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ARTICLE TYPE

Amino acid bioconjugation via iClick reaction of an oxanorbornadiene-masked alkyne with a $Mn^{I}(bpy)(CO)_3$-coordinated azide

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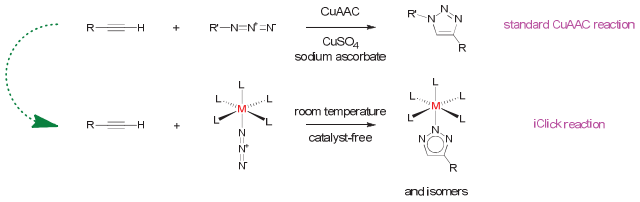
The catalyst-free room temperature iClick reaction of an unsymmetrically 2,3-disubstituted oxanorbornadiene (OND) as a "masked" alkyne equivalent with $[Mn(N_3)(bpy^{CH3,CH3})(CO)_3]$ leads to isolation of a phenylalanine ester bioconjugate, in which the model amino acid is linked to the metal moiety via a N-2-coordinated triazolate formed in a cycloaddition-retro-Diels-Alder (crDA) reaction sequence, in a novel approach to bioorthogonal coupling reactions based on metal-centered reactivity.

The site-selective modification of bio(macro)molecules is a key technology in the field of chemical biology. The plethora of functional groups present in peptides and proteins as well as oligonucleotides and carbohydrates but also other bioactive molecules requires specific bioorthogonal conjugation methods to introduce novel functionality to such systems.[1] Several different types of reactions, most of them based on "click" chemistry,[2] are now commonly utilized in this context. The most prominent is certainly the copper-catalyzed azide-alkyne cycloaddition (CuAAC), which selectively leads to 1,4-substituted triazoles.[3] However, the toxicity of copper is a concern for *in vitro* or *in vivo* applications and thus, catalyst-free variants have been developed, in particular based on cycloalkynes, in a reaction which has been termed strain-promoted azide-alkyne cycloaddition (SPAAC).[4] Other methods include the oxime ligation of aldehydes with aminoxy groups[5] or the inverse-electron demand Diels-Alder reaction of strained alkenes with tetrazines.[6]

When applied to metal complexes, these bioorthogonal coupling reactions usually take place in the periphery of the ligand sphere,[7, 8] at a position pointing away from the metal center. As an alternative, we are interested in novel, generally applicable methods for the conjugation of functional (organo)metal compounds to bio(macro)molecules which are based on an inherently metal-centered reactivity, which allows to tune the reaction kinetics by proper combination of metal center and (co)ligands. Metal-coordinated azides are a particularly attractive choice since they are easily accessible by ligand exchange from the corresponding halide complexes and might react with organic alkyne coupling partners already utilized in the context of other conjugation methods, leading to functionalized triazolate complexes in a catalyst-free process (Scheme 1). Some early work on cycloaddition reactions in the metal coordination sphere was summarized by Frühauf and additional applications were reviewed more recently.[9] Current research activities in the field, albeit still very limited, are especially focused on gold(I),[10] molybdenum(II),[11] and ruthenium(II) compounds.[12] In this context, Veige *et al.* introduced the term "iClick" (inorganic click) reaction for the cycloaddition of a metal-coordinated azide and an alkyne coupling partner.[13]



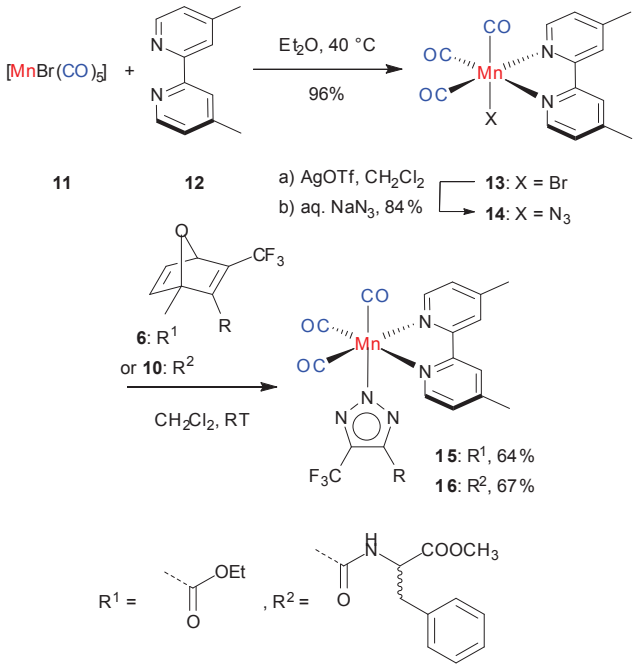
Scheme 1 Comparison of standard copper-catalyzed azide-alkyne cycloaddition reaction (CuAAC, top) and catalyst-free iClick reaction in the metal coordination sphere (bottom).

Besides their versatility, applications of iClick reactions in a biological context are still very rare. The groups of Gray and Metzler-Nolte reported on the coupling of linear phosphane gold(I) azides of the general formula $[(R_3P)AuN_3]$ to alkyne-functionalized dendrimers and peptides, respectively,[14] which leads to the gold-phosphane fragment coordinated to a carbon instead of a nitrogen atom of the triazolate. Another very interesting approach, recently described by Mirica *et al.*, is the iClick reaction of electron-poor alkynes with metal-azide fragments of enzyme active site models.[15] A major hurdle in the general application of this method to bioconjugation, however, is due to the fact that with the exception of the gold-based systems mentioned above, there seems to be a general requirement for the use of alkynes with strongly electron-withdrawing substituents like dimethyl acetylenedicarboxylate (DMAD) to ensure smooth coupling under mild conditions. This is a significant drawback, since such systems are very prone to Michael-type addition of nucleophiles like thiols and amines, which are highly abundant in biological systems.

Therefore, we wanted to explore "masked" alkynes in the form of functionalized oxanorbornadienes (ONDs) as a promising alternative.[16] In this context, 2,3-dicarboxy-7-oxanorbornadiene

dimethylester is easily accessible by Diels-Alder reaction of furan with dimethyl acetylenedicarboxylate (DMAD). However, the selective mono-functionalization of this compound turned out to be difficult, since both ester groups are equally labile towards hydrolysis, giving rise to inseparable product mixtures (data not shown). Therefore, we chose to replace one of the carboxylates by a trifluoromethyl group and prepared the corresponding oxanorbornadiene (OND) ester **6** in a four-step procedure from bromoacetic acid ethyl ester and 2-methylfuran (Scheme S1). Hydrolysis with dilute hydrochlorid acid led to acid **7**, which was then coupled to the amino group of phenylalanine methyl ester **9**, serving as a model system for functional oligopeptides, using EDCl and DMAP as the coupling agents, leading to conjugate **10** (Scheme 2).

Inspired by our ongoing interest in the biological activity of manganese(I) tricarbonyl complexes as molecular probes and delivery agents for carbon monoxide[7, 17] and further stimulated by the almost complete absence of reports on Mn azide compounds in iClick reactions,[18-20] $[Mn(N_3)(bpy^{CH3,CH3})(CO)_3]$ **14** was chosen as the coupling partner for ONDs **6** and **10**. This complex was easily prepared from manganese pentacarbonyl bromide **11** and 4,4'-dimethyl-2,2'-bipyridine **12** *via* the bromide complex $[MnBr(bpy^{CH3,CH3})(CO)_3]$ **13** by halide abstraction with silver triflate followed by addition of sodium azide (Scheme 2).



Scheme 2 Synthesis of manganese(I) azide complex **14** and room-temperature catalyst-free iClick reaction with "masked" alkynes **6** and **10** to give triazolate **15** and the corresponding amino acid bioconjugate **16**.

