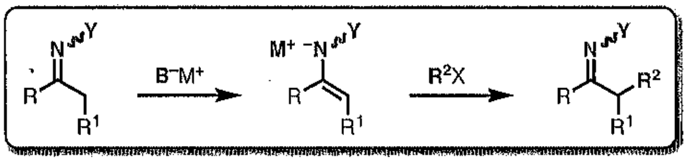
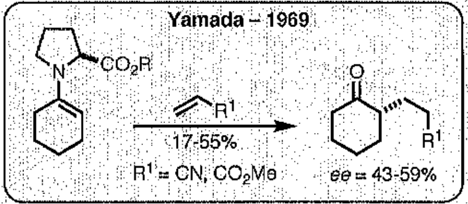
(Don Coltart)

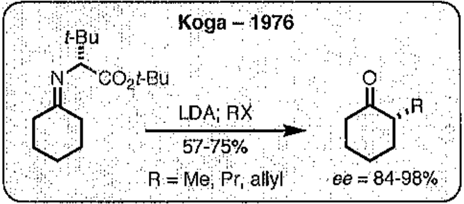
Asymmetric Ketone α-Alkylation

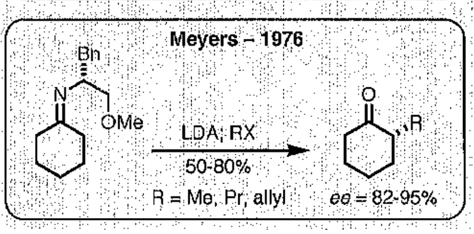
- Ketone α-alkylation is a fundamental synthetic transformation
- Azaenolates are often used in place of enolates:
  - Enhanced nucleophilicity
  - Greater regioselectivty for *C*-alkylation
  - Potential for asymmetric induction using chiral amines and their derivatives

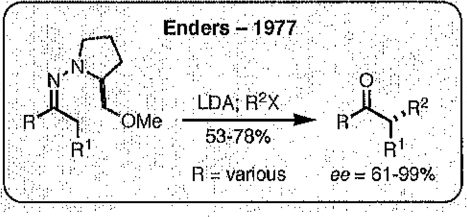


History



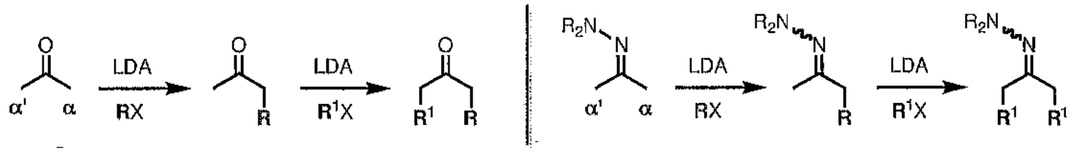




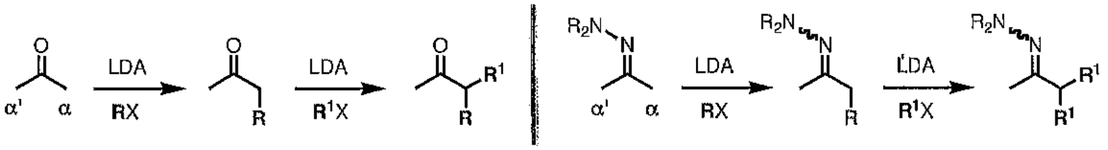


Regiochemistry of Bisalkylation

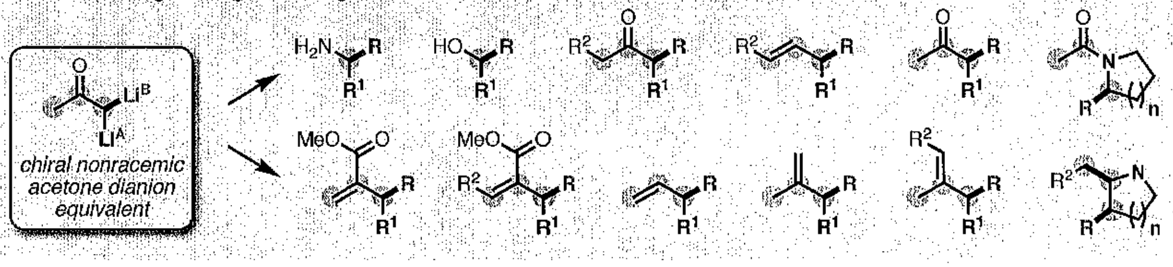
- Sequential bisalkylation of ketones/dialkyl hydrazones via kinetic deprotonation gives α, α′–regiochemistry



