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Review

Organotitanium Click Chemistry

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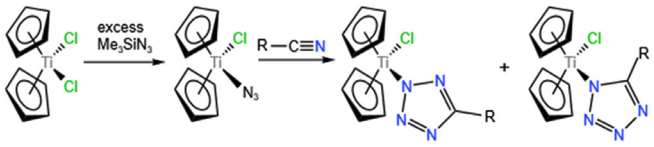
Abstract: The click chemistry of titanium exemplified by the "green" [3 + 2] cycloaddition of the [Ti-N_3] moiety with nitriles RCN to form a tetrazole ligand, is currently limited in scope, but the future of this open and wide field is bright, full of promising new synthetic approaches discussed herein, for pharmacological and bio orthogonal applications. This prediction is based on emerging click reaction possibilities from newly prepared titanium azides (complex **6**), to existing titanium azides, including the commercially available $Ti(N_3)_4$, $Cp_2Ti(N_3)_2$, $(^iPrO)_2Ti(N_3)_2$, and their multiple derivatives, participating in cycloaddition, exchange and other reaction types with alkynes, alkenes, nitriles, and related click synthons. Most of the organotitanium click reactions show nearly quantitative yields, as in the reaction of $Ti(O^iPr)_4$ with $(CH_3)_3SiN_3$. Structural, mechanistic, stereo control and other effects on reactivity are briefly discussed. The main emphasis in this review article is on recently discovered organotitanium complexes like 2-phenylindole titanium dichloride, easily modified by insertion reactions of small molecules like CO_2, SO_2 or even RN_3, serving as springboards of a new era in organotitanium click chemistry, by the original syntheses of non-toxic, potentially bioactive complexes.



Keywords: organotitanium, azide, click chemistry, cycloaddition, insertion, bioactive, pharmaceutical

1. Introduction

Titanium is relatively less known in click chemistry, in terms of catalytic effects or forming click-related coordination compounds, unlike other metals like copper, cobalt, ruthenium, palladium, platinum, osmium and even technetium, among several others.[1] The iconic click reaction, Cu(I)-catalyzed or not, is between an azide (RN_3) and a triple bond unsaturation (-C ≡ C- or -C ≡ N) in a [3 + 2] cycloaddition, to form triazole or tetrazole derivatives. These and several other related "green" reactions carried-out under modest conditions (room temperature, often in an aqueous

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medium), producing nearly quantitative yields, gave a tremendous impetus and progress in the important areas of bioorthogonal cell biology, medicinal chemistry, synthetic applications, organometallic chemistry, photo - and polymer chemistry, to mention only a few.

Several titanium compounds with azide functionality exist that could be utilized to expand the click chemistry of the metal. In dealing with azides in the laboratory, several safety precautions must be taken, because some of them tend to be explosive. Easily accessible titanium tetra azide $Ti(N_3)_4$ obtained quantitatively within minutes from TiF_4 and $(CH_3)_3SiN_3$ in acetonitrile at room temperature, features a linear azide coordination, whereas the 5- and 6-coordinated complexes $[P(C_6H_5)_4][Ti(N_3)_5]$ and $[P(C_6H_5)_4]_2[Ti(N_3)_6]$ respectively, demonstrate a bent azide configuration.[2] The structural difference of the linear vs. bent azide has been rationalized on the basis of the electron back-donation of the α-nitrogen atom. In the special case of tetracoordinate d° metals, all three electron pairs on the α-nitrogen atoms can donate electron density into three lobes of empty d-orbitals tetrahedrally arranged about the (+IV) central metal. In this model, azide acts as a tridentate ligand (Figure 1a), resulting in linear triple-bond conjugation. Usually the α-nitrogen atoms act as one electron pair donors (Figure 1b) with two sterically active free valence electron pairs resulting in strongly bent M-N-N ≡ N bond angles. This has been shown both computationally and by X-ray analysis to be the situation in the higher-coordinated (more stable) compounds $PPh_4[Ti(N_3)_5]$ and $(PPh_4)_2[Ti(N_3)_6]$. Likewise, the hexacoordinated complexes $(bpy)Ti(N_3)_4$ and $(phen)Ti(N_3)_4$ (bpy = bipyridine, phen = 1,10 phenanthroline) show bent azide groups.[3] In the important area of bis(cyclopentadienyl)titanium complexes, $Cp_2TiCF_3(N_3)$ demonstrates similarly a bent azide group.[4] Bending of the azide ligand may be important in the reactivity of these complexes. The majority of the new complexes we propose in this mostly conceptual overview will have a coordination number of five or six, therefore expected to feature bent azide ligands.

(a) (b)

Figure 1. Linear and bent configurations of titanium triazides

Other notable titanium azides are the tetrameric monoazidotitanium triisopropoxide $[(N_3)Ti(O^iPr)_3]_4$, derived from ligand disproportionation of the dimeric diazidotitanium diisopropoxide $[(N_3)_2Ti(O^iPr)_2]_2$ and $Ti(O^iPr)_4$.[5] The commercially available dimeric diazidotitanium diisopropoxide $[(N_3)_2Ti(O^iPr)_2]_2$ is synthesized from $Ti(O^iPr)_4$ and two equiv of $(CH_3)_3SiN_3$ in nearly quantitative yield.[6] We regard this simple reaction as a model in our vision of a new organotitanium click chemistry. It has all the expected characteristics of a click reaction: high yield, mild operational conditions, straightforward without unwanted byproducts, forming a solid product easily separated by simple filtration. In proposing several new organotitanium click complexes in the discussion section below, we take full advantage of the possibilities originating from this fundamental reaction. The crystal structure of $[(N_3)_2Ti(O^iPr)_2]_2$ could not be determined, but the crystal structure of $[(N_3)Ti(O^iPr)_3]_4$ features two bridging azides and the dimeric units are joined by a bridging azide and a bridging isopropoxide.

The reaction of Me_3SiN_3 with $Ti(NMe_2)_4$ at a molar ratio of 1.67 : 1 yields the unusual trimer $[Ti(NMe_2)(N_3)(\mu\text{-}NMe_2)]_3(\mu_3\text{-}N_3)(\mu_3\text{-}NH)$.[7] This structure contains a triply bridging azide and three terminal bent azides. The imido complex **1** reacts with a large excess of Me_3SiN_3 in pyridine at Room Temperature (RT) for two days to substitute only one chloride and yield the dimer **2**, Figure 2. It is remarkable that in **2** the bridging positions are adopted by azides, but not the chloride ligands.[8] Such a preferential bridge bonding of azide vs. chloride ligands is also exhibited in $[AsPh_4]_2[TiCl_4](N_3)_2]$[9] and $[(MeCp)TiCl_2(N_3)]_2$.[10] Furthermore, diazide **3** reacts at RT with cyclohexylamine ($CyNH_2$) in pyridine to form the dimeric azide **4** featuring both bridging and terminal azide groups.

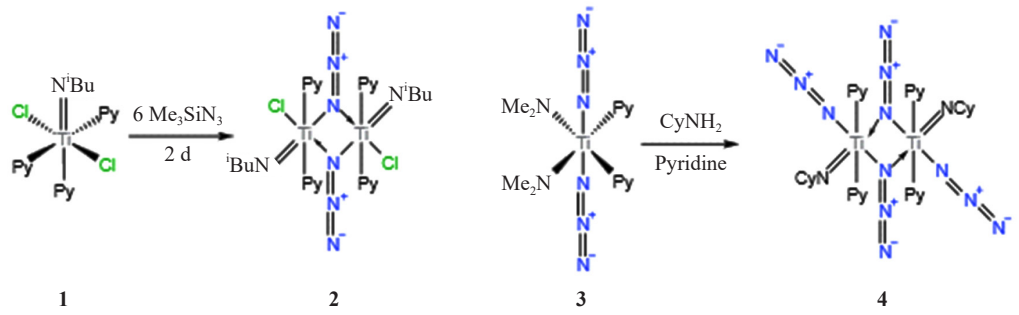


Figure 2. Reactions of complex **1** with excess Me_3SiN_3, and complex **3** with $CyNH_2$ in Pyridine

The first-ever mentioning of an "i-click" (inorganic click) reaction for a d° group 4 metal azide **6** with dipolarophile Dimethyl Acetylenedicarboxylate (DMAD) to afford the bis-triozalato complex **7** was in 2017, from a group in Bergen, Norway,[11] Figure 3, establishing the novelty of organotitanium click chemistry. Similar complexes of other transition metals (Ta, Mo, Mn, Re, Fe, Ru, Os, Co, Rh, Ir, Ni, Pd) had been known for some time. This is a key point, underlining the fact that click chemistry of several transition metals could be adapted to titanium, under certain conditions. These conditions were taken into account in proposing numerous new titanium click reaction pathways producing a bundle of organotitanium complexes discussed herein. In each case reference has been made to the relating original publication.

The most efficient way of preparing complex **6** with a quantitative yield is by the reaction of **5** with an excess of Me_3SiN_3 in CH_2Cl_2 overnight at RT. The effective use of a titanium di-isopropoxy derivative combined with excess Me_3SiN_3 to "click" the diazide **6** is a copycat of the previously mentioned "model" reaction of titanium tetraisopropoxide with Me_3SiN_3. Indeed, the chloride analogue of 5 could not react efficiently with NaN_3 to produce **6**. Complex **5** and related derivatives are active in copolymerization of cyclohexene oxide with CO_2.

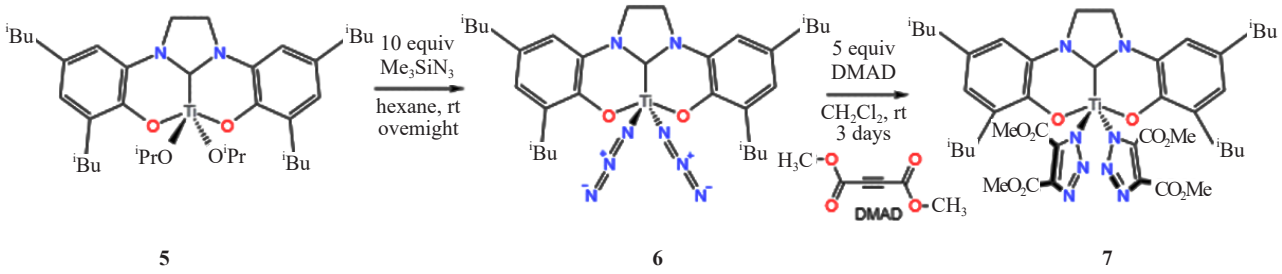
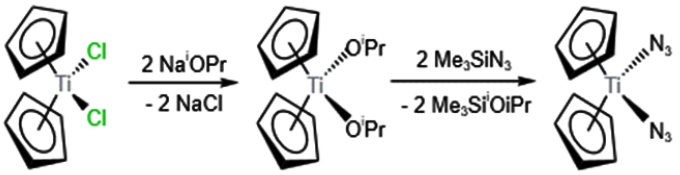


Figure 3. Synthesis of bis-triozalato titanium complex **7**

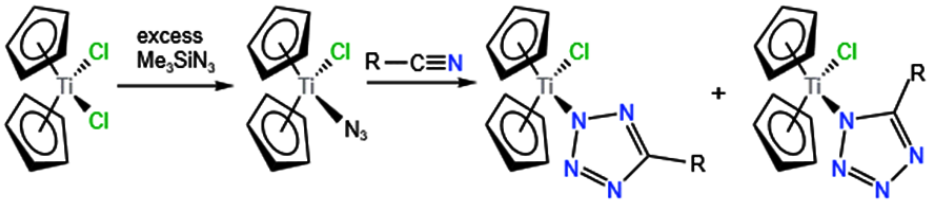
A similar click approach could be proposed for the preparation of the important building block bis(cyclo-pentadienyl)titanium diazide $Cp_2Ti(N_3)_2$ **10** (Figure 4), although the originally published low-yielding procedures utilized Cp_2TiCl_2 and NaN_3 in boiling acetone[12] or even water.[13]

By comparison, the direct reaction of bis(cyclopentadienyl)titanium dichloride Cp_2TiCl_2 **8** or the cyclo-pentadienyl titanium trichloride $CpTiCl_3$ with excess Me_3SiN_3 affords the substitution of a single chloride only[14] producing a monoazide **11**, Figure 5. The latter undergoes a [3 + 2] cycloadditon click reaction with nitrile RCN to yield two isomeric tetrazole derivatives, differentiated by the β- (**12**) or α-position (**13**) of the tetrazole ring carbon relative to the nitrogen atom bonded to titanium.[15]



8 **9** **10**

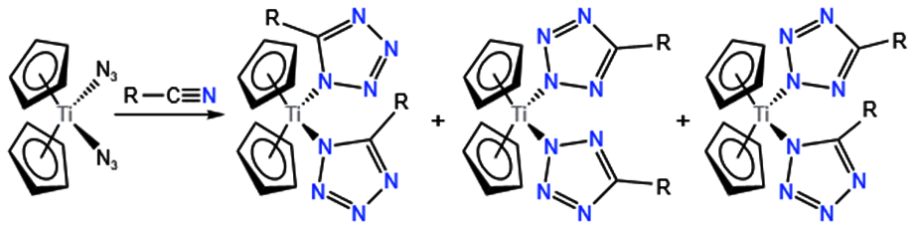
Figure 4. Proposed new approach for the formation of $Cp_2Ti(N_3)_2$ **10**



8 **11** **12** **13**

Figure 5. Single chloride substitution of Cp_2TiCl_2 **8** with excess Me_3SiN_3 to form monoazide **11**. Click reaction of **11** with RCN yielding two isomers, **12** and **13**

The same [3 + 2] cycloaddition reaction performed on the diazide **10** (Figure 6) is expected to yield three isomers. The first isomer **14** with two tetrazole rings, each having the ring carbon in the α-position next to the nitrogen bonded to titanium. A second isomer **15** with two tetrazole rings, each with the ring carbon in the β-position relative to the nitrogen bonded to titanium, and a third mixed isomer **16** with one tetrazole ring with carbon in the α- and another tetrazole ring with its carbon in the β-position relative to the nitrogen bonded to titanium.



