anti-Aminoallylation of Aldehydes via Ruthenium-Catalyzed Transfer Hydrogenative Coupling of Sulfonamido Allenes: 1,2-Aminoalcohols

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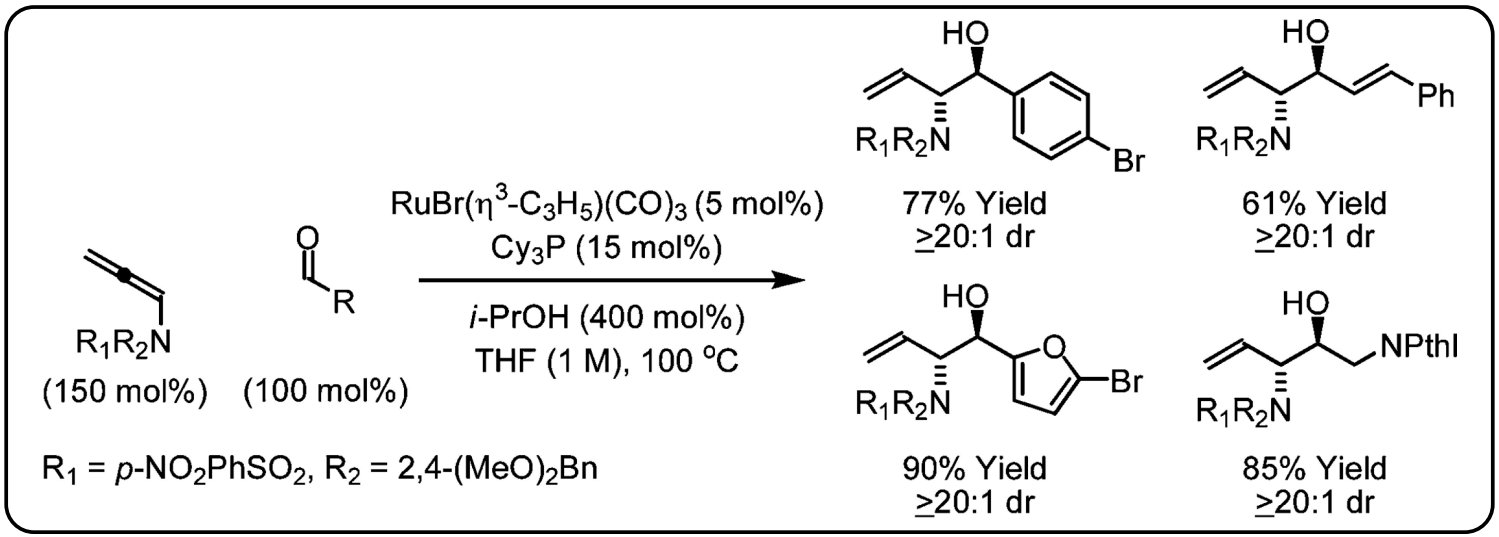
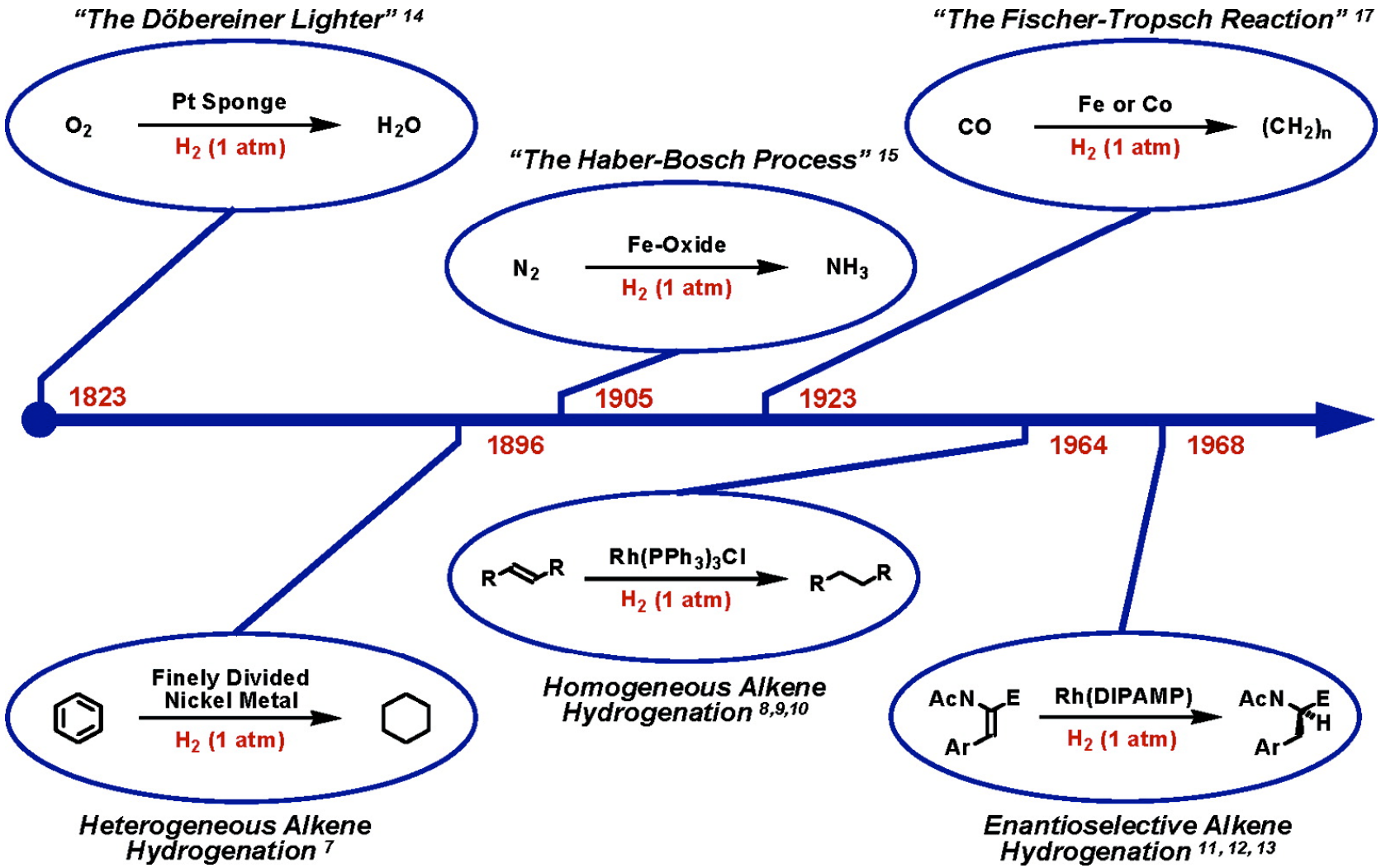
J. Am. Chem. Soc. **2009**, *131* , 5054–5055

