Understanding the Stability and Reactivity of Functionalised Organozinc Reagents: Applications to Amino Acid and Cyclic Peptide Synthesis

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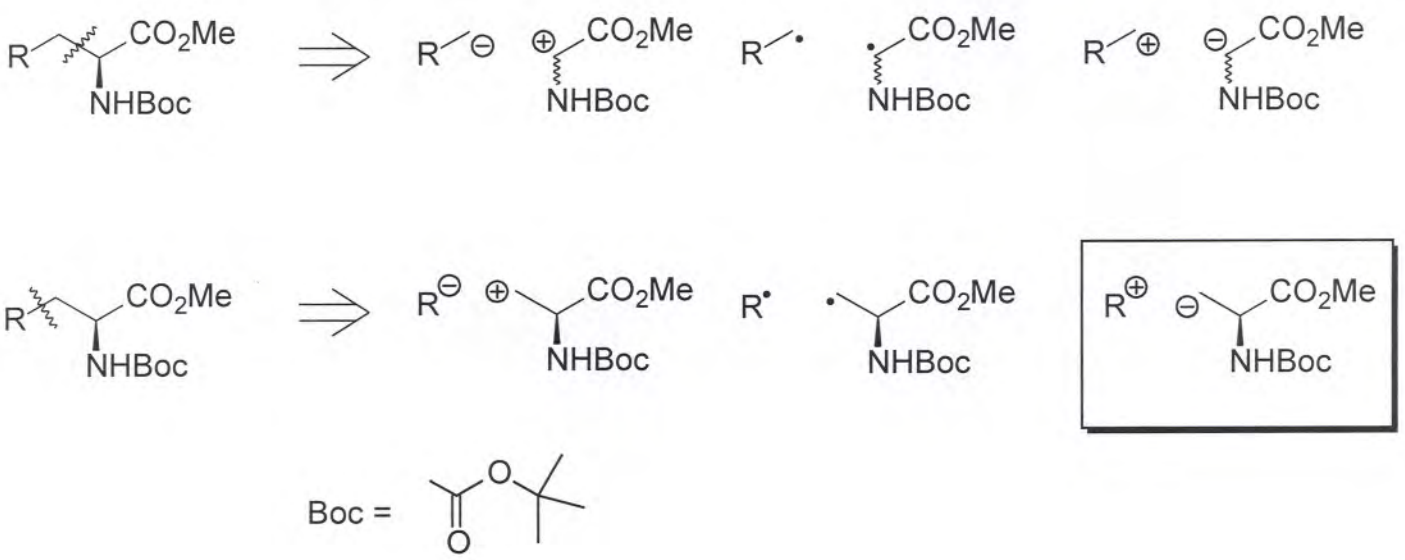
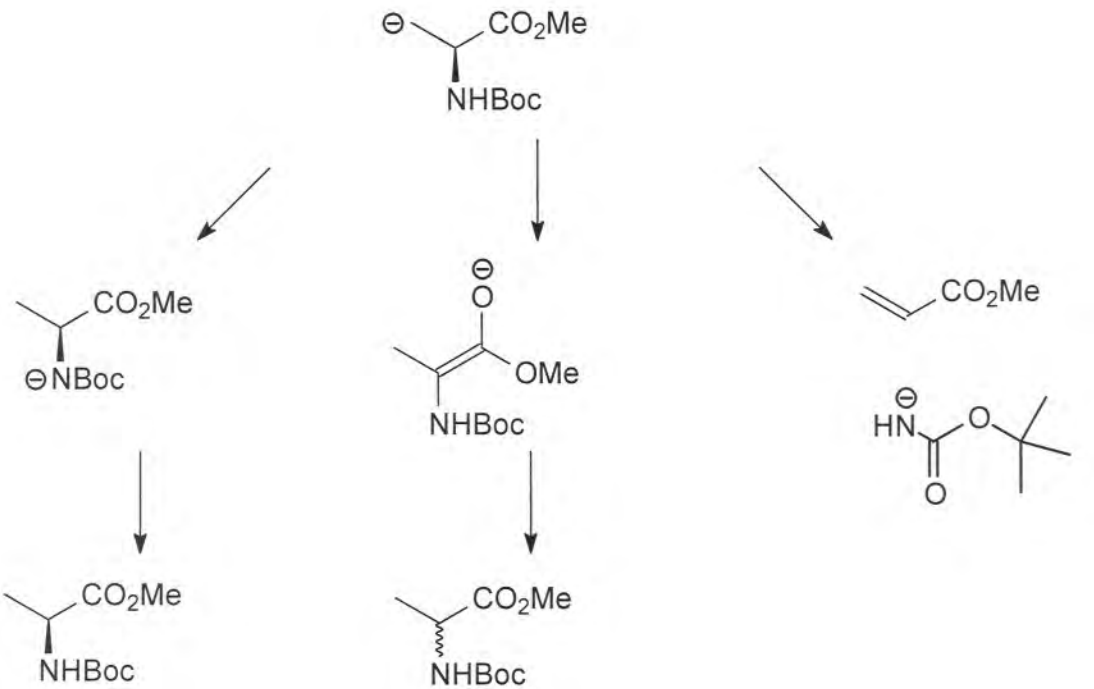
University of Sheffield

