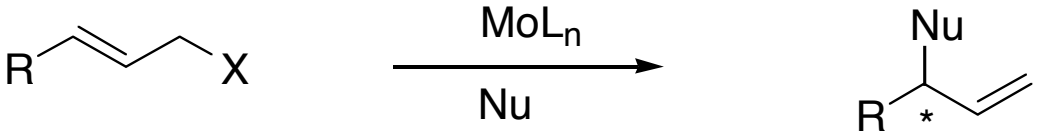
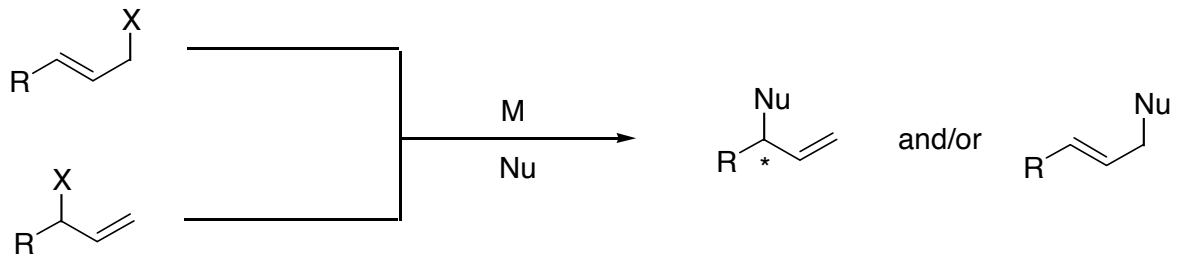
Molybdenum-Catalyzed Asymmetric Allylic Alkylation

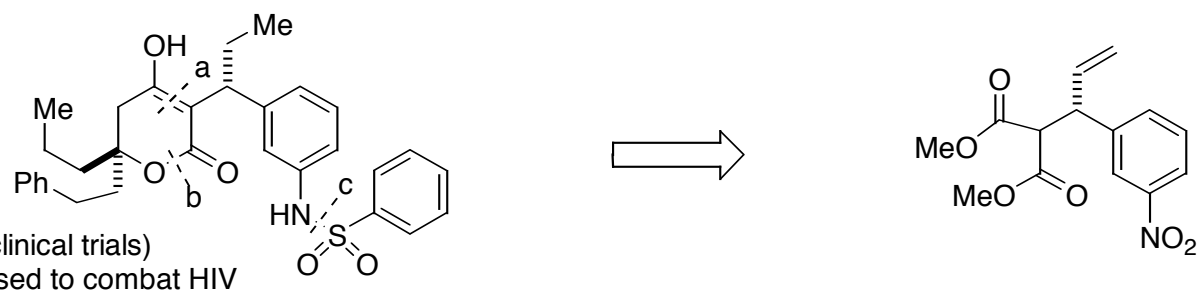


Tommy Bui
9/14/04

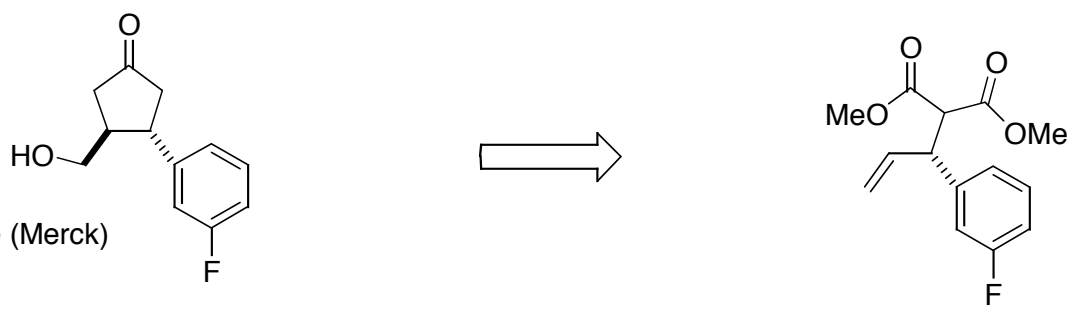
Asymmetric Allylic Alkylation from a Synthetic Viewpoint



- form a C-C bond with the creation of a new stereogenic center
- use readily accessible starting materials
- allow to an opportunity to perform dynamic kinetic transformation
- can be performed catalytically
- be able to predict the stereochemical outcome
- High regio-and enantioselectivity is achievable.

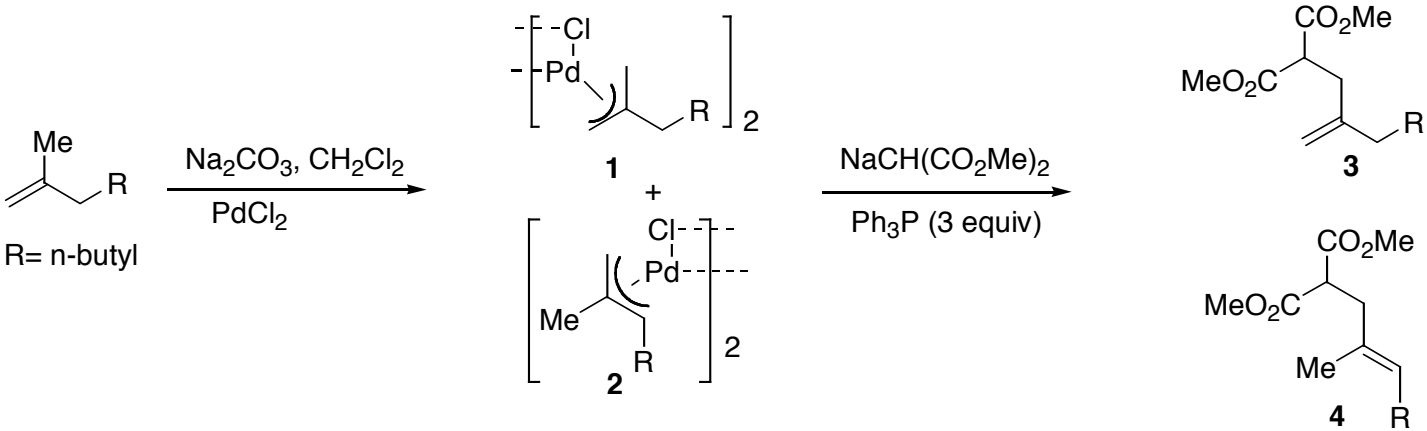


Typranavir (phase II clinical trials)
a therapeutic agent used to combat HIV



advanced intermediate (Merck)

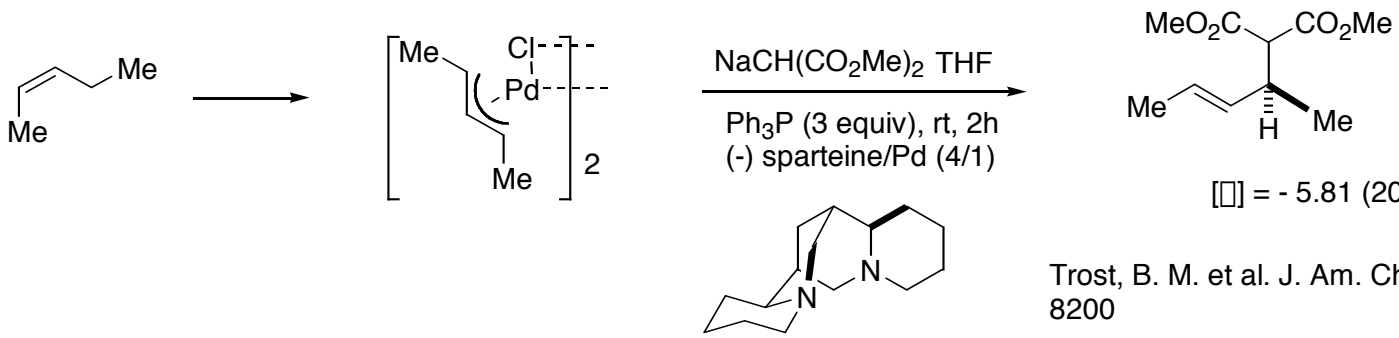
Allylic Alkylation from a Historical Viewpoint



63% isolated yield

Trost, B. M. et al. J. Am. Chem. Soc. 1973, 95, 292

Tsuji. J et al. J. Am. Chem. Soc. 1965, 84, 3275
(Addition of malonate Nu to cyclooctadiene activated by $PdCl_2$)

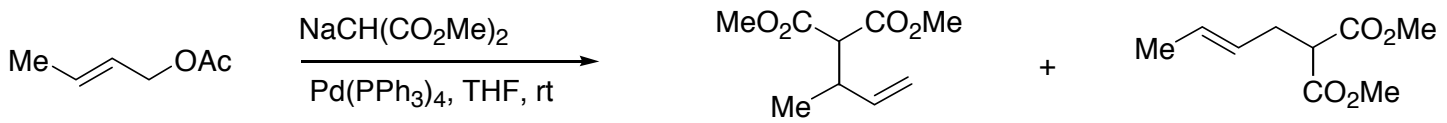


66% isolated yield

[□] = - 5.81 (20% optical yield)

Trost, B. M. et al. J. Am. Chem. Soc. 1973, 95, 8200

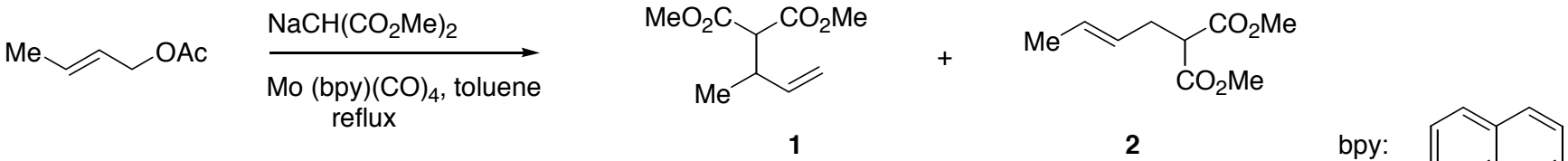
Regioselective Issue in Metal-Catalyzed Allylic Alkylation



1 **2**

89%, **1/2** = 50/50

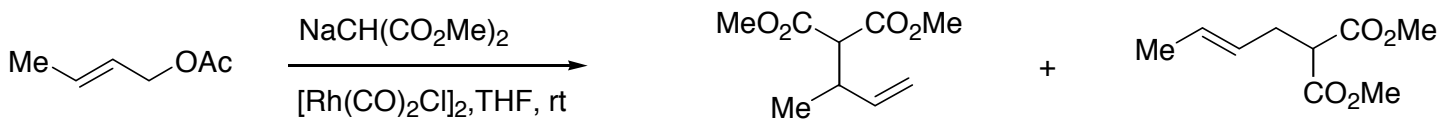
Keinan, E. et al. J.Chem. Soc. Chem. Comnun 1984, 648