Stirring of **6** with **14** in dichloromethane at room temperature for 5 d under exclusion of light led to the isolation of a light yellow solid product. The symmetrical and antisymmetrical C≡O stretching vibrations experienced only a small shift from 2006, 1927, and 1886 cm^{-1} in starting material **14** to 2026, 1929, and 1912 cm^{-1} in product **15**, which also showed an additional peak at 1727 cm^{-1} at essentially the same position as the ester C=O vibration in coupling partner **6**. Furthermore, the signal due to the coordinated azide ligand at 2049 cm^{-1} disappeared. In addition, the ^{19}F NMR signal of the CF_3 group in the masked alkyne coupling partner serves as a sensitive NMR spectroscopic marker. While it appears at -62.9 ppm in ester **6** and is unaffected by hydrolysis to free acid **7**, the reaction with metal azide complex **14** leads to a shift by 3.0 ppm, with product **15** now showing a single ^{19}F NMR peak at -59.9 ppm. Single crystals suitable for X-ray structure analysis could be obtained by diffusion of *n*-hexane into a dichloromethane solution of crude **15**. This confirmed the successful tandem cycloaddition/retro-Diels-Alder (crDA) reaction[16] of oxanorbornadiene **6** with metal azide **14** (Supporting information, Figure S1 and Table S1). However, in contrast to the gold(I) azides,[10, 14] where the metal is bound to the C4 carbon atoms of the triazole ring, the product of the reaction with the manganese(I)-coordinated azide is a nitrogen-coordinated triazolate with the metal bound to the central N-2 nitrogen atom.

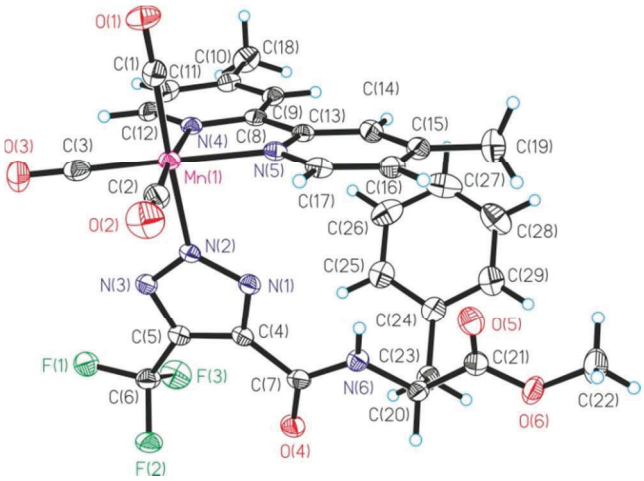


Fig. 1 Molecular structure of **16** with atomic displacement ellipsoids drawn at the 50% probability level.

Encouraged by these results, the OND-phenylalanine bioconjugate **10** was used as a model system for more complex bio(macro)molecules and reacted with azide complex **14** under similar conditions as identified above. Stirring at room temperature in dichloromethane for 7 d under exclusion of light to avoid decomposition of the $Mn(CO)_3$ moiety led to isolation of a yellow product in 67% yield. Again, the IR spectrum of **16** showed the absence of the azide band at around 2050 cm^{-1} and the C≡O peaks only marginally shifted compared to the starting material to 2025 and 1933 cm^{-1}. Two new bands were observed in the product at 1740 and 1680 cm^{-1} and assigned to the phenylalanine ester and amide C=O vibrations, respectively. The ^{19}F NMR also shows only a single peak at -59.6 ppm, which is shifted relative to the OND starting material by 6.2 ppm but at a position comparable to the corresponding CF_3 signal in **15**. The X-ray crystal structure confirms the connectivity of the phenylalanine-triazolate conjugate **16** resulting from the crDA reaction of **10** with **14** *via* the N-2 nitrogen atom of the aromatic heterocycle (Fig. 1). The octahedral coordination of the Mn(I) center is completed by the bpy ligand with a compressed N(4)-Mn(1)-N(5) angle of 79.05(8)° and three carbonyl ligands in a facial arrangement. No significant differences are seen in the Mn-C and C-O bond distances for the carbonyl groups *trans* to the triazolate *vs.* the bipy N donor atoms. Furthermore, bond lengths

in the crystal structures of **15** and **16** are comparable (Table S2). One notable difference between the two compounds, however, is the orientation of the mean plane of the triazolate (N(1)-N(2)-N(3)-C(4)-C(5)) relative to the pseudomirror plane between the two halves of the bpy ligand formed by the manganese center, the N(2) nitrogen of the triazolate and the mid-point of the central C-C bond of the bipy. In **15**, the triazolate is oriented almost perpendicular to this central axis of the bpy and essentially bisects the C(2)-Mn(1)-C(3) angle with a deviation of only 7.0°. In contrast, for **16**, this angle is increased to 59.1° and the triazolate mean plane is now in an almost eclipsed orientation relative to the C(3)-O(3) carbonyl ligand. A hydrogen bond exists between the ester carbonyl O(5) atom and the H(19b) proton of one of the bipyridine methyl groups with a O(5)-C(19) distance of 3.463 Å and a O(5)-H(19b)-C(19) angle of 125.6°. Since there are additional short intermolecular contacts, it is difficult to discern how much this intramolecular interaction contributes to the stabilization of the observed conformation. Only one other X-ray crystal structure of a triazolate coordinated to a *fac*-$Mn(CO)_3$ moiety is known in the literature,[19] with the octahedral ligand sphere of the metal however completed by a P-N chelating 1-dimethylamino-2-diphenylphosphinoethane ligand instead of a N-N coordinated bipy as in **15** and **16**. Other closely related compounds also structurally characterized retain the $Mn(bpy)(CO)_3$ coordination sphere but incorporate a sixth axial imidazole[21] or thiazole[22] ligand. Finally, the X-ray crystal structure of a tetrazolate complex with an $Mn(CO)_3$(P-P) core is based on the 1,2-bis(diethylphosphino)ethane ligand.[18] Besides these variations in the axial N ligand (triazolate *vs.* tetrazolate *vs.* imidazole *vs.* thiazole) and the nature of the chelator (N-N *vs.* P-N *vs.* P-P), there are very little differences in the Mn-N and M-C as well as C-O distances.

To further study the conformational preference of **15**, a relaxed surface scan was carried out with DFT at the RI-BP86 def2-TZVP/def2-TZVP/J level of theory. The perpendicular orientation of the triazolate mean plane relative to the central C2-C2' axis of the bpy ligand with the CF_3 group pointing towards the bpy turned out to be the lowest energy conformation. However, the parallel arrangement of the triazolate and the C2-C2' axis is higher in energy by only about 0.1 kcal mol^{-1}. A much less favorable orientation results from a perpendicular arrangement of the triazolate relative to the C2-C2' axis, but with the ester group pointing towards the bpy ligand, which is higher in energy by 0.9 kcal mol^{-1} compared to the one with the CF_3 aligned this way. Not surprisingly, the four possible conformations with an eclipsed orientation of the triazolate and a carbonyl ligand are transition states in the interconversion between the four minimum structures. However, the ones with the CF_3 group pointing towards the bpy are still somewhat lower in energy (by 0.3 kcal mol^{-1}) than those with the ester moiety in that orientation. With a maximum barrier height of 1.3 kcal mol^{-1}, the rotation around the Mn-N2 axis is much more facile than, for example, in ethane (ΔE ~ 2.9 kcal mol^{-1})[23] and thus the conformations are expected to freely interconvert at room temperature.

In summary, we have utilized a catalyst-free iClick reaction of an unsymmetrically 2,3-disubstituted oxanorbornadiene (OND) as a "masked" alkyne equivalent with a manganese(I) tricarbonyl azide complex to prepare a novel triazolate-linked $Mn(bpy)(CO)_3$-phenylalanine bioconjugate by simple stirring of the two reactants at room temperature for an extended period of time. Symmetrical binding *via* the triazolate N-2 nitrogen atom was demonstrated by X-ray crystallography, which additionally revealed weak interactions between the Phe phenyl ring and some bipy methyl and ring protons responsible for the observed solid-state conformation.

