Lewis Base Activation of Grignard Reagents with *N*-Heterocyclic Carbenes. Cu-Free Catalytic Enantioselective Additions to γ-Chloro-α,β-Unsaturated Esters

Lee, Y.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2006** ASAP

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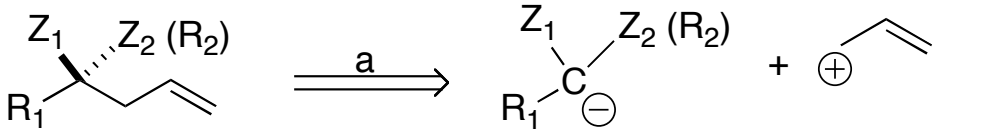
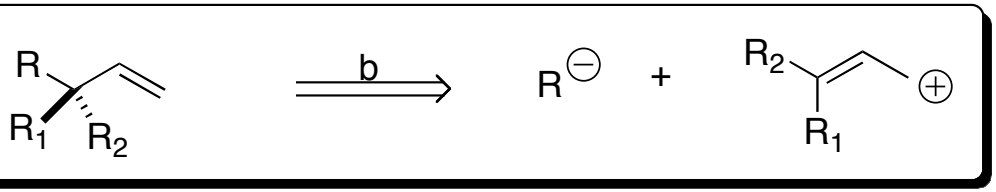
25 Nov 2006

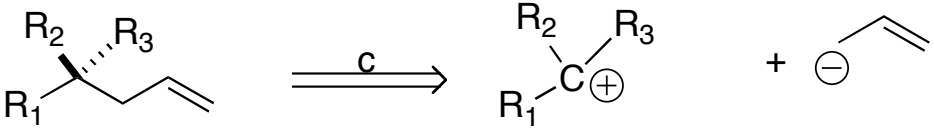
Electrophilic and Nucleophilic Allylic Alkylation

Electrophilic Allylation

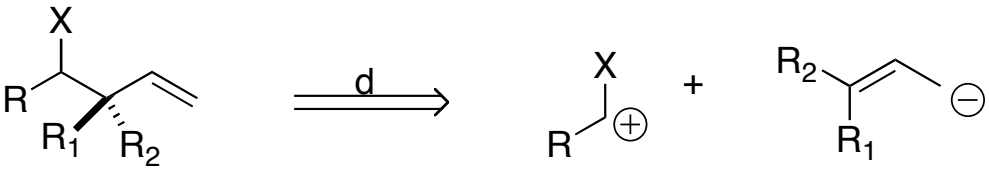




Nucleophilic Allylation



(allyl silanes as nucleophile)

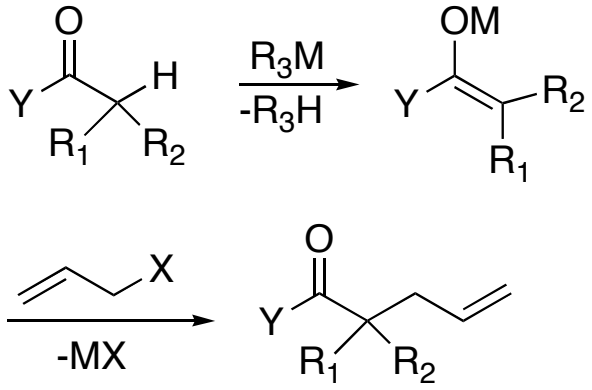


(γ-addition of allylic nucleophiles (allyl silanes and boronates) to aldehydes)

R, R_1, R_2, R_3 = alkyl, aryl; Z_1, Z_2 = electron withdrawing groups; X = electron donating group

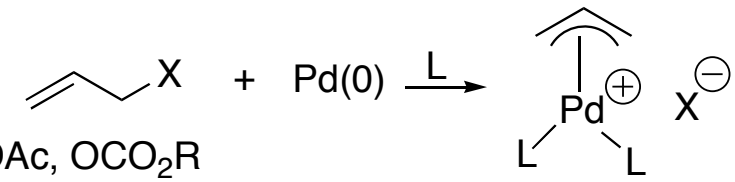
Electrophilic Allylic Alkylation: Path a