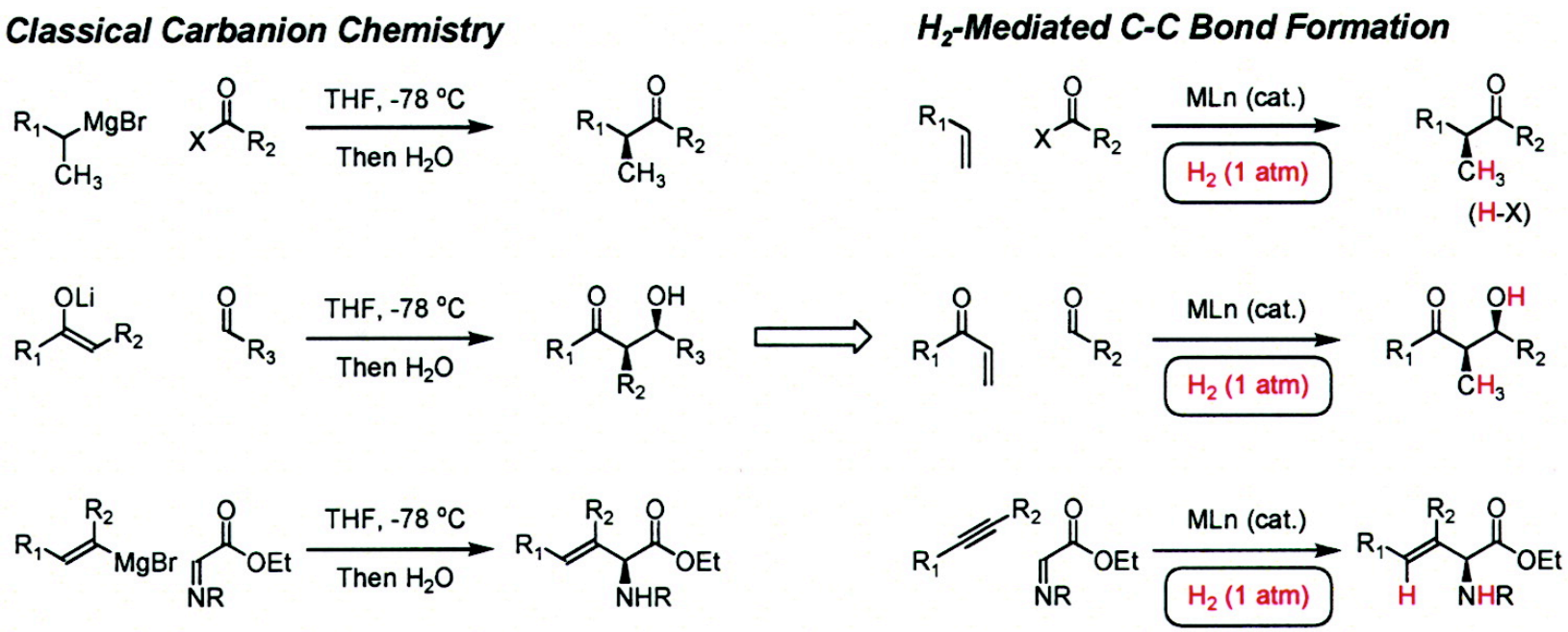


Timeline of Catalytic Hydrogenation

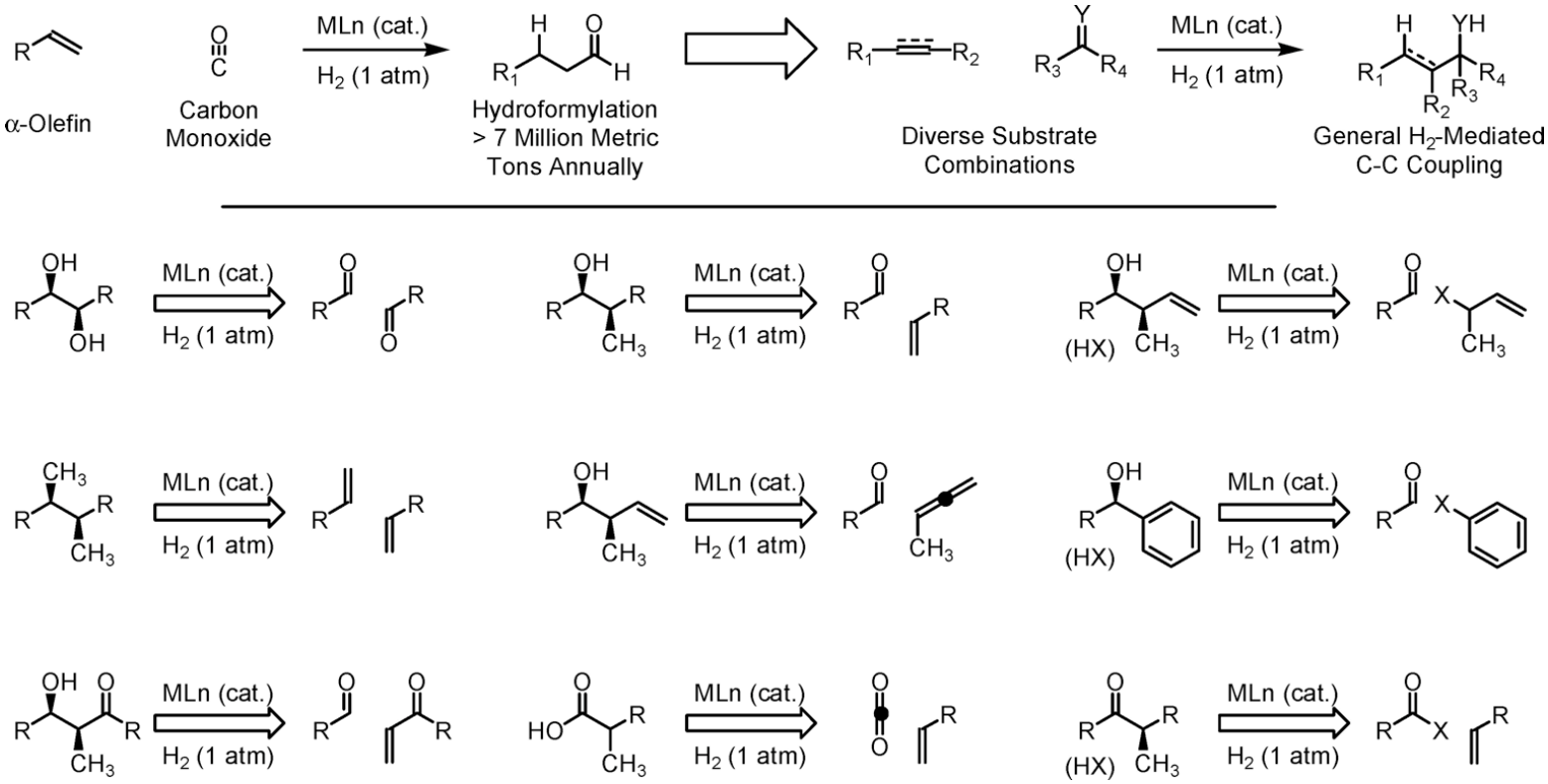


J. Org. Chem. ***2007***, *72, 1063*
Acc. Chem. Res. **2007**, *72*, 1063
Angew. Chem., Int. Ed. **2009**, *48*, 34

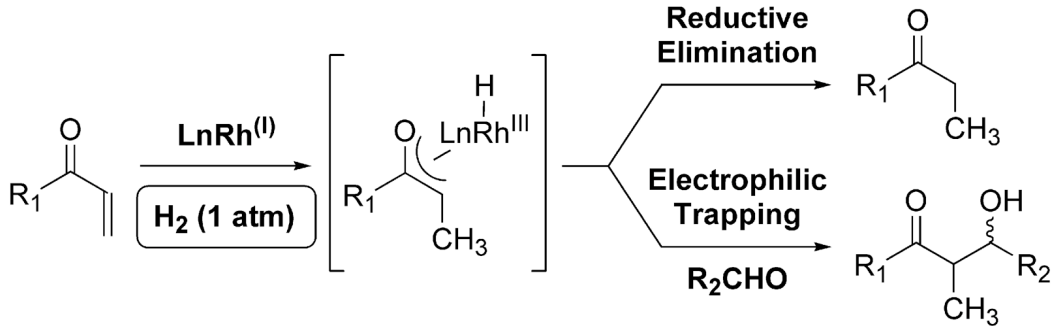
Old and New Paradigms in Organic Synthesis



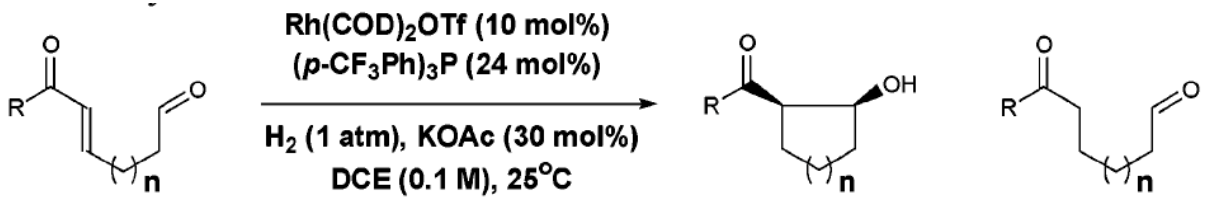
Old and New Paradigms in Organic Synthesis



Intramolecular Aldol Addition



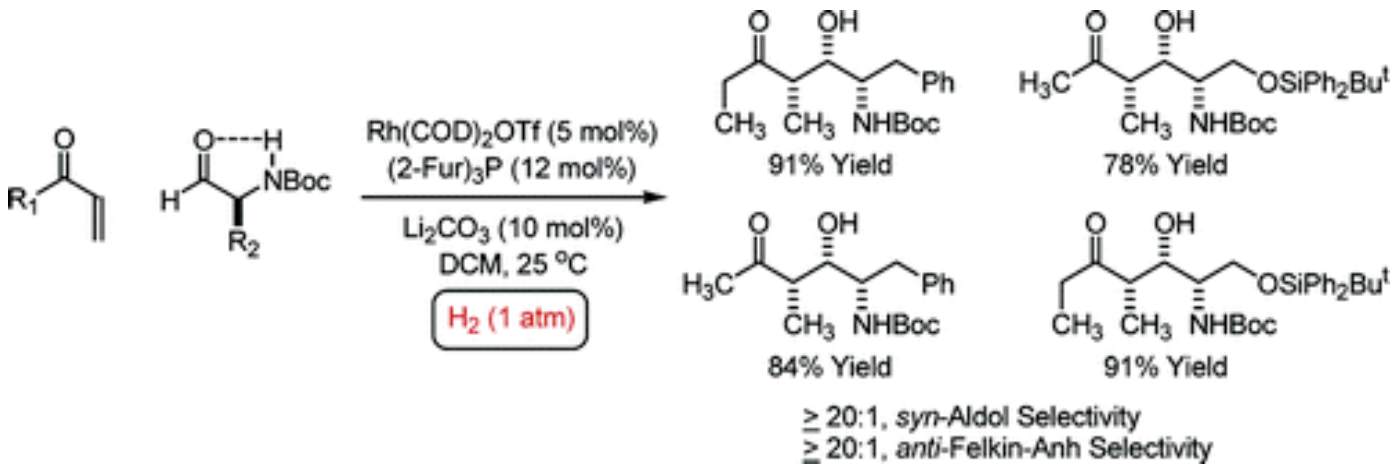
- ***Efficient Intra- and Intermolecular Catalytic Reductive Aldol Condensation***