- α, α–Bisalkylation not accessible in this way

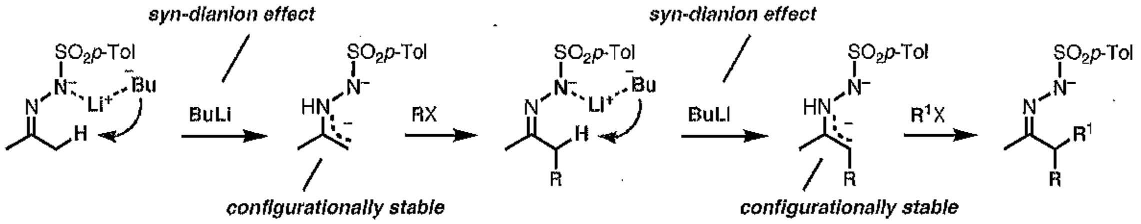


- Wide range of useful structural motifs will be accessible using well-established methods following bisalkylation, e.g.:

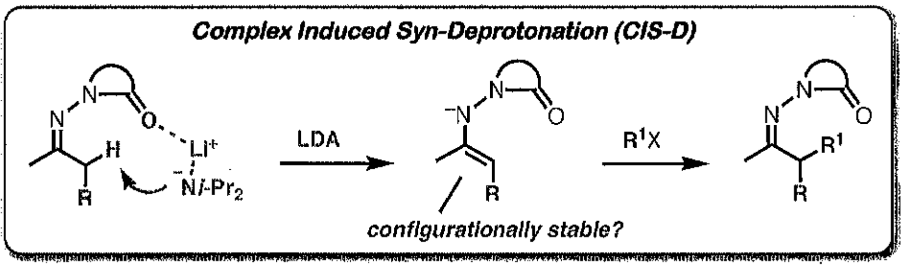


Complex Induced Syn-Deprotonation (CIS-D)

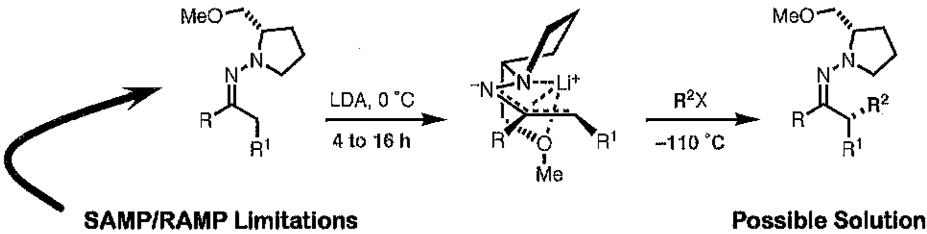
- α, α–Bis-alkylation of *N*-sulfonyl hydrazones is known – ***syn*-dianion effect**



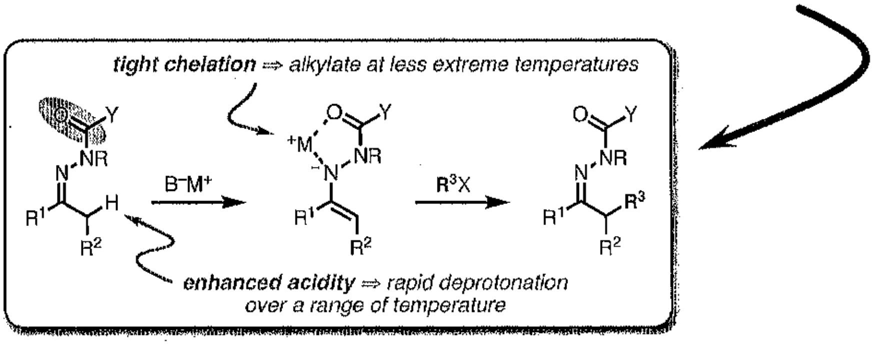
- Can we mimic the *syn*-dianion effect using a neutral coordinating element (e.g., neutral lone pair)
- Potentially simplified approach since dianion not required
- Similar complex-induced proximity effects are known (e.g., directed *ortho*-lithiation)


