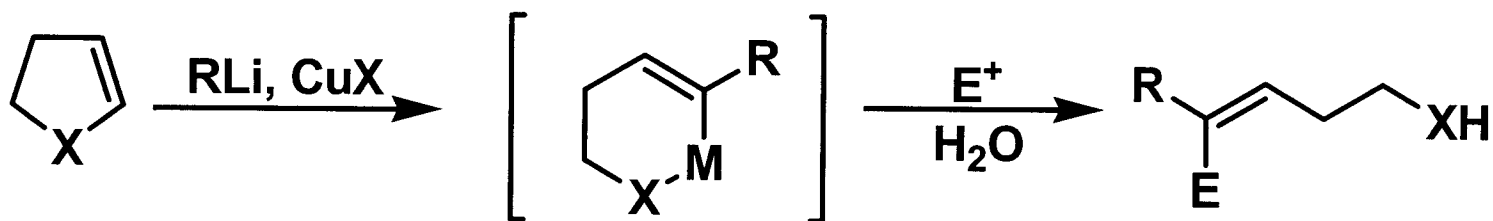


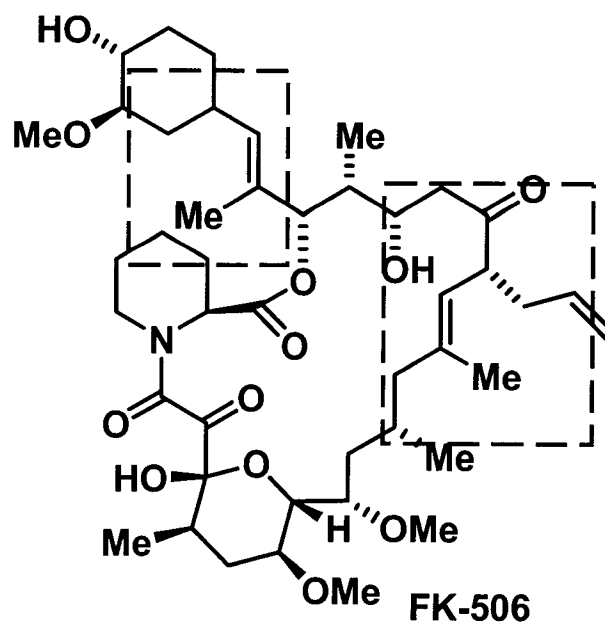
1,2-Metallate Rearrangement



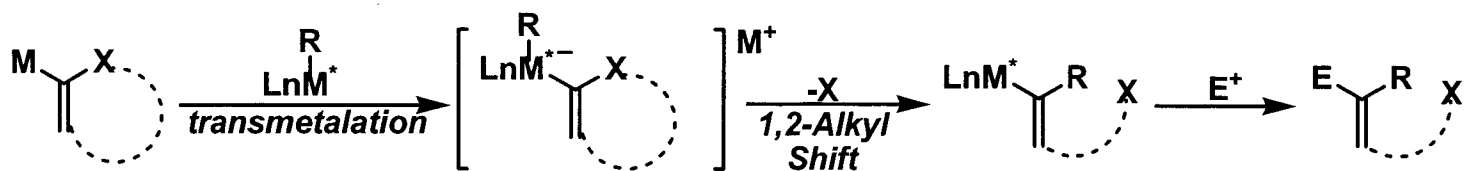
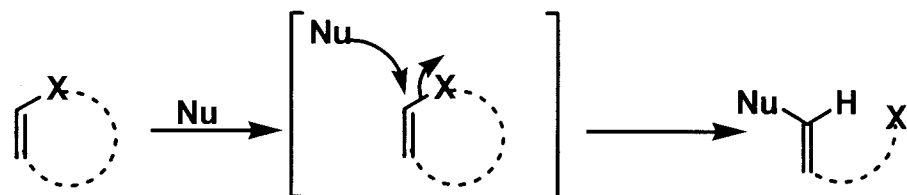
Christopher S. Regens
Group Meeting
1/18/2005

Why Do We Care?

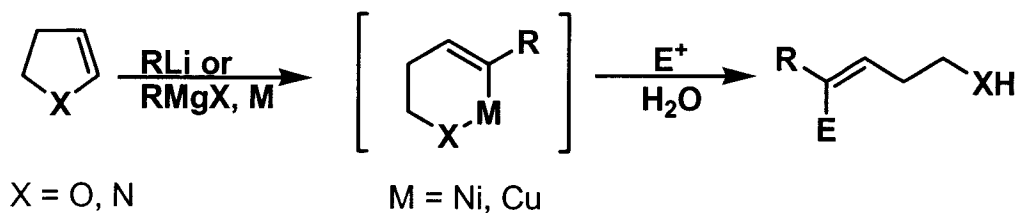
- Challenging to synthesize trisubstituted olefins (especially with *Z* geometry)
 - Common olefination procedures (Wittig and Peterson) give variable selectivities
- Trisubstituted olefin functional array common in natural products