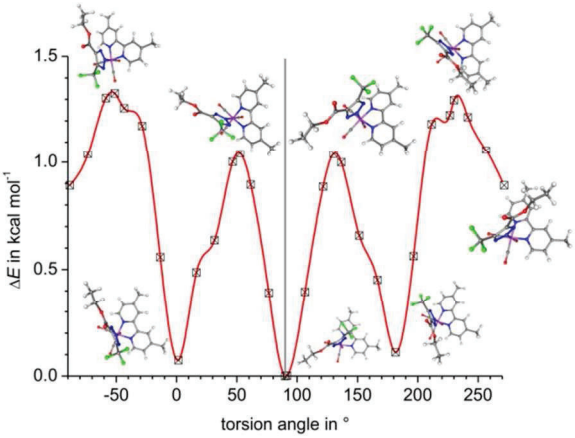


Fig. 2 Conformational energy diagram of **15** for variation of the torsion angle between the triazolate mean plane and the bpy C2-C2' axis calculated with DFT (RI-BP86, def2-TZVP/def2-TZVP/J).

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Notes and references

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† Electronic Supplementary Information (ESI) available: synthetic procedures, X-ray crystal structure of **15**, crystallographic data, and relevant bond distances and angles for **15** and **16**. CCDC 951372 (**15**) and 951371 (**16**). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b000000x/

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Amino acid bioconjugation via iClick reaction of an oxanorbornadiene-masked alkyne with a $Mn^{I}(bpy)(CO)_3$-coordinated azide

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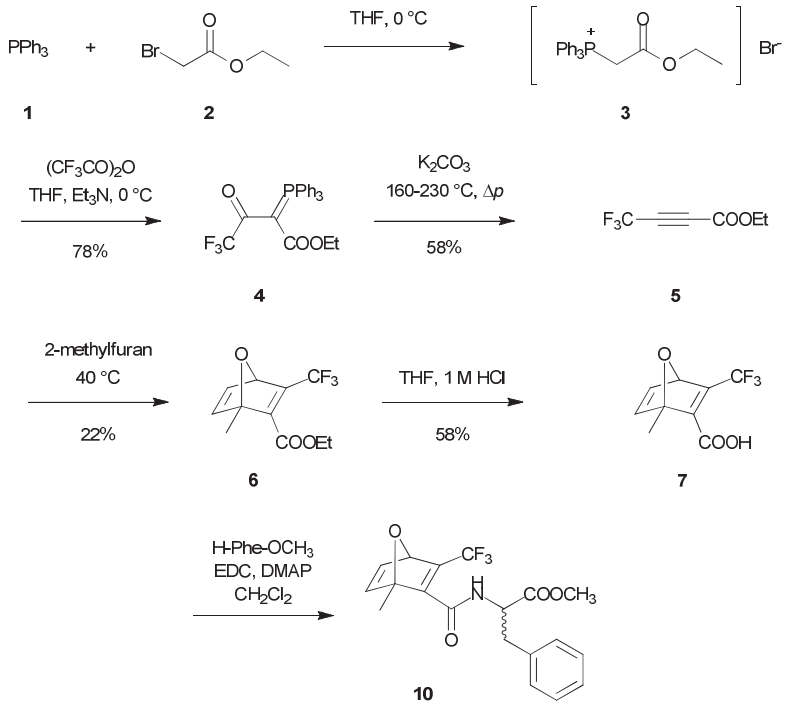
Supporting Information



Scheme S1 Synthesis of oxanorbornadiene(OND)-masked alkynes **6** and **10** for use in "iClick" reactions with metal-coordinated azides.

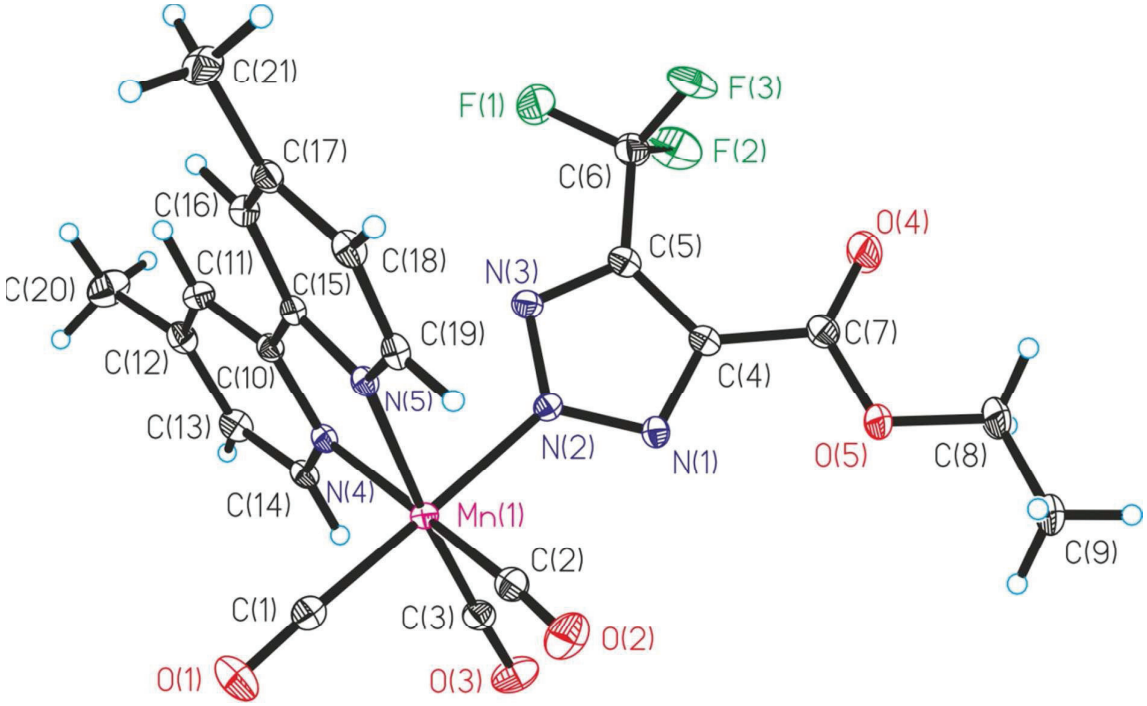


Fig. S1 Molecular structure of **15** with atomic displacement ellipsoids drawn at the 50% probability level.

Experimental

General remarks

Reactions were carried out in oven-dried Schlenk glassware under an atmosphere of pure dinitrogen and reaction vessels were protected from light by wrapping them with aluminium foil if necessary, in particular for the carbonyl complexes. All chemicals were purchased from commercial sources and used as received. Manganese pentacarbonyl bromide was supplied by Strem. IR spectra were measured on pure solid samples using a Nicolet 380 FT-IR spectrometer fitted with a smart iTR accessory. ^{1}H, ^{13}C, ^{19}F, and ^{31}P NMR spectra were recorded on Bruker Avance 200, DPX 200, DRX 300, Avance 400, and Avance 500 spectrometers (^{1}H, 199.93 and 500.13 MHz; ^{13}C, 50.27, 75.48 and 125.76 MHz; ^{19}F, 188.09, 376.50, and 470.59 MHz; ^{31}P, 80.93 MHz). The elemental composition of the compounds was determined with a Vario MICRO cube CHN analyzer.

HPLC analysis and purification

The analytical and preparative HPLC chromatography was performed on a Dionex Ultimate 3000 system equipped with a diode array detector and a ReproSil 100 column (C18, 5 μm, 4.6 mm or 10 mm diameter, 250 mm length) using a linear gradient gradient of 20–90% acetonitrile/water over 40 min at a flow rate of 0.6 mL min^{-1} for analytical and 3.0 mL min^{-1} for preparative chromatography.

