Recent Advances in Enantioselective Crotylations with Non-toxic Chiral Reagents

Literature Review

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Overview

1. Introduction
2. Type I Reagents
3. Type II Reagents
4. Type III Reagents
5. Conclusion
Introduction
Introduction: Definitions

- **Carbonyl crotylation**
  - Addition of $[M]CH_2CH=CHCH_3$ group to a carbonyl derivative
- **Chiral reagents/catalysts impart diastereo- and enantio- selectivity to crotylation products**
Introduction: Classification of Crotylumetals

- **Type I**
  - Syn/anti ratio of products reflects Z/E ratio of crotylumetal reagent
  - React via closed chair-like transition state
  - E.g. B, Si, Sn (thermal)

- **Type II**
  - Syn-selective products generated regardless of geometry of crotylumetal reagent
  - Undergo Lewis acid catalysis
  - React via open transition state
  - E.g. Sn, Si, Ti

- **Type III**
  - Anti-selective products generated regardless of geometry of crotylumetal reagent
  - Crotylumetal reagent generated in situ and equilibration gives more stable E-isomer
  - React via closed chair-like transition state
  - E.g. Ti, Cr, Zr
Type I Crotylmetals
Type I Crotylmetals: Diastereoselectivity

- React *via* a 6-membered closed, cyclic chair-like transition state (Zimmerman-Traxler model)
  - Metal coordinates to aldehyde oxygen *syn* to smallest substituent (H)
  - Aldehyde R group adopts pseudoequatorial position to minimise steric repulsion
Type I Crotylmetals: Enantioselectivity

- React *via* a 6-membered closed, cyclic chair-like transition state
  - Stereochemical outcome determined by chiral auxiliary on crotyl metal
Boron Reagents

disopinocampherylboranes  (lipo2boronyl)
Brown

tartrate-derived boronates
Roush

Corey

9-BBN-derived reagents
Soderquist
**Crotyleboranes: Aldehyde Crotylation**

- **B-crotyl-10-TMS-9-BBD** reagents are robust, versatile and recyclable
  - All 4 geometric and enantiomeric isomers can be prepared from **B-MeO-9-BBN**
  - **B-MeO-9-BBN** is resolved with pseudophendrine to give air-stable crystalline complexes 3
  - Crotyleboranes 6 are obtained from butene by reaction with Schlosser’s “superbase”, then addition to 4

**References**

Crotlylboranes: Aldehyde Crotylation

- **B-crotyl-10-TMS-9-BBD reagents are robust, versatile and recyclable**
  - Rapid reaction with aldehyde at low temperatures within 3 h, crotylborane geometry faithfully reflected
  - Choice of workup procedures
    - Oxidative workup with H₂O₂
    - Nonoxidative workup with appropriate enantiomeric form of pseudoephedrine allows recovery of chiral pseudophendrine complex 3 in 70-80% yield for recycling
  - Reacts *via* a chair-like TS
    - Formation of B-chiral *anti*-aldehyde complex *cis* to 10-TMS favoured
    - Using *R* reagent, this results in selective crotylation of the *re* face of RCHO observed

Crotarylboranes: Aldehyde Crotylation

- Application: One-Pot Asymmetric Synthesis of 2,3-disubstituted THFs
  - Sequential crotylboration-hydroboration-iodination-cyclisation reaction
  - Crotarylborane controls both enantio- and diastereo- selectivity of THF

Ramachandran, P. V.; Nair, H. M. G.; Gagare, P. D. JOC. 2012, 77, 5394.
Chiral biphenol organocatalyst for crotylboration of ketones

- High enantio- and diastereo-selectivity with low organocatalyst loadings
  - Cyclic boronates can be prepared and purified easily and stored for long periods of time
  - t-BuOH accelerates reaction and improves enantioselectivity

- Mechanistic studies and proposed catalytic cycle
  - RDS is liberation of catalyst from product \( k_{ex} \) \( \rightarrow \) addition of alcohol increases overall catalyst concentration, giving increased reaction rates and enantioselectivities
  - t-BuOH is a less coordinating alcohol \( \rightarrow \) less Lewis base-acid coordination to boronate so does not inhibit reaction

Crotylboration of aromatic N-silylimines with boronate complexes

- First report of Ipc-crotylboration complex
  - Addition of BF$_3$$\cdot$OEt$_2$ to generate trialkylboranes degrades silylimines
- Only aromatic imines tolerated

Crotylboration of N-aluminoimines with boronate complexes

- N-aluminoimines have higher stability than N-silylimines
- Aromatic N-aluminoimines give similar results to aromatic N-silylimines

