Asymmetric Iridium Catalysis in Synthesis

Dr John Bower

SCI Innovations in Chemical Synthesis

2nd December 2011

University of BRISTOL

Overview

Asymmetric Iridium Catalysis: three key areas covered today:

1. Asymmetric allylic substitution reactions.
2. Asymmetric hydrogenation of alkenes and heteroarenes.
3. Asymmetric hydrogenative and transfer hydrogenative C-C bond formation.

Iridium Catalysis: two key areas not covered today:

4. Aryl C-H functionalisation (esp. C-H borylation).
5. "Borrowing hydrogen" processes.

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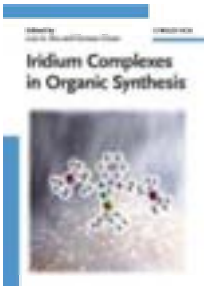
Key Texts



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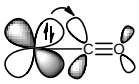
Iridium Catalysis: *Background*

Basic properties of iridium based catalyst systems:

Group IX	Oxidation states	π-Backbonding
Co 27		
Rh 45	I, III	Ph_3P, Ph_3P Rh Cl C≡O ν_{CO}, 1980 cm^{-1}
Ir 77	I, III and V	Ph_3P, Ph_3P Ir Cl C≡O ν_{CO}, 1965 cm^{-1}

Increase

This talk is organic focussed

Some mechanistic details are unclear

General trends will be highlighted

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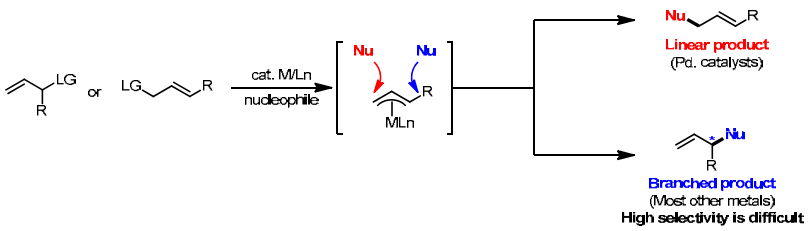
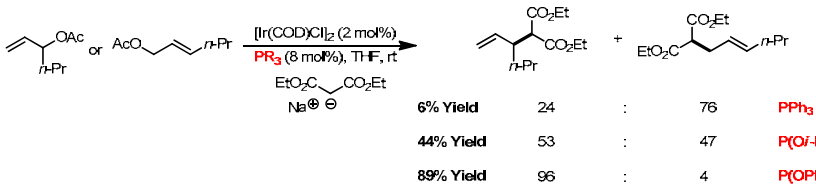
Allylic Substitution: *Background*

Metal catalysed allylic alkylation:



Ir-catalysed allylic alkylation: R. Takeuchi *et al*., *ACIEE*, **1997**, *36*, 263; *JACS*, **1998**, *120*, 8647



6% Yield	24	:	76	PPh_3
44% Yield	53	:	47	$P(O\textit{i}\text{-}Pr)_3$
89% Yield	96	:	4	$P(OPh)_3$

Increasing electron deficiency

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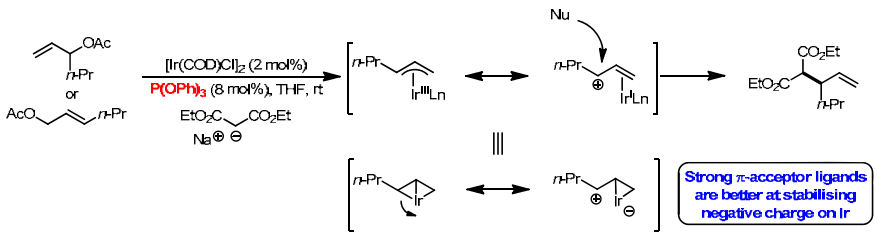
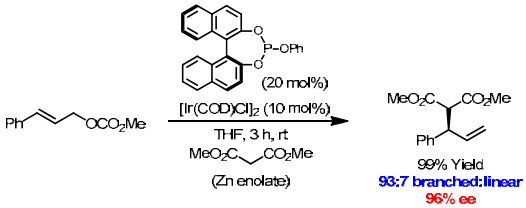
Allylic Substitution: *Early Asymmetric Examples*

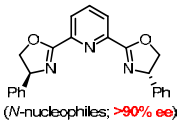
Mechanistic rationale:



Early asymmetric variants: Fuji *et al*., *Chem. Commun.*, **1999**, 2289.



See also:
Takemoto *et al*., *OL*, **2004**, *6*, 4631.



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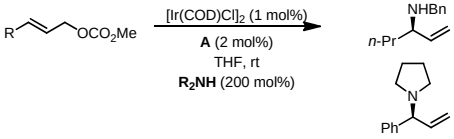
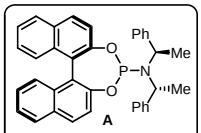
Allylic Substitution: *Phosphoramidite Ligands*

Phosphoramidite ligands:

Hartwig *et al. JACS*, **2002**, *124*, 15164

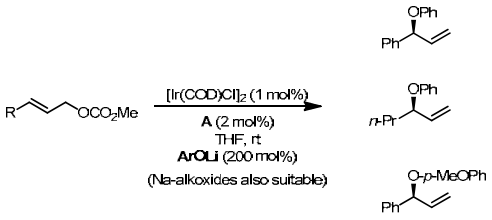




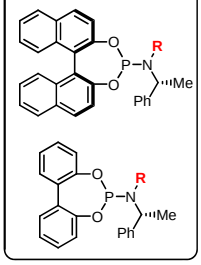
Very general ligand

Feringa *et al. ACIEE*, **1997**, *36*, 2620

Hartwig *et al. JACS*, **2003** *125*, 3426

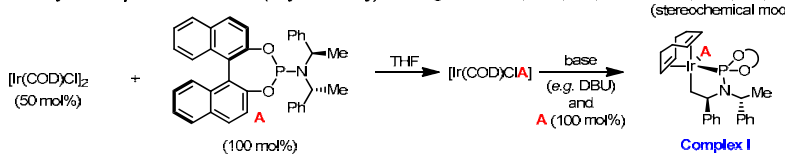


General architectures:



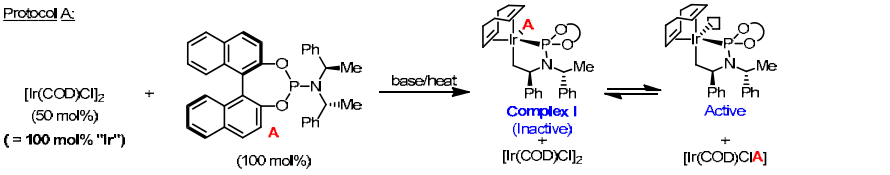
Allylic Substitution: *Metallacyclic Complexes*

Metallacyclic complexes form in situ (key discovery): Hartwig *et al. JACS*, **2003**, *125*, 14272; *JACS*, **2009**, *131*, 7228 (stereochemical model)