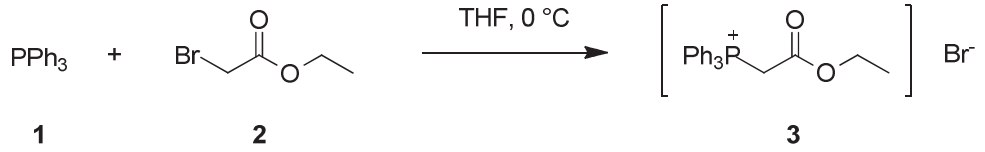
X-ray crystallographic data collection and refinement of structures 15 and 16

Clear light yellow single crystals of **15** were obtained by evaporation of a dichloromethane/*n*-hexane solution, those of **16** by diffusion of *n*-hexane into a solution of the compound in dichloromethane. A suitable single crystal was selected, soaked in perfluoro polyether oil, and mounted on a MiTeGen sample holder. Data were collected on a Nonius Kappa three circle diffractometer utilizing graphite monochromated Mo Kα radiation (λ = 0.71073 Å) from a rotating anode tube run at 50 kV and 30 mA, equipped with an APEXII area detector. The instrument was equipped with an open-flow N_2 Cryoflex II (Bruker) device and measurements were performed at 100 and 296 K, respectively. Using Olex2,[1] the structure was solved with the olex2.solve structure solution program,[2] using the Charge Flipping solution method. The model was refined with the olex2.refine refinement package using Gauss-Newton minimisation.[3]

Density functional theory calculations

DFT calculations were carried out on the Linux cluster of the Leibniz-Rechenzentrum (LRZ) in Munich with ORCA version 2.8,[4] using the BP86 functional with the resolution-of-the-identity (RI) approximation, a def2-TZVP/def2-TZVP/J basis set,[5] the `tightscf` and `grid4` options, and the COSMO solvation model with dimethylsulfoxide as the solvent for geometry optimization and subsequent calculation of vibrational frequencies to characterize the structure obtained as a minimum by inspection for absence of imaginary modes. Then, a relaxed surface scan was carried out in 15° steps for the full 360° rotation of the triazolate mean plane relative to the central C2-C2' axis of the 2,2'-bipyridine ligand while allowing all other variables to relax. The perpendicular orientation of the triazolate ring relative to the bpy C2-C2' axis with the CF_3 group pointing towards the bpy ligand is set to 90°. Clockwise rotation then gives negative angles and counter-clockwise rotation positive ones. The maxima on the resulting potential energy curve where then further characterized as transition states using the `optTS` keyword in separate runs.

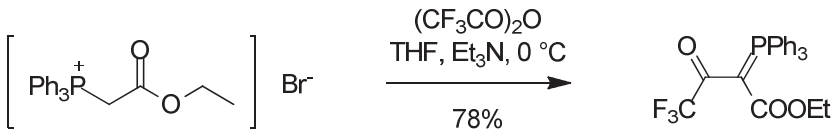
Synthesis of (carboxymethyl)triphenylphosphonium bromide (3)[6]



1 **2** **3**

Under a dinitrogen atmosphere, triphenylphosphane **1** (131.2 g, 0.50 mol) was dissolved in anhydrous degassed tetrahydrofuran (450 mL) in a 1 L flask and cooled in an ice bath. Then, bromoacetic acid ethyl ester **2** (56 mL, 84.3 g, 0.51 mol) was slowly added over 25 min at 0 °C. The reaction mixture turned turbid and was allowed to warm to room temperature with continued stirring overnight. The white solid which had precipiated was directly used in the next step without isolation.

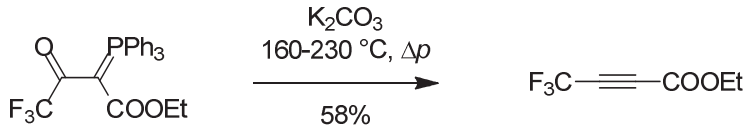
Synthesis of 4,4,4-trifluoro-3-oxo-2-(triphenylphosphoranylidene)butanoic acid ethyl ester (4)[6, 7]



3 **4**

The white phosphonium salt product **3** obtained in the previous step was dissolved again by addition of more anhydrous degassed tetrahydrofuran (450 mL). Then, the reaction mixture was cooled to 0 °C and triethylamine (150 mL, 108.9 g, 1.08 mol) was added dropwise over 20 min while keeping the temperature at 0 °C. Stirring was continued for another 30 min and then, trifluoroacetic acid anhydride (78 mL, 117.1 g, 0.56 mol) was added over 2 h while keeping the temperature at 0 °C. Then, the reaction mixture was allowed to warm up to room temperature overnight. The white solid which had precipitated was collected by filtration, washed with ice-cold tetrahydrofuran (3 × 150 mL) and discarded. The filtrate was concentrated under vacuum to obtain an orange oil which became solid upon cooling. This crude product was dissolved in hot methanol (900 mL) and then water (500 mL) added to precipitate the product. The flask was stored in a refrigerator at 4 °C overnight and the resulting solid collected by filtration, washed with ice-cold water (3 × 100 mL), and the pale yellow product dried under vacuum overnight. Yield: 78% (172.6 g, 0.39 mol). Elemental analysis (%): calc. for $C_{24}H_{20}F_3O_3P$: C 64.87, H 4.54, found: C 65.40, H 4.55; IR (ATR, cm^{-1}): 3072 (w), 2964 (w), 1695 (s), 1586 (s), 1439 (m), 1391 (m), 1256 (s), 1152 (s), 1073 (s), 1012 (m), 753 (m); ^{1}H NMR (199.93 MHz, $CDCl_3$): δ 7.45–7.72 (m, 15H, C_6H_5), 3.83 (q, 2H, CH_2CH_3, $^3J_{H\text{-}H}$ = 7.2 Hz), 0.89 (t, 3H, CH_2CH_3, $^3J_{H\text{-}H}$ = 7.1 Hz) ppm; ^{13}C NMR (75.48 MHz, $CDCl_3$): δ 175.0 (dd, $COCF_3$, $^2J_{C\text{-}F}$ = 34.2 Hz, $^2J_{C\text{-}P}$ = 6.2 Hz), 165.8 (d, C=O $^2J_{C\text{-}P}$ = 13.0 Hz), 133.3 (d, C-3, $^3J_{C\text{-}P}$ = 10.1 Hz), 132.5 (d, C-4, $^4J_{C\text{-}P}$ = 3.0 Hz), 128.9 (d, C-2, $^2J_{C\text{-}P}$ = 12.8 Hz), 124.1 (d, C-1, $^1J_{C\text{-}P}$ = 93.8 Hz), 118.0 (dd, CF_3, $^1J_{C\text{-}F}$ = 289.3 Hz, $^3J_{C\text{-}P}$ = 14.8 Hz), 70.1 (d, C=P, $^1J_{C\text{-}P}$ = 106.7 Hz) 60.0 (s, CH_2CH_3), 13.6 (s, CH_2CH_3); ^{19}F NMR (188.09 MHz, $CDCl_3$): δ -71.4 ($^3J_{P\text{-}F}$ = 1.7 Hz) ppm; ^{31}P NMR (80.93 MHz, $CDCl_3$): δ 19.5 ppm.

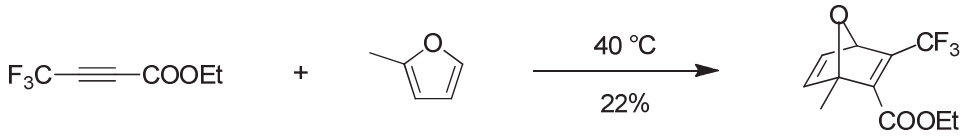
Synthesis of 4,4,4-trifluoro-2-butynoic acid ethyl ester (5)[6]



