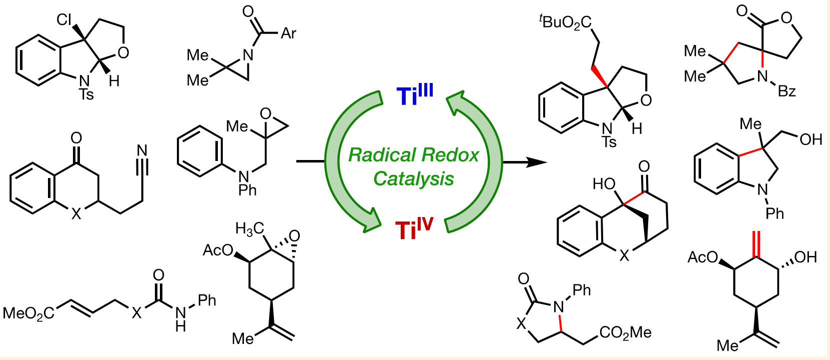
JOC The Journal of Organic Chemistry
JOCSynopsis
Cite This: J. Org. Chem. 2019, 84, 14369−14380
pubs.acs.org/joc

Recent Advances in Titanium Radical Redox Catalysis

Terry McCallum, Xiangyu Wu, and Song Lin*

Department of Chemistry and Chemical Biology, Cornell University, Ithaca, New York 14853, United States



ABSTRACT: New catalytic strategies that leverage single-electron redox events have provided chemists with useful tools for solving synthetic problems. In this context, Ti offers opportunities that are complementary to late transition metals for reaction discovery. Following foundational work on epoxide reductive functionalization, recent methodological advances have significantly expanded the repertoire of Ti radical chemistry. This Synopsis summarizes recent developments in the burgeoning area of Ti radical catalysis with a focus on innovative catalytic strategies such as radical redox-relay and dual catalysis.

1. INTRODUCTION

Radical-based chemistry has long been a cornerstone of synthetic organic chemistry.[1] The high reactivity of organic radicals has made possible myriad new reactions that cannot be readily achieved using two-electron chemistry. However, the high reactivity of organic radicals is a double-edged sword, as the selectivity of these fleeting intermediates can be difficult to control in the presence of multiple chemotypes. In addition, catalyst-controlled regio- and stereoselective reactions involving free-radical intermediates remain limited,[2] and the discovery of such processes is highly desirable. In light of these challenges, the development of catalytic strategies that enable new radical transformations with precise control over chemo-, regio-, and stereoselectivity could substantially impact organic synthesis.

Owing to their rich redox chemistry, titanium-based complexes have been widely used for the development of synthetically useful organic transformations involving redox processes. Among these reactions are the Sharpless epoxidation, the McMurry reaction, the pinacol coupling, the Barbier reaction, and the Pauson−Khand reaction.[3,4] In particular, the Ti$^{IV/III}$ redox couple offers unique opportunities to access radical intermediates in a chemoselective fashion. Although Ti^{III} complexes exhibit moderate reduction potentials [e.g., $E_{1/2}(Cp_2TiCl) = -0.65$ V vs SCE], they effect electron transfer via inner-sphere pathways by binding to a "hard" Lewis basic group in the substrate (e.g., epoxides and carbonyls). This mode of activation allows Ti to engage substrates that are outside the redox range of the catalyst and promote their reactions with high chemo- and stereoselectivity. Finally, from a green chemistry perspective, the abundance and low toxicity of Ti make its complexes highly attractive as reagents and catalysts in organic synthesis.[5]

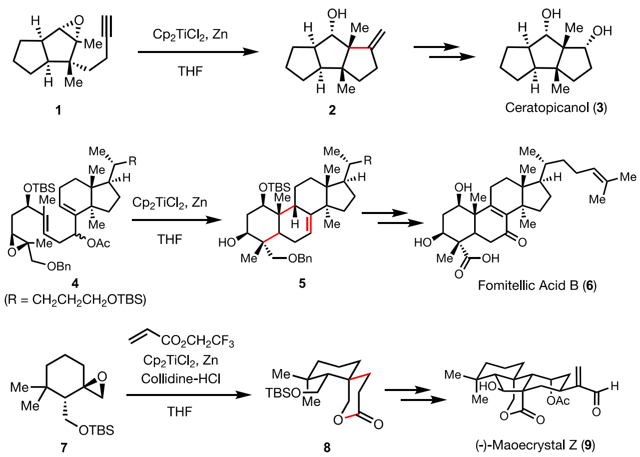
A classic example of Ti$^{IV/III}$-mediated reactivity is the reductive ring opening of epoxides. This process preferentially cleaves and functionalizes the more substituted C−O bond, providing complementary regioselectivity to Lewis acid promoted epoxide reactions. The synthetic value of Ti redox catalysis has been highlighted by their many uses in total synthesis (Scheme 1).[6−10] A small exhibition of the panoply is demonstrated in the synthesis of the linear triquinane skeleton of ceratopicanol,[11,12] the steroid core of fomitellic acid B,[13] and the spirocyclic core of (−)-maoecrystal Z.[14]

Recent years have seen great expansion of Ti$^{IV/III}$-mediated redox chemistry beyond epoxide functionalization. A wide range of new substrates have now been engaged in Ti^{III}-promoted single electron activities, including enones, nitriles, *N*-acylaziridines, chloroalkanes, and cyclopropyl ketones. These developments have opened new possibilities for the use of Ti radical redox catalysis in future synthetic endeavors. The aim of this Synopsis is to highlight recent advances in Ti$^{IV/III}$ redox catalysis (*c.* 2014) in three categories: net-reductive, redox-neutral (via radical redox-relay catalysis), and dual catalytic transformations. Much progress has also been made in the two-electron regime (i.e., Ti$^{IV/II}$ catalysis) in recent years, which has been systematically documented elsewhere and will not be covered herein.[15,16]

Received: September 10, 2019
Published: October 24, 2019

DOI: 10.1021/acs.joc.9b02465
J. Org. Chem. 2019, 84, 14369−14380

Scheme 1. Titanium-Mediated Transformations in Natural Product Synthesis



2. NET-REDUCING METHODOLOGY

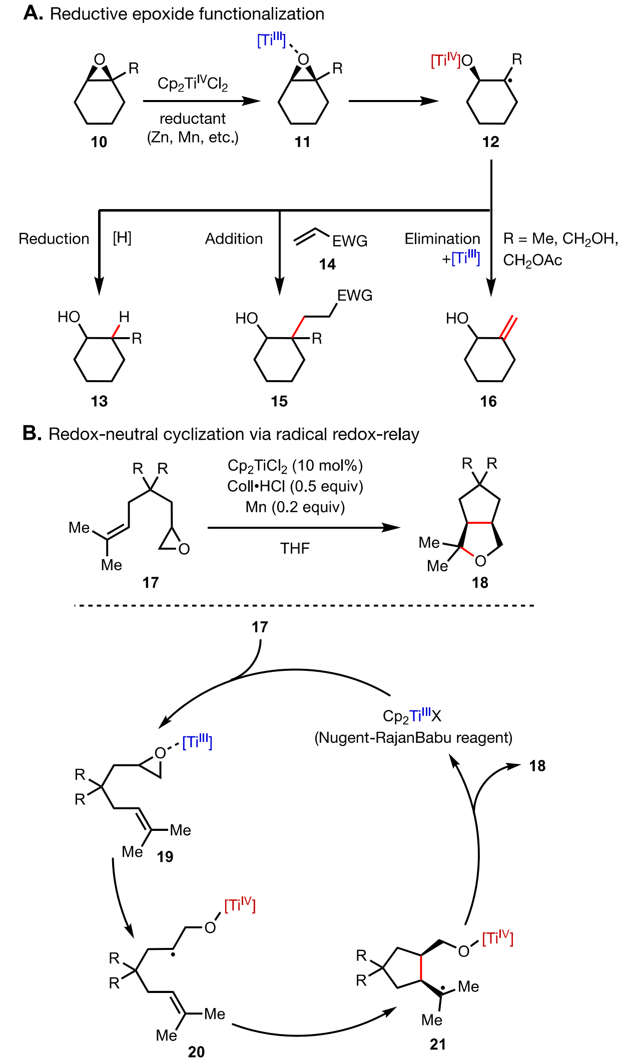
2.1. Background. In their seminal contributions, Nugent and RajanBabu described the functionalization of epoxides via titanocene-mediated reduction.[17,18] The central mechanistic basis entails inner-sphere single electron transfer (SET) from $Cp_2Ti^{III}Cl$ (generated from $Cp_2Ti^{IV}Cl_2$ via metal reduction) to the epoxide (e.g., **10**; Scheme 2A), resulting in homolysis of a C−O bond to form the more stable C-centered radical tethered to a Ti^{IV}-alkoxide (**12**). Subsequently, innate radical reactivities can take place to complete the transformation. For example, in the presence of a H atom donor, alcohol **13** is formed. In the presence of an electron-deficient alkene (**14**), **12** undergoes Giese-type radical addition to yield **15**.[17,18] Both hydrogenation and alkene addition reactions can be made catalytic in Ti using Mn or Zn as the terminal reductant.[7] With a leaving group at the *β*-position of the radical center (**12**, R = CH_2OH, CH_2OAc), Ti^{III}-mediated elimination can take place, giving allylic alcohol **16**.[19,20] The same type of products can also form via *β*-hydrogen atom abstraction by Ti^{III} (**12**, R = Me).[19,21]

When using epoxides with a pendent trisubstituted alkene (**17**), the Ti^{III}-promoted epoxide ring opening (**20**) followed by *5-exo-trig* cyclization gives 3° radical **21**. Subsequently, homolytic radical substitution takes place, furnishing a new C−O bond and regenerating $Cp_2Ti^{III}Cl$ (Scheme 2B). This process yields bicyclic tetrahydrofuran **18** and constitutes a seminal example of redox-neutral methodology using Ti^{IV}/Ti^{III} redox catalysis.[22−24]

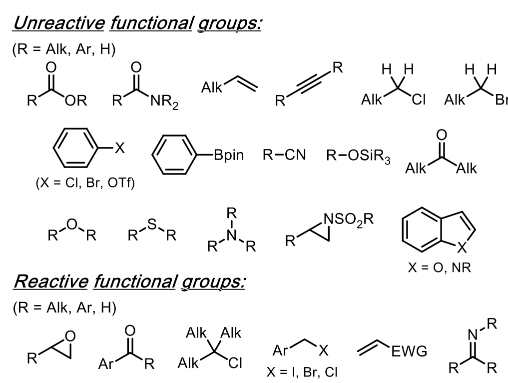
Various common functional groups are compatible with the relatively mild reaction conditions of Ti^{IV}/Ti^{III} catalysis (Scheme 3). Substituents resilient to single-electron reduction are well tolerated, including esters, amides, protected alcohols (−OTMS, −OAc, acetals), (thio)ethers, simple alkenes, alkynes, nitriles, free and protected amines, *N*-sulfonylaziridines, and heterocycles. Importantly, substituents that are often reactive under late-transition-metal catalysis, such as 1° bromo- and chloroalkanes, aryl halides, and boronates, are compatible with Ti chemistry.[5,25] Functional groups that are reactive under Ti^{III} activation include epoxides, aryl aldehydes and ketones, imines, enones, acrylates and acrylonitriles, *N*-acylaziridines, and activated alkyl halides.