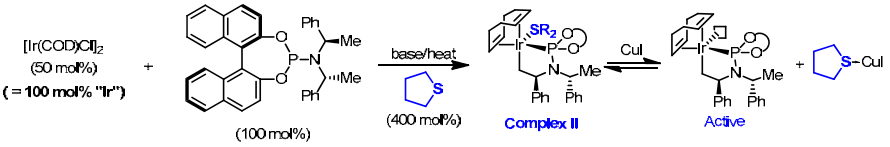


Active complexes can be generated in situ:

Protocol A:

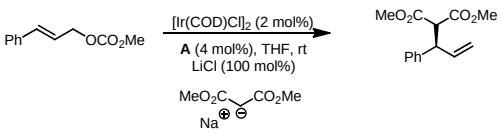


Protocol B: Hallmchen *et al. ACIEE*, **2004**, *43*, 4595

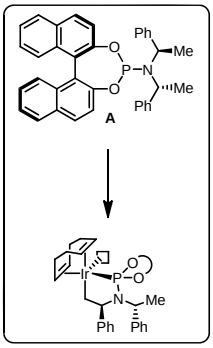


Allylic Substitution: *Enolates*

No catalyst preformation:

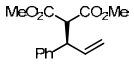


98% Yield
91:9 branched:linear
86% ee

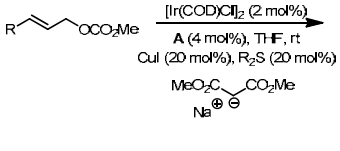


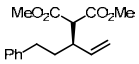
Catalyst preformed in situ (protocol B):

Helmchen *et al. ACIEE*, **2004**, *43*, 4595

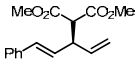


88% Yield
99:1 branched:linear
96% ee





92% Yield
81:19 branched:linear
96% ee

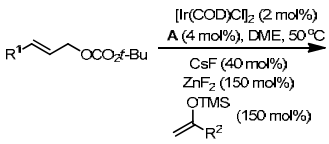


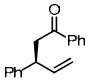
92% Yield
98:2 branched:linear
96% ee

Allylic Substitution: *Carbon Nucleophiles*

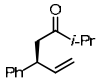
Unstabilised enolate equivalents react well:

(A) Silyl enol ethers: Hartwig *et al. JACS* **2005**, *127*, 17192.

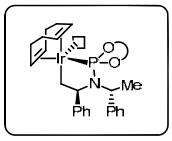




84% Yield
93:7 branched:linear
94% ee

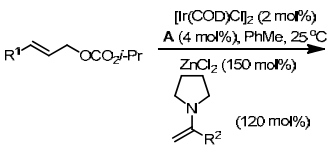


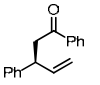
46% Yield
95:5 branched:linear
91% ee



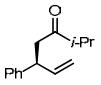
Lewis acid required to "mop up" HO*t*-Bu or HO*i*-Pr

(B) Enamines: Hartwig *et al. JACS* **2007**, *129*, 7720.





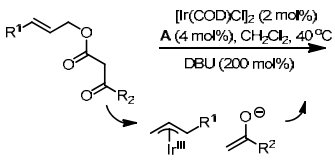
91% Yield
99:1 branched:linear
94% ee

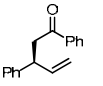


86% Yield
99:1 branched:linear
95% ee

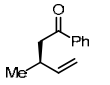
68% Yield
95:5 branched:linear
94% ee

(C) Decarboxylative generation: You *et al. OL* **2007**, *9*, 4339.

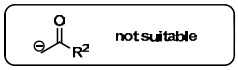




83% Yield
99:1 branched:linear
95% ee

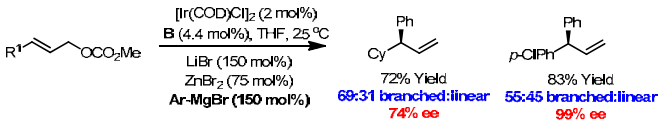


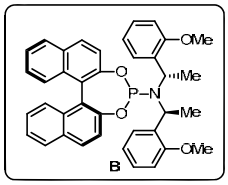
61% Yield
94:6 branched:linear
90% ee



Allylic Substitution: *Carbon Nucleophiles*

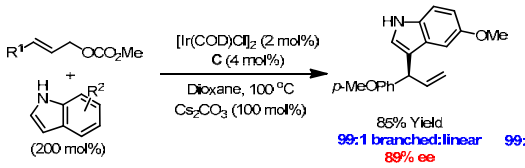
Aryl Zinc reagents: Alexakis *et al.*, *Chem. Eur. J.* **2009**, *15*, 1205.

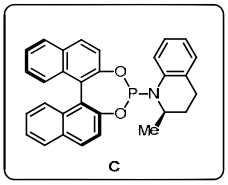




Branch selective arylation is very challenging

C-Functionalisation of heteroarenes: You *et al.* *Synthesis* **2009**, 2076.

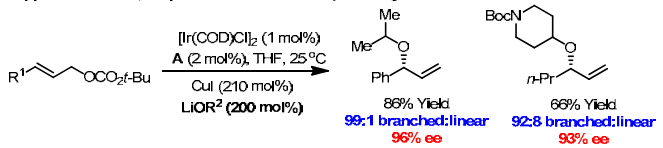


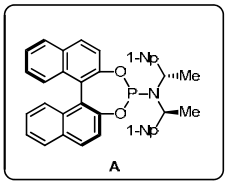


***N*-allylation not observed**

Allylic Substitution: *Oxygen Nucleophiles*

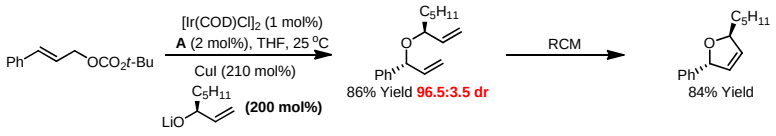
Copper alkoxides (for phenoxides see earlier): Hartwig *et al.* *ACIEE* **2004**, *43*, 4794.



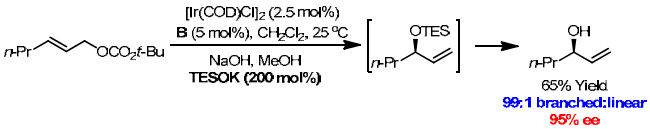


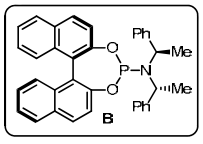
Copper moderates alkoxide basicity (K_3PO_4/alcohol also effective) *ACIEE* **2008**, *47*, 1928.

Catalyst controlled diastereoselectivity:



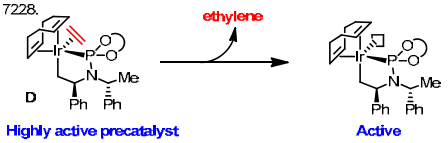
Alcohol synthesis: Carreira *et al.* *ACIEE* **2006**, *45*, 6204.