- ***No Stoichiometric Byproducts, i.e. Complete Atom Economy***



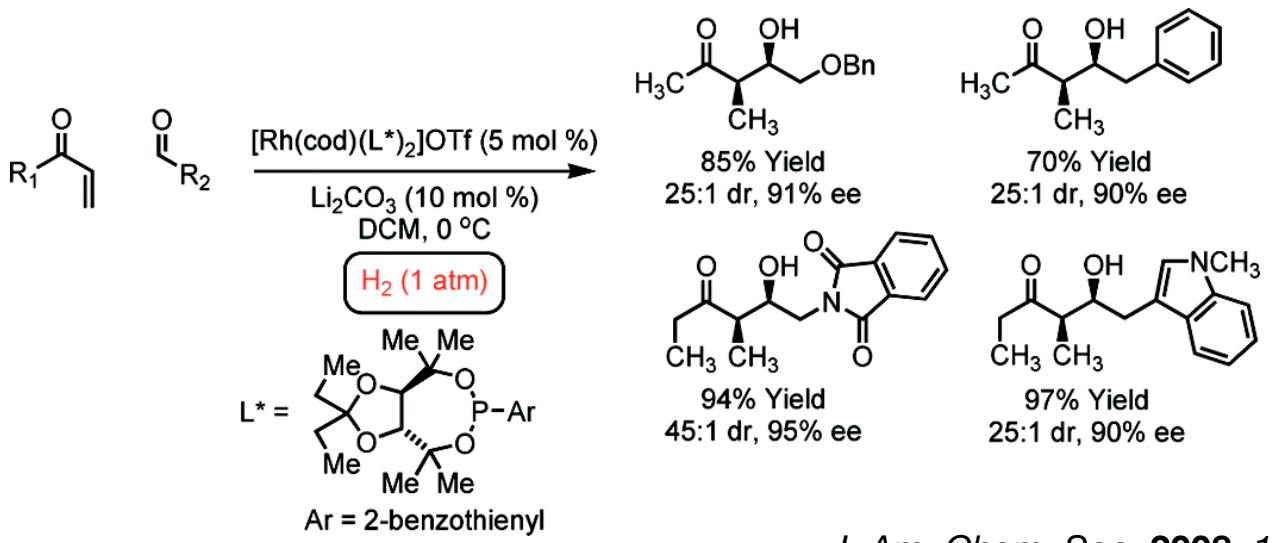
substrate	product (syn:anti)	1,4-reduction
1a, $n = 2$, R = Ph	**1b**, 89% (10:1)	**1c**, 0.1%
2a, $n = 2$, R = *p*-MeOPh	**2b**, 74% (5:1)	**2c**, 3%
3a, $n = 2$, R = 2-naphthyl	**3b**, 90% (10:1)	**3c**, 1%
4a, $n = 2$, R = 2-thiophenyl	**4b**, 76% (19:1)	**4c**, 2%
5a, $n = 2$, R = 2-furyl	**5b**, 70% (6:1)	**5c**, 10%
6a, $n = 1$, R = Ph	**6b**, 71% (24:1)	**6c**, 1%
7a, $n = 2$, R = CH_3	**7b**, 65% (1:5)	