4 **5**

Solid 4,4,4-trifluoro-3-oxo-2-(triphenylphosphoranylidene)butanoic acid ethyl ester **4** (50.0 g, 113 mmol) was placed in a 250 mL three-neck flask and mixed with potassium carbonate (10.0 g, 72 mmol). After addition of a magnetic stirring bar, the flask was fitted *via* a wide-bore glass tube to a Schlenk flask which was cooled by immersion in liquid dinitrogen in a Dewar vessel. This setup was connected to the vacuum line *via* an efficient cold trap also immersed in liquid dinitrogen. The pressure was carefully reduced to $1.5 \cdot 10^{-2}$ mbar and the solid mixture then heated with an oil bath to 50 °C over 10 min. Then, the temperature was rised to 160 °C over 2 h. At a bath temperature of 150 °C, the mixture started to melt. This temperature was kept until melting of the mixture was complete. Heating was then continued for 2.5 h at 230 °C and the product collected in the cooled Schlenk flask. It is mandatory to ensure that there is always sufficient liquid dinitrogen present in the Dewar and cold trap. The collected yellow liquid was cooled to room temperature. If some material already solidifies in the glass tube, it can be removed by melting with a heatgun. The crude material was purified by fractional destillation and the product collected as a colorless oil with a boiling point of 89–94 °C at atmospheric pressure. Yield: 58% (10.99 g, 66 mmol). Elemental analysis (%): calc. for $C_6H_5F_3O_2$: C 43.39, H 3.03, found: C 43.55, H 3.09; IR (ATR, cm^{-1}): 1728 (s), 1266 (s), 1154 (s), 1020 (m); ^{1}H NMR (500.13 MHz, $CDCl_3$): δ 4.32 (q, 2H, CH_2, $^3J_{H\text{-}H}$ = 7.2 Hz), 1.34 (t, 3H, CH_3, $^3J_{H\text{-}H}$ = 7.2 Hz) ppm; ^{13}C NMR (125.76 MHz, $CDCl_3$): δ 151.1 (d, *C*OO, $^4J_{C\text{-}F}$ = 1.5 Hz), 113.8 (q, *C*F_3, $^1J_{C\text{-}F}$ = 260.1 Hz,), 77.1 (m, *C*CO), 70.3 (q, *C*CF_3, $^2J_{C\text{-}F}$ = 54.7 Hz), 63.9 (s, *C*H_2), 14.2 (s, *C*H_3) ppm; ^{19}F NMR (188.12 MHz, $CDCl_3$): δ -52.3 ppm.

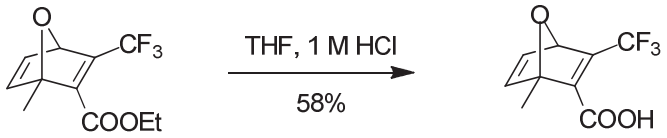
Synthesis of 1-methyl-3-trifluoromethyl-7-oxabicyclo[2.2.1]hepta-2,5-dien-2-carboxylic acid ethyl ester (6)[8]



5 **6**

Under dinitrogen, 2-methylfuran (5.91 g, 72 mmol) and 4,4,4-trifluoro-2-butynoic acid ethyl ester **5** (10.0 g, 60 mmol) were stirred without any solvent at 40 °C for 7 d. The resulting crude product was purified by two runs of column chromatography on silica, first using *n*-hexane/ethyl acetate (5:1, v/v) and then *n*-hexane/ethyl acetate (8:1, v/v) as the eluent. The product was obtained as a colorless oil. Yield: 22% (3.30 g, 13 mmol). Elemental analysis (%): calc. for $C_{11}H_{11}F_3O_3$: C 53.23, H 4.47, found: C 52.76, H 4.51; IR (ATR, cm^{-1}): 2988 (w), 1726 (m), 1667 (w), 1461 (w), 1382 (w), 1273 (s), 1237 (s), 1201 (s), 1126 (s), 1087 (m), 1020 (w), 854 (w); ^{1}H NMR (199.93 MHz, $CDCl_3$): δ 7.15 (dd, 1H, H-5, $^3J_{H\text{-}H}$ = 5.2 Hz, $^3J_{H\text{-}H}$ = 1.8 Hz), 7.04 (d, 1H, H-6, $^3J_{H\text{-}H}$ = 5.2 Hz), 5.52 (d, 1H, H-4, $^3J_{H\text{-}H}$ = 1.8 Hz), 4.16–4.42 (m, 2H, CH_2CH$_3$), 1.81 (s, 3H, CCH_3), 1.31 (t, 3H, CH$_2$CH_3, $^3J_{H\text{-}H}$ = 7.1 Hz) ppm; ^{13}C NMR (125.77 MHz, $CDCl_3$): δ 163.5 (q, *C*OO, $^4J_{C\text{-}F}$ = 1.4 Hz), 153.4 (q, C-2, $^3J_{C\text{-}F}$ = 5.0 Hz), 150.7 (q, C-3, $^2J_{C\text{-}F}$ = 37.0 Hz), 147.0 (s, C-6), 144.2 (s, C-5), 123.1 (q, *C*F$_3$, $^1J_{C\text{-}F}$ = 269.2 Hz), 94.5 (s, C-1), 82.7 (q, C-4, $^3J_{C\text{-}F}$ = 2.5 Hz), 62.1 (s, *C*H$_2$), 15.5 (s, *C*H$_3$), 14.3 (s, *C*H$_3$); ^{19}F NMR (188.12 MHz, $CDCl_3$): δ -62.9 ppm.

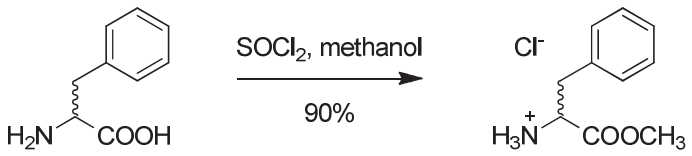
Synthesis of 1-methyl-3-trifluoromethyl-7-oxabicyclo[2.2.1]hepta-2,5-dien-2-carboxylic acid (7)



6 **7**

1-Methyl-3-trifluoromethyl-7-oxabicyclo[2.2.1]hepta-2,5-dien-2-carboxylic acid ethyl ester **6** (2.01 g, 8.1 mmol) was dissolved in tetrahydrofuran (50 mL) and cooled in an ice bath. Then, sodium hydroxide (0.80 g, 20 mmol) in water (20 mL) was added dropwise over 15 min and the mixture stirred at room temperature overnight. The volume of the solution was reduced to half and then water (50 mL) added. The mixture was extracted with ethyl acetate (2 × 50 mL) and the combined organic phases discarded. The aqueous phase was adjused to pH = 2 with 1 M hydrochloric acid and extracted with ethyl acetate (3 × 100 mL). These combined organic phases were dried over magnesium sulfate, filtered and the solvent removed under reduced pressure. The resulting brown oil was dissolved in *n*-hexane (150 mL), some insoluble brown material removed by filtration, and the solvent removed under reduced pressure to obtain a yellow solid. Yield: 58% (1.04 g, 4.7 mmol). Elemental analysis (%): calc. for $C_9H_7F_3O_3$: C 49.10, H 3.20, found: C 49.65, H 3.41; IR (ATR, cm^{-1}): 2834 (w), 1696 (s), 1650 (m), 1427 (m), 1314 (s), 1277 (s), 1125 (s), 919 (m), 853 (m); ^{1}H NMR (500.13 MHz, $CDCl_3$): δ 7.09–7.11 (m, 1H, H-5), 6.98 (d, 1H, H-6, ^3J = 5.2 Hz), 5.50 (d, 1H, H-4, $^3J_{H\text{-}H}$ = 2.0 Hz), 1.80 (s, 3H, CCH_3) ppm; ^{13}C NMR (75.48 MHz, $CDCl_3$): δ 167.9 (*C*OOH), 153.6 (q, C-3, $^2J_{C\text{-}F}$ = 37.5 Hz), 152.1 (q, C-2, $^3J_{C\text{-}F}$ = 4.9 Hz), 146.8 (s, C-6), 143.9 (s, C-5), 121.5 (q, *C*F$_3$, $^1J_{C\text{-}F}$ = 269.7 Hz), 94.4 (s, C-1), 82.6 (q, C-4, $^3J_{C\text{-}F}$ = 2.6 Hz), 15.4 (s, C*C*H$_3$) ppm; ^{19}F NMR (470.59 MHz, $CDCl_3$): δ -62.9 ppm.

