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Titanium Redox Catalysis: Insights and Applications of an Earth-Abundant Base Metal

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Abstract

π -acid ancillary ligands, reactants, or products can stabilize reactive low valent Ti intermediates through backbonding, and present opportunities for the development of vast new classes of Ti-catalyzed redox reactions with practical applications.

Graphical Abstract

Titanium is the second-most abundant transition metal in the Earth's crust.^{1,2} Despite this, Ti is largely underappreciated in the field of "base metal" catalysis. Nonetheless, Ti has many qualities that makes it appealing for continued method development. For example, the byproduct of workup from most Ti-catalyzed reactions, TiO_2 , is generally nontoxic, unlike late transition metals such as Ni.³ Additionally, Ti can access structures (*e.g.* metal-ligand multiple bonds) and elementary reaction steps (*e.g.* [2+2] cycloadditions) not commonly available to first row late transition metals, potentially allowing access to new types of catalytic transformations. Furthermore, there is extensive precedent of elegant and useful stoichiometric Ti-mediated coupling reactions that provides a basis for new catalytic methods.⁴

However, a significant challenge of designing new catalytic reactions with Ti is the thermodynamic stability of its highest oxidation state, Ti^{4+} , as well as its high oxophilicity. As a result, there are few Ti-catalyzed reactions that actually capitalize on metal-based redox events; instead, catalysis with Ti has largely been dominated by olefin polymerization⁵ and hydrofunctionalization,⁶ reactions that do not require formal redox changes at the metal.

The focus of this article is to highlight catalytic Ti coupling reactions that involve formal redox events at the metal, both old and new. There are several powerful classes of Ti redox catalytic reactions that have made an impact in the field of organic chemistry, and we seek to

establish design principles shared amongst these reactions that may lead to continued innovation in this promising field.

C-C Bond Forming Reactions

The most ubiquitous Ti redox catalytic reaction in organic synthesis is the Kulinkovich reaction, which yields cyclopropanols from the reaction of alkyl Grignard reagents with esters (Figure 1a).⁷ Computational⁸ and some mechanistic studies⁹ have elucidated the general mechanism of the Kulinkovich reaction as outlined in Figure 1b.¹⁰ Initiation of the reaction via alkylation of $\text{Ti}(\text{O}^i\text{Pr})_4$ followed by β -hydride abstraction leads to the formation of an η^2 -olefin complex, **1**, similar to the synthesis of the Negishi reagent.¹¹ Due to significant backbonding this complex is best described as a Ti^{IV} titanacyclop propane, which serves to “mask” a potential low-valent Ti^{II} intermediate. This titanacyclop propane then undergoes insertion of the ester to give an oxotitanacyclobutane, **2**, and then β -oxo-elimination followed by α,γ -coupling leads to the formation of a cyclopropoxide **4**. Further alkylation by the Grignard reagent closes the catalytic cycle.

Many new advances in Kulinkovich-type reactions have been developed since its initial discovery and a number of reviews highlight this work as well as other divergences from the use of $\text{Ti}(\text{OiPr})_4$ type-catalysts.¹² Two major modifications of the reaction, by de Meigere¹³ and Szymoniak,¹⁴ have been developed allowing for the synthesis of cyclopropylamines from amides and nitriles, respectively (Figure 2a). New ligand systems have also been utilized to promote the enantioselective synthesis of cyclopropanols (although with moderate ee's).^{9a} Numerous natural products have been synthesized using this reaction (Figure 2b),¹⁵ and the reaction has been developed for large/process scale use (> 1kg).¹⁶

Additionally, masked Ti^{II} species can catalyze alkyne cyclotrimerization (Figure 3a). Ladipo¹⁷ and Rothwell¹⁸ explicitly studied the mechanism and selectivity of this reaction using calixerene and aryloxide ligands, respectively, although this reaction can be catalyzed across a very broad spectrum of Ti complexes.¹⁹ The overall catalytic cycle for the trimerization of alkynes using the (DMSC) TiCl_2 catalyst developed by Ladipo is shown in Figure 3b.^{17b} In these reactions, arene-backbonded species such as **8** are often the resting state of the catalytic cycle.¹⁷ Calixarene ligands give high regioselectivity for 1,2,4 benzene products (Figure 3c),¹⁷ and can also incorporate alkenes as a third coupling partner to give cyclohexadiene products.²⁰