J. Am. Chem. Soc. **2002**, *124*, 15156

Intermolecular Aldol Addition

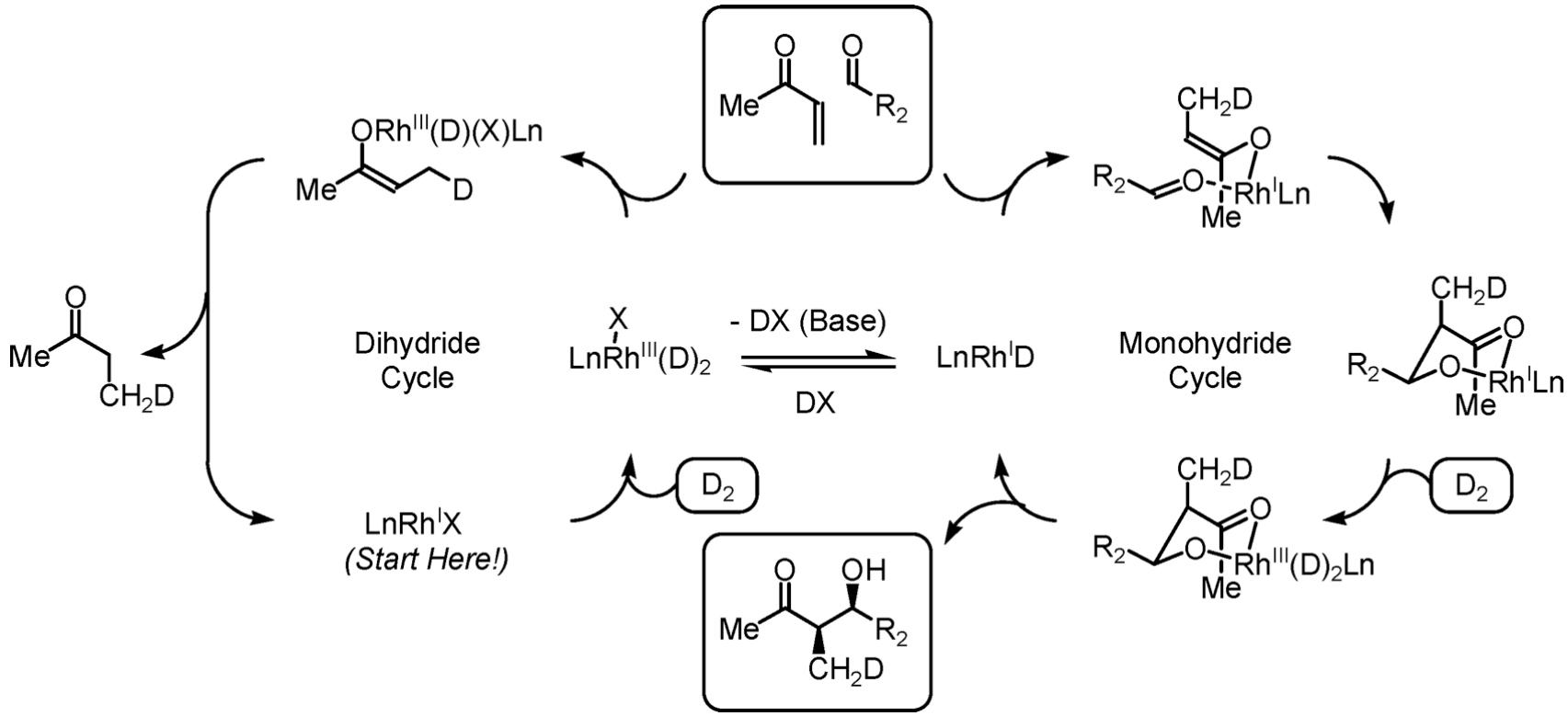


J. Am. Chem. Soc. **2006**, *128*, 17051

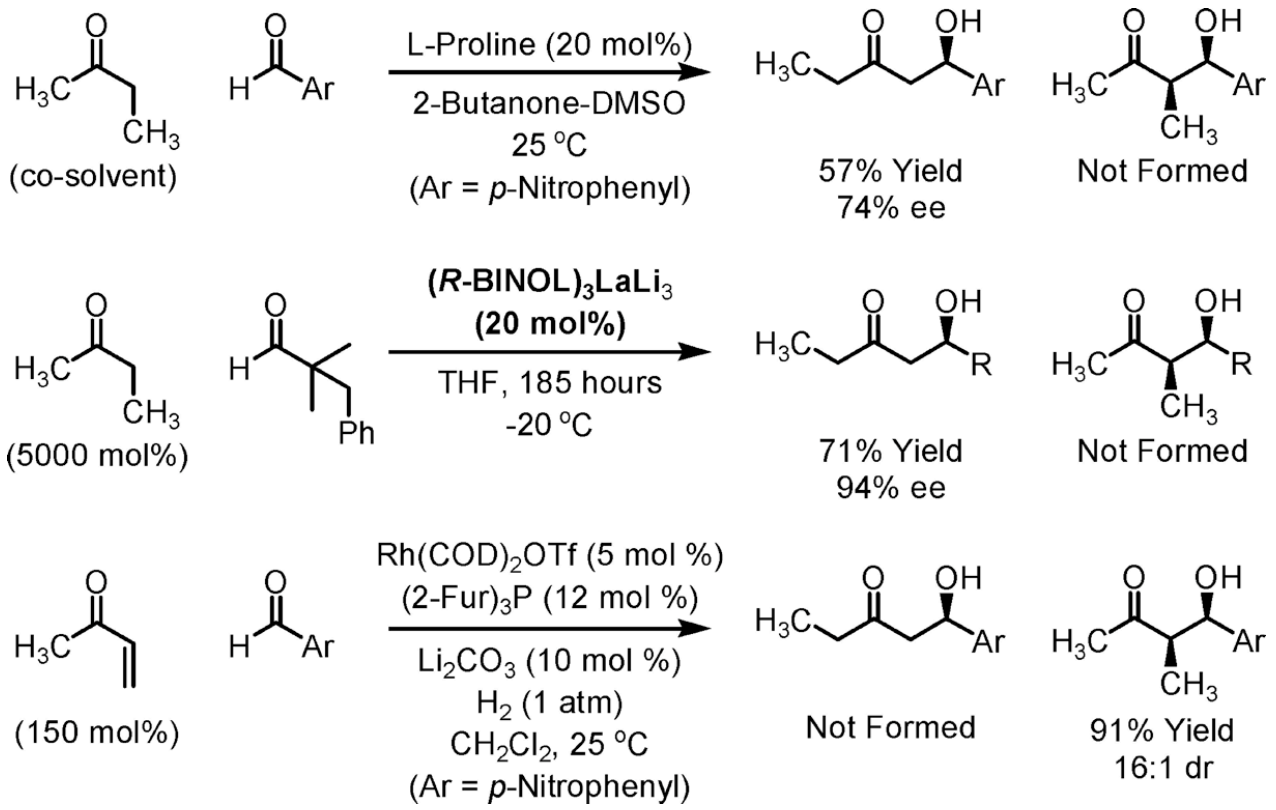


J. Am. Chem. Soc. **2008**, *130*, 2746

Intermolecular Aldol Addition

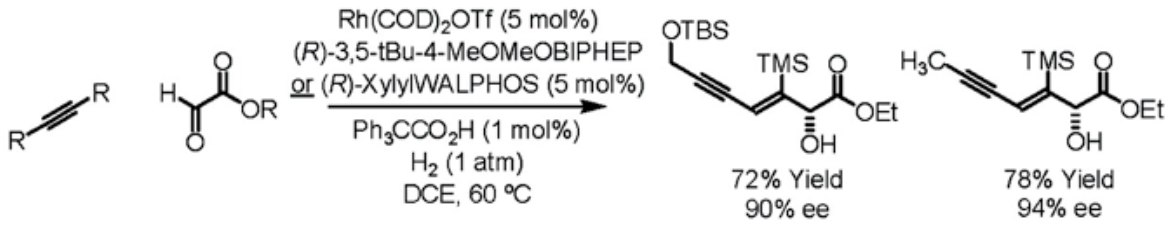


How Does it Compare to Other Methods?

