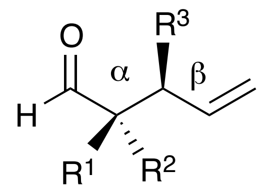
Enantio- and Diastereodivergent Dual Catalysis: α-Allylation of Branched Aldehydes

Krautwald, S.; Sarlah, D.; Schafroth, M. A.; Carreira, E. M.

Science **2013**, *340*, 1065–1068.



all stereoisomers

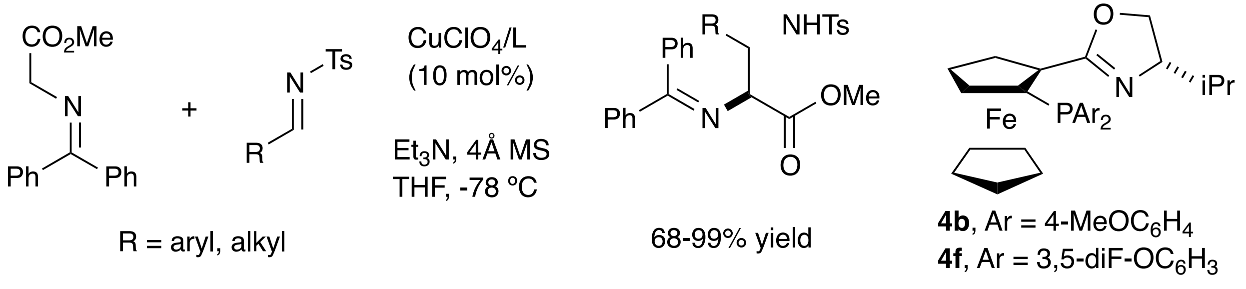
Kyu Ok Jeon

Wipf Group – Current Literature

Jul-13-2013

Access to the complete set of stereoisomer

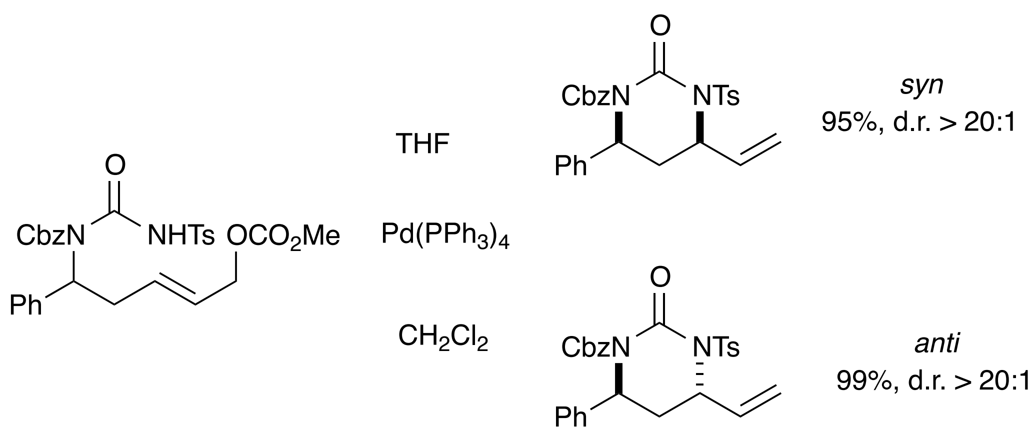
- Change of solvent, the use of additives, and selection of distinct catalysts



Ligand **4b** : *anti:syn* = 90->95:10-5 90-99% ee (*anti*)

Ligand **4f** : *anti:syn* = 93->95:7-5 96-99% ee (*syn*)

Yan, X.-X.; Peng, Q.; Li, Q.; Zhang, K.; Yao, J.; Hou, X.-H.; Wu, Y.-D. *J. Am. Chem. Soc.* **2008**, *130*, 14362–14363.



Morgen, M.; Bretzke, S.: Li, P.; Menche, D. *Org. Lett*. **2010**, *12*, 4494–4497.