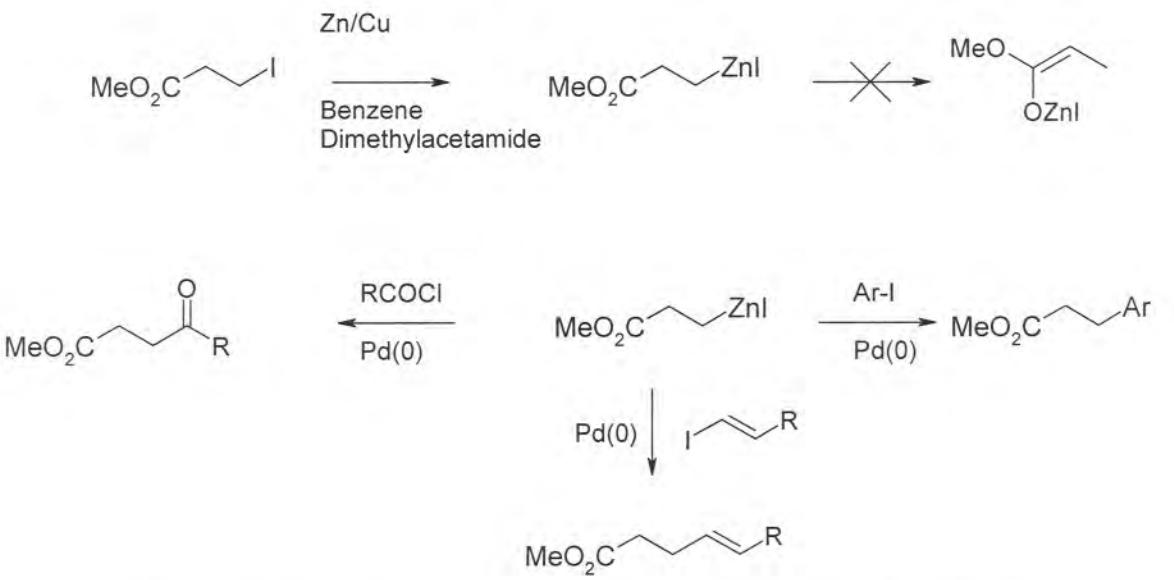
Amino Acid Disconnections



Instability of β-Amino Anions

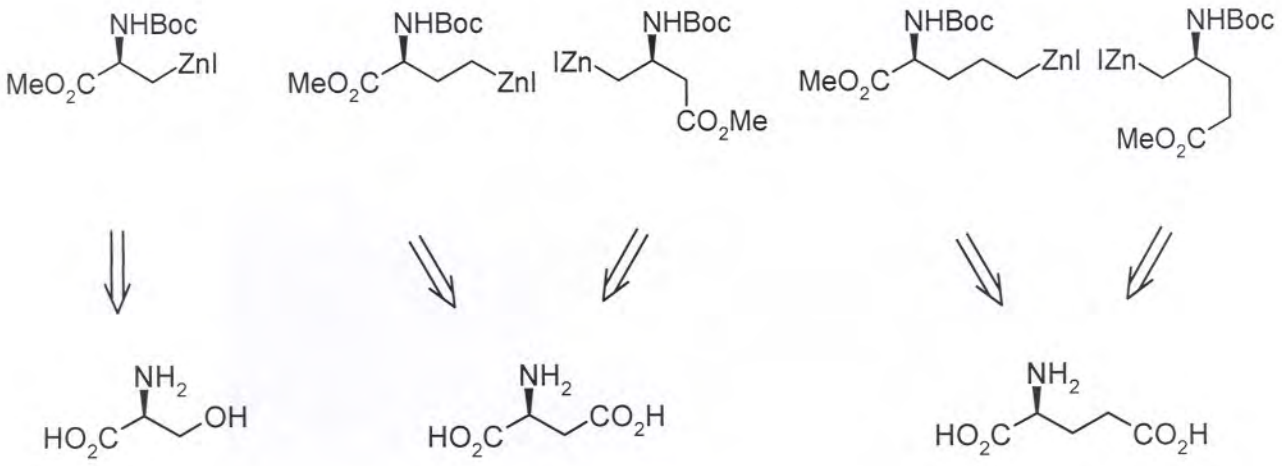


Reactions of Simple Organozinc Reagents

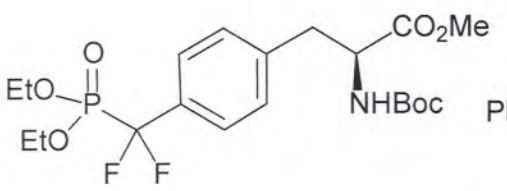


Y. Tamaru, H. Ochiai, T. Nakamura and Z.-i. Yoshida, Org. Synth. 1988, 67, 98

Amino Acid Derived Zinc Reagents

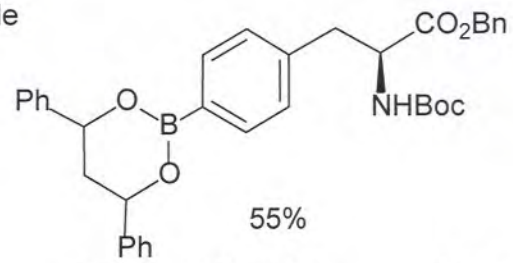


Synthesis of Phenylalanine Derivatives



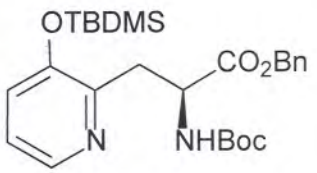
56 %

Tetrahedron Lett., 1994, **35**, 551



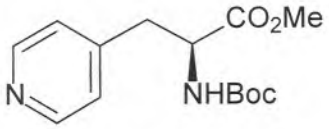
55%

Synlett., 1996, 167



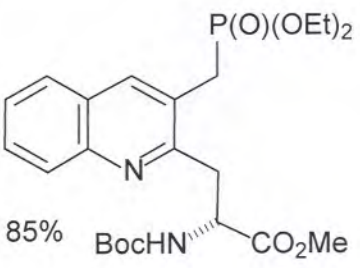
74%

J. Org. Chem., 1995, **60**, 2640



