Recent Advances in Enantioselective Crotylations with Non-toxic Chiral Reagents

Literature Review

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14 December 2012

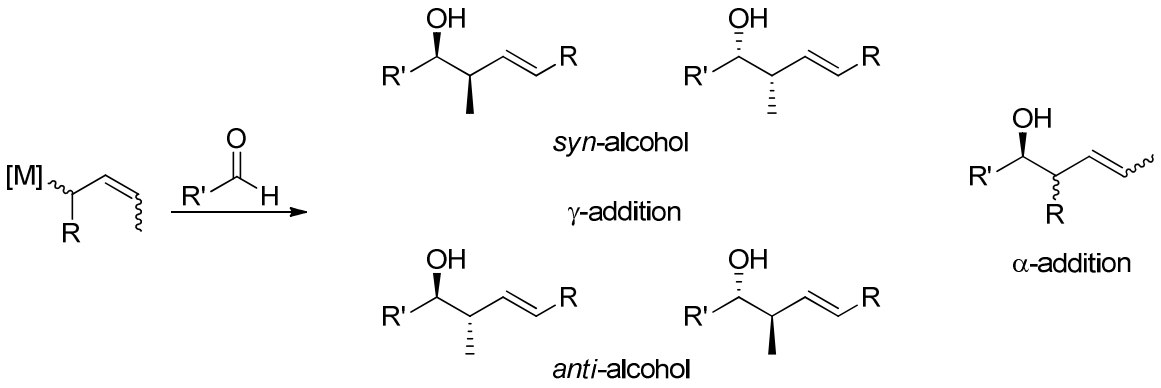
Overview

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



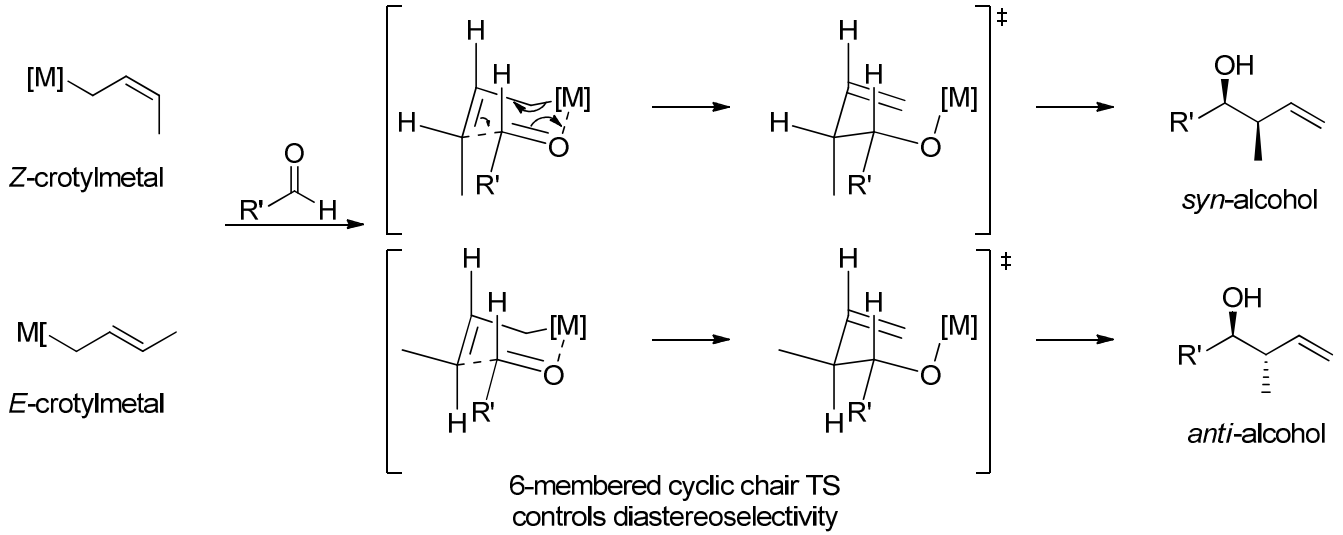
Introduction: Classification of Crotylmetals

- Type I
  - *Syn*/*anti* ratio of products reflects *Z*/*E* ratio of crotylmetal reagent
  - React *via* closed chair-like transition state
  - E.g. B, Si, Sn (thermal)
- Type II
  - *Syn*-selective products generated regardless of geometry of crotylmetal 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 crotylmetal reagent
  - Crotylmetal 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

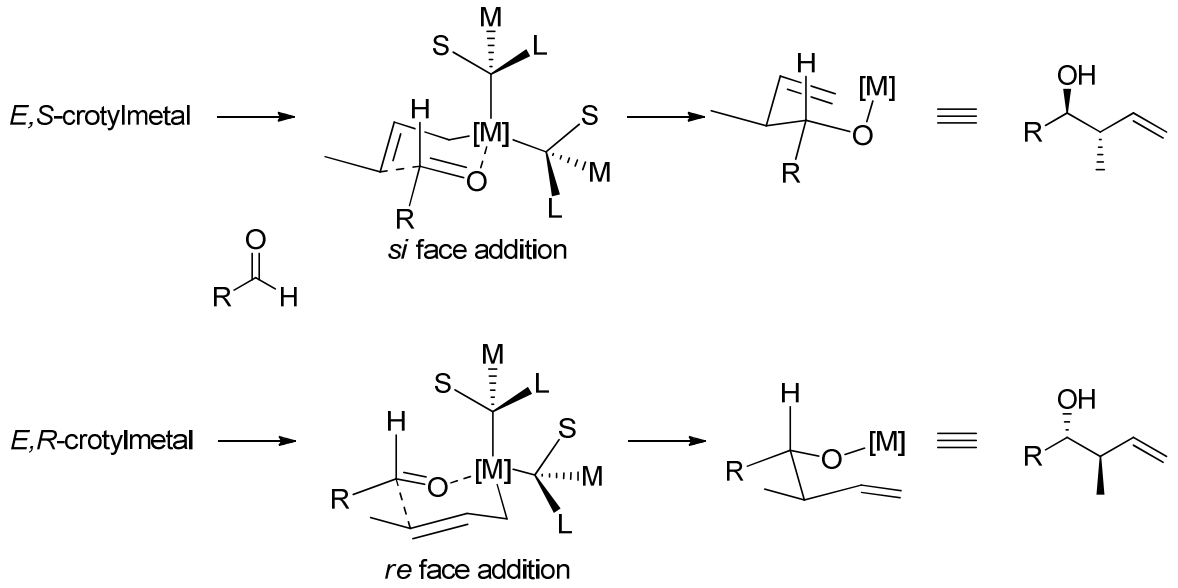
Type I Crotylmetals: Diastereoselectivity

- 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

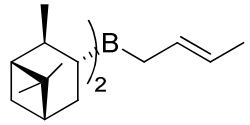


Type I Crotylmetals: Enantioselectivity

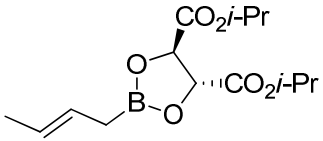
- React *via* a 6-membered closed, cyclic chair-like transition state
  - Stereochemical outcome determined by chiral auxiliary on crotyl metal



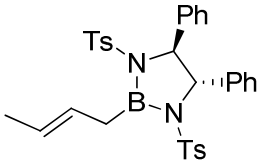
Boron Reagents



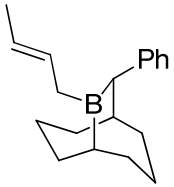
diisopinocampheyboranes
($Ipc_2Bcrotyl$)
Brown



tartrate-derived boronates
Roush



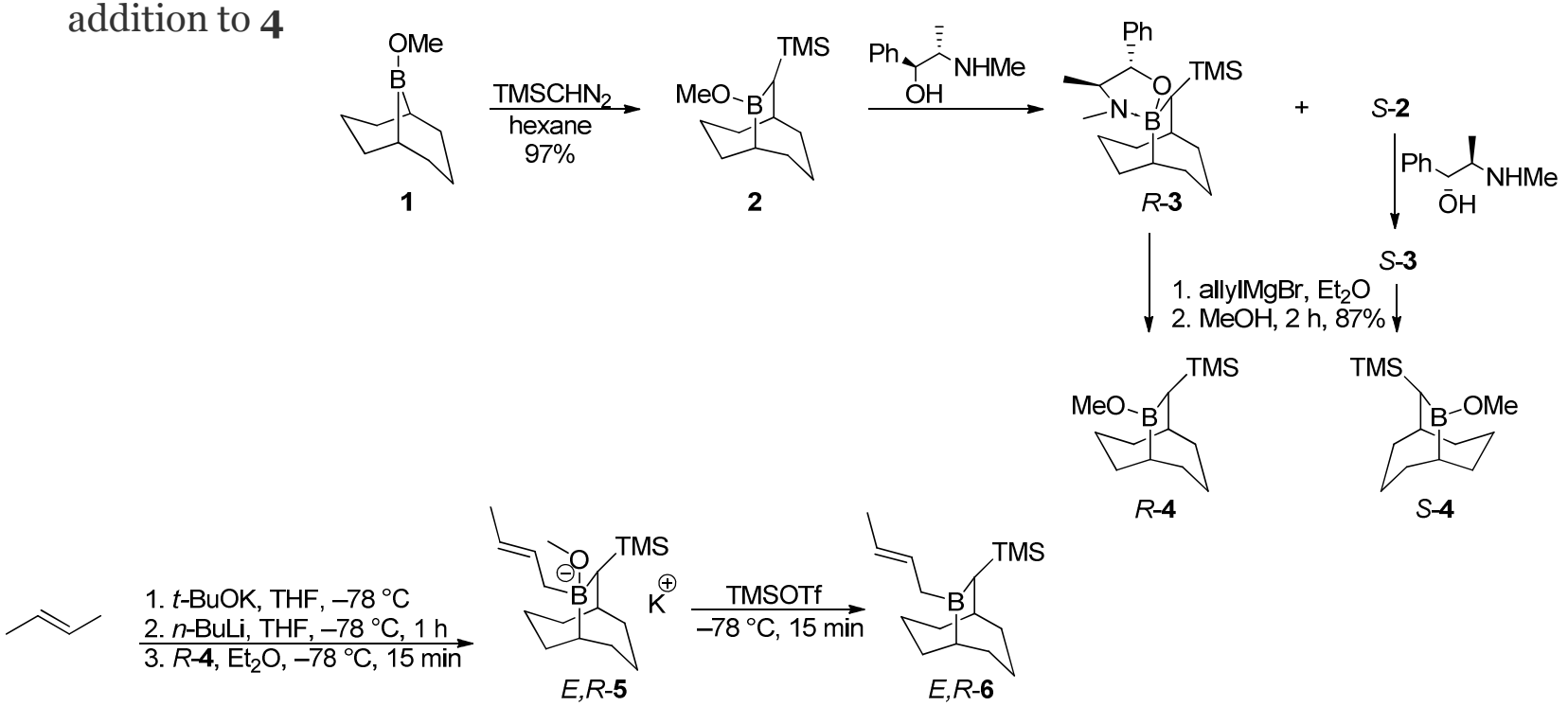
Corey



9-BBN-derived reagents
Soderquist

Crotylboranes: Aldehyde Crotylation

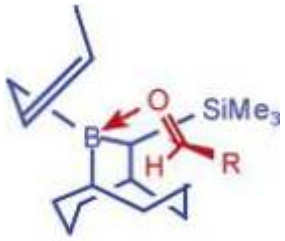
- *B*-crotyl-10-TMS-9-BBD reagents are robust, versatile and recyclable
  - All 4 geometric and enantiomeric isomers can be prepared from *B*-MeO-9-BBN
  - *B*-MeO-9-BBN is resolved with pseudophendrine to give air-stable crystalline complexes **3**
  - Crotylboranes **6** are obtained from butene by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