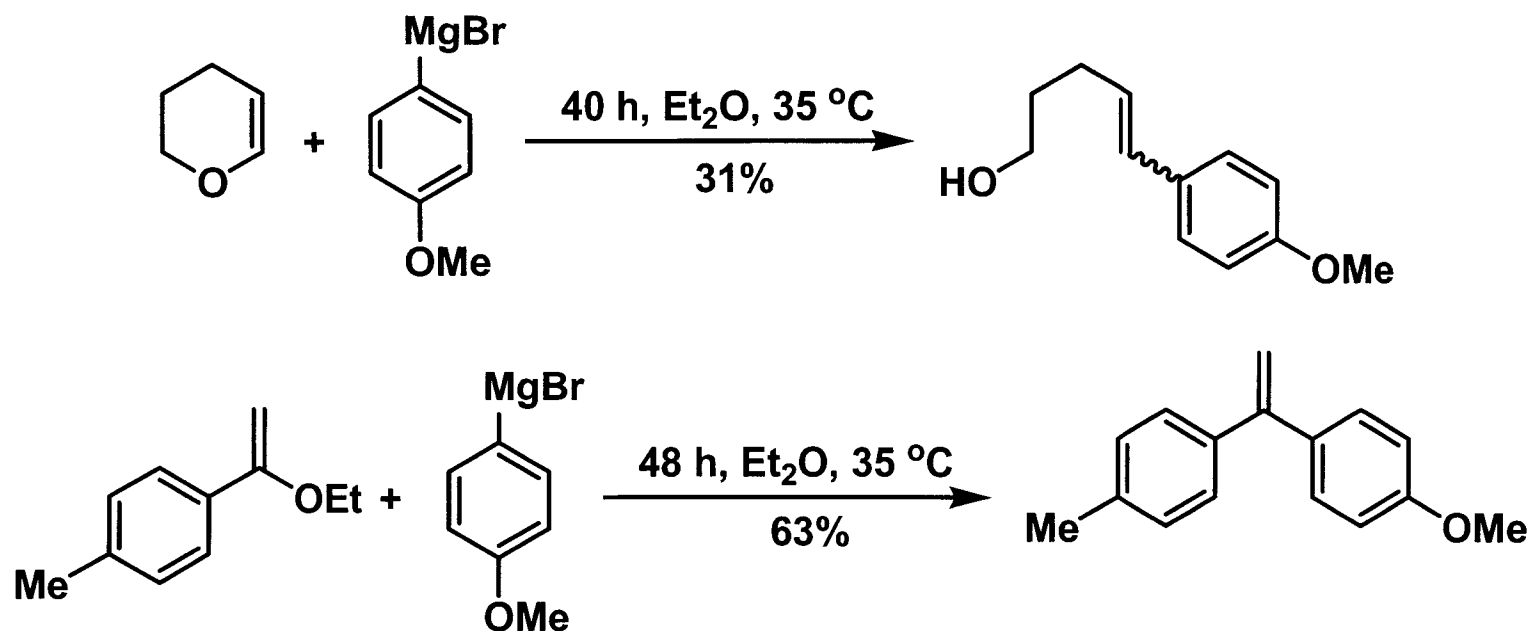
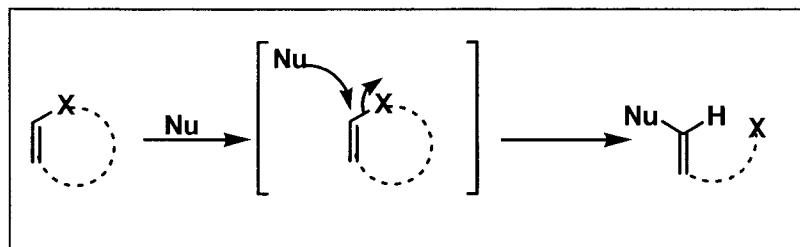
Metallate Rearrangement: General Reaction