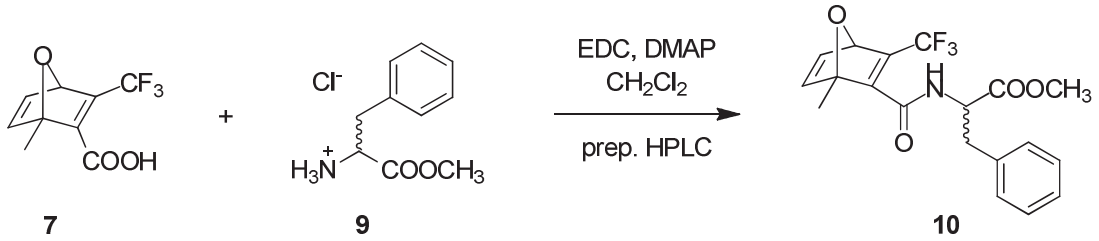
Synthesis of DL-phenylalanine methylester hydrochloride (9)



8 **9**

Under cooling with ice, thionylchloride (10 mL, 16.4 g, 138 mmol) was added dropwise to anhydrous methanol (60 mL). Then, a suspension of DL-phenylalanine **8** (5.0 g, 30 mmol) in methanol (30 mL) was added under cooling with ice and the resulting mixture heated to reflux for 14 h. After cooling to room temperature, the solvent was removed under vacuum and the remaining white residue redissolved in a minimum amount of methanol. This solution was added dropwise into diethylether (250 mL). A white precipitate formed which was filtered off, washed with diethylether (3 × 25 mL), and dried under vacuum to give the product as a white solid. Yield: 90% (5.8 g, 27 mmol). Elemental analysis (%): calc. for $C_{10}H_{14}ClNO_2$: C 55.69, H 6.54, N 6.49, found: C 55.39, H 6.57, N 6.48; IR (ATR, cm^{-1}): 2914 (s), 2840 (s), 2620 (m), 1744 (s), 1238 (s), 741 (s), 701 (s); ^{1}H NMR (200.13 MHz, DMSO-d_6): δ 8.78 (s, 2H, NH_2), 7.23–7.35 (m, 5H, C$_6H_5$), 4.22 (dd, 1H, H-α, ^3J = 7.6 Hz, ^3J = 5.6 Hz), 3.65 (s, 3H, CH_3), 3.22 (dd, 1H, H-β, ^3J = 14.0 Hz, ^3J = 5.7 Hz), 3.10 (dd, 1H, H-β, ^3J = 13.8 Hz, ^3J = 7.4 Hz) ppm; ^{13}C NMR (50.62 MHz, DMSO-d_6): δ 169.3 (C=O), 134.7 (C_6H_5), 129.3 (C_6H_5), 128.5 (C_6H_5), 127.2 (C_6H_5), 53.2 (OCH_3), 52.5 (C-α), 35.8 (C-β) ppm.

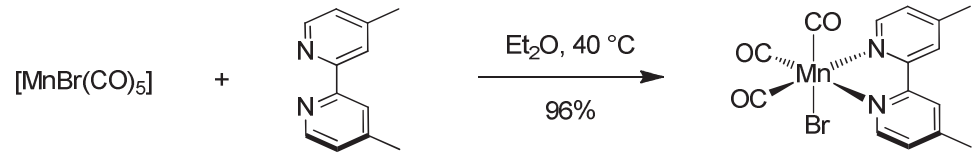
Synthesis of *N*-((1-methyl-3-trifluoromethyl-7-oxabicyclo[2.2.1]hepta-2,5-dien-2-yl)-carbonyl)-L-phenylalanine methyl ester (10)



7 **9** **10**

1-Methyl-3-trifluoromethyl-7-oxabicyclo[2.2.1]hepta-2,5-dien-2-carboxylic acid **7** (510 mg, 2.3 mmol) and DL-Phenylalanine methylester hydrochloride **9** (500 mg, 2.3 mmol) were dissolved in dichloromethane (20 mL). Then, 4-(*N*,*N*-dimethylamino)pyridine (DMAP, 567 mg, 4.6 mmol) was added to the solution. After cooling in an ice bath, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDCl, 396 mg, 2.1 mmol) was added and the reaction mixture stirred at 0 °C for 30 min. It was then allowed to warm to room temperature overnight. The reaction was quenched by addition of 2 M hydrochloric acid (~2 mL) until the pH has dropped to 1–2, and then the mixture is extracted with dichloromethane (2 × 15 mL). The combined organic layers were dried over magnesium sulfate and concentrated under vaccum. The resulting orange oil was redissolved in dichloromethane (10 mL) and extracted with 0.1 M aqueous sodium hydrogen carbonate (3 × 10 mL). The organic phase was separated, dried over magnesium sulfate, and the solvent removed under vacuum. A part of the oily orange crude product was dissolved in a mixture of acetonitrile and water and purified in several batches by preparative HPLC as described above. The product was obtained as a white solid after lyophilization of the combined batches on a scale of about 50 mg. Due to the small amount of sample purified this way, no elemental analysis was carried out. IR (ATR, cm^{-1}): 3275 (m), 1741 (m), 1631 (s), 1549 (m), 1273 (w), 1168 (m), 1111 (s); ^{1}H NMR (199.93 MHz, CD_3OD): δ isomer A: 7.20–7.30 (m, 5H, C_6H_5), 7.12–7.19 (m, 1H, H-5), 6.99 (d, 1H, H-6, ^3J = 5.2 Hz), 5.50 (t, 1H, H-4, ^3J = 1.8 Hz), 4.90–4.98 (m, 1H, H-α), 3.72 (s, 3H, COOCH_3), 3.18–3.28 (m, 2H, H-β), 1.56 (s, 3H, CCH_3) ppm; isomer A*: 7.20–7.30 (m, 5H, C_6H_5), 7.12–7.19 (m, 1H, H-5), 6.95 (d, 1H, H-6, ^3J = 5.2 Hz), 5.50 (t, 1H, H-4, ^3J = 1.8 Hz), 4.68–4.79 (m, 1H, H-α), 3.71 (s, 3H, COOCH_3), 2.87–3.02 (m, 2H, H-β), 1.26 (s, 3H, CCH_3) ppm; ^{19}F NMR (188.12 MHz, CD_3OD): δ isomer A: -65.67, isomer A:* -65.87 ppm; no ^{13}C NMR spectra were recorded due to the low amount of sample available; HPLC: t_r = 22.4 min.

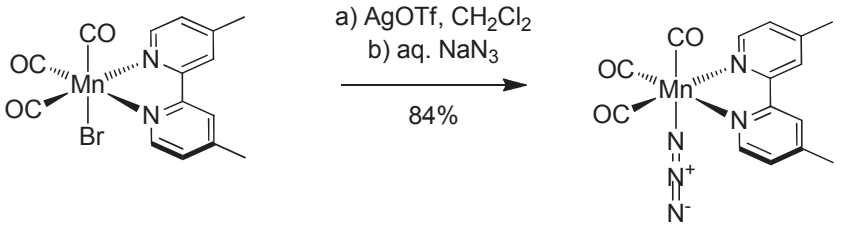
Synthesis of (*OC*-6-33)-bromotricarbonyl(4,4'-dimethyl-2,2'-bipyridine)manganese(I) [MnBr(bpy^{CH3,CH3})(CO)$_3$] (13)[9]



11 **12** **13**

Manganese pentacarbonyl bromide **11** (500 mg, 1.82 mmol) and 4,4'-dimethyl-2,2'-bipyridine (370 mg, 2.01 mmol) were dissolved in diethyl ether (40 mL) and heated to reflux for 3 h under exclusion of light. The precipitate formed was filtered off, washed with diethyl ether (3 × 10 mL), and dried under vacuum to obtain a yellow powder. Yield: 96% (705 mg, 1.75 mmol). Elemental analysis (%): calc. for $C_{15}H_{12}Br_1Mn_1N_2O_3$: C 44.69, H 3.00, N 6.95, found: C 44.97, H 3.03, N 6.97; IR (ATR, cm^{-1}): 2021 (s), 1939 (s), 1926 (s), 1892 (s), 1620 (m), 827 (m); ^{1}H NMR (200.13 MHz, DMSO-d_6): δ 8.98 (d, 2H, H-6/6', ^3J = 5.4 Hz), 8.48 (s, 2H, H-3/3'), 7.54 (d, 2H, H-5/5', ^3J = 5.2 Hz), 2.52 (s, 6H, CH_3) ppm; ^{13}C NMR (50.32 MHz, DMSO-d_6): δ 154.8 (C-2), 152.7 (C-6), 151.0 (C-3), 127.5 (C-5), 123.8 (C-4), 20.6 (*C*H$_3$) ppm. As commonly encountered with similar manganese carbonyl complexes, the ^{13}C NMR signals of the coordinated carbonyl ligands could not be observed.