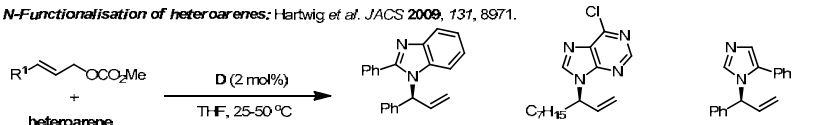


Allylic Substitution: *Nitrogen Nucleophiles*

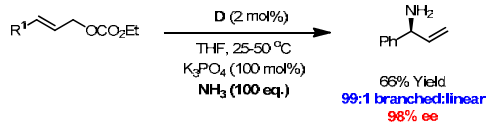
Hartwig *et al. JACS* **2009**, *131*, 7228.



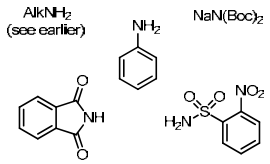
N-Functionalisation of heteroarenes: Hartwig *et al. JACS* **2009**, *131*, 8971.



Allylic amination: Hartwig *et al. JACS* **2009**, *131*, 11312.



Other suitable N-nucleophiles:



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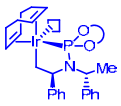
Allylic Substitution: *Summary*

1. Chiral metallacyclic catalysts are highly effective for branch selective allylic functionalisation:

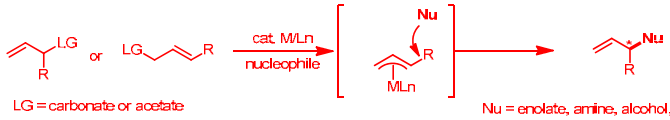


Vacant coordination site required

Electron deficient ligand required

Catalysts are prepared in situ from commercial materials

2. A wide range of nucleophiles are tolerated:



LG = carbonate or acetate

Nu = enolate, amine, alcohol, electron righ aryl, organo zinc reagents etc.

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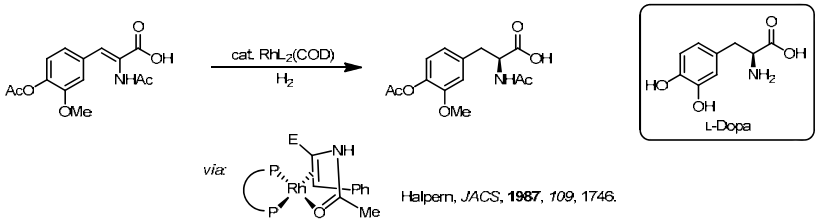
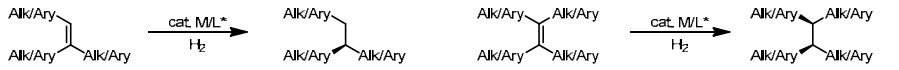
Asymmetric Hydrogenation: *The Problem*

Conventional processes are limited to substrates with coordinating groups:



Asymmetric hydrogenation of unfunctionalised alkenes not achievable with Rh or Ru:

Desirable transformations



1 new stereocentre

2 new stereocentres

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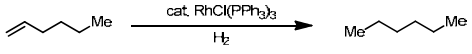
Asymmetric Hydrogenation: *Towards Effective Catalysts*

Wilkinson, *J. Chem. Soc. (A)*, **1966**, 1711.



$IrCl(PPh_3)_3$ ineffective because PPh_3 binds too tightly and does not dissociate

Crabtree, *Acc. Chem. Res.* **1979**, *12*, 331.

>100 times more active than Wilkinson's catalyst

Reduces tri- and tetrasubstituted alkenes

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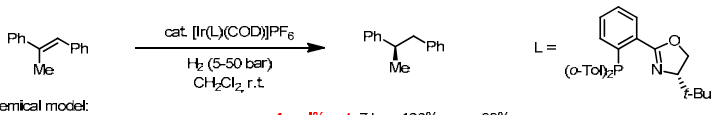
Asymmetric Hydrogenation: *The Solution*

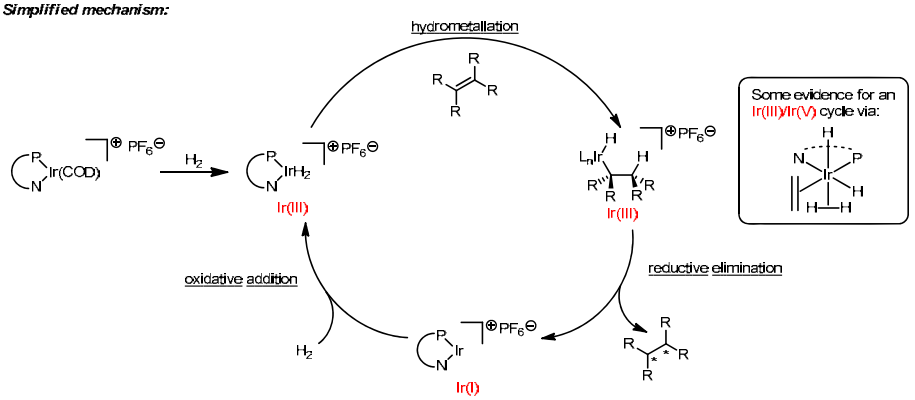
Pfaltz, Blackmond *et al.*, *Chirality*, **2000**, *12*, 442.



Stereochemical model:
Andersson *et al. JACS* **2006**, *128*, 2995.

4 mol% cat; 7 bar: 100% conv. 98% ee

Simplified mechanism:



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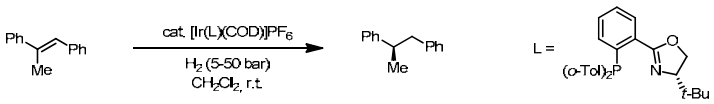
Asymmetric Hydrogenation: *Anion Effects*

Pfaltz, Blackmond *et al.*, *Chirality*, **2000**, *12*, 442.

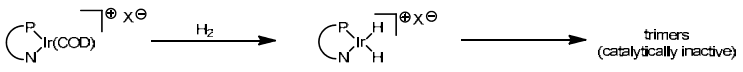


4 mol% cat; 7 bar: 100% conv. 98% ee

1 mol% cat; 7 bar: 45% conv. 98% ee

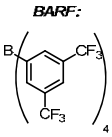
Initial rates similar ⇨ Catalyst deactivates

Deactivation pathway: Pfaltz *et al. Chem. Eur. J.* **2004**, *10*, 4685.