1 **2**

75%, **1/2** = 95/5

Trost, B.M. et al. J. Am. Chem. Soc. 1982, 104, 5543



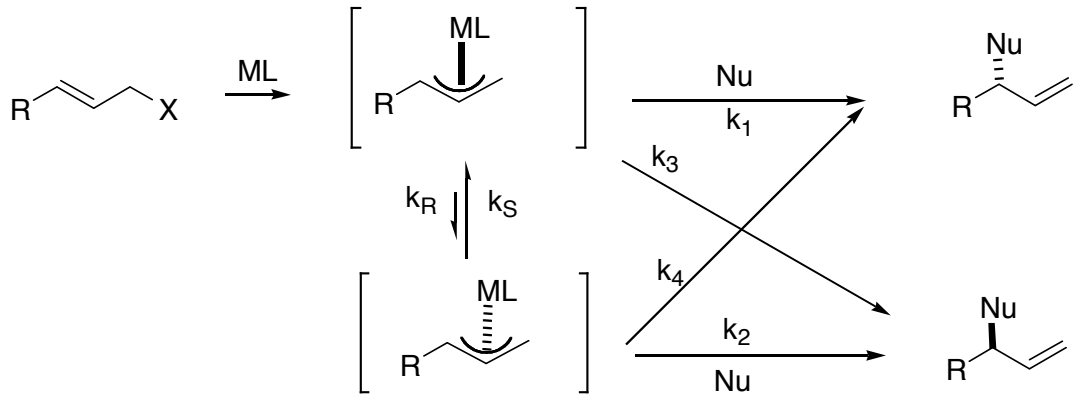
1 **2**

87%, **1/2** = 97/3

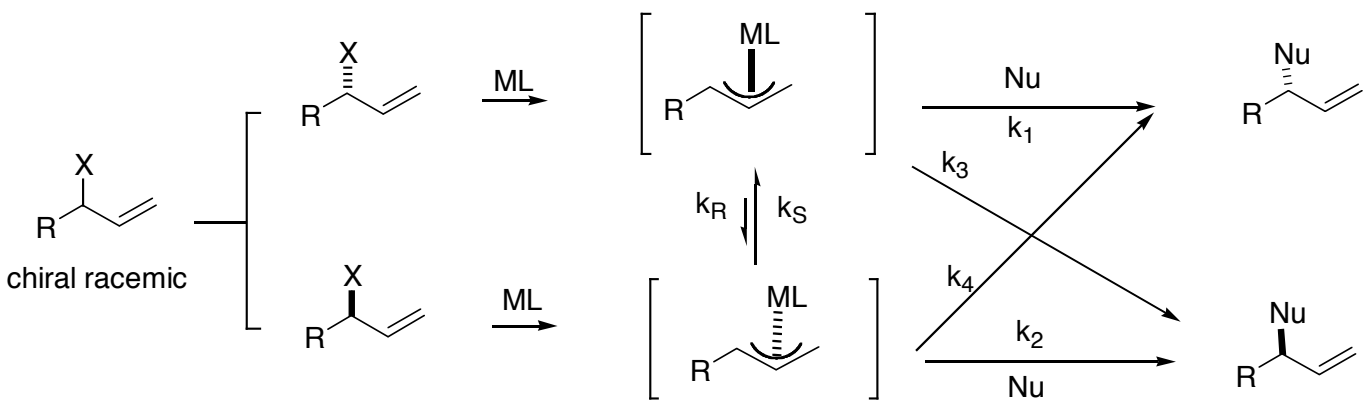
Martin, S. F. et al. J. Am. Chem. Soc. 2004, 6, 1321

General Mechanism

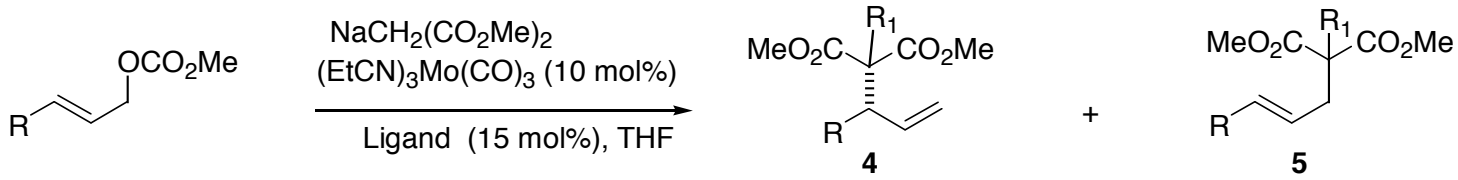
Linear

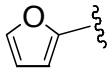


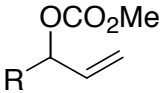
Branched substrate



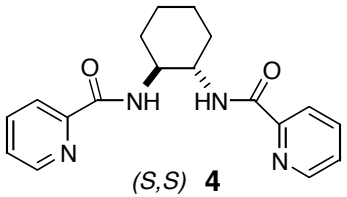
Molybdenum-Catalyzed Asymmetric Allylic Alkylation



entry	R	R_1	T, ^{0}C	time, h	yield	**4/5**	ee%
1	Ph	H	reflux	3	88	32/1	99
2	Ph	H	rt	3	70	49/1	99
3	Ph	Me	reflux	4	67	24/1	98
4		Me	reflux	2	71	32/1	97



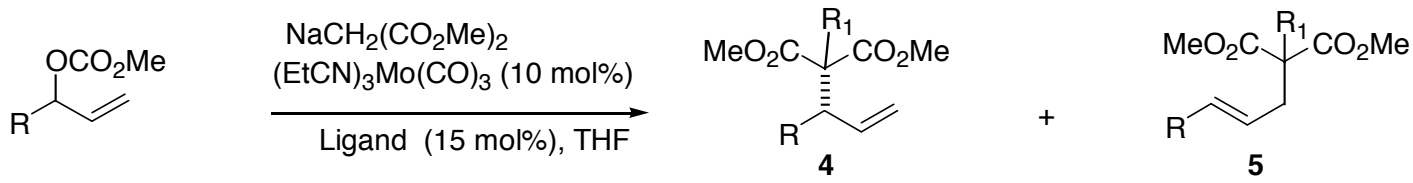
entry	R	R_1	T, ^{0}C	time, h	yield	**4/5**	ee%
1	Ph	H	reflux	3	70	13/1	92
2	Ph	H	rt	3	61	32/1	97
3	2-thienyl	H	reflux	2	78	19/1	88
4	2-pyridyl	H	reflux	2	69	8/1	87
5	2-pyridyl	Me	reflux	2	71	5/1	94
6	2-thienyl	Me	reflux	2	71	13/1	75



(S,S) **4**

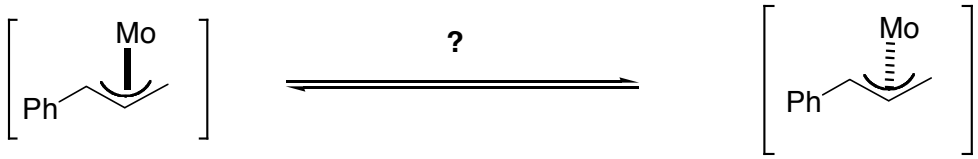
Trost, B.M. et al. *J. Am. Chem. Soc.* 1998, 120, 1104

Linear versus Branched : Mechanistic Implication



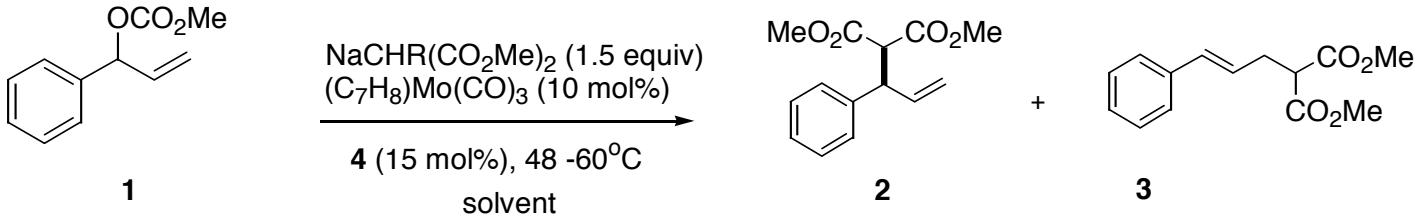
	entry	R	R_1	T, ^{0}C	time, h	yield	**4/5**	ee%
linear SM	1	Ph	H	reflux	3	88	32/1	99
	2	Ph	H	rt	3	70	49/1	99
branched SM	3	Ph	H	reflux	3	70	13/1	92
	4	Ph	H	rt	3	61	32/1	97

Whether □-allyl molybdenum complexation or the subsequent nucleophilic attack determines the stereochemical outcome of the product.

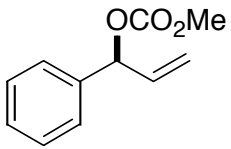


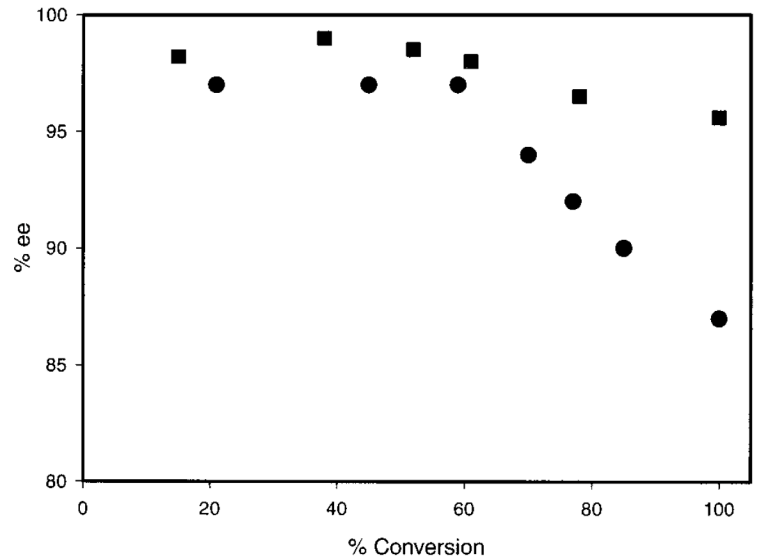
Trost, B.M. et al. *J. Am. Chem. Soc.* 1998, 120, 1104

Branched Substrates: Solvent Effects on Enantioselectivity



entry	Solvent	T, ^{0}C	**2/3**	ee%
1	THF	48	25/1	87
2	Toluene	60	46/1	97
3	MeCN	48	23/1	83

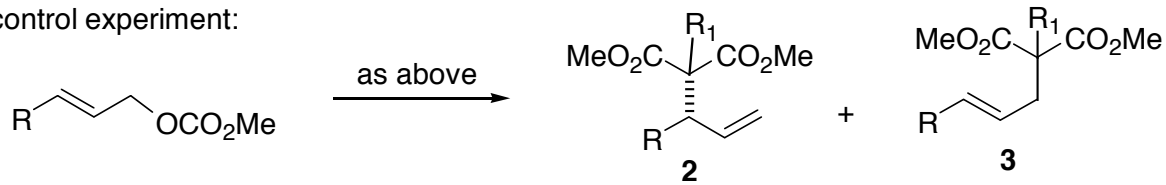




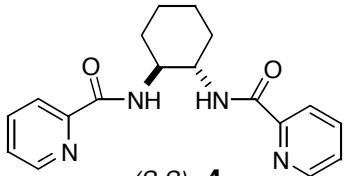
Reactions of **1** in THF (circles) and in toluene (squares)

(S) isomer is the fast-reacting enantiomer, 98% ee and 35/1 branched/linear selectivity during the first half of the reaction according to chiral HPLC traces and independent synthesis of **1**

control experiment:



2/3 = 35/1, 97% ee

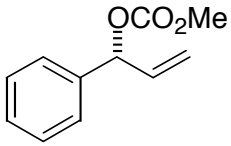


(S,S) **4**

Hughes, D.L .(Merck). *J. Org. Chem.* 2002, 67, 2762

Branched Substrates: Matched and Mismatched Cases

Matched case

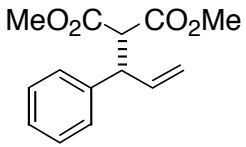


(R)-ent. 1

obtained by kinetic resolution

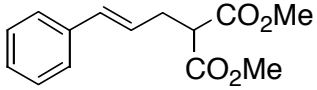
$NaCHR(CO_2Me)_2$ (1.5 equiv)
$(C_7H_8)Mo(CO)_3$ (10 mol%)

(R,R) 4 (15 mol%), 48 °C
THF



(S) **2**

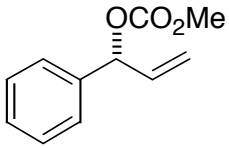
+



3

2/3 = 55/1, > 99% ee

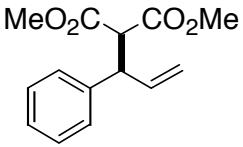
Mismatched case



(R)-ent. 1

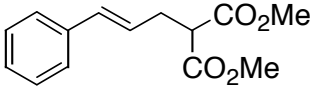
same rxn conditions

(S,S) 4



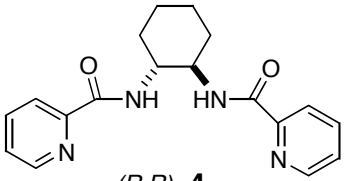
(R) **2**

+

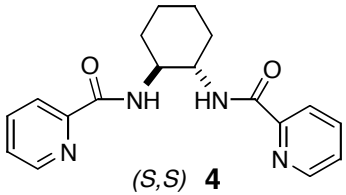


3

2/3 = 12/1, 70% ee



(R,R) **4**



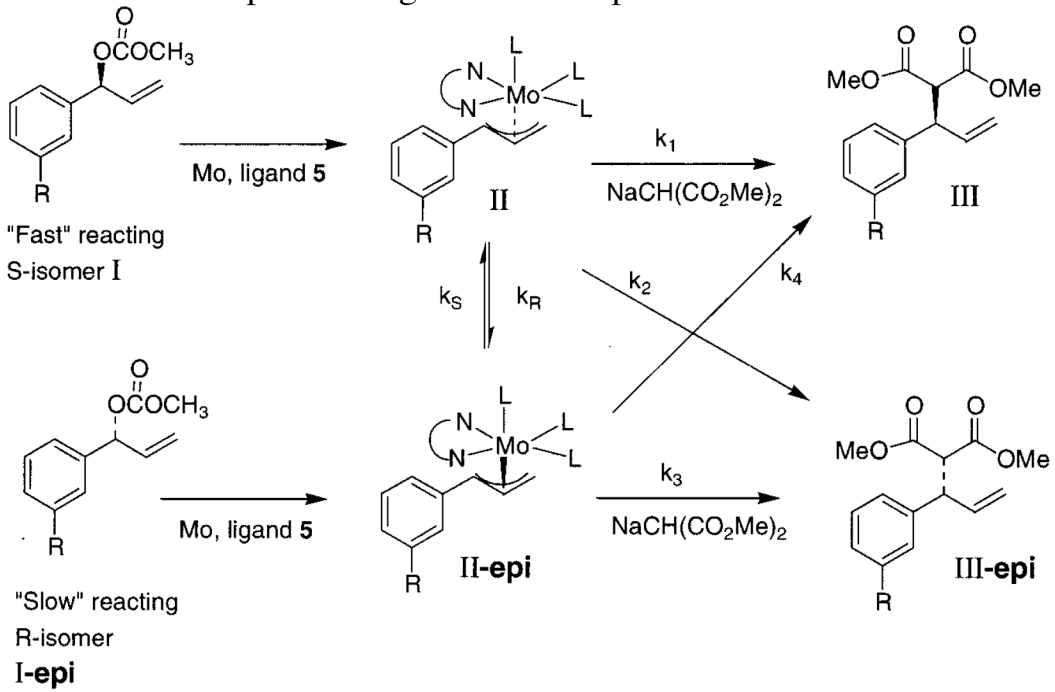
(S,S) **4**

"modest stereochemical memory effect"

Hughes, D.L .(Merck). *J. Org. Chem.* 2002, 67, 2762

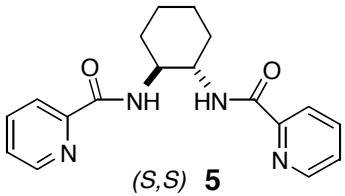
Possible Explanation for Solvent Effects on Selectivity

Since both carbonate enantiomers give the same major alkylated product when the same catalyst enantiomer is used, diastereomeric equilibration must take place along the reaction path.



If K_S and K_R are fast relative to k1,k2,k3, and k4, then enantioselectivity is under Curtin-Hammett control. Thus, the concentration of II and II-epi diastereomers is not important.

Experimentally, the two carbonate enantiomers do not give the same ee and branched/linear ratio. This suggests that the rate of equilibration of II and II-epi must be competitive with the nucleophilic displacement steps.



Hughes, D.L .(Merck). *J. Org. Chem.* 1998, 120, 1104

Efforts towards Understanding Molybdenum-Ligand Interactions

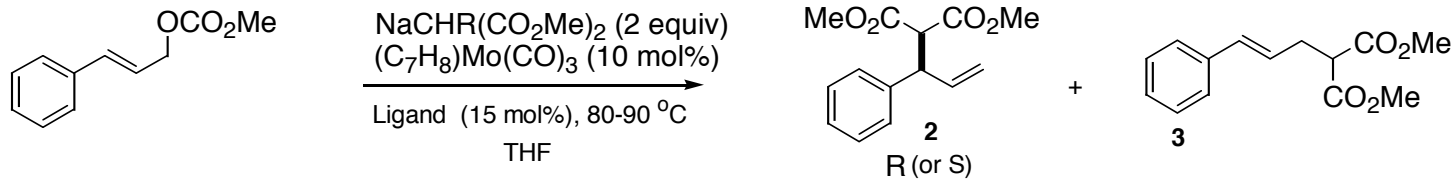


Table 1: chelating effects

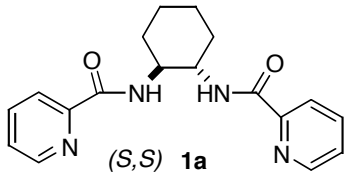
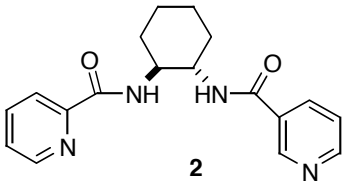
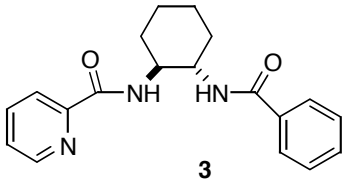
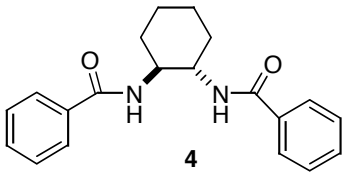
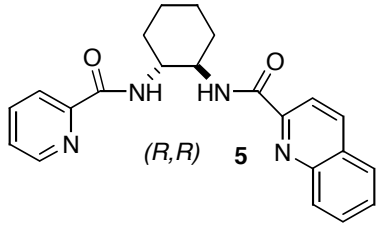
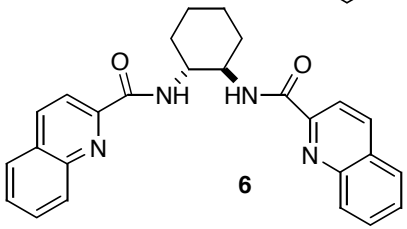
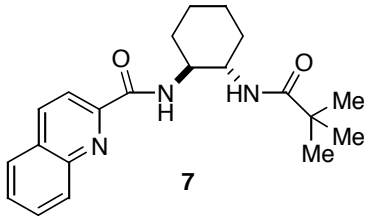
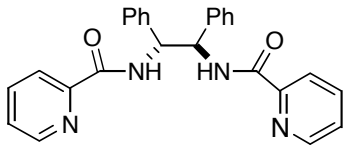
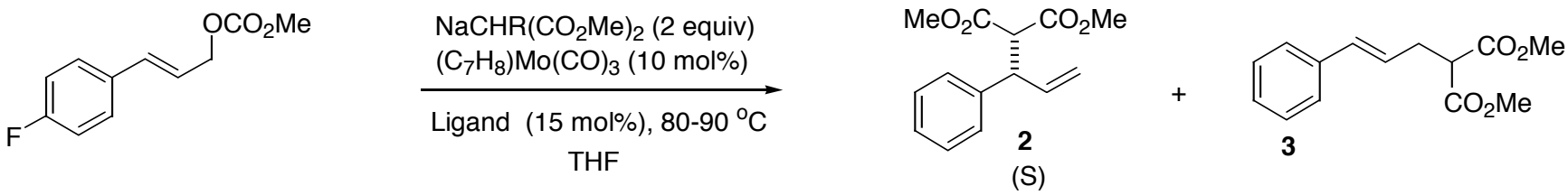
entry	ligand	yield (%)	**2/3**	ee%
1	 (S,S) **1a**	95	35/1	97 (R)
2	 **2**	93	46/1	99
3	 **3**	90	60/1	99
4	 **4**	35	1/1	24

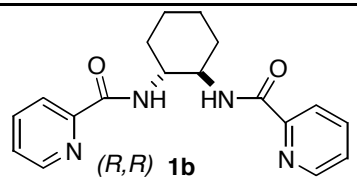
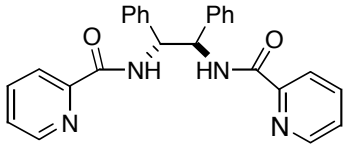
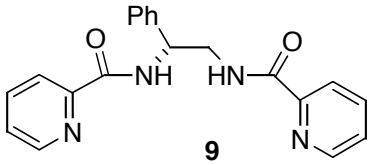
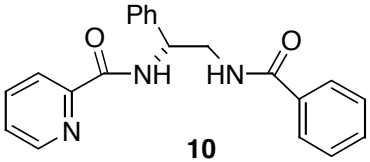
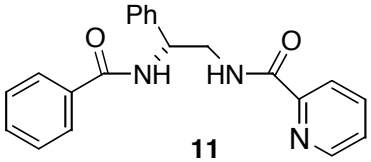
Table 1: steric effects

entry	ligand	yield (%)	**2/3**	ee%
5	 (R,R) **5**	29	19/1	98 (S)
6	 **6**	trace	-	-
7	 **7**	95	30/1	98
8	 **8**	95	19/1	99

Trost, B.M. and Hughes, D.L.(Merck) *Angew. Chem. Int. Ed.* 2002, 41, 1929

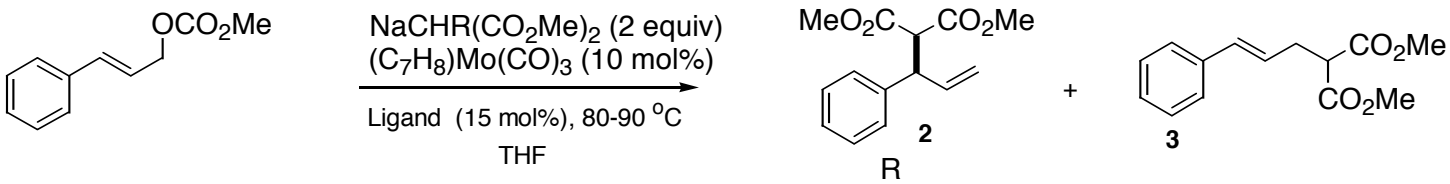
Variation in the Chiral Backbone of Ligands