Direct allylation of enolates

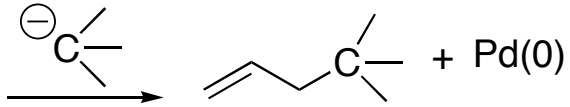


R_1, R_2 = alkyl, aryl, acyl
R_3 = alkyl, $N(alkyl)_2$
Y = alkyl, aryl, OR, NR_2, OM
X = LG

Palladium-catalyzed allylic substitution

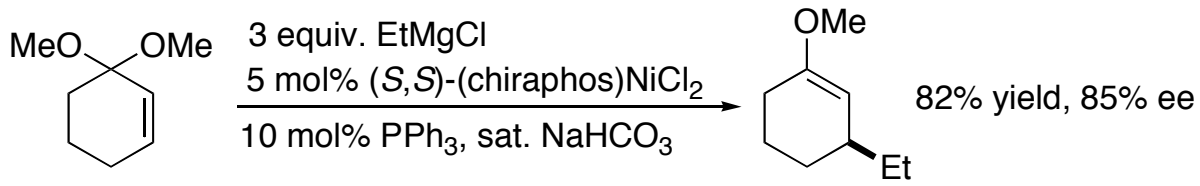


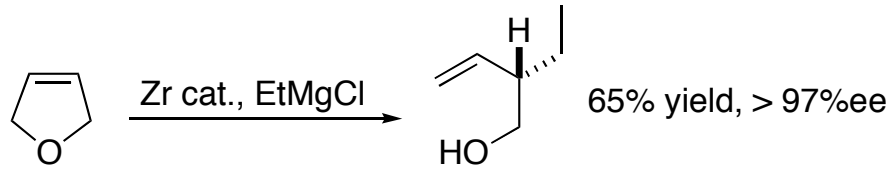
X = OAc, OCO_2R

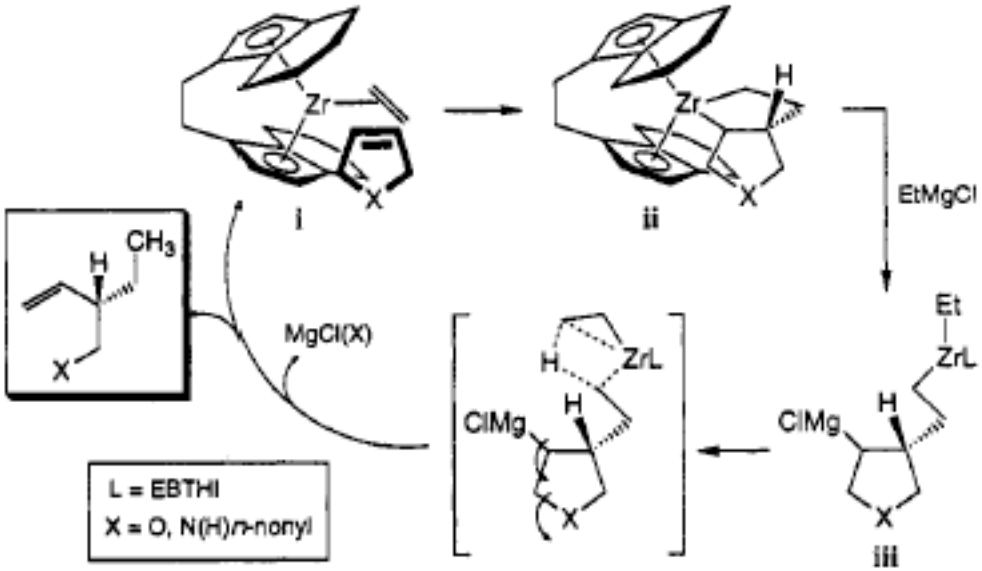