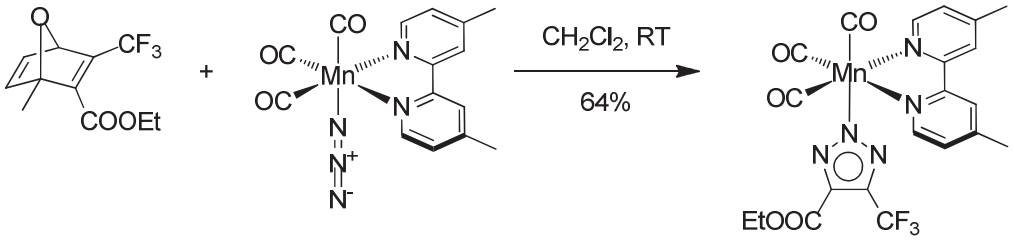
Synthesis of (*OC*-6-33)-azidotricarbonyl(4,4'-dimethyl-2,2'-bipyridine)manganese(I) [Mn(N_3)(bpy^{CH3,CH3})($CO)_3$] (14)



13 **14**

[MnBr(bpy^{CH3,CH3})($CO)_3$] **13** (300 mg, 0.74 mmol) was dissolved in anhydrous degassed dichloromethane (60 mL). Then, silver trifluoromethanesulfonate (228 mg, 0.89 mmol) was added and the mixture stirred under exclusion of light at room temperature for 3 h. The white solid which had precipitated was filtered off and an aqueous solution of sodium azide (138 mg, 2.12 mmol) added. Stirring was continued under exclusion of light overnight. Then, the two phases were separated and the organic phase washed with water (3 × 15 mL). The organic phase was dried over magnesium sulfate and the solvent removed under reduced pressure to obtain the product as a yellow solid which was dried under vacuum. Yield: 84% (228 mg, 0.62 mmol). Elemental analysis (%): calc. for $C_{15}H_{12}Mn_1N_5O_3$: C 49.33, H 3.31, N 19.18, found: C 49.30, H 3.28, N 18.62; IR (ATR, cm^{-1}): 2049 (m), 2006 (s), 1927 (s), 1886 (s), 1620 (s); ^{1}H NMR (200.13 MHz, DMSO-d_6): δ 8.92 (d, 2H, H-6/6', ^3J = 6.0 Hz), 8.53 (s, 2H, H-3/3'), 7.57 (d, 2H, H-5/5', ^3J = 6.0 Hz), 2.53 (s, 6H, CH_3) ppm; ^{13}C NMR (50.32 MHz, DMSO-d_6): δ 154.6 (C-2), 152.3 (C-6), 151.3 (C-3), 127.7 (C-5), 123.8 (C-4), 20.6 (*C*H_3) ppm. As commonly encountered with similar manganese carbonyl complexes, the ^{13}C NMR signals of the coordinated carbonyl ligands could not be observed.

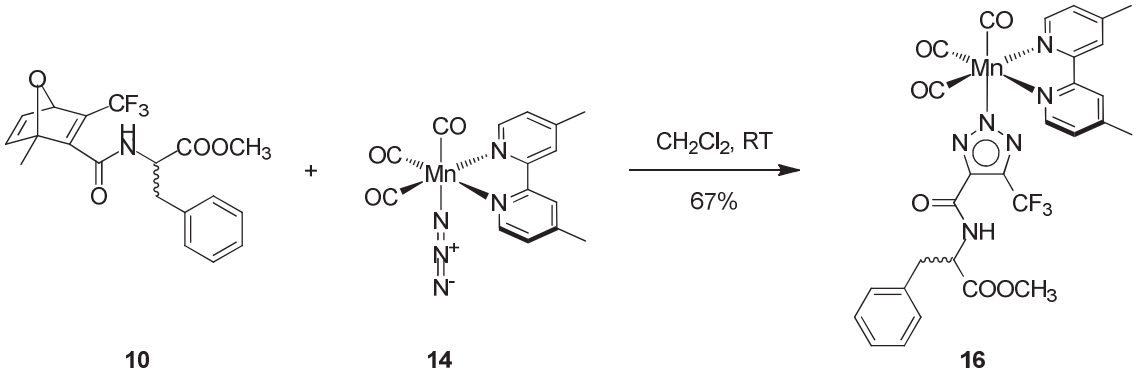
Synthesis of (*OC*-6-33)-(4-carbethoxy-5-trifluoromethyl-2*H*-1,2,3-triazolato-N^2) tricarbonyl(4,4'-dimethyl-2,2'-bipyridine)manganese(I) [Mn(triazolate^{COOEt,CF3})(bpy^{CH3,CH3})(CO)$_3$] (15)



6 **14** **15**

1-Methyl-3-trifluoromethyl-7-oxabicyclo[2.2.1]hepta-2,5-dien-2-carboxylic acid ethyl **6** ester (63.7 mg, 0.27 mmol) and [Mn(N$_3$)(bpy^{CH3,CH3})(CO)$_3$] **14** (50.0 mg, 0.14 mmol) were dissolved in degassed anhydrous dichloromethane (20 mL) and the mixture stirred for 5 d at room temperature under exclusion of light. Then, the solvent was removed under pressure and the resulting yellow solid washed with *n*-hexane (3 × 5 mL) and dried in vacuum. Diffusion of *n*-hexane into a solution of the crude product in dichloromethane gave yellow single crystals which were suitable for X-ray structure analysis. Yield: 64% (47.0 mg, 0.09 mmol). Elemental analysis (%): calc. for $C_{21}H_{17}F_3Mn_1N_5O_5$: C 47.47, H 3.22, N 13.18, found: C 46.70, H 3.35, N 12.04; IR (ATR, cm^{-1}): 2026 (s), 1929 (s), 1912 (s), 1727 (m), 1622 (w), 1546 (w), 1433 (w), 1307 (m), 1154 (m), 1130 (m), 1048 (m), 824 (w); ^{1}H NMR (500.13 MHz, $CDCl_3$): δ 9.06 (d, 2H, H-6/6', ^3J = 5.6 Hz), 7.82 (s, 2H, H-3/3'), 7.31 (d, 2H, H-5/5', ^3J = 5.7 Hz), 4.23 (q, 2H, CH_2CH$_3$, ^3J = 7.2 Hz), 2.53 (s, 6H, CH_3), 1.26 (t, 3H, CH$_2$CH_3, ^3J = 7.1 Hz) ppm; ^{13}C NMR (125.76 MHz, $CDCl_3$): δ 161.2 (C=O), 155.8 (C-2), 153.6 (C-6), 150.7 (C-4), 127.3 (C-5), 122.5 (C-3), 60.6 (*C*H$_2$), 21.6 (*C*H$_3$), 14.2 (*C*H$_3$); ^{19}F NMR (376.50 MHz, $CDCl_3$): δ -59.9 ppm. As commonly encountered with similar manganese carbonyl complexes, the ^{13}C NMR signals of the coordinated carbonyl ligands could not be observed. Furthermore, no peaks could be detected for the CF$_3$ and triazolate C-4 and C-5 carbon atoms.