-Common metals: Al, B, Cu, Ni, Zn and Zr



Background

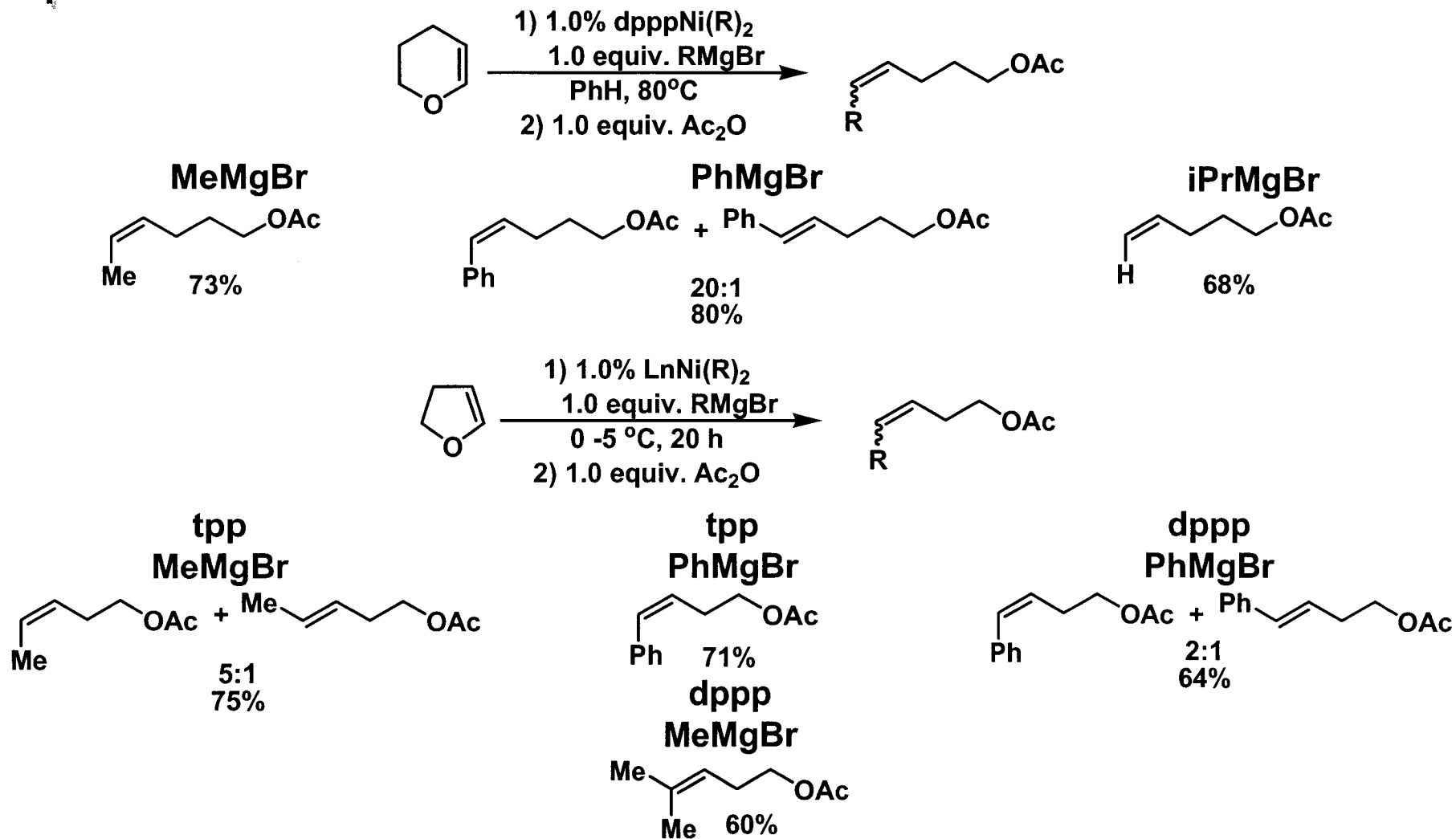


Reactions were plagued by long reaction times

Hill, C.M., Walker, R.A., Hill, M.E. *J. Am. Chem. Soc.* **1951**, 73, 1663

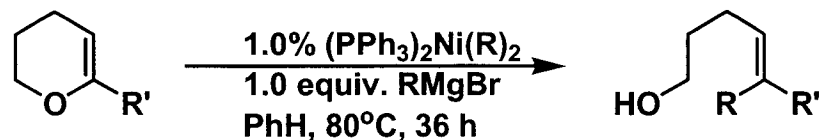
Hill, C.M., Senter, G.W., Haynes, L., Hill, M.E. *J. Am. Chem. Soc.* **1953**, 76, 4538

Nickel-Catalyzed Rearrangement of Grignard Reagents with Dihydropyran and Dihydrofuran



Rearrangement proceeded with inversion of configuration

Stereoselective Nickel-Catalyzed Rearrangement of Dihydropyran

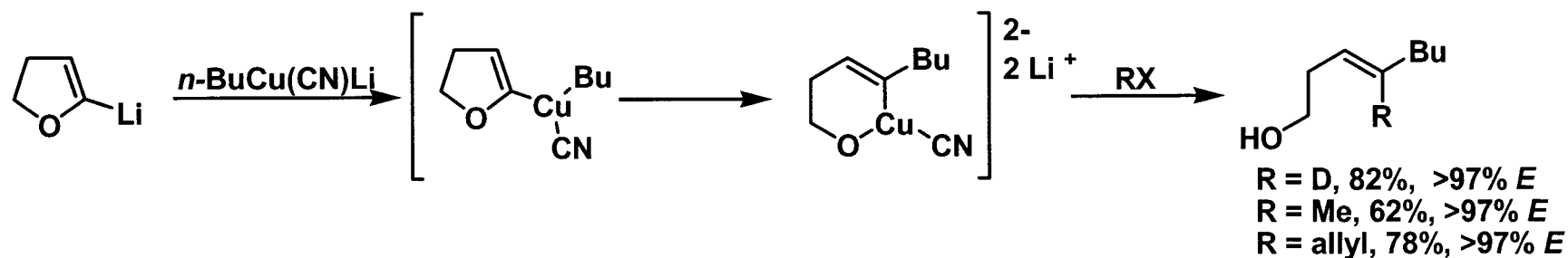


<u>Dihydropyran*</u>	<u>Grignard Reagent</u>	<u>Product (Yield %)*</u>
 (4)	PhMgBr $\text{Me}_3\text{SiCH}_2\text{MgCl}$	 (6) R = Ph (70%) (7) R = CH_2SiMe_3 (54%)
 (18)	MeMgBr PhMgBr	 (19) R = Me (35%) (20) R = Ph (56%)
 (8)	MeMgBr PhMgBr	 (9) R = Me (39%) (10) R = Ph (49%)
 (11)	MeMgBr	 (12) (45%)

• Limitations

- Prolonged reflux in benzene destroyed catalysts
- Reaction is limited to Grignard reagents lacking β -hydrogens
- Dihydrofurans rearrange to the exocyclic isomer under prolonged heating

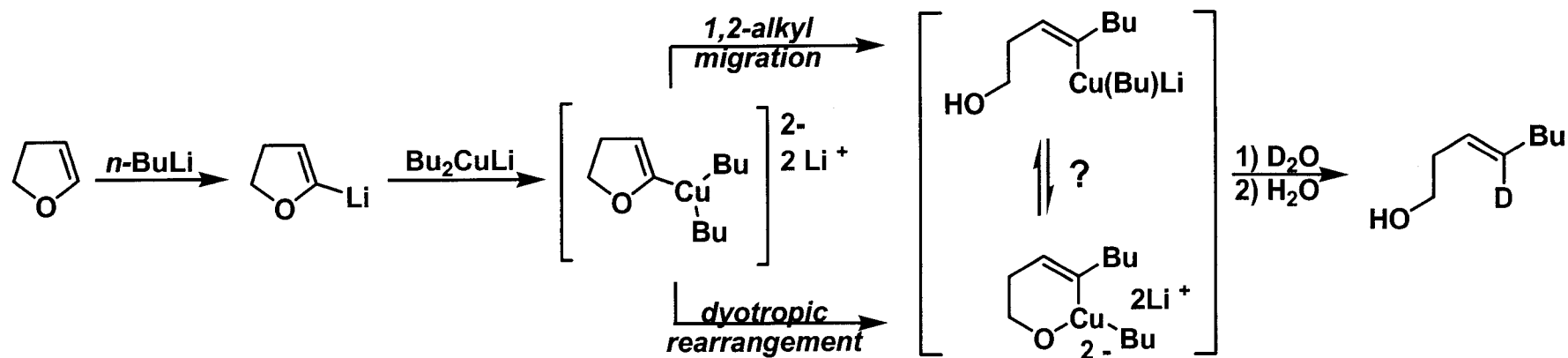
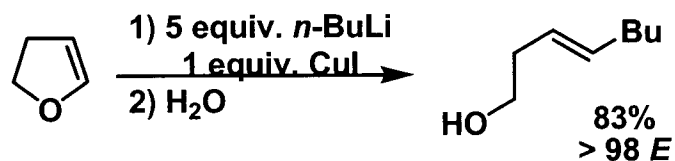
Organocuprate Catalyzed Rearrangement