"soft" C nucleophiles: malonates, β-ketoesters

Zr- and Ni-Catalyzed Asymmetric Allylic Addition

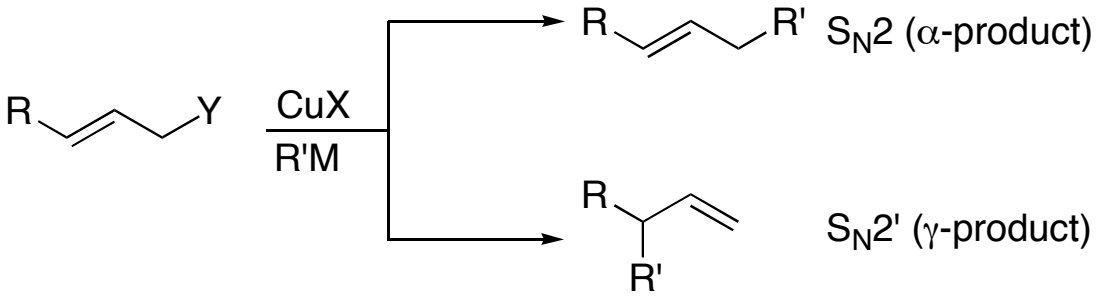




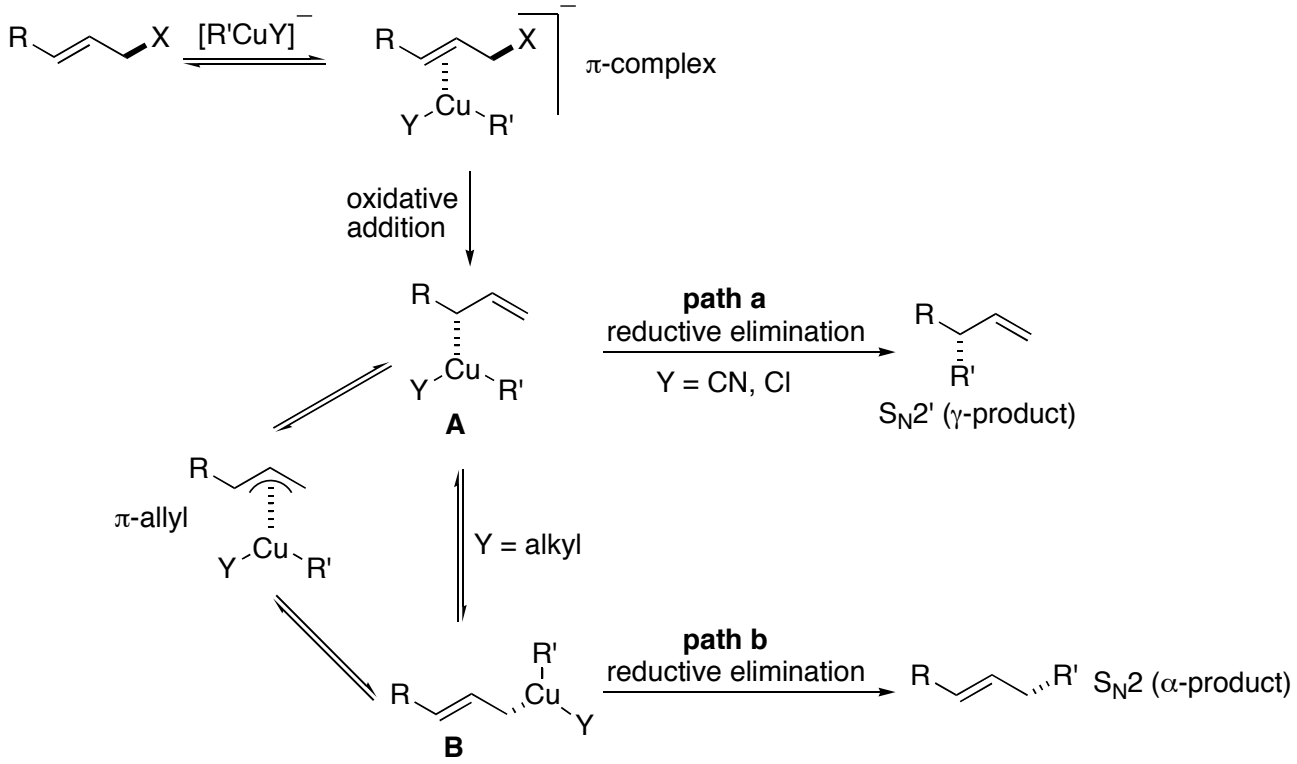


Hoveyda *et.al. J. Am. Chem. Soc.* **1998**, *120*, 7649-7650
Hoveyda *et.al. J. Am. Chem. Soc.* **1993**, *115*, 6997-6998