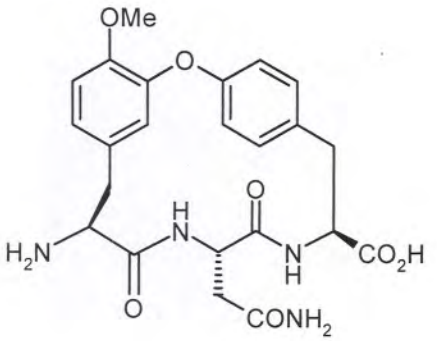
56%

J. Med. Chem., 1996, **39**, 1991
Synlett, 1997, 169

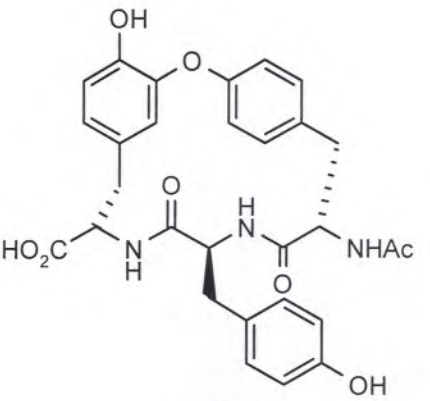


Biorg. Med. Chem. Lett., 1996, **6**, 1635

Synthesis of Macrocyclic Tripeptides

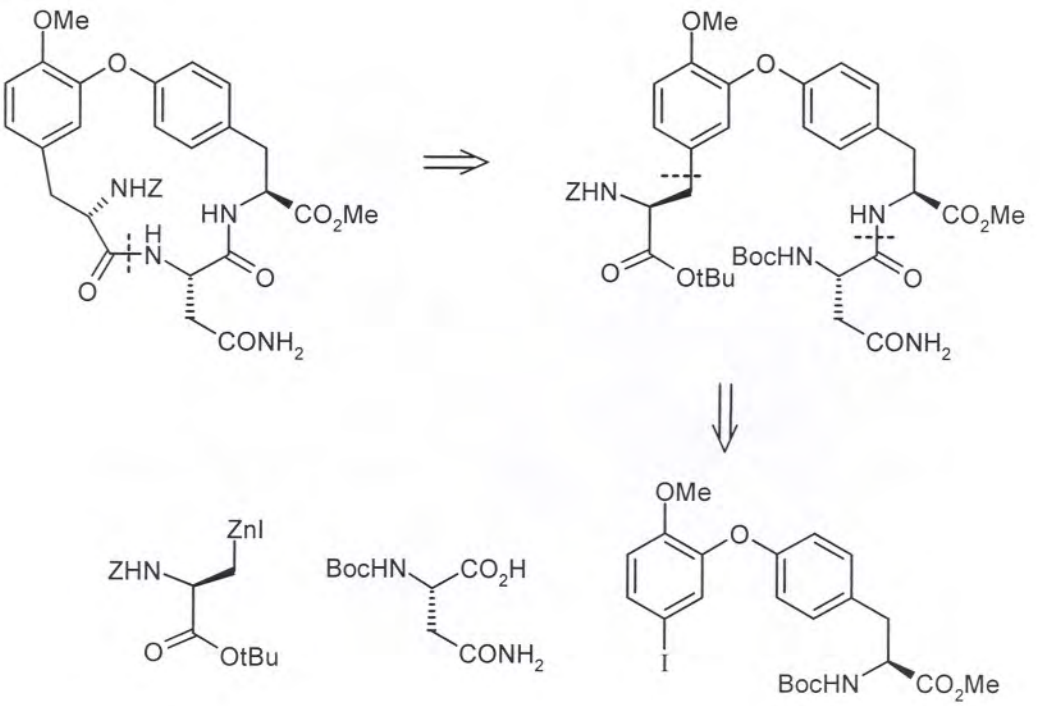


OF4949-III

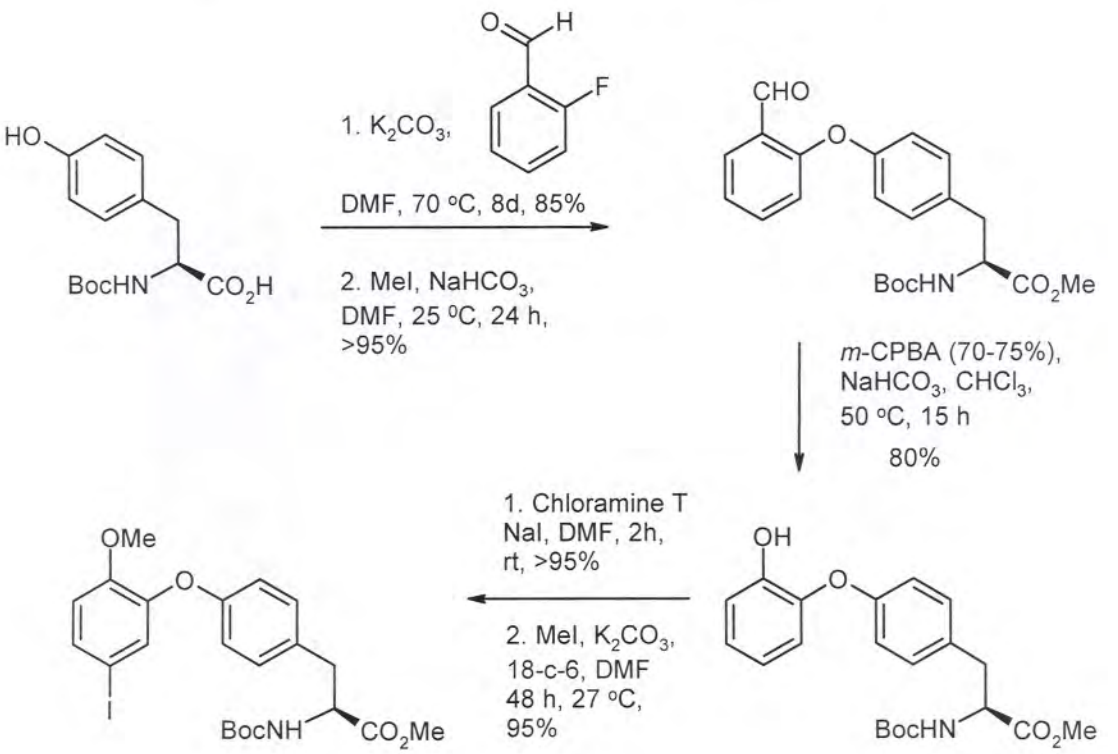


K-13

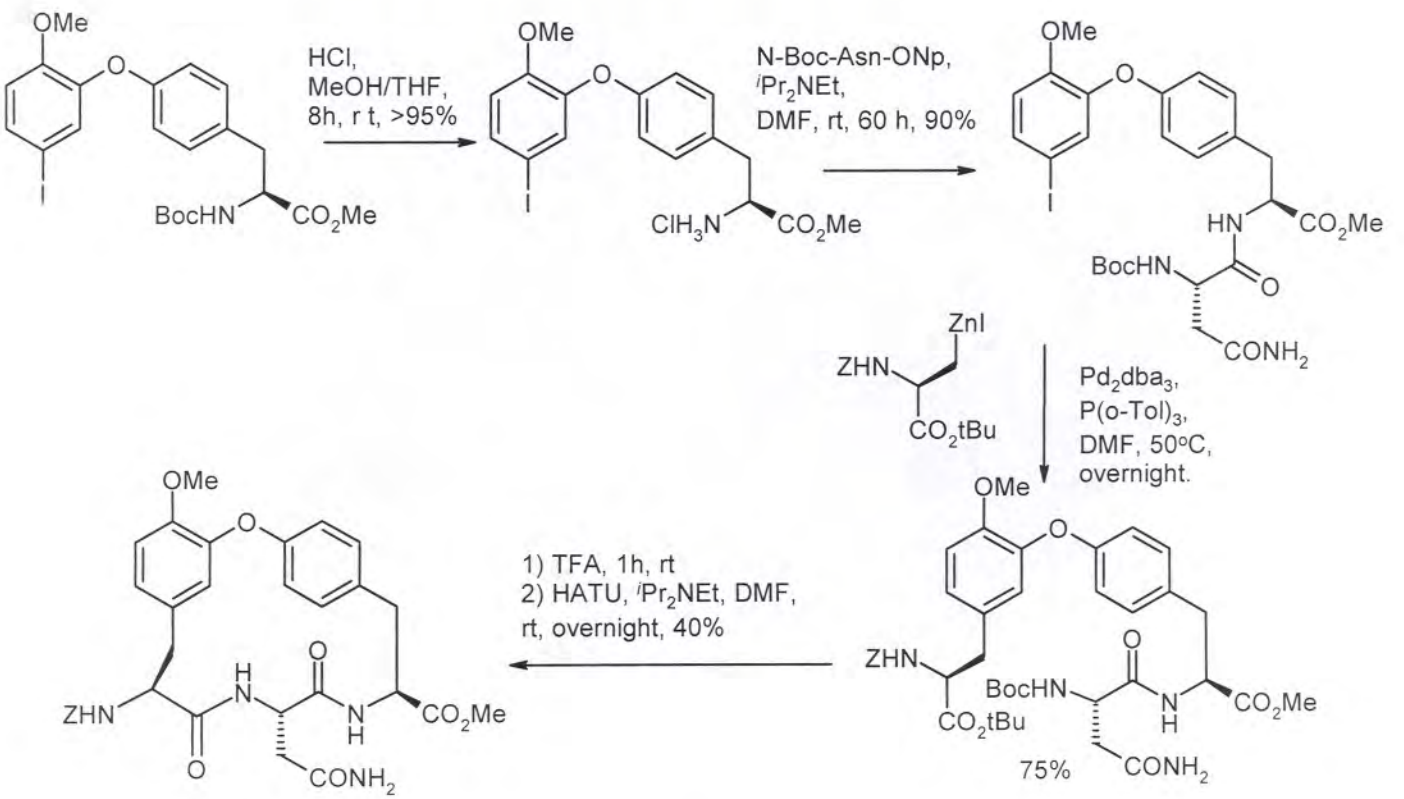
Retrosynthesis for OF4949-III



Synthesis of *O*-Aryltyrosine

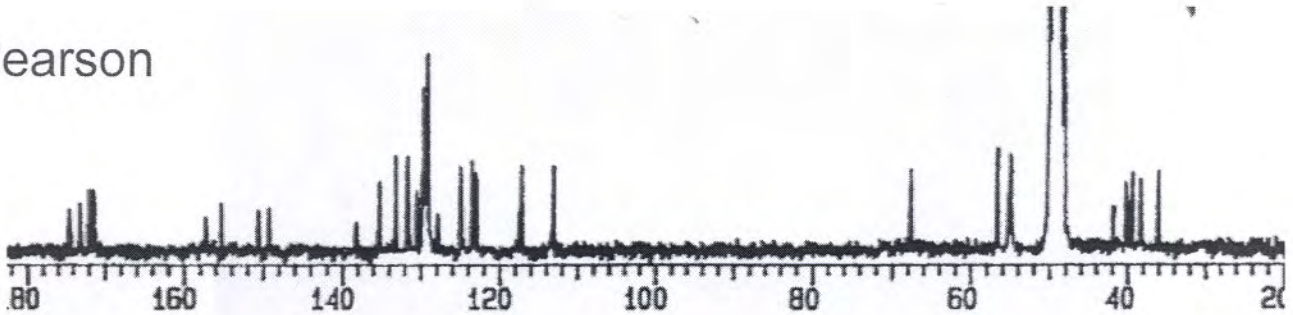


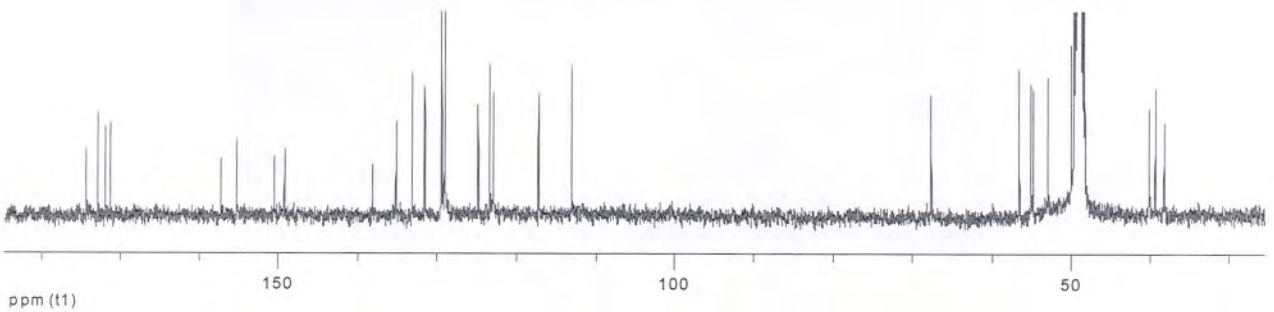
Synthesis of OF4949-III

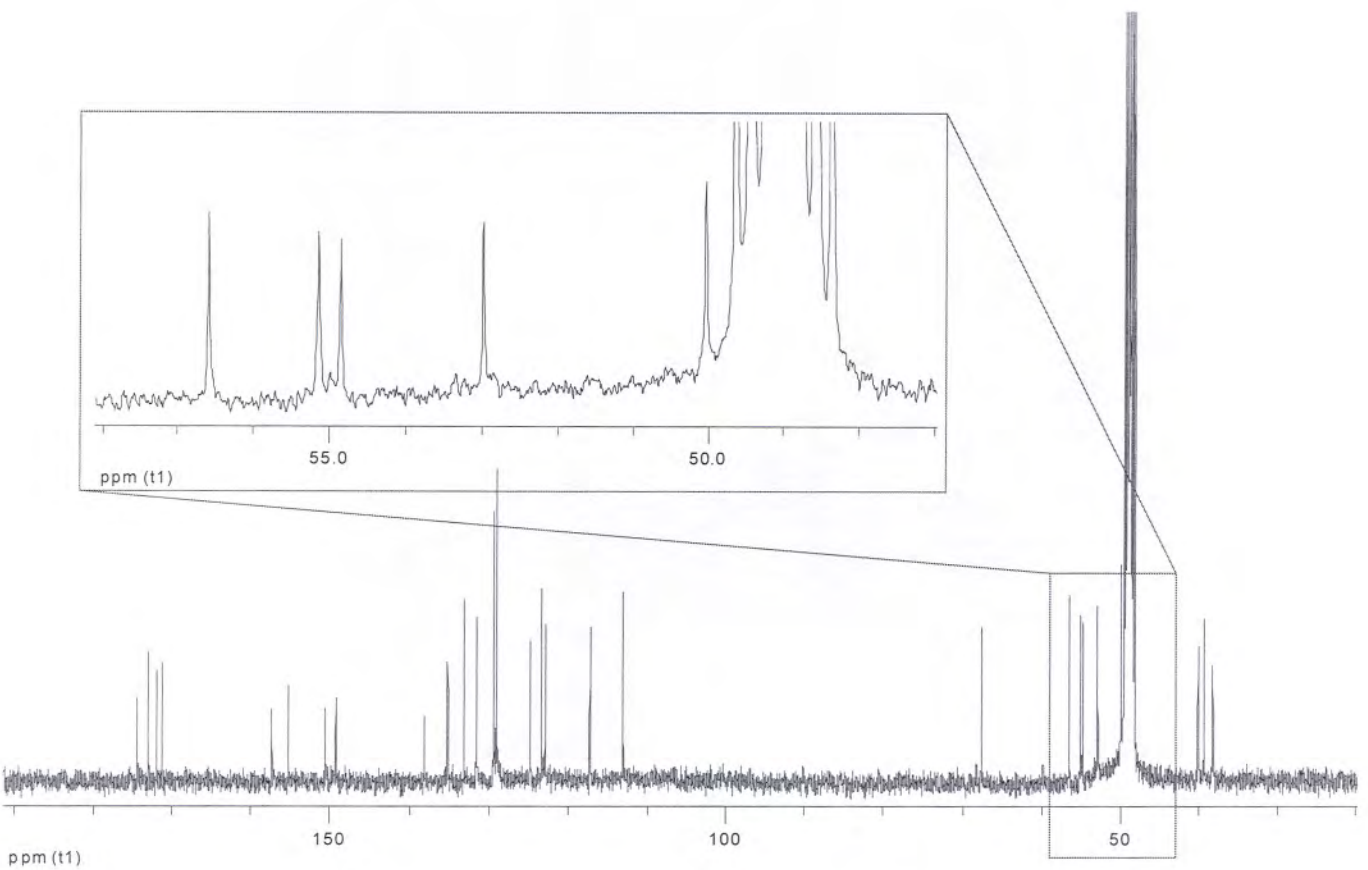


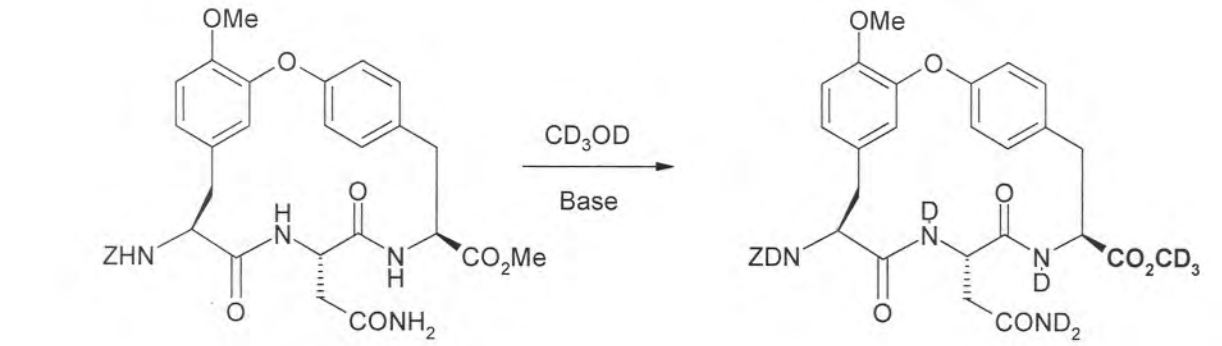
Comparison of ^{13}C Data with Literature data