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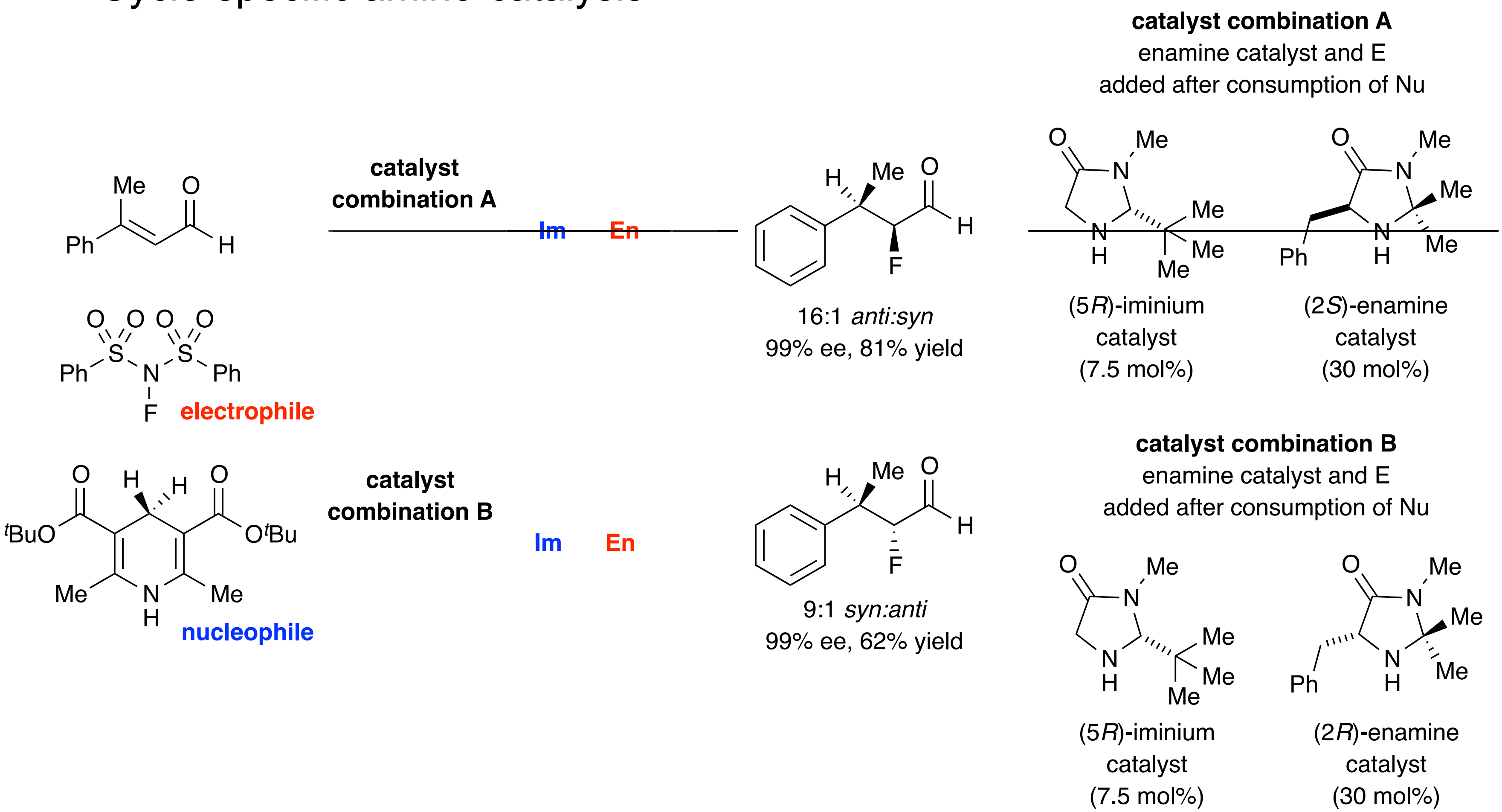
Access to the complete set of stereoisomer

- Cycle-specific amino-catalysis



Huang, Y.; Walji, A. M.; Larsen, C. H.; MacMillan, W. C. *J. Am. Chem. Soc.* **2005**, *127*, 15051–15053.