	Increasing Dissociation			
$X^{\ominus}$	$OTf^{\ominus}$	$BF_4^{\ominus}$	$PF_6^{\ominus}$	$BARF^{\ominus}$
TOF (h^{-1})	0	300	1700	4600

BARF:



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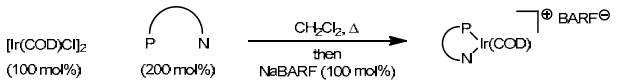
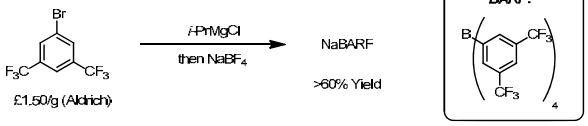
Asymmetric Hydrogenation: *Catalyst Preparation*

Catalyst preparation:



red complexes
(good air and moisture stability)

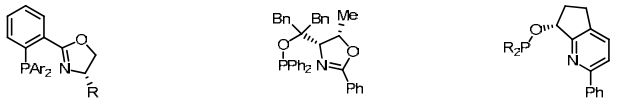
NaBARF £250/g (Aldrich) or: Bergman *et al. Organometallics* **2005**, *24*, 3579.



£1.50/g (Aldrich)

>60% Yield

Commonly employed ligands:

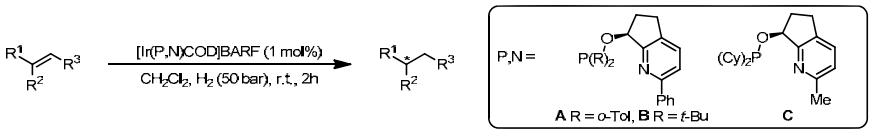


R = *i*-Pr, *t*-Bu
(commercial)
Williams-Helmchen-Pfaltz ligand

(commercial)

R = *t*-Bu or *o*-Tol

Asymmetric Hydrogenation: *Trisubstituted Alkenes*



>99% Yield, 98% ee
A

>99% Yield, >99% ee
A

>99% Yield, 97% ee
A

>99% Yield, 64% ee
C

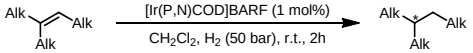
>99% Yield, >99% ee
A

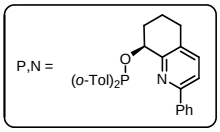
>99% Yield, 80% ee
A

>99% Yield, >99% ee
B

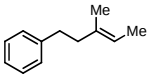
>99% Yield, 89% ee
A

Asymmetric Hydrogenation: *Trialkyl Alkenes*

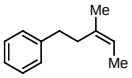




Pfaltz *et al*. *Science* **2006**, *311*, 642; *ACIEE* **2008**, *47*, 2298

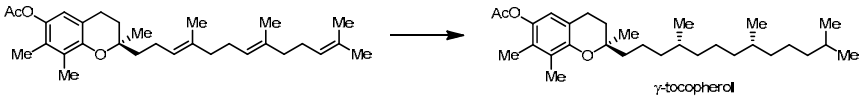


>99% Yield, 93% ee



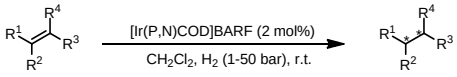
>99% Yield, 98% ee

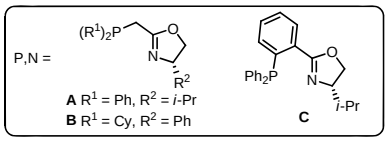
>99% Yield, 98% ee



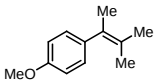
γ-tocopherol
>98% dr

Asymmetric Hydrogenation: *Tetrasubstituted Alkenes*

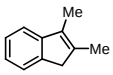




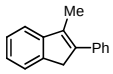
Pfaltz *et al*. *ACIEE* **2007**, *46*, 8274



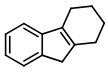
>99% Yield, 97% ee
B



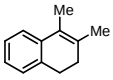
>99% Yield, 94% ee
A



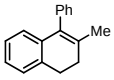
20% Yield, 88% ee
A



>99% Yield, 94% ee
C



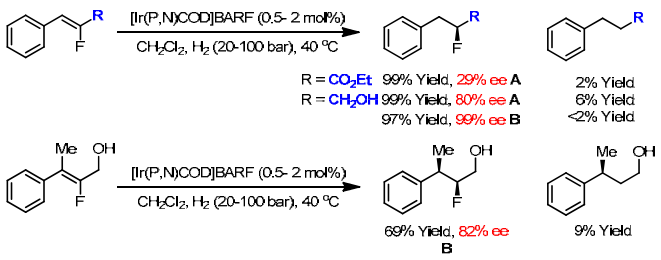
>99% Yield, 73% ee
A

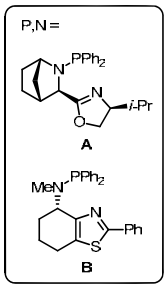


32% Yield, 91% ee
B

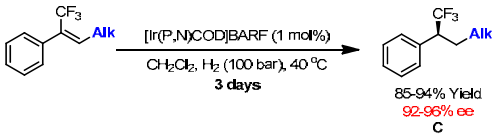
Asymmetric Hydrogenation: *Fluorinated Alkenes*

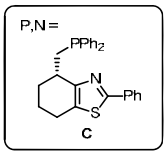
Vinyl fluorides: Andersson *et al. JACS*, **2007**, *129*, 4536.





Trifluoromethylalkenes: Andersson *et al. Adv. Synth. Cat.*, **2009**, *351*, 375.





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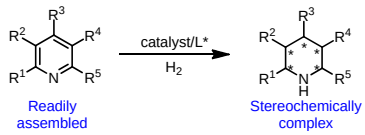
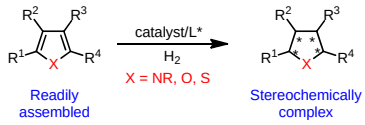
Asymmetric Hydrogenation: *Heteroarenes*

General concept:





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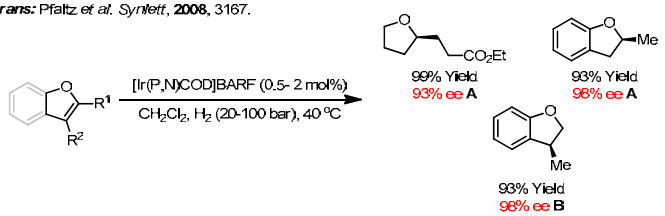
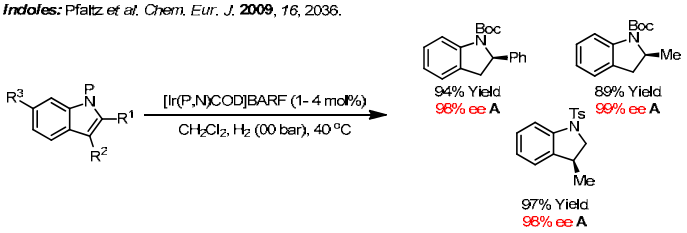
Asymmetric Hydrogenation: *Indoles and Furans*

Furans: Pfaltz *et al. Synlett*, **2008**, 3167.