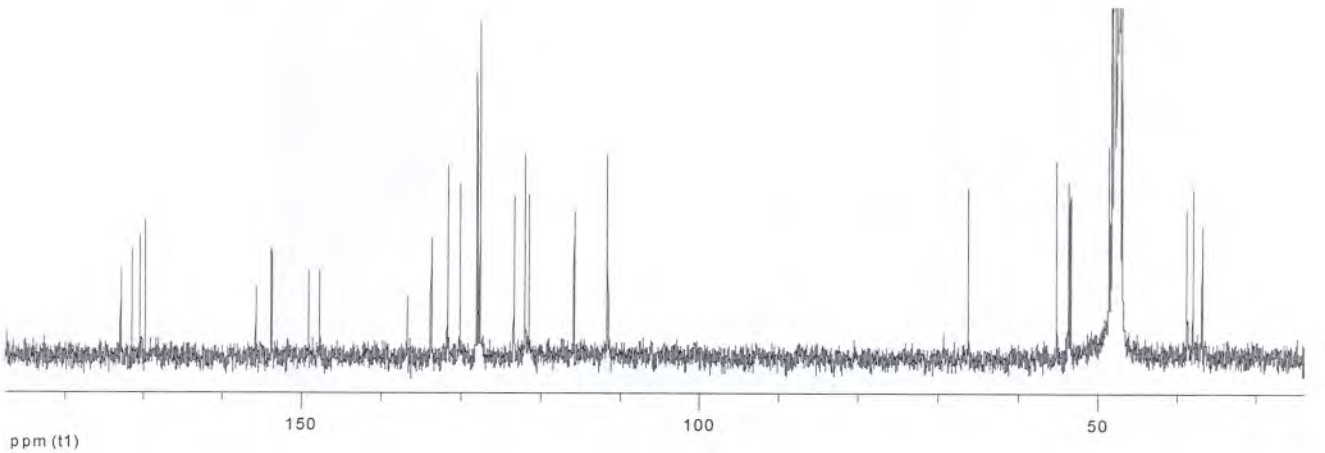
Pearson



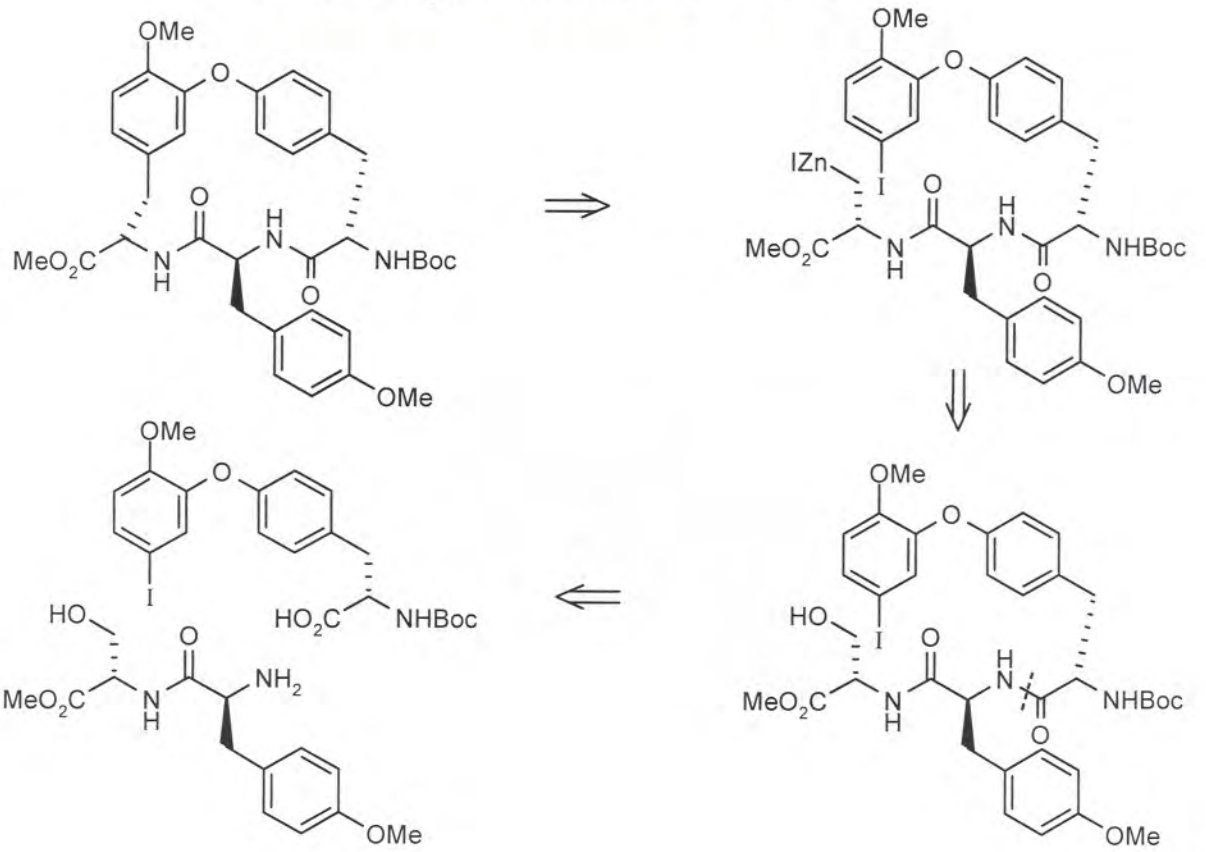




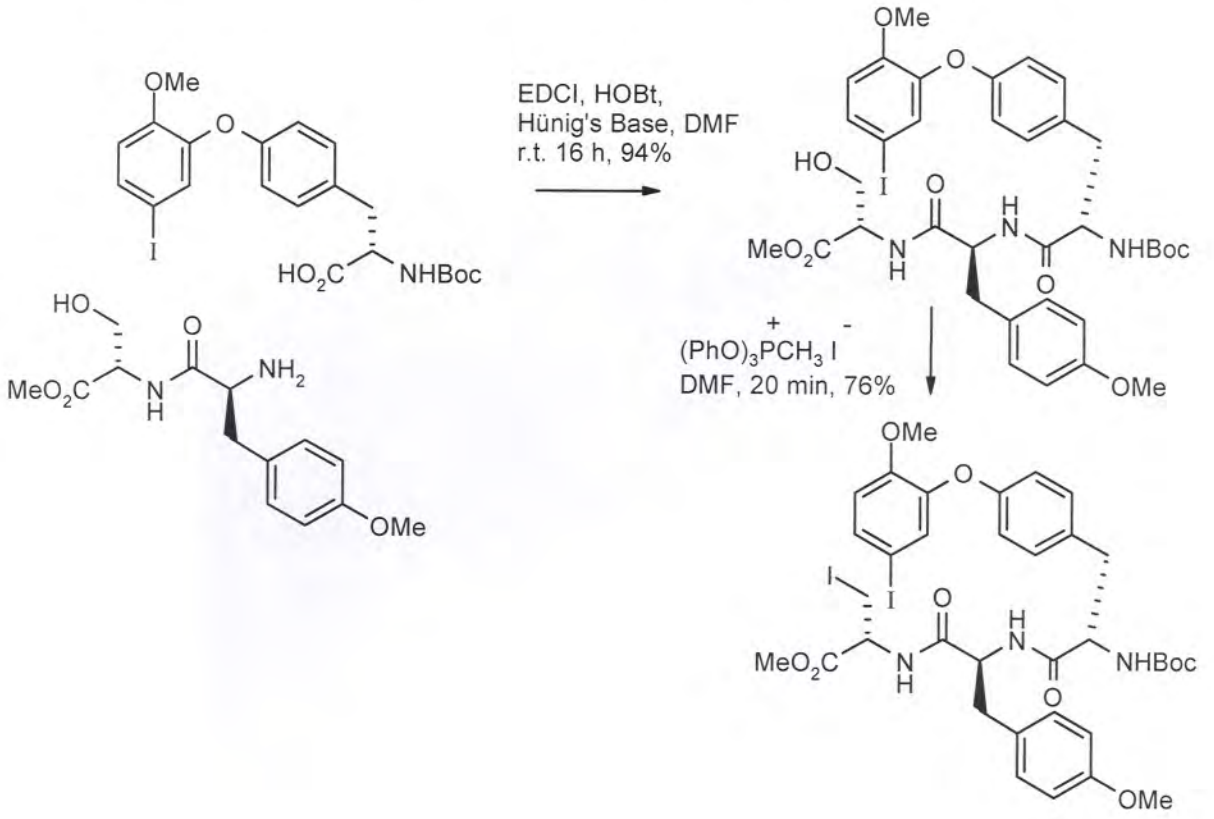




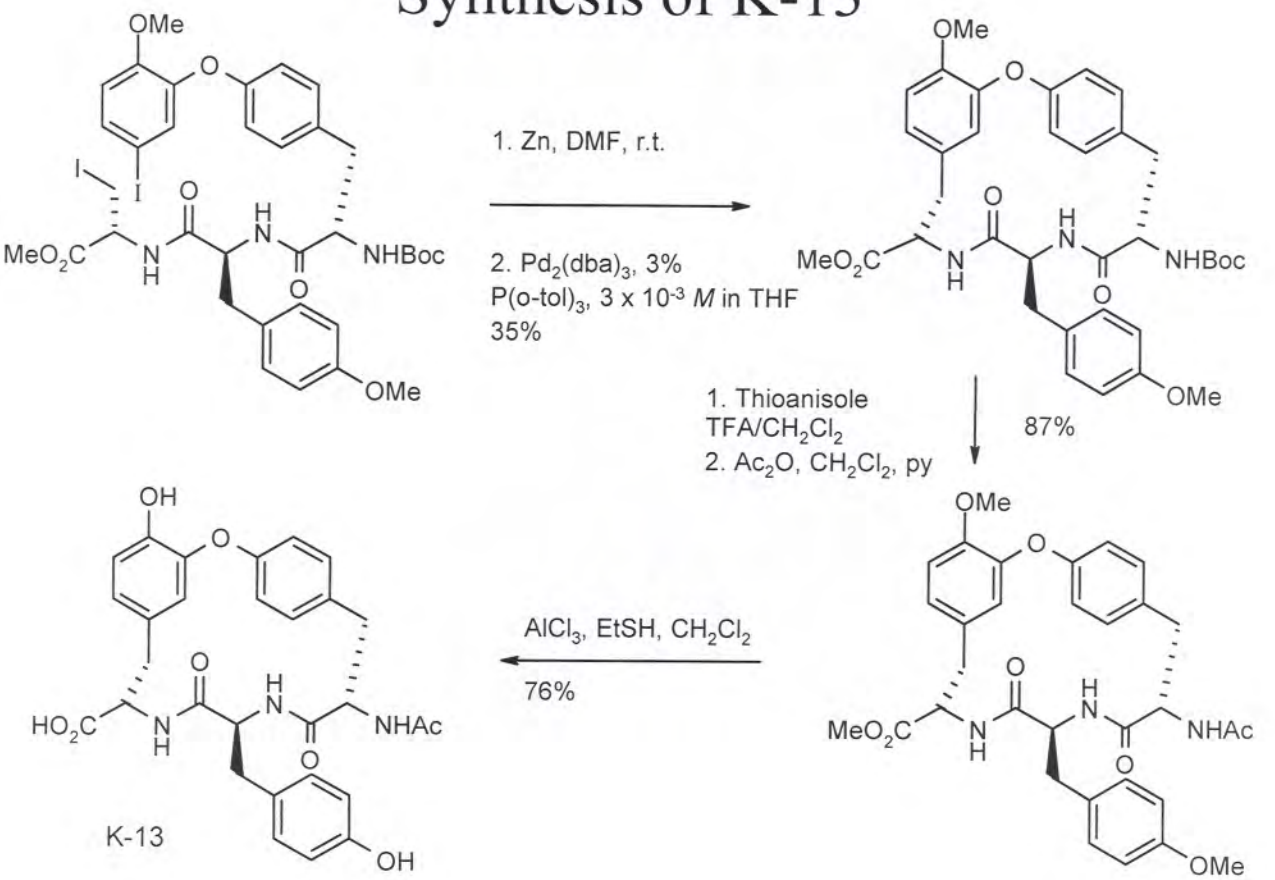
Retrosynthesis for K-13



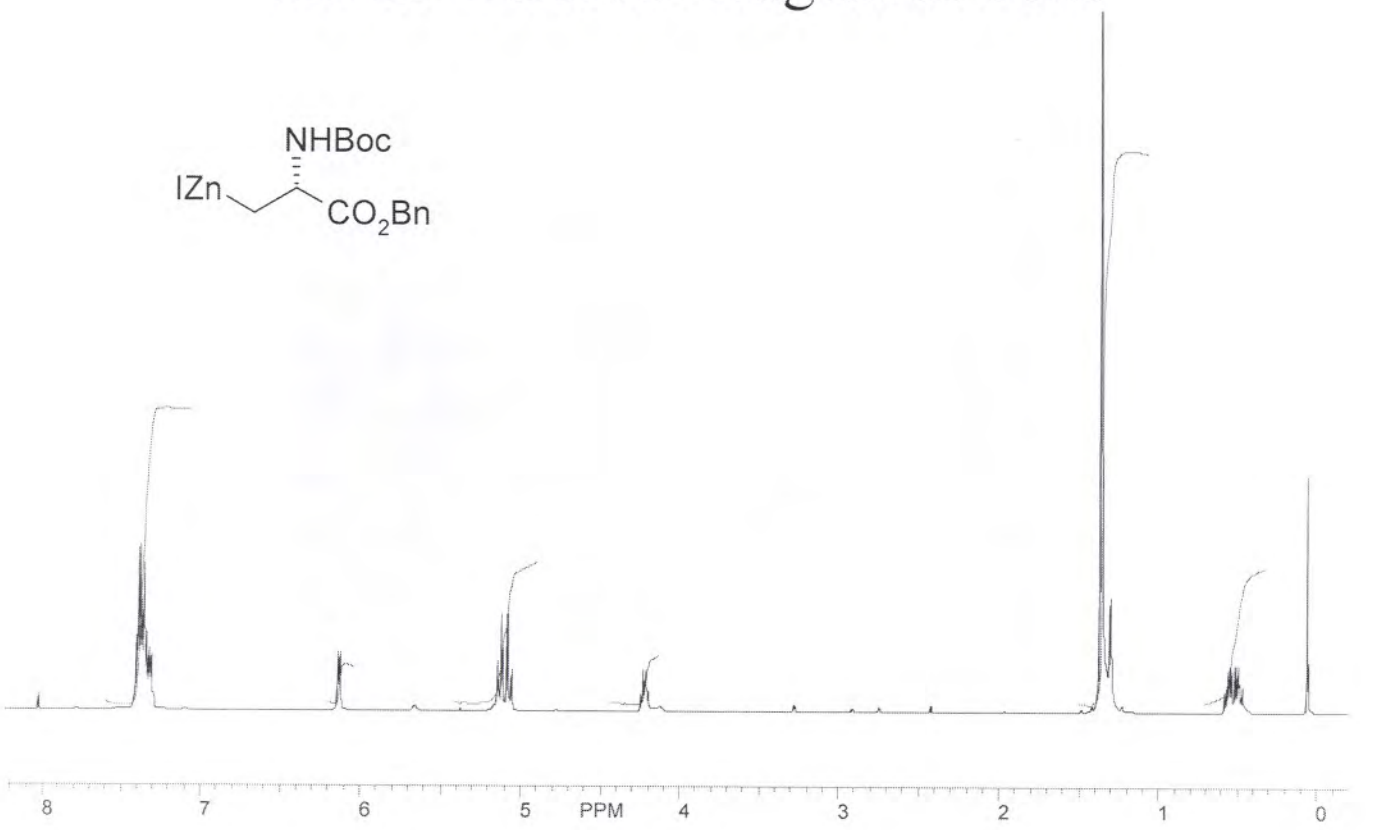
Synthesis of the Macrocyclic Precursor



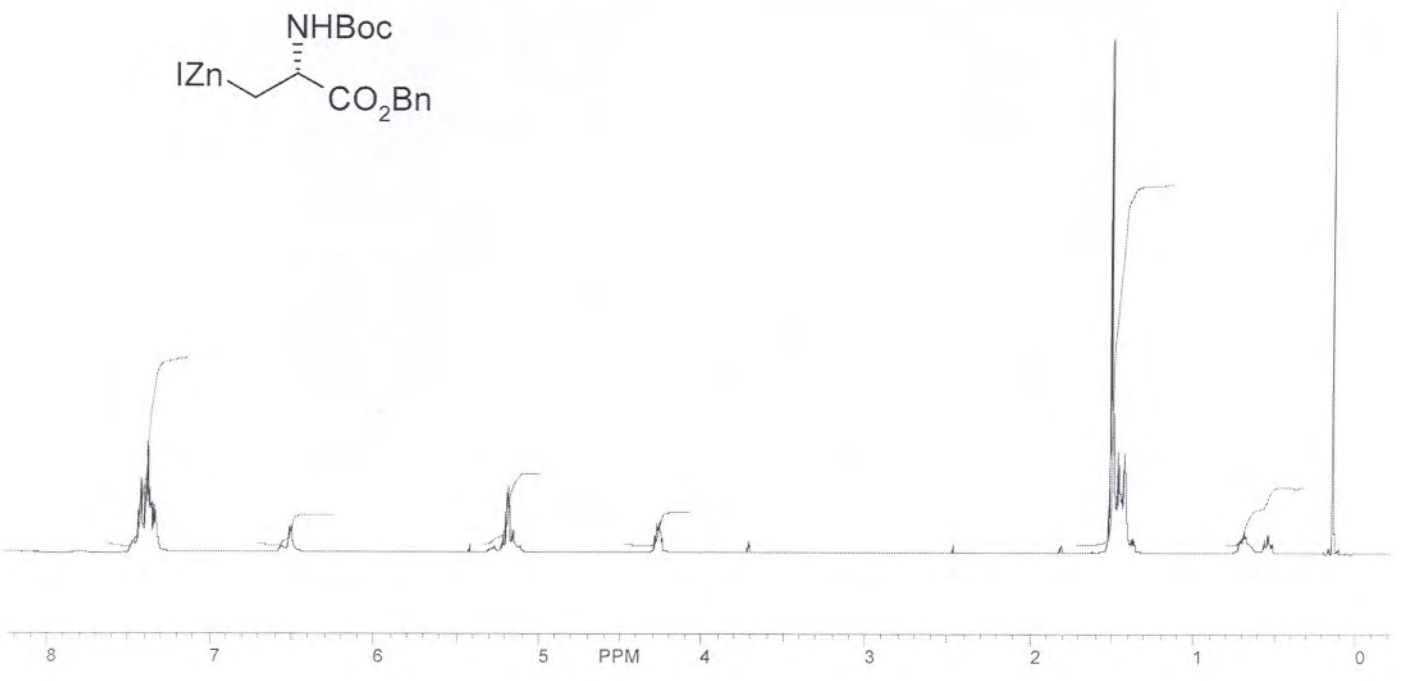
Synthesis of K-13



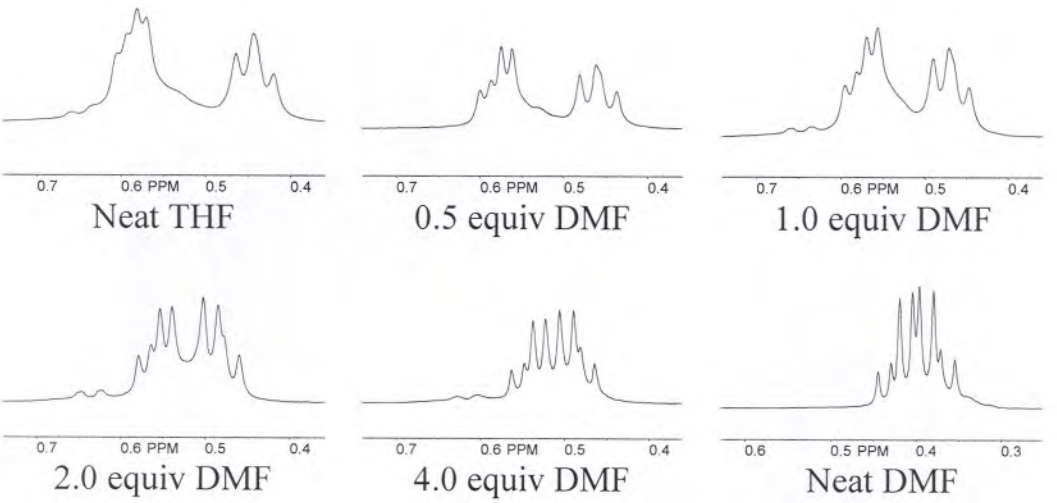
Serine-Derived Reagent in DMF



Serine-Derived Reagent in THF

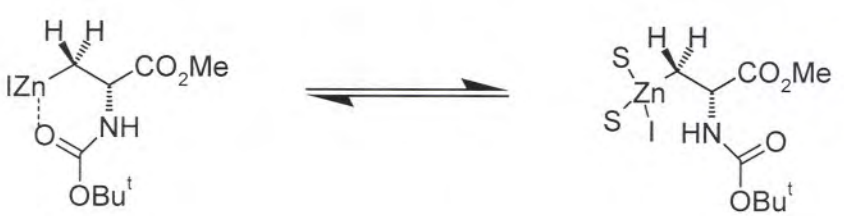


Solvent Dependence of NMR Spectra

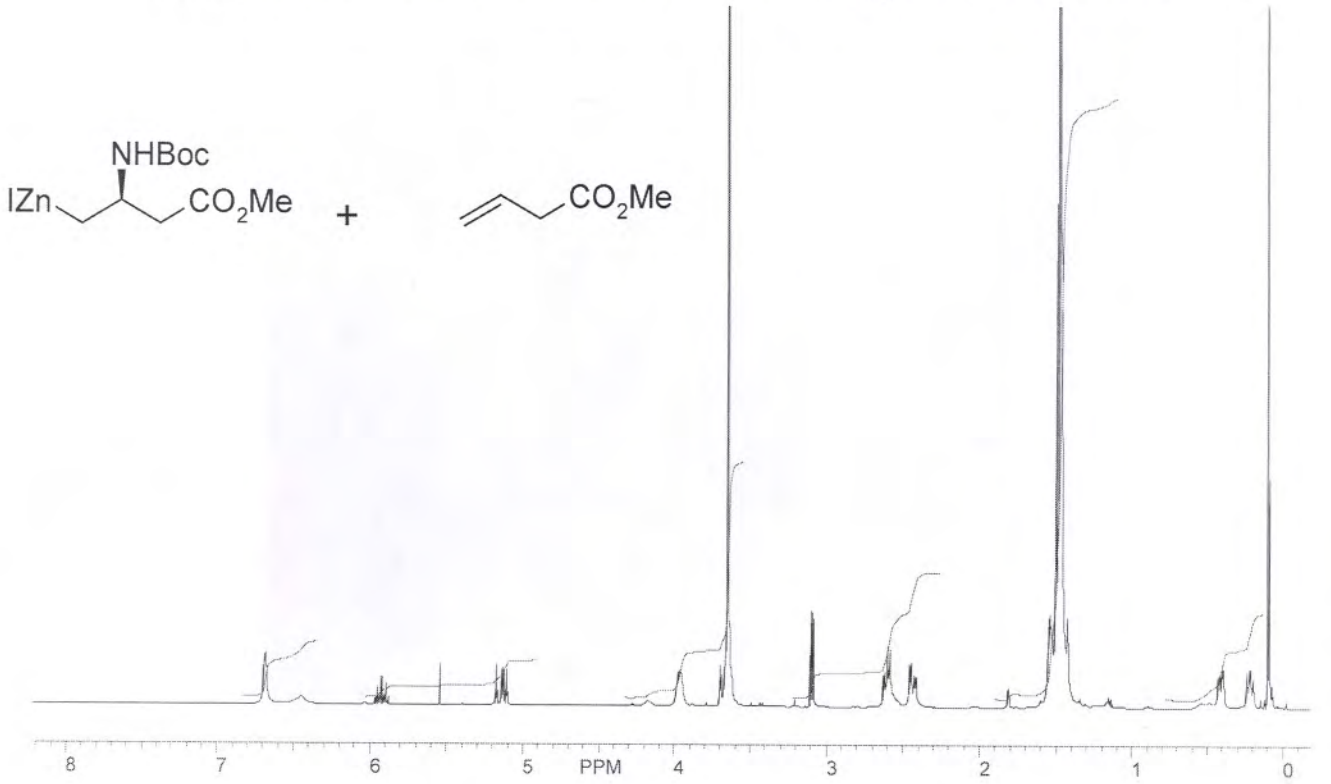


Interpretation of ^{1}H NMR data

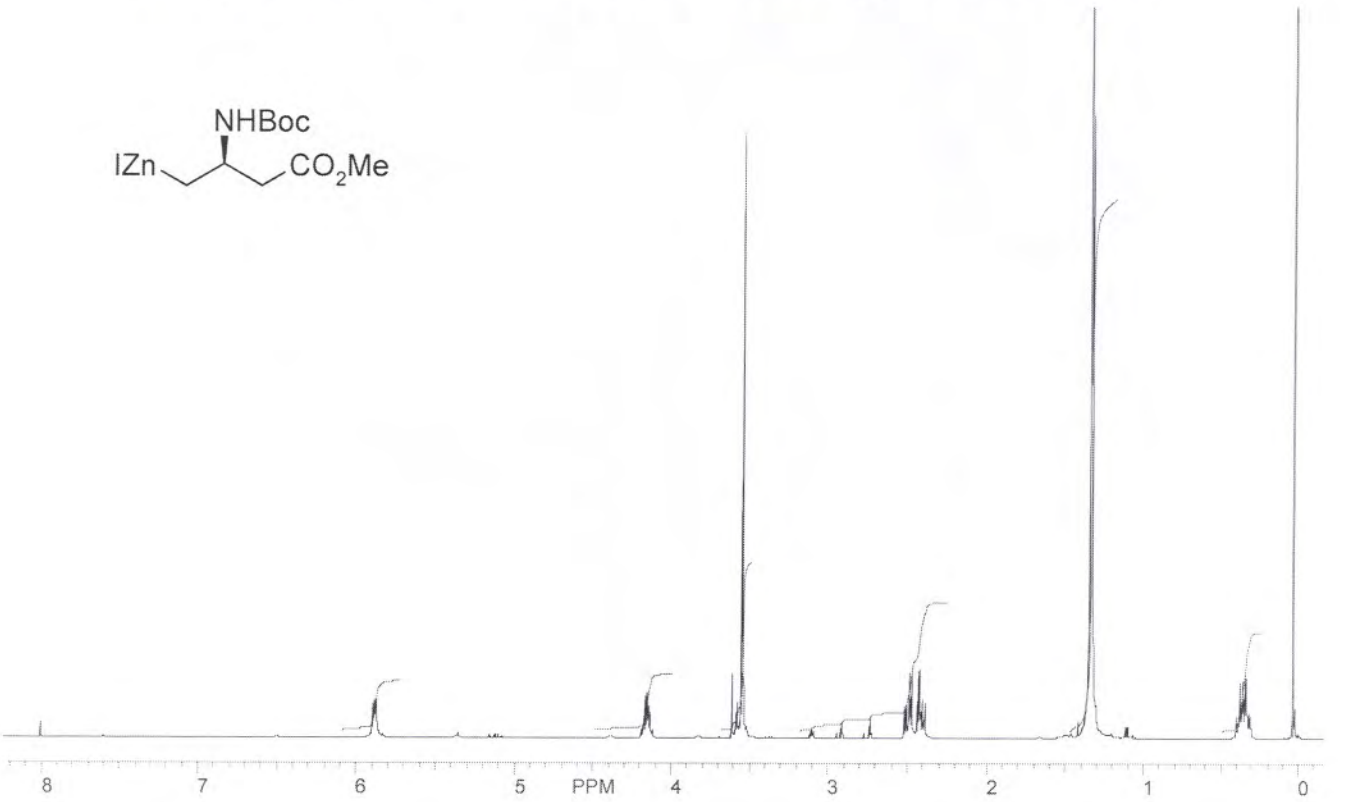
