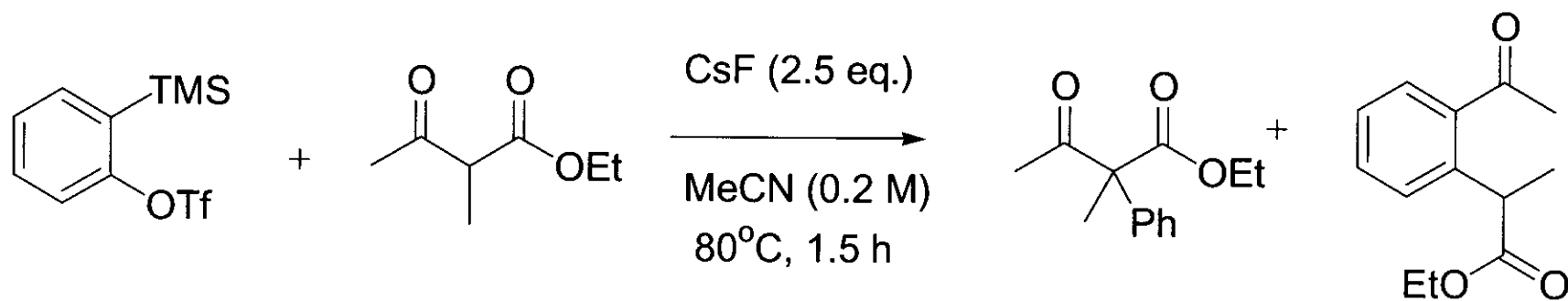


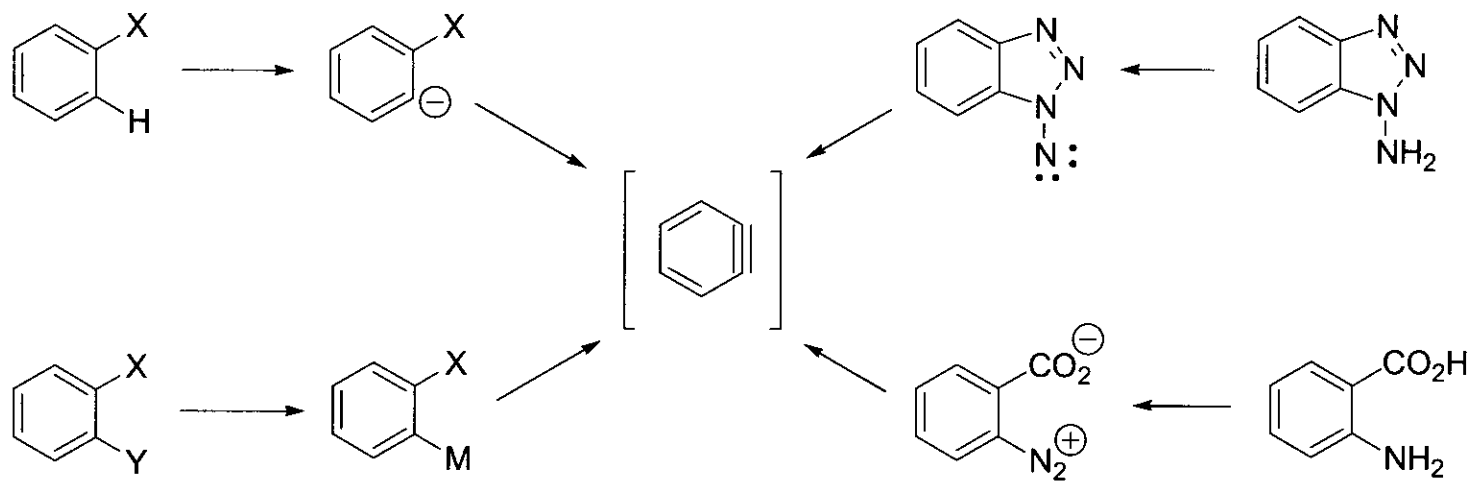
The Direct Acyl-Alkylation of Arynes

Stoltz, B.M.; Tambar, U.K. *JACS*, **ASAP**

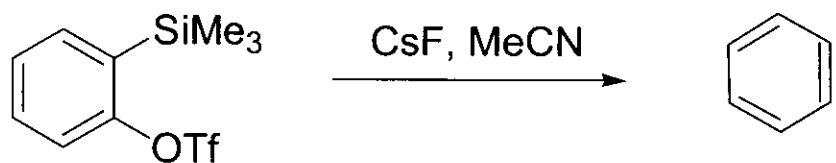


Introduction