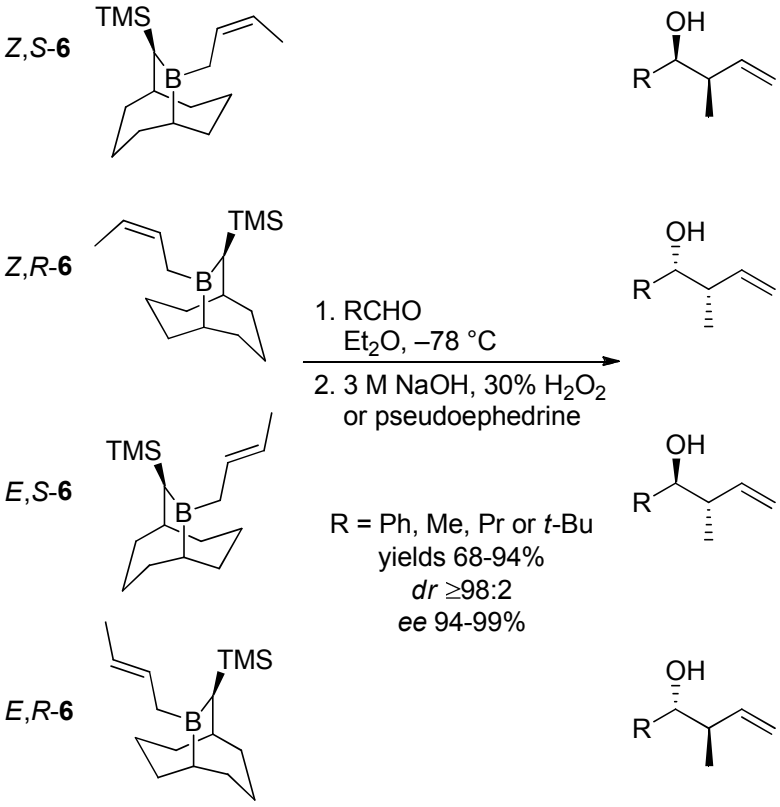


Burgos, C. H.; Canales, E.; Matos, K.; Soderquist, J. A. *JACS* **2005**, *127*, 8044.

Crotylboranes: 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

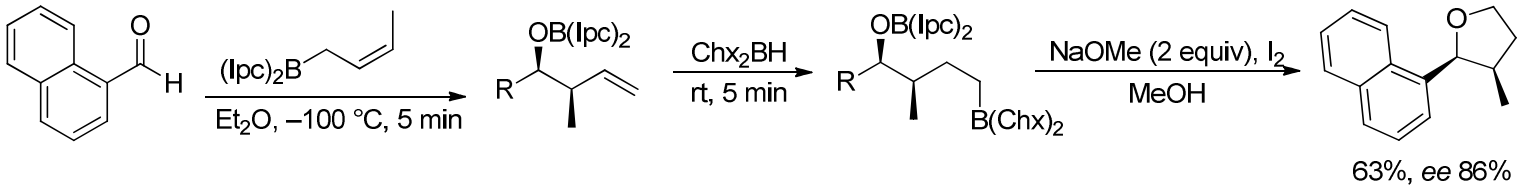


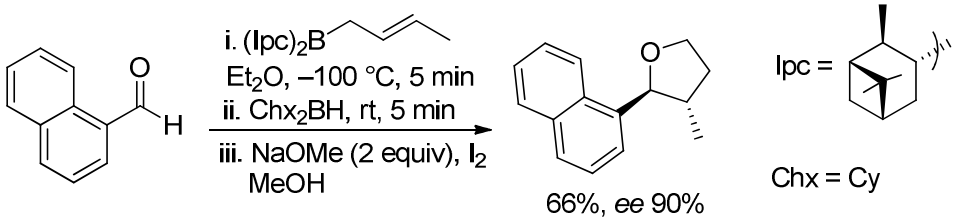


Burgos, C. H.; Canales, E.; Matos, K.; Soderquist, J. A. *JACS* **2005**, *127*, 8044.

Crotylboranes: Aldehyde Crotylation

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

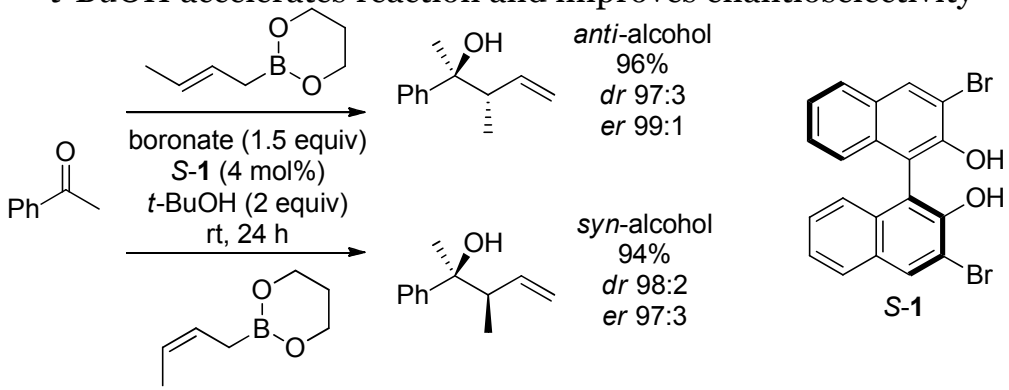




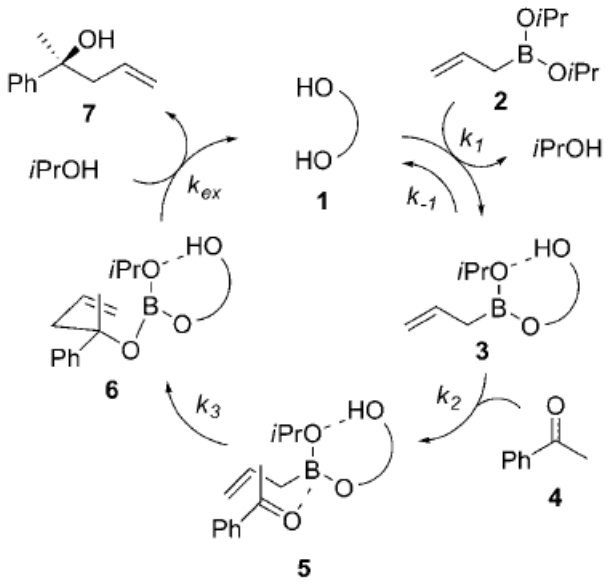
Ramachandran, P. V.; Nair, H. M. G.; Gagare, P. D. *JOC.* **2012**, *77*, 5394.

Crotylboronates: Ketone Crotylation

- 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



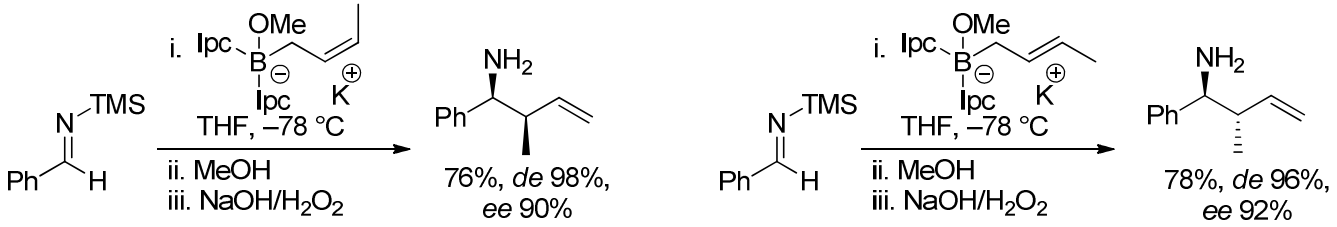
  - Mechanistic studies and proposed catalytic cycle
    - RDS is liberation of catalyst from product (k_{ex}) → addition of alcohol increases overall catalyst concentration, giving increased reaction rates and enantioselectivities
    - *t*-BuOH is a less coordinating alcohol → less Lewis base-acid coordination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



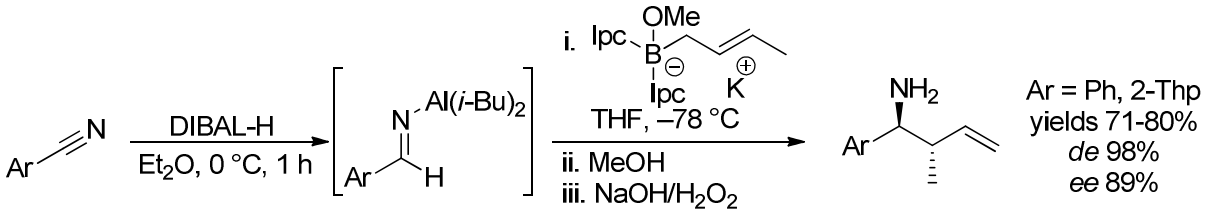
Barnett, D. S.; Moquist, P. N.; Schaus, S. E. *Angew. Chem. Int. Ed.* **2009**, *48*, 8679.