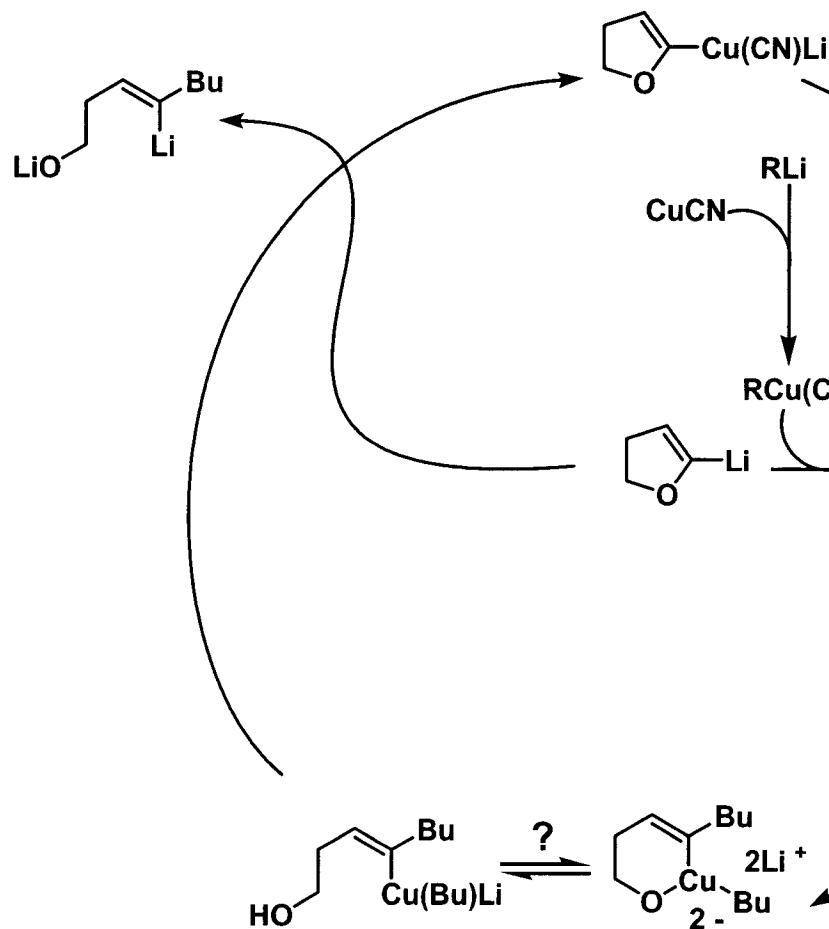
entry	α -lithio enol ether	RM (4 equiv.)	equiv. CuCN		R (% yield)
1		<i>n</i> -BuLi	0.1		<i>n</i> -Bu (82%)
2		<i>t</i> -BuLi	0.1		<i>s</i> -Bu (88%)
3		<i>o</i> -MeOC ₆ H ₄ Li	0.5		<i>o</i> -MeOC ₆ H ₄ (47%)
4		Me ₂ C=C(CH ₂) ₂ MgBr	1.0		Me ₂ C=C(CH ₂) ₂ (75%)
5		MeLi	0.1		Me (52%)
6		PhLi	1.0		Ph (25%)
7		CH ₂ =C(Me)Li	0.07		CH ₂ =C(Me) (79%)
8		PhCH ₂ MgBr	1.0		PhCH ₂ (60%)
9		PhMe ₂ SiLi	0.2		PhMe ₂ Si (92%)
10		Me ₃ SnLi	0.2		Me ₃ Sn (78%)

Copper catalyzed rearrangement proceeds with inversion of configuration

Mechanism: Organocuprate Rearrangement

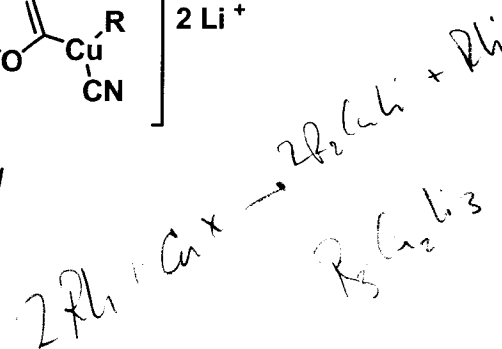


Mechanism: Proposed Catalytic Cycle

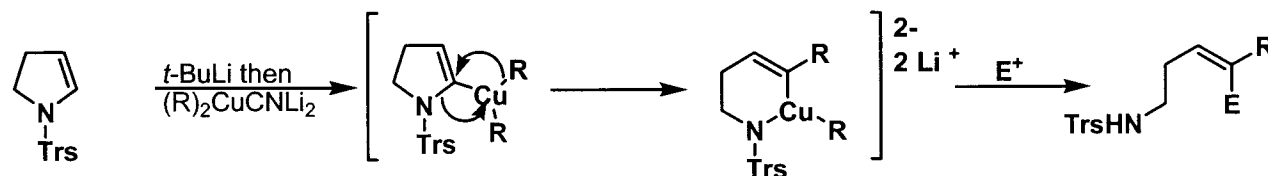


• Key Steps

- Formation of the higher order cyanocuprate intermediate
- Subsequent transmetalation displacing the alkenyl ligand