10 **14** **15** **16**

Figure 6. Three isomers from the cycloaddition of RCN with diazide **10**

The click chemistry of the azide complexes **10** and **11** may be expanded in multiple ways, by applying a variety of suitable reaction partners (dipolarophiles, acetylides, nitriles, etc.), many of them known partners of other metal azides as well. Moreover, the organotitanium click chemistry is not limited to chemical transformations of complexes **10** and **11** or others mentioned above. In this paper we are introducing new organotitanium click complexes originating from our serendipitous discovery of the ortho-metallation of various heteroaromatic ligands with $TiCl_4$ or $ZrCl_4$, starting with the ortho-titanation of 2-pheylindole:[16]

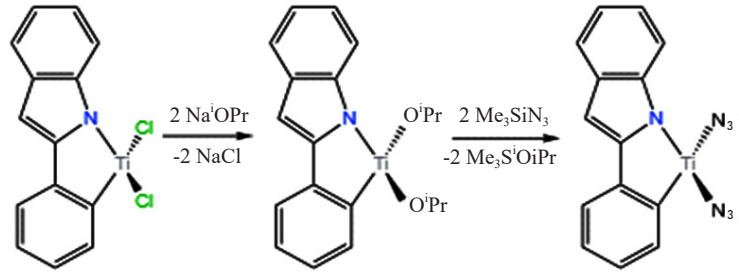


Figure 7. Synthesis of 2-phenylindole titanium diazide **19**

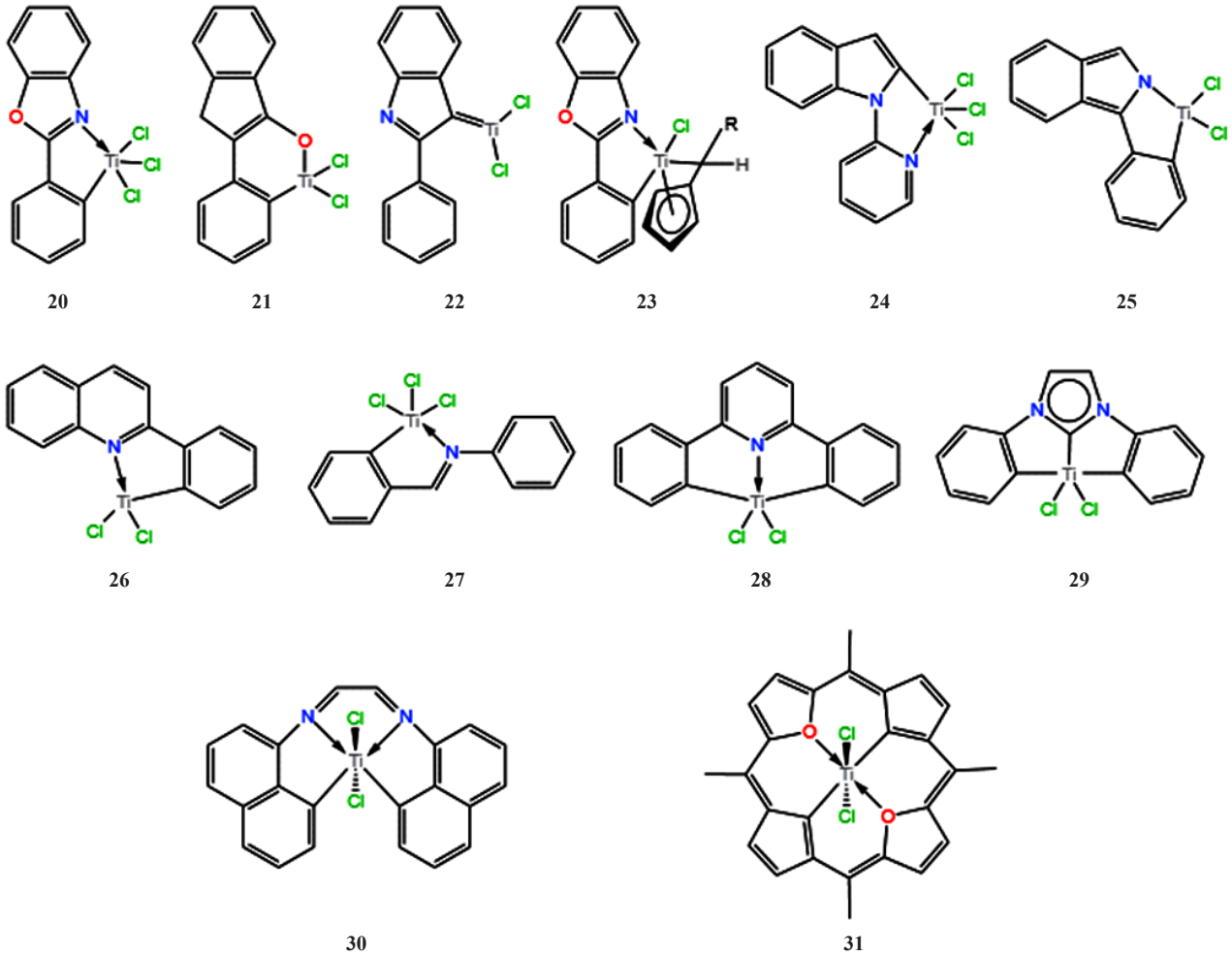


Figure 8. Selected organotitanium complexes available for click reactions

2. Discussion

2.1 *New organotitanium complexes--synthons in click reactions*

The orthometallation reaction of $TiCl_4$ or $ZrCl_4$ with suitable hetreroaromatic ligands featuring pendant phenyl,

naphthyl or other aryl groups like 2-phenylindole,[17] is a most valuable tool for accessing new building blocks for organotitanium and -zirconium click chemistry. For example the orthotitanated 2-phenyl indole titanium dichloride **17** in Figure 7 follows an identical reaction pattern as Cp_2TiCl_2 **8** in Figure 5, or even that of complex **5** in Figure 3, to yield the corresponding new diazide **19**, over the intermediate diisopropoxy derivative **18**. Complex **19** may be further prone to azide insertion into the actve Ti-C σ-bond, vide infra.

Besides this "model" building-block **17**, a number of selected organotitanium chlorides **20** through **31** depicted in Figure 8, are also accessible through the titanation reaction.[16-18] These organotitanium chlorides may serve as building blocks for attaining new organotitanium azides, simply undergoing the same strategic pathway outlined in Figure 7. The list of organotitanium complexes in Figure 8 contains a monocloride (**23**), several dichlorides (**21**, **22**, **25**, **26**, **28**, **29**, **30**, **31**) and trichlorides (**20**, **24**, **27**). In the following discussion, all click chemical transformations applicable to dichlorides will be represented by the framework of complex **17**, and click transformations of trichlorides by the framework of complex **20**. It is assumed that the remaining complexes in each category undergo identical transformations with their corresponding counterparts.

2.2 *Click reactions of titanium monochloride complexes*

The reaction of complex **20** with 6-tert-butyl fulvene in the presence of Mg in THF affords the mono-chloride[19] complex **23**, Figure 9. When three or more equiv. of Me_3SiN_3 react with complex **23** something extraordinary and unprecedented happens! Me_3SiN_3 attacks three distinctly different reactive sites of complex **23** simultaneously, in three separate modes of action: a. A chloride substitution reaction, forming the Ti-N_3 functionality, under Me_3SiCl elimination, b. The insertion into the Ti-C (alkyl) bond ultimately creating a relatively stable azide[20] **33** in the solid state, and c. The insertion into the Ti-C (phenyl) bond forming a transient azide **32**, which gives up N_2 readily to form complex **33**. The latter is stable in the solid state at ambient temperature, but in solution decomposes gradually giving-up additional N_2, forming complex **36**. Mechanistically, precursors of complex **36** decomposition are the transient intermediates **34** and **35**.

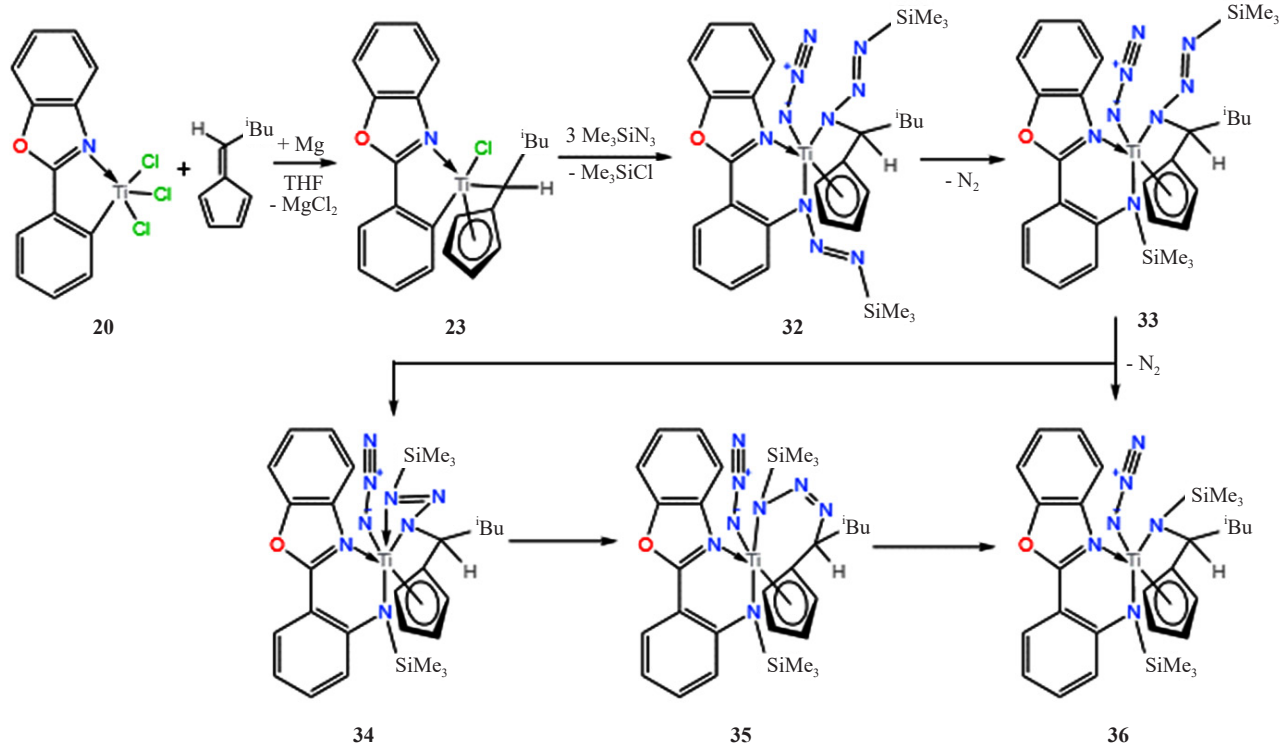


Figure 9. Reaction of complex **20** with 6-tert-butyl fulvene in the presence of Mg in THF, followed by azidation of product **23** with excess Me_3SiN_3

Azide **36** Figure 10 undergoes a [3 + 2] cycloaddition with benzonitrile PhCN to form the click isomeric tetrazole pair **37** and **38**. Other alkyl nitriles RC ≡ N and even thiocyanates RSC ≡ N show comparable behavior.

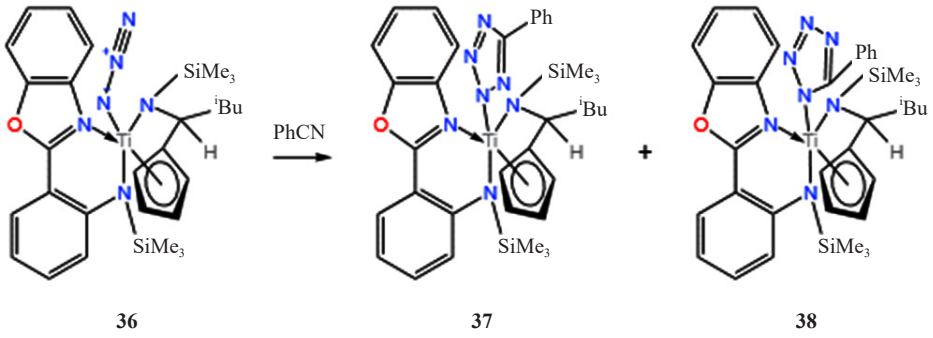


Figure 10. Cycloaddition of benzonitrile with complex **36**

Typical click reactions of complex **36** with several unsaturated reagents are depicted in Figure 11. First, the reaction with CS_2, ultimately yields the S-coordinated thiotriazoline titanium complex **39**.