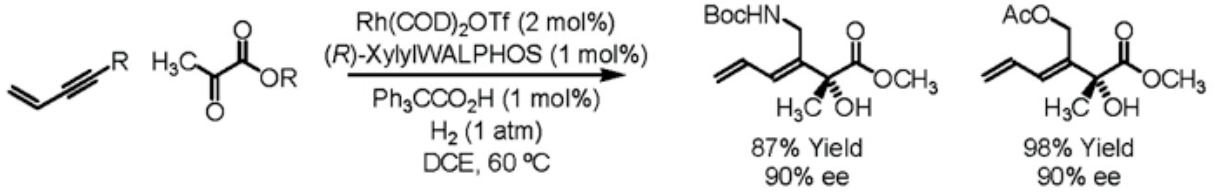


J. Org. Chem. ***2007****, 72, 1063*

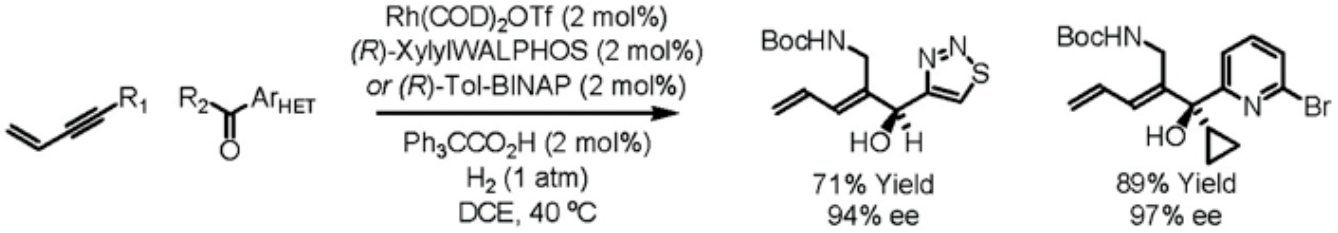
Alkyne-Carbonyl/Imine Coupling



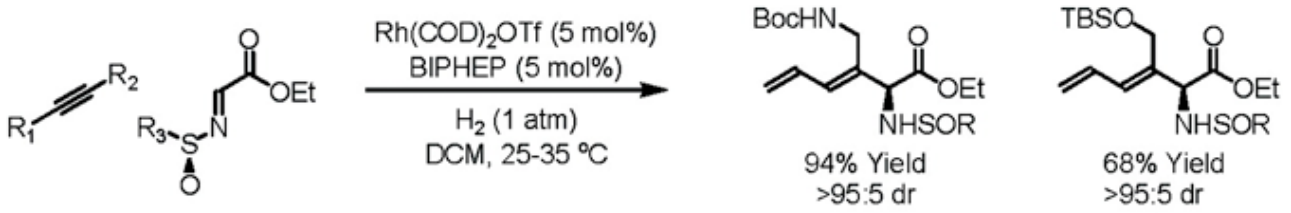
Org. Lett. **2007**, *9*, 3754



J. Am. Chem. Soc. **2006**, *128*, 718

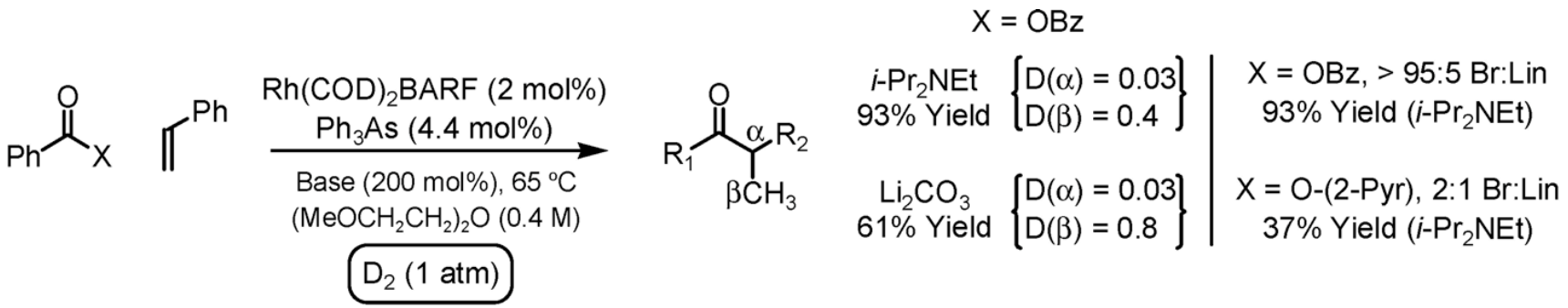


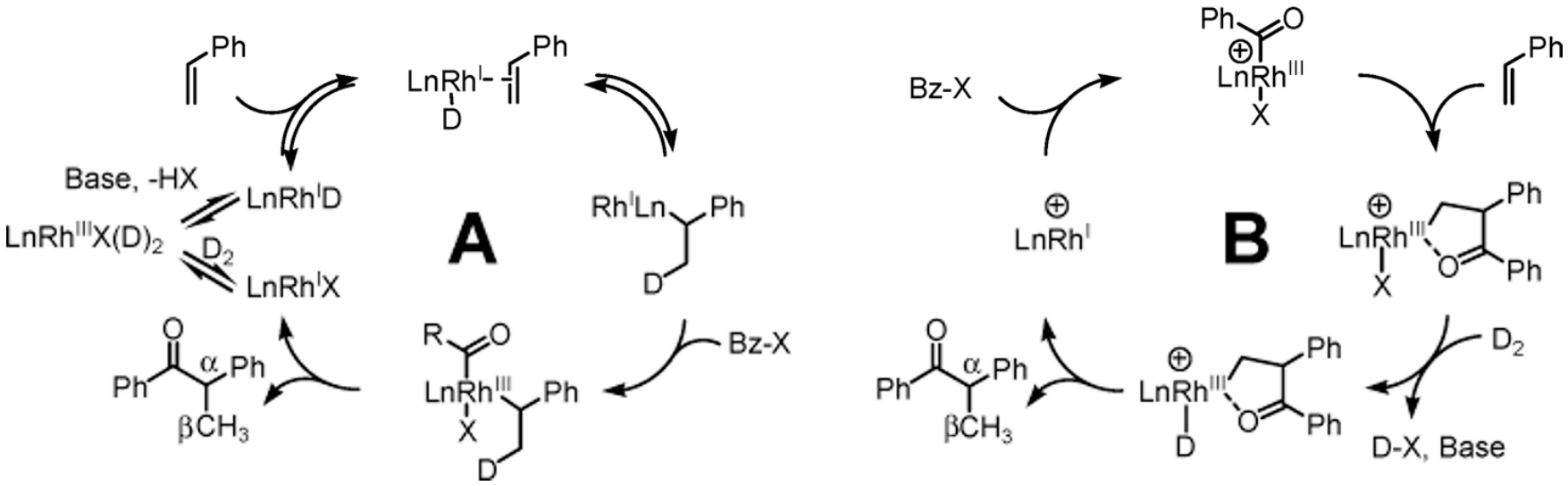
J. Am. Chem. Soc. **2006**, *128*, 16448



