complexes, and additional data on the kinetic experiments (PDF)

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The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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■ DEDICATION

This publication is dedicated to Prof. Dr. Dr. h.c. mult. Helmut Werner on the occasion of his 85th birthday.

■ REFERENCES

(1) Thirumurugan, P.; Matosiuk, D.; Jozwiak, K. Click Chemistry for Drug Development and Diverse Chemical-Biology Applications. *Chem. Rev.* **2013**, *113*, 4905−4979.

(2) Lim, R. K. V.; Lin, Q. Bioorthogonal chemistry: Recent progress and future directions. *Chem. Commun.* **2010**, *46*, 1589−1600.

(3) Ramil, C. P.; Lin, Q. Bioorthogonal chemistry: Strategies and recent developments. *Chem. Commun.* **2013**, *49*, 11007−11022.

(4) Tang, W.; Becker, M. L. Click" reactions: A versatile toolbox for the synthesis of peptide-conjugates. *Chem. Soc. Rev.* **2014**, *43*, 7013−7039.

(5) Lang, K.; Chin, J. W. Cellular incorporation of unnatural amino acids and bioorthogonal labelling of proteins. *Chem. Rev.* **2014**, *114*, 4764−4806.

(6) Pfeiffer, H.; Rojas, A.; Niesel, J.; Schatzschneider, U. Sonogashira and "Click" reactions for the *N*-terminal and side chain functionalization of peptides with $[Mn(CO)_3(tpm)]^+$-based CO releasing molecules (tpm = tris(pyrazolyl)methane). *Dalton Trans* **2009**, 4292−4298.

(7) Zagermann, J.; Klein, K.; Merz, K.; Molon, M.; Metzler-Nolte, N. Synthesis and Characterization of the Azido-Functionalized Ruthenocene Analogue $[TpmRu(p\text{-}N_3C_6H_4)Tp]Cl$ and Its Attachment to Biomolecules by Copper-Catalyzed Azide-Alkyne Cycloaddition. *Eur. J. Inorg. Chem.* **2011**, *2011*, 4212−4219.

(8) Lo, K. K.-W.; Chan, B. T.-N.; Liu, H.-W.; Zhang, K. Y.; Li, S. P.-Y.; Tang, T. S.-M. Cyclometalated iridium(III) polypyridine dibenzocyclooctyne complexes as the first phosphorescent bioorthogonal probes. *Chem. Commun.* **2013**, *49*, 4271−4273.

(9) Pai, S.; Radacki, K.; Schatzschneider, U. Sonogashira, CuAAC, and oxime ligations for the synthesis of Mn(I) tricarbonyl Photo CORM peptide conjugates. *Eur. J. Inorg. Chem.* **2014**, *2014*, 2886−2895.

(10) Del Castillo, T. J.; Sarkar, S.; Abboud, K. A.; Veige, A. S. 1,3-Dipolar cycloaddition between a metal-azide (PPh_3PAuN_3) and a metal acetylide ($Ph_3PAuCCPh$): An inorganic version of a click reaction. *Dalton Trans* **2011**, *40*, 8140−8144.

(11) Heckler, J. E.; Deligonul, N.; Rheingold, A. L.; Gray, T. G. Gold(I) triazolyls: Organometallic synthesis in air and aqueous media. *Chem. Commun.* **2013**, *49*, 5990−5992.

(12) Robilotto, T. J.; Deligonul, N.; Updegraff, J. B.; Gray, T. G. Azido, Triazolyl, and Alkynyl Complexes of Gold(I): Syntheses, Structures, and Ligand Effects. *Inorg. Chem.* **2013**, *52*, 9659−9668.