THF	DMF
• Broad signals	Sharp signals
• Large chemical shift difference	Small chemical shift difference
• Different values for J_{AX} and J_{BX}	Similar values for J_{AX} and J_{BX}



Aspartic Acid-Derived Reagent in THF



Aspartic Acid-Derived Reagent in DMF

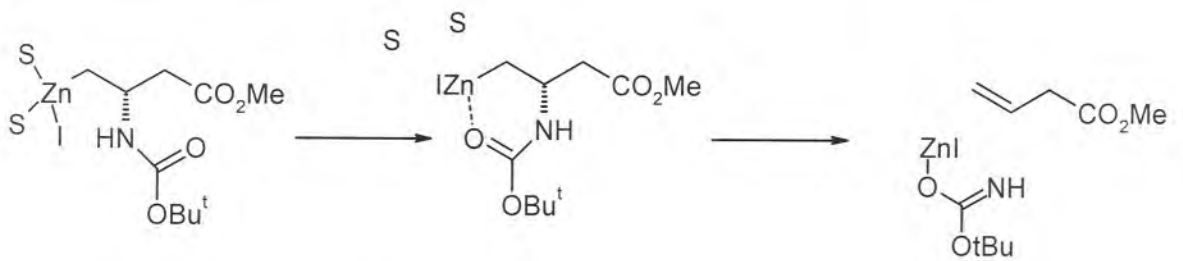


Kinetics of Decomposition

- Faster decomposition in THF than in DMF
- Simple first order kinetics in both THF and DMF
- Large negative $\Delta S^{\#}$ in THF indicating a highly ordered transition state

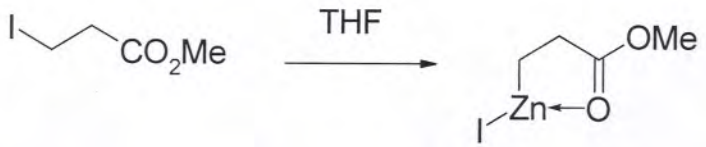
	$\Delta H^{\ddagger}$	$\Delta S^{\ddagger}$
	kJ mol^{-1}	J K^{-1} mol^{-1}
THF-d_8	+ 70	- 85
DMF-d_7	+ 90	- 31

Tentative Mechanism for Elimination



- Elimination proceeds *via* coordination of carbamate group to zinc, to give a highly ordered transition structure, hence the negative *entropy* of activation.
- THF interacts more weakly with the zinc than does DMF, as indicated by ^{1}H NMR. Thus, the disruption of DMF coordination to zinc in forming the transition structure also accounts for the higher *enthalpy* of activation in this solvent.
- The release of coordinated DMF partially compensates for the formation of the highly ordered transition structure, so the *entropy* of activation is less negative in this solvent.