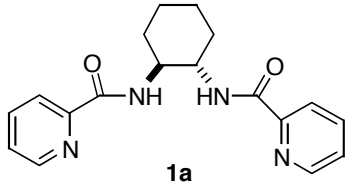


entry	ligand	yield (%)	2/3	ee%
1	 (R,R) **1b**	93	13/1	96 (S)
2	 **8**	84	10/1	94
		two fold increase in rate		
3	 **9**	92	6/1	91
5	 **10**	43	9/1	77
6	 **11**	72	8/1	90

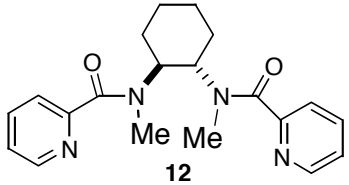
Trost, B.M. and Hughes, D.L.(Merck) *Angew. Chem. Int. Ed.* 2002, 41, 1929

The Role of the Secondary Amide Nitrogens

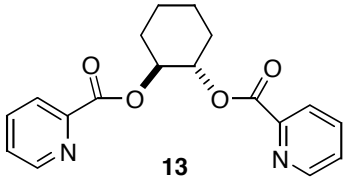




2/3 = 35/1 95% yield 97% ee



200-fold less active than **1a**
poor enantioselecitivity

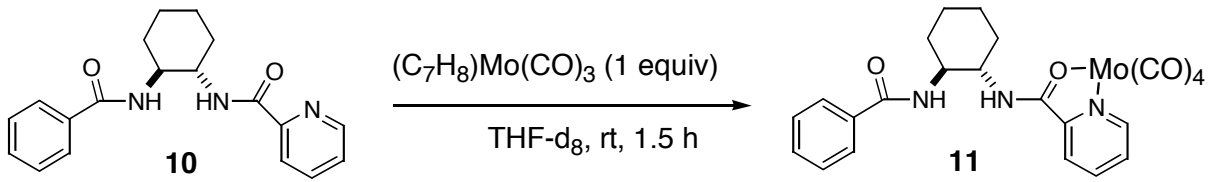


no observable reaction

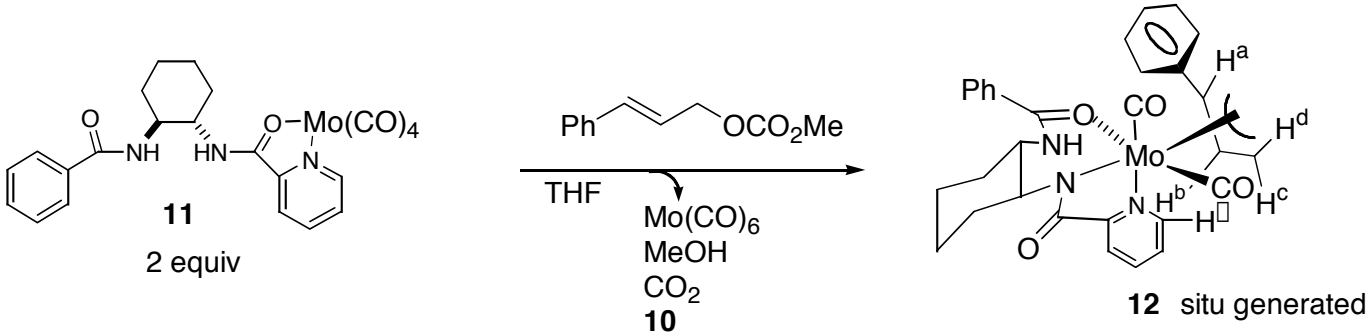
Amide nitrogens is crucial for achieving catalytic activity

Trost, B.M. and Hughes, D.L.(Merck) *Angew. Chem. Int. Ed.* 2002, 41, 1929

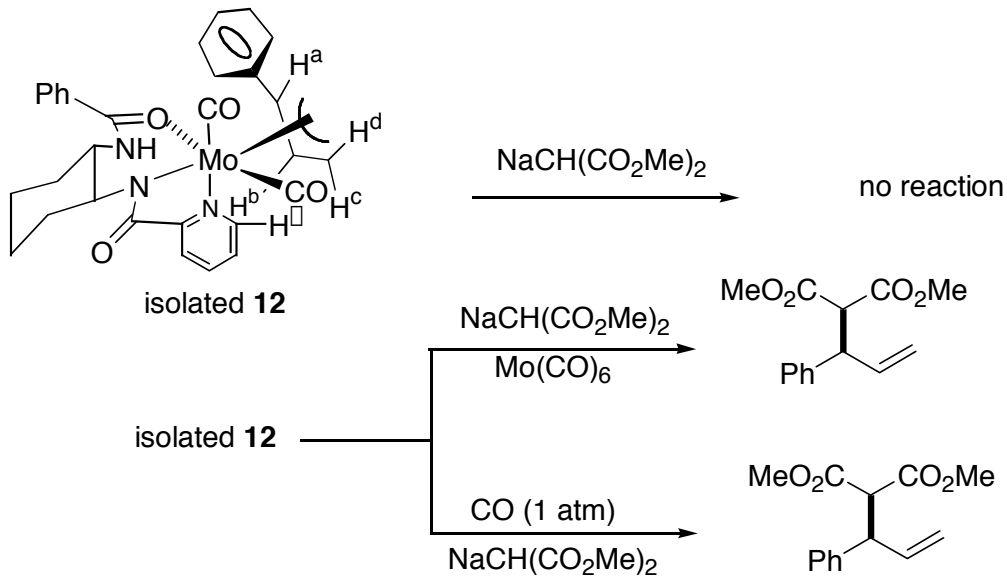
Attempt to identify the Catalytically Active Species



^{15}NNMR
Amide nitrogens: 133 ppm, 123 ppm
118 ppm, 119 ppm (free ligand)
Pyridine nitrogen: 273 ppm
304 ppm (free ligand)



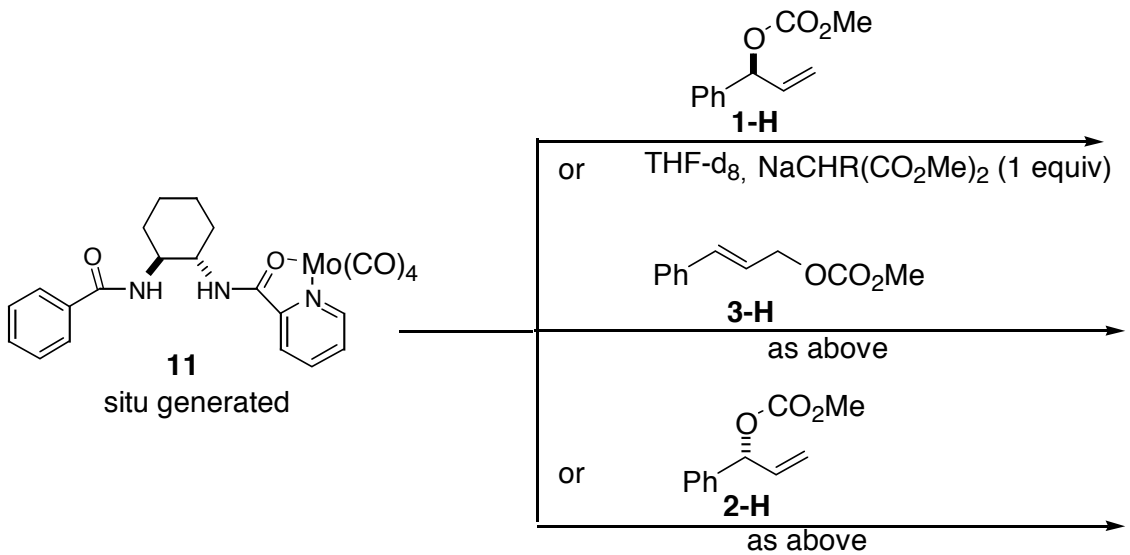
Amide N: 130 ppm, 175 ppm
118 ppm, 119 ppm (free ligand)
Pyridine N: 263 ppm
304 ppm (free ligand)

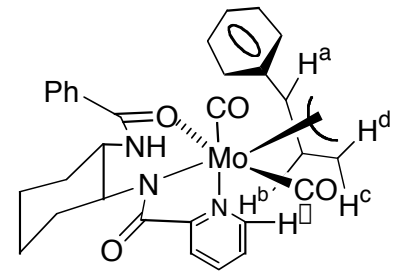


A CO source is needed for achieving catalytic activity.

Trost, B.M.; Hughes, D.L. (Merck) *J. Am. Chem. Soc.* 1998, 124, 1656

Solution and Solid State Studies of the Reactive Intermediate

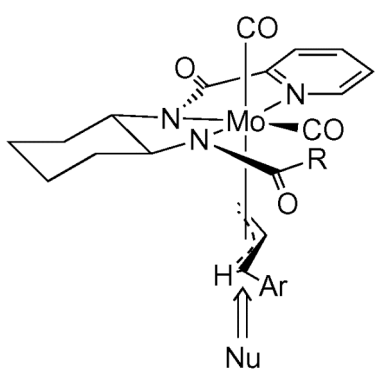




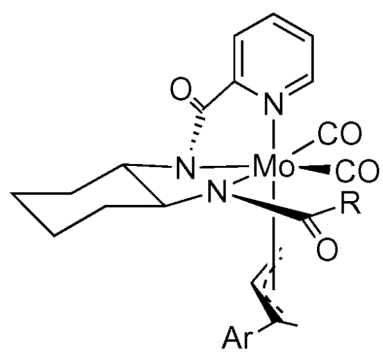
12

Amide N: 130 ppm, 175 ppm
118 ppm, 119 ppm (free ligand)
Pyridine N: 263 ppm
304 ppm (free ligand)

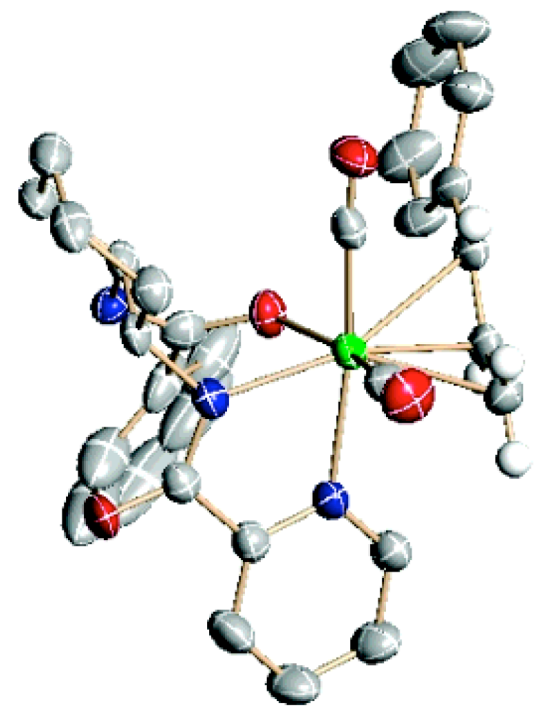
Other structures:



A

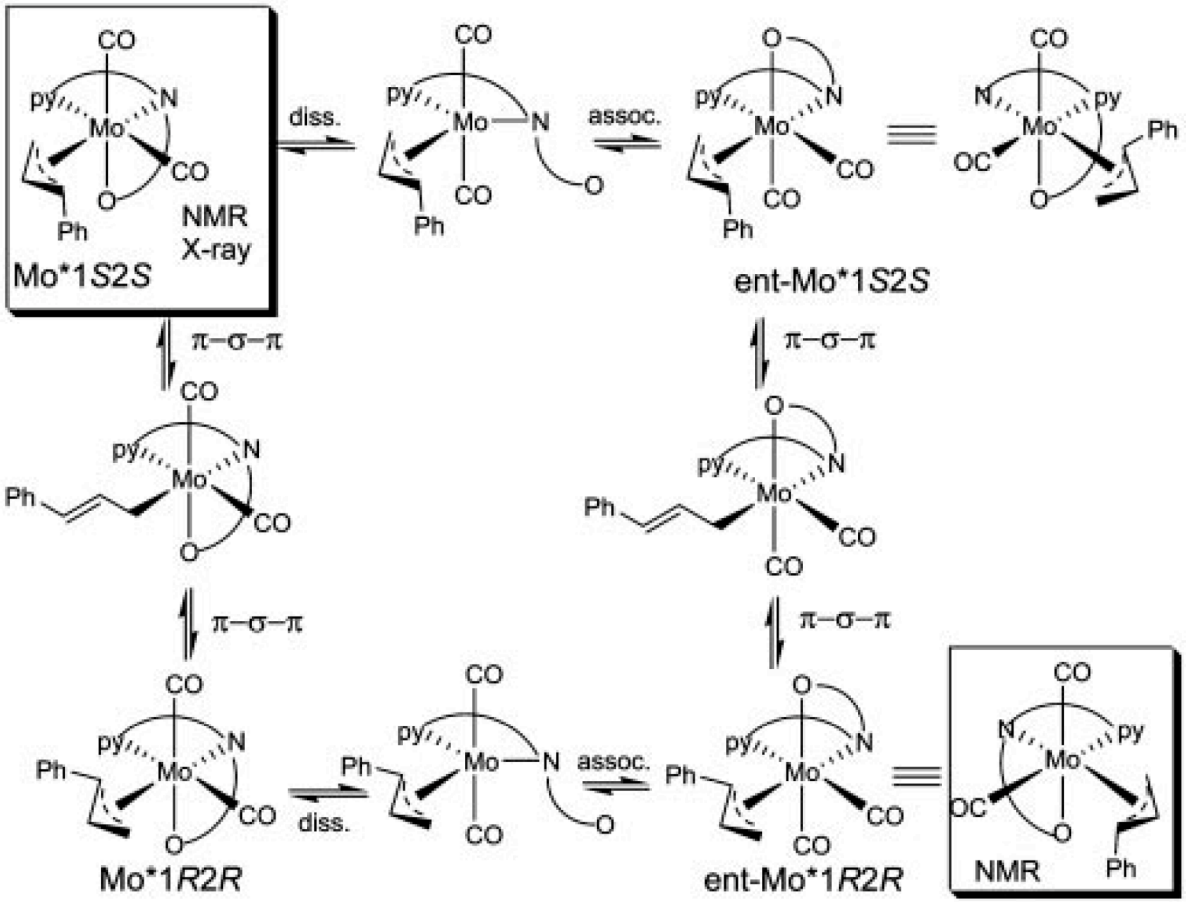


B



Trost, B.M.; Hughes, D.L. (Merck) *J. Am. Chem. Soc.* 2002, 124, 12656
Hughes, D.L. (Merck) Pro. *Nat. Acad. Sci.* 2004, 101, 5379

Possible Pathways for π-allyl Intermediates to Interconvert



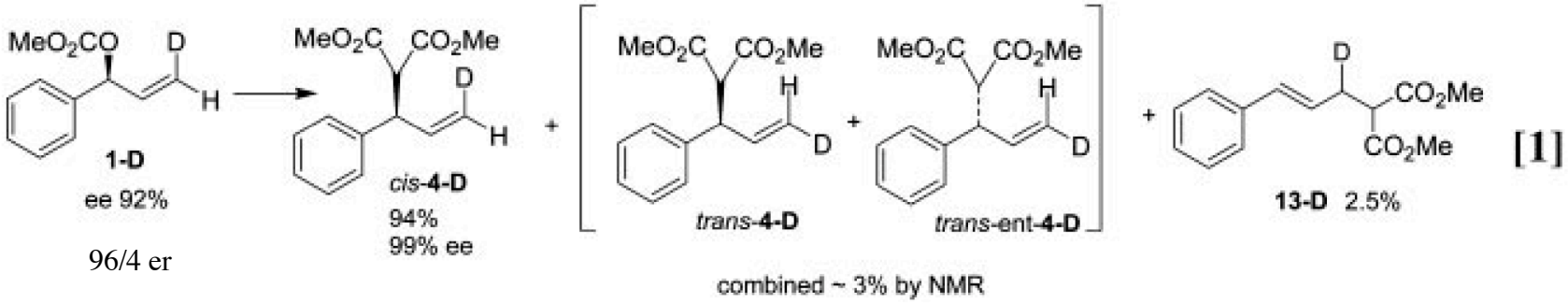
Mechanistic possibilities:

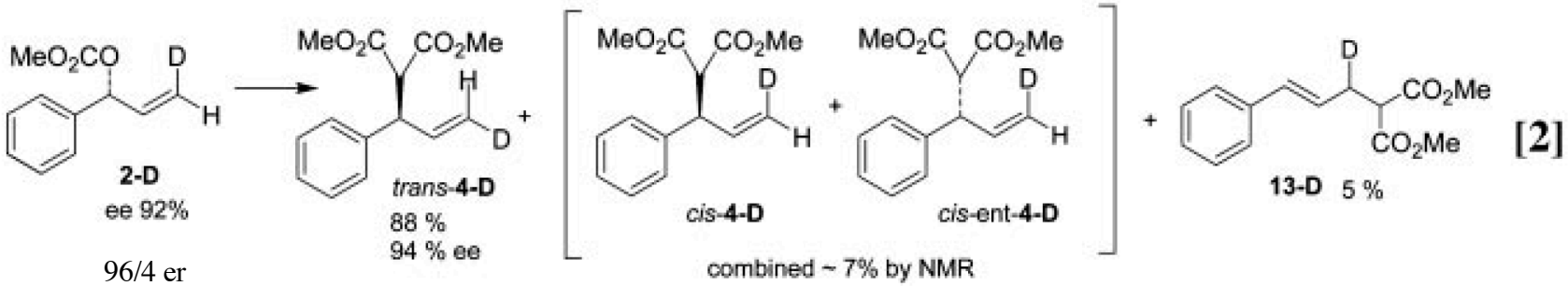
1. Mo*1S2S isomer recrystallizes preferentially and Nu attacks Mo*1R2R isomer with inversion.
2. Mo*1S2S and Mo*1R2R are in rapid equilibrium, and Mo*1R2R is the more reactive intermediate and reacts by inversion (selectivity is under Curtin-Hammett control).
3. Mo*1S2S isomer in solution and crystal and the nucleophilic addition occurs with retention of configuration.

Trost, B.M.; Hughes, D.L. (Merck) *J. Am. Chem. Soc.* 2002, 124, 12656

Hughes, D.L. (Merck) Pro. *Nat. Acad. Sci.* 2004, 101, 5379

Deterium-Labeling Experiments



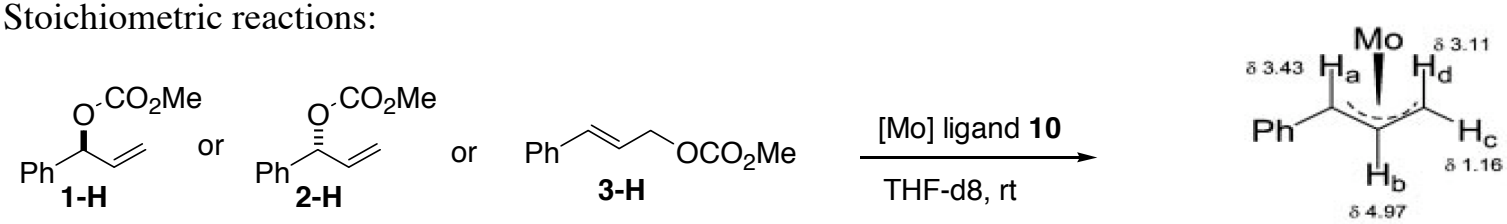


1. In reaction [1] about 3% of trans-4-D corresponds well with the 4% enantiomer present in the SM. This means that little or no scrambling of the deuterium occurs in the reaction.
2. In reaction [2], about 7% nontransposed product indicates that no more than 3% of the reaction can occur with scrambling of the label since the SM has 96/4 er.
   and reacts by inversion (selectivity is under Curtin-Hammett control).

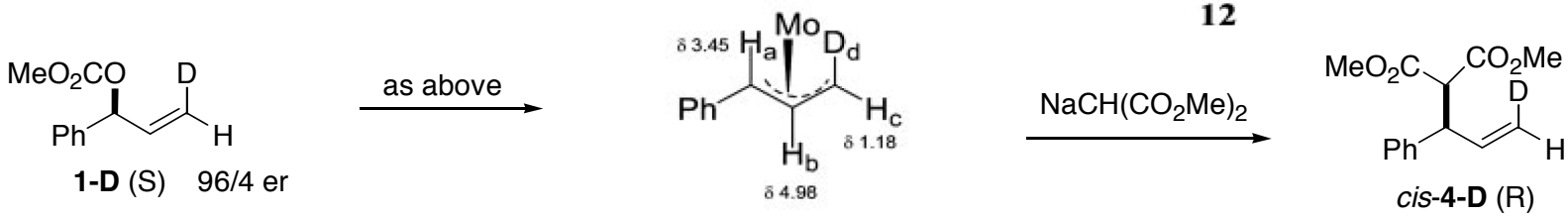
Hughes, D.L. (Merck) Pro. *Nat. Acad. Sci.* 2004, 101, 5379

^{1}H NMR Studies of π-Allyl Molybdenum Complexes

Stoichiometric reactions:

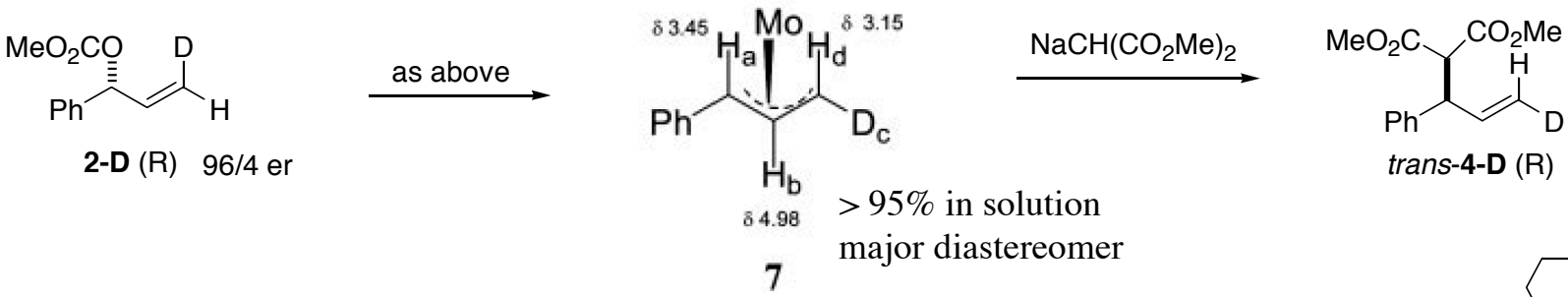


[1]