Use of arynes in organic chemistry is limited due to the harsh conditions needed to generate them.



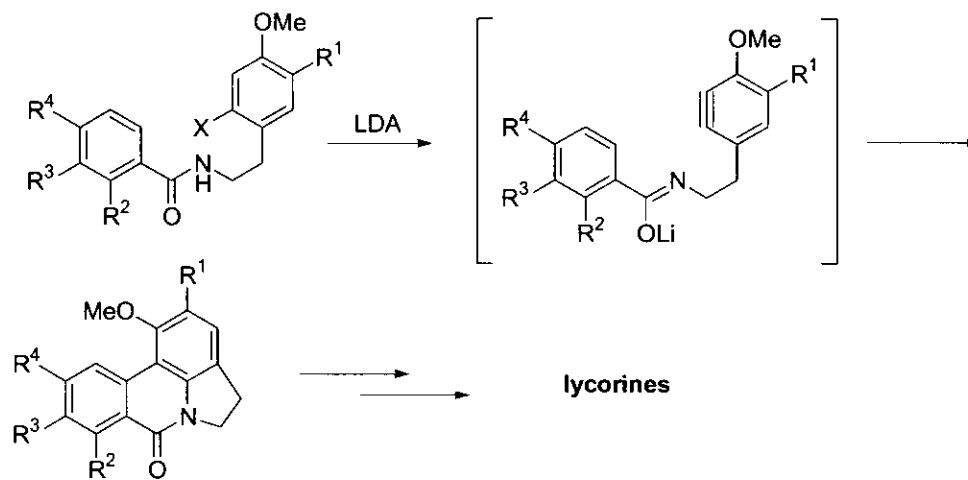
1983 Kobayashi introduced a mild method:



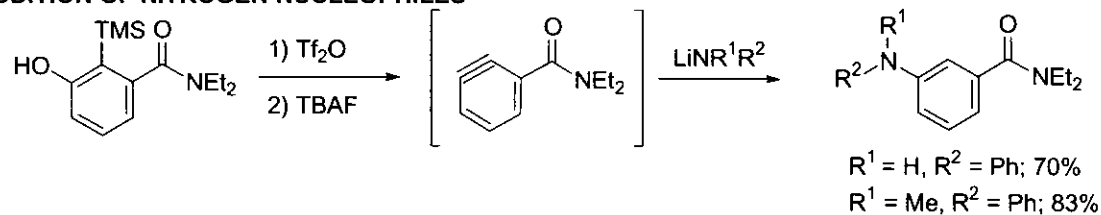
Santelli, M.; Pellissier, H. *Tetrahedron*, **2003**, *59*, 701