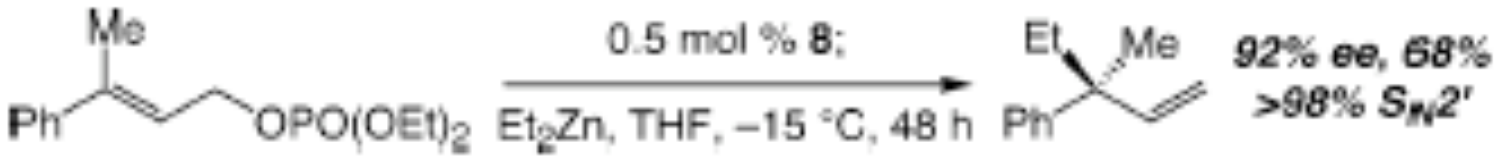
Copper-Catalyzed Allylic Substitution

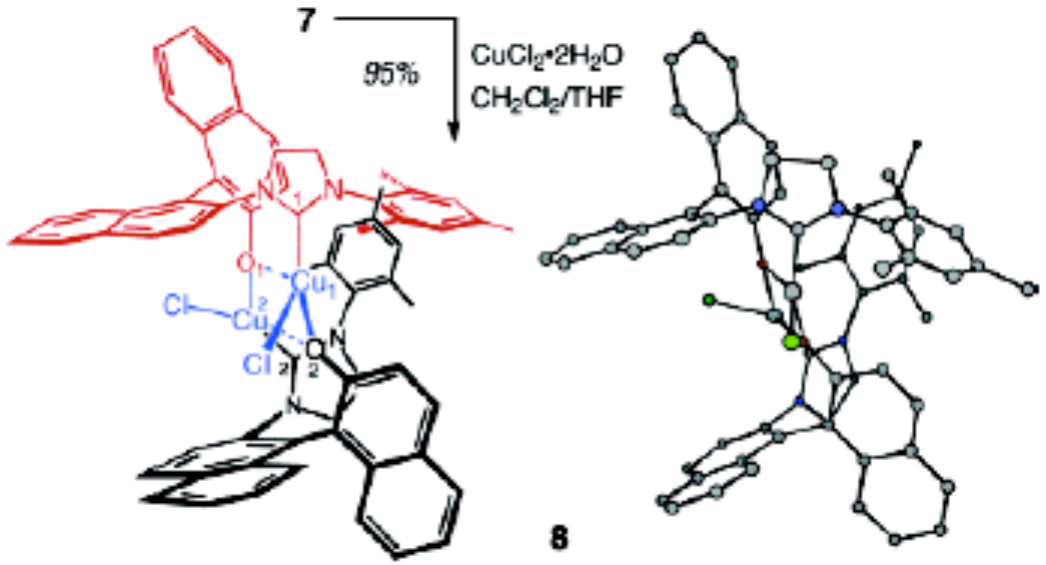


R' = alkyl, aryl, vinyl, allyl
M = Li, MgX, $Ti(OR)_3$, ZnX, etc.
Y = Cl, Br, OC(O)R'', SO_2Ph, OR'', $OP(O)(OR'')_2$, etc.