Following the initial establishment of reactivity, Gansäuer further applied Ti^{III}-mediated epoxide ring opening in

Scheme 2. Transformations of Epoxides with $Cp_2Ti^{III}Cl$



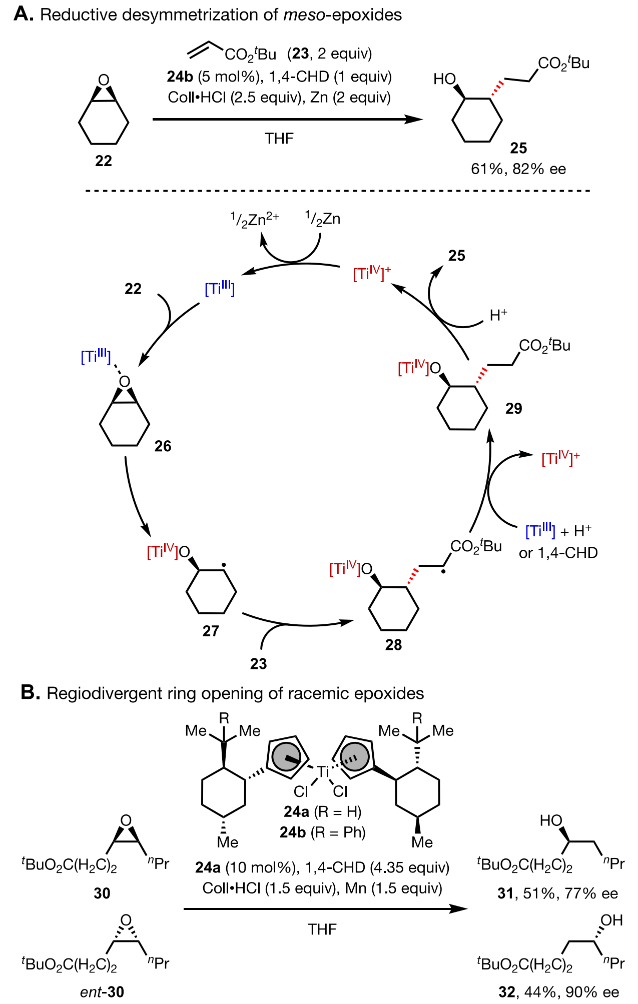
Scheme 3. General Functional Group Compatibility with Ti^{III}



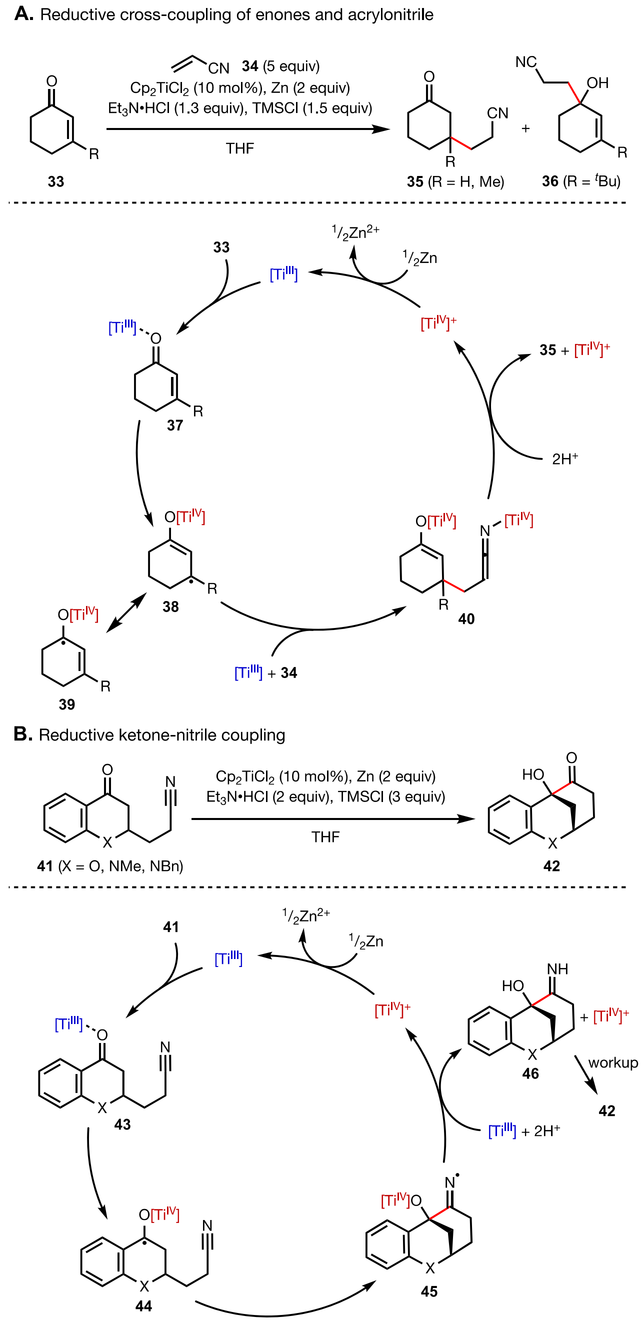
enantioselective synthesis. For example, the desymmetrization of *meso*-epoxides (**22**) was achieved using chiral titanocenes such as Kagan's complex (**24a**) in Giese-type addition reactions (Scheme 4A).[26−28] The concept of regiodivergent epoxide ring opening was also developed using catalyst **24a**, in which the racemate of linear unsymmetrical epoxides (**30** and *ent*-**30**) are converted to a pair of regioisomeric alcohol products (**31** and **32**) in high enantiomeric excess in the

DOI: 10.1021/acs.joc.9b02465
J. Org. Chem. 2019, 84, 14369−14380

Scheme 4. Net-Reducing Enantioselective (A) and Regiodivergent (B) Epoxide Opening Reactions



Scheme 5. Reductive Coupling of Ketones with Nitriles



presence of 1,4-cyclohexadiene (CHD) as the H atom donor (Scheme 4B).[29−32]

Extensive studies by Gansäuer and others on the mechanism of Ti^{III} activation of epoxides led to major findings summarized below. (1) The regioselectivity of reductive ring opening of epoxides favors the more substituted and stable alkyl radical (3° > 2° > 1°).[33,34] (2) Upon reduction of $Cp_2Ti^{IV}Cl_2$ by Mn or Zn, $Cp_2Ti^{III}Cl$ exists in an equilibrium between monomeric and dimeric complexes.[35] (3) $Cp_2Ti^{III}Cl$ undergo reaction with epoxides at rates on the order of 0.5−3.9 M^{-1} s^{-1}, which is often the rate-determining step of the overall reaction.[36,37] (4) Protonated amine salts, such as Coll·HCl and Et_3N·HCl, likely promote the reaction by breaking up off-cycle Ti adducts (e.g., Ti^{III} dimers).[36−38]

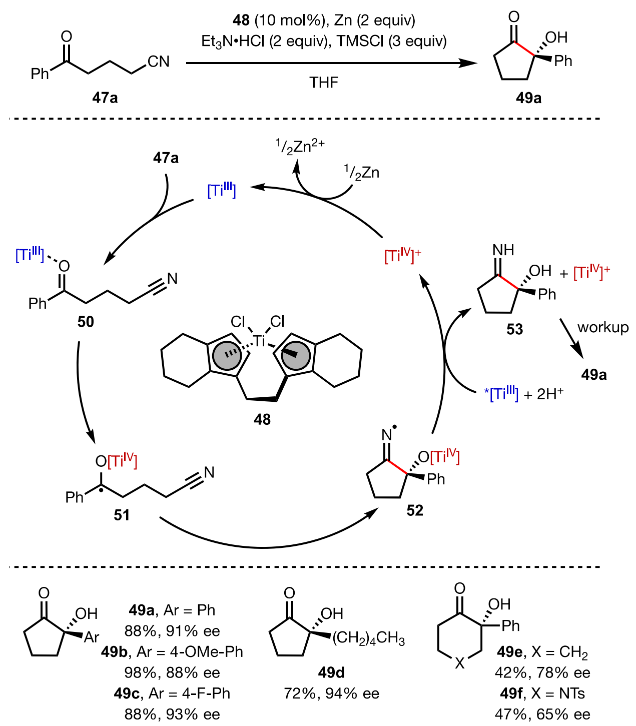
2.2. Reductive Ketone−Nitrile Coupling. Ti^{III} is capable of reductively activating conjugated aldehydes and ketones to form the corresponding ketyl radicals.[39] Recently, Streuff explored this reactivity in the reductive cross coupling of enones with acrylonitriles (Scheme 5A).[40] In these reactions, the in situ generated Ti^{III} binds to the cyclic enone (**33** to **37**), which triggers the inner-sphere SET to provide resonance stabilized ketyl radical **38**/**39**. This intermediate subsequently undergoes addition to acrylonitrile (**34**). In this step, Streuff proposes that Ti^{III} also activates **34** through binding of the CN group. Upon formation of **40**, protonation of both Ti^{IV}-enolate and Ti^{IV}-ketenimine groups gives rise to C−C coupling product **35**. Interestingly, increasing the size of the R group in **33** imparts a steric bias that results in predominant formation of 1,2-addition product **36** from intermediate **39**.