Complex Induced Syn-Deprotonation (CIS-D)

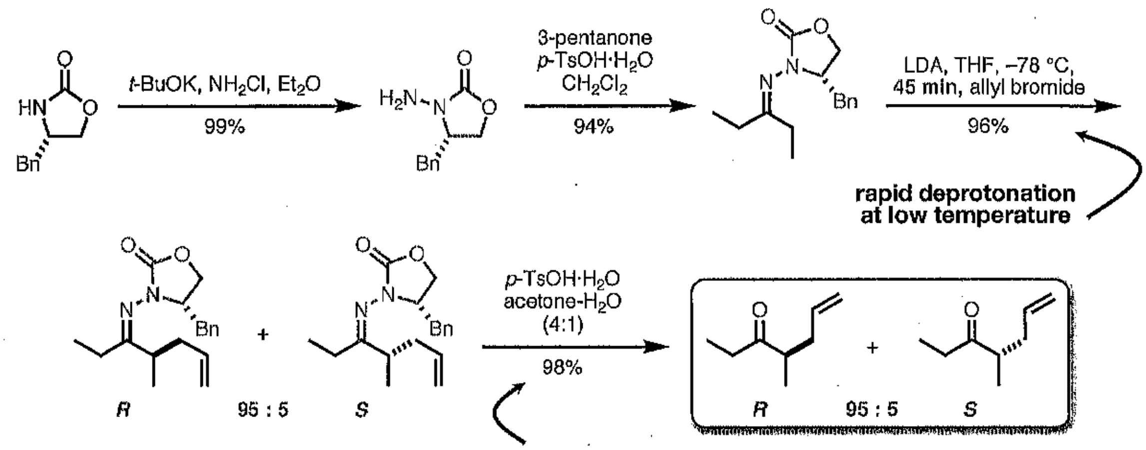
Asymmetric Ketone α-Alkylation



SAMP/RAMP Limitations	**Possible Solutions**
• Dialkyl hydrazones are weakly acidic (LDA, 4 to 16 h)	• Incorporate an electron withdrawing group
• Extreme low temperature (– 110 °C) needed for alkylation selectivity	• Generate a more tightly chelated aza-enolate intermediate
• Auxiliary removal/recycling is difficult	• Eliminate "amine" function
• Large scale applications are not practical	• Large scale applications will be possible