Crotylboronates: Imine Crotylation

- Crotylboration of aromatic N-silylimines with boronate complexes
  - First report of Ipc-crotylboronate complex
    - Addition of $BF_3.OEt_2$ to generate trialkylboranes degrades silylimines
  - Only aromatic imines tolerated



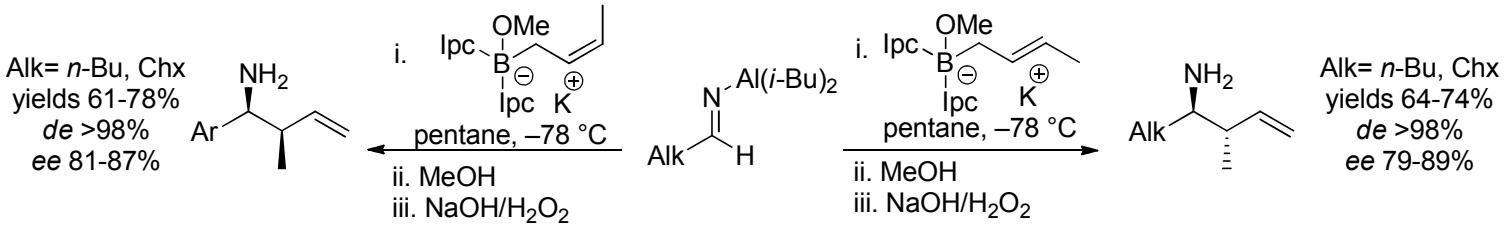
- Crotylboration of N-aluminoimines with boronate complexes
  - N-aluminoimines have higher stability than N-silylimines
  - Aromatic N-aluminoimines give similar results to aromatic N-silylimines



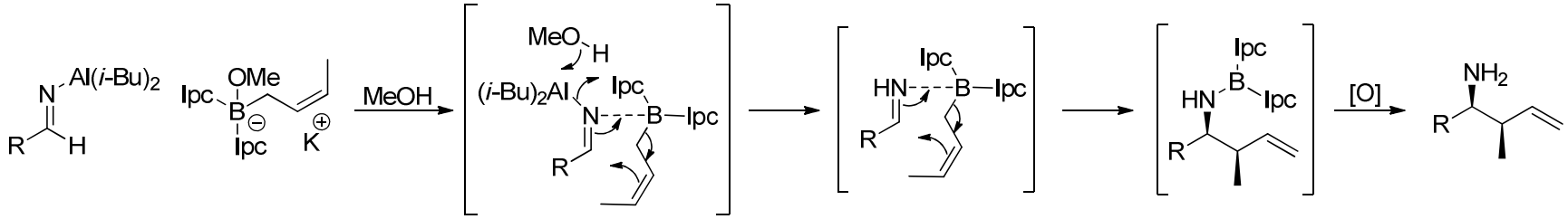
Ramachandran, P. V.; Burghardt, T. E. *Chem. Eur. J.* **2005**, *11*, 4387.

Crotylboronates: Imine Crotylation

- Crotylboration of N-aluminoimines with boronate complexes
  - Aliphatic N-aluminoimines can undergo crotylboration in pentane

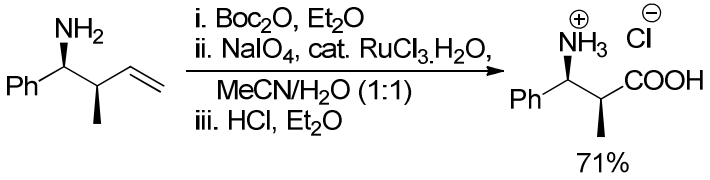


- Proposed mechanism
  - MeOH liberates "naked" aldimine
  - Reacts *via* a chair-like TS
  - Alkaline oxidative work-up yields β-methyl homoallylic imine

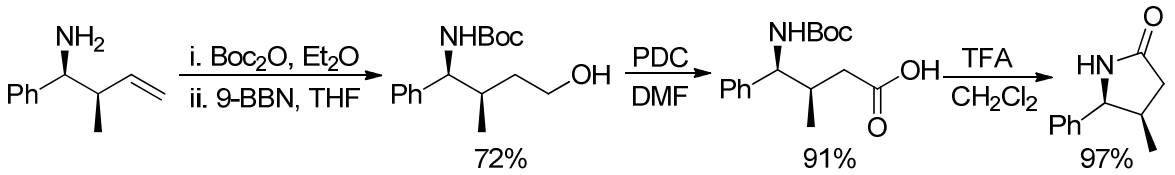


Crotylboronates: Imine Crotylation

- Application: Synthesis of β-Amino acids

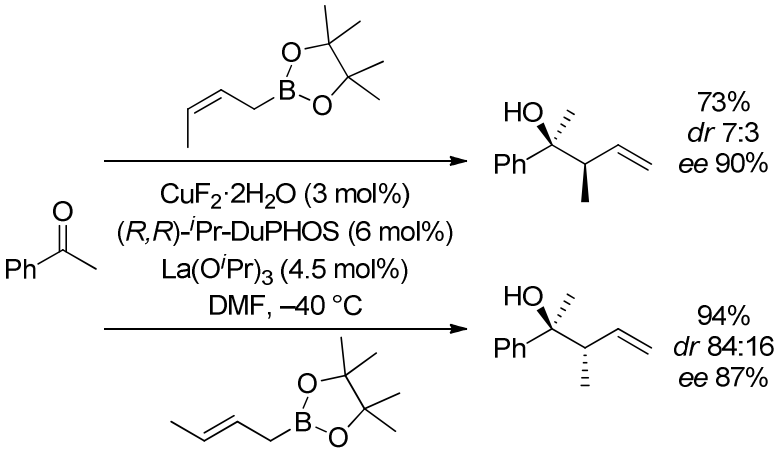


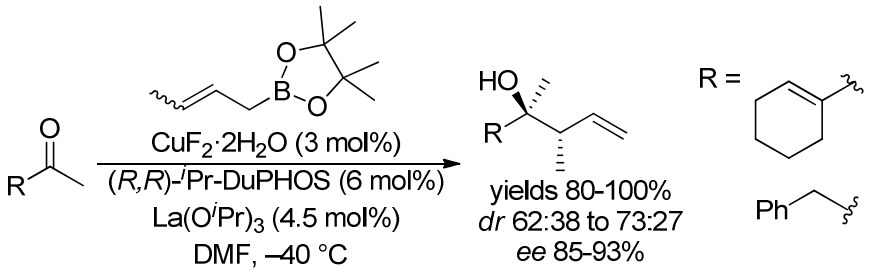
- Application: Synthesis of γ-lactams



Crotylboronates + Cu catalyst: Ketone Crotylation

- Chiral Cu catalyst effects enantioselective crotylboration of ketones
  - Geometry of product differs for aromatic and aliphatic ketones
    - For aromatic ketones, crotylboration was stereospecific i.e. geometry of crotylboronate was transferred
    - For aliphatic ketones, the major product was the *anti*-alcohol

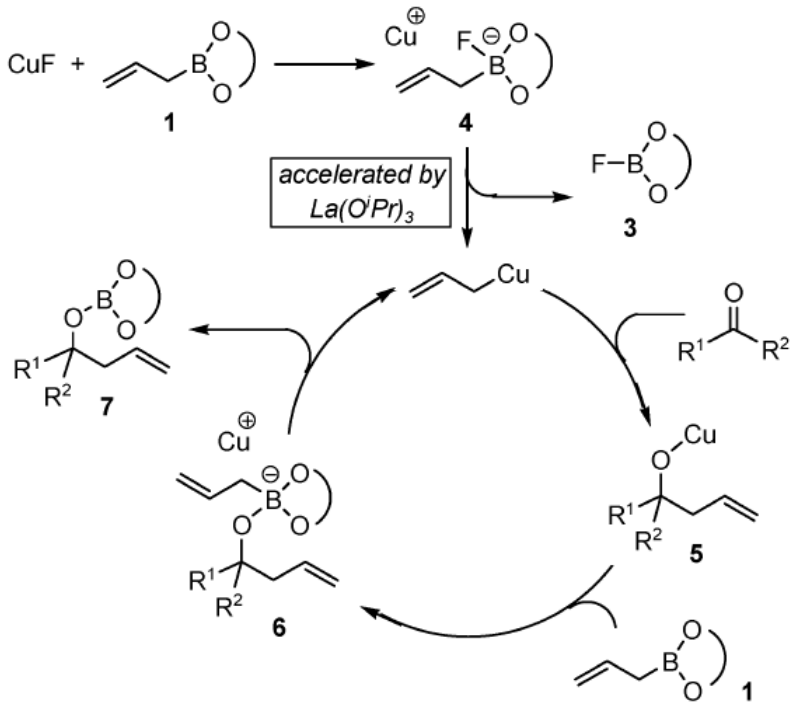




Kanai, M.; Wada, R.; Shibuguchi, T.; Shibasaki, M. *Pure Appl . Chem.* **2008**, *80*, 1055.