Early studies showed that Ti^{III}-mediated epoxide ring opening could trigger radical cyclization onto a tethered nitrile group.[41] Streuff expanded on this reactivity in the intramolecular reductive coupling of ketones and nitriles to form α-hydroxyketones. For example, chromones and quinolones with pendent nitrile groups (**41**) can undergo reductive ketone−nitrile cyclization to yield product **42** (Scheme 5B).[42−44] In this reaction, ketyl radical **44** generated from Ti^{III}-activation of ketone **41** adds to the nitrile group to furnish intermediate **45**. Subsequent reduction of the *N*-centered radical, protonation, and imine hydrolysis led to product **42**. Streuff further

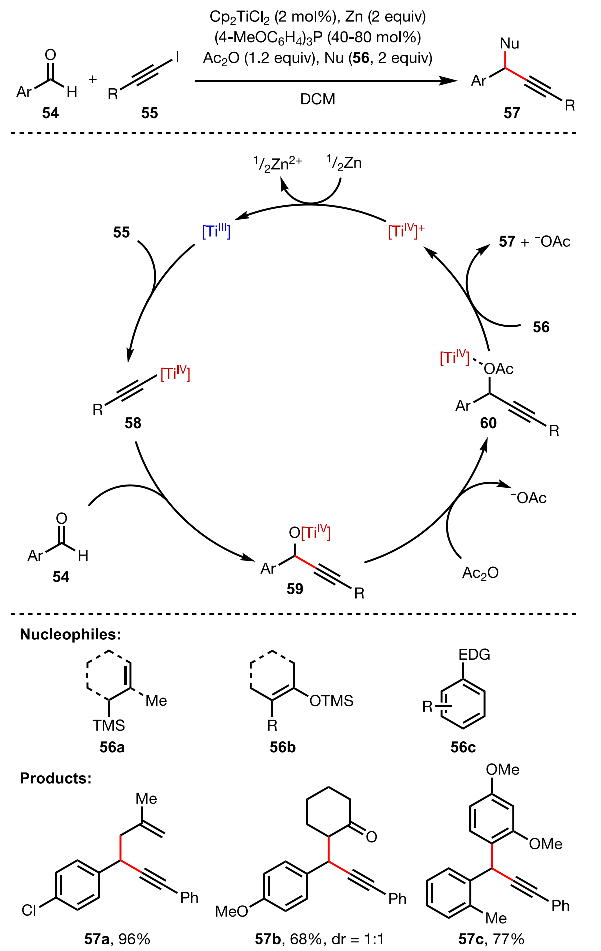
DOI: 10.1021/acs.joc.9b02465
J. Org. Chem. 2019, 84, 14369−14380

developed an enantioselective variant of the reductive ketone–nitrile cyclization using Brintzinger's *ansa*-titanocene complex (**48**), providing efficient access to enantioenriched α-hydroxyketones (**49**) with a fully substituted stereocenter (Scheme 6).[45,46]

Scheme 6. Enantioselective Reductive Ketone−Nitrile Coupling



Scheme 7. Ti-Catalyzed Three-Component Coupling of Acetylides, Aldehydes, and Nucleophiles



2.3. Three-Component Coupling of Aldehydes, Iodoacetylides, and π-Nucleophiles.

Ashfeld advanced Ti-promoted redox–Lewis acid relay catalysis for the three-component coupling of aldehydes (**54**), iodoacetylides (**55**), and nucleophiles (**56**; Scheme 7).[47−51] In this reaction, the Ti catalyst is proposed to take on multiple roles in the mechanism by behaving as both a Lewis acid and a single-electron reductant. The reaction begins with the reductive activation of **55** by $Cp_2Ti^{III}Cl$ to form Ti^{IV}-acetylide **58**. This intermediate can undergo transmetalation with $ZnCl_2$—generated from the reduction of $Cp_2Ti^{IV}Cl_2$ by Zn—to form Zn^{II}-acetylide. The metal acetylides (**58**, Ti^{IV} or Zn^{II}, Ti^{IV} depicted in Scheme 7 for clarity) then proceed to add to aldehyde **54**, giving propargyl alkoxide **59**. After reaction with Ac_2O, acetate **60** undergoes ionization, likely assisted by a Lewis acid (Ti^{IV} or Zn^{II}), and subsequent nucleophilic addition to furnish three-component coupling product **57** with two newly constructed C–C bonds. Carbon nucleophiles such as allylsilanes (**56a**), silyl enol ethers (**56b**), and electron-rich arenes (**56c**) have proven suitable coupling partners in this reaction.

2.4. Giese Radical Addition of *N*-Acyl Aziridines.

In 2017, Gansäuer expanded the scope of titanocene-based reactivity from epoxides to *N*-acylaziridines, achieving their reductive ring opening followed by Giese-type addition to electron-deficient alkenes (Scheme 8).[52] For example, aziridine **61a** can be activated by $Cp^*_2Ti^{III}Cl$ through Ti–carbonyl coordination (**63**) and subsequent SET, resulting in ring rupture and formation of radical intermediate **64**. This intermediate then adds to acrylate **23**, leading to adduct **65** after further reduction by Ti^{III}. Upon the final protonation step, the overall reaction gives rise to protected δ-amino acid **62a**. The formation of an intermediate radical during the reaction was demonstrated in the 5-*exo-dig* cyclization of **61b**. Aziridines with various *N*-protecting groups (**61c–f**) proved suitable substrates.

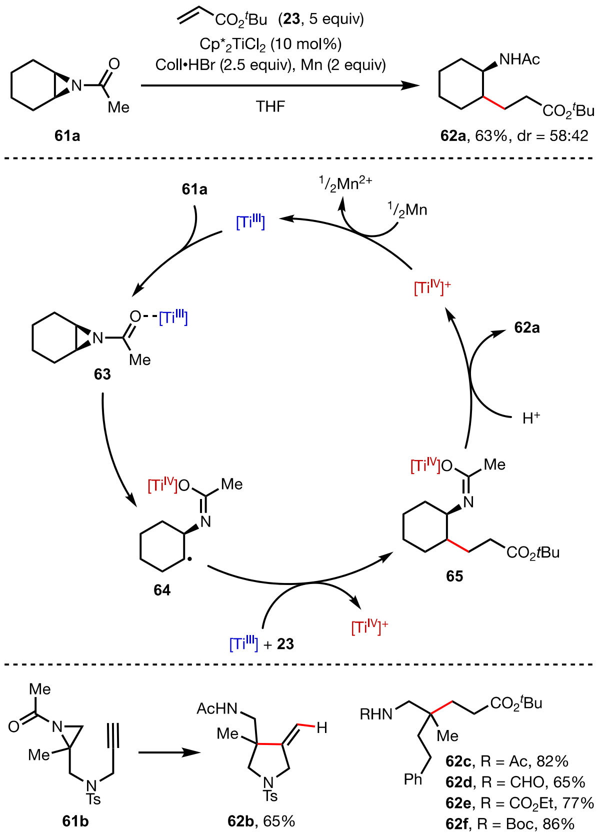
2.5. Activation of Chloroalkanes toward Giese-Type Radical Addition.

In 2018, our team expanded the scope of Ti^{III}-catalysis to the reductive activation of unactivated 2° and 3° chloroalkanes (Scheme 9).[25] $C(sp^3)$–Cl bonds are traditionally challenging to engage in C–C forming reactions due to their high bond dissociation energy (BDE ~ 85 kcal/mol). Recent advances in Ni catalysis have made possible cross-coupling reactions of unactivated chloroalkanes;[53] however, this strategy is currently not amenable to reactions with 3° substrates due to competing β-H elimination.

In a related previous work by Zheng, hemiaminals (**66**) were shown to undergo reductive Giese reaction in the presence of $Cp_2Ti^{III}Cl$ via α-chlorolactam intermediates (**67**, Scheme 9A).[54] This reaction, however, is limited to activated substrates with an α-N atom that can stabilize key radical intermediate derived from **67**. In our work, the reaction scope is extended to unactivated chloroalkanes (**69**) using a half-sandwich $Cp^*Ti^{III}Cl_2$ complex. The increased reactivity in comparison to titanocene-type catalysts is attributed to the smaller steric profile of $Cp^*Ti^{III}Cl_2$. The reaction begins with activation of

DOI: 10.1021/acs.joc.9b02465
J. Org. Chem. 2019, 84, 14369−14380

Scheme 8. Reductive Giese-Type Addition of *N*-Acyl-Protected Aziridines



the substrate C−Cl bond by Ti^{III} via inner-sphere Cl atom (**72**) transfer to generate the corresponding C-centered radical (**73**). This intermediate is difficult to access through outer-sphere SET pathways owing to the high redox potentials of chloroalkanes (E_{pc} > −2.5 V vs $Fc^{+/0}$). Finally, nucleophilic radical **73** adds to electron-deficient alkene **70** to generate product **71**.

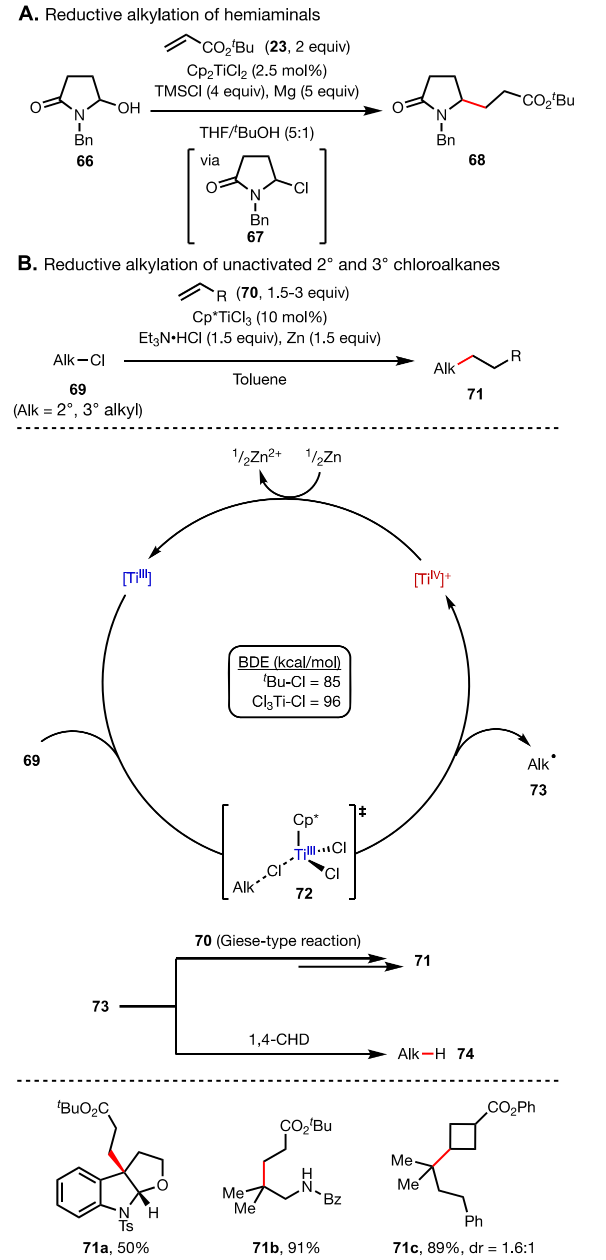
This methodology is applicable to the alkylation of a catalog of readily available chloroalkanes (**69a−c**) using various alkene acceptors, including bicyclobutanes (giving **71c**). The intermediacy of an alkyl radical was supported through reduction with CHD to form **74**. This reaction also provides a mild protocol for the reductive hydrodechlorination of chloroalkanes.