Reactions of Arynes

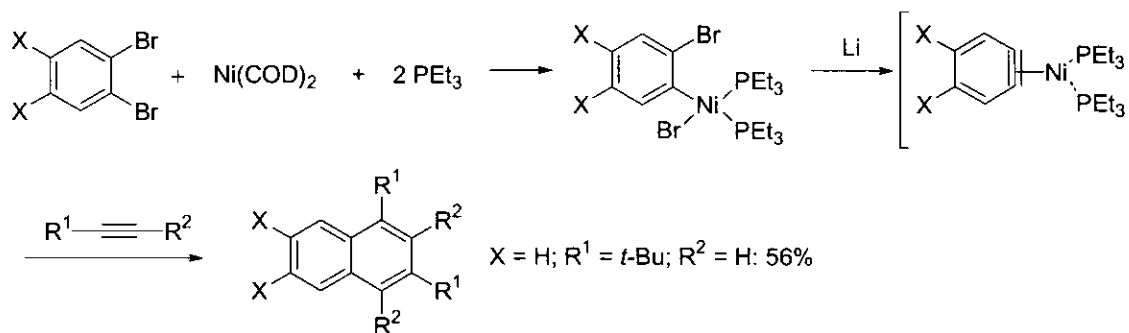
PERICYCLIC REACTIONS



ADDITION OF NITROGEN NUCLEOPHILES

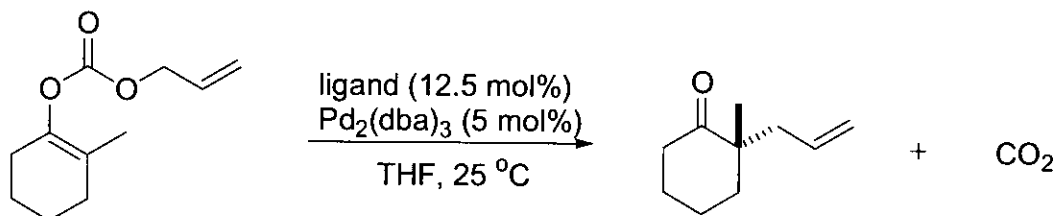


TRANSITION METALCATALYZED REACTION



Santelli, M.; Pellissier, H. *Tetrahedron*, **2003**, *59*, 701

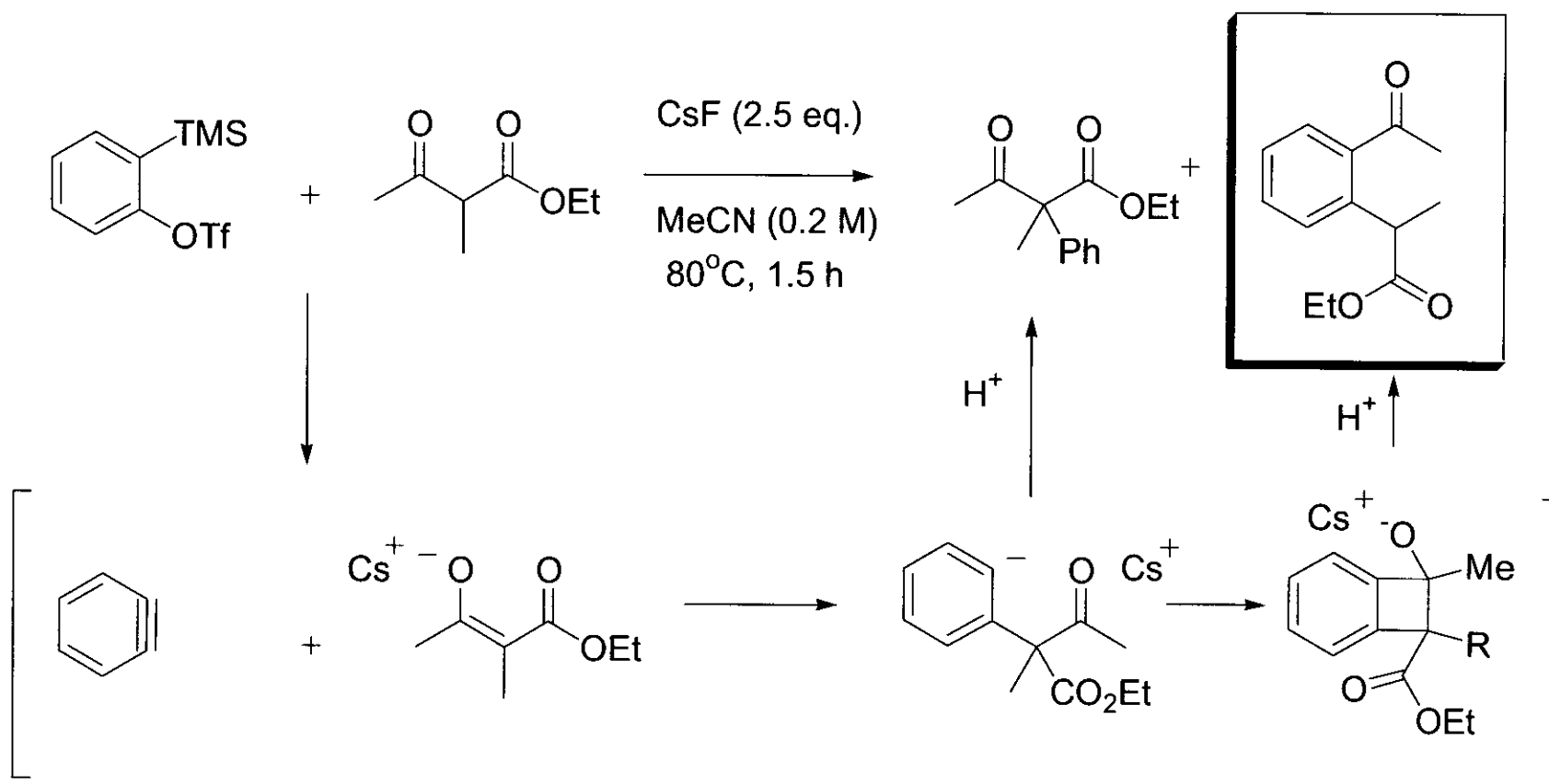
Previous Stoltz Chemistry



entry	ligand	time (h)	% yield	% ee
