Ti (II) Mediated Reactions in Organic Chemistry

Chris Tarr
University of North Carolina
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Outline of Topics Covered

• Background

• Cyclopropanation Reactions

• Olefin/Acetylene Functionalizations

• Reductive Couplings
Advantages of Titanium

• Titanium (IV) reagents are cheap and readily available

• Low toxicity compared to other transition metal catalysts

• Less reactive than Li or Mg organometallics

• More reactive than corresponding B or Zn organometallics
Notable Applications Not Covered

- **Sharpless Asymmetric Epoxidation (Ti IV)**

  \[
  
  \begin{align*}
  \text{R} &= \text{CH}_2\text{OH} \\
  \text{R} &= \text{CH}_2\text{OH}
  \end{align*}
  \]


- **Lewis Acid Catalysis (Ti IV)**

  \[
  \begin{align*}
  \text{R} &= \text{CH}_2\text{OH} \\
  \text{R} &= \text{CH}_2\text{OH}
  \end{align*}
  \]


- **McMurry Coupling (Ti III → Ti I)**

  \[
  \begin{align*}
  \text{R} &= \text{CH}_2\text{OH} \\
  \text{R} &= \text{CH}_2\text{OH}
  \end{align*}
  \]


- **Tebbe Reagent (Ti IV)**

  \[
  \begin{align*}
  \text{Cp}_2\text{TiCl}_2 + 2\text{AlMe}_3 &\rightarrow \text{Cp}_2\text{TiCl}_{\text{2AlMe}_2} \\
  \text{R} &= \text{R'}
  \end{align*}
  \]

Generation of Ti(II) from Ti(IV)

- Bercaw accessed and characterized the first Ti(II)-ethylene adduct: X-ray crystal structure verifies existence as monomer

- Ti(II) was able to dimerize ethylene; however, was not effective as a promoter for further polymerization
- Two limiting resonance structures: Ti(II) species may react as either a 1,2-dianion or a pi-bound alkene

Generation of Ti(II) via Reductive Alkylation

- Ti(IV) converted to Ti(II) via reductive alkylation: an organolithium or organomagnesium compound can be used to generate a dialkyl titanium complex which can lead to a Ti(II) species

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Kulinkovich Reaction

- Kulinkovich reaction: a facile method for cyclopropanol synthesis from esters

\[
\begin{align*}
\text{1. EtMgBr (3 equiv)} & \quad \text{Ti(IV) can also be used catalytically (2 equiv. of Grignard reagent required)} \\
\text{Ti(O/iPr)}_4 & \quad \text{Et}_2\text{O, -78°C} \\
\text{2. H}_3\text{O}^+ & \quad \text{OH} \\
\end{align*}
\]

Representative Examples

- Kulinkovich cyclopropanation

Mechanism of Kulinkovich Reaction

Mechanism of Kulinkovich Reaction

Ti(OiPr)$_4$ + 2 EtMgBr → \[ \begin{array}{c} \text{H} \\ \text{Ti(OiPr)$_2$} \end{array} \] → C$_2$H$_6$ + \[ \begin{array}{c} \text{Ti(OiPr)$_2$} \\ \text{R'O$_2$Me} \end{array} \] → Ti(OiPr)$_2$ + \[ \begin{array}{c} \text{MeO} \\ \text{R'} \end{array} \] → EtMgBr + \[ \begin{array}{c} \text{R'O$_2$Me} \\ \text{Ti(OiPr)$_2$} \end{array} \] → \[ \begin{array}{c} \text{HO} \\ \text{R} \end{array} \] → H$_3$O$^+$

Kulinkovich, O. *Pure Appl. Chem.* 2000, 72, 1715.
de Meijere Mechanism

- **de Meijere modification:** access to cyclopropylamines

1. EtMgBr (2 equiv.)
   \[ \text{Ti(OiPr)}_4 \]
   \[ \text{Et}_2\text{O} \]

2. \( \text{H}_3\text{O}^+ \)

- **Key mechanistic difference**

Substrate Scope

- de Meijere modification

Computational Study on Selectivity of Kulinkovich Reaction

- Computed with B3LYP/HW3 method
- Cyclopropane forming step, determines stereochemistry and is the rate determining step
- T.S. cis is 2.5 kcal/mol more favored because of agostic interaction between ester R group and Ti