3. REDOX-NEUTRAL METHODOLOGY: RADICAL REDOX-RELAY CATALYSIS

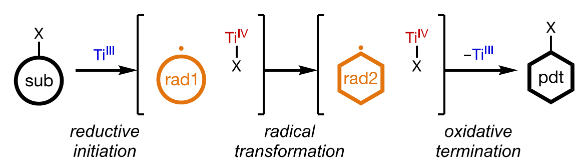
3.1. Background. Previous examples highlighted herein demonstrate the ability of Ti^{III}-complexes to promote reactions wherein the substrates undergo net-reductive transformations. In these reactions, the Ti catalysts are turned over by stoichiometric reducing metals (e.g., Mn, Zn). In principle, overall redox-neutral reactions could also be achieved by means of a sequence of self-sustained reduction and oxidation steps regulated by a redox-active catalyst in the absence of an extraneous stoichiometric reductant. This redox relay strategy could facilitate the development of dual catalytic processes that may not be feasible otherwise (see section 4).

Transition-metal-catalyzed redox-neutral transformations are by no means a novel concept. For example, Pd-mediated cross coupling reactions are net-redox neutral processes that consist of multiple elementary steps (e.g., oxidative addition, transmetalation, reductive elimination) during which the oxidation state of the catalyst cycles between Pd^{II} and Pd^{0}. Radical redox-relay catalysis borrows from the same principle but operates in a single-electron manifold.[55] In the context of $Ti^{IV/III}$ catalysis (Scheme 10), Ti^{III} reductively activates the substrate to generate a radical intermediate (rad 1) while the catalyst is

Scheme 9. Reductive Giese-Type Addition of Tertiary and Secondary Chloroalkanes



Scheme 10. General Principle of Radical Redox-Relay Catalysis by $Ti^{IV/III}$

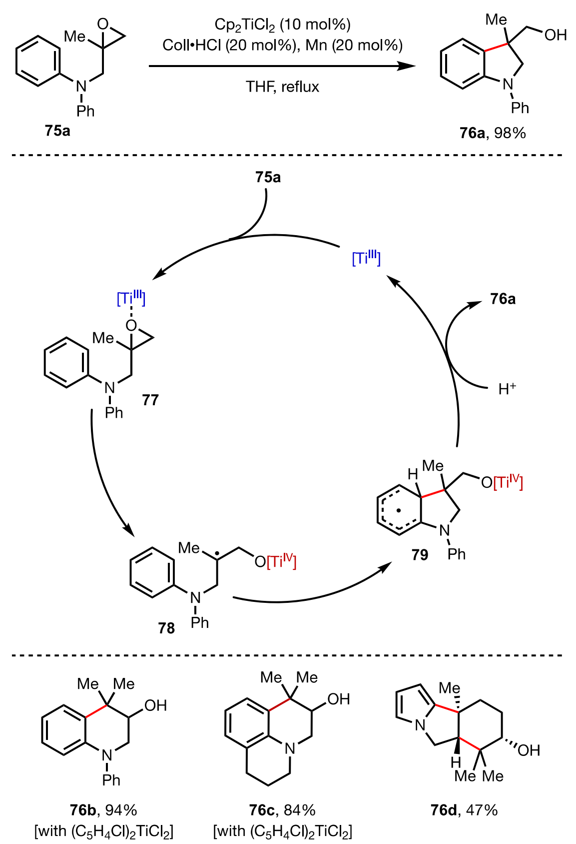


DOI: 10.1021/acs.joc.9b02465
J. Org. Chem. 2019, 84, 14369−14380

oxidized to Ti^{IV}. Rad 1 undergoes subsequent transformations to rad 2 before returning an electron to the catalyst to furnish the product and regenerate Ti^{III}. In this mechanism, Ti promotes electron-transfer and bond-forming/cleaving events in an inner-sphere manner, thus allowing catalyst-control over the reaction stereoselectivity. This section will review new transformations made possible by recent developments in Ti-promoted radical redox-relay catalysis as well as the enantioselective processes that they enable.

3.2. Redox-Neutral Epoxide Arylation. Expanding upon their previous work on reductive epoxide chemistry, Gansäuer and Flowers II developed early examples of Ti-catalyzed radical redox-relay in the context of epoxide arylation (Scheme 11).[56−63] This methodology leverages the known capabilities

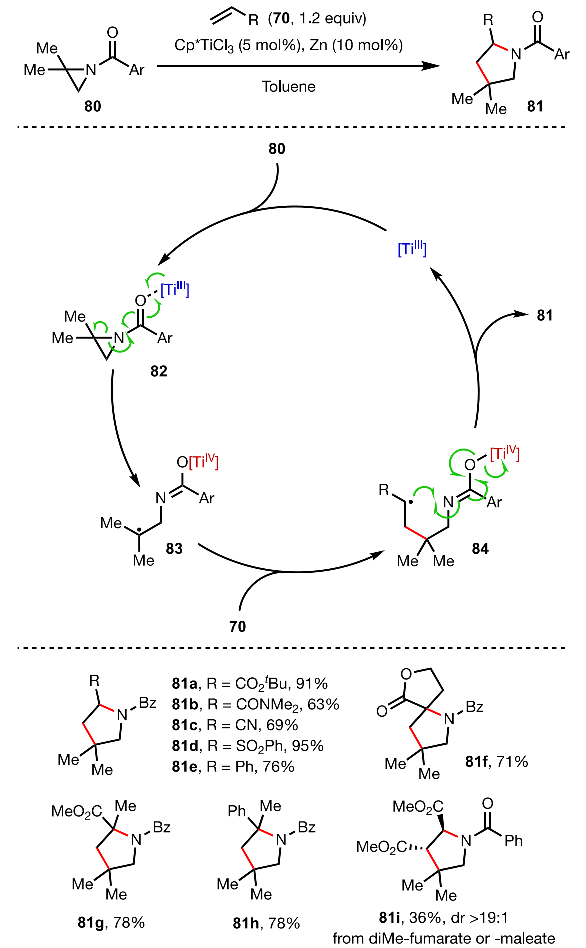
Scheme 11. Redox-Neutral Arylation of Epoxides



of $Cp_2Ti^{III}X$ of inducing reductive ring opening of epoxides (**75a**−**78**) and C-centered radicals of undergoing cyclization to π-systems (**78**−**79**) to achieve intramolecular C(sp^2)−C(sp^3) coupling. The strong tendency of the aryl-based radical (**79**) to undergo rearomatization provides the driving force for catalyst turnover. Specifically, the cyclohexadienyl motif in **79** transfers an electron and a proton to the pendent Ti^{IV}-alkoxide, which occurs consecutively or in concert, to furnish the bicyclic product and regenerate the Ti^{III} catalyst. This reaction was applied to the synthesis of indolines (**76a**) and tetrahydroquinolines (**76b**,**c**) as well as cascade cyclizations to form polycyclic products (**76d**).

3.3. Formal [3 + 2] Cycloaddition of *N*-Acylaziridines and Alkenes. Coinciding with Gansäuer's report on the reductive alkylation of *N*-acylaziridines (Section 2.4), in 2017, we employed this new class of substrates for Ti^{III} catalysis in the redox-neutral formal [3 + 2] cycloaddition with radical acceptor alkenes (Scheme 12).[64] In contrast to Gansäuer's net-reducing transformation using $Cp_2Ti^{IV}Cl_2$ and stoichiometric

Scheme 12. Formal [3 + 2] Cycloaddition of *N*-Acylaziridines with Alkenes



Mn, our protocol uses half-sandwich $Cp^*Ti^{IV}Cl_3$ with substoichiometric Zn and provides cyclic pyrrolidines as products.

The proposed catalytic cycle begins with coordination of the Ti catalyst to the *N*-acylaziridne (**80**−**82**). Subsequent inner-sphere SET causes ring rupture, giving an alkyl radical tethered to a Ti^{IV}-azaenolate group (**83**). This nucleophilic radical undergoes addition to an electron-deficient alkene (**83** to **84**), which is followed by cyclization of the ensuing electrophilic C-centered radical onto the nucleophilic Ti^{IV}-azaenolate to construct the desired C−N bond (**84** to **81**) and regenerate Ti^{III}. This overall reaction displays perfect atom economy through the redox cycling of an electron.

The distinct chemoselectivity shown in our and Gansäuer's reports is intriguing, given that the reactions employ very similar conditions. We hypothesize that the use of less bulky Cp^*TiCl_3 instead of $Cp^*_2TiCl_2$ alleviates any steric repulsion between the catalyst and the substrate during the C−N cyclization event (**84**−**81**), thus allowing it to occur more readily. A variety of aziridines and radical acceptors such as styrenes and acrylates are successfully engaged in the [3 + 2] cycloaddition reaction (**81a**−**h**). The stepwise radical addition mechanism is validated using dimethyl maleate and dimethyl fumarate, both giving predominantly *trans*-**81i**. Together with

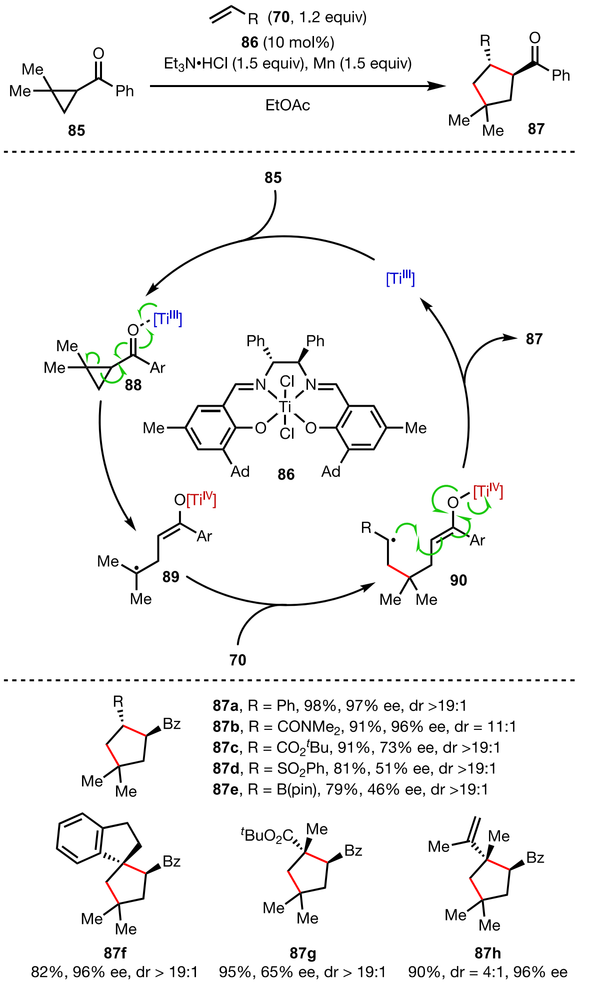
DOI: 10.1021/acs.joc.9b02465
J. Org. Chem. 2019, 84, 14369−14380

Gansäuer's complementary method, this reaction represents an important expansion of Ti^{III} catalysis and demonstrates the ability of catalyst control of reaction chemoselectivity.