Synthesis of (*OC*-6-33)-tricarbonyl(4,4'-dimethyl-2,2'-bipyridine)(*N*-((5-trifluoro-2*H*-1,2,3-triazolato-4-yl)carbonyl)-L-phenylalanine methyl ester-N^2) manganese(I) [Mn(triazolate$^{CO\text{-}Phe\text{-}OCH3,CF3}$)(bpy^{CH3,CH3})$(CO)_3$] (16)



N-(1-Methyl-3-trifluoromethyl-7-oxabicyclo[2.2.1]hepta-2,5-dien-2-yl)carbonyl)-L-phenyl-alanine methyl ester **10** (35.0 mg, 0.09 mmol) and [Mn(N_3)(bpy^{CH3,CH3})$(CO)_3$] **14** (22.4 mg, 0.06 mmol) were dissolved in dichloromethane (5 mL) and stirred at room temperature under exclusion of light for 7 d. Then, the solvent was removed under vacuum and the crude product purified by column chromatography on silica using ethyl acetate/petroleum ether (1:1, v/v) as the eluent. Single crystals suitable for X-ray structure analysis were grown by diffusion of *n*-hexane into a solution of the compound in dichloromethane. Yield: 67% (28.4 mg, 0.04 mmol). Elemental analysis (%): calc. for $C_{29}H_{24}F_3Mn_1N_6O_6$: C 52.42, H 3.64, N 12.65, found: C 53.94, H 4.18, N 11.61; IR (ATR, cm^{-1}): 2025 (s), 1933 (s), 1909 (s), 1740 (m), 1680 (m), 1485 (m), 1159 (m), 1129 (m), 1060 (m); ^{1}H NMR (199.93 MHz, $CDCl_3$): δ 8.95 (t, 2H, H-3/3', ^3J = 5.3 Hz), 7.79 (d, 2H, H-6/6', ^3J = 8.1 Hz), 7.00–7.35 (m, 5H, C_6H_5), 6.88 (d, 2H, H-5/5', ^3J = 7.4 Hz), 4.88 (m, 1H, H-α), 3.68 (s, 3H, COOCH_3), 3.10 (d, 2H, H-β, ^3J = 4.9 Hz), 2.45 (d, 6H, CH_3, ^4J = 7.8 Hz) ppm; ^{13}C NMR (50.27 MHz, $CDCl_3$): δ 155.9 (C-2/2'), 153.3 (C-6/6'), 153.2 (C-3/3'), 136.4 (C-1), 129.7 (C-3/5), 128.5 (C-2/6), 127.2 (C-4), 127.0 (C-5/5'), 122.6 (C-4/4'), 52.6 (C-α), 52.1 (COO*C*H3), 38.3 (C-β), 21.50 (*C*H_3) ppm; ^{19}F NMR (188.12 MHz, $CDCl_3$): δ -59.6 ppm. As commonly encountered with similar manganese carbonyl complexes, the ^{13}C NMR signals of the coordinated carbonyl ligands could not be observed. Furthermore, no peaks could be detected for the CF_3 and triazolate C-4 and C-5 carbon atoms due to low concentration because of the small amout of sample.

Table S1 Crystallographic data for complexes **15** and **16**

Compound	**15**	**16**
Empirical formula	$C_{21}H_{17}F_3Mn_1N_5O_5$	$C_{29}H_{24}F_3Mn_1N_6O_6$
Formula weight	531.33	664.48
Dimensions (mm)	0.49 × 0.15 × 0.11	0.65 × 0.41 × 0.38
Crystal system	Orthorhombic	Monoclinic
Space group	*Pbca*	$P2_1$
a (Å)	16.0897(7)	9.2447(8)
b (Å)	14.5131(6)	15.2085(12)
c (Å)	19.1832(8)	10.6362(9)
α (°)	90	90
β (°)	90	98.280(3)
γ (°)	90	90
V (Å^3)	4479.5(3)	1479.8(2)
Z	8	2
ρ_{calc} (g cm^{-3})	1.576	1.491
T (K)	100	296
μ (mm^{-1})	0.658	0.518
λ (Å) (Mo K_α)	0.71073	0.71073
$2\Theta_{max}$ (°)	27.12	26.00
Reflections measured	59029	18131
Unique refl. / [$I > 2\sigma(I)$]	4957 / 3800	5767 / 5342
Data completeness	0.999	0.993
Variables	318	408
R ($I > 2\sigma(I)$)	0.0306	0.0329
wR ($I > 2\sigma(I)$)	0.0783	0.0750
Largest difference map peak/hole in e Å^{-3}	0.408 / -0.417	0.342 / -0.269
Goodness of fit (GOF)	1.043	1.037

Table S2 Selected bond lengths [Å] and angles (°) for complexes **15** and **16**

	15		**16**
Mn1-C1	1.8173(19)	Mn1-C1	1.811(2)
Mn1-C2	1.8046(19)	Mn1-C2	1.792(3)
Mn1-C3	1.807(2)	Mn1-C3	1.802(3)
Mn1-N2	2.0448(15)	Mn1-N2	2.0368(18)
Mn1-N4	2.0418(15)	Mn1-N4	2.0362(19)
Mn1-N5	2.0422(15)	Mn1-N5	2.032(2)
C1-O1	1.146(2)	C1-O1	1.136(3)
C2-O2	1.147(2)	C2-O2	1.142(3)
C3-O3	1.147(2)	C3-O3	1.142(3)
N1-N2	1.338(2)	N1-N2	1.320(2)
N2-N3	1.340(2)	N2-N3	1.332(3)
N3-C5	1.338(2)	N3-C5	1.336(3)
C4-C5	1.395(3)	C4-C5	1.375(3)
C7-O4	1.202(2)	C7-O4	1.219(3)
C1-Mn1-N2	178.79(7)	C1-Mn1-N2	177.73(10)
C2-Mn1-N4	175.07(7)	C2-Mn1-N4	175.01(10)
C3-Mn1-N5	172.79(7)	C3-Mn1-N5	174.95(10)
C1-Mn1-N5	94.91(7)	C1-Mn1-N5	92.17(9)
C1-Mn1-C3	90.77(8)	C1-Mn1-C3	90.46(11)
N2-Mn1-C3	90.08(7)	N2-Mn1-C3	91.78(9)
N2-Mn1-N5	84.18(6)	N2-Mn1-N5	85.57(7)
C2-Mn1-C3	87.70(8)	C2-Mn1-C3	88.25(12)
C2-Mn1-N5	96.93(7)	C2-Mn1-N5	96.19(10)
N4-Mn1-C3	96.87(2)	N4-Mn1-C3	96.45(10)
N4-Mn1-N5	78.70(6)	N4-Mn1-N5	79.05(8)
C1-Mn1-N4	90.06(7)	C1-Mn1-N4	94.44(9)
C1-Mn1-C2	88.02(8)	C1-Mn1-C2	87.18(11)
N2-Mn1-N4	88.98(6)	N2-Mn1-N4	84.93(7)
N2-Mn1-C2	92.88(7)	N2-Mn1-C2	93.27(9)

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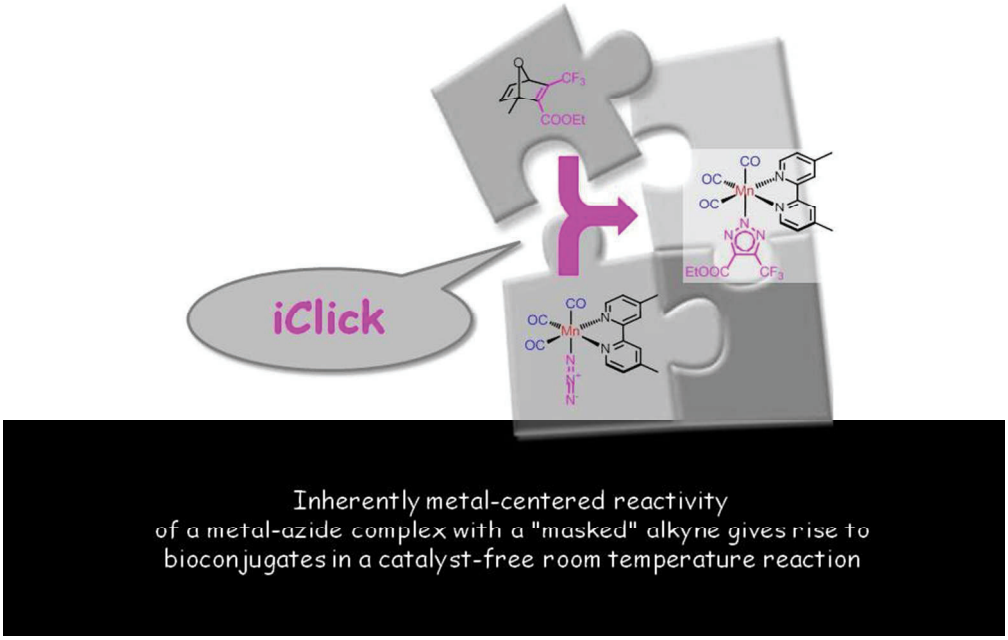

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