Ligand Exchange in Kulinkovich Reaction

- Allows for a wider range of substitution in cyclopropanols

- Substrates with which alkene exchange has been successful

Intramolecular Nucleophilic Acyl Substitution

- Typically difficult to balance the necessary reactivity and functional group tolerance
- Exchange of the initial alkene with a second alkene tethered to an ester leads to new products with *trans* alkyl/(aryl) groups

Additional INAS reactions

- Generation of fused bicyclic cyclopropanols

\[
\begin{align*}
\text{alkyne} \quad &\xrightarrow{\text{Ti(OiPr)}_2} \quad \text{cyclopropanol} \\
\text{alkene} \quad &\xrightarrow{\text{Ti(OiPr)}_2} \quad \text{methylene-lactone} \\
&\xrightarrow{\text{Ti(OR)}_3} \quad \text{cyclohexene} \quad \text{OH}
\end{align*}
\]

- Use of an alkyne versus an alkene leads to methylene-lactone or \(\alpha,\beta\)-unsaturated carbonyl

\[
\begin{align*}
\text{alkyne} \quad &\xrightarrow{\text{Ti(OiPr)}_2} \quad \text{cyclopropanol} \\
\text{alkene} \quad &\xrightarrow{\text{Ti(OiPr)}_2} \quad \text{methylene-lactone} \\
&\xrightarrow{\text{Ti(OR)}_3} \quad \text{cyclohexene} \quad \text{OH}
\end{align*}
\]

Enantioselective Catalytic Kulinkovich Reaction

• Corey demonstrated limited success in achieving an asymmetric reaction based on catalyst control
• Very limited catalyst screen and substrate scope
• Only moderate yields and enantiomeric induction are achieved

TADDOL-based pre-catalyst
Ar = 3,5-bis(trifluoromethyl)phenyl

With ethyl acetate substrate:
65% yield
70-80% ee

Substrate controlled INAS Reaction

- Stereoselectivity can be transferred from starting material to the final products


Cyclopropylamines from Nitriles

- Initial adduct can lead to tertiary amines and ketones
- Addition of a BF$_3$ Lewis acid results in the formation of cyclopropylamines

Cyclopropylamines from Nitriles

- Nitriles can easily be installed in carbohydrate backbones; this strategy allows the synthesis of cyclopropylamine substituted sugars

First Access to Spirocyclopropyl Iminosugar

- Iminosugars are potent glycosidase inhibitors and have been identified as possible anti-diabetes, anti-retroviral, and anti-tumor targets
- High cytotoxicities preclude their use
- Cyclopropane ring is a key pharmacophore that induces binding in other bioactive molecules

Vinylogous Kulinkovich Reaction

- Cha has recently developed a procedure for a vinylogous Kulinkovich reaction
- When toluene and a Lewis acid are employed, a vinyl cyclopropane is formed
- Reaction produces a spirocyclic cyclopropane ring with no directly bound heteroatom

Ring Expansions to Cyclobutanones

- Acid mediated ring expansion/cyclization of Kulinkovich reaction products

\[
\begin{align*}
\text{CHO} & \xrightarrow{\text{H}^+} \text{HO} \\
\text{HO} & \xrightarrow{\text{R} \text{ClTi(OiPr)}_3} \text{HO}
\end{align*}
\]


- Pinacol-type rearrangement to access chiral \(\alpha\)-substituted cyclobutanones

\[
\begin{align*}
\text{R} & \xrightarrow{\text{EtMgBr}} \text{OH} \\
\text{OH} & \xrightarrow{\text{CITi(OiPr)}_3} \text{OH} \\
\text{OH} & \xrightarrow{\text{MsCl, pyridine}} \text{R}
\end{align*}
\]

>90% chirality transfer

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  • Olefin/Acetylene Functionalizations

• Reductive Couplings
Olefin-imide Coupling

• Ti (II) can react with imides, however only poor regioselectivity is obtained.

• Intramolecular trapping provides poor diastereoselectivity; however, reduction with $\text{H}_2/\text{PtO}_2$ leads to the same product arising from both diastereomers.