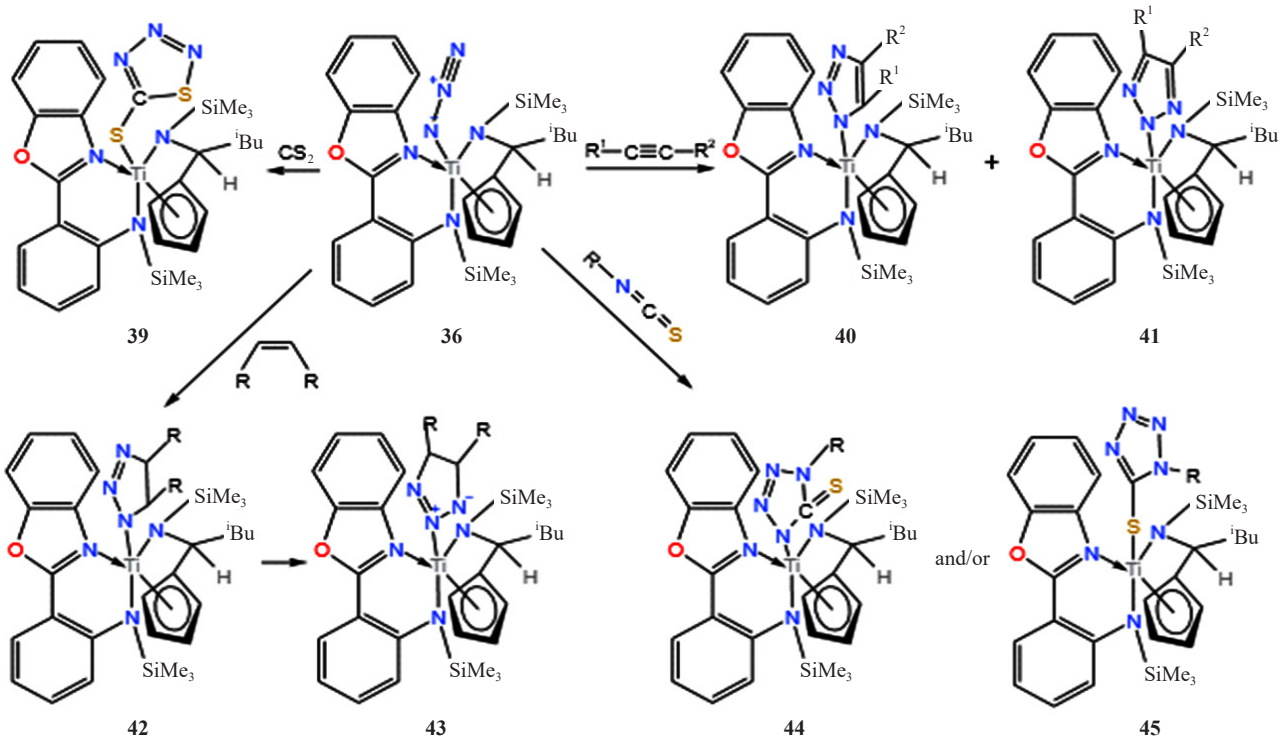


Figure 11. Typical click reactions of complex **36** with unsaturated organic compounds

The latter is the isomerization product of an originally formed N-bound 1,2,3,4-thiatriazoline thionate.[21] On the right top side of Figure 11, the equation represents the reaction of complex **36** with disubstituted acetylenes $R^1C \equiv CR^2$. Better known examples are with $R^1 = R^2 = CO_2Me$,[22] Ph, and CF_3[23] affording two isomers in each case, one isomer

with titanium coordinated to the α-N of the triazole ring and the other with the titanium coordinated to β-N. Likewise, an alkene[24] derivative will yield complex **42**, which isomerizes promptly to complex **43**, featuring coordination of the triazole ring to titanium through the middle nitrogen atom of the triazol ring.

Cycloaddition reactions with isothiocyanates RNCS[25] give rise to N-coordinated thiotetrazole complexes **44** and S-coordinated tetrazole complexes **45**. Isocyanates RNCO[22] follow the same reaction pattern, yielding the corresponding oxygenated isomers replacing sulfur.

2.3 *The role of insertion reactions into the active Ti-C σ-bond*

Insertion reactions into the active Ti-C σ-bonds of the complexes, as in complex **32**, take center stage in all chemical manipulations involving each and every complex in Figure 8. The insertion reaction may occur independently, i. e., before any click reaction (for example complex 17 to **49**, Figure 12); At the same time with a substitution reaction, as in complex **17** to **51** (a transient intermediate) and **52**; or in complex **18** to **53** and **54**; Finally, insertion and substitution may take place in sequence (insertion first, complex **17** to **49**, and then substitution, **49** to **50**). Please note that the reaction of Me_3SiN_3 with chloride complexes in Figure 2 results in a single chloride substitution only, as in monochlorides **50** and **52**, vide supra. The remaining chloride functionality in these monoazide complexes (**50**, **52**) may participate in secondary substitution reactions, exchanging the chloride of the complex with new functional groups like nitriles, alkoxides, amides, etc. Unlike the single chloride substitution of **17** and **49** in reactions with Me_3SiN_3, substitution of both isopropoxy groups of complex **18** with Me_3SiN_3 takes place.

Small molecules like CO, CO_2, CS_2, SO_2, $SOCl_2$, SO, COS, NO, NO_2, N_2O, are the usual partners in these insertion reactions, along with several click reagents such as nitriles, isonitriles, alkenes, alkynes, aldehydes, ketones, etc. The insertion reactions constitute a prime advantage, and they are introduced here for the first time in organotitanium click chemistry. Among the advantages of the insertion reactions are: (a) A substantial increase of the number of new material combinations to be created, (b) Improvement of their thermal stability, sensitivity to air and moisture, and (c) Increase of complex solubility in selected solvents, particularly water under physiological conditions. Consequently, ease of handling in planned click reactions and enhanced reactivity may be realized.

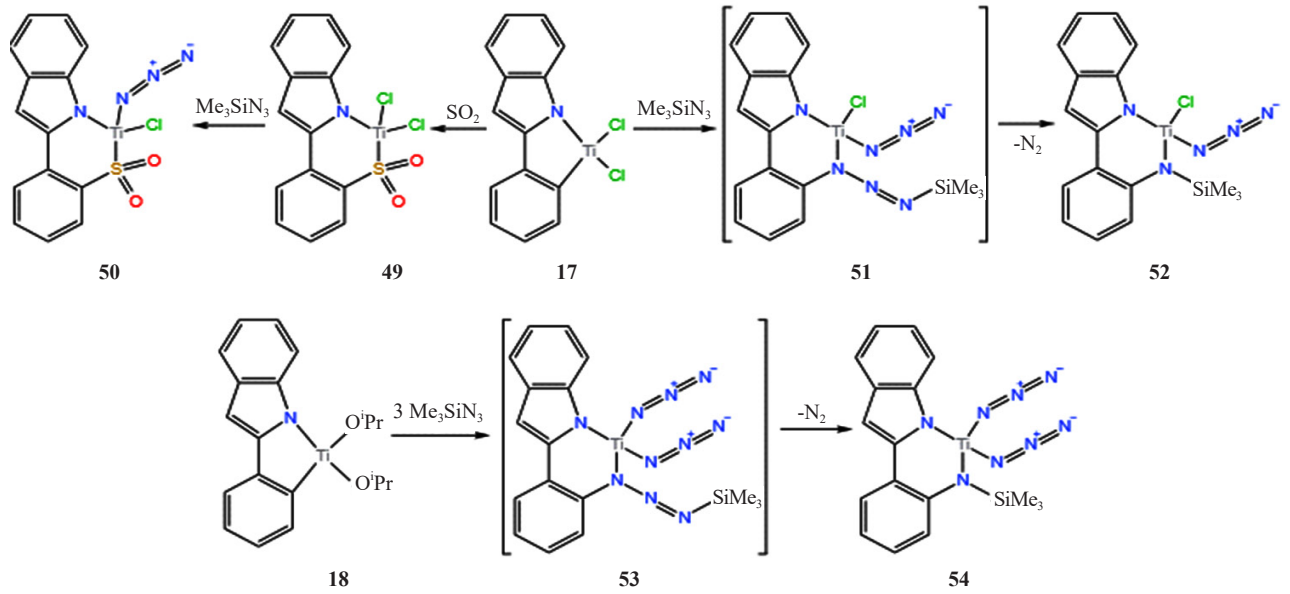


Figure 12. Insertion reactions enhancing organotitanium click chemistry

To further simplify our discussion, we will select as base reactants organotitanium frameworks (included in Figure

2) modified previously by an insertion reaction with any one of the above mentioned small molecules, as represented by complex **49** or **50**.

2.4 *Organotitanium diazide click reactions*

Selected click reactions starting with diazide complex **55** are depicted in Figure 13. Complex **55** is prepared from dichloride **49** following the procedure outlined in Figure 9. The reaction of complex **55** with nitriles RCN[26] yields three isomers, compare with the analogous reaction with $Cp_2Ti(N_3)_2$, Figure 6. Complex **56** is one of the three isomers with a mixed coordination mode for the two tetrazole rings to titanium (one ring with α-N and the other with β-N). The second isomer (not shown) has both tetrazole rings with α-N bonding to titanium, and the third isomer (also not shown) has both rings β-N bonding. This statistical bonding distribution may be rationalized on the basis of each of the three isomers deriving from the transient ionic resonance structure **62**. Likewise, three isomers are formed by the reaction of **55** with an alkyne[19] R^1 - C ≡ C - R^2, with product complex **57** showing two different N-triazole coordination modes to the titanium central atom. Reaction with CS_2 initially forms the N-coordinated thiotriazole rings **58**, which transform to S-coordination **59**. By comparison, the isothianate[21] RNCS reaction result in N- coordination **60**, and both N- and S-coordination, complex **61**.

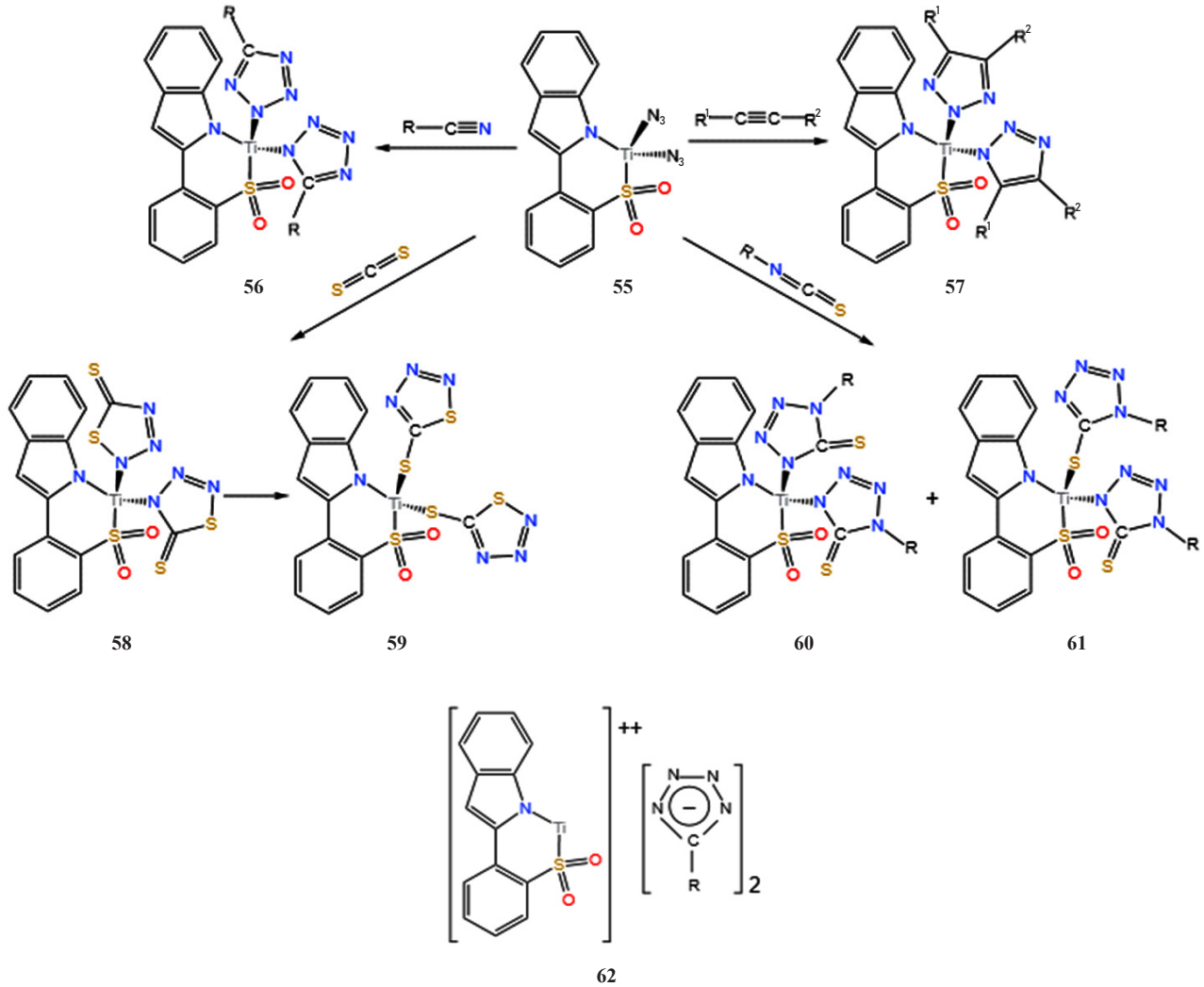
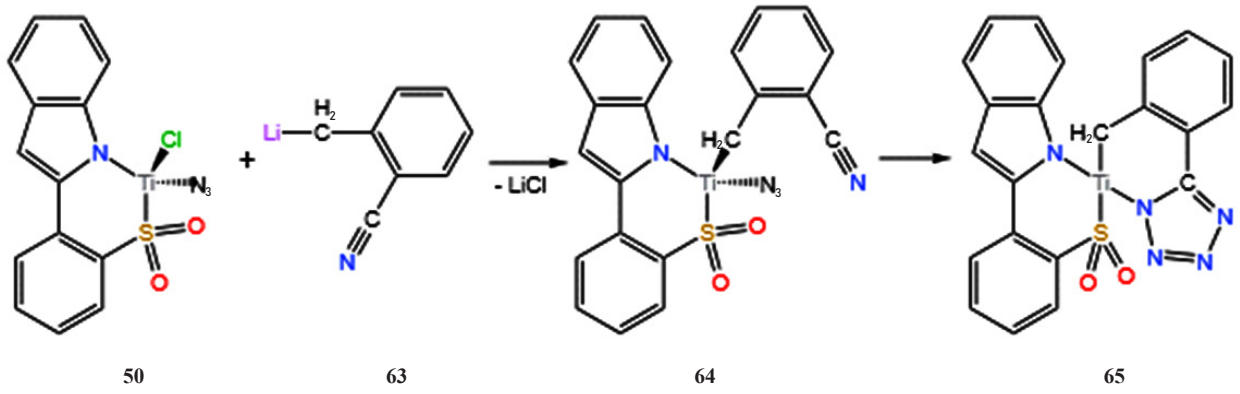


Figure 13. Click reactions of diazide complex **55** with unsaturated compounds

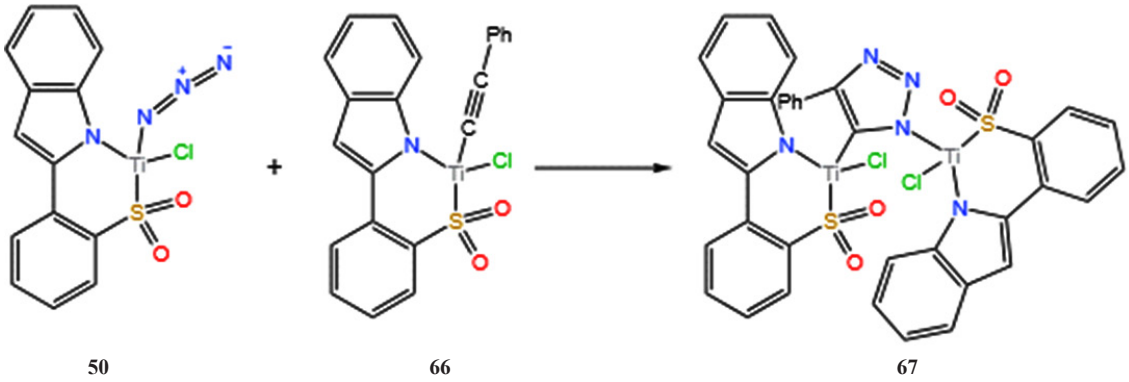
2.5 *Organotitanium monoazide click reactions*

An interesting example of adding a new functionality into a chloroazide **50** is shown in Figure 14. The lithiated o-tolunitrile **63** reacts with complex **50** to afford the azido-complex **64**, stable in the solid state, but in solution it undergoes an intramolecular 1,3-cycloaddition[23] yielding the tetrazole complex **65**. Chlorozide **50** interacts further with the alkyne group of complex **66** to produce the bimetallic complex **67**, linking the two reagents through the newly created triazole ring in the 1,5-positions, Figure 15.