DOI: 10.1021/acs.inorgchem.9b01304
Inorg. Chem. XXXX, XXX, XXX−XXX

(13) Frühauf, H.-W. Organotransition metal [3 + 2] cycloaddition reactions. *Coord. Chem. Rev.* **2002**, *230*, 79−96.
(14) Fehlhammer, W. P.; Beck, W. Azide chemistry - An inorganic perspective, Part II. [3 + 2]-Cycloaddition reactions of metal azides and related systems. *Z. Anorg. Allg. Chem.* **2015**, *641*, 1599−1678.
(15) Rosan, A.; Rosenblum, M. Reaction of dicarbonyl (^{5}-cyclopentadienyl)(olefin)iron cations with sodium azide. *J. Organomet. Chem.* **1974**, *80*, 103−107.
(16) Daniel, T.; Knaup, W.; Dziallas, M.; Werner, H. Osmiumkomplexe vom Halbsandwichtyp mit Oximen, Iminen und Azavinylidenen als Liganden. *Chem. Ber.* **1993**, *126*, 1981−1993.
(17) Chang, C.-W.; Lee, G.-H. Synthesis of Ruthenium Triazolato and Tetrazolato Complexes by 1,3-Dipolar Cycloadditions of Ruthenium Azido Complex with Alkynes and Alkenes and Regiospecific Alkylation of Triazolates. *Organometallics* **2003**, *22*, 3107−3116.
(18) Singh, K. S.; Kreisel, K. A.; Yap, G. P. A.; Kollipara, M. R. Synthesis of arene ruthenium triazolato complexes by cycloaddition of the corresponding arene ruthenium azido complexes with activated alkynes or with fumaronitrile. *J. Organomet. Chem.* **2006**, *691*, 3509−3518.
(19) Pachhunga, K.; Therrien, B.; Kollipara, M. R. Synthesis of benzene ruthenium triazolato complexes by [3 + 2] cycloaddition reactions of activated alkynes and fumaronitrile to benzene ruthenium azido complexes. *Inorg. Chim. Acta* **2008**, *361*, 3294−3300.
(20) Chen, C.-K.; Tong, H.-C.; Hsu, C.-Y. C.; Lee, C.-Y.; Fong, Y. H.; Chuang, Y.-S.; Lo, Y.-H.; Lin, Y.-C.; Wang, Y. Synthesis and Reactivity of Ruthenium Azido Complexes Containing a Hydridotris(pyrazolyl)borate Ligand and Dimerization of Terminal Alkynes in Organic and Aqueous Media. *Organometallics* **2009**, *28*, 3358−3368.
(21) Liu, F.-C.; Lin, Y.-L.; Yang, P.-S.; Lee, G.-H.; Peng, S.-M. [3 + 2] Cycloadditions of Molybdenum(II) Azide Complexes with Nitriles and an Alkyne. *Organometallics* **2010**, *29*, 4282−4290.
(22) Liu, F.-C.; Liang, J.-E.; Jin, J.-Y.; Lin, Y.-L.; Chu, Y.-J.; Yang, P.-S.; Lee, G.-H.; Peng, S.-M. Reactions of molybdenum(II) azides Mo(η^3-C_3H_5)$(CO)_2(L_2)(N_3)$ (L_2 = en, dppe) toward dipolarophiles. *J. Organomet. Chem.* **2013**, *735*, 1−9.
(23) van Berkel, S. S.; Dirks, T. J.; Debets, M. F.; van Delft, F. L.; Cornelissen, J. J. L. M.; Nolte, R. J. M.; Rutjes, F. P. J. T. Metal-Free Triazole Formation as a Tool for Bioconjugation. *ChemBioChem* **2007**, *8*, 1504−1508.
(24) van Berkel, S. S.; Dirks, T. J.; Meeuwissen, S. A.; Pingen, D. L. L.; Boerman, O. C.; Laverman, P.; Van Delft, F. L.; Cornelissen, J. J. L. M.; Rutjes, F. P. J. T. Application of Metal-Free Triazole Formation in the Synthesis of Cyclic RGD-DTPA Conjugates. *ChemBioChem* **2008**, *9*, 1805−1815.