Olefin-imide Coupling

• Cha also developed a diastereoselective cyclization between imides and substituted tethered olefins

![Chemical structure]

\[ \text{m, n} = 1, 2 \]

\[ R = \text{Me, Ph} \]

• When \( R = \text{H} \), poor diastereoselectivities are achieved; however, larger \( R \) groups such as Me or Ph higher diastereoselectivities were obtained

Olefin-imide Coupling


![Chemical structures and reaction schemes](image-url)
Addition of Imine-Based Titanocyclopropanes

- Addition to an imine followed by trapping with acetylene leads to allyl and alkynyl amines, as well as pyrroles
- Asymmetric induction from chiral R group

- Stereochemical model for observed products

Diastereoselectivity of Allyl Amine Formation

\[
\text{Ar} \text{N} \text{Ti(OiPr)}_2 \xrightarrow{\text{R} \equiv \equiv} \text{ArHN} \text{OMe}\]

<table>
<thead>
<tr>
<th>R</th>
<th>d.r.</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TMS</td>
<td>97:3</td>
<td>81</td>
</tr>
<tr>
<td>Hexyl</td>
<td>98:2</td>
<td>82</td>
</tr>
<tr>
<td>Ph</td>
<td>98:2</td>
<td>84</td>
</tr>
<tr>
<td>CO\textsubscript{2}Et</td>
<td>96:4</td>
<td>63</td>
</tr>
<tr>
<td>SO\textsubscript{2}Tol</td>
<td>94:6</td>
<td>28</td>
</tr>
</tbody>
</table>

Diastereoselectivity of Allenyl Amine Formation

\[
\text{Ar} \quad \text{R/R'/X} \quad \text{d.r.} \quad \text{Yield}
\begin{array}{|c|c|c|}
\hline
\text{Ph} & \text{H/H/Br} & 98:2 & 74 \\
\text{o-iodophenyl} & \text{H/H/Br} & 98:2 & 61 \\
\text{1-naphthyl} & \text{H/H/Br} & 98:2 & 59 \\
\text{p-OTBS-phenyl} & \text{H/H/Br} & 98:2 & 62 \\
\text{Ph} & \text{Hexyl/H/OP(O)(OEt)_2} & 98:2 & 49 \\
\text{Ph} & \text{Ph/H/OP(O)(OEt)_2} & 98:2 & 62 \\
\hline
\end{array}
\]

Diene Functionalization

- Titanium can add into a diene to form a cyclopentenyltitanium species which can add to an aldehyde with good regio- and diastereoselectivity.
- The resulting species can be opened via protonolysis.

Good asymmetric induction was achieved by tethering a chiral 8-phenylmenthol ester to the diene backbone.

Addition to Acetylenes

- Reaction of alkynes with Ti(II) allows for trapping with two subsequent electrophiles

- Reaction with dichlorophosphites leads to cyclic phosphites

- Reaction with sec-BuOH followed by a second electrophile leads to one C-C or C-X and one C-H bond

Regioselectivity of Titanacyclopropene Opening

- When unsymmetrical acetylenes are used to form the titanacyclopropene, electrophilic ring opening can occur with a high degree of regioselectivity

Cross Coupling Reactions

- Recently, the Ti(II)-cyclopropene complex has been found to undergo a newly developed cross coupling reaction

- Treatment with aryl iodide and a Ni(COD)$_2$ complex leads to a mixture of mono- and di-arylated products with mono-coupled products predominating

Yields 40 – 80%
Selectivities range from 10:1 to 1:1

Enyne Cyclization

- A tethered alkyne and alkene can be used in an annulation reaction

- Depending on the substitution of enyne, 1,2-difunctionalized rings and variously functionalized bicyclic rings can be achieved

Diversity of Enyne Cyclization Manifold

1,2 substituted acrylynes can also undergo titanium mediated cyclization to form exocyclic cyclopentenes, [3.3.0]-bicyclooctanes, and [3.1.0]-bicyclohexanes.

Asymmetric Metallo-ene Reaction

Normal Metallo-ene Reaction

- Metallo-ene reaction, difficult to achieve enantioselectivity

Titanium (II) Equivalent

- Ti-mediated cyclization: does allow for asymmetric induction
- Camphor esters gave poor ee's; however, chiral acetals gave high ee's
- Acetals offer a convenient synthetic handle for further product manipulation

Siloxy-enyne Cyclization

- Phillips and co-workers developed a siloxy-enyne cyclization.
- Cleavage of the C-Si bond allows for the installation of an \textit{anti}-methyl group alpha to a hydroxy group.
- This strategy has been applied to natural product synthesis.