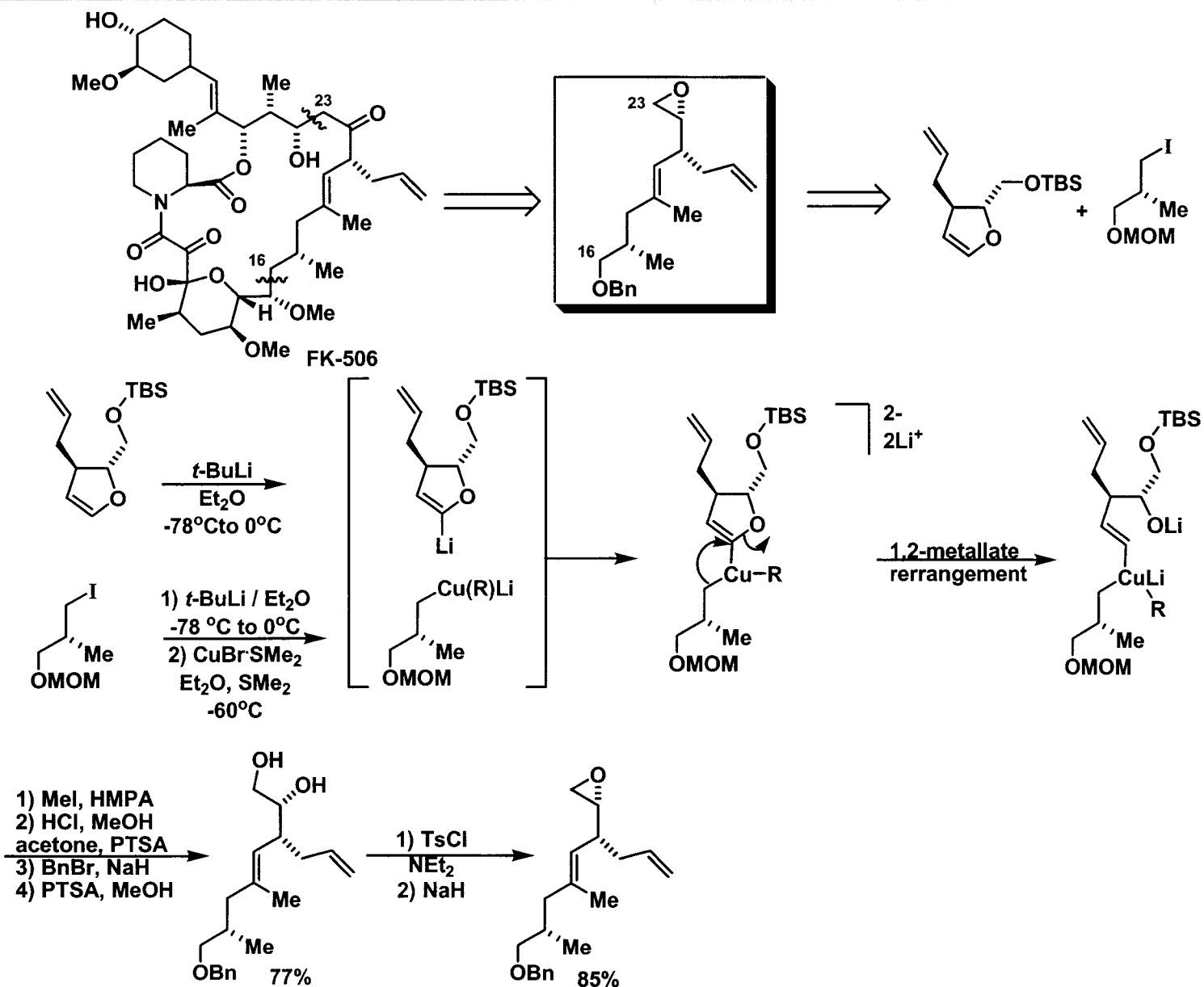
Cuprate Rearrangement: Synthesis of Homoallyl Amines



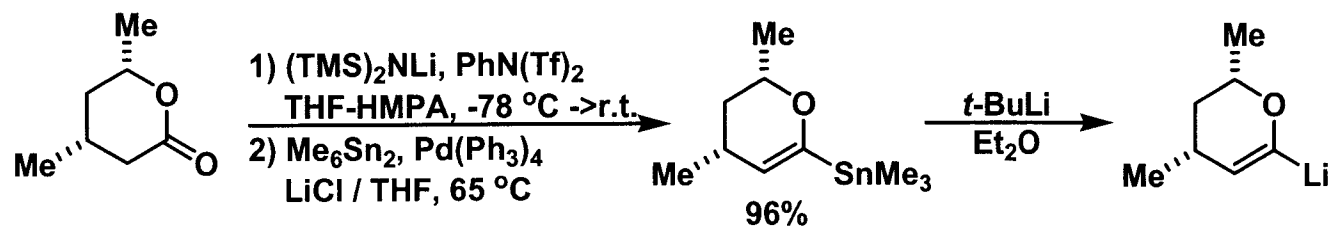
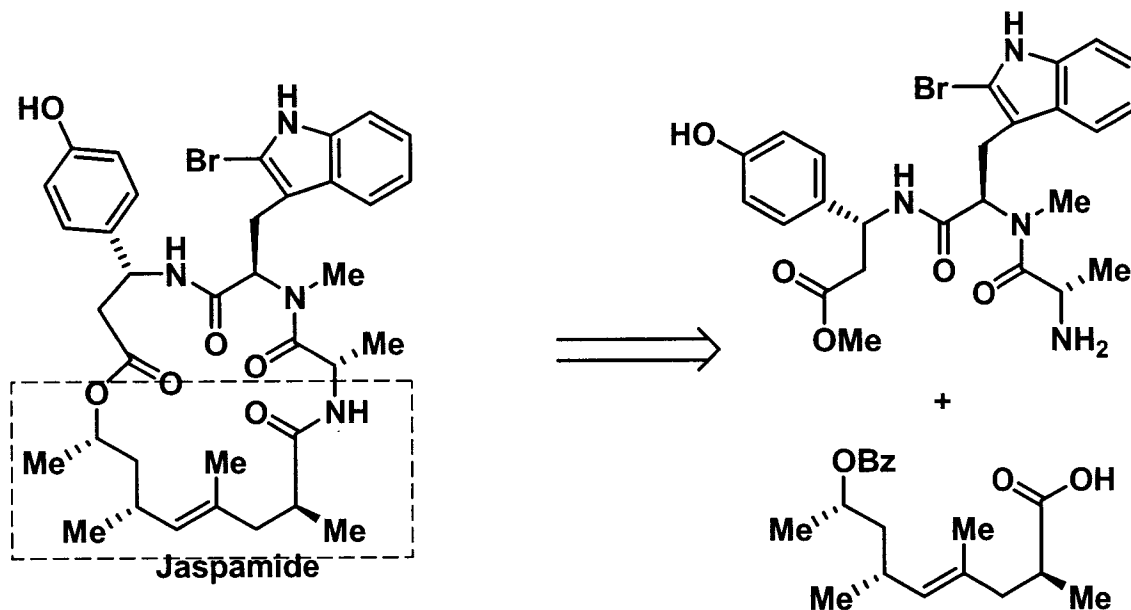
entry	cuperate	electrophile	Product		% yield
			R	E	
1	$(\text{CH}_2=\text{CH})_2\text{CuCNLi}_2$	H_2O	$\text{CH}_2=\text{CH}$	H	66
2	$(t\text{-Bu})_2\text{CuCNLi}_2$	H_2O	t-Bu	H	93
3	$(t\text{-Bu})_2\text{CuCNLi}_2$	MeI	t-Bu	Me	92
4	$(t\text{-Bu})_2\text{CuCNLi}_2$	allyl bromide	t-Bu	allyl	88
5	$(t\text{-Bu})_2\text{CuCNLi}_2$	I_2	t-Bu	I	92
6	$(t\text{-Bu})_2\text{CuCNLi}_2$	Me_3SnCl	t-Bu	Me_3Sn	80