(25) Laverman, P.; Meeuwissen, S. A.; van Berkel, S. S.; Oyen, W. J. G.; van Delft, F. L.; Rutjes, F. P. J. T.; Boerman, O. C. In-depth evaluation of the cycloaddition-retro-Diels-Alder reaction for in vivo targeting with [^{111}In]-DTPA-RGD conjugates. *Nucl. Med. Biol.* **2009**, *36*, 749−757.
(26) Henry, L.; Schneider, C.; Mützel, B.; Simpson, P. V.; Nagel, C.; Fucke, K.; Schatzschneider, U. Amino acid bioconjugation via iClick reaction of an oxanorbornadiene-masked alkyne with a $Mn^I(bpy)(CO)_3$-coordinated azide. *Chem. Commun.* **2014**, *50*, 15692−15695.
(27) Schmid, P.; Maier, M.; Pfeiffer, H.; Belz, A.; Henry, L.; Friedrich, A.; Schönfeld, F.; Edkins, K.; Schatzschneider, U. Catalyst-free room-temperature iClick reaction of molybdenum(II) and tungsten(II) azide complexes with electron-poor alkynes: Structural preferences and kinetic studies. *Dalton Trans* **2017**, *46*, 13386−13396.
(28) Waag-Hiersch, L.; Mößeler, J.; Schatzschneider, U. Electronic influences on the stability and kinetics of Cp* rhodium(III) azide complexes in the iClick reaction with electron-poor alkynes. *Eur. J. Inorg. Chem.* **2017**, *2017*, 3024−3029.
(29) Powers, A. R.; Ghiviriga, I.; Abboud, K. A.; Veige, A. S. Au-iClick mirrors the mechanism of copper catalyzed azide-alkyne cycloaddition (CuAAC). *Dalton Trans* **2015**, *44*, 14747−14752.
(30) Cruchter, T.; Harms, K.; Meggers, E. Strain-promoted azide-alkyne cycloaddition with ruthenium(II)-azido complexes. *Chem. - Eur. J.* **2013**, *19*, 16682−16689.
(31) Farrer, N. J.; Sharma, G.; Sayers, R.; Shaili, E.; Sadler, P. J. Platinum(IV) azido complexes undergo copper-free click reactions with alkynes. *Dalton Trans* **2018**, *47*, 10553−10560.
(32) Paul, P.; Nag, K. Sulfur-nitrogen-bonded metal chelates. 18. 1,3-Dipolar cycloadditions to coordinated azide in nickel(II) complexes of the types [Ni(S-N-N)(N_3)] and [S-N-N)Ni(N_3)Ni-(N-N-S)](ClO_4). *Inorg. Chem.* **1987**, *26*, 2969−2974.
(33) Paul, P.; Chakladar, S.; Nag, K. Stereochemical aspects of the cycloaddition reaction products of the coordinated azide in palladium complexes [Pd(N-N-S)(N_3)]. *Inorg. Chim. Acta* **1990**, *170*, 27−35.
(34) Kim, Y.-J.; Joo, Y.-S.; Kwak, Y.-S.; Han, W.-S.; Lee, S.-W. Reaction of phenyl palladium(II) azido complexes with DMAD (dimethyl acetylendicarboxylate): Synthesis and structures of *trans*-[PdL(C_6H_5){N_3C2−3,4-(C(O)OMe)$_2$}] (L = PMe_3, PEt_3). *Bull. Korean Chem. Soc.* **2001**, *22*, 647−650.
(35) Kreutzer, P.; Weis, C.; Boehme, H.; Kemmerich, T.; Beck, W.; Spencer, C.; Mason, R. [2 + 3] Cycloaddition reactions of azido metal complexes and crystal structure of the cycloadduct of $(Ph_3P)Pd(N_3)_2$ with benzonitrile. *Z. Naturforsch., B: J. Chem. Sci.* **1972**, *27*, 745−747.