The last major class of successful Ti redox-catalyzed C-C bond forming reactions is the Pauson-Khand synthesis of cyclopentenones (Scheme 4a).²¹ While a broad range of transition metals catalyze the Pauson-Khand reaction, the Ti-catalyzed variant was initially studied by Buchwald using Me_3SiNC ,²² and later expanded toward the general use of CO.²³ The mechanism of this reaction was studied in detail, and is presented in Figure 4b.^{23b} The reaction begins with a $\text{Cp}_2\text{Ti}(\text{CO})_2$ precatalyst **9** which undergoes ligand exchange with the alkyne of an enyne to give an η^2 -titanacyclop propene, **10**. The second CO is then displaced by incoming olefin and is then inserted into this metallacycle to give the intermediate titanacyclopentene, **11**. Coordination and insertion of CO gives the ring-expanded titanacyclohexenone, **12**, which can then undergo reductive elimination with coordination of

another equivalent of CO to give the bicyclic cyclopentone product and $\text{Cp}_2\text{Ti}(\text{CO})$. Much like in the Kulinkovich reaction, a key feature of the Ti-catalyzed Pauson-Khand reaction is the ability of a reaction component to stabilize low-valent Ti intermediates through backbonding: in this case, either incoming CO ligands or the alkyne triple bond.

The reaction was later developed to give asymmetric products using the ETBHI (EBTHI = ethylene *bis*(tetrahydroindenyl) ligand giving ee's from 70–95%²⁴ (Figure 4c). Different coupling partners such as allenes have also been incorporated, and the reaction is tolerant of a variety of functional groups including ethers, esters, and tertiary amines.^{23b,24c} TMS-substituted alkynes were not tolerated with this system due to steric hindrance, although less encumbered dimethylsilanes^{23b} are viable substrates. TMS-substitution was realized later by using less sterically hindered mono-Cp aryloxide Ti complexes.²⁵

C-O Bond Forming Reactions

Typically titanium C-X redox-forming events are quite challenging due to the stability of Ti-O and Ti-N bonds. Remarkably, Buchwald²⁶ and Crowe²⁷ both reported stoichiometric and catalytic C-O bond forming hetero Pauson-Khand reactions for the synthesis of bicyclic γ -butyrolactones from tethered enals and enones (Figure 5a). These reactions initially form an oxatitanacyclopropane **14** from an aldehyde or ketone and Ti^{II} that can then follow the classical Pauson-Khand mechanism (Figure 5b). The key step in these catalytic reactions is the surprising CO-induced C-O reductive elimination from an oxatitanacyclohexanone intermediate **16**: normally, one would envision that the Ti-O bond would be very stable due to the oxophilicity of Ti. This reaction again demonstrates the utility of a backbonding reagent such as CO in masking low valent Ti intermediates and driving catalytic reactions forward.

Notably Crowe^{27b} was able to enantioselectively cyclize alkyl ketones and aldehydes using C_2 -symmetric (EBTHI) $\text{Ti}(\text{CO})_2$, although in both cases only moderate ee's were achieved. In each of these procedures, 20–100 mol % PMe_3 was used as an additive to allow for lower catalyst loadings. Interestingly, aldimines are incompatible with this reaction—this seems to be a result of CO being unable to insert into the azatitanacyclopentane,^{27a} which highlights the subtle stereoelectronic balance required for productive reactivity.

C-B Bond Forming Reactions

Although there are significantly fewer examples with Ti than late transition metals, hydroboration and borylation are increasingly important reactions as they yield precursors for various C-C and C-X coupling reactions. In the mid 1990s, Hartwig reported catalytic borylation reactions using low-valent Ti precatalysts (Figure 6a).²⁸ $\text{Cp}_2\text{Ti}(\text{CO})_2$ is an efficient and highly anti Markovnikov-selective precatalyst for the hydroboration of alkynes to vinylboranes with catecholborane, while Cp_2TiMe_2 and the σ -borane complex $\text{Cp}_2\text{Ti}(\text{HBCat})_2$ (HBCat = catecholborane) catalyze the hydroboration of alkenes to alkylboranes.

Each of these reactions has been extensively studied both experimentally²⁹ and computationally,³⁰ and both hinge on important steps involving masked Ti^{II} complexes

similar to the Pauson-Khand and Kulinkovich reactions. The mechanism for alkene borylation is shown in Figure 6b: in this case the diborane σ -complex, **17**, which stabilizes the $\text{Cp}_2\text{Ti}^{\text{II}}$ fragment through a 3-center-2-electron bond, loses borane to make a monoborane adduct **18** and reacts with an alkene to make an alkene-borane intermediate **19**, which likely has important contributions from the Ti^{IV} alkyl hydride resonance structure.^{30b} **19** can then undergo reductive elimination to liberate the alkylborane product.