3.4. Enantioselective Formal [3 + 2] Cyclization of Cyclopropyl Ketones and Alkenes.

As a logical extension of the *N*-acylaziridine reaction (Section 3.3), we reported in 2018 the formal [3 + 2] cycloaddition of cyclopropyl ketones (**85**) with alkenes (Scheme 13).[65] This reaction employs

Scheme 13. Enantioselective Dormal [3 + 2] Cyclization of Cyclopropyl Aryl Ketones and Alkenes



readily available Ti(salen) catalysts (e.g., **86**) and constructs polysubstituted cyclopentane products. The proposed mechanism starts from a low-valent Ti^{III} catalyst coordinating with the cyclopropyl ketone (**85** to **88**), which triggers SET to generate the Ti^{IV} enolate appended radical **89**. Upon addition to alkene **70**, the resultant intermediate **90** undergoes cyclization to liberate desired product **87** and regenerate Ti^{III}.

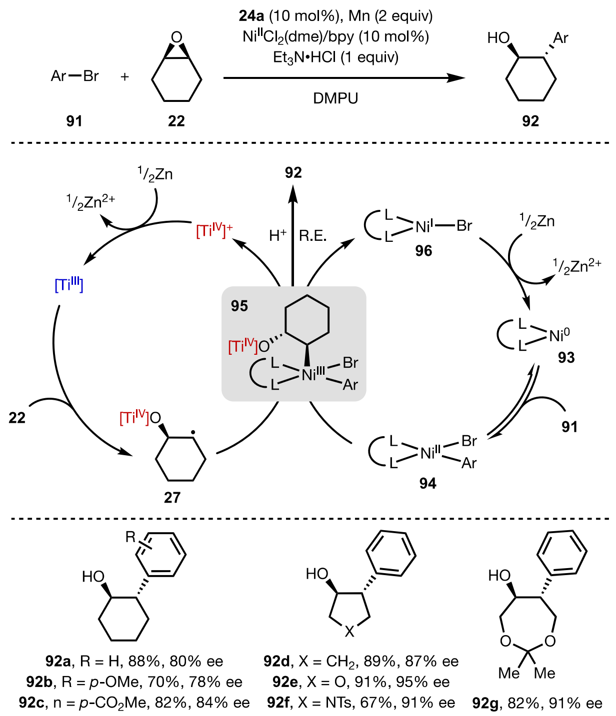
Ti(salen) complexes are readily made chiral, making it possible to render the cycloaddition reaction enantioselective. Using catalyst **86**, various polysubstituted cyclopentanes, including those with quaternary stereocenters (**87f–h**), are constructed with excellent enantioselectivity and diastereoselectivity. At the current stage, electron-deficient alkenes such as acrylates and vinylboronates provide products in lower enantioselectivity (**87c–e**, 46–73% ee). Nonetheless, these electrophiles give rise to interesting structures that are challenging to access using known methods.

4. TI-MEDIATED DUAL CATALYSIS

4.1. Ti^{III}/Ni^{0}-Catalyzed Reductive Arylation of Epoxides.

In 2014, Weix reported the cross-electrophile coupling of epoxides (**22**) with aryl bromides (**91**) to access *β*-aryl alcohols (**92**; Scheme 14) using a catalytic combination of Ni and Ti complexes (**24a**).[66,68] This work merges two well-established radical reactions, Ni-mediated $C(sp^2)-C(sp^3)$ cross coupling[67] and Ti^{III}-promoted epoxide reduction. In the proposed dual catalytic cycle, Ni^0 (**93**) undergoes oxidative addition to aryl halide **91** to form the Ni^{II}–aryl complex **94**. Meanwhile, Ti^{III} activates epoxide **22** to generate alkyl radical **27**. Intermediate **94** reacts with **27** to form Ni^{III} complex **95**, which undergoes reductive elimination to liberate desired arylation product **92**. Both catalysts (**24a** and **96**) are subsequently turned over by Mn. Finally, using Kagan's complex (**24a**) rendered the arylation highly enantioselective (**92a–g**).[68]

Scheme 14. Enantioselective Ti/Ni Dual Catalyzed Arylation of *meso*-Epoxides

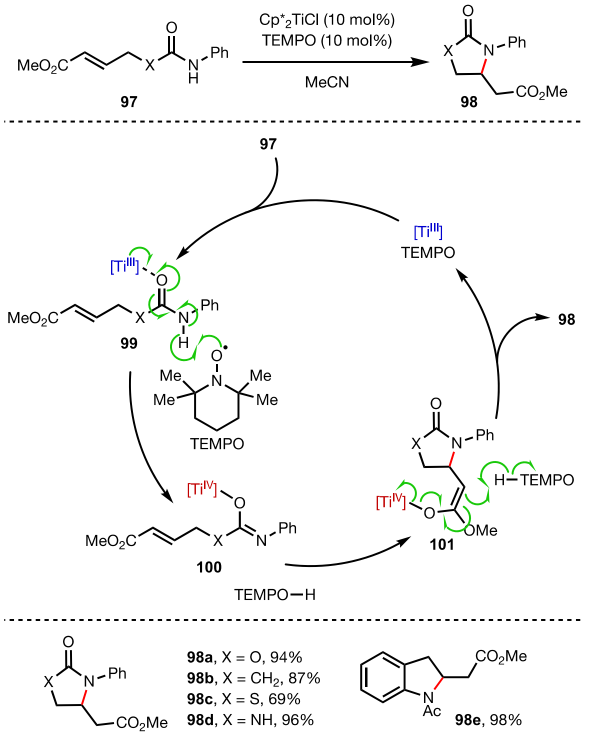


4.2. Conjugate Amination via Proton-Coupled Electron Transfer (PCET).

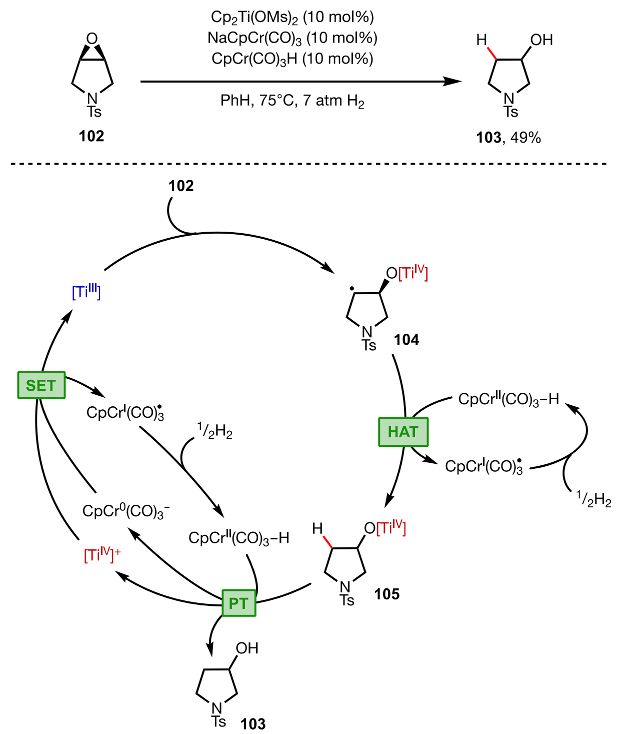
In 2015, Knowles demonstrated Ti^{III}-promoted bond-weakening catalysis in the context of intramolecular conjugate aminations (Scheme 15).[69] Amide substrates such as **97** have an estimated N–H bond dissociation free energy (BDFE) of 99 kcal/mol, making it challenging to cleave homolytically. Association of $Cp^*_2Ti^{III}Cl$ to the amide (**99**), however, drastically lowers the BDFE of the N–H bond to 66 kcal/mol. This bond-weakening effect enables a PCET event to occur in the presence of a weak H atom abstractor such as TEMPO, furnishing TEMPO-H (BDFE = 67 kcal/mol) along with a Ti^{IV}-azaenolate (**100**). This intermediate then undergoes intramolecular conjugate addition to form the desired C–N bond. The resultant Ti^{IV}-enolate (**101**) and TEMPO-H undergo proton and electron transfer events to liberate product **98** along with the $Cp^*_2Ti^{III}Cl$ and TEMPO catalysts.

DOI: 10.1021/acs.joc.9b02465
J. Org. Chem. 2019, 84, 14369–14380

Scheme 15. Dual Catalytic Conjugate Amination via PCET



Scheme 16. Ti/Cr-Catalyzed Reductive Epoxide Ring Opening



On thermodynamic grounds, the catalytic duo Ti^{III} and TEMPO are incompatible with one another and could undergo radical annihilation to form TEMPO−Ti^{IV} adducts. Indeed, such an adduct is observed when treating TEMPO with $Cp_2Ti^{III}Cl$, an inactive catalyst combination in the cyclization reaction. The sterically congested $Cp^*{}_2Ti^{III}Cl$, however, can coexist with TEMPO as a radical pair. In fact, electron spin resonance analysis of the mixture of these two catalysts showed signals characteristic of both open-shell species.

4.3. Dual Ti^{III}/Cr^{II} Catalysis for the Ring-Opening Hydrogenation of Epoxides. The heterogeneous nature of Ti^{III}-catalyzed reductive functionalization of epoxides using stoichiometric metal reductants (Scheme 4) makes them challenging to be adopted beyond laboratory scales. To address this limitation, Norton and Gausäuer developed a dual catalytic system encompassing Ti^{III}-mediated epoxide ring opening and Cr-promoted HAT (Scheme 16).[74] Specifically, upon reductive activation of epoxide 102, radical 104 accepts an H atom from cocatalyst $CpCr^{II}(CO)_3$-H. The resultant intermediate 105 reacts with another molecule of $CpCr^{II}(CO)_3$-H via proton transfer (PT) to furnish alcohol 103. The ensuing catalytic species $CpCr^0(CO)_3^-$ and Ti^{IV} undergo electron transfer with one another, returning Ti^{IV} to the active Ti^{III} oxidation state. The turnover of the active $CpCr^{II}(CO)_3$-H catalyst is achieved using H_2 as the terminal reductant. This dual catalytic strategy is reminiscent of Gausäuer's previous reports on hydrogenation of epoxides using Ti and Rh/Ir cocatalysis[70−73] but removes the need for stoichiometric metal reductants