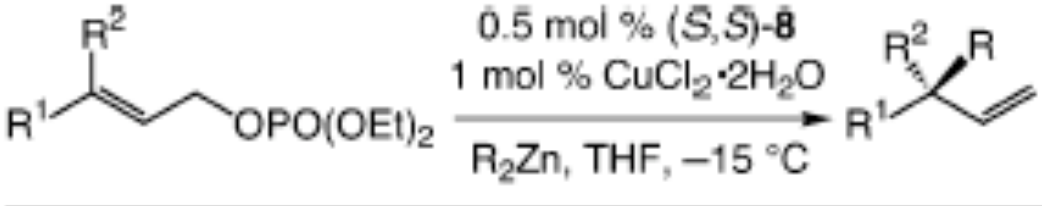
Cu-Catalyzed AAA w/ *N*HC-Based Chiral Ligands

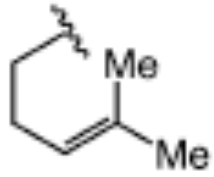


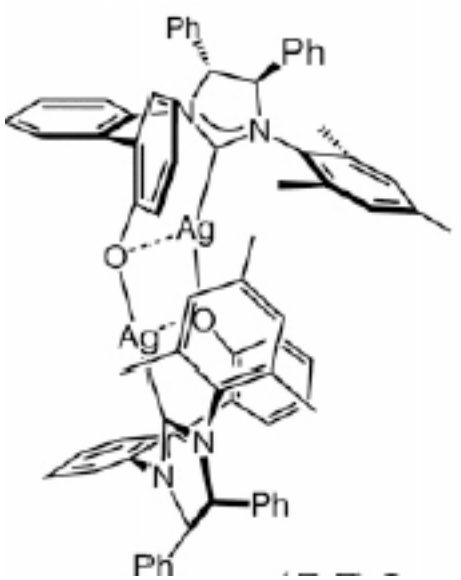


Hoveyda *et.al. J. Am. Chem. Soc.* **2004**, *126*, 11130-11131

Cu-Catalyzed AAA w/ *N*HC Ligands Bearing Chiral Diamine Backbone

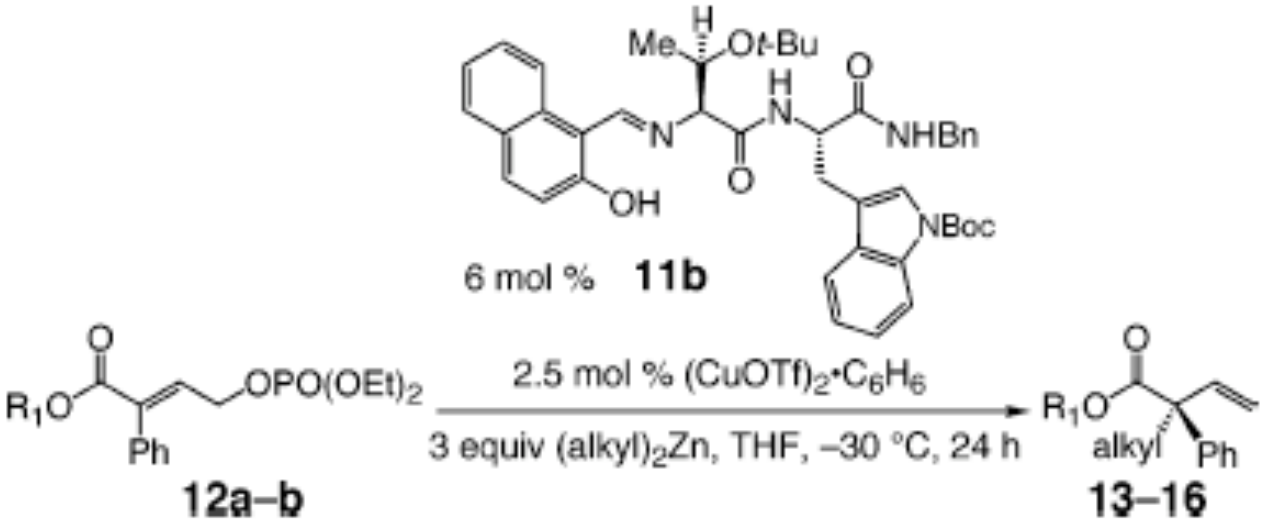


entry	R^1	R^2	alkylzinc	conv (%);[b] time (h)	yield (%);[c] ee (%)[d]
1	C_6H_5	Me	Et_2Zn	>98; 2	94; 97
2[e]	C_6H_5	Me	*i*-Pr_2Zn	>98;12	74; 98
3	Cy	Me	Et_2Zn	>98; 24	76; 97
4		Me	Et_2Zn	>98; 16	82; 94