Additionally, Smith discovered that $\text{Cp}^*\text{Ti}(\text{n}^2\text{-C}_2\text{H}_4)$ is capable of catalyzing the dehydrogenative borylation of ethylene to yield vinyl boranes (Figure 6c).³¹ This reaction proceeds through a alkene borane/alkyl hydride intermediate **20** similar to that proposed by Hartwig. In lieu of direct reductive elimination, **20** first undergoes β -H elimination to an alkene dihydride **21** (or direct β -H abstraction to give **18**), which can lose H_2 to form the borylated alkene titanacyclopropane adduct **22**. In fact, small amounts of dehydrogenative borylation products were also observed during hydroboration reactions.^{28,29} Smith utilized a nitrogen-based borane, HBOP (benzo-1,3,2-diazaborolane) because the more electron-rich and bulky alkyl-substituted titanocenes undergo rapid decomposition when hydroborations are attempted with HBcat, indicating that the general utility of oxygen-substituted boranes in Ti catalysis may be limited.

C-N Bond Forming Reactions

Despite the ubiquity of C-N bond forming hydroamination reactions,^{6b} until recently there were no examples of Ti-catalyzed oxidative C-N bond forming reactions. In 2016, we reported a Ti imido-catalyzed formal [2+2+1] oxidative coupling of alkynes with aryl diazenes to yield pyrroles (Figure 7a).³² This reaction is a synthetically attractive, modular route to pentasubstituted and electron-rich pyrroles, which are typically challenging moieties to access. In general, terminal, alkyl, aryl and TMS protected alkynes are all suitable substrates for this reaction. In the case of unsymmetrical alkynes mixtures of regioisomers were observed, with the 2,4-disubstituted regioisomer predominating in cases where there is significant steric differentiation between the halves of the alkyne.

Preliminary mechanistic investigation (Figure 7b) indicates that this reaction proceeds *via* [2+2] addition of an alkyne to a Ti imido **23**—analogous to the first step in Ti-catalyzed alkyne hydroamination—followed by second insertion of an alkyne into the resulting azatitanacyclobutene **24** to yield an azatitanacyclohexadiene **25**. This metallacycle then undergoes C-N reductive coupling to yield the product pyrrole and a Ti^{II} fragment that is likely stabilized by backbonding³³ into the pyrrole **26** or an incoming diazene/alkyne **27**, in a manner similar to that seen for the Pauson-Khand reaction. Finally, reoxidation to a Ti imido *via* diazene disproportionation closes the catalytic cycle.

Similarly, we have expanded upon this [2+2+1] reaction to include the multicomponent coupling of diazenes, alkynes and alkenes (Figure 8a).³⁴ We hypothesized that since alkenes readily undergo 1,2 insertion into Ti-C bonds but do not typically participate in [2+2] reactions with Ti imidos, that we would be able to selectively heterocouple them with alkynes to make dihydropyrroles, in direct analogy to the [2+2+1] pyrrole synthesis.

These reactions proceed to give the expected azatitanacyclohexene intermediate, **28**, but are unable to undergo C-N reductive coupling: sp^3 -C-N reductive elimination is significantly more challenging than sp^2 -C-N elimination (Figure 8b). As a result, new pathways are opened up to catalytically synthesize α -iminocyclopropanes (nucleophilic metallacycle collapse, **29**) or α - β -unsaturated imines (β -H elimination, **31**), each resulting in formal oxidative carboamination of the alkyne. In each case, we hypothesize that Ti backbonding into the resulting imine products (**30**, **32**) is likely key for productive catalysis, in analogy to the other examples provided herein. Interestingly, the mechanism of nucleophilic metallacycle collapse that yields the α -iminocyclopropane product is similar to that observed in the Kulinkovich cyclopropanation. Similar to Crowe's Pauson-Khand with ketones, small steric changes dramatically affect product distributions: for example, carboamination of 2-butyne yields exclusively iminocyclopropanes, while carboamination of 3-hexyne yields 50:50 a mixture of iminocyclopropane and α - β -unsaturated imine.

These oxidatively carboaminated alkyne products are synthetically useful: for example, α -imino functionalized cyclopropanes are versatile building blocks for a variety of applications including dihydropyrroles, dihydroazepines, and dihydropyridones (Scheme 6c).³⁵

Wolczanski recently reported another example of oxidative C-N bond formation catalyzed by Ti, the carbonylation of azides to give isocyanates (Figure 9a).³⁶ This reaction is similar to a strategy employed by Heyduk for Zr-catalyzed isocyanide imination.³⁷ Unlike the other reactions presented herein, this reaction hinges on the redox noninnocent behavior of the tetradentate (dadi) ancillary ligand, which cycles between a (dadi)⁴⁻ and (dadi)²⁻ state upon oxidation, instead of metal-based redox (Figure 9b). An important feature of this catalytic system is that the redox changes of the (dadi) ligand prevent strong binding of CO, which may partially explain why this reaction can be run at significantly lower temperature than the alkyne oxidative amination reactions. Thus, while redox noninnocent ancillary ligands aren't necessary for Ti redox catalysis, they may play a role going forward in accessing reactivity under milder conditions.