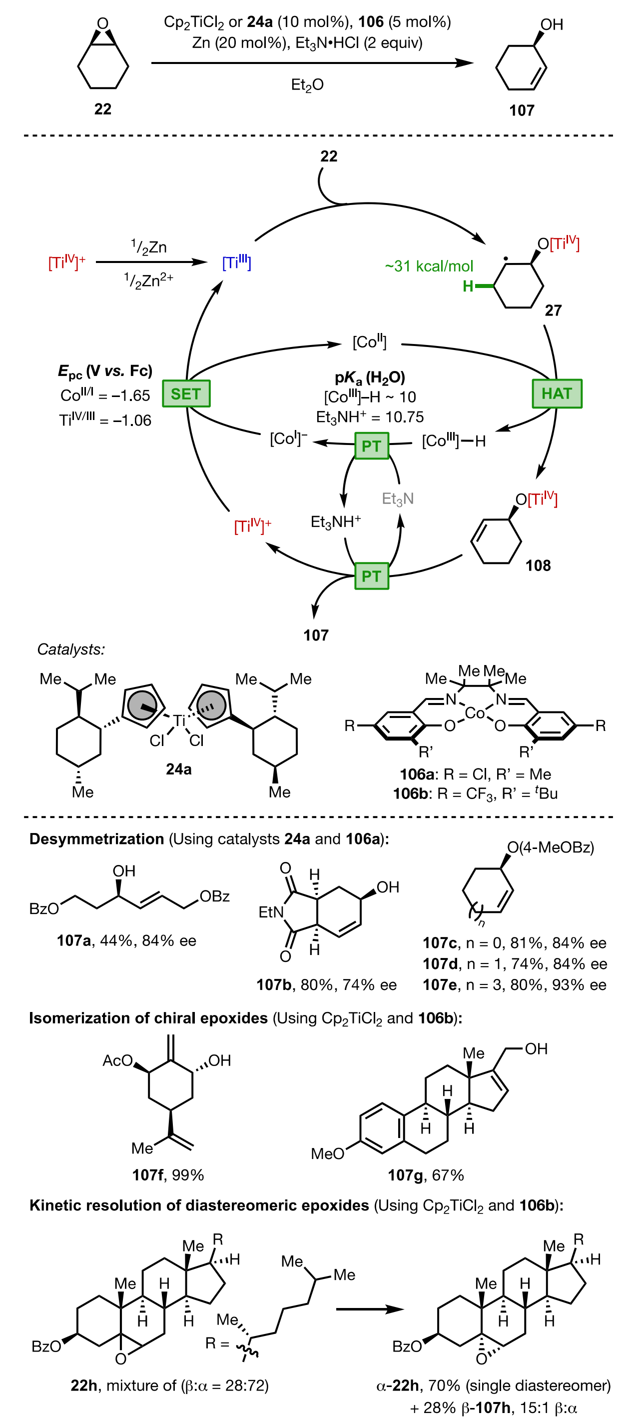
4.4. Dual Ti^{III}/Co^{II} Radical Redox-Relay Catalysis for the Isomerization of Epoxides to Allylic Alcohols. Our most recent foray into the realm of Ti redox-relay catalysis showcased the stereoselective isomerization of epoxides (**22**) to allylic alcohols (**107**) via dual Ti/Co catalysis (Scheme 17).[75] The reaction design combines Ti^{III}-promoted epoxide chemistry and Co^{II}-mediated HAT[76] in the same catalytic system. Specifically, Ti^{III} first induces reductive ring opening of epoxide **22** to give intermediate **27**. The radical character in **27** significantly weakens the adjacent C−H bond (BDE ∼ 31 kcal/mol),[77] which allows Co^{II} catalyst **106** to readily abstract the H atom and form a C═C bond. This step produces a formally Co^{III}−H intermediate and Ti^{IV}-alkoxide **108**. The final product formation and catalytic turnover can occur through a stepwise proton transfer/electron transfer (PT/ET) process. First, $Et_3N{\cdot}HCl$ protonates Ti^{IV}-alkoxide **108** to furnish allylic alcohol **103** and liberate the Ti^{IV} catalyst. Meanwhile, the acidic Co^{III}−H (pK_a = 10−15)[76] loses a proton to Et_3N to form the corresponding $[Co^I]^-$ intermediate. This intermediate is sufficiently reducing to give up an electron to Ti^{IV}, thus completing the turnover of both catalysts. This reaction itself is overall redox-neutral, and the proposed catalytic mechanism is self-sustaining without need for a stoichiometric reductant.

We successfully implemented this reaction design using Cp_2TiCl_2 and Co(salen) complexes. The optimal reaction conditions require only a catalytic amount of Zn, which functions to reduce the Ti^{IV} precursor to Ti^{III} to kick start the radical reaction. The scope of the reaction is broad with various epoxides prepared from cyclic or acyclic alkenes readily converted to the allylic alcohols.

The use of chiral Ti catalyst **24a** expands the scope of the reaction to the desymmetrization of *meso*-epoxides. Chiral linear and cyclic allylic alcohols are obtained with enantioselectivities ranging from 64 to 94% (**107a−e**). Compared with chiral base-mediated isomerization, our reaction operates under neutral conditions and preserves stereogenic centers that are sensitive to epimerization (e.g., **107b**). The reaction also gives allylic alcohol products (**107f,g**) from natural

DOI: 10.1021/acs.joc.9b02465
J. Org. Chem. 2019, 84, 14369−14380

Scheme 17. Enantioselective Epoxide Isomerization Using Dual Ti^{III}/Co^{II} Redox Catalysis



product derived epoxide sources such as (+)-carvone and estrone.

The epoxide isomerization reaction is also stereoselective. For example, when cholesterol-derived epoxide **22h** was subjected to the dual-catalytic system as a mixture of α/β-isomers, the β-anomer reacts at a much faster rate, generating alcohol **107h** in 15:1 dr, whereas the α-anomer was nearly fully recovered as a single diastereomer. This kinetic resolution activity is also demonstrated with several other substrates. Although the origin of the observed stereoselectivity is not clear at this stage, we reason that the large steric profile of the titanocene catalyst makes it sensitive to the steric properties of the epoxide substrates. This kinetic resolution activity has not been reported in previous reaction systems involving Ti^{III} and provides an efficient means to access diastereomerically pure epoxides that are challenging to synthesize directly using epoxidation.

This methodology represents another example of a Ti-mediated redox-neutral transformation in the absence of stoichiometric reductants, wherein catalyst turnover is achieved via redox-relay with a Co-cocatalyst.

5. OUTLOOK

During the past few decades, the knowledge and understanding with respect to titanocene-based redox transformations has greatly expanded. In recent years, this foundational work has transformed to a wide range of net-reducing and redox-neutral transformations, many of which are stereoselective. Ongoing methodological advancements, new catalyst development, and stereoselective synthesis will continue to enrich the synthetic value of Ti-redox radical catalysis. New studies concerned with the merger of Ti catalysis with other redox modules in dual catalytic systems as well as the use of photoredox catalysis[78] and electrochemistry[61] as a means to promote redox cycling of Ti will drive this growing field of research.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: songlin@cornell.edu.

ORCID

Terry McCallum: 0000-0002-8034-7180
Song Lin: 0000-0002-8880-6476

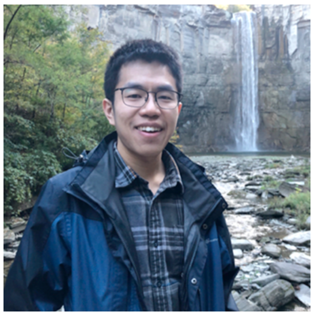
Notes

The authors declare no competing financial interest.

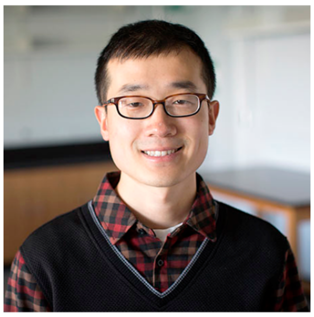
Biographies

Terry McCallum originates from Abitibi-Témiscamingue, Canada. He received his B.Sc. (2013) and Ph.D (2018) at the University of Ottawa, where he studied under the tutelage of Professor Louis Barriault in the field of photoredox gold catalysis. Terry is currently a postdoctoral researcher in Professor Song Lin's lab at Cornell University exploring new transformations in radical redox-relay catalysis.

DOI: 10.1021/acs.joc.9b02465
J. Org. Chem. 2019, 84, 14369−14380



Xiangyu Wu was born and raised in Jiangxi-Nanchang, China. He received his B.S. (2016) degree in chemistry from Nanjing University under supervision of Prof. Xuezhong Du. In 2016, he joined Prof. Song Lin's group at Cornell University for Ph.D. studies on transition-metal-catalyzed radical redox relay reactions.



Song Lin grew up in Tianjin, China, and received his B.S. degree from Peking University in 2008. After completing his Ph.D. at Harvard University with Prof. Eric Jacobsen, he joined the laboratory of Prof. Christopher Chang at UC Berkeley to carry out his postdoctoral studies. In July 2016, he moved to Cornell University to start his independent research career and is currently a Howard Milstein Faculty Fellow and Assistant Professor of Chemistry.

■ ACKNOWLEDGMENTS

Financial support was provided by Cornell University and the National Science Foundation (CHE-1751839). S.L. thanks the Alfred P. Sloan Foundation for a Sloan Fellowship.

■ REFERENCES

(1) (a) Renaud, P.; Sibi, M. P. *Radicals in Organic Synthesis*; Wiley-VCH: Weinheim, 2001. (b) Yan, M.; Lo, J. C.; Edwards, J. T.; Baran, P. S. Radicals: Reactive Intermediates with Translational Potential. *J. Am. Chem. Soc.* **2016**, *138*, 12692−12714. (c) Jasperse, C. P.; Curran, D. P.; Fevig, T. L. Radical Reactions in Natural Product Synthesis. *Chem. Rev.* **1991**, *91*, 1237−1286. (d) Ischay, M. A.; Yoon, T. P. Accessing the Synthetic Chemistry of Radical Ions. *Eur. J. Org. Chem.* **2012**, *2012*, 3359−3372.

(2) (a) Sibi, M. P.; Manyem, S.; Zimmerman, J. Enantioselective Radical Processes. *Chem. Rev.* **2003**, *103*, 3263−3296. (b) Curran, D. P.; Porter, N. A.; Giese, B. *Stereochemistry of Radical Reactions*; Wiley-VCH: Weinheim, 1996.

(3) Ramón, D. J.; Yus, M. In the Arena of Enantioselective Synthesis, Titanium Complexes Wear the Laurel Wreath. *Chem. Rev.* **2006**, *106*, 2126−2208.

(4) Gansäuer, A.; Bluhm, H. Reagent-Controlled Transition-Metal-Catalyzed Radical Reactions. *Chem. Rev.* **2000**, *100*, 2771−2788.

(5) CastroRodríguez, M.; RodríguezGarcia, I.; RodríguezMaecker, R. N.; PozoMorales, L.; Oltra, J. E.; Rosales Martínez, A. Cp2TiCl: An Ideal Reagent for Green Chemistry? *Org. Process Res. Dev.* **2017**, *21*, 911−923.

(6) Justicia, J.; Rosales, A.; Buñuel, E.; Oller-López, J. L.; Valdivia, M.; Haïdour, A.; Oltra, J. E.; Barrero, A. F.; Cárdenas, D. J.; Cuerva, J. M. Titanocene-Catalyzed Cascade Cyclization of Epoxypolyprenes: Straightforward Synthesis of Terpenoids by Free-Radical Chemistry. *Chem. - Eur. J.* **2004**, *10*, 1778−1788.