Crotyleboronates: Imine Crotylation

- Crotyleborination of N-aluminoimines with boronate complexes
  - Aliphatic N-aluminoimines can undergo crotyleborination in pentane

- Proposed mechanism
  - MeOH liberates “naked” aldime
  - Reacts via a chair-like TS
  - Alkaline oxidative work-up yields β-methyl homoallylic imine

Crotlylboronates: Imine Crotylation

- Application: Synthesis of β-Amino acids

\[
\begin{align*}
\text{NH}_2 & \quad \text{Ph} \quad \text{Ph} \quad \text{NH}_2 \\
\text{MeCN/H}_2\text{O (1:1)} & \quad \text{i. Boc}_2\text{O, Et}_2\text{O} \\
\text{ii. NaIO}_4, \text{cat. RuCl}_3\text{H}_2\text{O} & \\
\text{iii. HCl, Et}_2\text{O} & \quad \text{NH}_3 \quad \text{Cl} \\
\text{COOH} & \\
71\% 
\end{align*}
\]

- Application: Synthesis of γ-lactams

\[
\begin{align*}
\text{Ph} \quad \text{NMHR} & \quad \text{Ph} \\
\text{Ph} & \quad \text{Ph} \\
\text{Boc} & \quad \text{Boc} \\
\text{OH} & \quad \text{OH} \\
\text{DMF} & \\
91\% & \\
\text{HN} & \quad \text{HN} \\
97\% & \\
\end{align*}
\]

Chiral Cu catalyst effects enantioselective crotylboronation of ketones

- Geometry of product differs for aromatic and aliphatic ketones
  - For aromatic ketones, crotylboronation was stereospecific i.e. geometry of crotylboronate was transferred
  - For aliphatic ketones, the major product was the *anti*-alcohol

Chiral Cu catalyst effects enantioselective crotylboration of ketones

- Proposed catalytic cycle
  - CuF (generated by reducing CuF2 with 2 equiv of chiral phosphine) activates boronate
  - Crotylcopper as reactive intermediate since allylboronate, allyltrimethoxysilane and allyltributyltin all give identical enantioselectivity
  - Cocatalyst La(OiPr)3 accelerates transmetallation but does not participate in crotylation step
  - Crotylcopper regenerated by transmetallation of crotylation product

Chiral Cu catalyst effects enantioselective crotylboration of ketones

- Explanation of diastereoselectivity
  - Crotylcopper species are configurationally unstable, rapid equilibration via 1,3-metal transposition gives E-crotylcopper predominantly → leads to anti-product
  - Crotylation of aromatic ketones is faster than aliphatic ketones, so addition could proceed without equilibration of aromatic ketones, and after equilibration for aliphatic ketones

- Stereochemical model

**Crotyltrifluoroborates + Rh catalyst: Imine Crotylation**

- **Enantioselective Rh-catalysed crotylations of cyclic imines**
  - Cyclic imine structure facilitates efficient crotylation
    - Cyclic aldimines and ketimines both undergo enantioselective crotylations
  - Potassium crotyltrifluoroborate necessary for high enantioselectivity

Enantioselective Rh-catalysed crotylations of cyclic imines

Proposed catalytic cycle
- Stereoselectivity suggests that crotylRh(I) intermediates have configurational stability and react via chair-like TS
- Methanolysis of crotylBF3K and transmetalation forms crotylRh(I) intermediate
- Coordination of imine to minimise steric interactions
- Crotylation via 6-membered cyclic chair TS, then protonation gives product

Silicon Reagents

strained silacycles
Leighton
Ring strained crotylsilacycles are type I reagents
  o Si is more Lewis acidic, formation of pentacoordinate Si releases ring strain
  o Good yields with aliphatic aldehydes (67-83%)
    ▪ Moderate yields with aromatic and α,β-unsaturated aldehydes (52-67%)
    ▪ Limited tolerance for steric hindrance (no crotylation of pivaldehyde)
  o Reagents easily synthesised in bulk from diamine and crotyltrichlorosilane
    ▪ Crystalline reagents easy to store and handle (from p-bromobenzyl substituent)
    ▪ Moisture-sensitive but have unlimited shelf-life if stored in a glovebox
    ▪ Diamine can be recovered in 90% yield (atom economy)

\[
\begin{align*}
R = \text{BnCH}_2, \text{Me}_2\text{CHCH}_2, \text{Cy},
\text{BnOCH}_2, \text{PMBOCH}_2\text{CH}_2,
\text{Ph}, \text{p-CF}_3\text{C}_6\text{H}_4, \text{E-PhCHCH}
\end{align*}
\]

\[
\begin{align*}
\text{syn-product yields 61-83\%} & \quad \text{dr} > 15:1 \text{ to } > 25:1 \quad \text{ee 95-97\%} \\
\text{anti-product yields 52-83\%} & \quad \text{dr} > 15:1 \text{ to } > 25:1 \quad \text{ee 93-98\%}
\end{align*}
\]