50 **63** **64** **65**

Figure 14. Substitution reaction of chloro-azide **50** with lithiated tolunitrile **63**. Internal cycloaddition of azido complex **64**, rearranging to complex **65** in solution

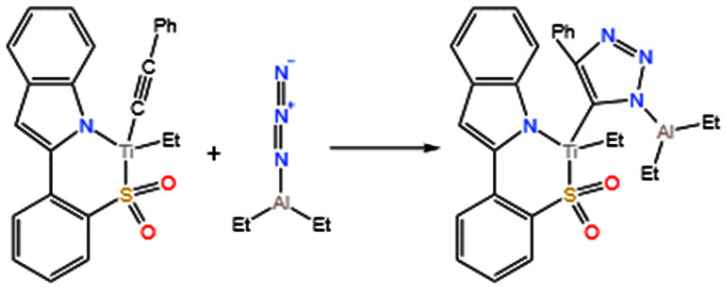


50 **66** **67**

Figure 15. Cycloaddition of the azido-complex **50** with the alkyne ligand of complex **66**

2.6 *Heterobimetallic complexes through click chemistry*

A hetrerobimetallic (Ti, Al) complex **70** with potential applications in α-olefin polymerization catalysis is prepared from the alkyne/alkane complex **68** and diethylaluminum azide **69**, Figure 16. Other bimetallic complexes may be considered, by engaging titanium click complexes **66**, **68** and related synthons with metal azides, for example $M(N_3)_2(PR_3)_2$ (M = Pd, Pt, Ni, Cu, etc., R = Ph, Me, Et), $Au(N_3)PPh_3$ and multiple others.[25] The click heterobimetallic complexes of titanium with other metals is an important and wide-open topic to be discussed in a separate report.

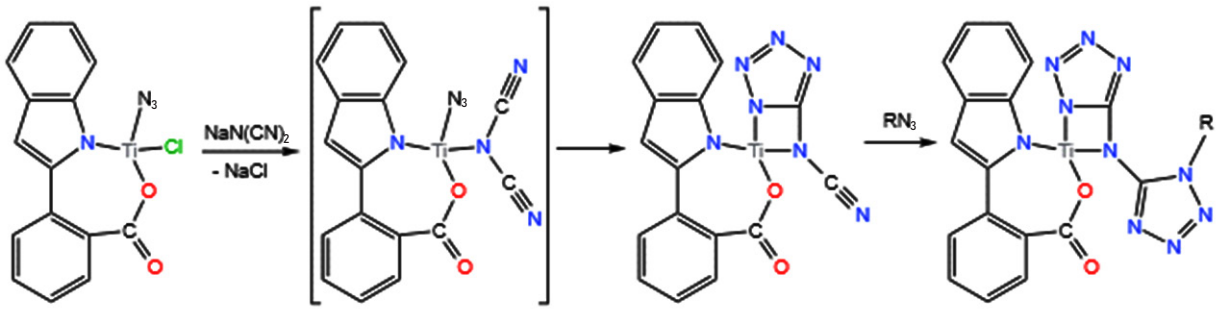


68 69 70

Figure 16. Cycloaddition of Et_2AlN_3 **69** with complex **68**

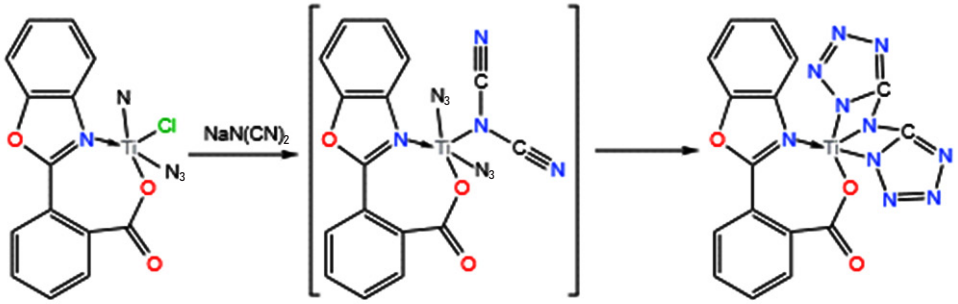
2.7 *Internal cyclization of azido azo(binitrile) titanium complexes*

Another illustrative example of the multiple available possibilities from utilizing complex **50** or its counterpart from a CO_2 insertion **71** is the reaction with sodium dicyanamide $NaN(CN)_2$ to form the transient intermediate azido azo(bisnitrile) 2-phenyl carboindole titanium complex **72**, which promptly undergoes a click intramolecular cycloaddition forming a terazole ring to yield complex **73**. The latter reacts further with an organic azide interacting with the remaining nitrile group, to form a pendant second tetrazole ring, complex **74**, Figure 17.



71 72 73 74

Figure 17. Reaction of complex **71** with sodium dicyanamide $NaN(CN)_2$, formation of transient intermediate **72**, internal cyclization to **73**, and external cylization to form complex **74**



75 76 77

Figure 18. Double intramolecular cycloaddition

A double intramolecular cycloaddition is enacted by the transient product **76**, from the substitution reaction of the chloro-diazide complex **75** with $NaN(CN)_2$ under NaCl elimination, to afford the most unusual complex **77**, featuring a fused titanadiazetidine-di-tetrazolato ring, and a carbonated 2-phenyl benzoxazole ligand, Figure 18.

2.8 *Click reactions with di- and tri-acetylides*

The reaction of dimethyl diacetylide Me-C ≡ C-C ≡ C-Me with complex **49** in the presence of Mg yields the titanacyclocumulene[25] **78**. Interaction with $B(C_6F_5)_3$ creates the zweitterionic complex **79**, a promising polyolefin catalyst. Further reaction with an organic triazide RN_3 will afford the coordinated triazole derivative 80, maintaining its zweitterionic character Figure 19. Phenyl or $-SiMe_3$ substituted titanacyclocumulenes will follow a different reaction pathway upon interaction with $B(C_6F_5)_3$.

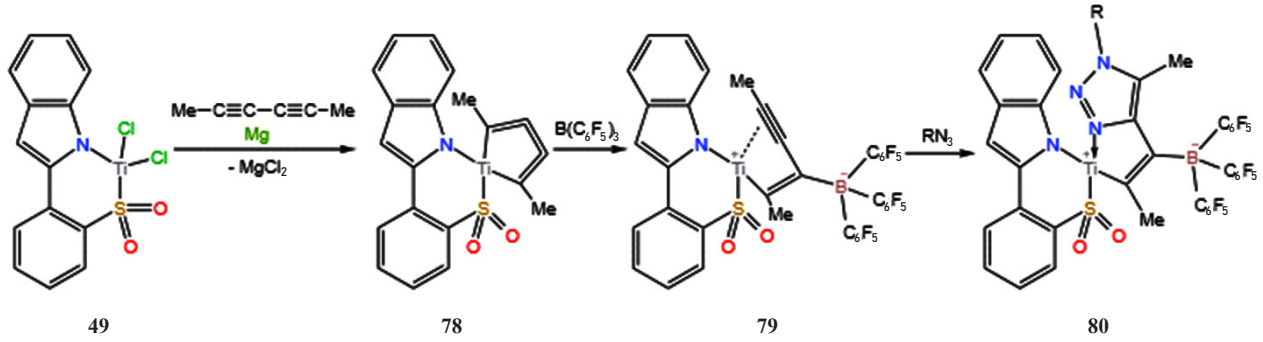


Figure 19. Dimethyl diacetylide reaction with complex **49**, after reduction with Mg. Formation of zweitterionic complex **79**

The dichloro complex **17** after carbonation forms **81**, which, as in the previous example, reacts with di-t-butyl hexatriyne, in the presence of magnesium, to afford a titanacyclopropene ring di-substituted with t-butyl alkynyl groups. These functionalities form triazole rings in the presence of two equivalents of RN_3, Figure 20. Using a di-t-butyl-tetradiyne instead, will generate complexes with one alkynyl group which reacts with one equivalent RN_3 to yield a single triazole ring.

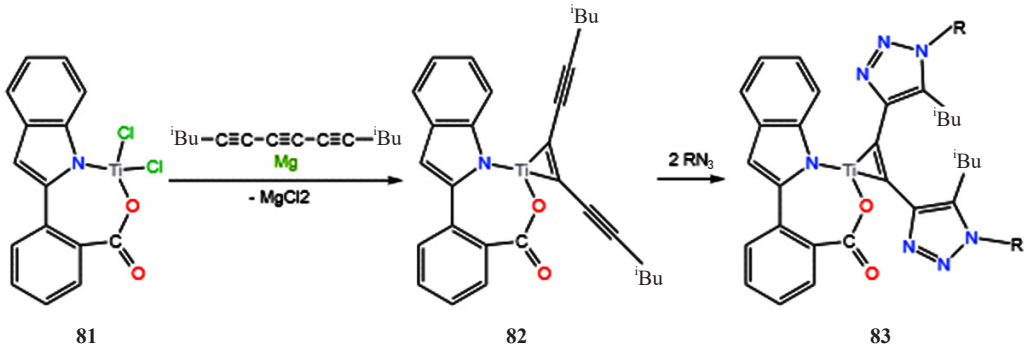
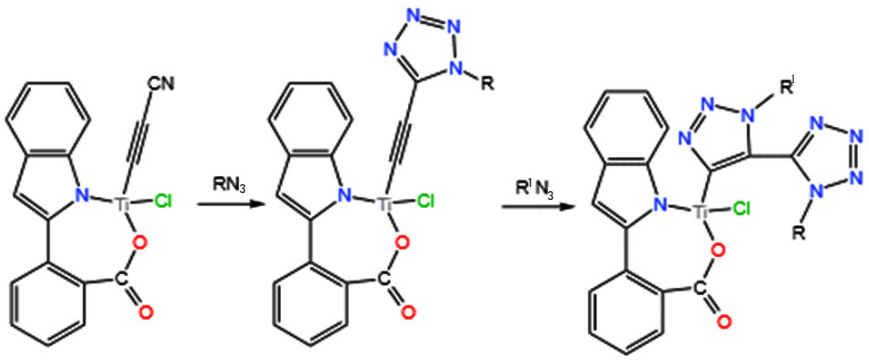


Figure 20. Di-t-butyl hexatriyne with complex **81** in the presence of Mg

2.9 *The alkynylonitrile ligand*

Formation of an uncommon carbon-to-carbon connected triazole-tetrazole ligand, coordinated to titanium by the

second triazole carbon, is accomplished by a two step [3 + 2] cycloadditions of two RN_3 equivalents to the titanium coordinated alkynylonitrile ligand of complex **84**, affording complexes **85** and **86**, Figure 21. We project the tetrazole rings are produced first, because of the end location of the nitrile and the perceived higher reactivity of RN_3 with the polar nitrile group over the triple bond. Complex **85** or even **84** could react with azide-functionalized biological molecules, e.g., peptides, to form a peptide-substituted anticancer drug.[26]

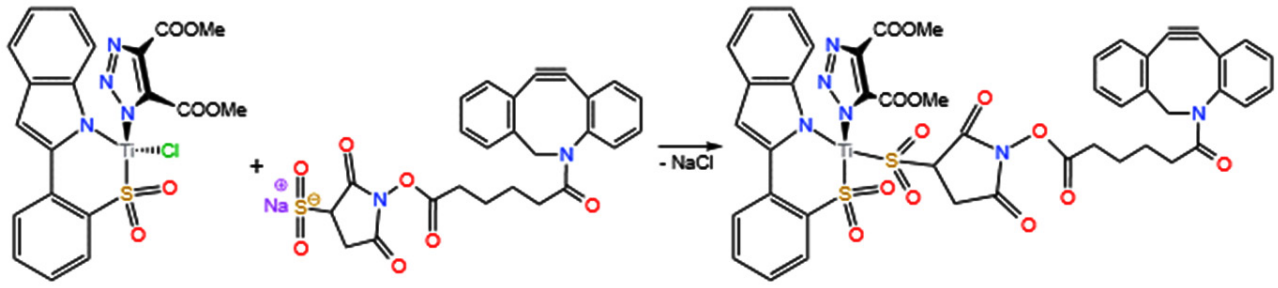


84 **85** **86**

Figure 21. Cycloadditions to the alkynylonitrile ligand of complex **84**

2.10 *SPAAC reactions*

Strain-Promoted Azide-Alkyne Cycloadition (SPAAC) reactions are widely employed in modifications of biomolecules in living systems, in many bioorthogonal applications, and in new drug development. The great advantage of this approach is the high energy of the strained cyclooctyne molecule as the reaction driving force, thus avoiding the use of cytotoxic copper (I) catalyst (CuAAC). The energy of cyclooctyne increases dramatically with two fused benzene rings (DBCO dibenzocyclooctyne) and a nitrogen atom in the ring, as in the commercially available DBCO-sulfo-NHS ester **88**, Figure 22. This product reacts further with complex **87** under NaCl elimination, to create the novel potential anticancer drug **89**, available also for site-selective cysteine-cyclooctyne conjugation.[27]



87 **88** **89**

Figure 22. Potential anticancer drug **89**

Complex **87** derives from **50** after reaction with Dimethyl Acetylenedicarboxylate (DMAD), as in Figure 3. Needless to say, any related chloro-azide complex, for example **51**, modified with DMAD or a different alkyne, would react with **88** similarly, affording unique bioorthogonal products.