Dictyostatin Synthesis

- Dictyostatin, an anti-cancer marine macrocycle synthesized by Phillips
- Two $3^\circ$ stereocenters set by siloxy-enyne reaction

**2+2+2 Cyclization**

- Trapping of cyclopentadienyl-titanium species with another unsaturated molecule results in a 2+2+2 cyclization

\[
\begin{align*}
\text{ArO}_2\text{Cl}_2 & \quad \text{Ti} \quad \text{Cl}_2 \\
\text{2 Na/Hg} & \quad \xrightarrow{\text{cyclization}} \\
\text{Ti(OAr)}_2 & \quad \xrightarrow{\text{product}} \\
\end{align*}
\]

- Rothwell developed a 2+2+2 reaction; however, the product is formed with only poor regioselectivity due to metal-assisted 1,5-hydride shifts under reaction conditions

\[
\begin{align*}
\text{Ph} = \text{Et} \quad \xrightarrow{(\text{ArO})_2\text{TiCl}_2} \\
\text{Et} & \quad \xrightarrow{\text{product}} \\
\end{align*}
\]

10% 55% 35%

2+2+2 Cyclization

- Cha developed a 2+2+2 coupling reaction with tethered acetylenes β-hydroxy olefins
- The reaction proceeds in good to moderate yields
- No double bond migration occurs, so initially formed cyclohexadienes can be isolated

Yields ~50-80%

Synthesis of Titanated Benzene Rings

Two Mechanisms for Alkyne Addition

Synthesis of Aromatic Rings

- Sato developed a regioselective coupling between an acetylene and a nitrile, followed by trapping with another unsaturated molecule.
- A single intermediate allows access to pyridine, furan, and pyrrole containing molecules.

Mechanism for Pyridine Formation

- Tosyl acetylenes lead to titanated pyridines, which allow for the regiocontrolled synthesis of tetrasubstituted pyridines
- Reaction conditions also allow for the preparation of chiral pyridine rings starting from the easily accessible optically active propargyl alcohols

Furan Formation

- Interception of the cyclopentadienyl intermediate with an aldehyde leads to an insertion, followed by protonolysis, ring closing, and aromatization
- The reaction produces moderate yields of tetrasubstituted furan rings

Pyrrole Formation

- Nitrile insertion leads to a di-imine product after hydrolysis, which under acidic conditions cyclizes to the formyl pyrrole.
- Trapping by two different nitriles leads to regioselective formation of the aldehyde at the least substituted side chain.

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Pinacol Coupling

- Pinacol reaction: coupling of two carbonyl radicals

\[
2 \text{RCHO} \rightarrow \text{RCHO} \rightarrow \text{ROH} \quad \text{dl selective}
\]

- Titanium mediated pinacol couplings lead to high selectivities for the \textit{dl} isomer over the \textit{meso} compound via a di-oxo-titanium intermediate

\[
2 \text{RCHO} + \text{TiX}_2 + \text{Cu} \rightarrow \text{ROL} \rightarrow \text{ROH} \quad \text{dl selective}
\]

\[
\text{TiI}_4 + \text{Cu} \rightarrow \text{TiI}_2 + 2\text{CuI}
\]

Pinacol Coupling (cont.)

\[
\begin{align*}
2 \text{RCHO} &\xrightarrow{\text{Til}_4, 2 \text{Cu}} \text{RCH(OH)CH(OH)R} \\
&= \text{dl} \\
&= \text{meso}
\end{align*}
\]

Reformatsky Reaction

- Reformatsky Reaction: An aldol surrogate, enolate is formed via insertion into a C-X bond

\[
\begin{align*}
\text{R} & \text{CH}_2 \text{X} \quad \text{Zn} \quad \rightarrow \quad \text{R} \quad \text{ZnX} \quad \rightarrow \quad \text{R} \quad \text{CHO}
\end{align*}
\]

- Mukaiyama et al. developed a Ti-based Reformatsky-type reaction that displays high diastereoselectivity

\[
\begin{align*}
\text{R} & \text{CH}_2 \text{Br} \quad \text{TiCl}_2 \quad \text{Cu} \quad \rightarrow \quad \text{R} \quad \text{CHO} \quad \rightarrow \quad \text{R} \quad \text{OH}
\end{align*}
\]

Kagayama, A. et al.
Substrate Scope for Reformatsky Reaction

Summary

• Titanium (II) complexes can easily be generated from readily available and inexpensive starting materials

• The chemistry of Ti (II) complexes allows entry into several intriguing reaction manifolds including:
  – Cyclopropanation
  – Alkene/acetylene/imine functionalization
  – Synthesis of novel aromatic rings
  – Various reductive coupling reactions

• Titanium (II) chemistry is amenable to the synthesis of interesting natural products
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• UNC Chemistry Department