Crotylboronates + Cu catalyst: Ketone Crotylation

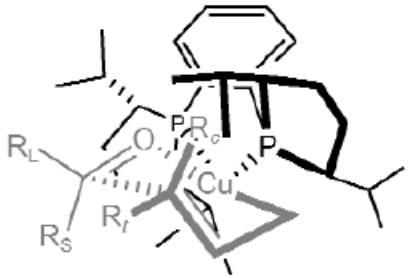
- Chiral Cu catalyst effects enantioselective crotylboration of ketones
  - Proposed catalytic cycle
    - CuF (generated by reducing CuF2 with 2 equiv of chiral phosphine) activates boronate
    - Crotylcopper as reactive intermediate since allyl-boronate, allyltrimethoxysilane and allytributyltin all give identical enantioselectivity
    - Cocatalyst La(O^{i}Pr)3 accelerates transmetallation but does not participate in crotylation step
    - Crotylcopper regenerated by transmetallation of crotylation product

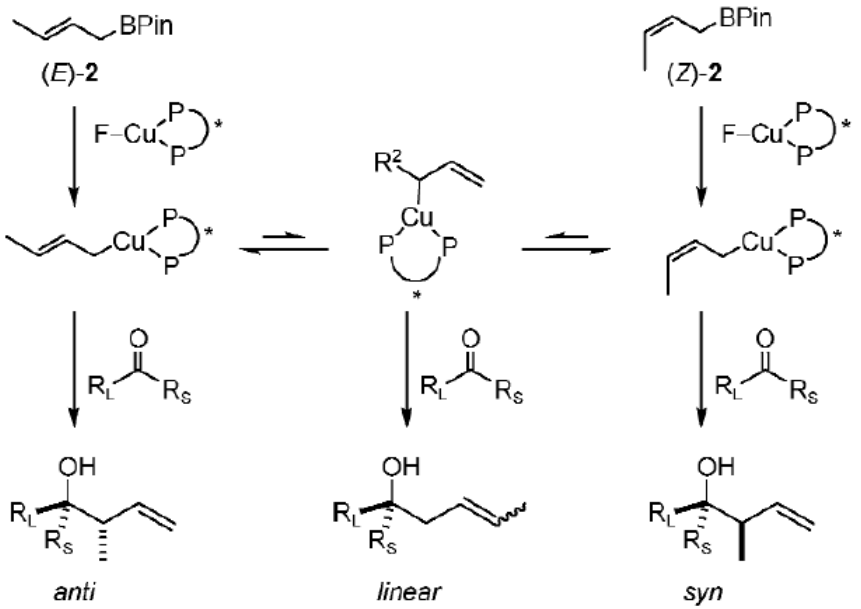


Kanai, M., Wada, R., Shibuguchi, T., Shibasaki, M., *Pure Appl . Chem.* **2008**, *80*, 1055.

Crotylboronates + Cu catalyst: Ketone Crotylation

- Chiral Cu catalyst effects enantioselective crotylboration of ketones
  - Explanation of diastereoselectivity
    - Crotylcopper speicies 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

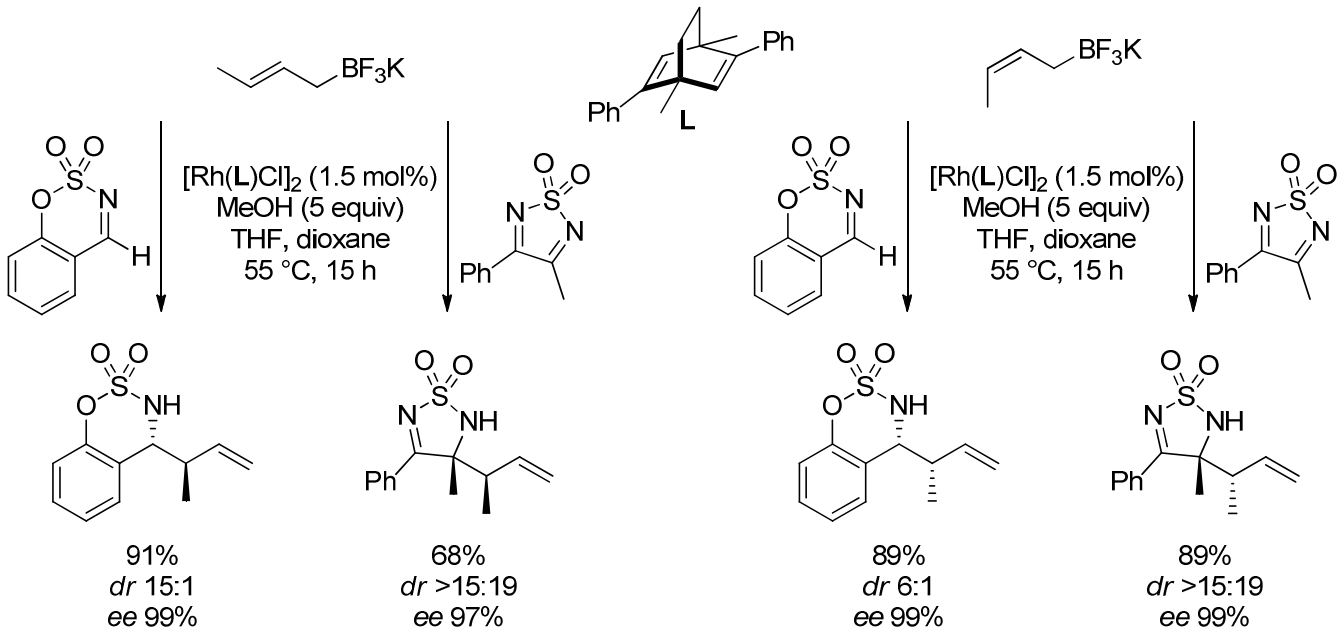




Kanai, M.; Wada, R.; Shibuguchi, T.; Shibasaki, M. *Pure Appl . Chem.* **2008**, *80*, 1055.

Crotyltrifluoroborates +Rh catalyst: Imine Crotylation

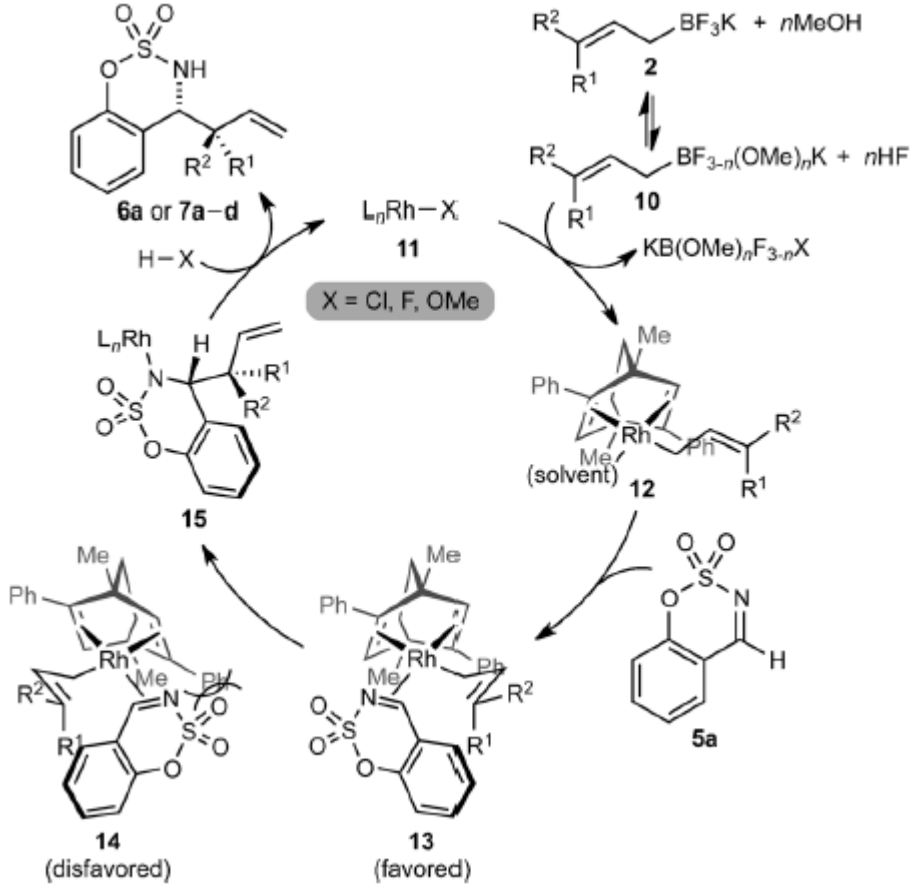
- Enantioselective Rh-catalysed crotylations of cyclic imines
  - Cyclic imine structure facilitates efficient crotylation
    - Cyclic aldimines and ketimines both undergo enantioselective crotylations
  - Potassium crotyltrifluoroborate necessary for high enantioselectivity



Luo, Y.; Hepburn, H. B.; Chotsaeng, N.,;Lam, H. W. *Angew. Chem. Int. Ed.* **2012**, *51*, 8309

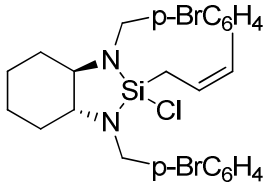
Crotyltrifluoroborates +Rh catalyst: Imine Crotylation

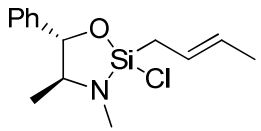
- Enantioselective Rh-catalysed crotylations of cyclic imines
  - Proposed catalytic cycle
    - Stereoselectivitysuggests that crotylRh(I) intermediates have configurational stability and react *via* chair-like TS
    - Methanolysis of crotylBF3K and transmetlalation forms crotylRh(I) intermediate
    - Coordination of imine to minimise steric interactions
    - Crotylation *via* 6-membered cyclic chair TS, then protonation gives product



Hackman, B. M. , Lombardi, P. J., Leighton, J. L., *Org. Lett.* **2004**, *23*, 4375.

Silicon Reagents

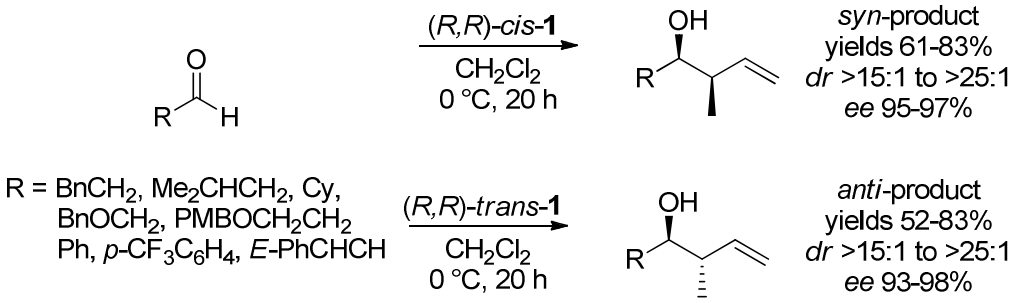


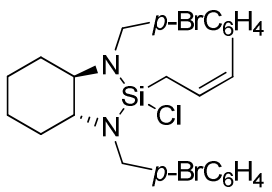


strained silacycles
Leighton

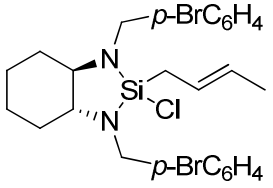
Strained Crotylsilanes: Aldehyde Crotylation

- Ring strained crotylsilacycles are type I reagents
  - Si is more Lewis acidic, formation of pentacoordinate Si releases ring strain
  - 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)
  - 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)