2.11 *A potent inhibitor of human α-1,3-fucosyltransferase*

The acetylene derivative of guanosine diphosphate β-L-fucose (GDP-fucose) Figure 23 is available for a click [3 + 2] coupling reaction with titanium azide complexes (**71**, Figure 24), producing a potent inhibitor of human α-1,3-fucosyltransferase[28] **90**.

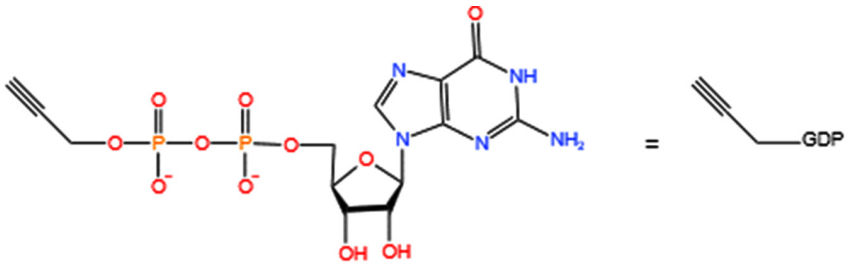
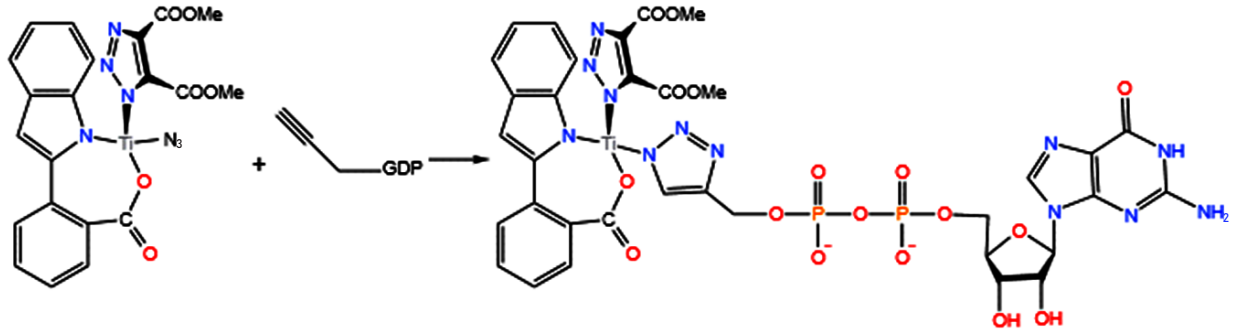


Figure 23. Guanosine diphosphate β-L-fucose (GDP-fucose)



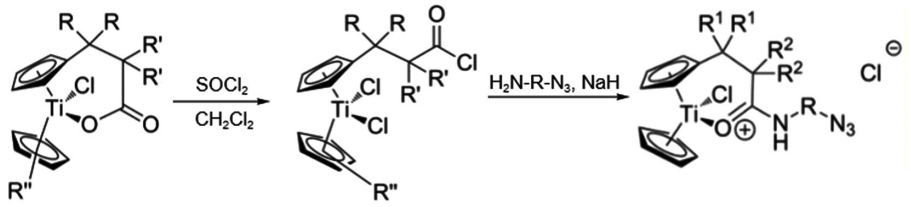
71 **90**

Figure 24. Cycloaddition of GDP-fucose with azido complex **71**, producing **90**, a potent inhibitor of human α-1,3-fucosyltransferase

This reaction requires the presence of either a soluble copper(I) (CuAAC), or more efficiently a heterogeneous copper-cluster-based Metal-Organic Framework (MOF) catalyst,[29] used for CO_2 chemical fixation and azide-alkyne cycloaddition. The presence of the heterogeneous MOF catalyst may be recommended/required in several other alkyne-azide cycloadditions described in the present account.

2.12 *Carboxylate titanocene azides and related compounds*

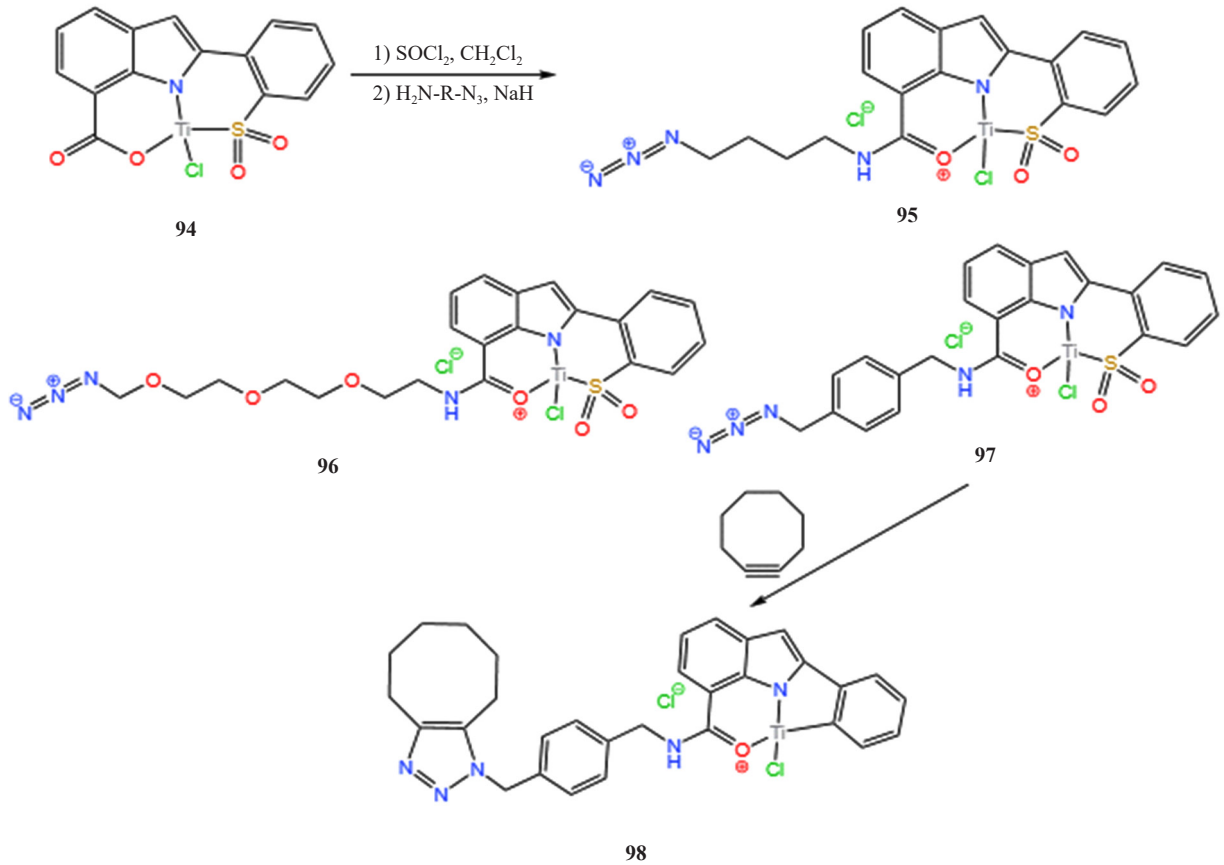
Carboxylate containing titanocene building blocks **91** react with $SOCl_2$ to form the corresponding acid chlorides, restoring the [$TiCl_2$] group as well, **92**, Figure 25. The acid chloride group is more electrophilic than the [$TiCl_2$] fragment and therefore many titanocenes containing ligands with pending ketone , ester, and amide groups can be prepared with classical organic acylation reactions (Friedel-Crafts reaction, esterification, amide synthesis).[30] The amide **93** (and ketone) substituted catalysts are cationic due to the intramolecular coordination of the carbonyl group. This feature is essential for the cytostatic and catalytic activity of these complexes. The titanocene acid chlorides react with amino azides in the presence of NaH without purification of the acid chlorides, producing the azides **93**, generally in good yields.



91 92 93

Figure 25. Carboxylate titanocene chloride **91** reacting with $SOCl_2$ to form acid chloride **92**. Further reaction with H_2N-R-N_3 and NaH yields complex **93**

The above described reaction sequence may be duplicated starting with complex **94**, the 7-carbolylate 2-phenyl indole ortho-titanated complex, deriving from 1-*H*-2-phenyl indole-7-carboxylic acid and $TiCl_4$[13] after insertion of SO_2 into the Ti-C bond. Reaction with three different aninoazides in the presence of NaH (Figure 26) afford the corresponding novel azides **95**, **96**, and **97**. These azides undergo a strain-driven 1,3-cycloaddition with cyclooctyne and derivatives under mild conditions, yielding products available for biorthogonal applications. For example, complex **98** is the reaction product of azide **97** with cyclooctyne.



94 95 96 97 98

Figure 26. The carboxylate titanium complex **94** forming azide **95**, followed by reaction with various amine azides to yield new bioorthogonal complexes **96**, **97**, and **98**, which click with octyne derivatives under mild conditions

Easily accessible carboxylate **81** will react with $SOCl_2$ to form a complex represented by the resonating structures **99A** and **99B**. Reaction with one equiv. of $H_2N(CH_2)_nN_3$ + NaH is expected to yield a mixture of azides **100** and **101**.

The [Ti-Cl] fragments in **100** and **101** are amenable to several desirable substitution reactions.[37]

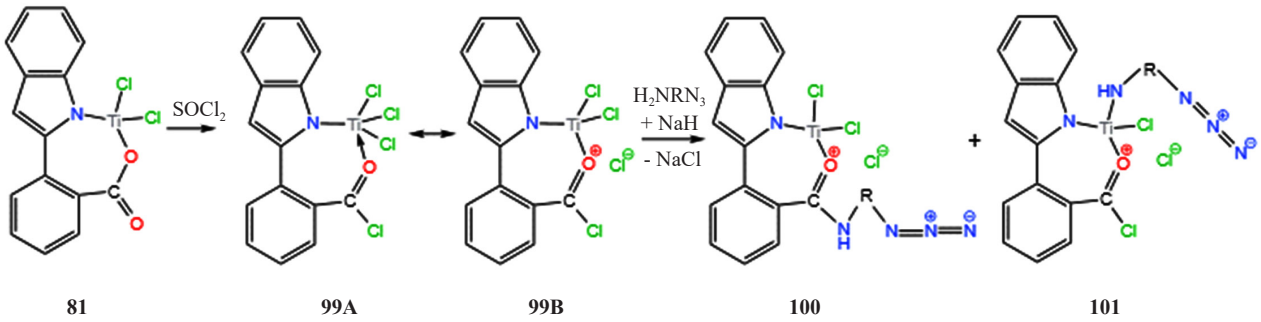


Figure 27. Organotitanium azides **100** and **101**, starting from complex **81**

The chemistry outlined in Figure 27 may be performed with any individual complex included in Figure 2 after CO_2 insertion, highlighting the wide range of possible applications available by this approach.

2.13 *Double cycloadditions with oxindole 1,6-heptatriene and fumaronitrile*

The oxindole based 1,6 heptatriene[38] **102** reacts with complex **55** in a double, CuAAC-catalyzed [3 + 2] cycloaddition to yield complex **103**, Figure 28, featuring two different indole frameworks. An electron- withdrawing acetyl group in N-protecting group R^2 of **102** favors the production of the ditriazole **103** over the asymmetric monotriazole derivative, which is expected to be optically active. Moreover, 3,3-disubstituted oxindoles (**102** framework) are widely present in natural products, drugs, and pharmaceutically active compounds.