(36) Kreutzer, P.; Weis, C.; Bock, H.; Erbe, J.; Beck, W. Cycloadditionsreaktionen am Azidliganden von Phosphan-Komplexen von Palladium(II), Platin(II) und Iridium(I). *Chem. Ber.* **1983**, *116*, 2691−2707.
(37) Kamijo, S.; Jin, T.; Huo, Z.; Yamamoto, Y. Regiospecific synthesis of 2-allyl-1,2,3-triazoles by palladium-catalyzed 1,3-dipolar cycloaddition. *Tetrahedron Lett.* **2002**, *43*, 9707−9710.
(38) Kamijo, S.; Jin, T.; Huo, Z.; Yamamoto, Y. Synthesis of triazoles from nonactivated terminal alkynes via the three-component coupling reaction using a Pd(0)-Cu(I) bimetallic catalyst. *J. Am. Chem. Soc.* **2003**, *125*, 7786−7787.
(39) Kamijo, S.; Jin, T.; Yamamoto, Y. Four-component coupling reactions of silylacetylenes, allyl carbonates, and trimethylsilyl azide catalyzed by a Pd(0)-Cu(I) bimetallic catalyst. Fully substituted triazole synthesis from seemingly internal alkynes. *Tetrahedron Lett.* **2004**, *45*, 689−691.
(40) Büchi, J.; Aebi, A.; Deflorin, A.; Hurni, H. Synthese und pharmakologische Wirkung einiger Thiosemicarbazone von 8-Hydroxychinolin-Derivaten. *Helv. Chim. Acta* **1956**, *39*, 1676−1683.
(41) Kovala-Demertzi, D.; Domopoulou, A.; Demertzis, M. A.; Valle, G.; Papageorgiou, A. Palladium(II) complexes of 2-acetylpyridine N(4)-methyl, N(4)-ethyl and N(4)-phenyl-thiosemicarbazones. Crystal structure of chloro(2-acetylpyridine N(4)-methylthiosemicarbazonato) palladium(II). Synthesis, spectral studies, in vitro and in vivo antitumour activity. *J. Inorg. Biochem.* **1997**, *68*, 147−155.
(42) Demoro, B.; Sarniguet, C.; Sanchez-Delgado, R. A.; Rossi, M.; Liebowitz, D.; Caruso, F.; Olea-Azar, C.; Moreno, V.; Medeiros, A.; Comini, M. A.; Otero, L.; Gambino, D. New organoruthenium complexes with bioactive thiosemicarbazones as co-ligands: potential anti-trypanosomal agents. *Dalton Trans* **2012**, *41*, 1534−1543.
(43) Adams, M.; Li, Y.; Khot, H.; De Kock, C.; Smith, P. J.; Land, K.; Chibale, K.; Smith, G. S. The synthesis and antiparasitic activity of aryl- and ferrocenyl-derived thiosemicarbazone ruthenium(II)-arene complexes. *Dalton Trans* **2013**, *42*, 4677−4685.
(44) Arancibia, R.; Klahn, A. H.; Lapier, M.; Maya, J. D.; Ibanez, A.; Garland, M. T.; Carrere-Kremer, S.; Kremer, L.; Biot, C. Synthesis, characterization and in vitro anti-Trypanosoma cruzi and anti-Mycobacterium tuberculosis evaluations of cyrhetrenyl and ferrocenyl thiosemicarbazones. *J. Organomet. Chem.* **2014**, *755*, 1−6.
(45) Cipriani, M.; Toloza, J.; Bradford, L.; Putzu, E.; Vietes, M.; Curbelo, E.; Tomaz, A. I.; Garat, B.; Guerrero, J.; Gancheff, J. S.; Maya, J. D.; Azar, C. O.; Gambino, D.; Otero, L. Effect of the metal ions on the anti *T. cruzi* activity and mechanism of action of 5-nitrofuryl-containing thiosemibarbazone metal complexes. *Eur. J. Inorg. Chem.* **2014**, *2014*, 4677−4689.
(46) Oliveira, A. A.; Perdigao, G. M. C.; da Silva, J. G.; Souza-Fagundes, E. M.; Beraldo, H. Indium(III) complexes with 2-