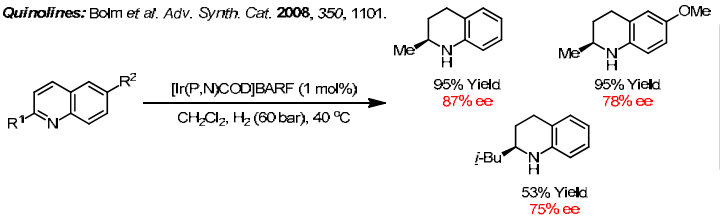
Indoles: Pfaltz *et al. Chem. Eur. J.* **2009**, *16*, 2036.



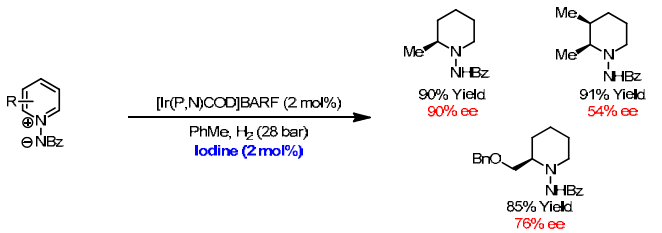
Approach also successful with enol ether and enamine substrates

Asymmetric Hydrogenation: *Quinolines and Pyridines*

Quinolines: Bolm *et al. Adv. Synth. Cat.* **2008**, *350*, 1101.

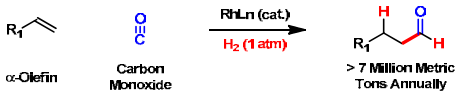


Iminopyridinium ylides: Charette *et al. JACS*, **2005**, *127*, 8966.



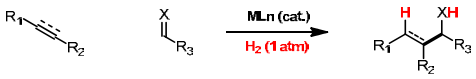
Hydrogenative C-C Bond Formation: *Background*

Alkene hydroformylation:



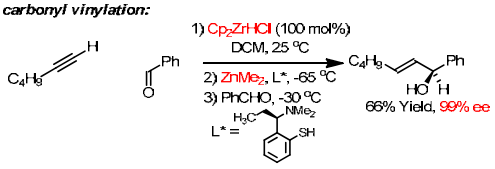
Largest volume application of homogeneous catalysis

C-C coupling via hydrogenation and transfer hydrogenation:

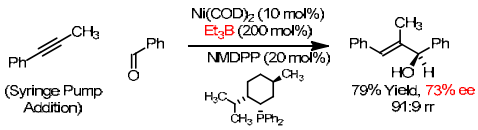


Hydrogenative C-C Bond Formation: *Vinylation*

Asymmetric carbonyl vinylation:

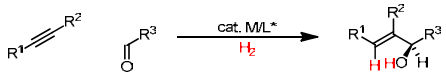


Oppolzer *JACS* **1993**, 1593
Wipf *JOC* **1998**, 6454
Walsh *JACS* **2002**, 1225



Montgomery *JACS* **1997**, 6098
Jamison *JACS* **2003**, 3442
Montgomery *JACS* **2004**, 3698

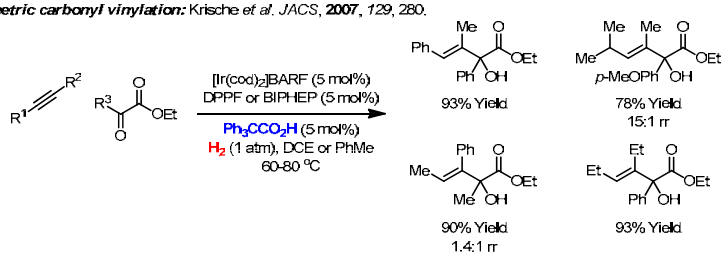
Hydrogenative approach:



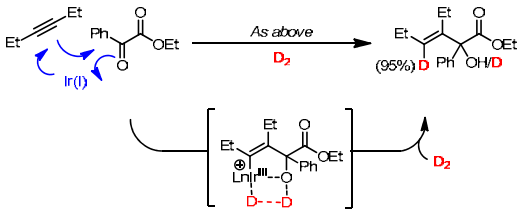
Byproduct free!

Hydrogenative C-C Bond Formation: *Vinylation*

Asymmetric carbonyl vinylation: Krische *et al. JACS*, **2007**, *129*, 280.

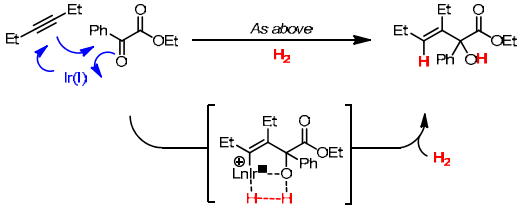


Mechanism:

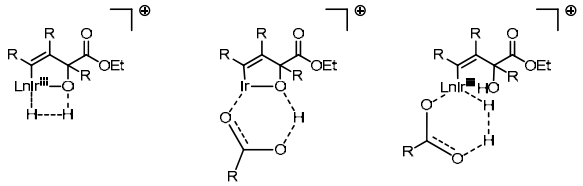


Hydrogenative C-C Bond Formation: *Vinylation*

Mechanism:



Role of acid co-catalyst:



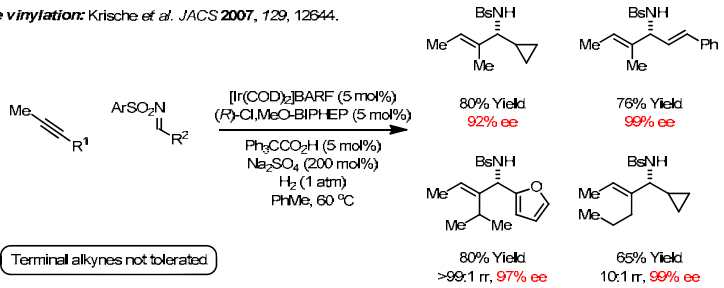
A
σ-Bond Metathesis
via 4-Centered TS

B
Protonolysis
via 6-Centered TS

C
σ-Bond Metathesis
via 6-Centered TS

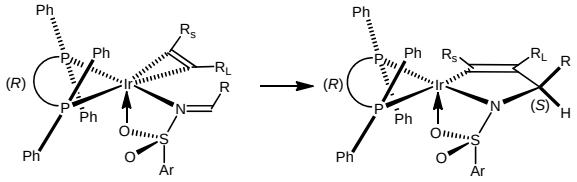
Hydrogenative C-C Bond Formation: *Vinylation*

Imine vinylation: Krische *et al. JACS* **2007**, *129*, 12644.