Classification of catalytic systems involving two catalysts

(A) Bifunctional catalyst

Catalyst

E **Nu**

both the nucleophile and electrophile
are activated separately
by discrete functional groups
on the same catalyst

(B) Double activation catalyst

Cat A **Cat B**

E **Nu**

both catalyst work in concert to
activate only one of the reacting partners

(C) Cascade catalyst

Cat A **Cat B**

E **E'** **Nu**

both catalysts activate
the same reacting partner,
but in a sequential fashion

(D) Synergistic catalyst (Dual catalyst)

Cat A **Cat B**

E **Nu**

the nucleophile and electrophile are
simultaneously activated by
two separate catalysts

Allen, A. E.; MacMillan, W. C. *Chem. Sci.* **2012**, *3*, 633–658.

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Dual and stereodivergent dual catalysis

A) ***dual catalysis***

A   **Cat 1**   **Cat1—E**

B   Cat 2   Cat2—**Nu**

C

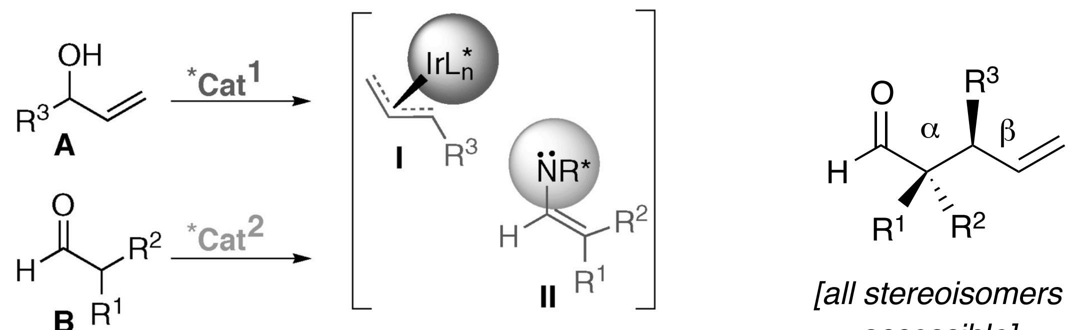
[reactant]   *[activated intermediates]*   *[product]*

B) ***stereodivergent dual catalysis (this work)***

$\mathbf{C}_{R,\,R}$ **Cat** $^{1}_{R}$ $\mathbf{C}_{R,\,S}$

Cat $^{2}_{R}$ **A + B**   Cat $^{2}_{S}$

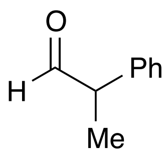
$\mathbf{C}_{S,\,R}$ **Cat** $^{1}_{S}$ $\mathbf{C}_{S,\,S}$



[all stereoisomers accessible]

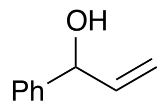
Krautwald, S.; Sarlah, D.; Schafroth, M. A.; Carreira, E. M. *Science* **2013**, *340*, 1065–1068.

Key experiments in the evaluation of diastereocontrol



1a
1.1 equiv

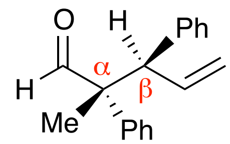
+



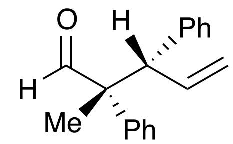
2a
0.25 mmol

2 mol% [{Ir(cod)Cl}$_2$]
8 mol% **ligand**

10 mol% **amine**
Cl_3CCO_2H
DCE, 25 °C, 24 h



(*R,R*)-3a
major
diastereoisomer

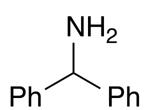


(*R,S*)-3a
minor
diastereoisomer

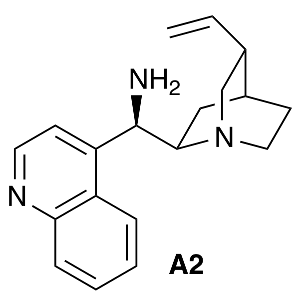
Key Experiments:

#1	#2	#3	#4
(*R*)-L + A1	**L1 + A2**	**L1 + A1**	**(*R*)-L + A2**
69%, 3:1 d.r.	69%, 1.3:1 d.r.	71%, 3:1 d.r.	77%, >20:1 d.r.
99% ee	68% ee/92% ee		99% ee
(*R*)-L: β-control	**A2**: α-control		**(*R*)-L + A2**: α & β-control