Hoveyda *et.al. J. Am. Chem. Soc.* **2005**, *127*, 6877-6882

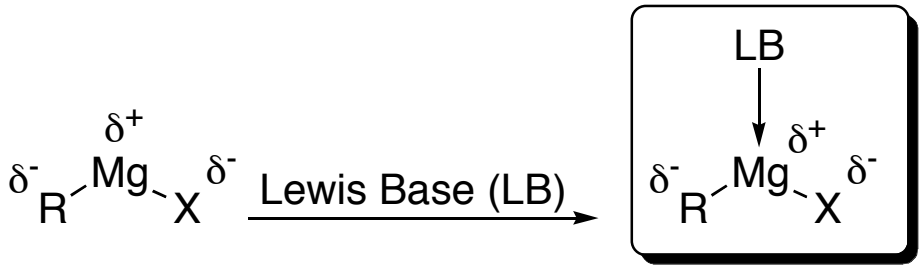
Cu-Catalyzed AAA w/ Amino Acid Based Ligands



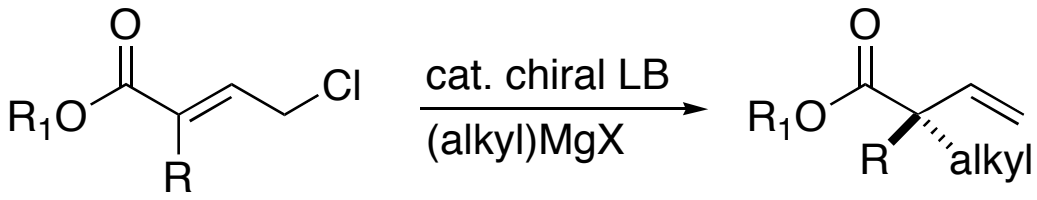
entry	R_1		$(alkyl)_2Zn$	product	yield[a] (%)	re[b] (%)	ee[c] (%)
1	Me	**12a**	Et_2Zn	**13**	95	>98	86
2	Me	**12a**	Me_2Zn	**14**	85	>98	94
3	*t*-Bu	**12b**	Et_2Zn	**15**	80	>98	79
4	*t*-Bu	**12b**	Me_2Zn	**16**	87[d]	>98	89

Hoveyda *et.al. Org. Lett.* **2005**, *7*, 1255-1258

Activation of Grignard Reagents by a Lewis Base



increased nucleophilicity and altered mode of reactivity *vs* RMgX



1) Catalyst turn over
2) Efficiency
3) Regio- and Enantioselectivity

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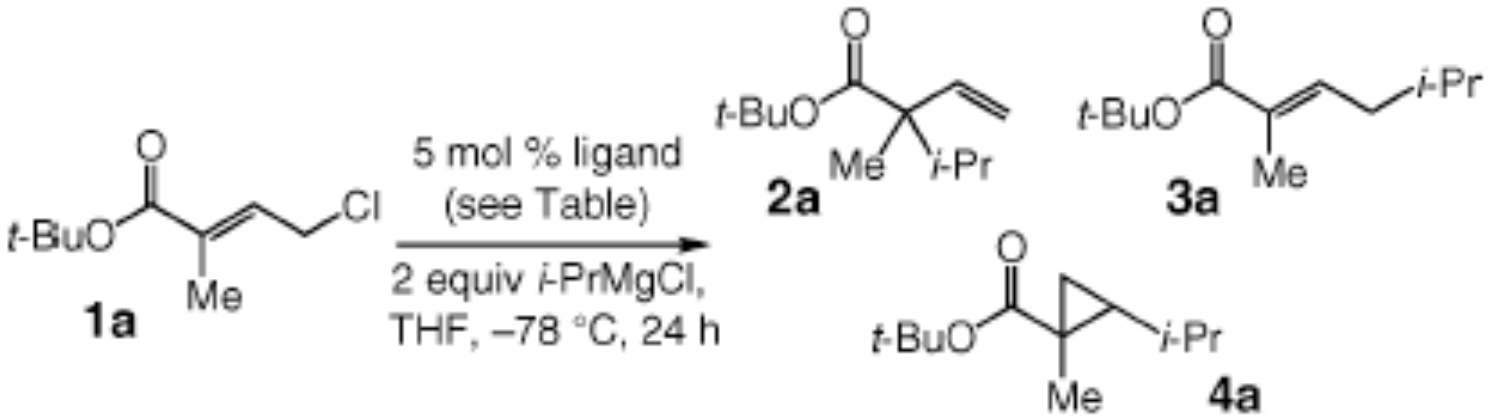
Activation of *i*-PrMgCl by Catalytic Amounts of Lewis Bases