(7) Gansäuer, A.; Justicia, J.; Rosales, A.; Worgull, D.; Rinker, B.; Cuerva, J. M.; Oltra, J. E. Transition-Metal-Catalyzed Allylic Substitution and Titanocene-Catalyzed Epoxypolyene Cyclization as a Powerful Tool for the Preparation of Terpenoids. *Eur. J. Org. Chem.* **2006**, *2006*, 4115−4127.

(8) Justicia, J.; Álvarez de Cienfuegos, L.; Campaña, A. G.; Miguel, D.; Jakoby, V.; Gansäuer, A.; Cuerva, J. M. Bioinspired terpene synthesis: a radical approach. *Chem. Soc. Rev.* **2011**, *40*, 3525−3537.

(9) Jiménez, T.; Morcillo, S. P.; Martín-Lasanta, A.; Collado-Sanz, D.; Cárdenas, D. J.; Gansäuer, A.; Justicia, J.; Cuerva, J. M. Combining the Power of Ti^{III}-Mediated Processes for Easy Access to Hydroxylated Polycyclic Terpenoids: Synthesis of Sesterstatin 1 and C−D Rings of Aspergilloxide. *Chem. - Eur. J.* **2012**, *18*, 12825−12833.

(10) Morcillo, S. P.; Miguel, D.; Campaña, A. G.; Álvarez de Cienfuegos, L.; Justicia, J.; Cuerva, J. M. Recent applications of Cp_2TiCl in natural product synthesis. *Org. Chem. Front.* **2014**, *1*, 15−33.

(11) Clive, D. L. J.; Magnuson, S. R. Synthesis of the Sesquiterpene (±)-Ceratopicanol: Use of Radicals Derived from Epoxides. *Tetrahedron Lett.* **1995**, *36*, 15−18.

(12) Clive, D. L. J.; Magnuson, S. R.; Manning, H. W.; Mayhew, D. L. Cyclopentannulation by an Iterative Process of Sequential Claisen Rearrangement and Enyne Radical Closure: Routes to Triquinane and Propellane Systems and Use in the Synthesis of (±)-Ceratopicanol. *J. Org. Chem.* **1996**, *61*, 2095−2108.

(13) Yamaoka, M.; Nakazaki, A.; Kobayashi, S. Total synthesis of fomitellic acid B. *Tetrahedron Lett.* **2009**, *50*, 6764−6768.

(14) Cha, J. Y.; Yeoman, J. T. S.; Reisman, S. E. A Concise Total Synthesis of (A)-Maoecrystal Z. *J. Am. Chem. Soc.* **2011**, *133*, 14964−14967.

(15) Davis-Gilbert, Z. W.; Tonks, I. A. Titanium redox catalysis: insights and applications of an earth-abundant base metal. *Dalton Trans* **2017**, *46*, 11522−11528.

(16) Beaumier, E. P.; Pearce, A. J.; See, X. Y.; Tonks, I. A. Modern applications of low-valent early transition metals in synthesis and catalysis. *Nat. Rev. Chem.* **2019**, *3*, 15−34.

(17) Nugent, W. A.; RajanBabu, T. V. Transition-Metal-Centered Radicals in Organic Synthesis. Titanium(III)-Induced Cyclization of Epoxyolefins. *J. Am. Chem. Soc.* **1988**, *110*, 8561−8562.

(18) RajanBabu, T. V.; Nugent, W. A. Selective Generation of Free Radicals from Epoxides Using a Transition-Metal Radical. A Powerful New Tool for Organic Synthesis. *J. Am. Chem. Soc.* **1994**, *116*, 986−997.

(19) Bermejo, F.; Sandoval, C. Cp_2TiCl-Promoted Isomerization of Trisubstituted Epoxides to *exo*-Methylene Allylic Alcohols on Carvone Derivatives. *J. Org. Chem.* **2004**, *69*, 5275−5280.

(20) Fernández-Mateos, A.; Madrazo, S. E.; Teijón, P. H.; González, R. R. Titanocene-Promoted Eliminations on Epoxy Alcohols and Epoxy Esters. *Eur. J. Org. Chem.* **2010**, *2010*, 856−861.

(21) Gordon, J.; Hildebrandt, S.; Dewese, K. R.; Klare, S.; Gansäuer, A.; RajanBabu, T. V.; Nugent, W. A. Demystifying $Cp_2Ti(H)Cl$ and Its Enigmatic Role in the Reaction of Epoxides with Cp_2TiCl. *Organometallics* **2018**, *37*, 4801−4809.

(22) Gansäuer, A.; Rinker, B.; Pierobon, M.; Grimme, S.; Gerenkamp, M.; Mück-Lichtenfeld, C. A Radical Tandem Reaction with Homolytic Cleavage of a TiAO Bond. *Angew. Chem., Int. Ed.* **2003**, *42*, 3687−3690.

(23) Gansäuer, A.; Rinker, B.; Ndene-Schiffer, N.; Pierobon, M.; Grimme, S.; Gerenkamp, M.; Mück-Lichtenfeld, C. A Radical Roundabout for an Unprecedented Tandem Reaction Including a Homolytic Substitution with a Titanium-Oxygen Bond. *Eur. J. Org. Chem.* **2004**, *35*, 233732351.

(24) Gansäuer, A.; Fleckhaus, A.; Lafont, M. A.; Okkel, A.; Kotsis, K.; Anoop, A.; Neese, F. Catalysis via Homolytic Substitutions with CCO and TiOO Bonds: Oxidative Additions and Reductive

DOI: 10.1021/acs.joc.9b02465
J. Org. Chem. 2019, 84, 14369−14380

Eliminations in Single Electron Steps. *J. Am. Chem. Soc.* **2009**, *131*, 16989−16999.

(25) Wu, X.; Hao, W.; Ye, K.-Y.; Jiang, B.; Pombar, G.; Song, Z.; Lin, S. Ti-Catalyzed Radical Alkylation of Secondary and Tertiary Alkyl Chlorides Using Michael Acceptors. *J. Am. Chem. Soc.* **2018**, *140*, 14836−14843.

(26) Cesarotti, E.; Kagan, H. B.; Goddard, R.; Krüger, C. Synthesis of new ligands for transition metal complexes: menthyl- and neomenthyl-cyclopentadienes. *J. Organomet. Chem.* **1978**, *162*, 297−309.

(27) Gansäuer, A.; Lauterbach, T.; Bluhm, H.; Noltemeyer, M. A Catalytic Enantioselective Electron Transfer Reaction: Titanocene-Catalyzed Enantioselective Formation of Radicals from *meso*-Epoxides. *Angew. Chem., Int. Ed.* **1999**, *38*, 2909−2010.

(28) Gansäuer, A.; Bluhm, H.; Lauterbach, T. Titanocene-Catalysed Enantioselective Opening of *meso*-Epoxides. *Adv. Synth. Catal.* **2001**, *343*, 785−787.

(29) Gansäuer, A.; Fan, C.-A.; Keller, F.; Keil, J. Titanocene-Catalyzed Regiodivergent Epoxide Openings. *J. Am. Chem. Soc.* **2007**, *129*, 3484−3485.

(30) Gansäuer, A.; Fan, C.-A.; Keller, F.; Karbaum, P. Regiodivergent Epoxide Opening: A Concept in Stereoselective Catalysis beyond Classical Kinetic Resolutions and Desymmetrizations. *Chem. - Eur. J.* **2007**, *13*, 8084−8090.

(31) Gansäuer, A.; Shi, L.; Otte, M. Catalytic Enantioselective Radical Cyclization via Regiodivergent Epoxide Opening. *J. Am. Chem. Soc.* **2010**, *132*, 11858.

(32) Funken, N.; Mühlhaus, F.; Gansäuer, A. General, Highly Selective Synthesis of 1,3- and 1,4-Difunctionalized Building Blocks by Regiodivergent Epoxide Opening. *Angew. Chem., Int. Ed.* **2016**, *55*, 12030−12034.

(33) Gansäuer, A.; Pierobon, M.; Bluhm, H. Catalytic, Highly Regio- and Chemoselective Generation of Radicals from Epoxides: Titanocene Dichloride as an Electron Transfer Catalyst in Transition Metal Catalyzed Radical Reactions. *Angew. Chem., Int. Ed.* **1998**, *37*, 101−103.

(34) Gansäuer, A.; Bluhm, H.; Pierobon, M. Emergence of a Novel Catalytic Radical Reaction: Titanocene-Catalyzed Reductive Opening of Epoxides. *J. Am. Chem. Soc.* **1998**, *120*, 12849−12859.

(35) Enemærke, R. J.; Larsen, J.; Skrydstrup, T.; Daasbjerg, K. Revelation of the Nature of the Reducing Species in Titanocene Halide-Promoted Reductions. *J. Am. Chem. Soc.* **2004**, *126*, 7853−7864.

(36) Daasbjerg, K.; Svith, H.; Grimme, S.; Gerenkamp, M.; Mück-Lichtenfeld, C.; Gansäuer, A.; Barchuk, A.; Keller, F. Elucidation of the Mechanism of Titanocene-Mediated Epoxide Opening by a Combined Experimental and Theoretical Approach. *Angew. Chem., Int. Ed.* **2006**, *45*, 2041−2044.

(37) Gansäuer, A.; Barchuk, A.; Keller, F.; Schmitt, M.; Grimme, S.; Gerenkamp, M.; Mück-Lichtenfeld, C.; Daasbjerg, K.; Svith, H. Mechanism of Titanocene-Mediated Epoxide Opening through Homolytic Substitution. *J. Am. Chem. Soc.* **2007**, *129*, 1359.

(38) Streuff, J.; Himmel, D.; Younas, S. L. Understanding titanium-catalysed radical-radical reactions: a DFT study unravels the complex kinetics of ketone-nitrile couplings. *Dalton Trans* **2018**, *47*, 5072−5082.

(39) Rossi, B.; Prosperini, S.; Pastori, N.; Clerici, A.; Punta, C. New Advances in Titanium-Mediated Free Radical Reactions. *Molecules* **2012**, *17*, 14700−14732.

(40) Streuff, J. A Titanium(III)-Catalyzed Redox Umpolung Reaction for the Reductive Cross-Coupling of Enones with Acrylonitriles. *Chem. - Eur. J.* **2011**, *17*, 5507−5510.

(41) Gansäuer, A.; Piestert, F.; Huth, I.; Lauterbach, T. Nitriles and Carbonyl Groups as Acceptors in Titanocene-Catalyzed Radical Cyclizations. *Synthesis* **2008**, *2008*, 3509−3515.

(42) Bichovski, P.; Haas, T. M.; Kratzert, D.; Streuff, J. Synthesis of Bridged Benzazocines and Benzoxocines by a Titanium-Catalyzed Double-Reductive Umpolung Strategy. *Chem. - Eur. J.* **2015**, *21*, 2339−2342.