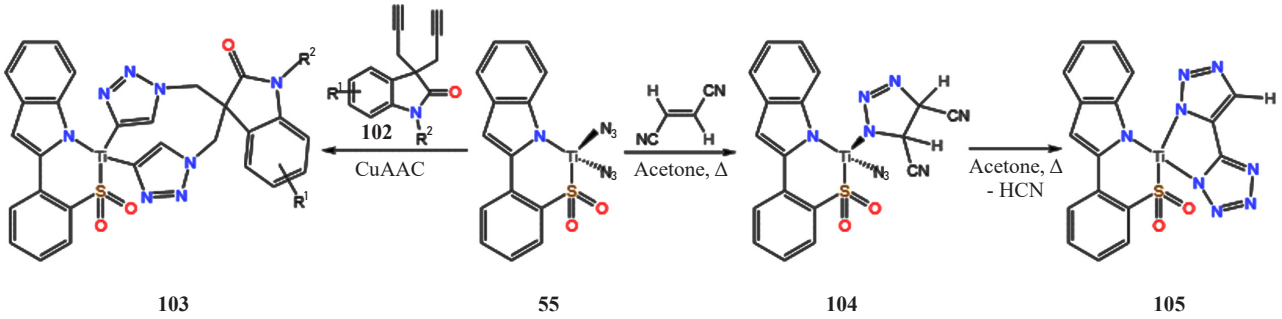


Figure 28. Double cycloaddition of diazidotitanium complex **55** with oxindole 1,6-heptatriene and fumaronitrile

The reaction of complex **55** with an excess of fumaronitrile in refluxing acetone affords complex **105**, which contains a bidentate ligand 5-(1,2,3-triazol-4-yl)-1,2,3,4-tetrazolate coordinated through the N(1) of the tetrazole ring and the N(3) of the triazole ring[39] (Figure 28). Complex **105** is the result of the cycloaddition reaction of the two azide groups of complex **55** with the C≡N and C=C of fumaronitrile. The first cycloaddition involves one Ti-N_3 moiety with the double bond of fumaronitrile, forming the transient intermediate **104**. The second cycloaddition occurs internally with the second Ti-N_3 moiety and the adjacent C≡N group.

2.14 *Orthogonal modifications of Titanocene Y*

Titanocene Y, used in initial clinical trials against breast and renal-cell cancer, has been modified by introduction of a targeting substituent, an alkyne[30] (complex **106**). The latter could be easily undergo [3 + 2] "click" cycloaddition with an azide and subsequently with an octyne-substituted biological molecule such as a protein. Similarly, incorporation of a pendant diazo group[37] (complex **107**) may enable Titanocene Y to become cysteine-selective through the activated alkene group. However, there are numerous other modifications of Titanocene Y, by introducing different targeting substituents into the molecule. Titanocene Y will react with Me_3SiN_3 to prepare the monoazide **109**, Figure 29. The corresponding diazide could be prepared by substitution of both chlorides in Titanocene Y, forming the diisopropoxide derivative, and then performing the reaction with Me_3SiN_3. The Ti-N_3 functionality of Titanocene Y would undergo a SPAAC reaction with a cycloalkyne, in this case with the most powerful known agent **108**,[40] Figure 29.

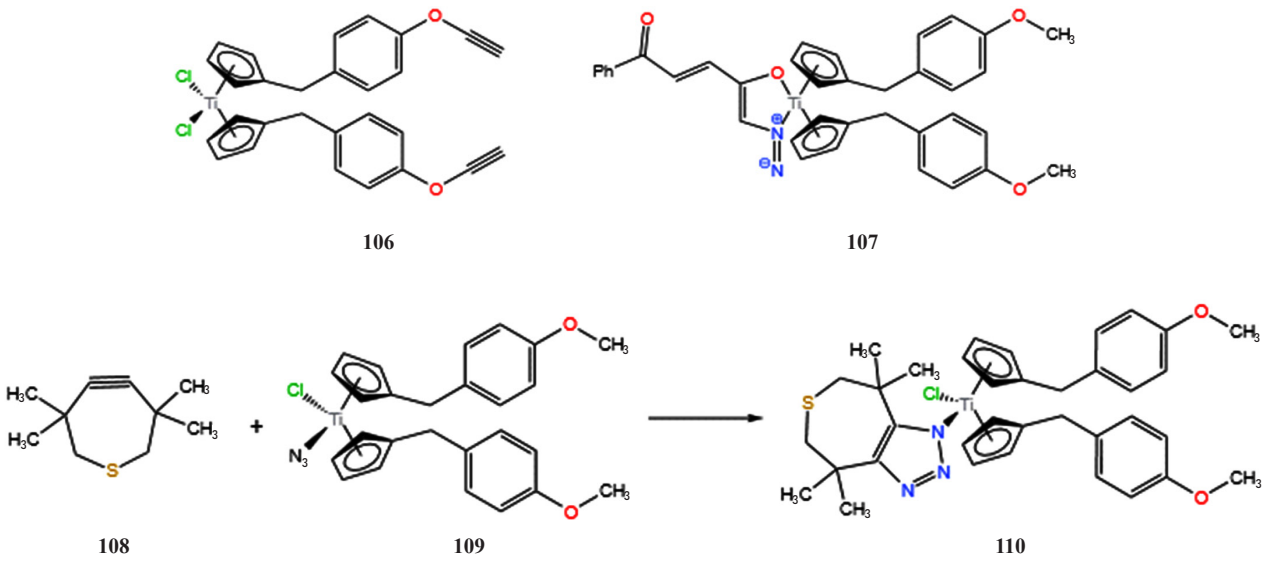


Figure 29. Orthogonal modifications of titanocene Y

Additional modifications of product **110** are available through substitution reactions of the chloride ligand, underlying the versatility of the approach. Moreover, the **106** Titanocene Y modification may react with diazide complexes **55**, **113** and the like to perform a double [3 + 2] click cycloaddition.

2.15 *Di(trimethylsilyl)acetyline titanium complex with heteroaromatic nitriles*

The reaction of complex **81** with di(trimethylsilyl)acetyline $Me_3Si-C\equiv C-SiMe_3$ in the presence of Mg will afford complex **111**, a starting material for homocoupling reactions with heteroaromatic nitriles like 2,6-dicyanopyridine[41] (Figure 30), 2-cyanofuran, or 2-cyanothiophene. Product **112**, carrying two cyano groups, is amenable to a double reaction with the titanium di(triazide) **113** to form the unusual bimetallic complex **114**, a potential therapeutic agent, originating from the two indole scaffolds connected by two tetrazole rings.

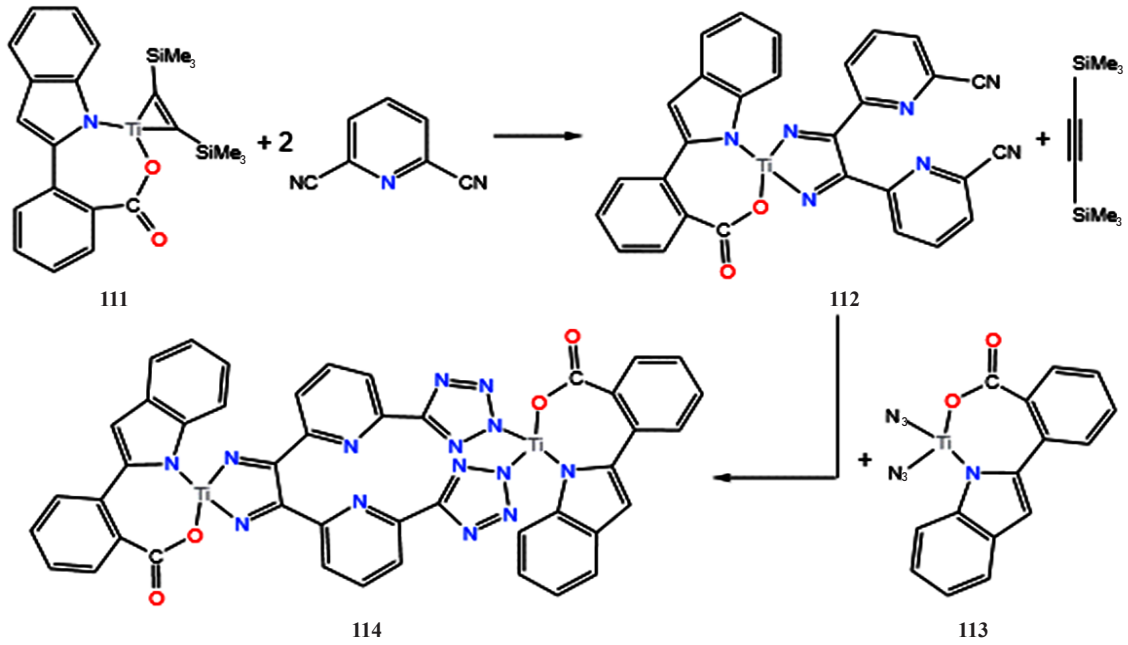


Figure 30. Complex **114**, featuring two indole scaffolds connected by two tetrazole rings

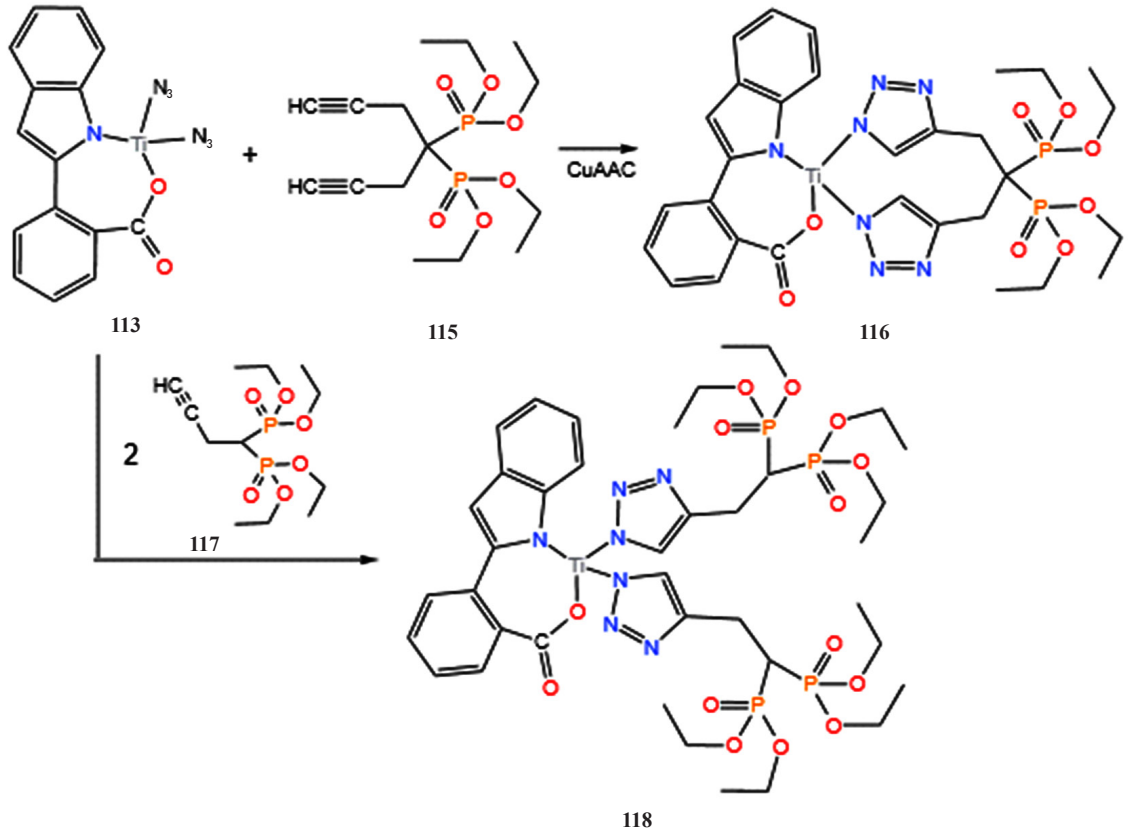


Figure 31. Reactions of mono- and di-propargyl phosphonates with diazido carboxylate titanium 2-phenyl indole complex **113**, producing complexes **116** and **118**, with improved aqueous solubility

2.16 *Double cycloadiition of dipropargil bisphosphonate with diazido carboxylate titanium 2-phenyl indole*

Dipropargyl bisphosphonate[42] **115** (Figure 31) is an interesting molecule in terms of increasing aqueous solubility and biocompatibility, when partnering with a bioactive molecule. Accordingly, the bis-triazide complex **113** will undergo a double [3 + 2] click cycloaddition to produce complex **116**, a potential drug candidate. Two equiv of propargyl bisphonate **117** will react similarly with bis-diazide **113**, introducing four phosphonate groups per Ti in the **118** molecule.

2.17 *Titanium complexes derived from N-alkynylheterocycles*

N-alkynylheterocycles of benzimidazole (**119A**) and indazole (**124A**) are converted to triazoles (**119**, **121**, **124**, Figure 32) by click chemistry.[43] These triazoles react with $TiCl_4$,[38] $Ti(NMe_3)_2Cl_2$ or $TiCl_3(THF)_3$[39] under specified reaction conditions to yield the corresponding titanium complexes, each one with its own individual titanium-to-ligand coordination pattern. Thus, benzimidazole complex **119** dissolved in toluene reacts with one equiv of $TiCl_4 \cdot NEt_3$ at elevated temperature to afford the five-coordinated organotitanium complex **120**. Carbene **121** reacts with $TiCl_4$[44] [or $Ti(NMe_3)_2Cl_2$[45]] at -15 °C to RT to form the hexa-coordinated complex **122** (Figure 32), with a prominent Ti-C σ-bond as well. Whereas room temperature for click reactions is the norm, lower starting temperature for carbene **121** is required, since it is highly reactive. The same carbene **121** in the presence of $TiCl_3(THF)_3$ creates the Ti^{+3} five-coordinated complex **123**. Finally, N,N-indazole triazole **124** forms a hexa-coordinated chelate compound **125**.