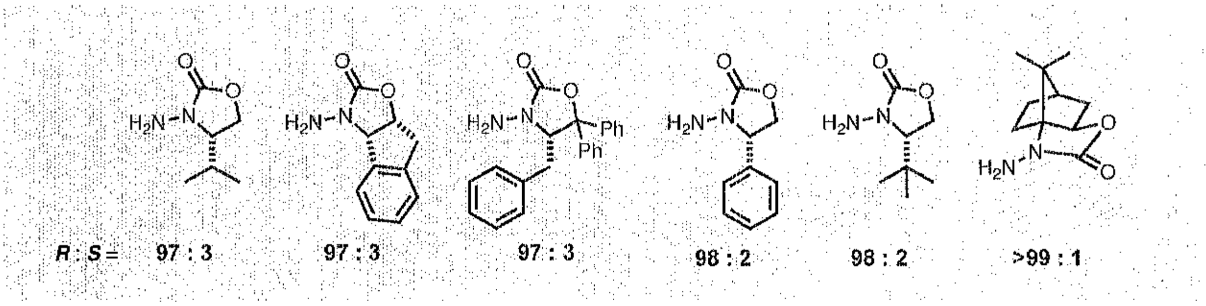


ACC Auxiliaries – Proof of Concept

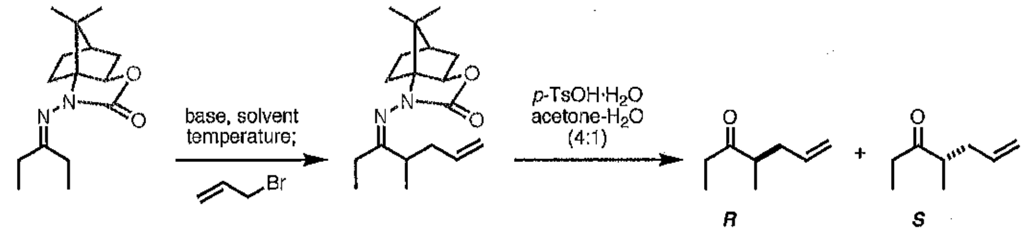


rapid deprotonation at low temperature

Non-oxidative auxiliary cleavage with quantitative recovery



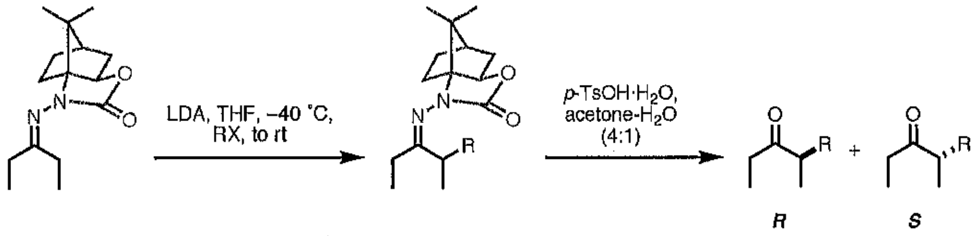
ACC Auxiliaries – Reaction Conditions

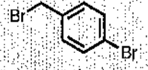
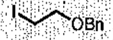
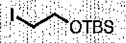
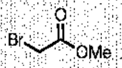
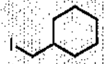


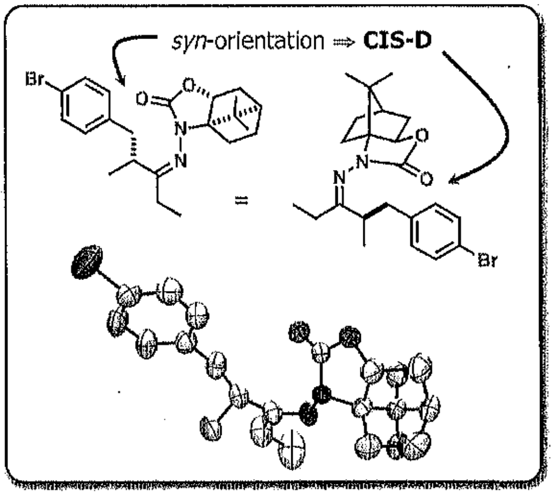
Base	Solvent	Temp (°C)	R : S
LDA	THF	−78 to rt	>99 : 1
LDA	Et_2O	−78 to rt	>99 : 1
LDA	toluene	−78 to rt	>99 : 1
LHMDS	THF	−78 to rt	87 : 13
NHMDS	THF	−78 to rt	82 : 18
KHMDS	THF	−78 to rt	82 : 18
LDA	THF	−110 to rt	>99 : 1
LDA	THF	−60 to rt	>99 : 1
LDA	THF	−40 to rt	>99 : 1
LDA	THF	−20 to rt	>99 : 1
LDA	THF	0 to rt	96 : 4

- Alkylation at temperatures up to −20 °C without erosion of stereoselectivity
- Large scale applications may be possible
- Preliminary test reaction conducted on 10 g scale:
  - 94% yield of ketone
  - >99 : 1 *R* : *S*
  - 97% recovery of auxiliary