Conclusions and Outlook

While still relatively uncommon, Ti redox catalytic reactions are poised to be an important tool going forward—particularly in reactions that involve substrates (alkenes, alkynes, CO, *etc*) or products (arenes, cumulenes, dienes, and double bonds) that can act as π -acids and stabilize otherwise high energy Ti^{II} intermediates. While new examples of Ti redox catalysis have been scarce over the intervening 20 years since the discovery of the Kulinkovich and Ti-catalyzed Pauson-Khand reactions, the recent discovery of several new C-N bond-forming reactions suggests that there is room for continued discovery. It is our opinion that by examining classical Ti- and other early transition metal-mediated reactions through the lens of 21st century organometallic catalysis, many new, useful catalytic reactions will be discovered. For example, Rosenthal has extensively studied the structure, reactivity and catalytic behavior of many π -acid stabilized masked Ti^{II} species;³⁸ these types of fundamental studies are poised to impact new avenues of Ti redox catalytic processes.

An ongoing challenge facing early transition metal catalysis is the often-empirical choice of ligands for a given reaction. This is clear in the examples above: many involve some type of reductive elimination of a titanacycle to yield a masked Ti^{II} species. Many questions remain in these reactions: what is the role, both from the perspective of electronics and sterics, of the ligand in promoting these unique transformations? In each case, starkly different ligands are used, with limited theoretical rationale behind the choice. Unlike the late transition metals,³⁹ parameterization of ligands for the early transition metals lags behind, which makes direct comparisons between disparate ligand sets (and as a result, the rational design and understanding of new catalytic reactions) particularly difficult. In this regard, there is a significant opportunity for impact by developing new free energy relationships such as the Ligand Donor Parameter (LDP) method designed by Aaron Odom.⁴⁰

Another important factor to consider going forward is designing new, reliable routes to the *in situ* generation of reduced Ti catalytic intermediates. Many low valent early transition metal complexes rely on strong reductants in their synthesis, which may preclude their use by nonspecialist researchers. Using simple Ti starting materials in conjunction with commonly-used organic reagents (*e.g.* Grignards in the case of Kulinkovich; alkynes in the case of C-N couplings) is an important consideration for developing widely-used chemistries.

In comparison to late transition metals, early transition metal catalysts will almost certainly always be limited by their oxophilicity and Brønsted basicity. However, it is best to view these reactions as complementary to late transition metal catalyzed reactions. Early transition metals provide access to new mechanisms and retrosynthetic disconnections, and yet can also access classical late transition metal transformations through different mechanisms (*e.g.* β -H abstraction *vs.* β -H elimination). Additionally, early metals often have *different* functional group tolerances than classical late metal systems—for example, aryl iodides are well tolerated in all of the C-N coupling reactions described above.

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a. Kulinkovich Cyclopropanation: **b. Generalized Mechanism:** **Figure 1.**

Mechanistic details of the Kulinkovich cyclopropanation.

a. Cyclopropylamines from Modified Kulinkovich Conditions:*de Meijre:* *Szymoniak:* **b. Kulinkovich Examples in Total Synthesis:**

Figure 2.
Modifications and applications of Kulinkovich cyclopropanations.

a. Alkyne Cyclotrimerization: **b. Generalized Mechanism:** **c. Catalysts for Selective Trimerization:**

Figure 3.
Alkyne cyclotrimerization catalyzed by low valent Ti^{II} .

a. Pauson-Khand Reaction: **b. Generalized Mechanism:** **c. Enantioselective Pauson-Khand:**

Figure 4.
Mechanistic details of the Ti-catalyzed Pauson-Khand reaction.

a. C-O Bond Formation in the Hetero Pauson-Khand:

b. Generalized Mechanism:

Figure 5.

Further elaborations of the Ti-catalyzed Pauson-Khand reaction yield lactone products.

a. Alkene/Alkyne Hydroboration: **b. Generalized Mechanism:** **c. Dehydrogenative Borylation:**

Figure 6.
Ti-catalyzed borylation reactions.

a. Ti-Catalyzed [2+2+1] Pyrrole Synthesis: **b. Generalized [2+2+1] Mechanism:** **c. Regioselectivity with Unsymmetric Alkynes:**

Figure 7.
Ti imido-catalyzed pyrrole syntheses.

b. Abbreviated Carboamination Mechanisms:

c. Carboaminated Products as Building Blocks:

Figure 8.
Oxidative alkyne carboamination via Ti redox catalysis.

a. Azide Carbonylation: **b. Proposed Mechanism:**

Figure 9.
Redox noninnocence opens an avenue for Ti-catalyzed nitrene carbonylation.