- Electron withdrawing group on nitrogen is necessary
- Slight excess of higher order cuprate is need to achieve good yields
- Lithiation of dihydropyrole prior to treatment with cuprate is required

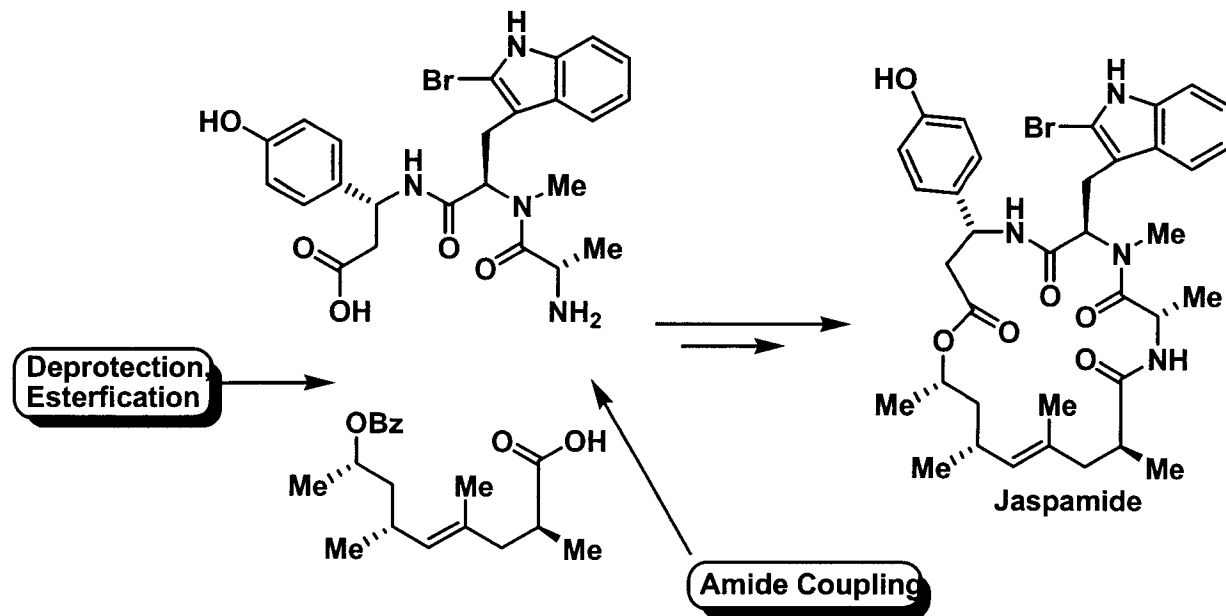
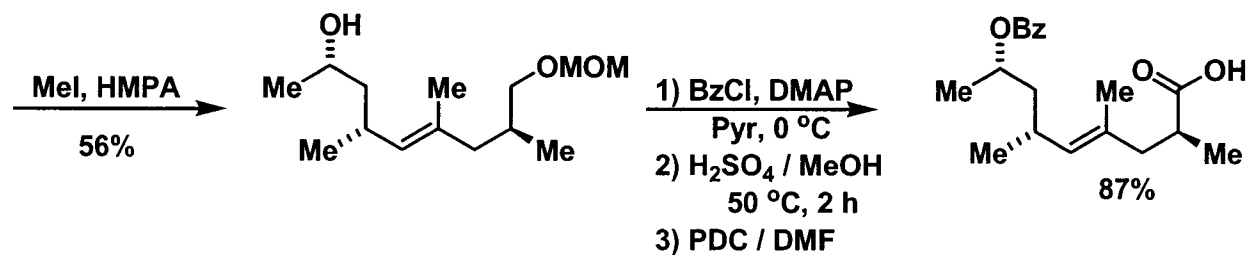
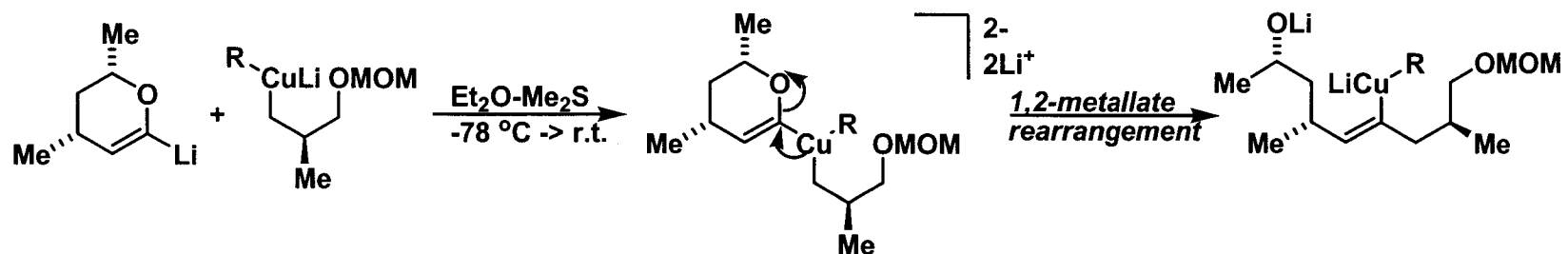
Synthesis of C16-C23 Fragment of FK-506