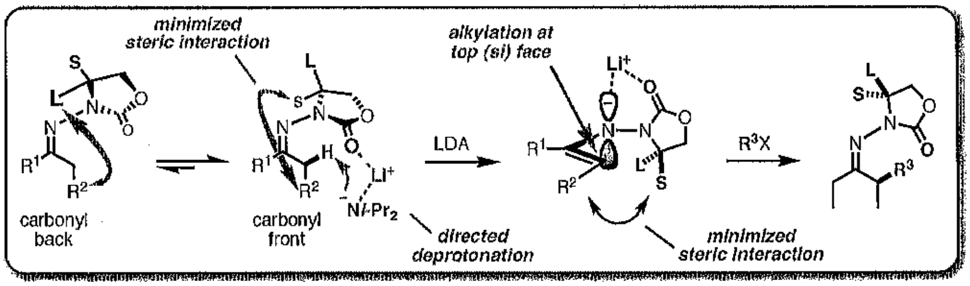
ACC Auxiliaries – Scope, Stereochemistry, and Evidence of CIS-D



Alkylating agent (RX)	Yield (%)	*R* : *S*
allylBr	96	>99 : 1
BnBr	99	>99 : 1
EtI	92	>99 : 1
PrI	94	98 : 2
	93	>99 : 1
	85	98 : 2
	87	99 : 1
	96	99 : 1
	94	97 : 3
	87	>99 : 1
	83	98 : 2