Terminal alkynes not tolerated

Stereochemical model:

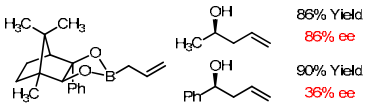


Favored mode of addition

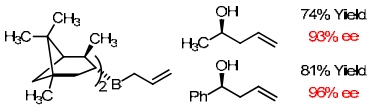
Hydrogenative C-C Bond Formation: *Allylation*

Asymmetric carbonyl allylation methods:

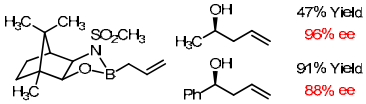
Hoffmann, *Angew. Chem., Int. Ed. Engl.* **1978**, 768



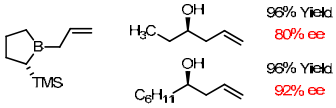
Brown, *J. Am. Chem. Soc.* **1983**, 2092



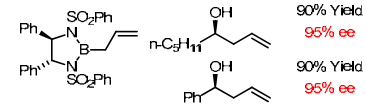
Reetz, *Pure Appl. Chem.* **1988**, 1607



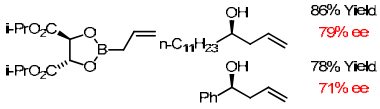
Masamune, *J. Am. Chem. Soc.* **1989**, 1892



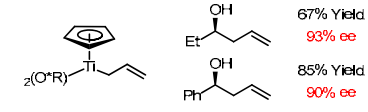
Corey, *J. Am. Chem. Soc.* **1989**, 5495



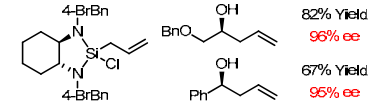
Roush, *J. Am. Chem. Soc.* **1985**, 8186



Duthaler, *Angew. Chem., Int. Ed. Engl.* **1989**, 494



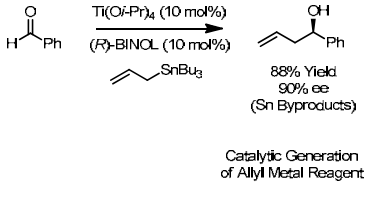
Leighton, *J. Am. Chem. Soc.* **2002**, 7920



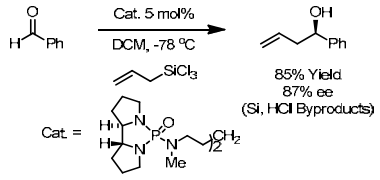
Hydrogenative C-C Bond Formation: *Allylation*

Catalytic protocols rely on the use of stoichiometric allyl metal reagents:

Umani-Ronchi *J. Am. Chem. Soc.* **1993**, 7001;
Keck, *ibid* **1993**, 8467.

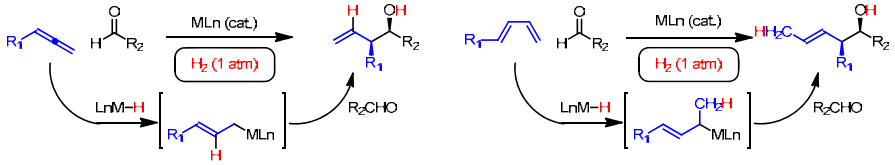


Denmark, *J. Am. Chem. Soc.* **2001**, 9488.



Catalytic Generation of Allyl Metal Reagent ?

Byproduct-free carbonyl allylation via hydrogenative coupling?



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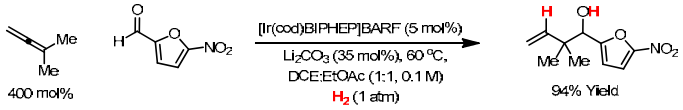
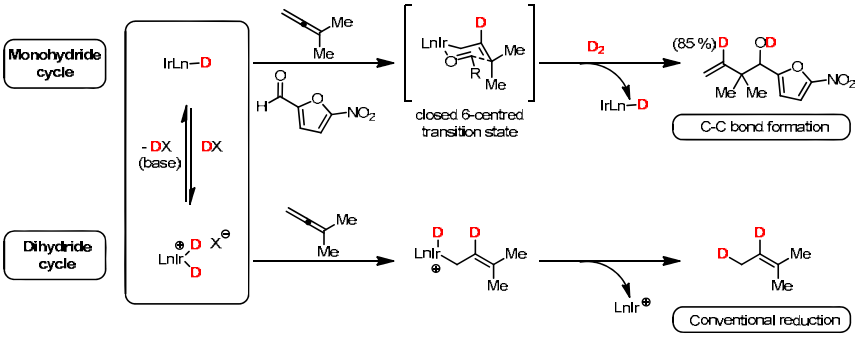
Hydrogenative C-C Bond Formation: *Allylation*

Krische *et al. JACS*, **2007**, *129*, 12678.





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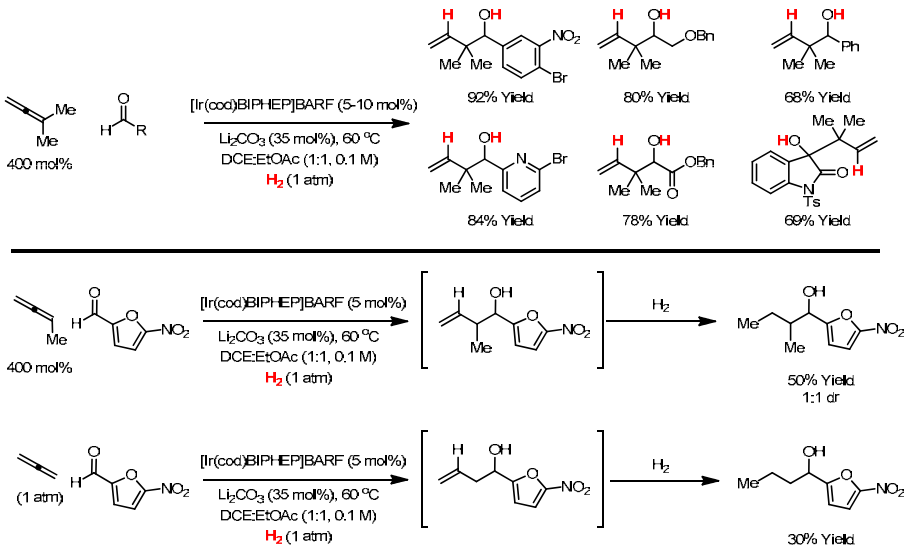
Hydrogenative C-C Bond Formation: *Allylation*



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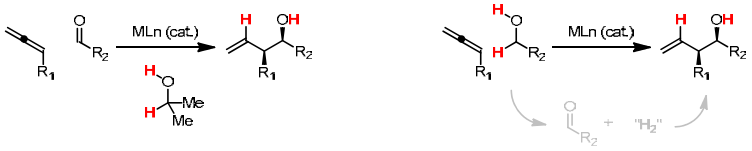
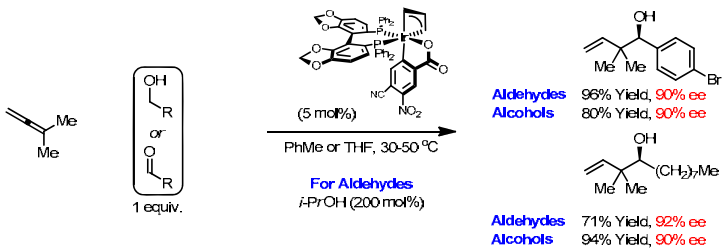
Transfer Hydrogenative C-C Bond Formation

Suppressing over reduction:



Enantioselective reverse prenylation: Krische *et al. JACS* **2007**, *129*, 15134; *JACS* **2009**, *131*, 6916.