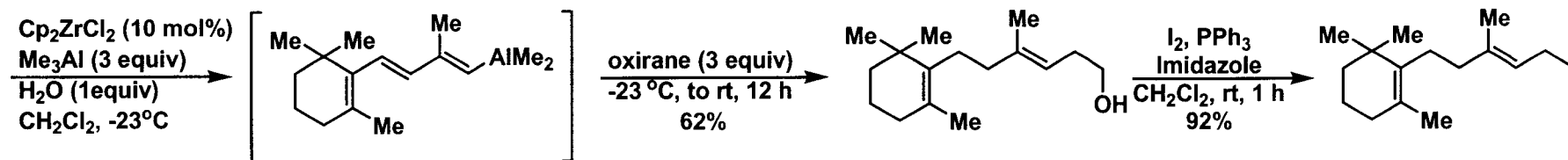
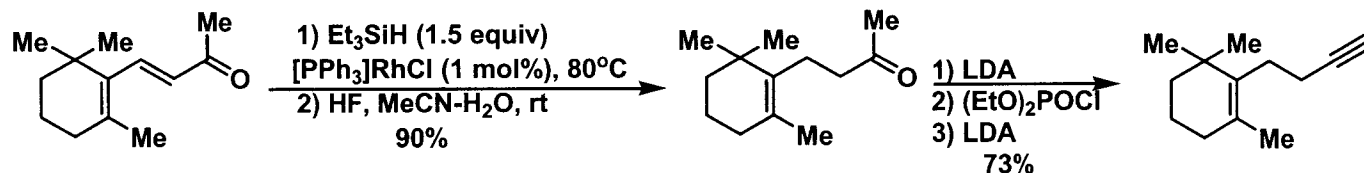
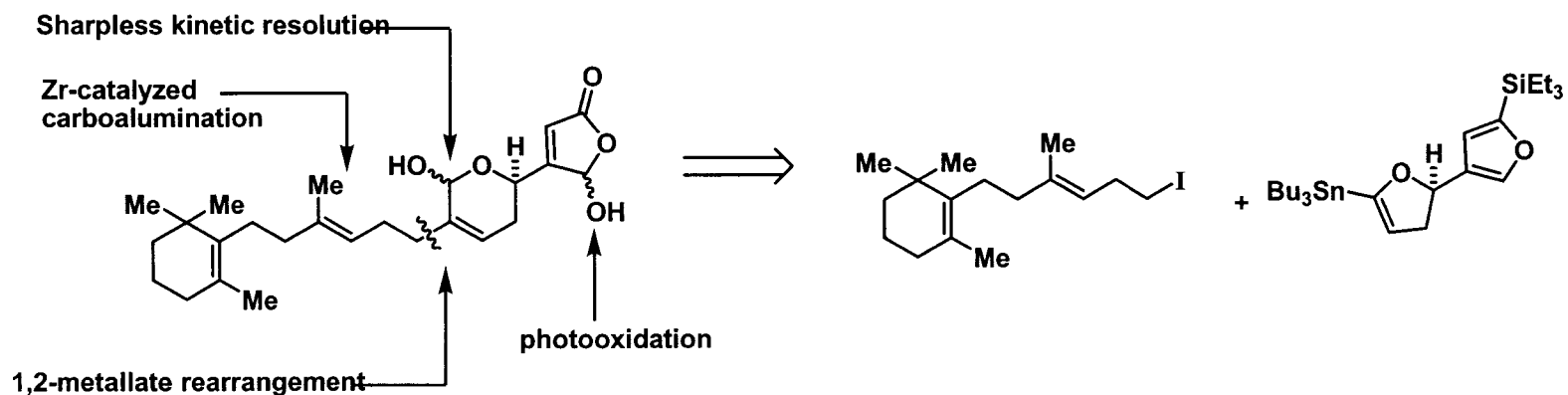
Application: Total Synthesis of Jaspamide