entry	Lewis Base	conv (%)[b]	**2**+**3** (%)[c]	**2**:**3**[c]	**4** (%)[c]
1	none	28	–	–	28
2	PPh_3	25	–	–	25
3	$(O)PPh_3$	30	7	<2:>98	23
4	 **5**	60	30	1:1	30

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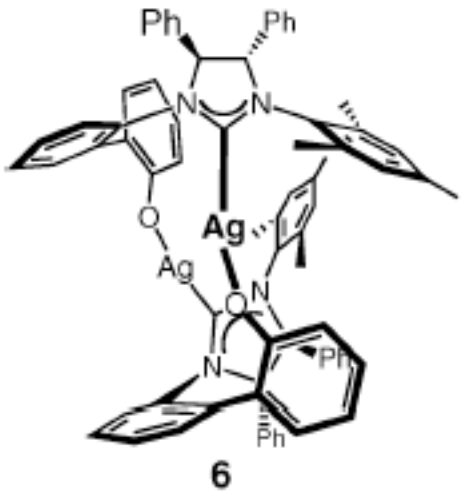
N-Heterocyclic Carbene (NHC)-Based Chiral Ligands



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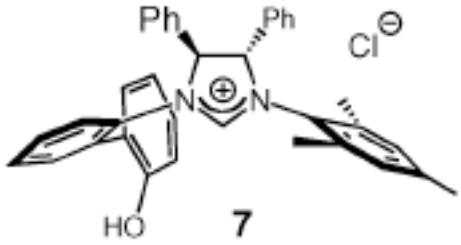

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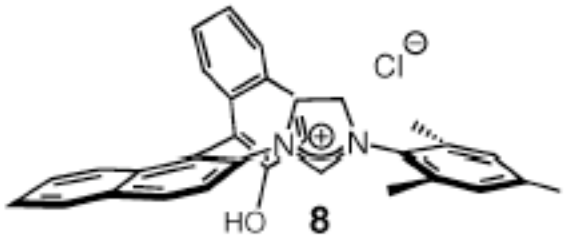

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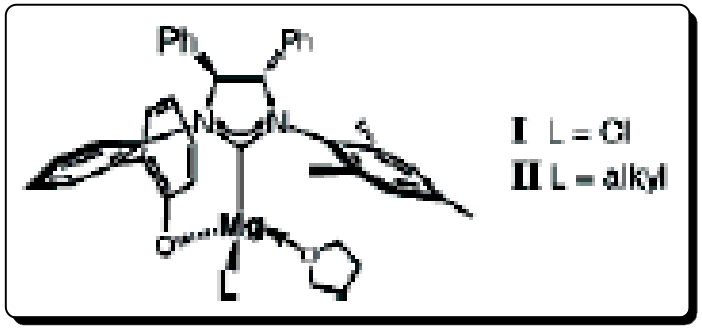