(*R,R*)-*cis*-**1**

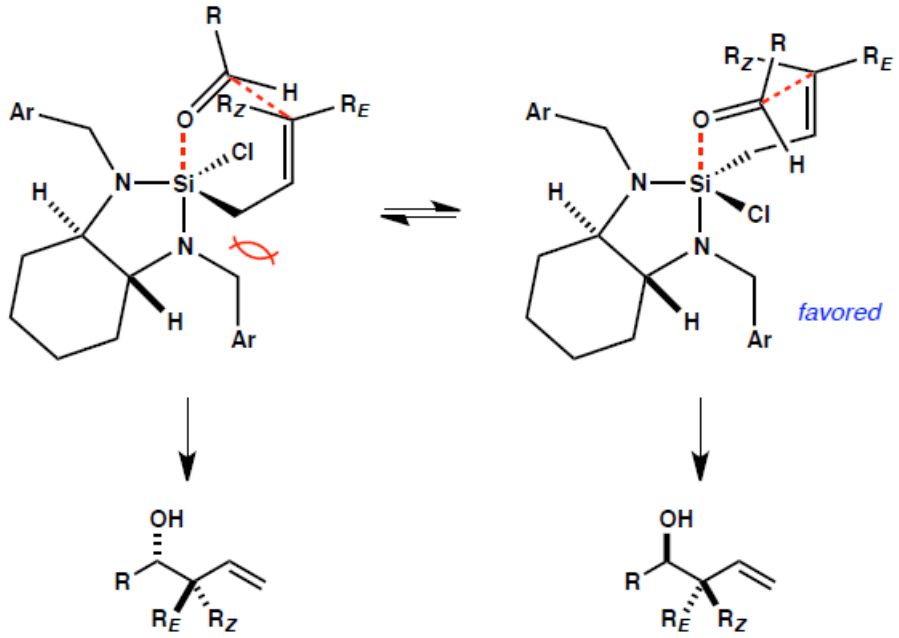


(*R,R*)-*trans*-**1**

Hackman, B. M. , Lombardi, P. J., Leighton, J. L., *Org. Lett.* **2004**, *23*, 4375.

Strained Crotylsilanes: Aldehyde Crotylation

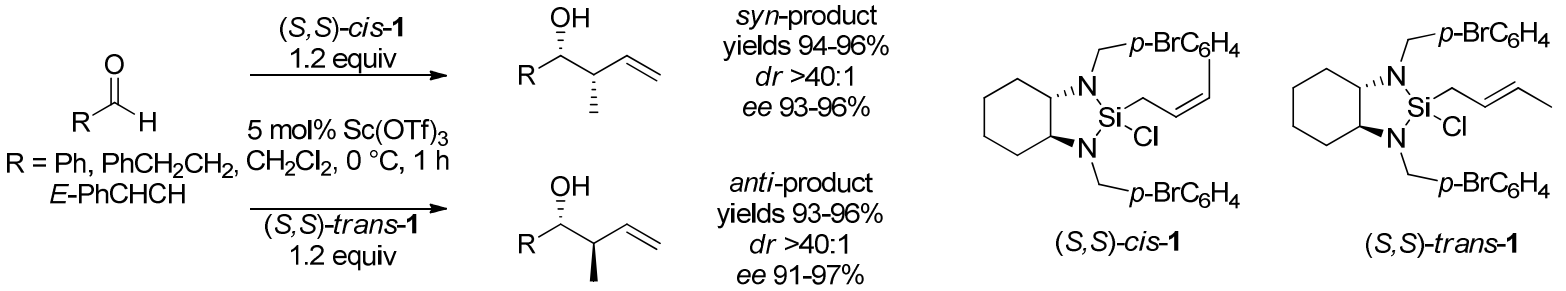
- Ring strained crotylsilacycles are type I reagents
  - Origin of Enantioselectivity
    - Steric interactions around pentacoordinate Si



Hackman, B. M. , Lombardi, P. J., Leighton, J. L., *Org. Lett.* **2004**, *23*, 4375.

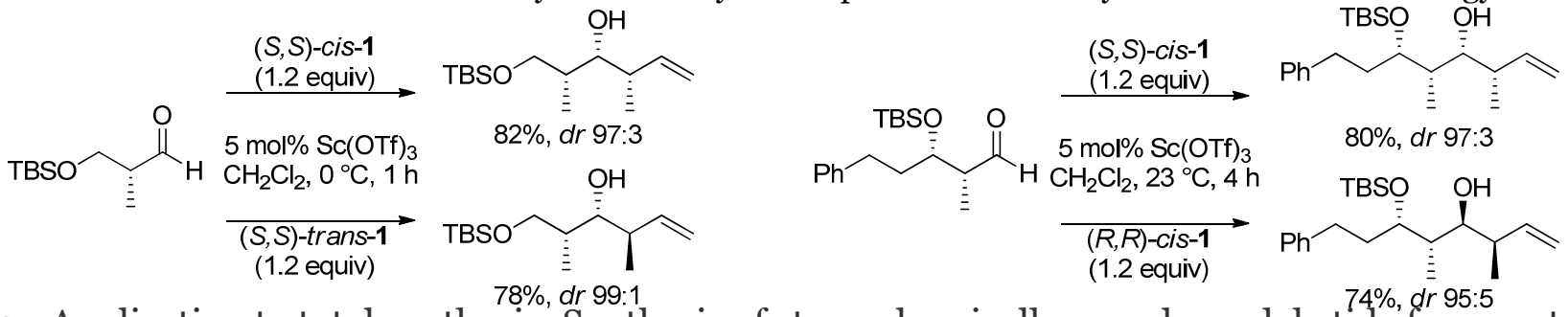
Strained Crotylsilanes: Aldehyde Crotylation

- 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 α,β-unsaturated aldehydes can be crotylated with high yields, diastereoselectivities and enantioselectivities

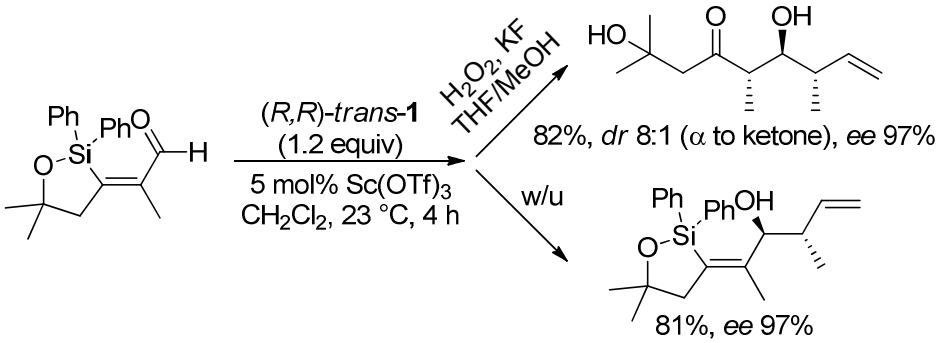


Strained Crotylsilanes: Aldehyde Crotylation

- EZ-CrotylMix is a commercially available reagent for aldehyde crotylation
  - Chiral aldehydes at the α- and β- positions can be crotylated with high diasteroselectivity
    - Reagent is able to override diastereofacial bias of chiral aldehydes
    - Access to stereochemical arrays which may not be possible selectively with Brown methodology



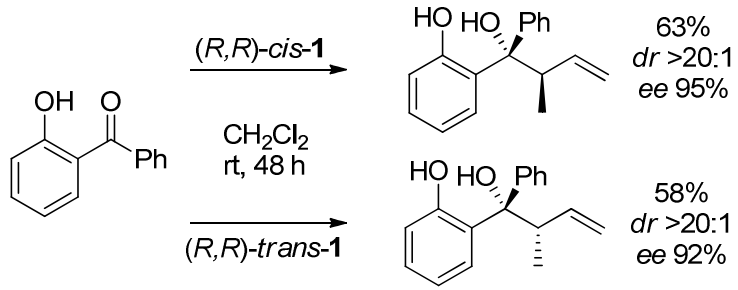
  - Application to total synthesis: Synthesis of stereochemically complex polyketide fragments



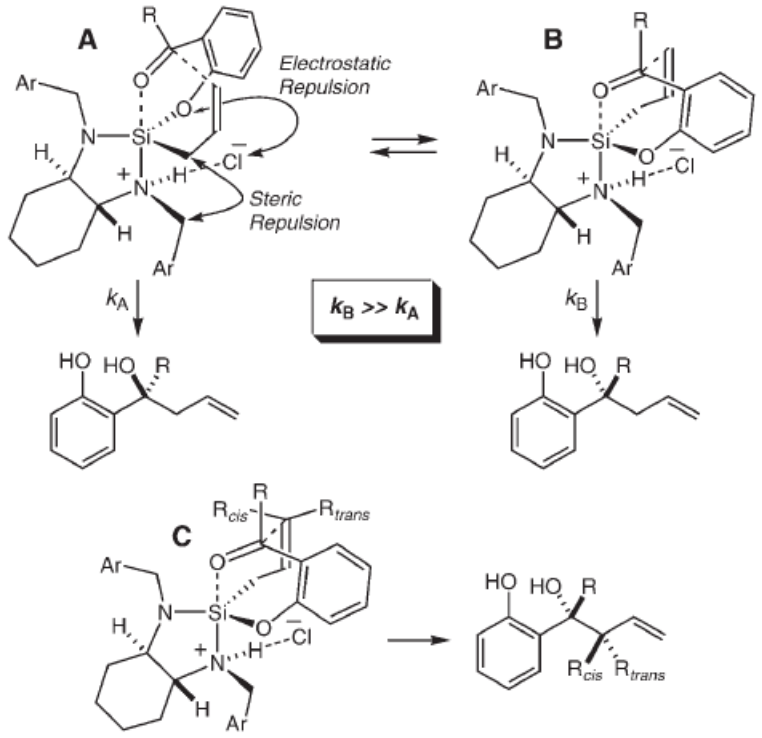
Kim, H.; Ho, S.; Leighton, J. L. *JACS* **2011**, *133*, 6517.