1	(R,R)-Troost ligand	5	92	64
2	(R)-BINAP	5	76	2
3	(R,R)-Me-DUPHOS	5	66	0
4	(R,R)-DIOP	2	59	2
5	(R)-MOP	3	47	13
6	(R)-QUINAP	2	97	61
7	(R)-Ph-PHOX	2	95	65
8	(R)-Bn-PHOX	5	94	63
9	(R)-i-Pr-PHOX	2	95	83

Stoltz, B.M.; Behenna, D.C. *J. Am. Chem. Soc.* **2004**, *126*, 15044

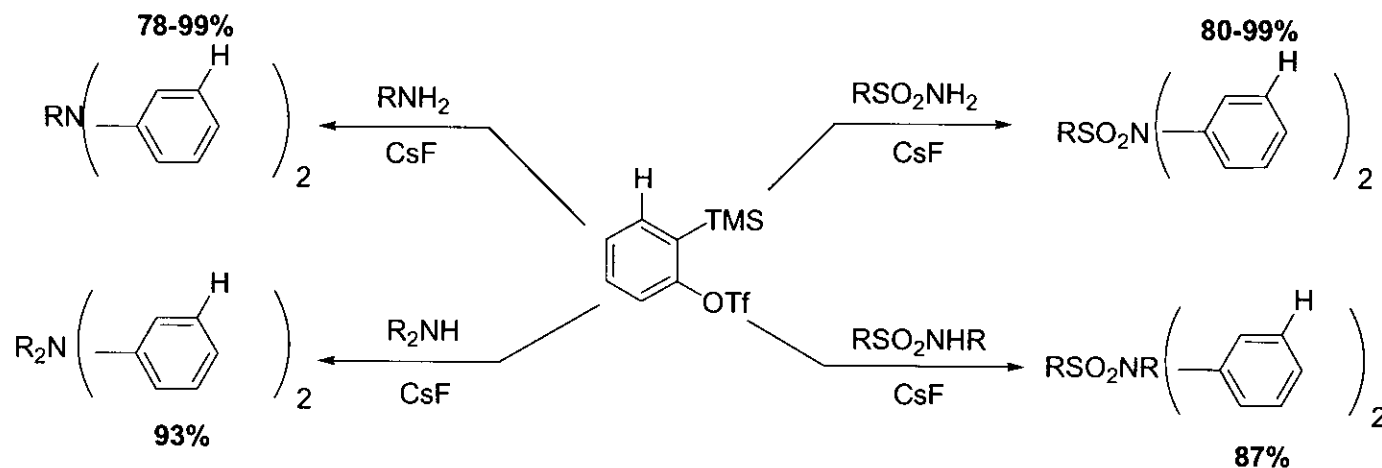
Initial Attempts at β -Ketoester Formation