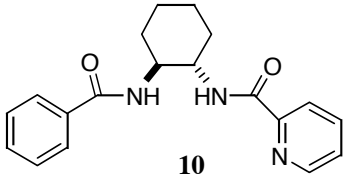
[2]

5 95% in solution
major diastereomer



[3]

7 > 95% in solution
major diastereomer

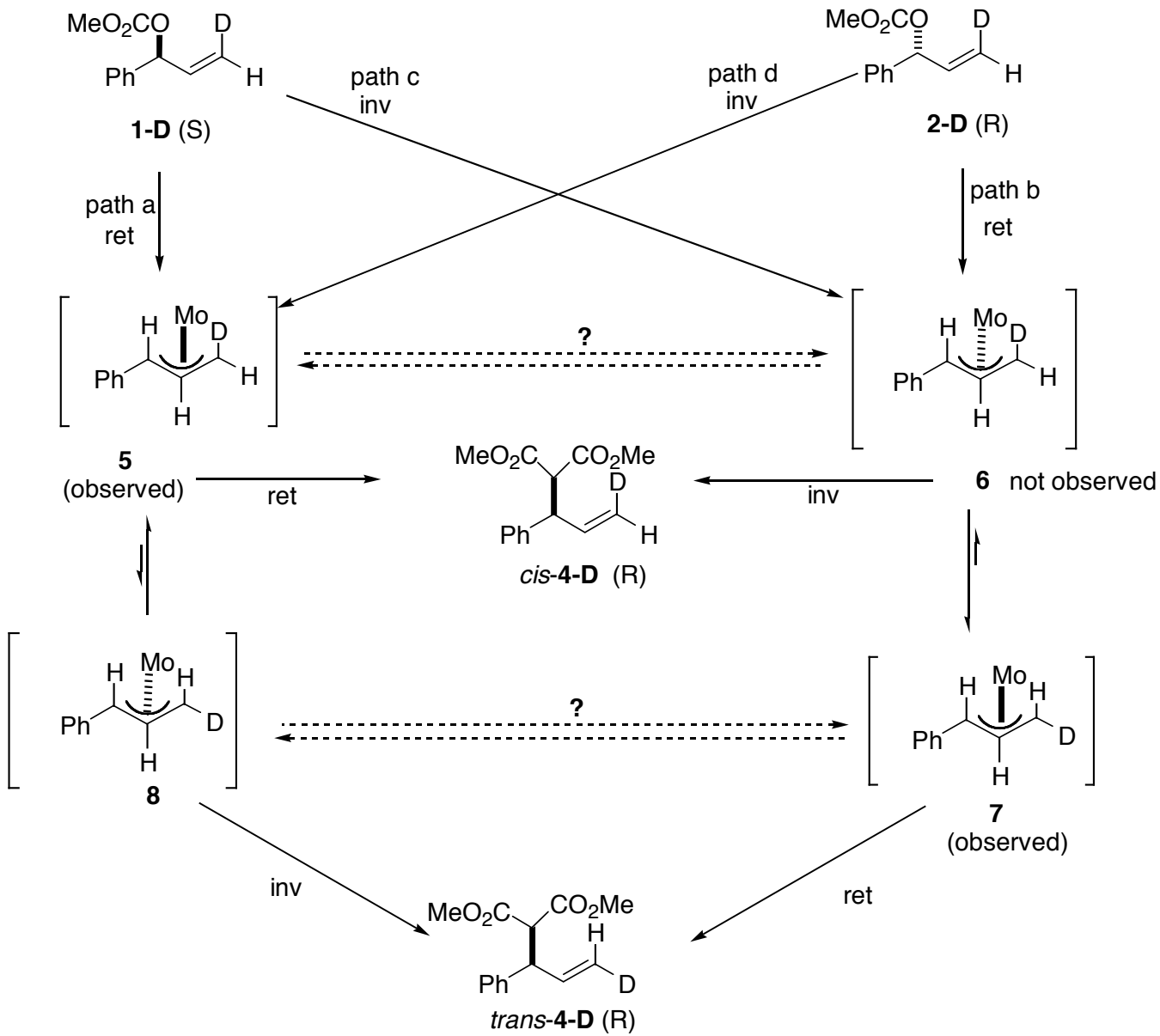


10

The results of experiments 1 & 2 confirm that the reaction proceeds by retention-retention pathway.

Hughes, D.L. (Merck) Pro. *Nat. Acad. Sci.* 2004, 101, 5379

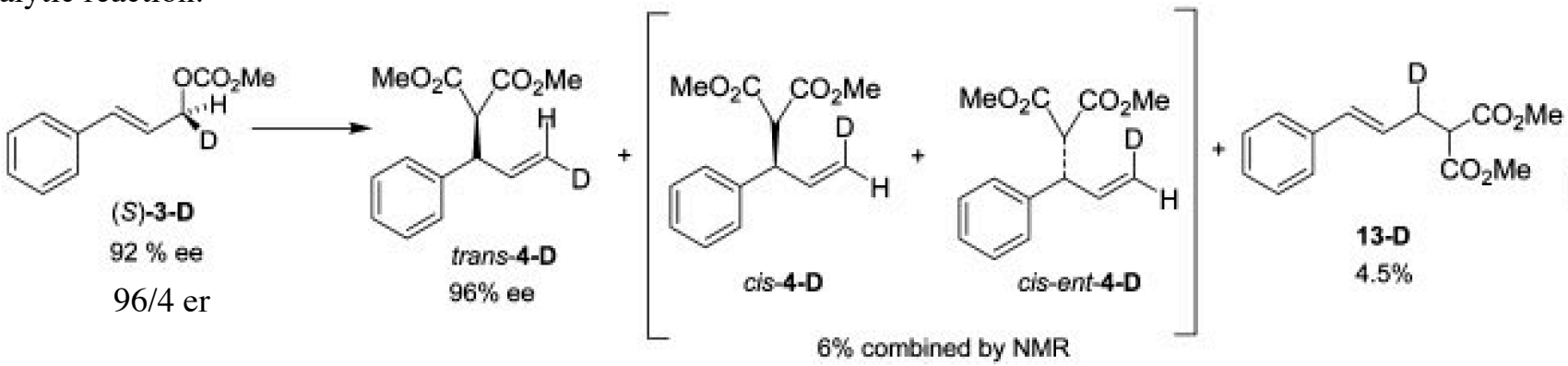
Mechanistic Pathways for the Formation of Cis-4-D and Trans-4-D Products



Hughes, D.L. (Merck) Pro. *Nat. Acad. Sci.* 2004, 101, 5379

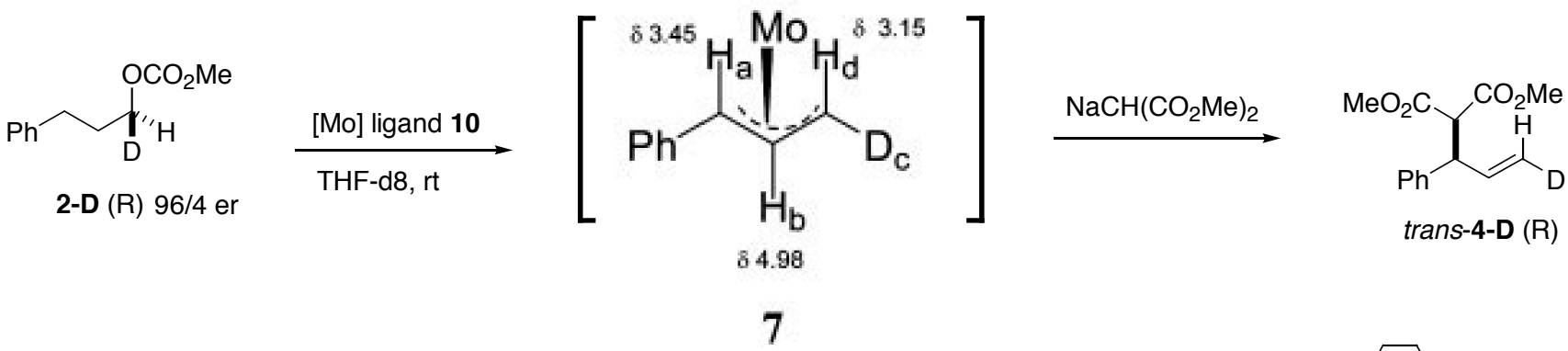
Linear Chiral Allylic Substrates

Catalytic reaction:

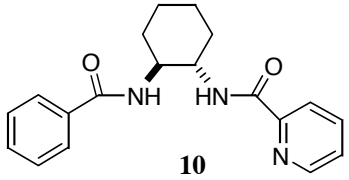


Less than 2% of oxidative addition occurred with inverted stereochemistry

Stoichiometric reaction:



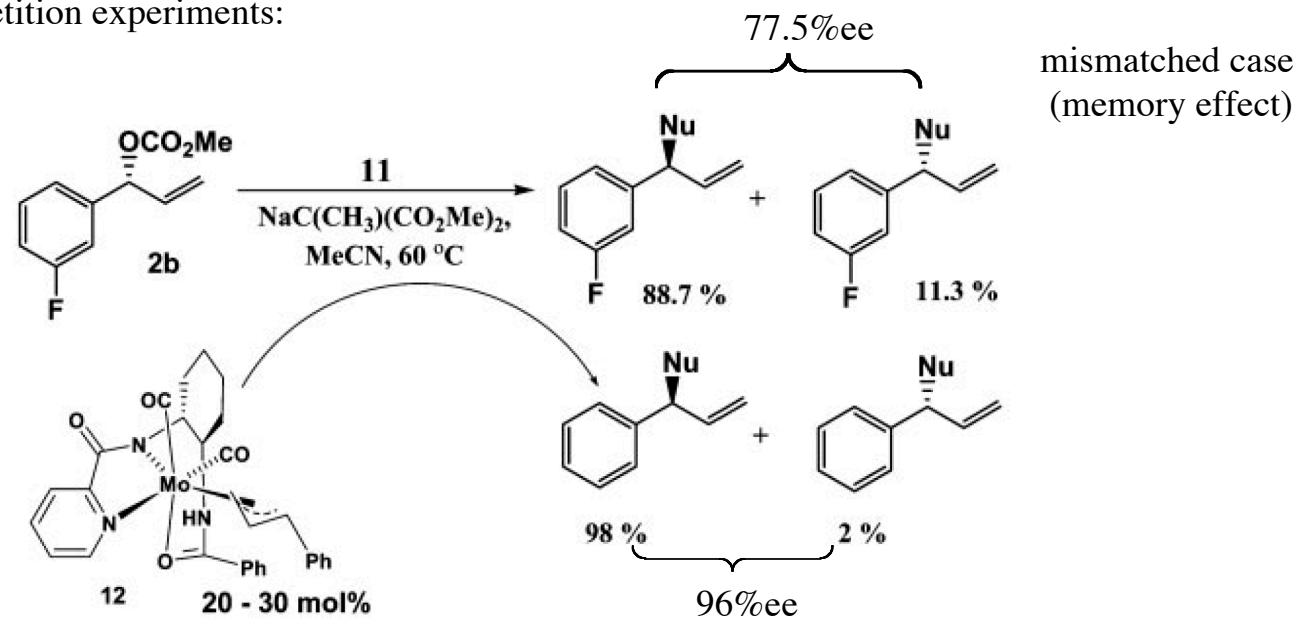
Again, the reaction proceeds by a double retention pathway.