J. Am. Chem. Soc. **2005**, *127*, 11269

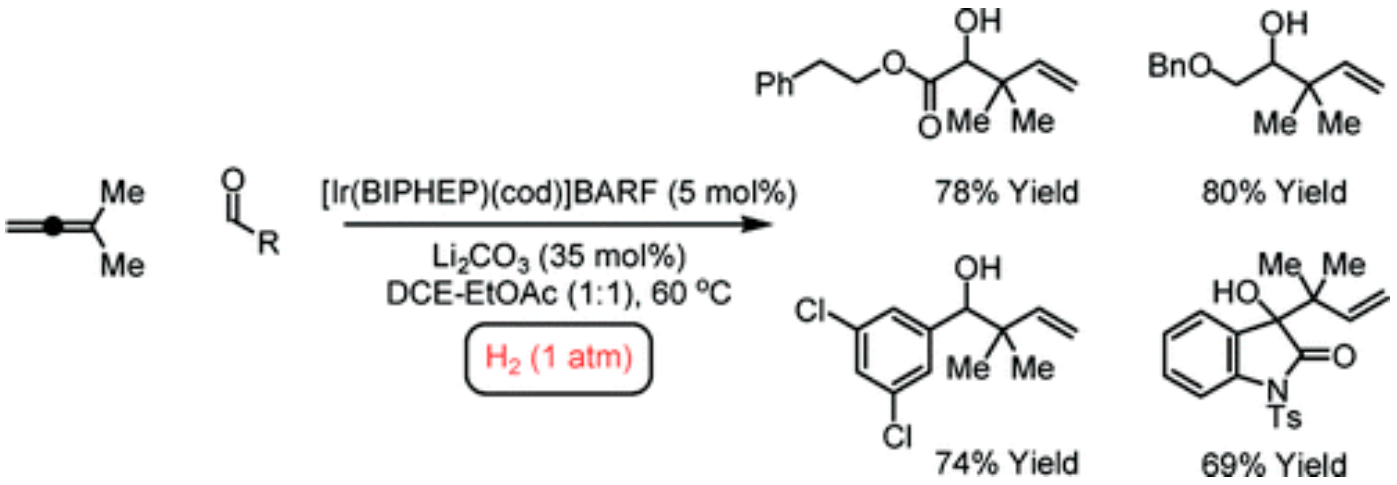
Coupling of Styrene and Carboxylic Acid Anhydride





Angew. Chem. Int. Ed. **2006**, *45*, 6885

Allene - Carbonyl Coupling



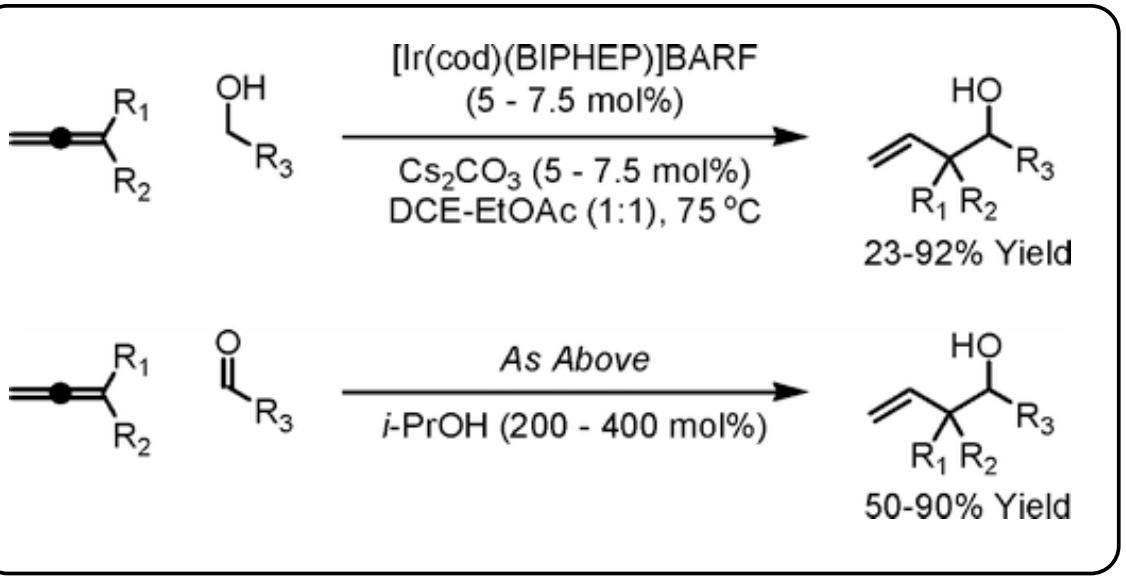
J. Am. Chem. Soc. **2007**, *129*, 12678

C-C coupling under transfer hydrogenation conditions

J. Am. Chem. Soc. **2007**, *129*, 15134

For diene/alkyne coupling, see:

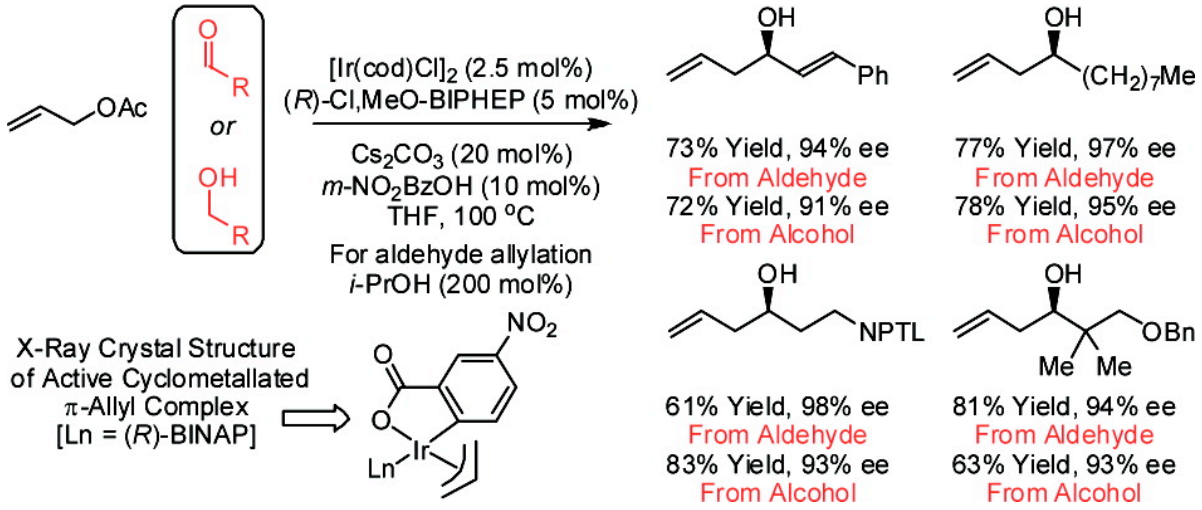
Org. Lett. **2008**, *10*, 1033
J. Am. Chem. Soc. **2008**, *130*, 6338
J. Am. Chem. Soc. **2008**, *130*, 14120
Org. Lett. **2008**, *10*, 2705

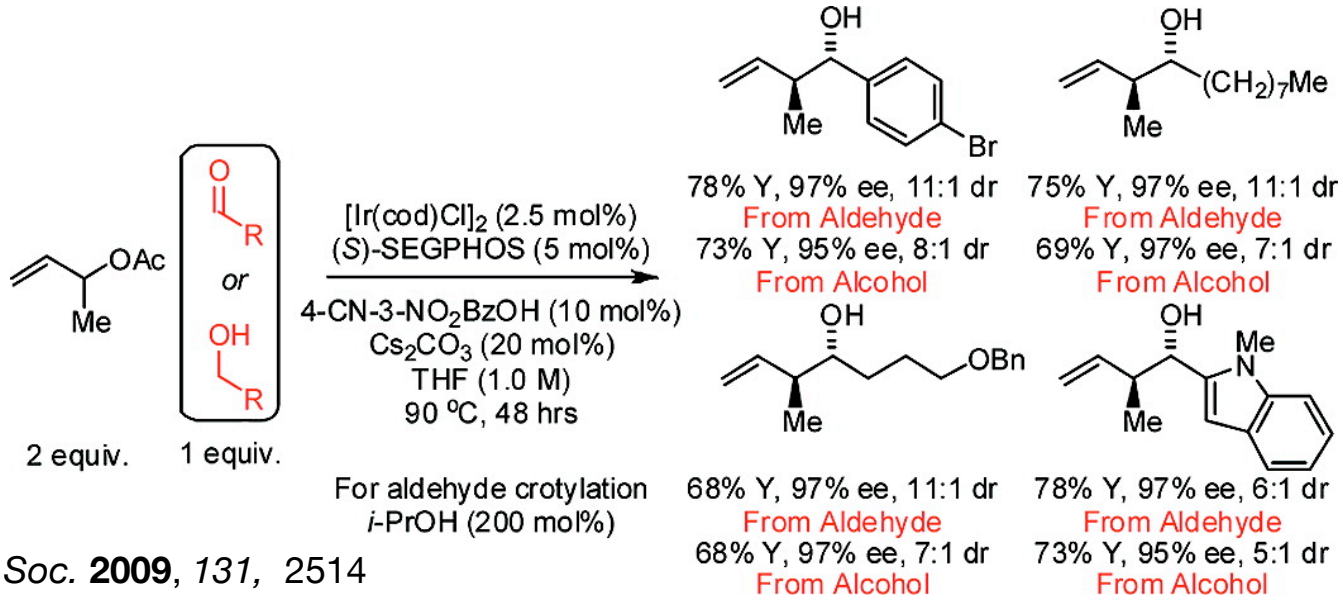


Allylation/Crotylation under Transfer Hydrogenation Conditions

- low-valent Ir(I) and moderately π-acidic ligands promote allylation versus *O*-alkyation (for etherification, Ir (III) and phosphoroamidates)
- reaction proceeds most likely *via* metallated benzoate intermediate

J. Am. Chem. Soc. **2008**, *130*, 6340
J. Am. Chem. Soc. **2008**, *130*, 14891





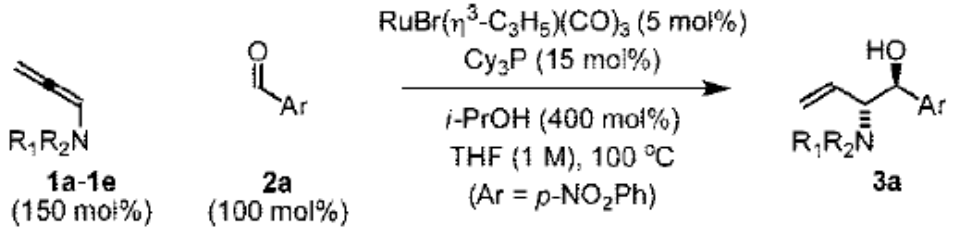
J. Am. Chem. Soc. **2009**, *131*, 2514

Title Paper - Reaction Optimization

Pre-Catalyst Screen:

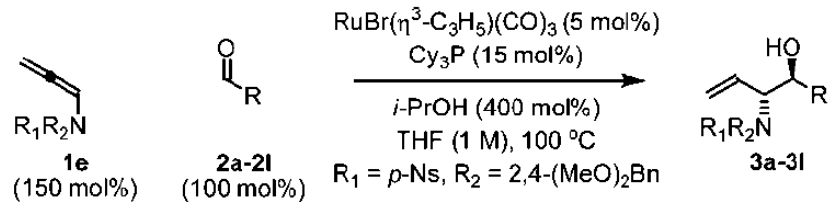
$Ru(O_2CCF_3)_2(CO)(PPh_3)_2$, $RuHCl(CO)(PPh_3)_3$, $RuH_2(CO)(PPh_3)_2$, $RuCl_2(CO)_2(PPh_3)_2$, and **$RuBr(\eta^3\text{-}C_3H_5)(CO)_3$**

Nitrogent-Substitution:



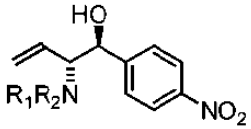
entry	allene	R_1	R_2	**3a** % yield (dr)
1	**1a**	*p*-toluenesulfonyl	benzyl	92 (5:1)
2	**1b**	phthalimido	—	37 (3:1)
3	**1c**	Boc	benzyl	71 (8:1)
4	**1d**	*o*-nitrobenzenesulfonyl	benzyl	50 (≥20:1)
5	**1e**	*p*-nitrobenzenesulfonyl	2,4-dimethoxybenzyl	91 (≥20:1)

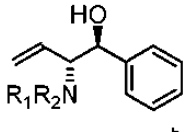
Title Paper - Reaction Scope

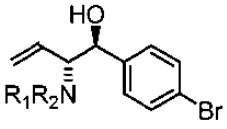


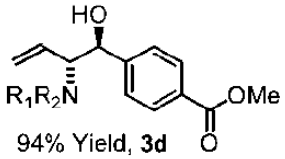
2a, R = *p*-NO_2Ph
2b, R = Ph
2c, R = *p*-BrPh
2d, R = *p*-(CO_2Me)Ph
2e, R = *p*-(COMe)Ph
2f, R = 2-(5-BrFuryl)
2g, R = CH=CHPh
2h, R = CH=CHMe
2i, R = $CH=CHCH_2OBn$
2j, R = CH_2OBn
2k, R = CH_2NPhth
2l, R = *n*-Hexyl

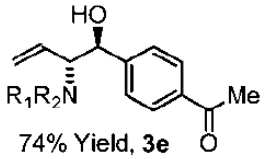
Coupling to Aryl Aldehydes

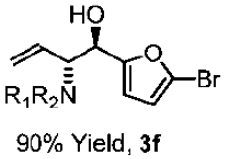

91% Yield, **3a**


70% Yield, **3b**[b]

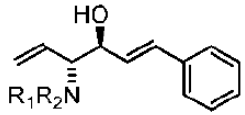

77% Yield, **3c**

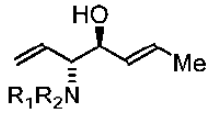

94% Yield, **3d**

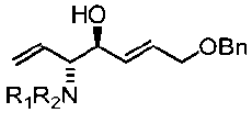

74% Yield, **3e**


90% Yield, **3f**

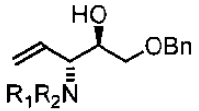
Coupling to Enals

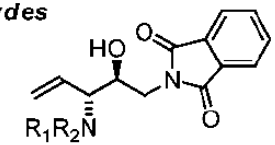

61% Yield, **3g**[b]

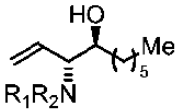

63% Yield, **3h**[b]


65% Yield, **3i**[b]

Coupling to Aliphatic Aldehydes

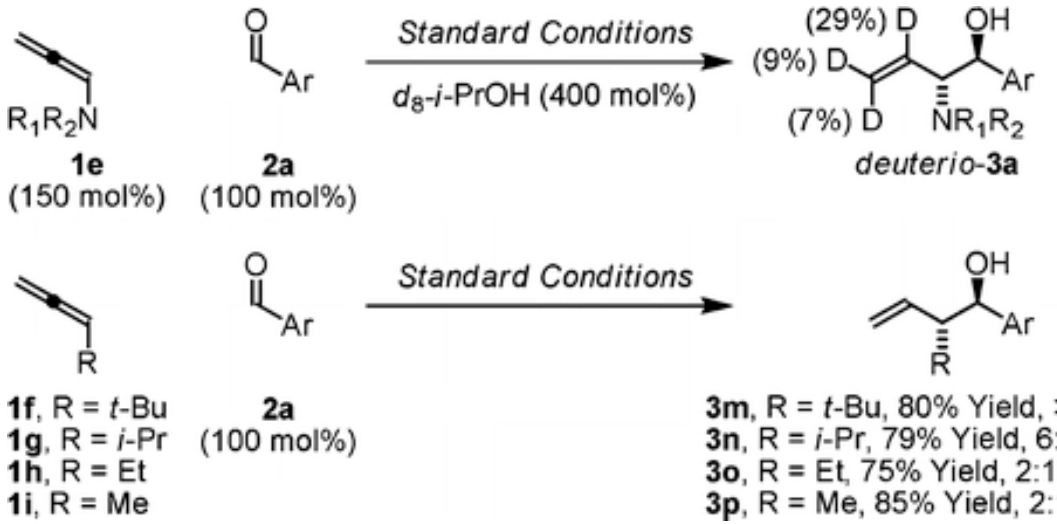

77% Yield, **3j**


85% Yield, **3k**

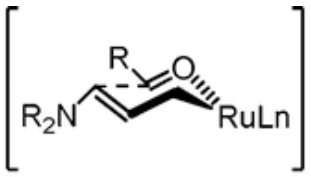

69% Yield, **3l**[b]

Title Paper - Mechanistic Studies

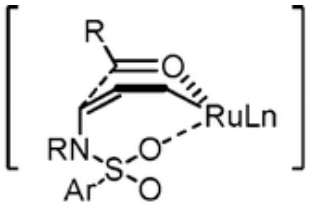
Deuterium-Labeling:



Mechanistic Proposal for anti-Selectivity:

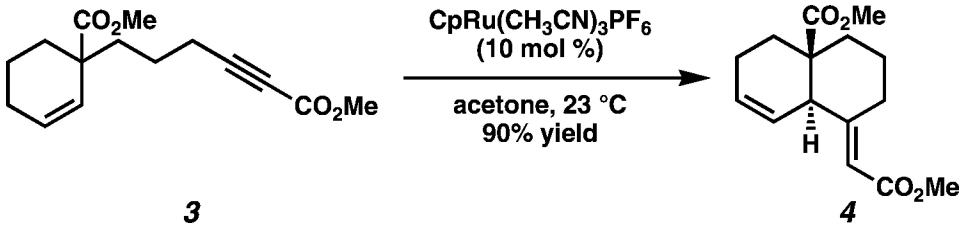


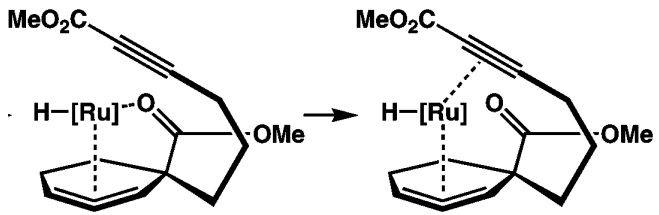
E-Allylruthenium
Chair-Like Transition Structure



Z-Allylruthenium
Boat-Like Transition Structure

Recent Precedence for X=O Chelation with Ru





B. M. Trost, E. M. Ferreira, A. C. Gutierrez
J. Am. Chem. Soc. **2008**, *130*, 16176

Summary

- Transfer hydrogenative coupling of allenyl amides with aldehydes gave 1,2-aminoalcohol in high yield and *anti*-selectivity.

- Selectivity in these reactions can be rationalized by a chair-like TS model.

- Asymmetric variant of this transformation awaits discovery.