DOI: 10.1021/acs.inorgchem.9b01304
Inorg. Chem. XXXX, XXX, XXX−XXX

acetylpyridine-derived thiosemicarbazones exhibit cytotoxic activity against human leukemia and solid tumor cell lines. *Polyhedron* **2017**, *135*, 72−78.
(47) Hamper, B. C.; Harrison, T.; Overman, L. E. Acetylenic esters from s-acylmethylenephosphoranes: Ethyl 4,4,4-trifluorotetrolate. *Org. Synth.* **1992**, *70*, 246−255.
(48) Kislukhin, A. A.; Higginson, C. J.; Finn, M. G. Aqueous-phase deactivation and intramolecular [2 + 2 + 2] cycloaddition of oxanorbornadiene esters. *Org. Lett.* **2011**, *13*, 1832−1835.
(49) Kowol, C. R.; Reisner, E.; Chiorescu, I.; Arion, V. B.; Galanski, M.; Deubel, D. V.; Keppler, B. K. An electrochemical study of antineoplastic gallium, iron and ruthenium complexes with redox noninnocent α-N-heterocyclic chalcogensemicarbazones. *Inorg. Chem.* **2008**, *47*, 11032−11047.
(50) McDermott, J. X.; White, J. F.; Whitesides, G. M. Thermal decomposition of bis(phosphine)platinum(II) metallocycles. *J. Am. Chem. Soc.* **1976**, *98*, 6521−6528.
(51) Drew, D.; Doyle, J. R.; Shaver, A. G. Cyclic diolefin complexes of platinum and palladium. *Inorg. Synth.* **2007**, *28*, 346−349.
(52) Still, B. M.; Kumar, P. G. A.; Aldrich-Wright, J. R.; Price, W. S. ^{195}Pt NMR - theory and application. *Chem. Soc. Rev.* **2007**, *36*, 665−686.
(53) D'Alessio, A.; Proietti, G.; Sica, G.; Scicchitano, B. M. Pathological and molecular features of glioblastoma and its peritumoral tissue. *Cancers* **2019**, *11*, 469.
(54) Wang, Y.; Kong, X.; Guo, Y.; Wang, R.; Ma, W. Continuous dose-intense Temozolomide and cisplatin in recurrent glioblastoma patients. *Medicine* **2017**, *96*, No. e6261.
(55) Akslen, L. A.; Andrersen, K. J.; Bjerkvig, R. Characteristics of human and rat glioma cells grown in a defined medium. *Anticancer Res.* **1988**, *8*, 797−804.
(56) Alam, M. N.; Huq, F. Comprehensive review on tumour active palladium compounds and structure-activity relationships. *Coord. Chem. Rev.* **2016**, *316*, 36−67.
(57) Fanelli, M.; Formica, M.; Fusi, V.; Giorgi, L.; Micheloni, M.; Paoli, P. New trends in platinum and palladium complexes as antineoplastic agents. *Coord. Chem. Rev.* **2016**, *310*, 41−79.
(58) Churusova, S. G.; Aleksanyan, D. V.; Rybalkina, E. Y.; Susova, O. Y.; Brunova, V. V.; Aysin, R. R.; Nelyubina, N. V.; Peregudov, A. S.; Gutsul, E. I.; Klemenkova, Z. S.; Kozlov, V. A. Highly cytotoxic palladium(II) pincer complexes based on picolinylamides functionalized with amino acids bearing ancillary S-donor groups. *Inorg. Chem.* **2017**, *56*, 9834−9850.
(59) Fulmer, G. R.; Miller, A. J. M.; Sherden, N. H.; Gottlieb, H. E.; Nudelman, A.; Stoltz, B. M.; Bercaw, J. E.; Goldberg, K. I. NMR Chemical Shifts of Trace Impurities: Common Laboratory Solvents, Organics, and Gases in Deuterated Solvents Relevant to the Organometallic Chemist. *Organometallics* **2010**, *29*, 2176−2179.
(60) Harris, R. K.; Becker, E. D.; Cabral de Menezes, S. M.; Goodfellow, R.; Granger, P. NMR nomenclature. Nuclear spin properties and conventions for chemical shifts. *Pure Appl. Chem.* **2001**, *73*, 1795−1818.

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Inorg. Chem. XXXX, XXX, XXX−XXX