Stoltz, B.M.; Tambar, U.K. *J. Am. Chem. Soc.* **2005**, ASAP

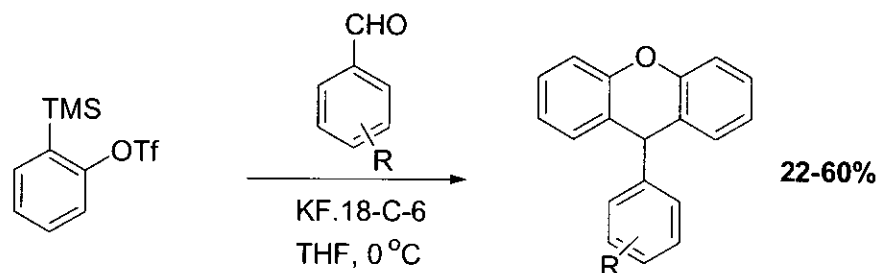
Aryne Insertion into X-H and X-C Bonds

Insertion into heteroatom-hydrogen bonds:



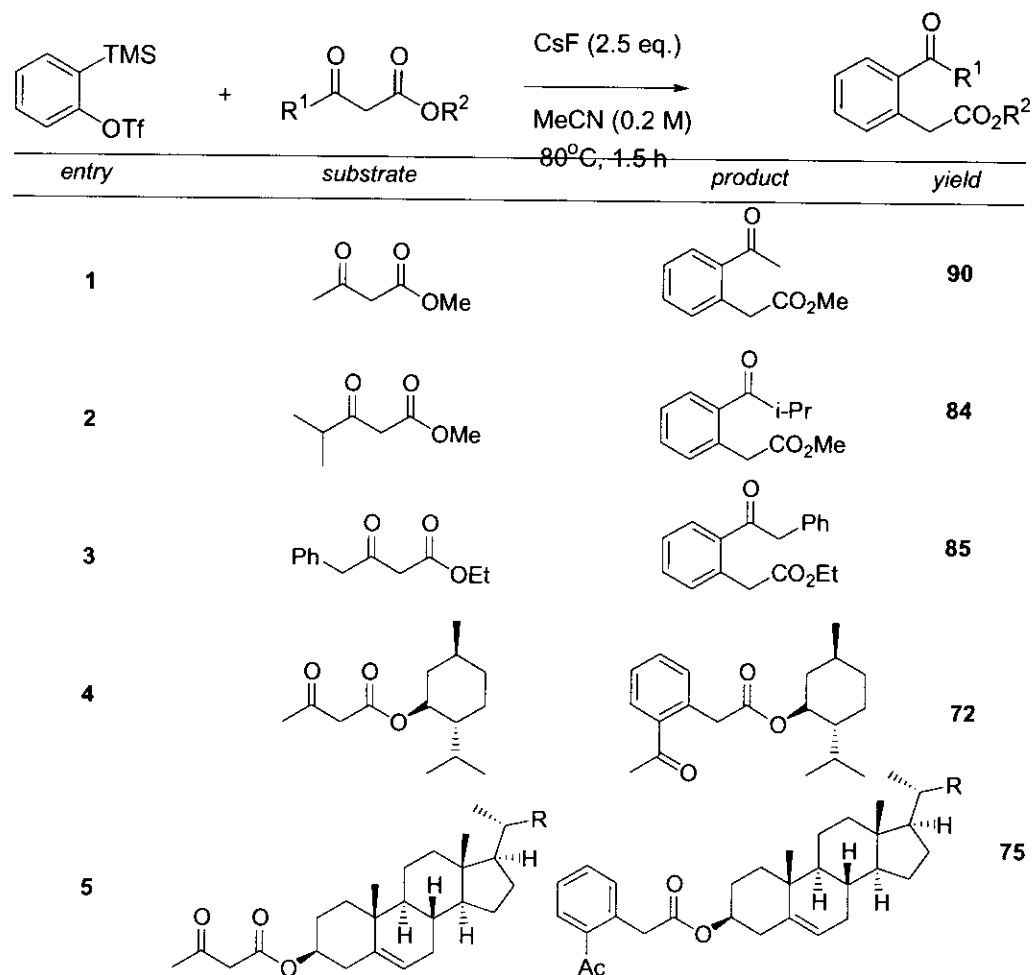
Larock, R.C.; Liu, Z. *Org. Lett.* **2003**, *5*, 4637