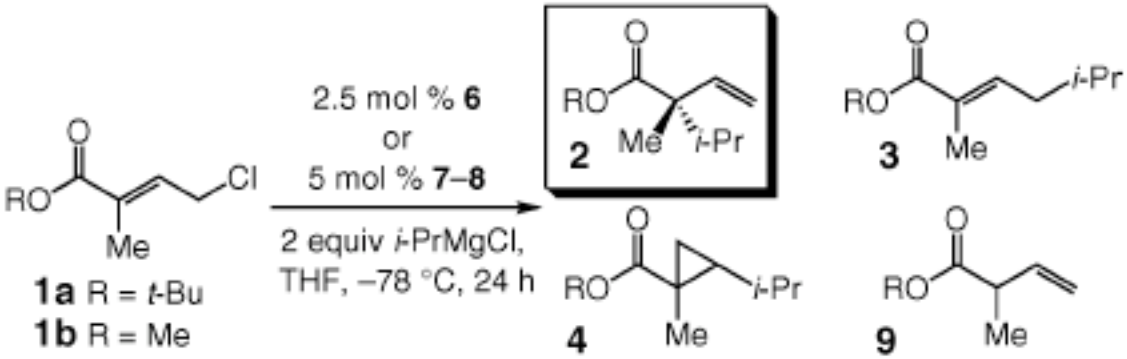

entry	R	chiral ligand	conv (%)[b]	% 2[b]	2:3[b]	ee 2 (%)[c]	% 4[b]	% 9[b]
1	*t*-Bu	**6**	87	7	1:2.9	89	18	42
2	*t*-Bu	**7**	>98	56	3.5:1	93	28	<2
3	*t*-Bu	**8**	59	5	1:4.9	–12	29	<2
4	Me	**7**	***>98***	***82***	***9:1***	***97***	***9***	***<2***

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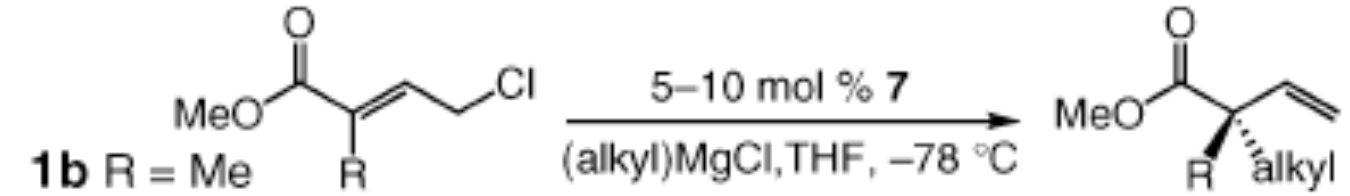
Quaternary Center Formation by Enantioselective Allylic Alkylations



1b R = Me
10 R = Et, **11** R = *n*-Bu

entry	R	(alkyl)MgCl	mol % **7**	conv (%)[b]; time (h)	S_N2':S_N2[b]	cycloprop. (%)[b]	S_N2' yield (%)[c]	ee (%)[d]
1	Me	*i*-PrMgCl	5	>98; 24	9.0:1	9	80	97
2	Me	*c*-pentMgCl	5	95; 48	4.3:1	12	57	75
3	Me	*c*-hexMgCl	5	95; 24	11.5:1	27	63	94
4	Me	*n*-BuMgCl	8	93; 48	6.1:1	28	34	63
5	Et	*i*-PrMgCl	5	>98; 24	10.1:1	7	73	97
6	*n*-Bu	*i*-PrMgCl	5	>98; 24	10.1:1	7	75	98
7	Et	*c*-pentMgCl	10	>98; 48	7.3:1	8	66	90
8	*n*-Bu	*c*-pentMgCl	10	>98; 60	3.5:1	13	59	85
9	Et	*c*-hexMgCl	10	>98; 48	13.3:1	19	60	96
10	*n*-Bu	*c*-hexMgCl	10	84; 48	11.5:1	13	57	96
11	Et	*n*-BuMgCl	10	>98; 60	7.3:1	26	35	79

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Summary

- First Example of Asymmetric Allylic Alkylation involving Grignard Reagents to Generate Quaternary Stereocenters

- Needs Further Understanding of Mechanism and Origin of Enantioselectivity