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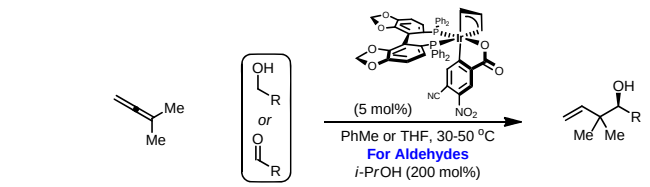
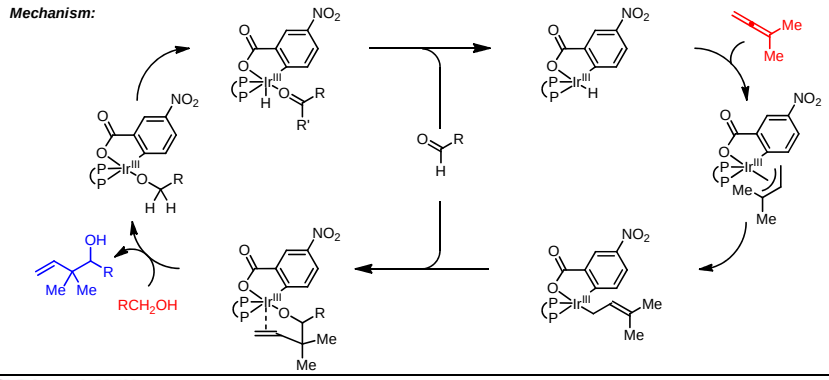
Transfer Hydrogenative C-C Bond Formation



Mechanism:



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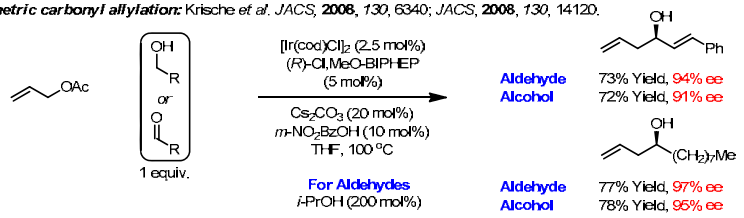
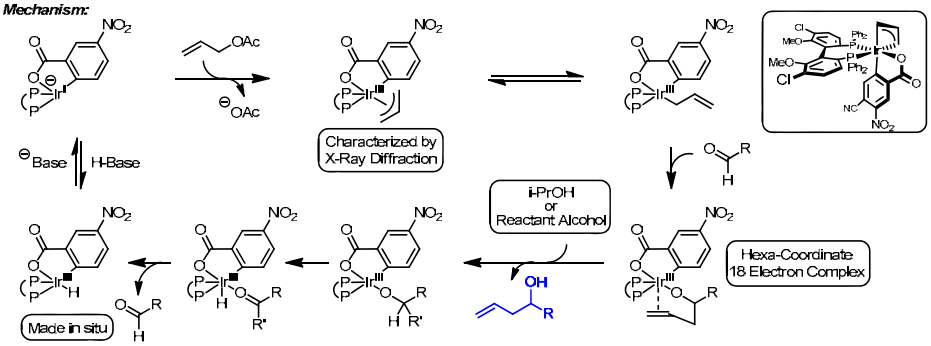
Transfer Hydrogenative C-C Bond Formation: *Allylation*

Asymmetric carbonyl allylation: Krische *et al. JACS*, **2008**, *130*, 6340; *JACS*, **2008**, *130*, 14120.



Mechanism:



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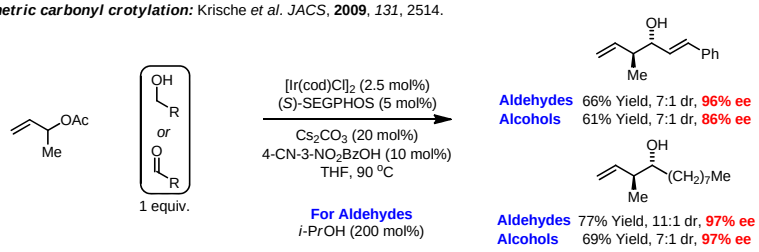
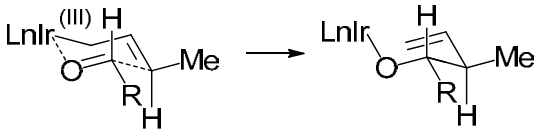
Transfer Hydrogenative C-C Bond Formation: *Crotylation*

Asymmetric carbonyl crotylation: Krische *et al. JACS*, **2009**, *131*, 2514.





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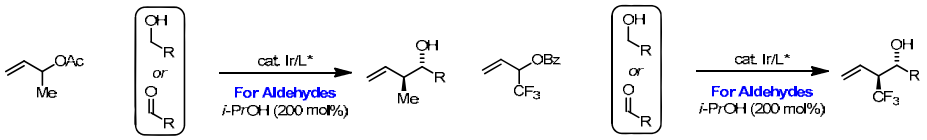
Transfer Hydrogenative C-C Bond Formation: *Crotylation*

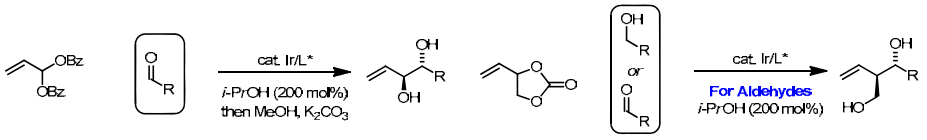
Asymmetric carbonyl crotylation:
Krische *et al. JACS*, **2009**, *131*, 2514.

Asymmetric carbonyl trifluoromethylallylation:
Krische *et al. ACIEE*, **2011**, *50*, 4173.



Asymmetric carbonyl hydroxyallylation:
Krische *et al. JACS*, **2010**, *132*, 1760.

Asymmetric carbonyl hydroxymethylallylation:
Krische *et al. JACS*, **2010**, *132*, 4562.



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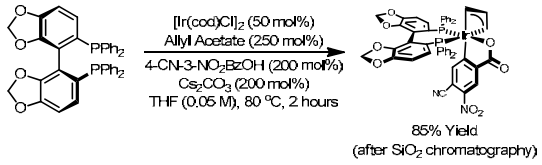
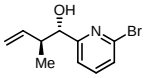
Transfer Hydrogenative C-C Bond Formation: *Catalyst Recycling*

Catalysts are easy to prepare: Krische *et al. JOC*, **2011**, *76*, 2350.