Strained Crotylsilanes: Ketone Crotylation

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



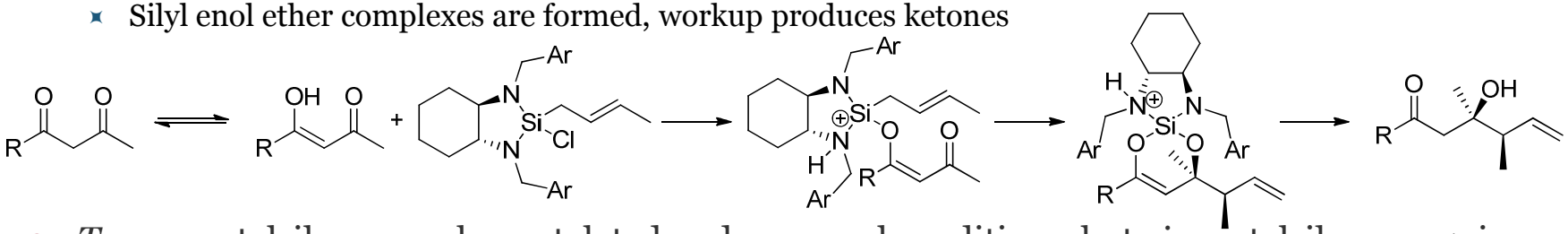
  - Mechanism
    - Phenol displaces chloride from silane; HCl generated protonates one of the amino groups → intramolecular reaction + increase Lewis acidity of silane
    - Ketone and protonated amino groups occupy apical positions on trigonal bipyramidal intermediate; TS **A** has more unfavourable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



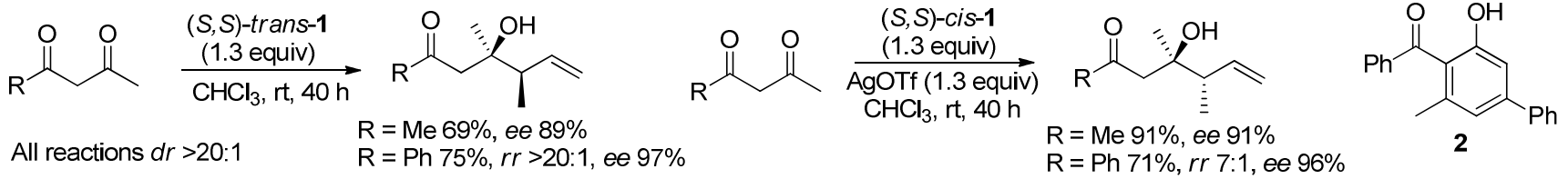
Burns, N. Z.; Hackman, B. M.; Ng, P. Y.; Powelson, I. A. Leighton, J. L. *Angew. Chem. Int. Ed.* **2006**, *45*, 3811.

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



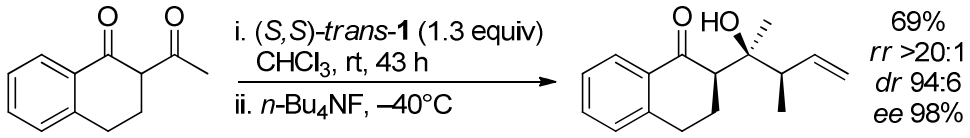
  - *Trans*-crotylsilanes can be crotylated under normal conditions, but *cis*-crotylsilanes require pre-activation with AgOTf
    - Knoevenagel condensation is a competing side reaction in the complexation of *cis*-crotylsilane with benzoylacetone, side product **2** is observed in significant amounts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



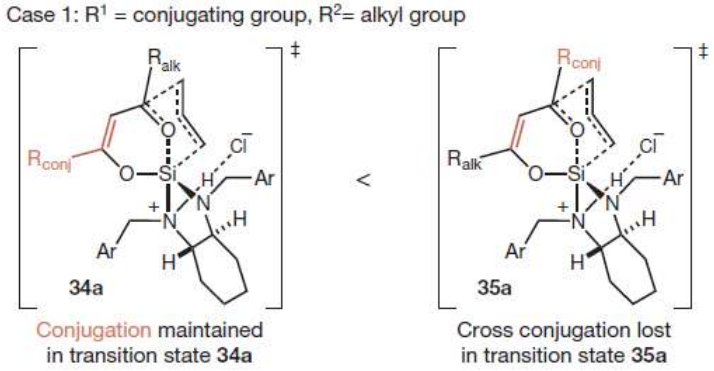
Chalifoux, W. A.; Reznik, S. K.; Leighton, J. L. *Nature* **2012**, *487,* 86.

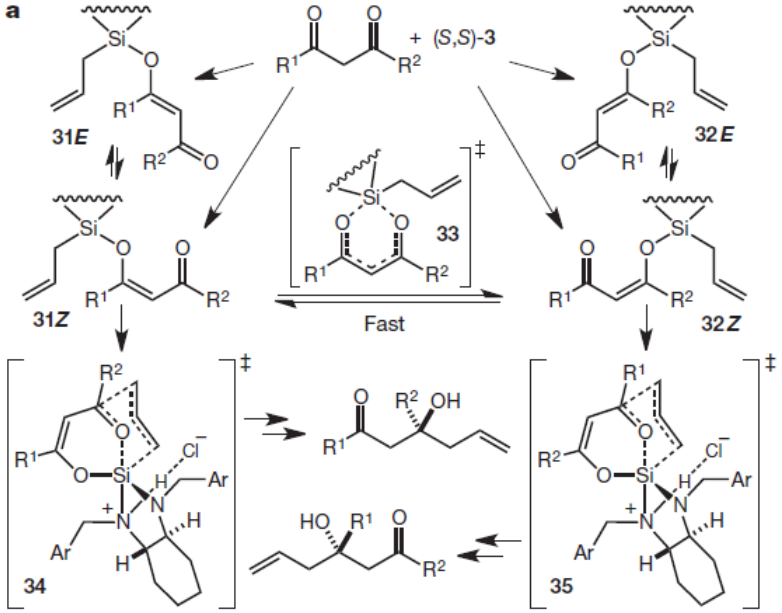
Strained Crotylsilanes: β-Diketone Crotylation

- 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 diastereocontrol in tautomerisation to ketone



  - Mechanism and regioselectivity
    - Conversion between all β-siloxyenones 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

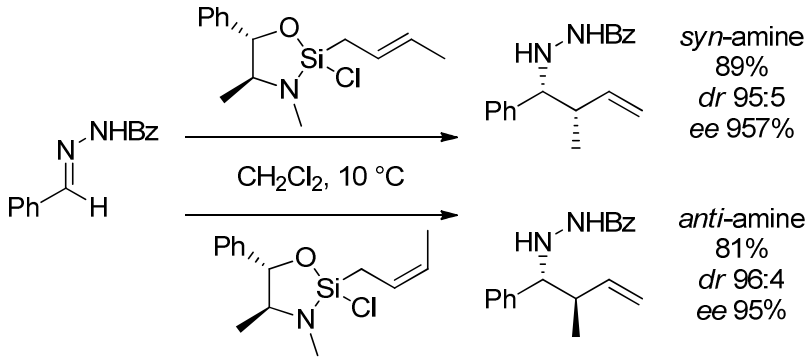




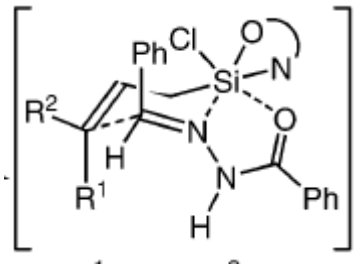
Chalifoux, W. A.; Reznik, S. K.; Leighton, J. L. *Nature* **2012**, *487*, 86.

Strained Crotylsilanes: Acylhydrazone Crotylation

- Ring strained crotylsilacycles crotylate acylhydrazones with unusual diastereoselectivity
  - *Cis*-crotylsilanes give *anti*-amines and *trans*-crotylsilanes give *syn*-amines



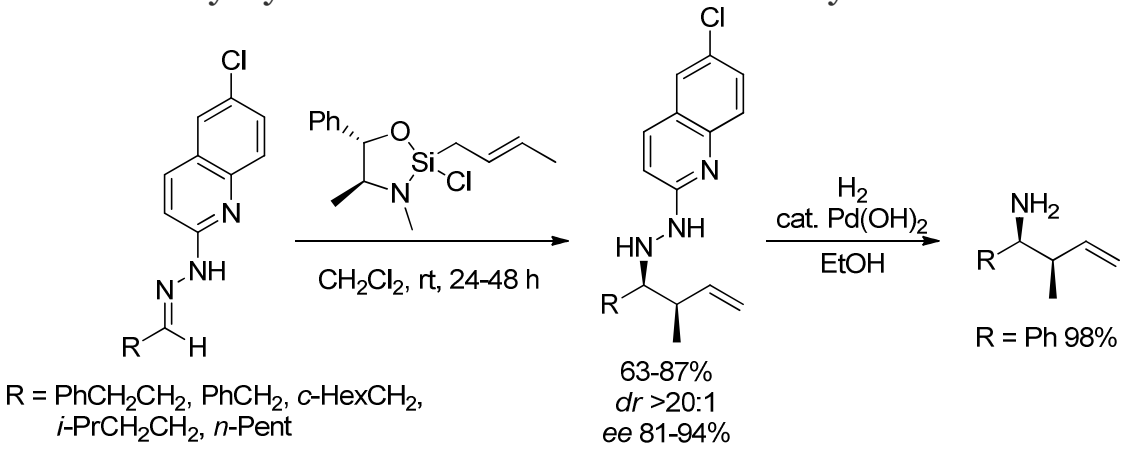
  - Mechanistic explanation
    - Two-point binding/double activation of crotylsilane and acylhydrazone
    - Secondary interaction between Lewis basic amide and Lewis acidic silane
    - Ph group is pseudoaxial instead of pseudoequatorial as expected
    - Opposite diastereoselectivity observed



Berger, R.; Rabbat, P. M. A.; Leighton, J. L. *JACS* **2003**, *125*, 9596.