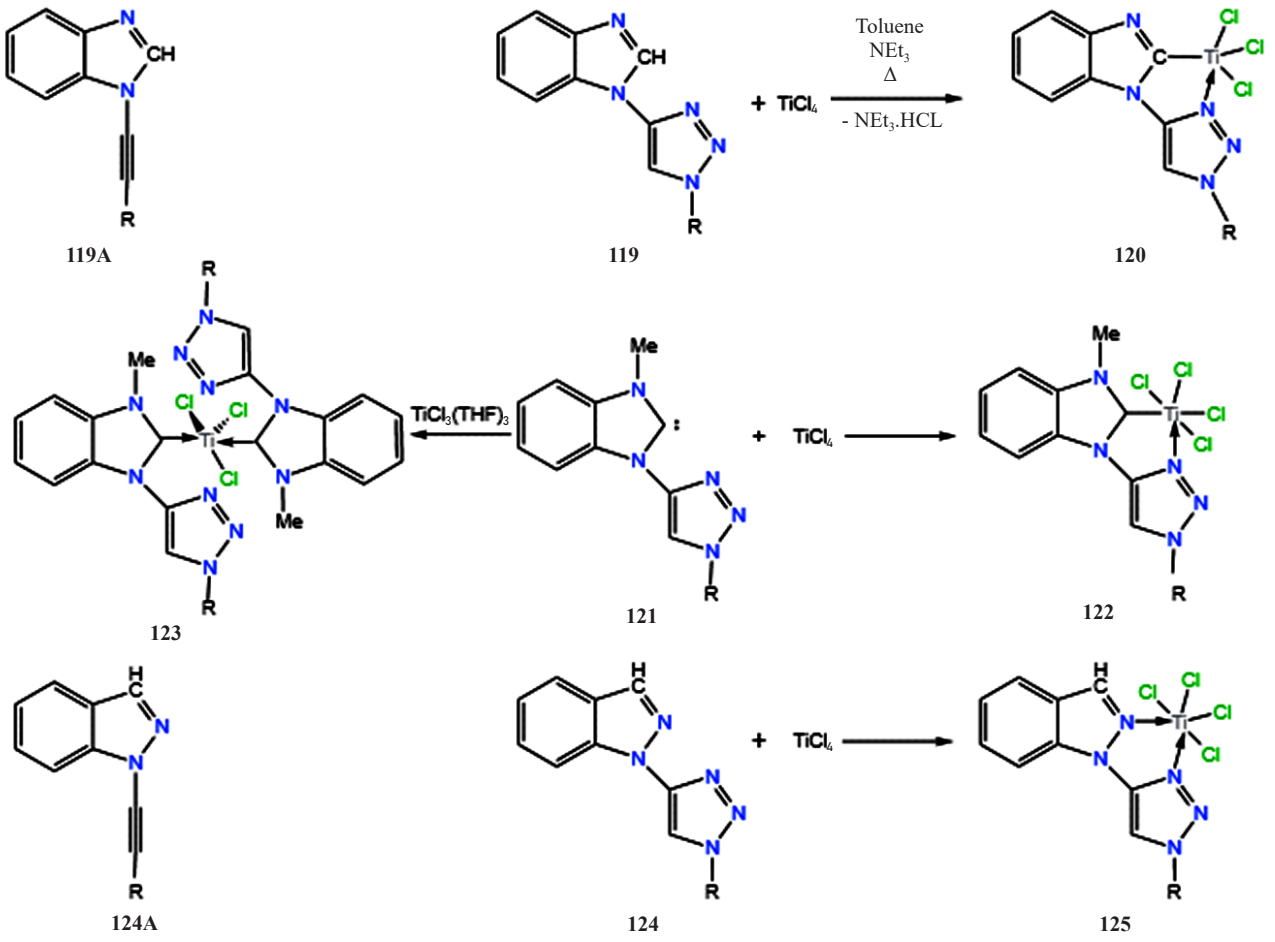
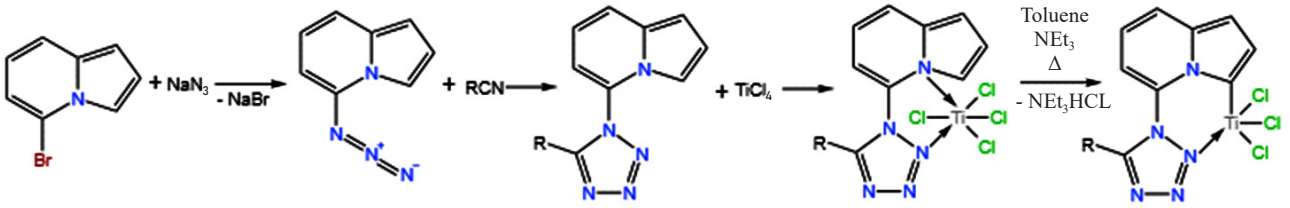


Figure 32. Titanium complexes of N-alkynylheterocycles

Titanium azides of these N-alkynylheterocycles are formed by reaction with Me_3SiN_3 as previously described, making them attractive building blocks for bioorthogonal applications.

Indolizines are also versatile building blocks for natural product synthesis, possessing a large range of bioactivities and interesting photophysical properties.[46] Commercially available 5-bromo-indolizine **126**, reacts with NaN_3 to form azide **127**, Figure 33. Further reaction with a nitrile RCN affords the 5-tetrazole-indolizine **128**. The latter forms a hexacoordinated titanium tetrachloride complex **129**, which, at elevated temperature in the presence of NEt_3 or pyridine, transforms to the organotitanium complex **130**, a novel building block for bioorthogonal synthetic applications.

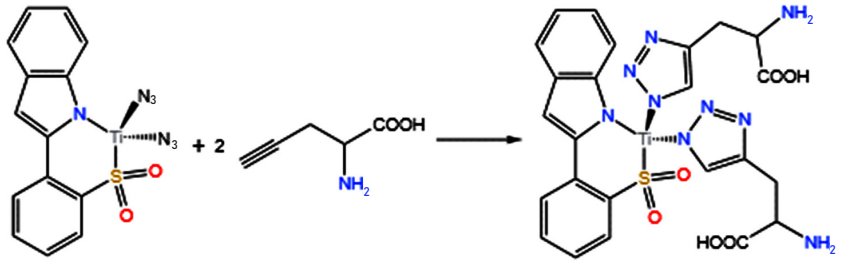


126 **127** **128** **129** **130**

Figure 33. From 5-bromo-indolizine **126** to the organotitanium complex **130**

2.18 *An organotitanium aminoacid*

Two equivalents of L-propargyl glycine[47] **131** "click" with the diazide complex **49** (Figure 34) to form an organotitanium aminoacid **132**, which could find bioorthogonal application participating in peptide synthesis. Several other variations of this approach may be considered, including monosubstitution and the use of alternate titanium azides (**113**).

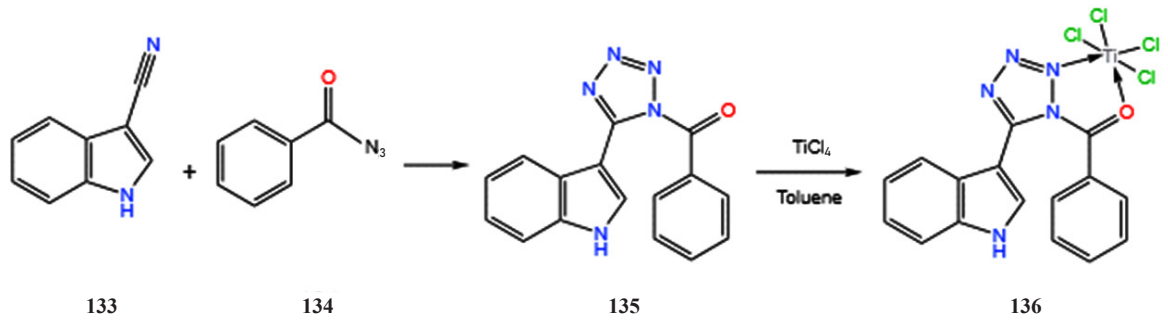


49 **131** **132**

Figure 34. Synthesis of organotitanium aminoacid **132**

2.19 *Titanium complex from the cycloaddition of 3-cyanoindole with benzoyl azide*

3-Cyanoindole (indole 3-carbonitrile) **133** reacts with benzoyl azide **134** producing the indole-3-tetrazole-4-benzoyl ligand **135**, coordinating with $TiCl_4$ in toluene to afford complex **136**, Figure 35. Acyl azides like **134** are conveniently synthesized by the one-step conversion of esters with diethylalumnum azide.[48]

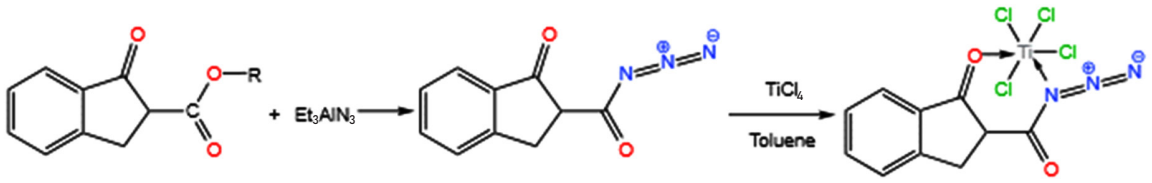


133 134 135 136

Figure 35. Cycloaddition of 3-cyanoindole **133** with benzoyl azide **134**. Ligand **135** reacting with $TiCl_4$ to afford complex **136**

2.20 *Diethylaluminum azide azidation of 1-indanone-2-carboxylic acid ester. Azide and other potentially bioactive heterocyclic titanium complexes*

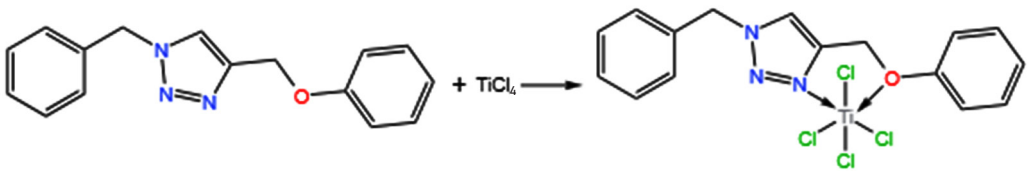
1-Indanone-2-carboxylic acid ester **137** will undergo azidation with diethylaluminum azide Et_2AlN_3 affording **138**, which will interact with $TiCl_4$ to form the hexacoordinated complex **139**, Figure 36. Both products **138** and **139** are prone to an α-alkynylation in the 2-position of the indanone framework by Br-C≡C-EWG (EWG = Electron Withdrawing Group, i. e. alkyl esters, ketones, amides, and sulfones).[49]



137 138 139

Figure 36. 1-Indanone-2-carboxylic acid ester **136** azidation with Et_2AlN_3 to afford azide **138**, complexing with $TiCl_4$

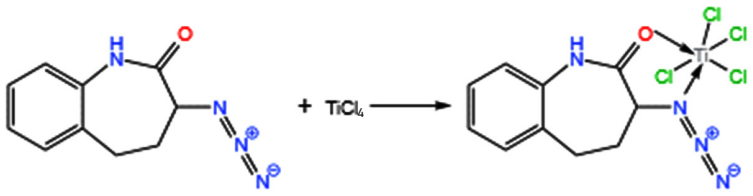
The reaction between phenyl propargyl ether and benzylazide[50] in the presence of 5 mol% of sodium ascorbate and 1 mol% of copper(II) sulfate in a 2:1 mixture of water and tert-butyl alcohol furnished the 1,4-disubstituted triazole product **140** in 91% yield after stirring for eight hours at RT. Product **140** ligates promptly with $TiCl_4$ affording the hexacoordinated complex **141**, Figure 37.



140 141

Figure 37. 1,4-Disubstituted triazole-ether **140** forming titanium complex **141**

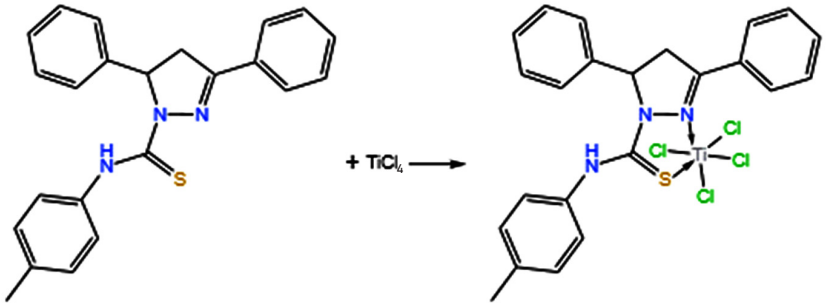
The cyclic amide-azide **142**[51] undergoes a similar facile ligation with $TiCl_4$ to produce complex **143**, Figure 38.



142 143

Figure 38. Coordination of amide-azide **142** with $TiCl_4$

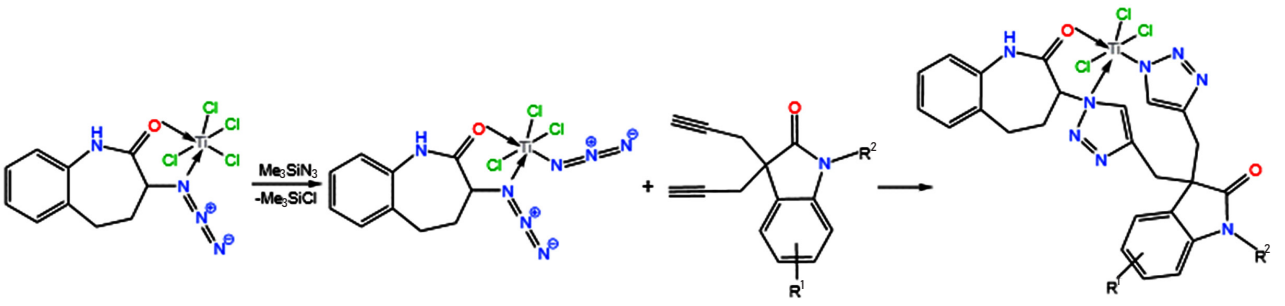
Pyrazolinethiocarbamoyl complexes have shown antivirus activity,[52] including coronavirus. A representative ligand **144** coordinates with $TiCl_4$ to form the corresponding titanium coordination compound **145**, Figure 39.



144 145

Figure 39. Pyrazolinethiocarbamoyl ligand **144**, corresponding $TiCl_4$ complex **145**

Reaction with Me_3SiN_3 with anyone of the above mentioned titanium coordination compounds (**136**, **139**, **141**, **143**, **145**) will introduce the [Ti-N_3] functionality into the molecule, transforming them into attractive partners in a variety of click reactions. For example, complex **143** will form **146**, which reacts the dialkyne oxindole **102** affording the di-triazole complex **147**, Figure 40. The cycloaddition reaction is expected to take place stepwise, with one of the azide functionality reacting with a triple-bond first creating a transient intermediate, which reacts further intramolecularly to yield **147** as the final product.