Strained Crotylsilanes: Aldehyde Crotylation

- Ring strained crotylsilacycles are type I reagents
  - Origin of Enantioselectivity
    - Steric interactions around pentacoordinate Si

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EZ-CrotylMix is a commercially available reagent for aldehyde crotylation
- EZ-CrotylMix is a mixture of the desired crotylsilane with Sc(OTf)$_3$ in a 25:1 ratio
  - 650 mg of EZ-CrotylMix for 1.0 mmol of aldehyde = 1.1 equiv of silane and 4.4 mol% of Sc(OTf)$_3$
- Sc(OTf)$_3$-catalysed reaction
  - Lewis acid binds to aminochlorosilane Lewis acid to boost reactivity while keeping enantioselectivity
- Increased substrate scope compared to previous methodology without Sc(III) catalysis
  - Aromatic, sterically hindered and $\alpha,\beta$-unsaturated aldehydes can be crotylated with high yields, diastereoselectivities and enantioselectivities

EZ-CrotylMix is a commercially available reagent for aldehyde crotylation

- Chiral aldehydes at the α- and β- positions can be crotylated with high diastereoselectivity
  - Reagent is able to override diastereofacial bias of chiral aldehydes
  - Access to stereochemical arrays which may not be possible selectively with Brown methodology

- Application to total synthesis: Synthesis of stereochemically complex polyketide fragments

Ring strained crotylsilacycles can crotylate 2’-hydroxyphenylketones with high diastereo- and regio- selectivity.

**Mechanism**

- Phenol displaces chloride from silane; HCl generated protonates one of the amino groups → intramolecular reaction + increase Lewis acidity of silane
- Ketone and protonated amino groups occupy apical positions on trigonal bipyramidal intermediate; TS A has more unfavourable steric and electrostatic interactions, TS B gives allylation product
- TS C shows chair-like TS giving crotylation product

Strained Crotylsilanes: β-Diketone Crotylation

- Ring strained crotylsilacycles can crotylate β-diketones with high regio-, diastereo- and enantio- selectivity
  - Crotylchlorosilane and β-diketone react to form β-siloxyenone complex
    - Enol form of β-diketone displaces chloride from chlorosilane → crotylsilane activated by HCl generated + tethering strategy allows intramolecular crotylation
    - Silyl enol ether complexes are formed, workup produces ketones

- Trans-crotylsilanes can be crotylated under normal conditions, but cis-crotylsilanes require pre-activation with AgOTf
  - Knoevenagel condensation is a competing side reaction in the complexation of cis-crotylsilane with benzoylaceton, side product 2 is observed in significant amounts
  - Preactivation of cis-crotylsilane with AgOTf accelerates complexation

Strained Crotylsilanes: β-Diketone Crotylation

- Ring strained crotylsilacycles can crotylate β-diketones
  - Substitution on α-C is tolerated, and high levels of diastereoselectivity can be achieved
    - Quenching of silyl enol ether with aTBAF at low temperature gives excellent diastereoccontrol in tautomerisation to ketone
  - Mechanism and regioselectivity
    - Conversion between all β-siloyenones is rapid, so regioselectivity is governed by Curtin-Hammett kinetics
    - Relative energies of the TS where non-conjugated ketone is crotylated is lower since conjugation is maintained in TS → major product

Ring strained crotylsilacycles crotylete acylhydrazones with unusual diastereoselectivity

- Cis-crotylsilanes give anti-amines and trans-crotylsilanes give syn-amines

Mechanistic explanation
- Two-point binding/double activation of crotylsilane and acylhydrazone
- Secondary interaction between Lewis basic amide and Lewis acidic silane
- Ph group is pseudoaxial instead of pseudoequatorial as expected
- Opposite diastereoselectivity observed
Ring strained crotysilacycles croltylate N-heteroarylhydrazones with unusual diastereoselectivity

- Improvement over acylhydrazone method which was only amenable to aromatic hydrazones

- Again, unusual diastereoselectivity observed
  - Coordination of heteroatom to crotysilane requires loss of aromaticity, but possible with heteroarenes

- Product can be hydrogenated to give corresponding amine
  - N-N bond in N-arlyhydrazides susceptible to metal-catalysed hydrogenation
Chiral dinitrones catalyse crotylations with crotyltrichlorosilanes