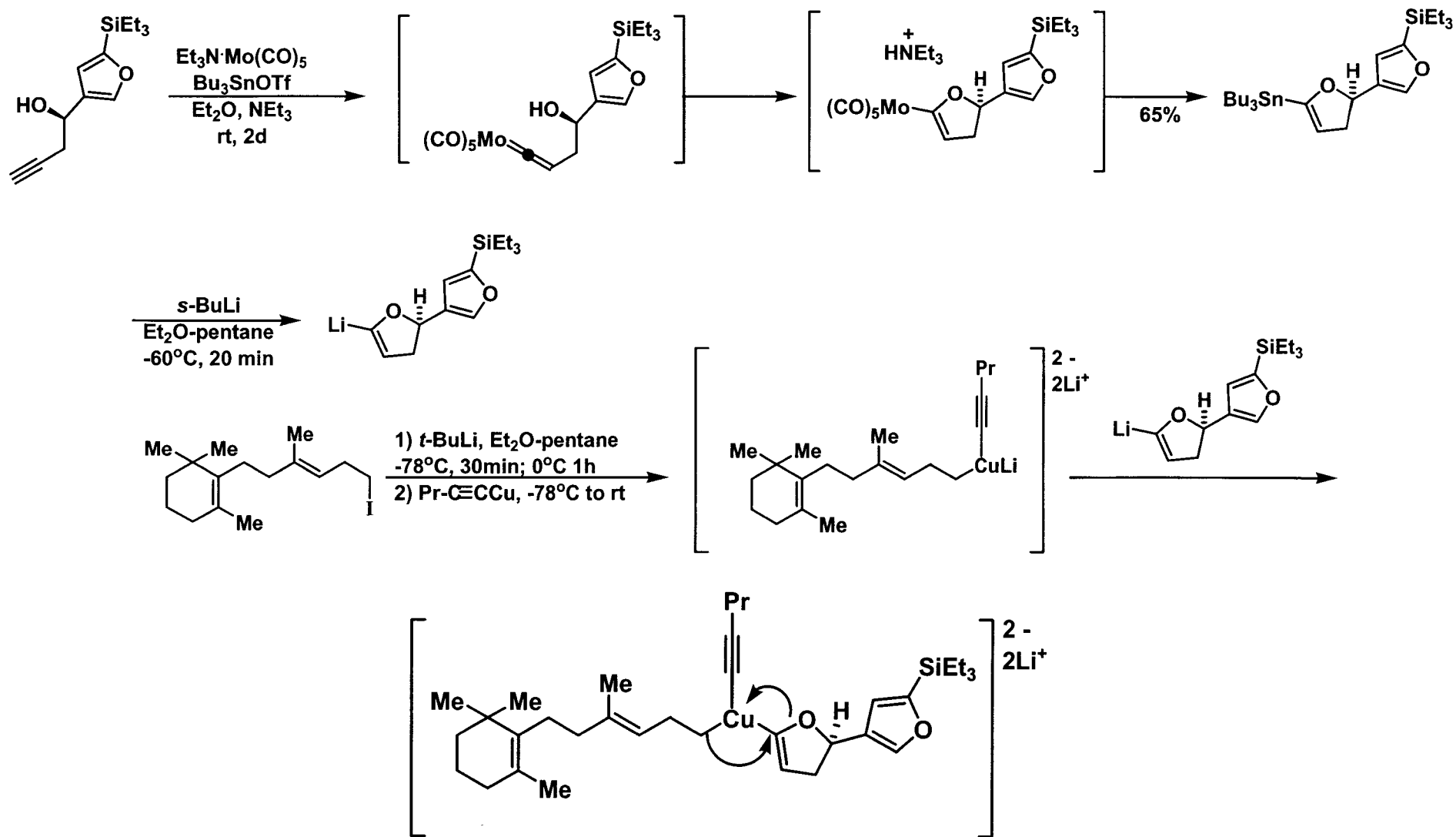
Jaspamide: Cuprate Rearrangement



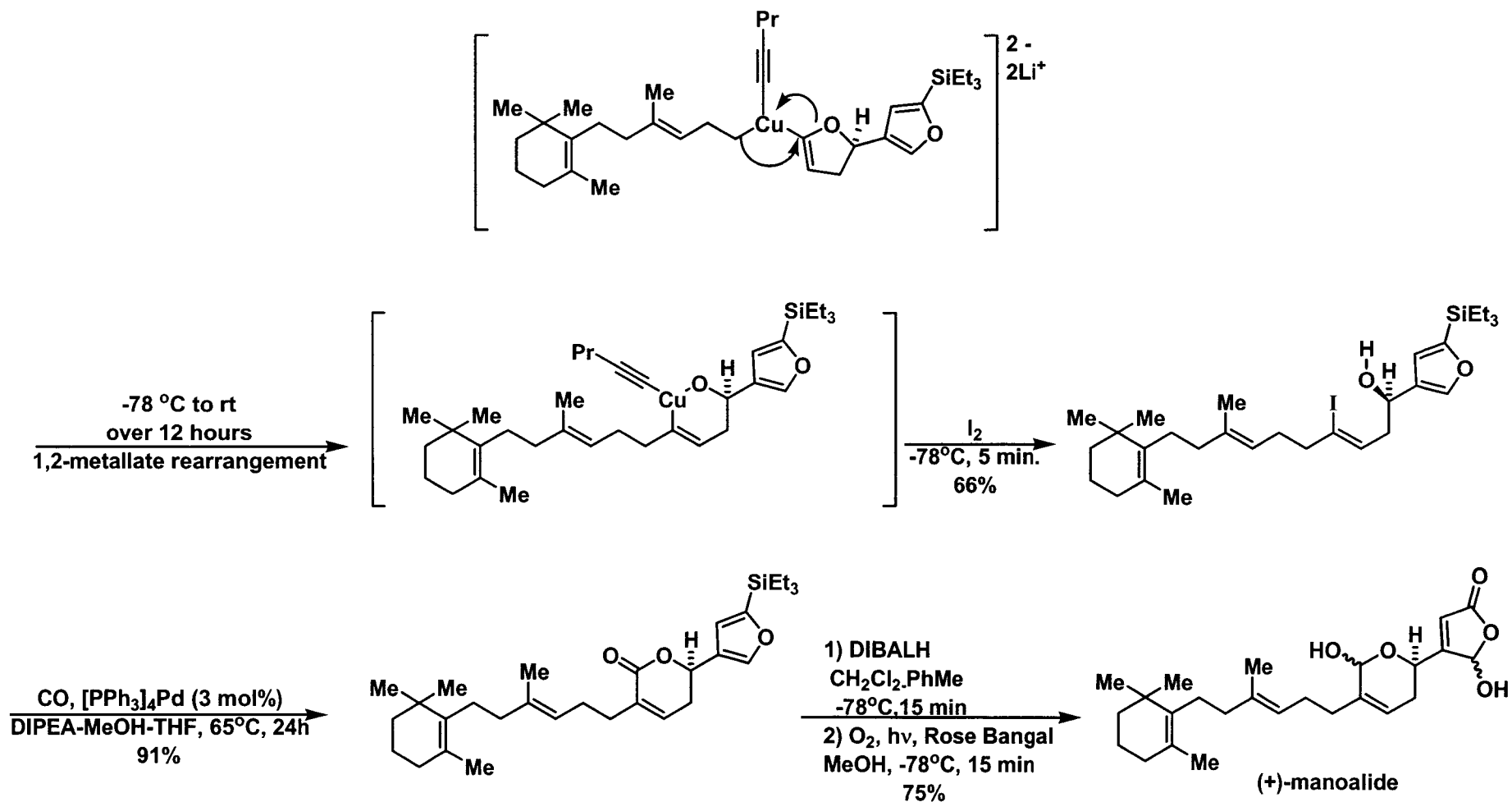
Application: Total Synthesis of (+)-Manoalide



(+)-Manoalide: 1,2-Metalate Rearrangement



(+)-Manoalide: Final Steps



(+)-manoalide was synthesized in 12% overall yield 12 steps longest linear

Conclusion

- **Advantages**

- Stereoselective formation of trisubstituted and disubstituted olefins
- Complex metal reagents prepared from relatively simple starting material

- **Disadvantages**

- Reactive starting materials (i.e. RLi, and RMgBr).
- Limited scope

- **Future Directions**

- Use of functionalized Grignard reagents