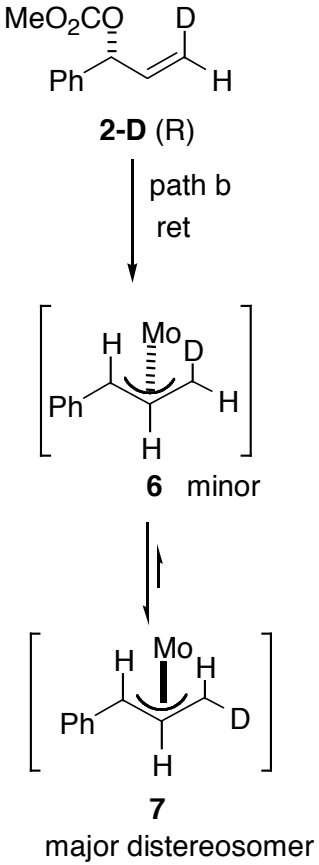


Hughes, D.L. (Merck) Pro. *Nat. Acad. Sci.* 2004, 101, 5379

The X-ray Structure of the Protio Complex vs its Solution Structure

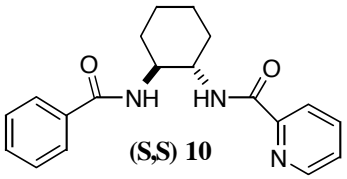
Competition experiments:

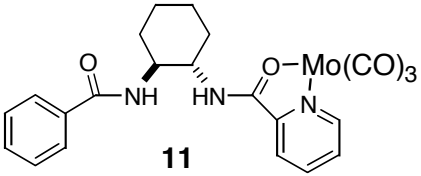




If **12** was the minor isomer and required equilibration to the major isomer (**7**) before undergoing nucleophilic addition, then both the 3-F substituted and unsubstituted products should exhibit a memory effect and have similar, low ee.

If **12** is the major complex (**7**) and requires no equilibration, then a high ee should result.

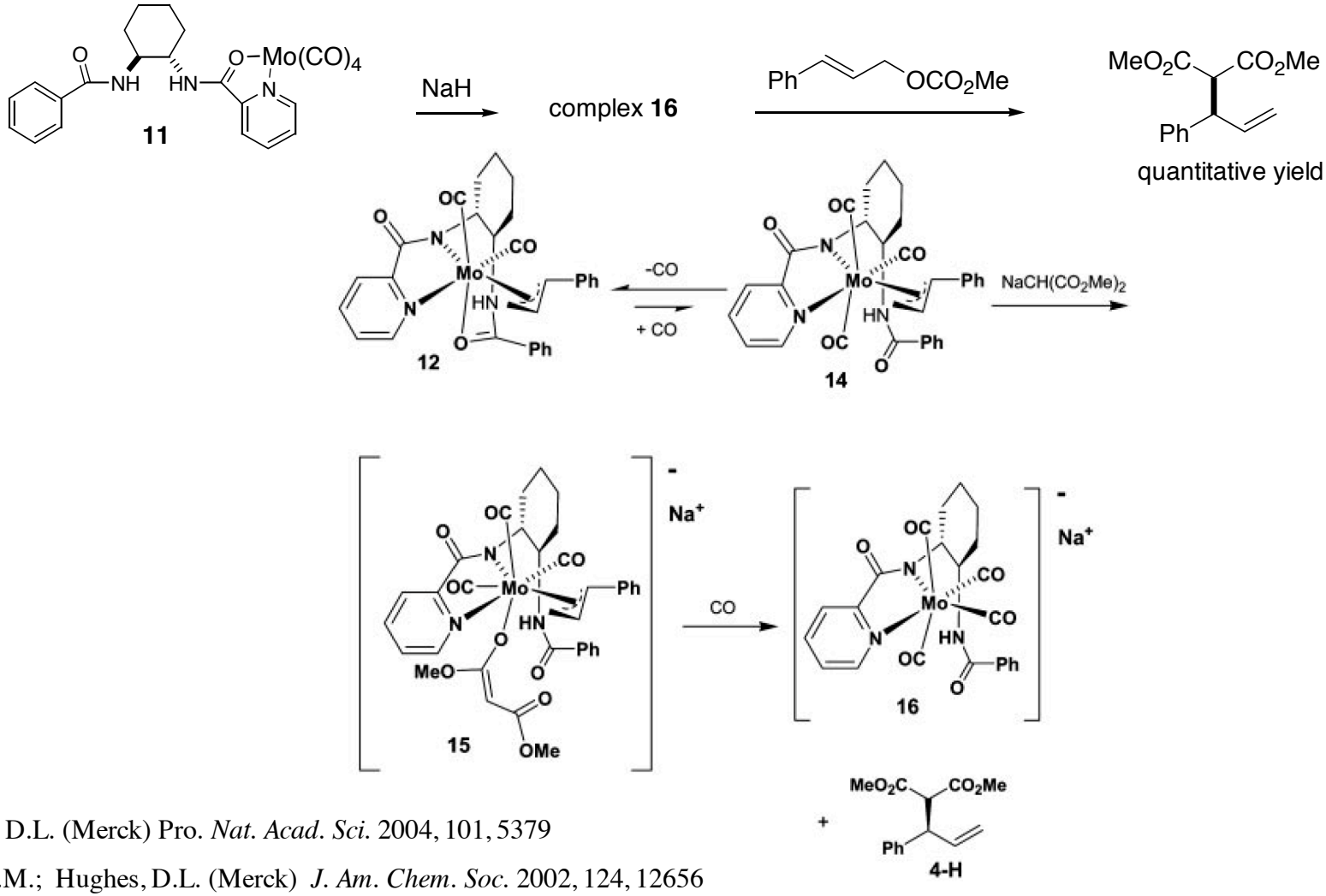




Hughes, D.L. (Merck) Pro. *Nat. Acad. Sci.* 2004, 101, 5379

Proposed Mechanism for Product Formation

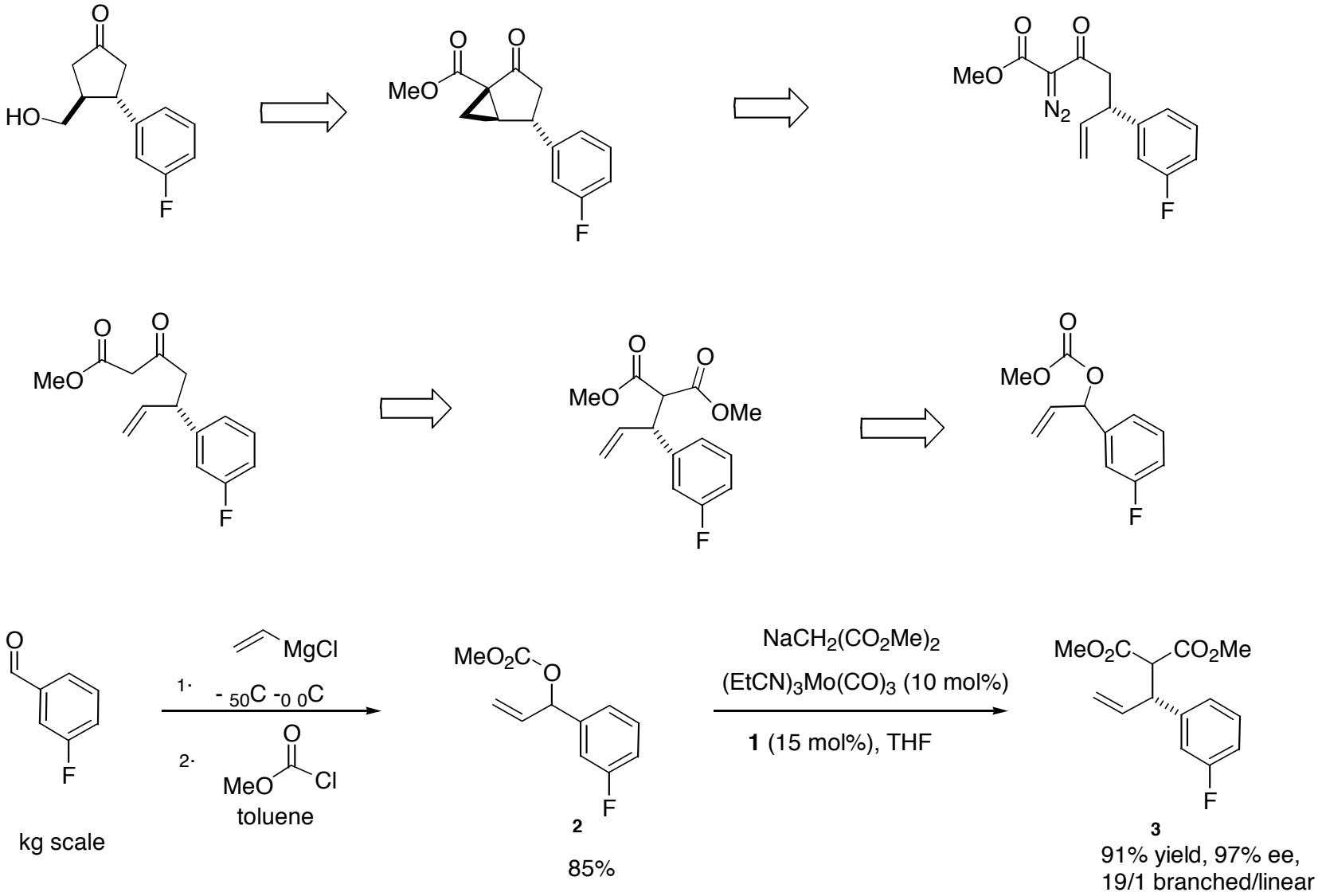
- The ligand binds to Mo in a tridentate fashion
- CO is imperative for the reaction to take place
- Allyl substrates react with overall retention of configuration
- S,S catalyst gives product with R configuration
- Independent synthesis of **16** which has activity the same as that of **12**



Hughes, D.L. (Merck) Pro. *Nat. Acad. Sci.* 2004, 101, 5379

Trost, B.M.; Hughes, D.L. (Merck) *J. Am. Chem. Soc.* 2002, 124, 12656

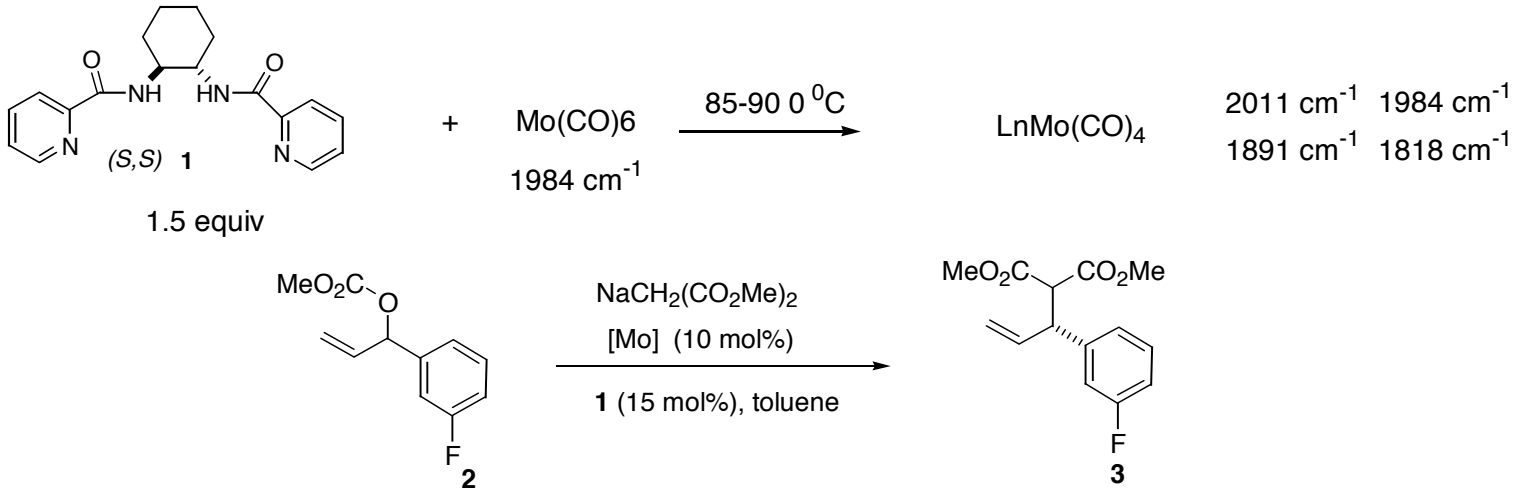
Application of Molybdenum-Catalyzed Asymmetric Allylic Alkylation



Heating $(EtCN)_3Mo(CO)_3$ can generate ethylene and HCN, thus raising a safety issue.