Strained Crotylsilanes: N-Heteroaryl Hydrazone Crotylation

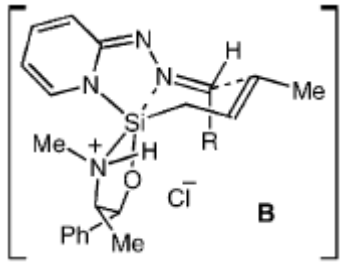
- Ring strained crotylsilacycles crotylate N-heteroarylhydrazones with unusual diastereoselectivity
  - Improvement over acylhydrazone method which was only amenable to aromatic hydrazones



R = $PhCH_2CH_2$, $PhCH_2$, *c*-$HexCH_2$, *i*-$PrCH_2CH_2$, *n*-Pent

63-87%
dr >20:1
ee 81-94%

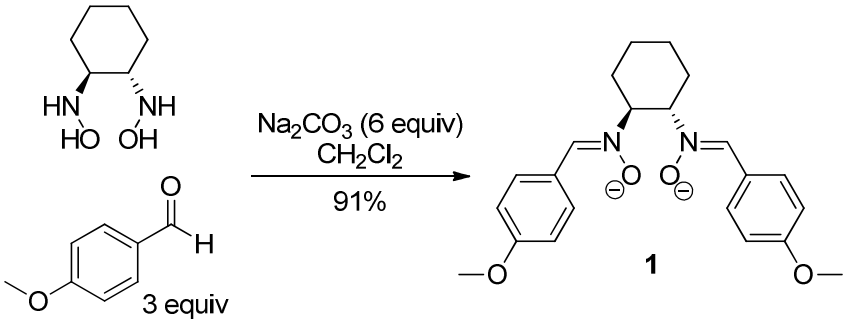
  - Again, unusual diastereoselectivity observed
    - Coordination of heteroatom to crotylsilane requires loss of aromaticity, but possible with heteroarenes
  - Product can be hydrogenated to give corresponding amine
    - N-N bond in N-arylhydrazides susceptible to metal-catalysed hydrogenation



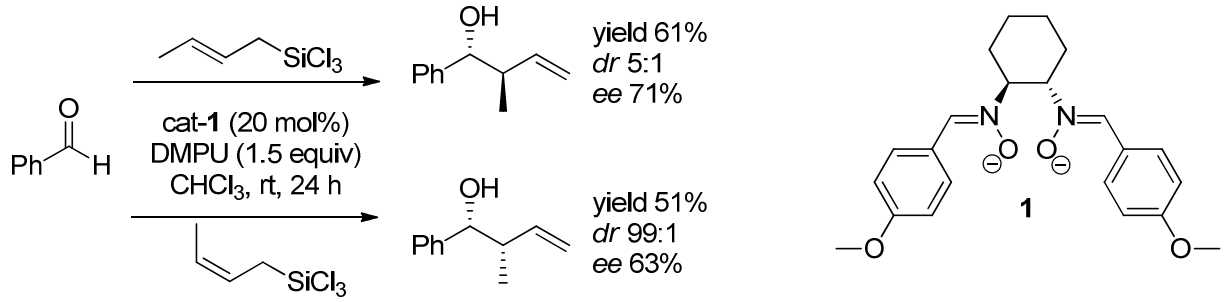
Feske, M. I.; Santanilla, A. B. S.; Leighton, J. L. *Org. Lett.* **2010**, *12*, 688.

Crotyltrichlorosilanes: Aldehyde Crotylation

- 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*-$MeOC_6H_4$ 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)

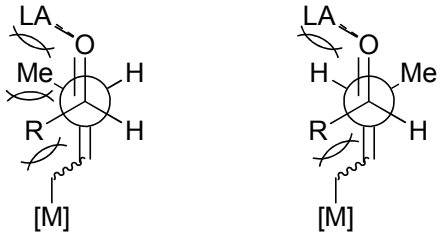


Oh, Y. S., Kotani, S., Sugiura, M., Nakaima, M., *Tetrahedron: Asymmetry* **2010**, *21*, 1833.

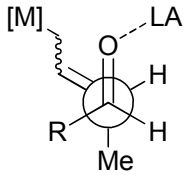
Type II Crotylmetals

Type II Crotylmetals: 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)

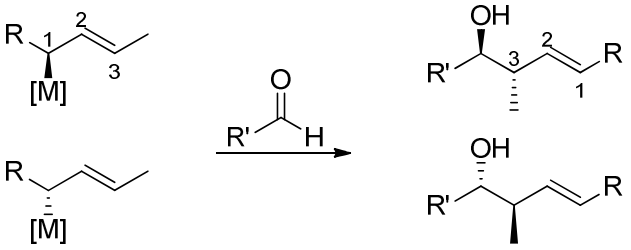


syn favoured antiperiplanar



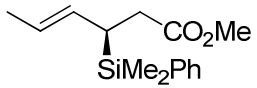
stereoelectronically favoured synclinal

- 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



Yamamoto, Y.; Yatagai, H.; Naruta, Y.; Maruyama, K. *JACS* **2005**, *102*, 7107; Denmark, S.E., Eber, E. U., *Helv. Chim. Acta* **1983**, *66*, 1655.

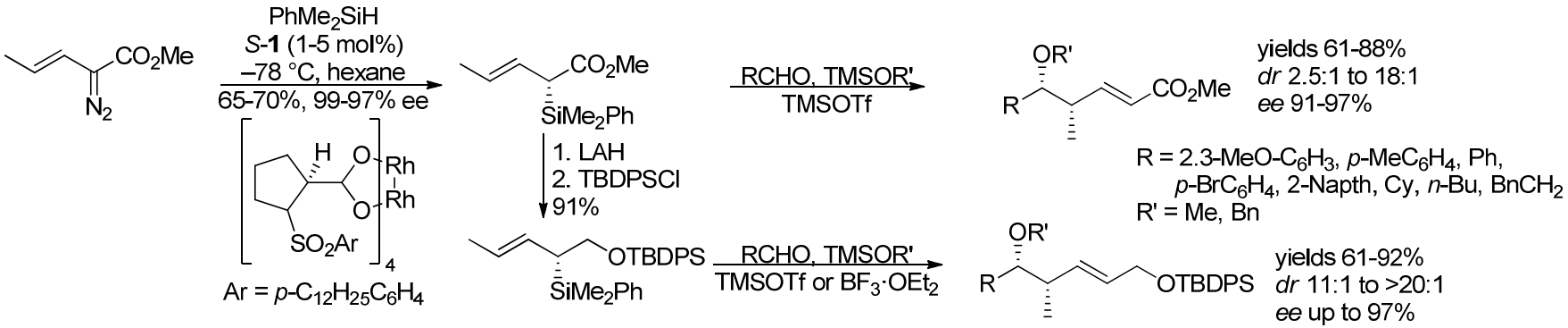
Silicon Reagents



chiral crotylsilanes
Panek

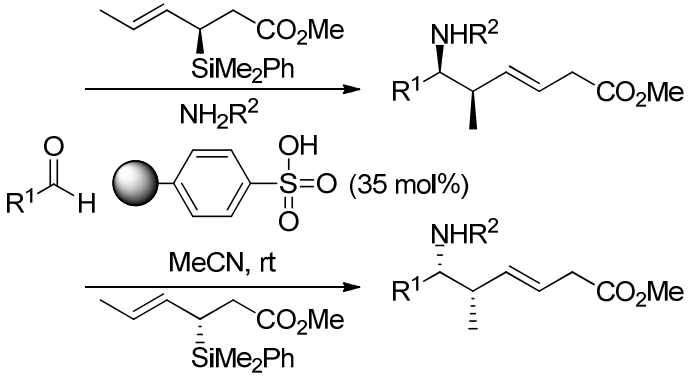
Crotylsilanes: Aldehyde Crotylation

- 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



Crotylsilanes: Imine Crotylation

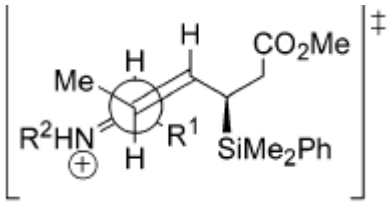
- 3-Component Enantioselective Synthesis of Homoallylic Carbamates
  - Condensation of aldehyde with carbamate generates N-acyliminium → crotylated *in situ* by chiral silane
    - Catalysed by Brønsted acid macroporous polystyrene-bound sulfonic acid (MP-TsOH)



R^1 = Ph, *m*-$MeOC_6H_4$, *p*-$MeOC_6H_4$, *p*-$ClOC_6H_4$, *p*-$MeOC_6H_4$, Cy
R^2 = CO_2Me, CO_2Et, Cbz

yields 57-83%
dr >20:1 except R^1 = *p*-$MeOC_6H_4$ 4:1
ee up to 89%

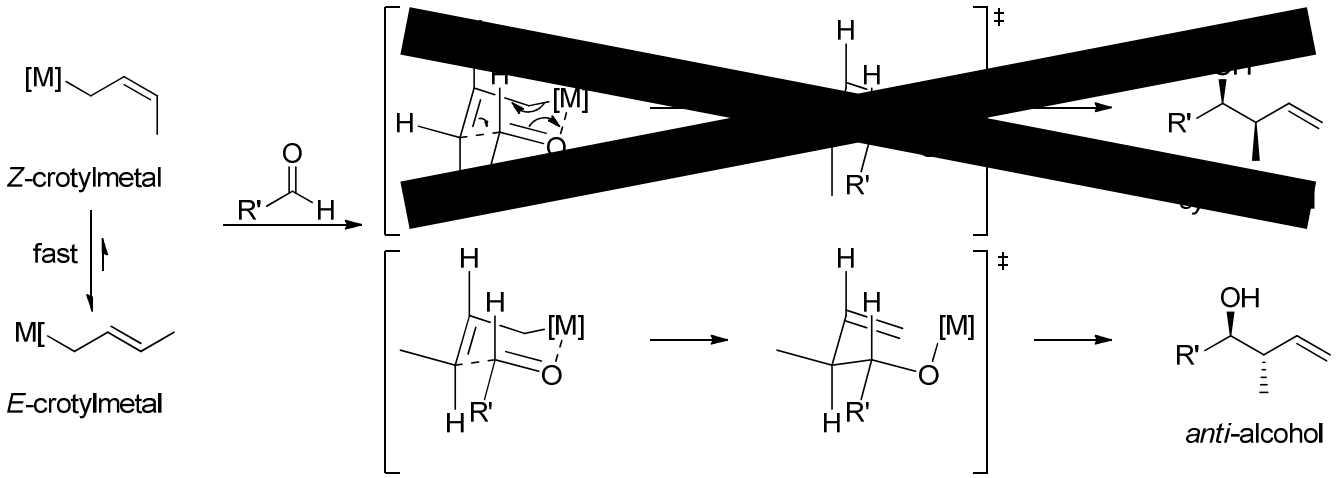
  - Stereochemical outcome rationalised by open transition state
    - Antiperiplanar TS with least Gauche interactions favoured