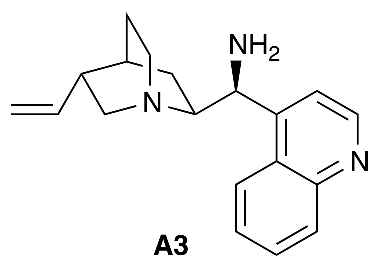
amine:



A1

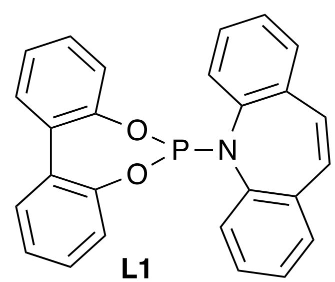


A2

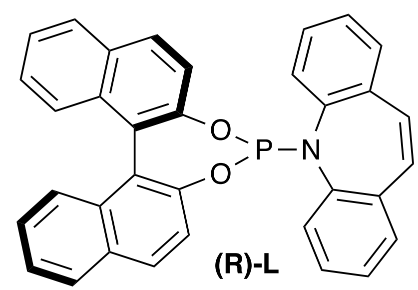


A3

(P, olefin) ligand



L1



(R)-L

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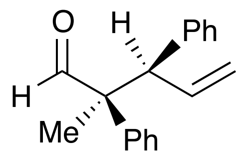
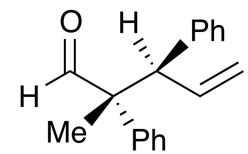
*Stereodivergent dual catalytic synthesis of all stereoisomers of **3a***



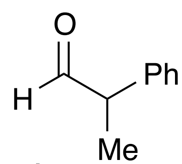
(*S,R*)-3a
80% yield
>99% ee
20:1 d.r.

(*R*)-L
A3

(*R*)-L
A2

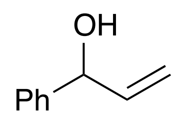


(*R,R*)-3a
77% yield
>99% ee
>20:1 d.r.

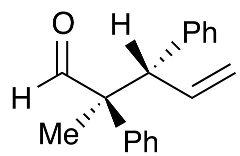


1a

+



2a

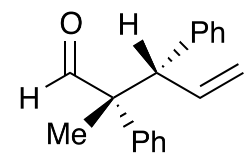


(*S,S*)-3a
71% yield
>99% ee
>20:1 d.r.

(*S*)-L
A3

Condition:
2 mol% [{Ir(cod)Cl}$_2$]
8 mol% **ligand**
10 mol% **amine**
Cl_3CCO_2H
DCE, 25 ºC, 24 h

(*S*)-L
A2



(*R,S*)-3a
78% yield
>99% ee
15:1 d.r.

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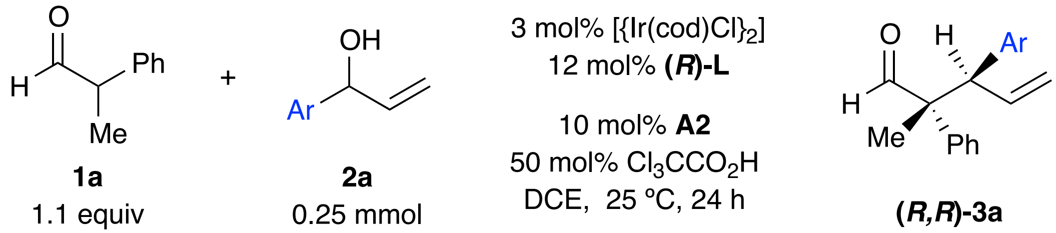
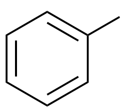
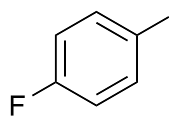
Allylic alcohol scope of the allylation