- Chiral dinitrones act as Lewis base catalysts
  - Polar N-O bond enables catalyst to nucleophilically activate chlorosilane reagents
  - Electron-rich p-MeOC₆H₄ group on dinitrone gave best catalyst performance
  - Catalyst can be recovered by FCC after isolation of product

- Reacts via a chair-like TS
  - DMPU additive increases enantioselectivity and yield (mechanism as yet unknown)

Type II Crotylemetalss
Type II Crotymetals: Selectivity

- Diastereoselective crotylation
- Under Lewis acid catalysis
- React via an open, acyclic transition state
  - Yamamoto proposed antiperiplanar TS from crotylstannane studies
    - Steric preference by minimising gauche interactions
  - Denmark proposed synclinal TS from crotylsilanes studies
    - Stereoelectronic preference (secondary orbital interactions)

- Stereospecific anti-$S_E$’ crotylation
  - Configuration of methyl substituent at 3-position consistent with electrophile attacking the C=C bond anti- to the leaving metal group

Silicon Reagents

\[ \text{chiral crotylsilanes} \]

Panek
**Vinylogous Aldol Products from Chiral Crotylsilnaes**

- Chiral crotylsilanes formed by enantioselective Rh(II) carbenoid Si-H insertion
- Lewis-acid promoted crotylations give *syn*-products
  - Activated aromatic aldehydes less selective than deactivated substrates
  - Branched aliphatic aldehydes more selective than straight chain substrates
- Increased selectivity can be achieved by
  - Switch substituents Si atom to *n*-Bu3
  - Use TBDPS ether instead of ester silane
Crotysilanes: Imine Crotylation

- **3-Component Enantioselective Synthesis of Homoallylic Carbamates**
  - Condensation of aldehyde with carbamate generates N-acyliminium $\rightarrow$ crotylated *in situ* by chiral silane
    - Catalysed by Brønsted acid macroporous polystyrene-bound sulfonic acid (MP-TsOH)
  - Stereochemical outcome rationalised by open transition state
    - Antiperiplanar TS with least Gauche interactions favoured

![Chemical structure](image)

Type III Crotylmetals
Type III Crotylmetals: Diastereoselectivity

- React via a 6-membered closed, cyclic transition state akin to Type I
- But crotylmetal is configurationally labile, and rapidly isomerises to $E$-isomer so anti-product is obtained
Crotyltitanates in Total Synthesis

- Stereoselective Synthesis of the Octalactin Lactone Using Enantioselective Crotyltitanations
  - Crotyltitantions used in 2 key steps
  - 9 steps, 28% overall yield
  - Octalactin lactone used in the convergent approach to octalactins A and B by Buszek and Clardy

Crotylboronates + Indium catalyst

- Indium(I)-catalysed asymmetric *anti*-selective hydrazone crotylation
  - Complete α-selectivity contrasts exclusive γ-selectivity in the absence of catalyst, or under Lewis- or Brønsted- acid catalysis
  - Use of racemic crotylboronate provides enantiomerically enriched *anti*-product

- Mechanism
  - Formation of chiral In(I)-semicorrin complex
  - B-to-In transmetallation (with hydrazone acting as Lewis base to activate boronate)
  - C-C bond formation *via* cyclic TS
  - α-chloroallylation also possible with this chemistry

Crotylation with butadiene

- Direct enantio- and diastereo-selective C-H crotylation of benzylic alcohols *via* hydrohydroxyalkylation of butadiene

- Transfer hydrogenation conditions: 1° alcohols act as hydrogen donor and aldehyde precursors
- Advantages:
  - Butadiene is cheap and readily available chemical feedstock
  - No stoichiometric by-products, bypass the use of premetallated reagents for carbonyl crotylation
- *Anti*-diastereoselectivity arises from steric demand of counterion derived from acid-base reaction of Ru catalyst with chiral acid A
- When using aldehydes as substrates, 1,4-butanediol is required as a terminal reductant, with similar yields and selectivities observed

Crotylation with butadiene

- Direct enantio- and diastereo-selective C-H crotylation of benzylic alcohols *via* hydrohydroxyalkylation of butadiene
  - Proposed Mechanism

Conclusion
Conclusion

- Type I crotylmetalts are most commonly used in asymmetric crotylations due to their high diastereoselectivity and enantioselectivity allowing access to all 4 stereoisomeric products with excellent stereocontrol via chair-like TS.
- Type II and III crotylations are less commonplace, but the ability to control both diastereo- and enantio- selectivity from racemic starting materials or a mixture of geometric isomers is useful.
The End

THANK YOU!