Type III Crotylmetals

Type III Crotylmetals: Diastereoselectivity

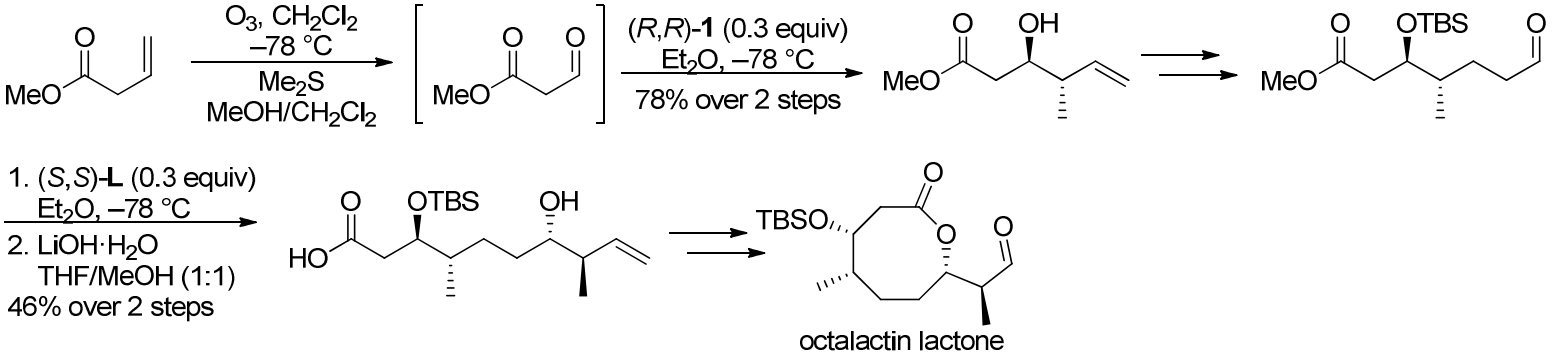
- React *via* a 6-membered closed, cyclic transition state akin to Type I
- But crotylmetal is configurationally labile, and rapidly isomerises to *E*-isomer so *anti*-product is obtained

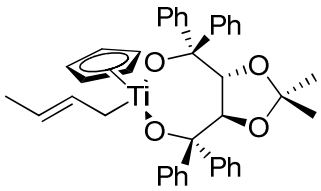


Yamamoto, Y., Yatagai, H., Naruta, Y., Maruyama, K. *JACS* **2005**, *102*, 7107; Denmark, S.E., Eber, E. U., *Helv. Chim. Acta* **1983**, *66*, 1655.

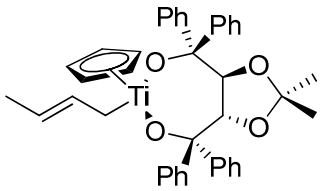
Crotyltitanates in Total Synthesis

- 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

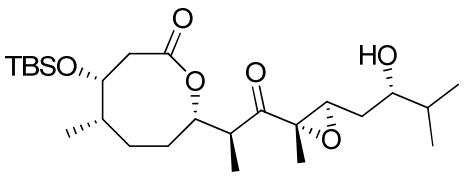




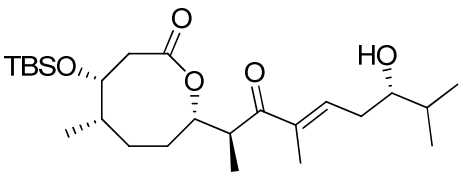
(*R*,*R*)-**1**



(*S*,*S*)-**1**



(–)-octalactin A

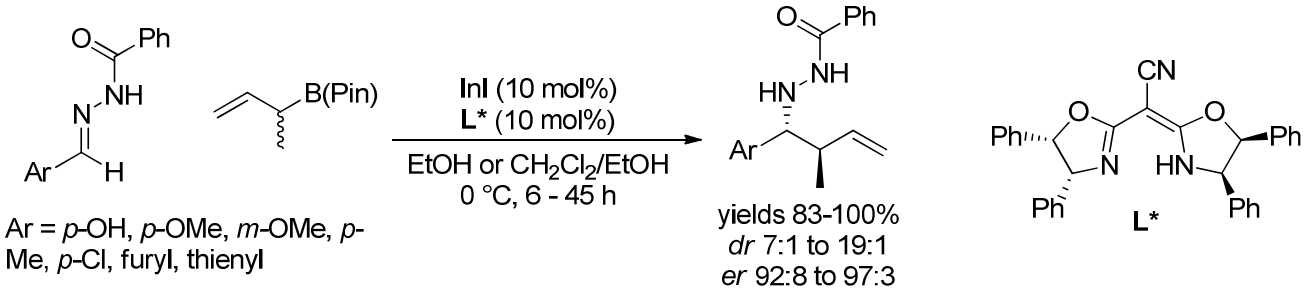


(–)-octalactin B

Dinh, M.-T.; BouzBouz, S.; Pegliion, J.-L.; Cossy, J.; *Synlett*, **2005**, 2851.

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



Ar = *p*-OH, *p*-OMe, *m*-OMe, *p*-Me, *p*-Cl, furyl, thienyl

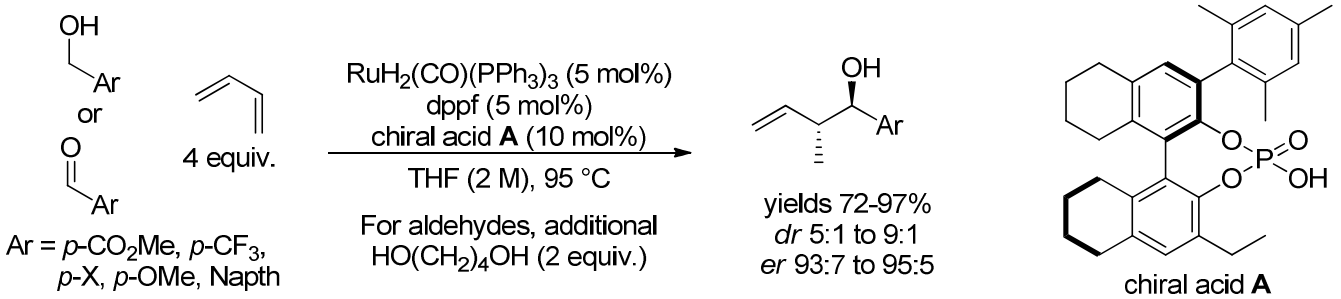
yields 83-100%
dr 7:1 to 19:1
er 92:8 to 97:3

  - 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

Chakrabarti, A.; Konishi, H.; Yamaguchi, M.; Schneider, U.;Kobayashi, S. *Angew. Chem. Int. Ed.* **2010**, *49*, 1838.

Crotylation with butadiene

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

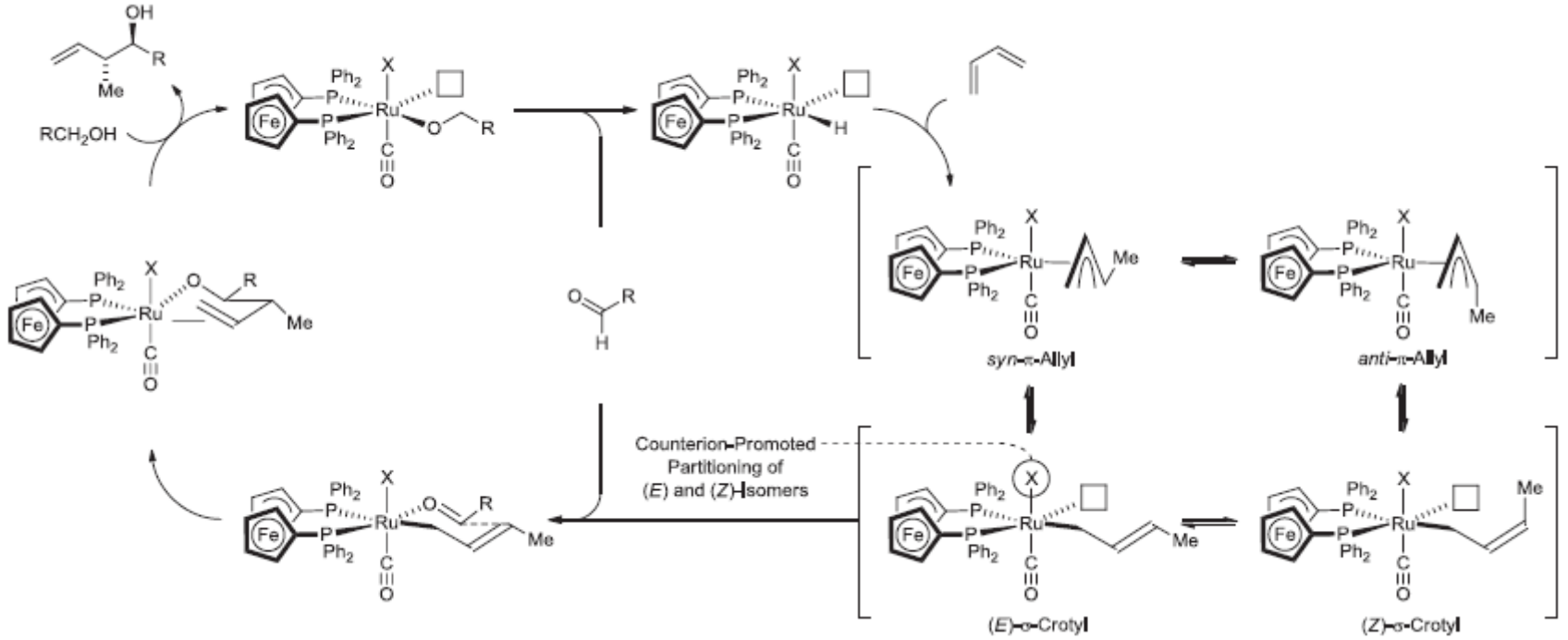


- Transfer hydrogenation conditions: 1° alcohols act as hydrogen donor and aldehyde precursors
- Advantages:
  - Butadiene is cheap and readily available chemical feedstock
  - No stoichiometric by-products, bypass the use of premetallated reagents for carbonyl crotylation
- *Anti*-diastereoselectivity 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

Zbieg, J.R.; Yamaguchi, E.; McInturff, E. L.; Irische, M. J. *Science*, **2012**, *336*, 324.

Crotylation with butadiene

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



Zbieg, J.R.; Yamaguchi, E.; McInturff, E. L.; Irische, M. J. *Science*, **2012**, *336*, 324.

Conclusion

Conclusion

- Type I crotylmetals 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!