(43) Streuff, J.; Gansäuer, A. Metal-Catalyzed M-Functionalization of Michael Acceptors through Reductive Radical Addition Reactions. *Angew. Chem., Int. Ed.* **2015**, *54*, 14232−14242.

(44) Bichovski, P.; Haas, T. M.; Keller, M.; Streuff, J. Direct conjugate alkylation of α,β-unsaturated carbonyls by Ti^{III}-catalysed reductive umpolung of simple activated alkenes. *Org. Biomol. Chem.* **2016**, *14*, 5673−5682.

(45) Wild, F. R. W. P.; Zsolnai, L.; Huttner, G.; Brintzinger, H. H. *ansa*-Metallocene derivatives IV. Synthesis and molecular structures of chiral *ansa*-titanocene derivatives with bridged tetrahydroindenyl ligands. *J. Organomet. Chem.* **1982**, *232*, 233−247.

(46) Streuff, J.; Feurer, M.; Bichovski, P.; Frey, G.; Gellrich, U. Enantioselective Titanium(III)-Catalyzed Reductive Cyclization of Ketonitriles. *Angew. Chem., Int. Ed.* **2012**, *51*, 8661−8664.

(47) Gianino, J. B.; Ashfeld, B. L. Titanocene-Catalyzed Multicomponent Coupling Approach to Diarylethynyl Methanes. *J. Am. Chem. Soc.* **2012**, *134*, 18217−18220.

(48) Lepore, A. J.; Pinkerton, D. M.; Ashfeld, B. L. Relay Redox and Lewis Acid Catalysis in the Titanocene-Catalyzed Multicomponent Assembly of 1,5-Enynes. *Adv. Synth. Catal.* **2013**, *355*, 1500−1504.

(49) Campos, C. A.; Gianino, J. B.; Ashfeld, B. L. Bifunctional Titanocene Catalysis in Multicomponent Couplings: A Convergent Assembly of β-Alkynyl Ketones. *Org. Lett.* **2013**, *15*, 2656−2659.

(50) Campos, C. A.; Gianino, J. B.; Bailey, B. J.; Baluyut, M. E.; Wiek, C.; Hanenberg, H.; Shannon, H.; Pollok, K. E.; Ashfeld, B. L. Design, Synthesis, and Evaluation of Curcumin-Derived Arylheptanoids for Glioblastoma and Neuroblastoma Cytotoxicity. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 6874−6878.

(51) Gianino, J. B.; Campos, C. A.; Lepore, A. J.; Pinkerton, D. M.; Ashfeld, B. L. Redox and Lewis Acid Relay Catalysis: A Titanocene/Zinc Catalytic Platform in the Development of Multicomponent Coupling Reactions. *J. Org. Chem.* **2014**, *79*, 12083−12095.

(52) Zhang, Y.-Q.; Vogelsang, E.; Qu, Z.-W.; Grimme, S.; Gansäuer, A. Titanocene-Catalyzed Radical of *N*-Acylated Aziridines. *Angew. Chem., Int. Ed.* **2017**, *56*, 12654−12657.

(53) González-Bobes, F.; Fu, G. C. Amino Alcohols as Ligands for Nickel-Catalyzed Suzuki Reactions of Unactivated Alkyl Halides, Including Secondary Alkyl Chlorides, with Arylboronic Acids. *J. Am. Chem. Soc.* **2006**, *128*, 5360−5361.

(54) Zheng, X.; Dai, X.-J.; Yuan, H.-Q.; Ye, C.-X.; Ma, J.; Huang, P.-Q. Umpolung of Hemiaminals: Titanocene-Catalyzed Dehydroxylative Radical Coupling Reactions with Activated Alkenes. *Angew. Chem., Int. Ed.* **2013**, *52*, 3494−3498.

(55) Huang, H.-M.; Garduño-Castro, M. H.; Morrill, C.; Procter, D. J. Catalytic cascade reactions by radical relay. *Chem. Soc. Rev.* **2019**, *48*, 4626−4638.

(56) Gansäuer, A.; Behlendorf, M.; von Laufenberg, D.; Fleckhaus, A.; Kube, C.; Sadasivam, D. V.; Flowers, R. A., II. Catalytic, Atom-Economical Radical Arylation of Epoxides. *Angew. Chem., Int. Ed.* **2012**, *51*, 4739−4742.

(57) Gansäuer, A.; Kube, C.; Daasbjerg, K.; Sure, R.; Grimme, S.; Fianu, G. D.; Sadasivam, D. V.; Flowers, R. A., II. Substituent Effects and Supramolecular Interactions of Titanocene(III) Chloride: Implications for Catalysis in Single Electron Steps. *J. Am. Chem. Soc.* **2014**, *136*, 1663−1671.

(58) Gansäuer, A.; von Laufenberg, D.; Kube, C.; Dahmen, T.; Michelmann, A.; Behlendorf, M.; Sure, R.; Seddiqzai, M.; Grimme, S.; Sadasivam, D. V.; Fianu, G. D.; Flowers, R. A., II. Mechanistic Study of the Titanocene(III)-Catalyzed Radical Arylation of Epoxides. *Chem. - Eur. J.* **2015**, *21*, 280−289.

(59) Gansäuer, A.; Hildebrandt, S.; Michelmann, A.; Dahmen, T.; von Laufenberg, D.; Kube, C.; Fianu, G. D.; Flowers, R. A., II. Cationic Titanocene(III) Complexes for Catalysis in Single-Electron Steps. *Angew. Chem., Int. Ed.* **2015**, *54*, 7003−7006.

(60) Hildebrandt, S.; Gansäuer, A. Synthesis of Dihydropyrrolizine and Tetrahydroindolizine Scaffolds from Pyrroles by Titanocene(III) Catalysis. *Angew. Chem., Int. Ed.* **2016**, *55*, 9719−9722.

(61) Liedtke, T.; Spannring, P.; Riccardi, L.; Gansäuer, A. Mechanism-Based Condition Screening for Sustainable Catalysis in

DOI: 10.1021/acs.joc.9b02465
J. Org. Chem. 2019, 84, 14369−14380

Single-Electron Steps by Cyclic Voltammetry. *Angew. Chem., Int. Ed.* **2018**, *57*, 5006−5010.
(62) Richrath, R. B.; Olyschläger, T.; Hildebrandt, S.; Enny, D. G.; Fianu, G. D.; Flowers, R. A., II.; Gansäuer, A. Cp_2TiX Complexes for Sustainable Catalysis in Single-Electron Steps. *Chem. - Eur. J.* **2018**, *24*, 6371−6379.
(63) Mühlhaus, F.; Weihbarth, H.; Dahmen, T.; Schnakenburg, G.; Gansäuer, A. Merging Regiodivergent Catalysis with Atom-Economical Radical Arylation. *Angew. Chem., Int. Ed.* **2019**, *58*, 14208−14212.
(64) Hao, W.; Wu, X.; Sun, J. Z.; Siu, J. C.; MacMillan, S. N.; Lin, S. Radical Redox-Relay Catalysis: Formal [3 + 2] Cycloaddition of *N*-Acylaziridines and Alkenes. *J. Am. Chem. Soc.* **2017**, *139*, 12141−12144.
(65) Hao, W.; Harenberg, J. H.; Wu, X.; MacMillan, S. N.; Lin, S. Diastereo- and Enantioselective Formal [3 + 2] Cycloaddition of Cyclopropyl Ketones and Alkenes via Ti-Catalyzed Radical Redox Relay. *J. Am. Chem. Soc.* **2018**, *140*, 3514−3517.
(66) Zhao, Y.; Weix, D. J. Nickel-Catalyzed Regiodivergent Opening of Epoxides with Aryl Halides: Co-Catalysis Controls Regioselectivity. *J. Am. Chem. Soc.* **2014**, *136*, 48−51.
(67) Weix, D. J. Methods and Mechanisms for Cross-Electrophile Coupling of Csp^2 Halides with Alkyl Electrophiles. *Acc. Chem. Res.* **2015**, *48*, 1767−1775.
(68) Zhao, Y.; Weix, D. J. Enantioselective Cross-Coupling of *meso*-Epoxides with Aryl Halides. *J. Am. Chem. Soc.* **2015**, *137*, 3237−3240.
(69) Tarantino, K. T.; Miller, D. C.; Callon, T. A.; Knowles, R. R. Bond-Weakening Catalysis: Conjugate Aminations Enabled by the Soft Homolysis of Strong N-H Bonds. *J. Am. Chem. Soc.* **2015**, *137*, 6440−6443.
(70) Gansäuer, A.; Fan, C.-A.; Piestert, F. Sustainable radical reduction through catalytic hydrogen atom transfer. *J. Am. Chem. Soc.* **2008**, *130*, 6916−6917.
(71) Gansäuer, A.; Otte, M.; Piestert, F.; Fan, C.-A. Sustainable radical reduction through catalyzed hydrogen atom transfer reactions (CHAT-reactions). *Tetrahedron* **2009**, *65*, 4984−4991.
(72) Gansäuer, A.; Otte, M.; Shi, L. Radical Cyclizations Terminated by Ir-Catalyzed Hydrogen Atom Transfer. *J. Am. Chem. Soc.* **2011**, *133*, 416−417.
(73) Velasco, J.; Ariza, X.; Badia, L.; Bartra, M.; Berenguer, R.; Farras, J.; Gallardo, J.; Garcia, J.; Gasanz, Y. Total Synthesis of Entecavir. *J. Org. Chem.* **2013**, *78*, 5482−5491.
(74) Yao, C.; Dahmen, T.; Gansäuer, A.; Norton, J. Anti-Markovnikov alcohols via epoxide hydrogenation through cooperative catalysis. *Science* **2019**, *364*, 764−767.
(75) Ye, K.-Y.; McCallum, T.; Lin, S. Bimetallic Radical Redox-Relay Catalysis for the Isomerization of Epoxides to Allylic Alcohols. *J. Am. Chem. Soc.* **2019**, *141*, 9548−9554.
(76) Crossley, S. W. M.; Obradors, C.; Martinez, R. M.; Shenvi, R. A. Mn-, Fe-, and Co-Catalyzed Radical Hydrofunctionalizations ofOlefins. *Chem. Rev.* **2016**, *116*, 8912−9000.
(77) West, J. G.; Sorensen, E. J. Development of a Bio-Inspired Dual Catalytic System for Alkane Dehydrogenation. *Isr. J. Chem.* **2017**, *57*, 259−269.
(78) Zhang, Z.; Richrath, R. B.; Gansäuer, A. Merging Catalysis in Single Electron Steps with Photoredox Catalysis - Efficient and Sustainable Radical Chemistry. *ACS Catal.* **2019**, *9*, 3208−3212.

DOI: 10.1021/acs.joc.9b02465
J. Org. Chem. 2019, 84, 14369−14380