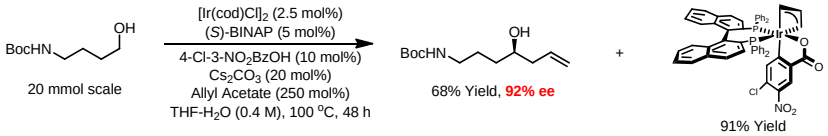
85% Yield
(after SiO_2 chromatography)

Using preformed catalyst:



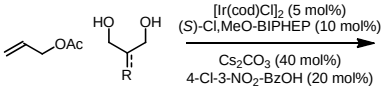
RCHO 75% Yield, 14:1 dr, **98% ee**
RCH_2OH 50% Yield, >20:1 dr, **97% ee**
No product observed with in situ catalyst!

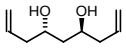
Catalyst can often be prepared in situ and then recycled: Krische *et al. OL*, **2011**, *13*, 2484



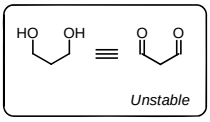
Transfer Hydrogenative C-C Bond Formation: *Bidirectional*

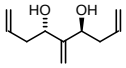
Bidirectional allylation: Krische *et al. ACIEE* **2009**, *48*, 5018.



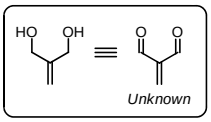


70% Yield
≥ 99% ee, ≥ 30:1 dr

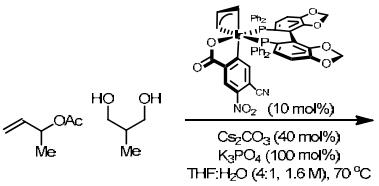


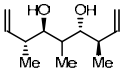


66% Yield
≥ 99% ee, 20:1 dr



Bidirectional crotylation: Krische *et al. JACS*, **2011**, *133*, 12795.



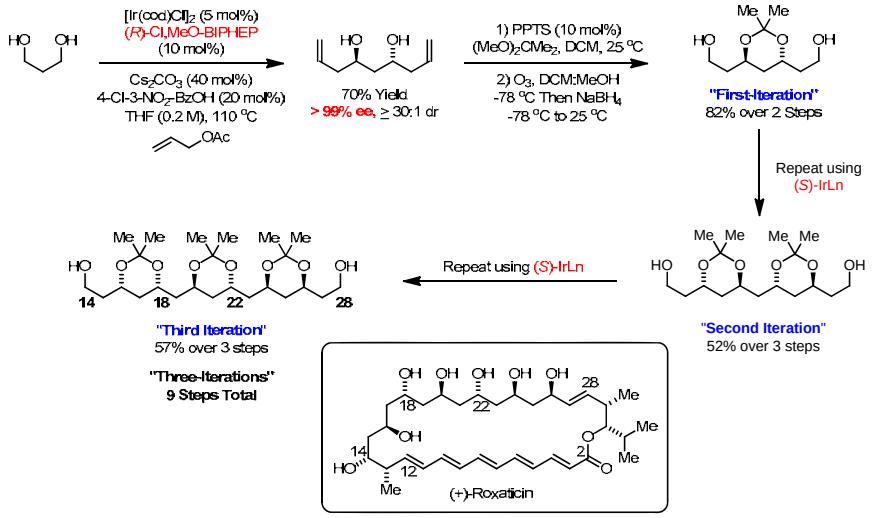


62% Yield
≥ 99% ee, 6:1 dr

Predominantly 1 of 16 possible stereoisomers!

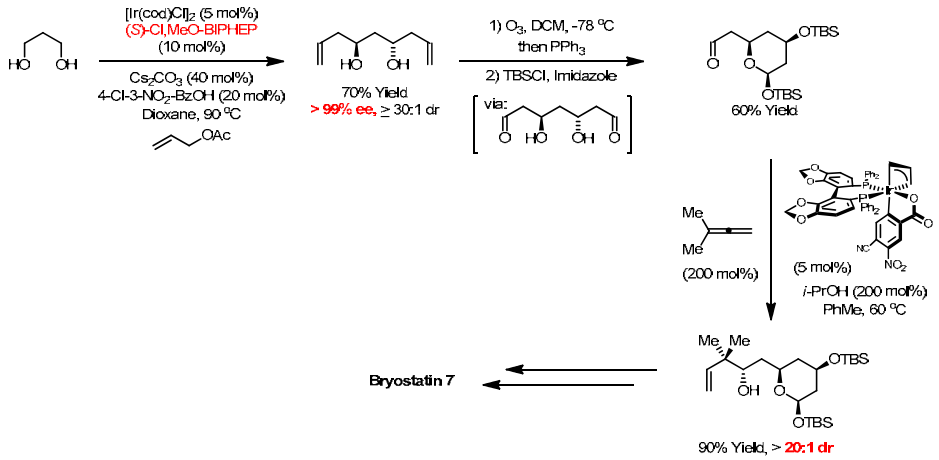
Transfer Hydrogenative C-C Bond Formation: *Roxaticin*

Iterative bidirectional allylation: Krische *et al*. *JACS*, **2010**, *132*, 15559.



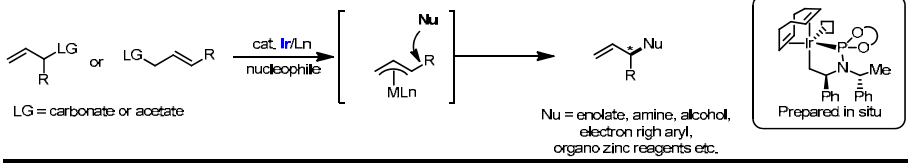
Transfer Hydrogenative C-C Bond Formation: *Bryostatin*

Synthesis of Bryostatin 7 fragment: Krische *et al*. *JACS*, **2011**, *133*, 13876.



Iridium Catalysis: *Summary*

1. Asymmetric allylic functionalisation

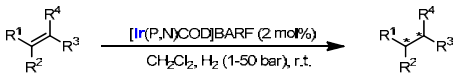


LG = carbonate or acetate

Nu = enolate, amine, alcohol, electron righ aryl, organo zinc reagents etc.

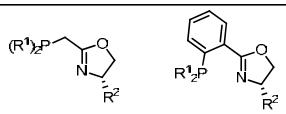
Prepared in situ

2. Asymmetric hydrogenation



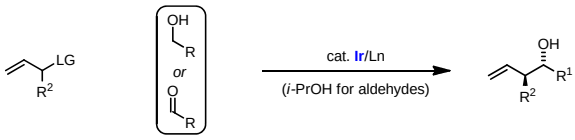
tri- and tetrasubsituted alkenes (and aromatics)

P,N =

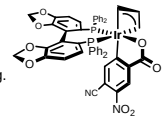


modular ligands

3. Transfer hydrogenative C-C bond formation



e.g.



Prepared in situ

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