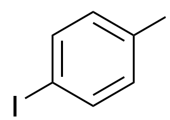




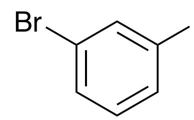
3a: 86% (>20:1)
>99% ee



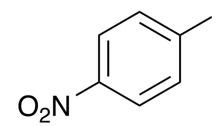
3b: 79% (>20:1)
>99% ee



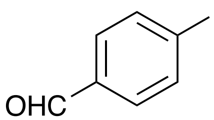
3c: 86% (>20:1)
>99% ee



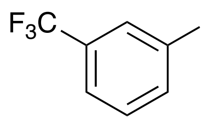
3d: 72% (>20:1)
>99% ee



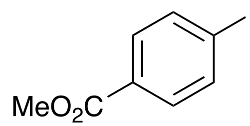
3e: 51% (15:1)
>99% ee



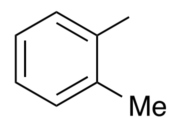
3f: 72% (>20:1)
>99% ee



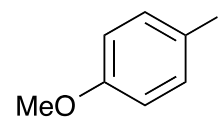
3g: 64% (>20:1)
>99% ee



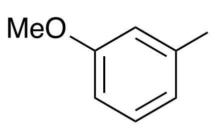
3h: 71% (>20:1)
>99% ee



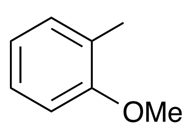
3i: 72% (>20:1)
>99% ee



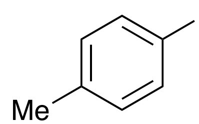
3j: 42% (>20:1)
>99% ee



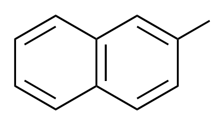
3k: 67% (>20:1)
>99% ee



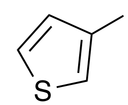
3l: 53% (>20:1)
>99% ee



3m: 67% (>20:1)
>99% ee



3n: 83% (14:1)
>99% ee



3o: 64% (>20:1)
>99% ee

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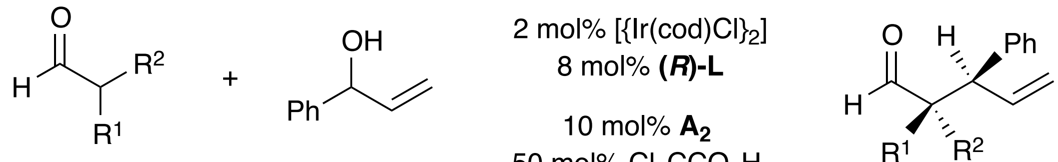
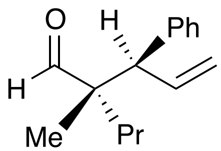
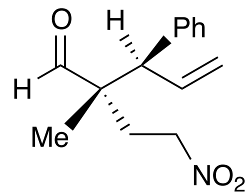
Aldehyde scope of the allylation



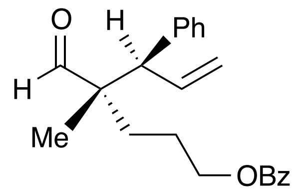
1a 1.1 equiv | **2a** 0.25 mmol | **3**



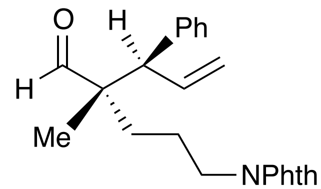
3p: 76% (6:1) >99% ee



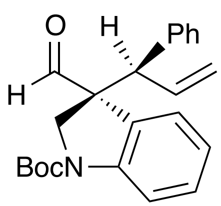
3q*: 53% (6.5:1) >99% ee



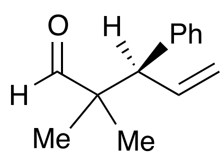
3r*: 62% (4:1) >99% ee



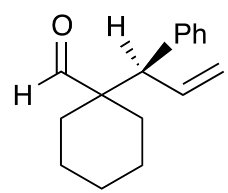
3s*: 74% (4.5:1) >99% ee



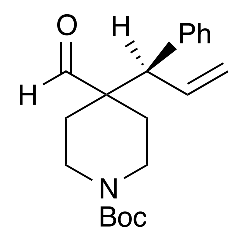
3t: 77% (>20:1) >99% ee



3u: 85% >99% ee



3v: 72% >99% ee



3w: 72% >99% ee

* 20 mol% **A2** and 100 mol% Cl_3CCO_2H were used.