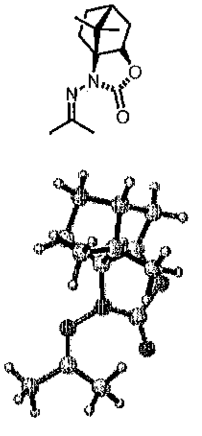


ACC Auxiliaries – Stereochemical Model

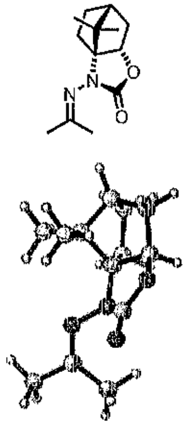


N–N Conformation

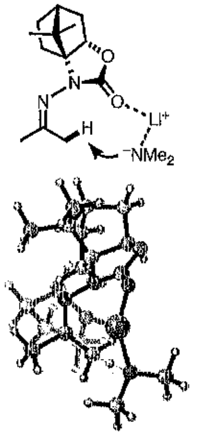
Deprotonation Transition States



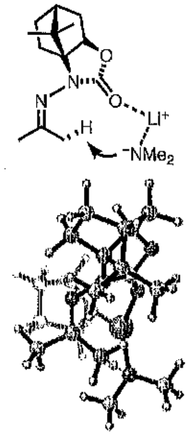
ΔH_{rel} = 3.5 kcal/moll



ΔH_{rel} = 0 kcal/moll

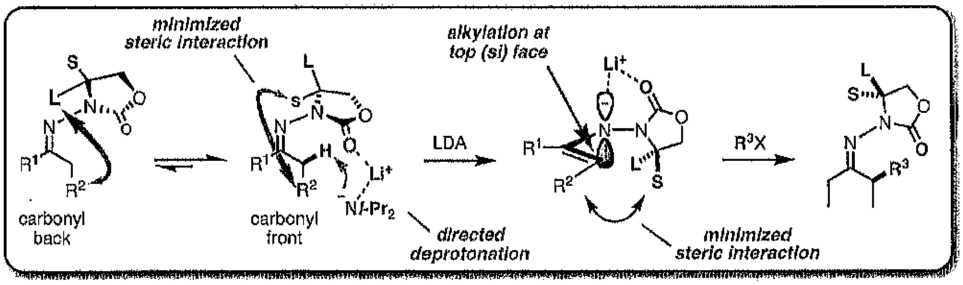


$\Delta H^{\ddagger}_{rel}$ = 0 kcal/moll

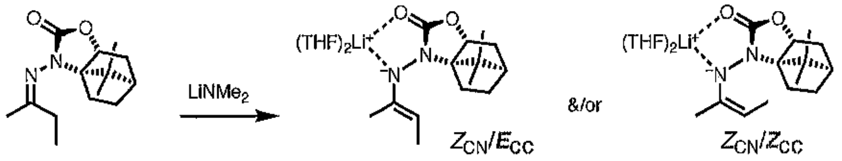


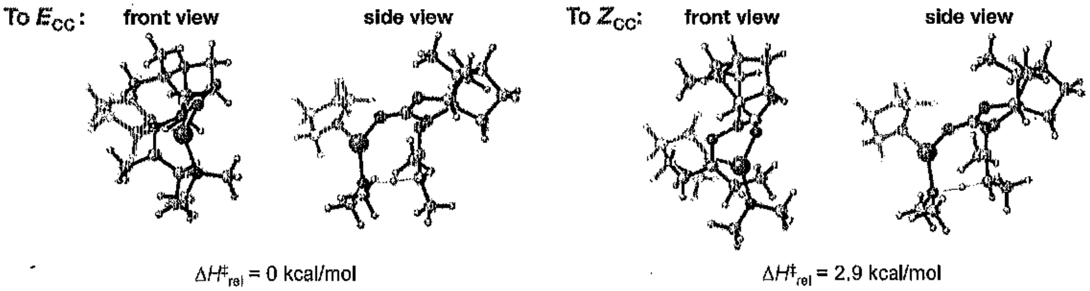
$\Delta H^{\ddagger}_{rel}$ = 3.5 kcal/moll

ACC Auxiliaries – Stereochemical Model



Deprotonation Transition States Leading to E_{CC} and Z_{CC} Azaenolates

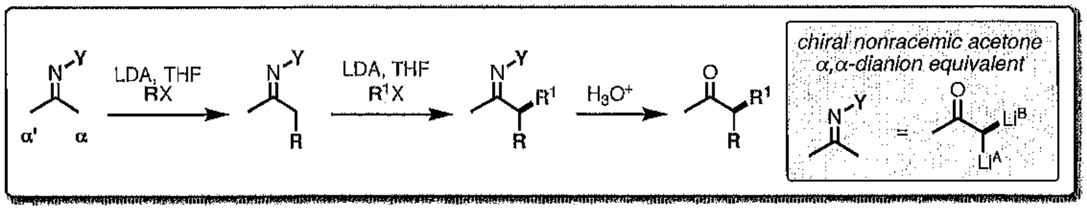


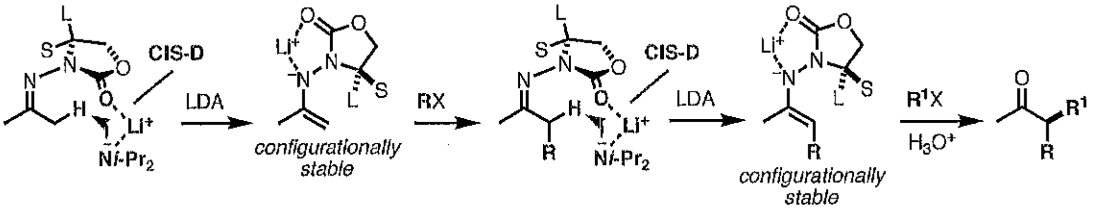


$\Delta H^{\ddagger}_{rel} = 0$ kcal/mol

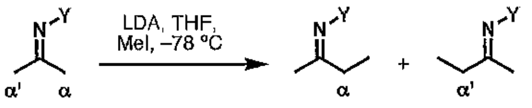
$\Delta H^{\ddagger}_{rel} = 2.9$ kcal/mol

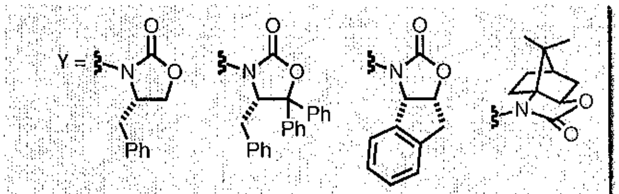
ACC Auxiliaries – Asymmetric α,α–Bisalkylation