143 146 102 147

Figure 40. A common reaction pathway of an easily accessible diazide with a dialkyne

The chiral lithium complex **148**[53] was converted to the chiral benzenesulfonylpyrrolidine titanium dichloride complex **149** by treatment with an equivalent amount of $TiCl_4$. Complex **149** converts to the diazide **151**, Figure 41, over the intermediate formation of the di-isopropoxide **150**, reminiscent of Figure 4. Reaction of complex **151** with dipolarophile DMAD may follow.

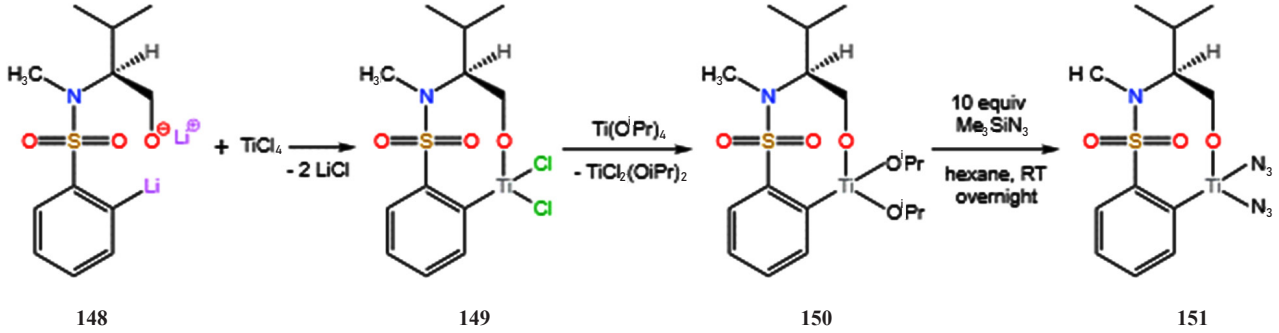


Figure 41. Synthesis of chiral organotitanium diazide **151**

2.21 *The essential role of $Ti(NMe_2)_4$ in complex formation*

Two equivalents of the isopropoxy tosylsulfonamide **152** undergo an exchange reaction with $Ti(NR_2)_4$ (R = Me or Et) to form complex **153**.[54] The bis-azide complex **154** is obtained from **153** in the presence of excess Me_3SiN_3,[55] Figure 42.

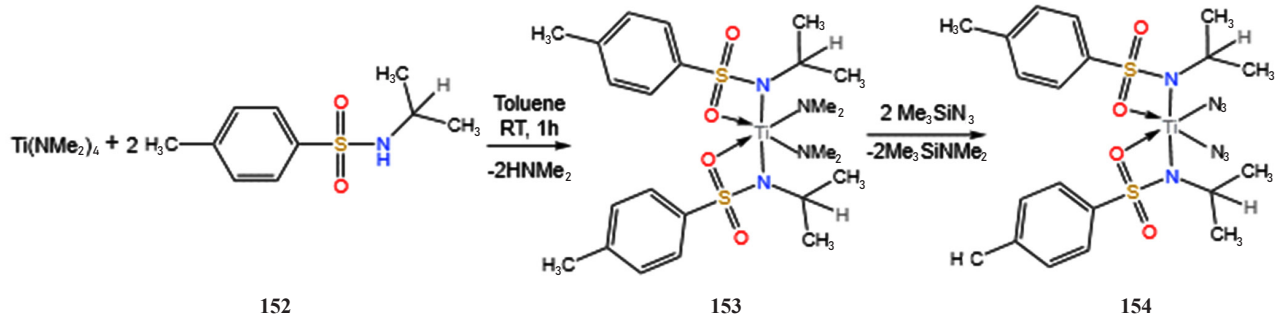
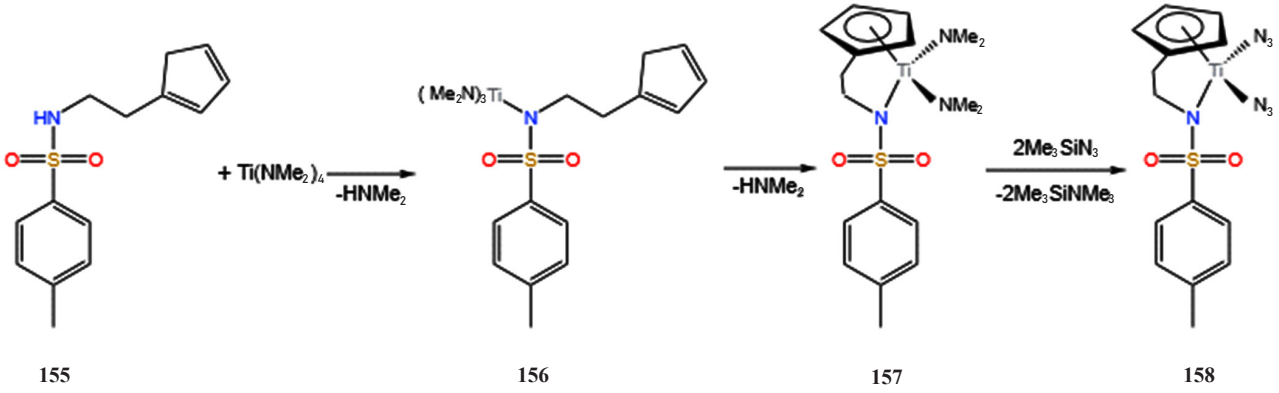


Figure 42. Exchange reaction of $Ti(NMe_2)_4$ with isopropoxy tosylsulfonamide **152**

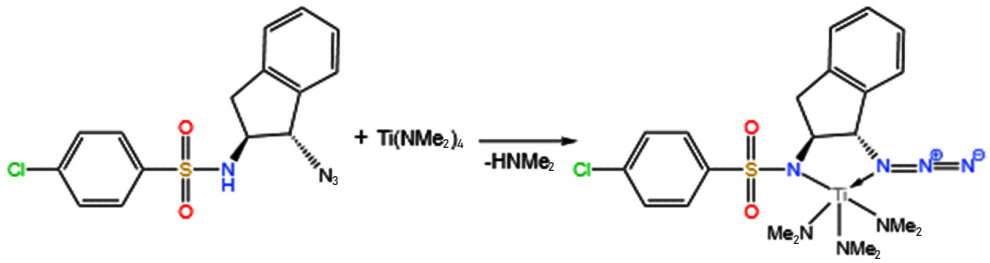
In a similar fashion, the cyclopentadienylsulfonamido ligand **155**[56] reacts with $Ti(NMe_2)_4$ at RT in toluene to form the intermediate **156**, by elimination of one equivalent $HNMe_2$. The reaction is completed at RT by a second equivalent $HNMe_2$ elimination, and formation of the cyclopentadienylsulfonamido complex **157**. It reacts further with Me_3SiN_3 to afford the corresponding diazide **158**, Figure 43.

More than a dozen sulfonylamines carrying a pendant triazide group in the β-alkyl position, formed in a regioselective manner, have been prepared by the ring opening of several aziridines with NaN_3 in a DMF/H_2O solution, under specified conditions.[57] Representing the group, β-azidosulfonylamine **159** reacts as described above with $Ti(NMe_2)_4$ to produce complex **160**, having a characteristic azide bridge bonding, Figure 44. Additional triazide functionalities may be introduced into the coordination sphere of complex **160** by an exchange reaction using Me_3SiN_3.



155 156 157 158

Figure 43. Synthesis of the cyclopentadienylsulfonamido diazide **158**



159 **160**

Figure 44. β-Azidosulfonylamine **159** undergoing exchange with $Ti(NMe_2)_4$

2.22 *Titanium complexes with pharmacologically active heterocyclic compounds*

Several heterocyclic compounds, in particular those known for their pharmacological properties, coordinate promptly with $TiCl_4$ in toluene under mild conditions to afford 1 : 1 coordination complexes, precursors to additionally planned click reactions, as described previously in this review article. Among them, 1-phenyl indazolle[58] forms the hexacoordinated complex **161**, 1-benzyl-4-phenyl triazole[59] forms complex **162**, the products of 4-fluorobenzonitrille with different alkenes and alkynes[60] will afford complexes of the type **163**, and 1,4 disubstituted 1,2,3-triazoles[55] will produce complex **164**.

2.23 *Proposed beneficial effect of the azide group in ortho-metallation*

A $TiCl_4$ complex formed with 2-phenyl pyridine **165** is expected to undergo phenyl titanation at elevated temperature, in a similar fashion as its Pd, Rh and Ir counterparts, mimicking the orthotitanation mechanism of 2-phenylindole.[16, 17] It is proposed that phenyl titanation of 2-phenyl pyridine will be greatly facilitated by an exchange of a chloride with an azide group to yield **166**. The organotitanium azide **167** will form at an elevated temperature in the presence of NEt_3, Figure 45.

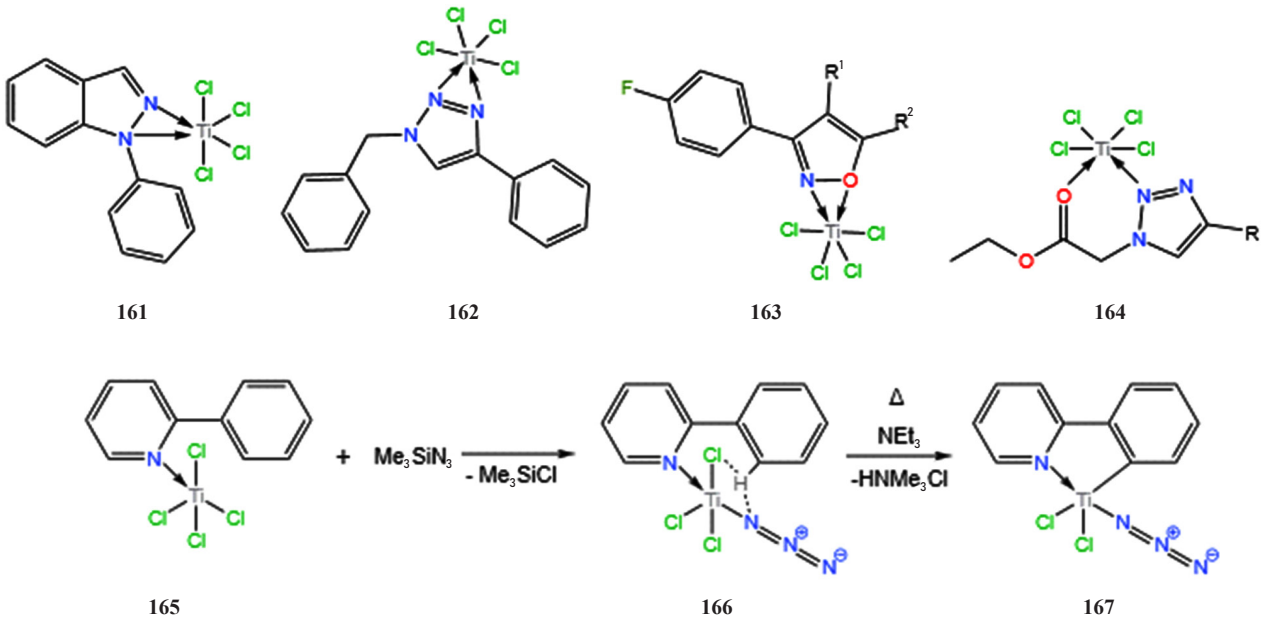


Figure 45. Orthotitanation of 2-phenyl pyridine titanium tetrachloride complex **165**, aided by the azide intermediate **166**

3. Conclusions and future perspectives

Organotitanium click chemistry is intertwined with azide click chemistry, originating from the facile creation of [Ti-N_3] moieties in multiple organotitanium complexes. Azide click chemistry is widely used in pharmaceutical and biotech fields, due to its mild conditions, fast speed, and biocompatibility. Moreover, unlike other transition metals, the high tolerance of titanium in the human body[36] is a determining factor in pharmaceutical applications of organotitanium click complexes.

Over three dozen documented new examples of organotitanium click chemistry have been proposed, responsible for synthesis of a plethora of new organotitanium complexes and derivatives, suitable for pharmacological and bioorthogonal applications. The majority of these proposals were inspired by the comparative chemistry of titanium and other transition metals, an approach supported by recent findings, e.g., the synthetic pathway illustrated in Figure 3 applicable to several transition metals, and the orthometallation of 2-phenyl indole, enacted separately by Ti, Rh, Ir, and Pd reactants.

After considering the click chemistry prospects of existing titanium azides, both inorganic and metallocene-based, we introduce a recently discovered class of organotitanium chloride complexes shown in Figure 2, easily replacing a chloride ligand with an azide via Me_3SiN_3 exchange, forming monoazide complexes. Diazide complexes may be formed starting with a [Ti(O^iPr)$_2$] moiety and applying excess Me_3SiN_3. These new azides undergo cycloaddition reactions with nitriles, isonitriles, cyanates, isocyanates, isothiocyanates, CS_2, alkynes, alkenes, etc.

A notable synthetic approach is the exchange reaction between Ti(NR_2)$_4$ (N = Me, Et) and several sulfonylamides, affording complexes with the general formula (sulfonylamide)$_x$Ti(NR_2)$_{4-x}$. The [Ti-NR_2] functionality converts readily to [Ti-N_3] in the presence of Me_3SiN_3.

Insertion of small molecules (SO_2, CO_2, even RN_3 among several other) into the active Ti-C σ-bond of the organotitanium complexes has now been introduced to click chemistry protocol for the first time. Insertion improves the properties (aqueous solubility, thermal and air stability) of the complexes, making them attractive for targeted applications, and increases the number of possible product variations almost exponentially.

The new organotitanium click chemistry described in the present review will enrich our knowledge in this important area of chemistry, with expected desirable ramifications in bioorthogonal and pharmacological applications.

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Conflict of interest

The author declares that he has no conflict of interest.

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