Palucki, M .(Merck). *J. Org. Chem.* 2002, 67, 5008

Searching for Different Molybdenum Precatalysts



Entry	Solvent	Activation Time (h)	Activation Temp(°C)[c]	% ee of 3[b]	Branched : Linear	% Assay Yield[d]
1	toluene	0.75	85	95	95 : 5	77
2	toluene	4	85	97	95 : 5	91(84)
3	toluene	15	85	89	92 : 8	91

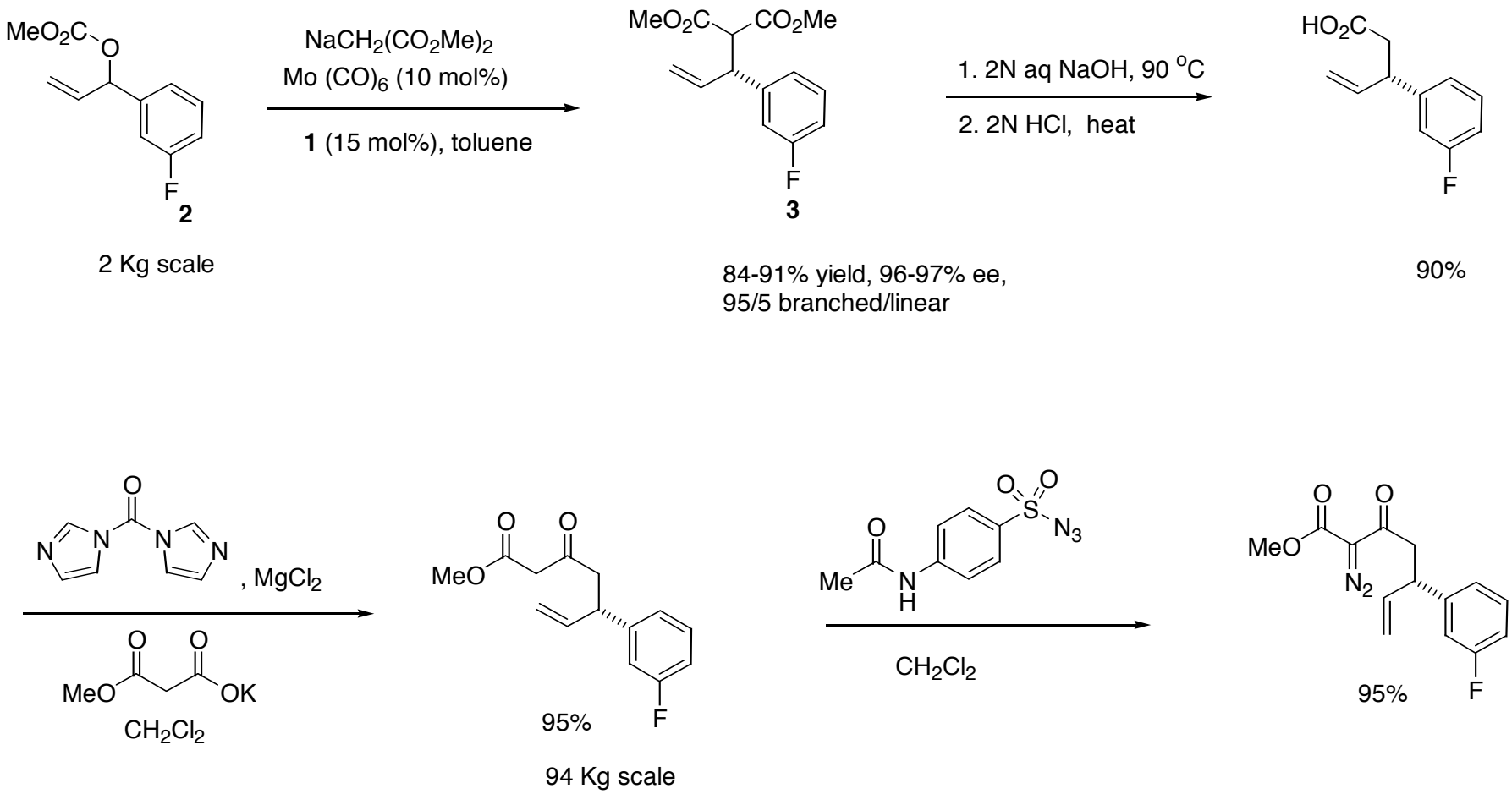
[a] Reaction conditions: 10 mol% $Mo(CO)_6$, 15 mol% ligand **1**, 2.0 equiv dimethyl sodiomalonate, 0.15 M substrate **2**, reaction time: 8–12 h.
[b] Determined by HPLC using a chiral column (CHIRALPAK AD, 25 cm × 4.6 mm, 10 μm particle diameter).
[c] The activation temperature [$Mo(CO)_6$ + ligand **1** in solvent] is also the alkylation reaction temperature.
[d] Yield in parentheses represent isolated product yield with purity > 95% as determined by HPLC and ^1H NMR.

Entry	Mo-precatalyst[b]	Solvent	Activation Time (h)	Activation Temp(°C)[c]	% ee of 3[d]	Branched:Linear	% Assay Yield of 3
1	$(EtCN)_3Mo(CO)_3$	toluene	0.5	85	95	93 : 7	84
2	$(C_7H_8)Mo(CO)_3$	toluene	0.5	85	96	96 : 4	87
3	$Mo(CO)_6$	toluene	4	85	97	95 : 5	91

[a] Results represent the average of two or more runs.
[b] $(EtCN)_3Mo(CO)_3$ was prepared using a literature procedure, see reference 7.
[c] The activation temperature [$Mo(CO)_6$ + ligand **1** in solvent] is also the subsequent alkylation reaction temperature.
[d] Determined by HPLC using a chiral column (CHIRALPAK AD, 25 cm × 4.6 mm, 10 μm particle diameter).

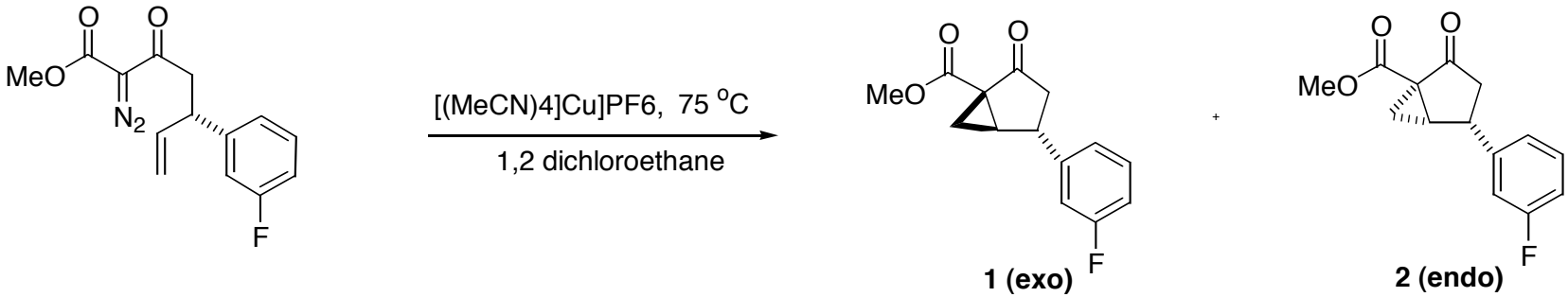
Palucki, M .(Merck). *Adv. Synth. Catal.* 2001, 343, 46

Molybdenum-Catalyzed Asymmetric Allylic Alkylation in Large Scale Synthesis

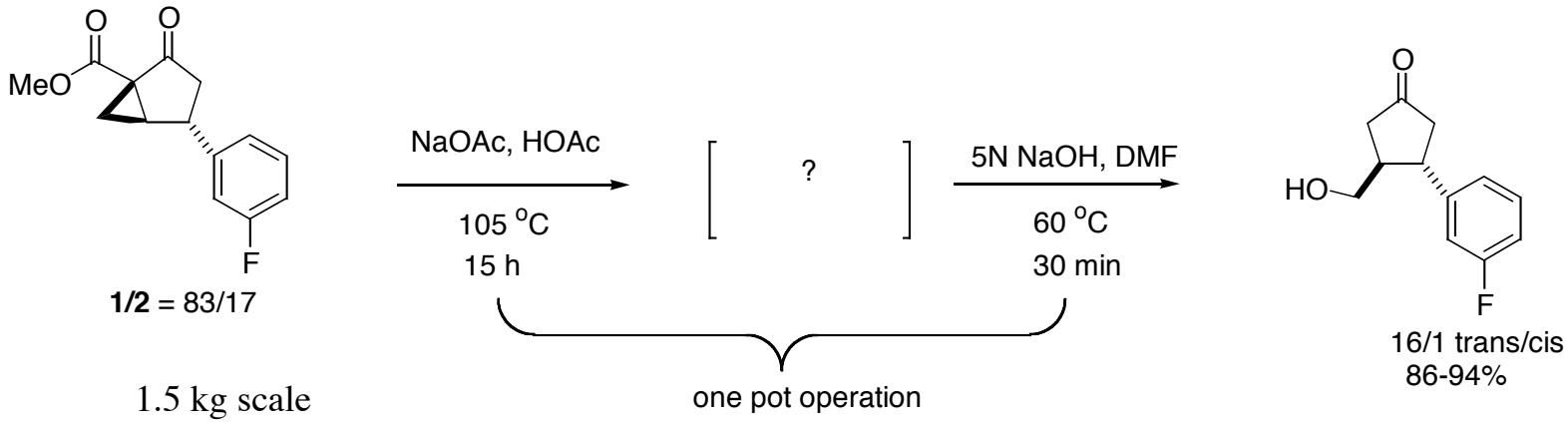


Palucki, M .(Merck). *J. Org. Chem.* 2002, 67, 5008

Completion of the Synthesis



1/2 = 83/17, 98% yield



1/2 = 83/17

1.5 kg scale

16/1 trans/cis
86-94%

56% overall yield starting from 3-fluorobenzaldehyde.

Palucki, M .(Merck). *J. Org. Chem.* 2002, 67, 5008

Summary

- Molybdenum-catalyzed allylic alkylation is a general reaction.
- Ligands and solvents can greatly influence both regio-and enantioselectivity
- The reaction proceeds by a retention-retention pathway.
- Modest stereochemical memory effect is observed in the case of chiral racemic substrates.
- Labeling, solution, and solid state studies have shed light on the identity of the catalytically active species.
- The reaction has great potential for synthetic application.