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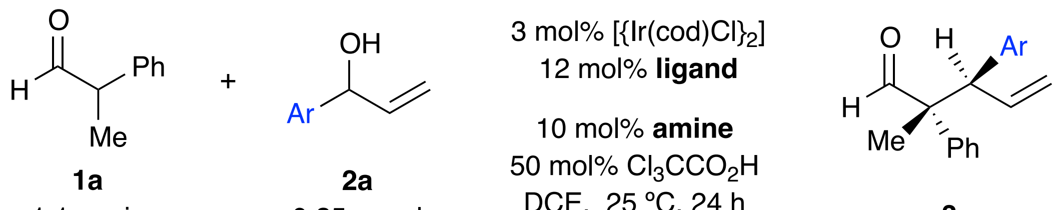
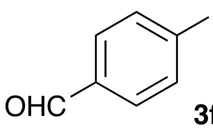
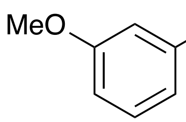
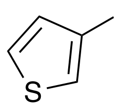
Representative examples of stereodivergence

stereoisomeric products obtained by catalyst permutation



1a 1.1 equiv | **2a** 0.25 mmol | **3**

	(*R*)-L + A2	(*R*)-L + A3	(*S*)-L + A2	(*S*)-L + A3
 **3f**	**(*R,R*)-3f** 72% (>20:1) >99% ee	**(*S,R*)-3f** 67% (20:1) >99% ee	**(*R,S*)-3f** 63% (20:1) >99% ee	**(*S,S*)-3f** 75% (>20:1) >99% ee
 **3k**	**(*R,R*)-3k** 67% (>20:1) >99% ee	**(*S,R*)-3k** 73% (15:1) >99% ee	**(*R,S*)-3k** 67% (>20:1) >99% ee	**(*S,S*)-3k** 73% (14:1) >99% ee
 **3o**	**(*R,R*)-3o** 64% (>20:1) >99% ee	**(*S,R*)-3o** 70% (11:1) >99% ee	**(*R,S*)-3o** 64% (10:1) >99% ee	**(*S,S*)-3o** 70% (>20:1) >99% ee

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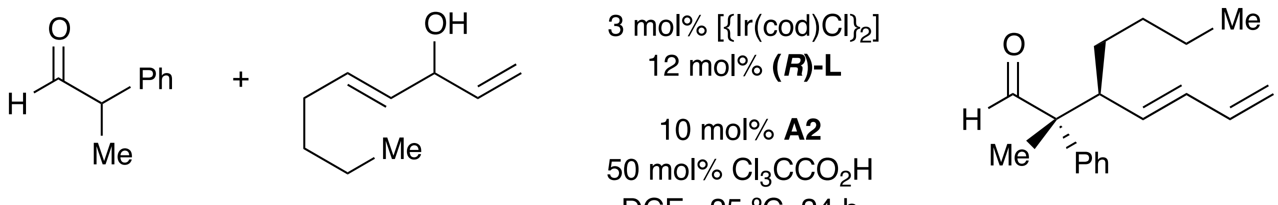
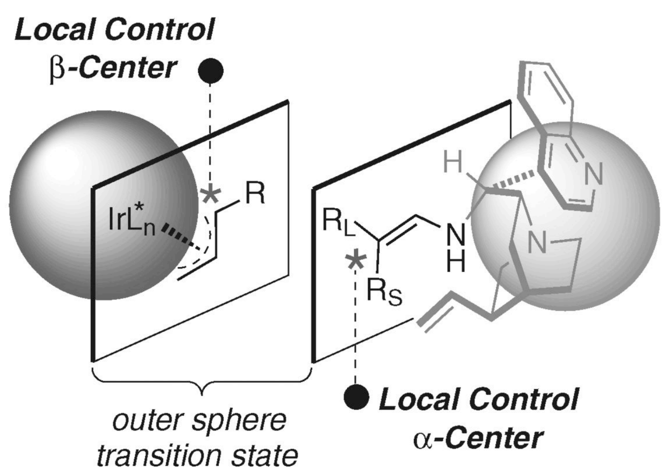
*Synthesis of diene **3x** and analysis*



1a 1.1 equiv | **2x** 0.25 mmol | **3x** 57% (5:1 d.r.) 98% ee



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Conclusion

- The authors have demonstrated an enantioselevtive α-allylation of branched aldehydes.
- This method delivers γ,δ-unsaturated aldehyde products bearing vicinal quaternary/tertiary stereocenters in good yields and excellent selectivities.