Insertion into heteroatom-carbon bonds:



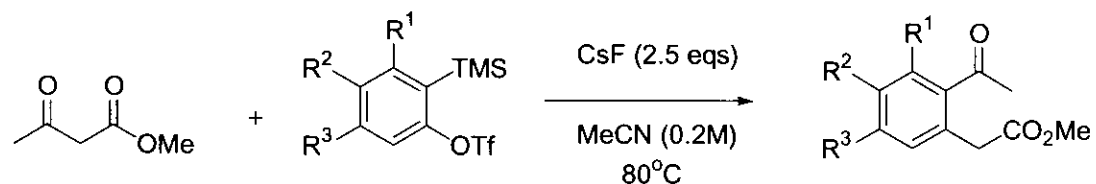
Kunai, A.; et.al. *Org. Lett.* **2004**, *6*, 4049

Acyl-Alkylation of Benzyne



Stoltz, B.M.; Tambar, U.K. *J. Am. Chem. Soc.* **2005**, ASAP

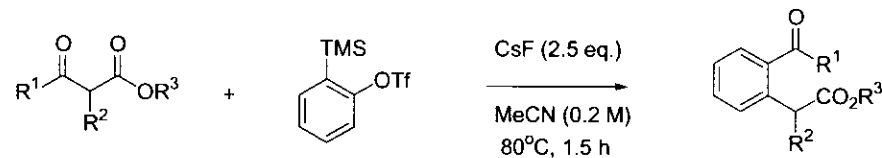
Acyl-Alkylation of Substituted Arynes



<i>entry</i>	<i>aryne</i>	<i>product</i>	<i>yield</i>
1			95
2			82
3			75

Stoltz, B.M.; Tambar, U.K. *J. Am. Chem. Soc.* **2005**, ASAP

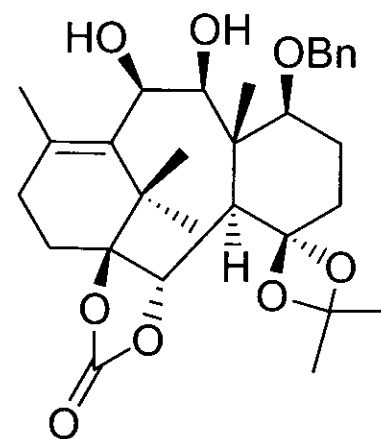
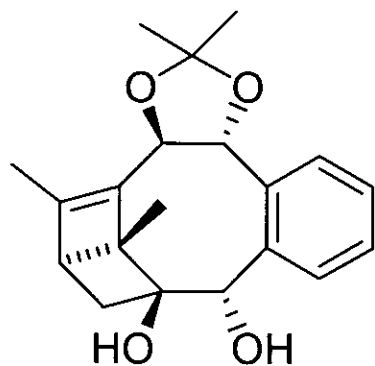
Ring Expansion of Cyclic β -Ketoesters



entry	substrate	product	yield
1			50
2			61
3			65
4			45
5			69

Stoltz, B.M.; Tambar, U.K. *J. Am. Chem. Soc.* **2005**, ASAP

Occurrence in Natural Products



Yet, L.; *Chem. Rev.* **2000**, *100*, 2963

Conclusion

- ❖ Stoltz and coworkers developed a mild, direct process for the acyl-alkylation of arynes.
- ❖ Provides access to *o*-substituted arenes.
- ❖ Cyclic β -ketoesters can be expanded to form medium-sized carbocycles—prevalent in natural products.
- ❖ The utility of this reaction is begin explored in natural product synthesis.