Internal Coordination in Functionalised Organozinc Halides

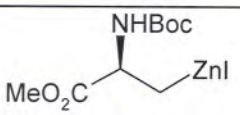
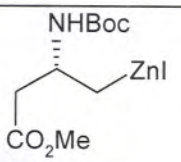
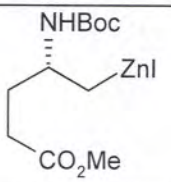


ν_{max} 1746 cm^{-1} ν_{max} 1642 cm^{-1}

$\delta_{C=O}$ 171.6 $\delta_{C=O}$ 175.8

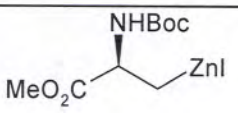
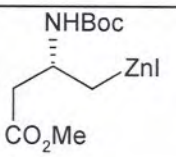
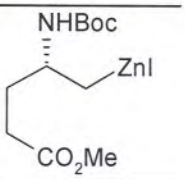
^{13}C NMR Data

- Chemical shift differences of the carbonyl groups of the β-amino zinc reagents in d_8-THF relative to the parent iodides.

$\Delta\delta$ ($\delta_{(R\text{-}ZnI)}$ - $\delta_{(R\text{-}I)}$)			
Ester	+5.347	+1.464	+ 0.675
Carbamate	+ 2.711	+3.747	+3.923

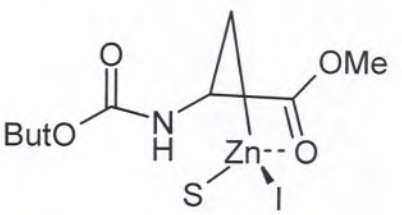
^{13}C NMR Data

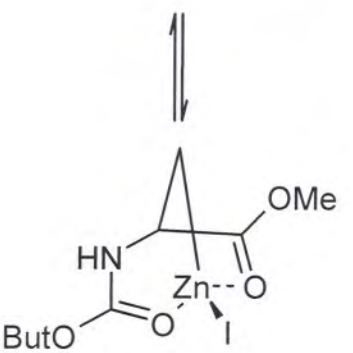
- Chemical shift differences of the carbonyl groups of the β-amino zinc reagents in d_7-DMF relative to the parent iodides.

$\Delta\delta$ ($\delta_{(R\text{-}ZnI)}$ - $\delta_{(R\text{-}I)}$)			
Ester	+5.786	+0.872	+0.115
Carbamate	-0.868	-0.535	-0.687

Unique Stability of Serine-Derived Reagent

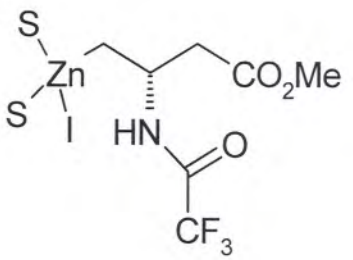
- For the serine-derived reagent in all solvents, co-ordination of ester to zinc occurs.



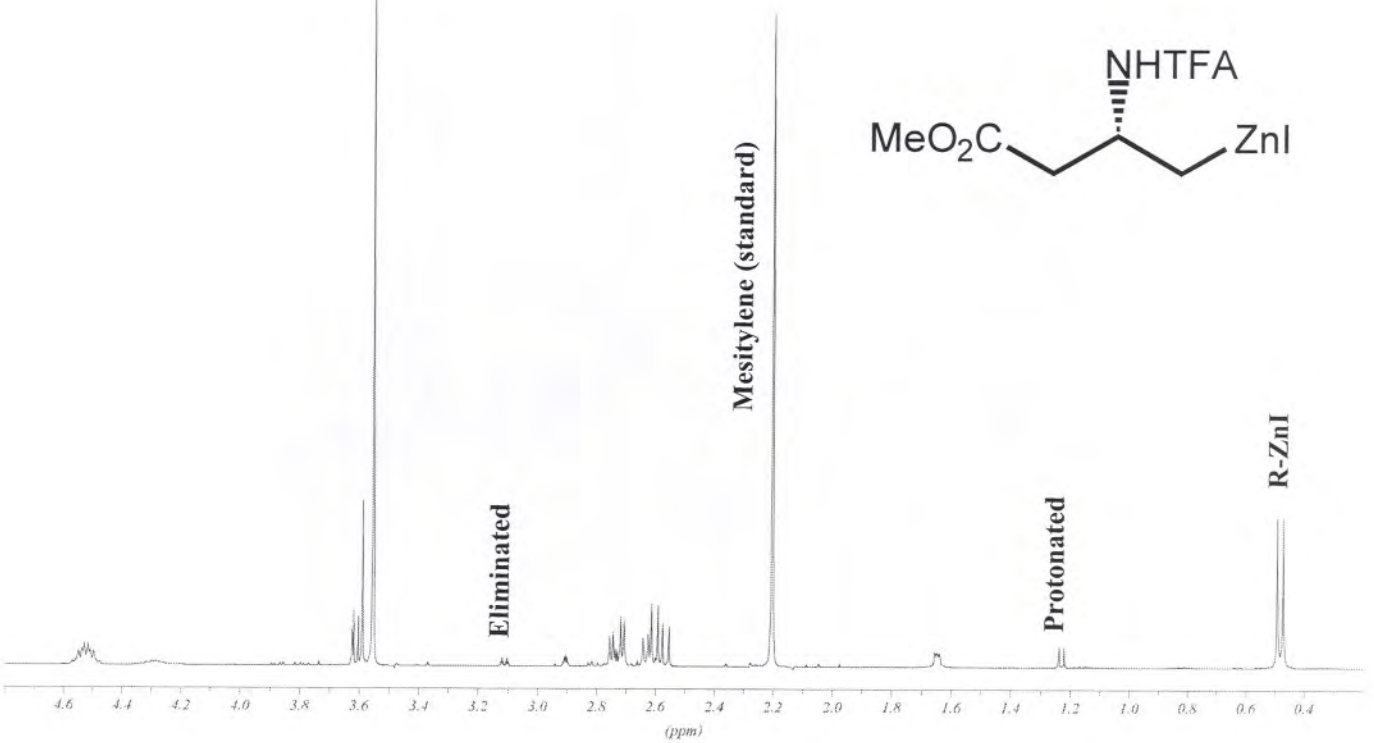


How to Minimise the Elimination

- The elimination reaction appears to be dependent on the Lewis basicity of the carbonyl function, not its ability as a leaving group.
- Therefore, we need to choose a group in which Lewis basicity is minimised.

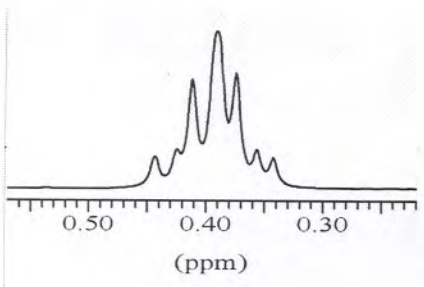


N-TFA Asp(OMe)-ZnI in d_7-DMF

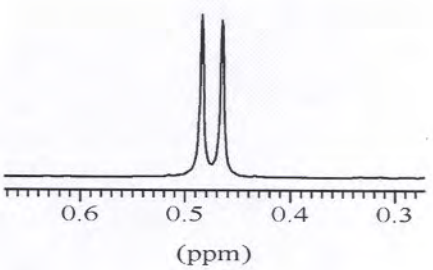


Comparison of CH_2ZnI signals

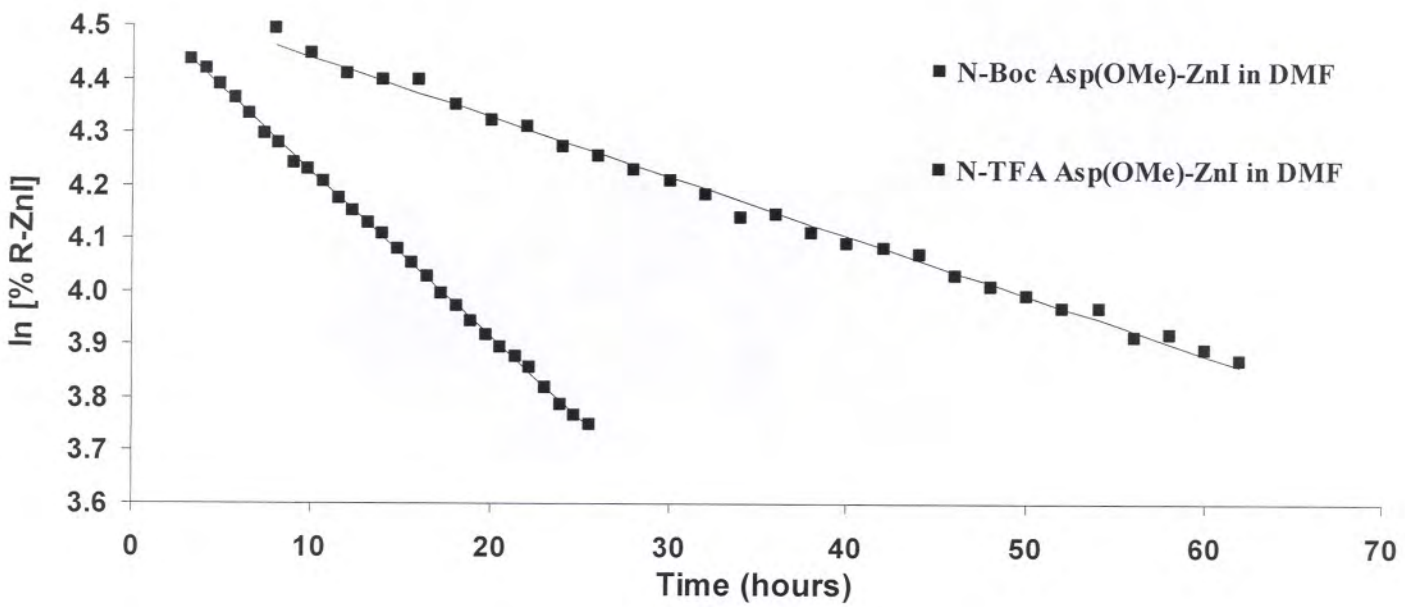
Methylene protons for N-Boc Asp(OMe)-ZnI in DMF