Regioselectivity of Monoalkylation

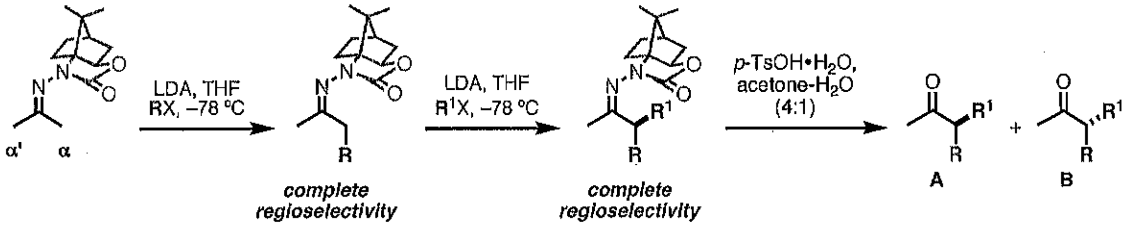




α : α'	91 : 9	98 : 2	91 : 9	>99 : 1
% yield	90	82	93	96

ACC Auxiliaries – Asymmetric α,α–Bisalkylation

Stereo- and Regioselectivity

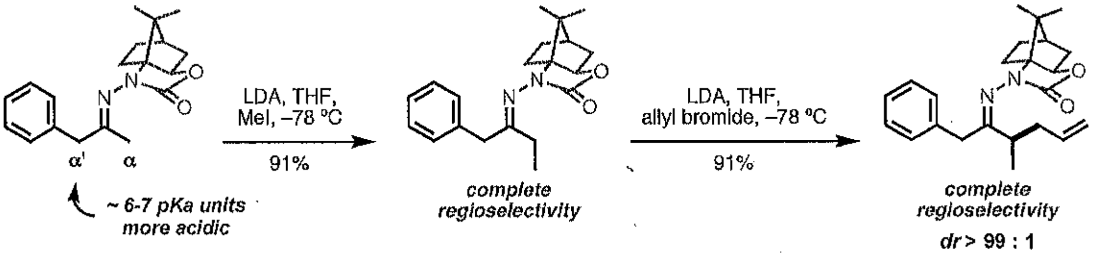


First Alkylation		Second Alkylation			Hydrolysis	
RX	% Yield	R^1X	% Yield	dr	% Yield	A : B
MeI	97	BnBr	93	>99:1	98	>99:1
BnBr	91	MeI	97	>99:1	98	>99:1
EtI	94	AllylBr	91	>99:1	95	n.d.
AllylBr	92	EtI	94	>99:1	96	n.d.
4-Br-$C_6H_4CH_2Br$	96	PrenylBr	89	>99:1	98	>99:1
PrenylBr	87	4-Br-$C_6H_4CH_2Br$	87	>99:1	98	>99:1
4-Br-$C_6H_4CH_2Br$	96	AllylBr	91	>99:1	98	>99:1
AllylBr	92	4-Br-$C_6H_4CH_2Br$	92	>99:1	97	>99:1

- CIS-D completely overrides the inherent preference of LDA to remove the most acidic proton
- Attempts to effect third α-alkylation not successful – CIS-D breaks down

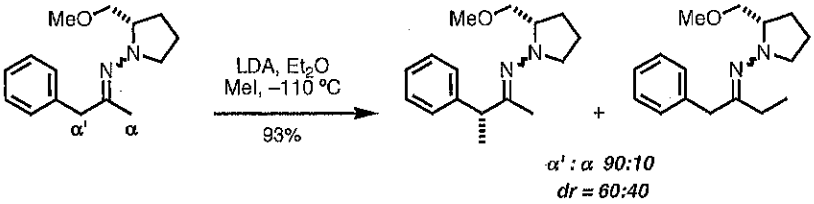
ACC Auxiliaries – CIS-D in Activated Ketones

α,α-Bisalkylation of α-Phenylacetone



- CIS-D completely overrides the inherent preference of LDA to remove the most acidic proton

Alkylation via SAMP Hydrazone



- Complimentary regiochemical outcome