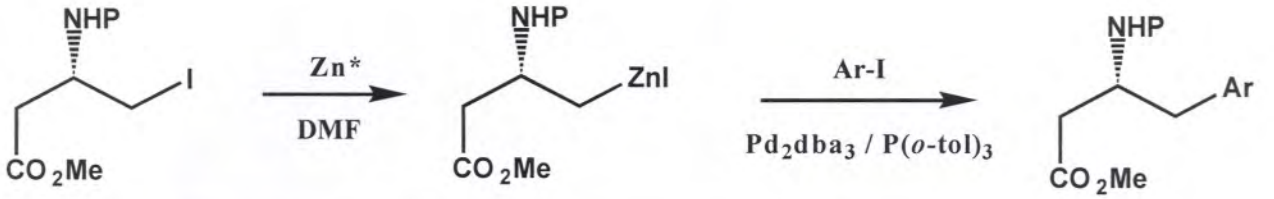
Methylene protons for N-TFA Asp(OMe)-ZnI in DMF



Decomposition of Organozinc Reagents



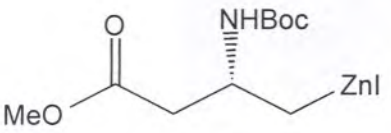
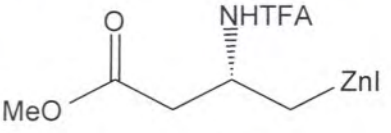
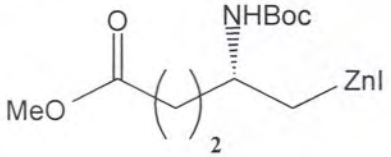
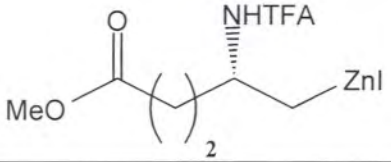
Yields from Palladium-Catalysed Cross Coupling of β–Amidozinc Reagents



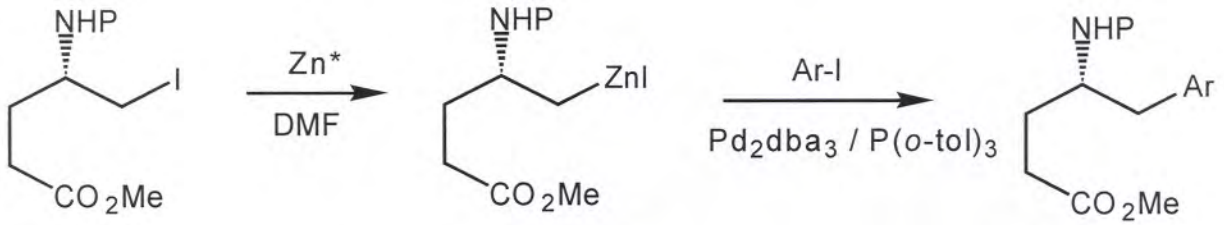
Ar	P = Boc Yield (%)	P = TFA Yield (%)
4-Me-Ph	73	64
4-MeO-Ph	68	69
Ph	73	72
4-CN-Ph	-	77
1-Naphthyl	61	70
4-Br-Ph	58	53

Jackson, R. F. W.; Rilatt, I. and Murray, P. J., *Chem. Commun.*, **2003**, 1242 – 1243.

Kinetic Behaviour of Organozinc Reagents

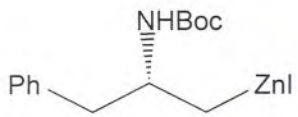
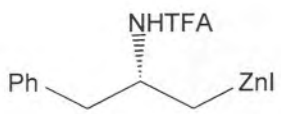
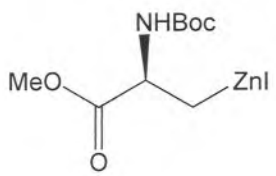
Organozinc Reagent	Rate of Decomposition (x 10^{-5} s^{-1})	Rate of Coupling (x 10^{-4} s^{-1})	Isolated Yield (%)
	0.87	Too fast to measure	63
	0.31	20.6	65
	2.84	41.3	70
	0.33	62.5	88

Palladium-Catalysed Cross Coupling of *β*–Amidozinc Reagents

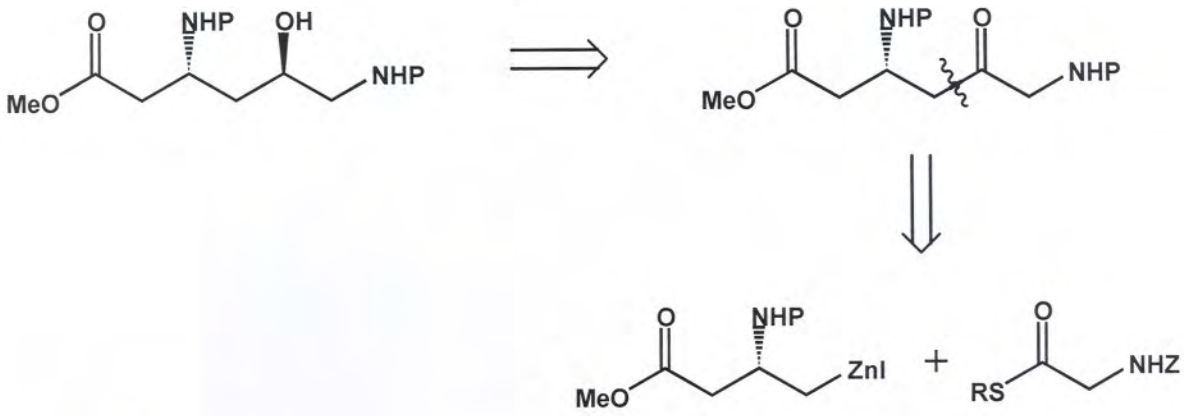


Ar	Yield with Boc (%)	Yield with TFA (%)
4-MeO-Ph	**68**	**79**
2-NH_2-Ph	**56**	**62**
2-F-Ph	**34**	**51**
4-Me-Ph	**68**	**79**
Ph	**68**	**88**

Reactivity of Organozinc Reagents

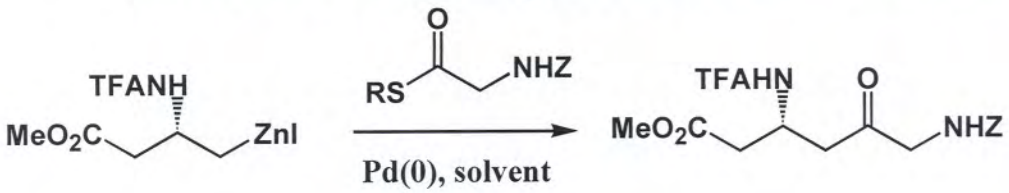
Organozinc Reagent	Rate of Decomposition (x 10^{-5} s^{-1})	Rate of Coupling (x 10^{-5} s^{-1})	Isolated Yield (%)
	1.1	Too fast to measure	74
	0.42	Too fast to measure	83
	0.2	8.5	44

Applications of Reagents



Negamycin fragment

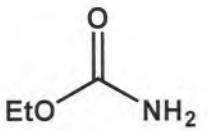
Kinetics of Coupling Reaction – Thiolesters



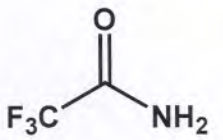
R	Solvent	Reaction Rate (x 10^{-5} s^{-1})	Reaction Time	Isolated Yield (%)
Ph	DMF	0.5	> 16 h	65
Ph	THF/DMF(6 eq)	1.0	~ 16 h	72
C_6F_5	DMF	1.7	~ 8 h	81
C_6F_5	THF/DMF(6 eq)	5.2	~ 3 h	94

Conclusions

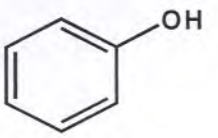
- TFA reagents more stable to elimination
- Ester coordination critical factor in reactivity
- Glutamic acid trifluoroacetamide a superior reagent
- More acidic proton of the trifluoroacetamide tolerated



pKa = 25 (DMSO)



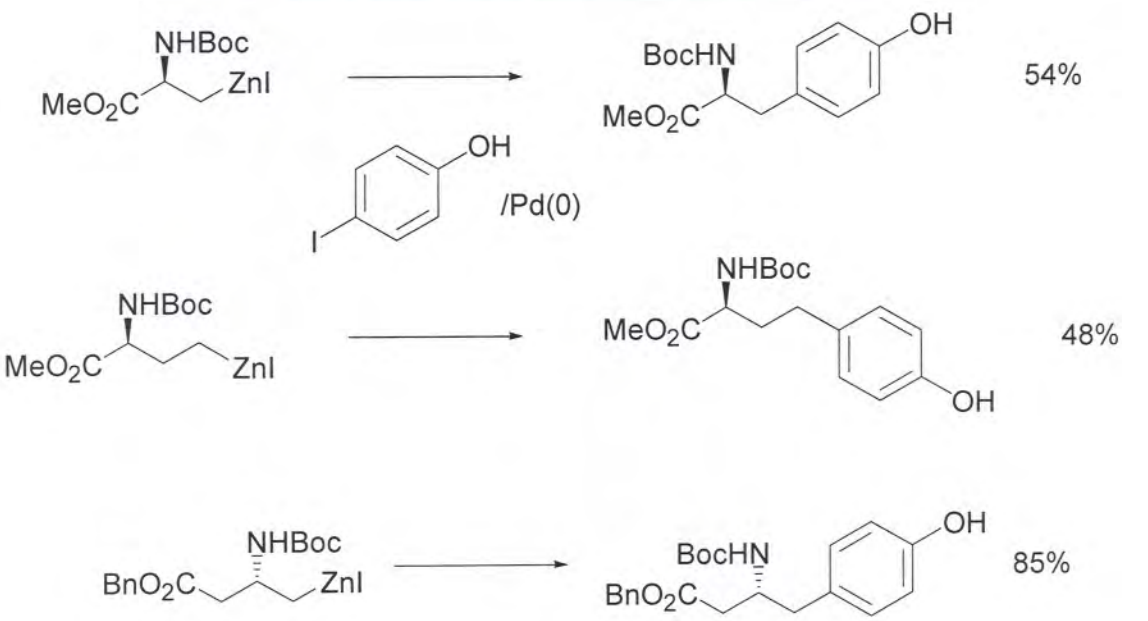
pKa = 17 (DMSO)



pKa = 18 (DMSO)

F. G. Bordwell, *Acc. Chem. Res*, 1988, **21**, 456-463

Coupling with Iodophenols



Org. Biomol. Chem., 2004, **2**, 110 – 113.

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