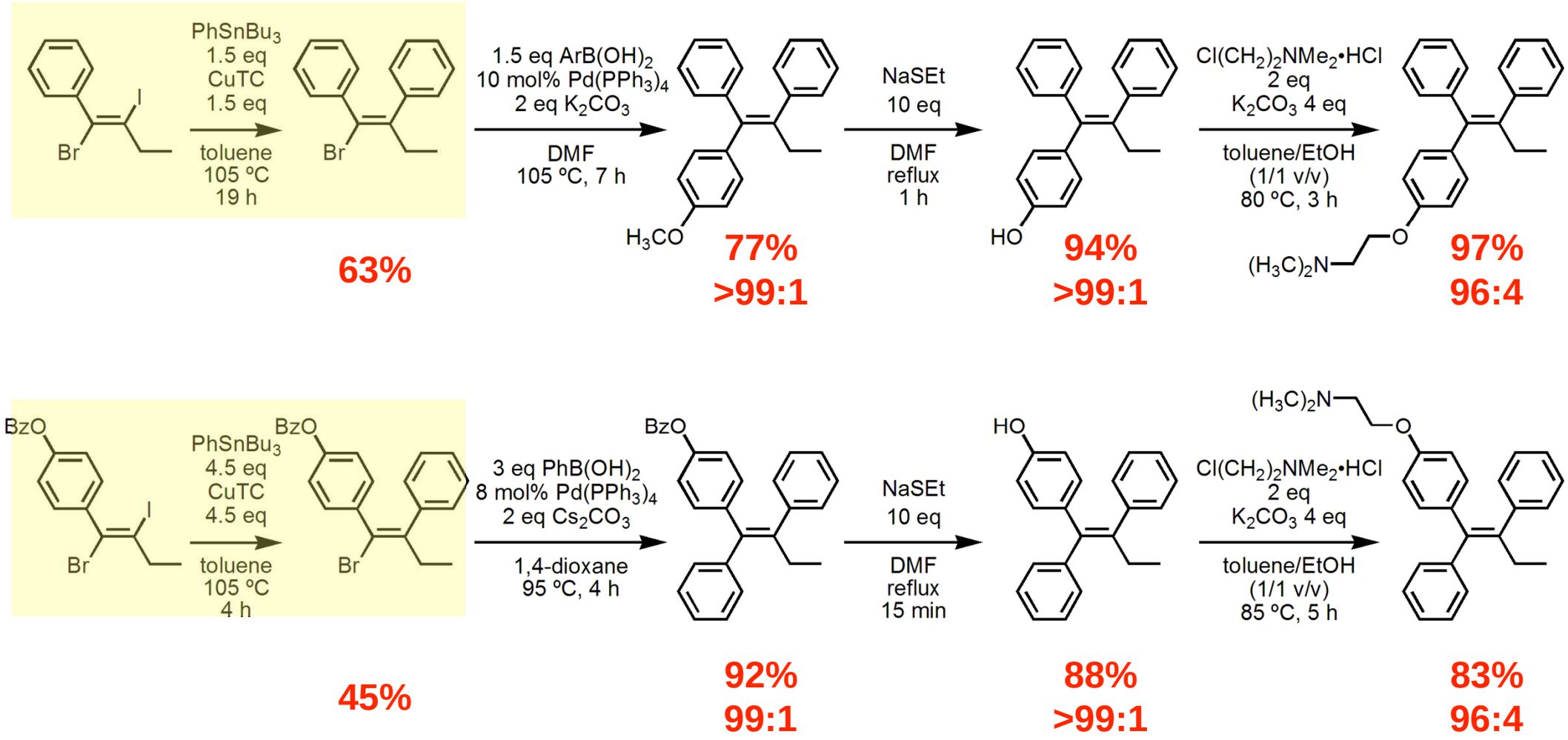
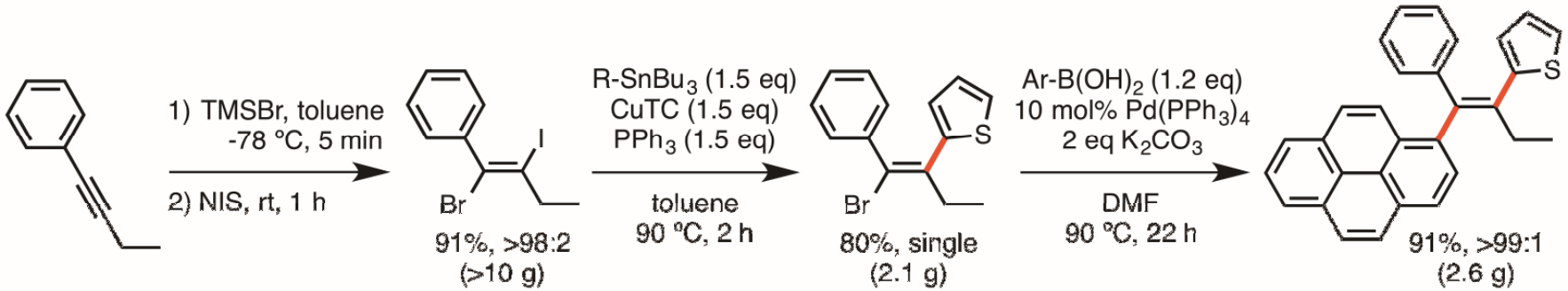
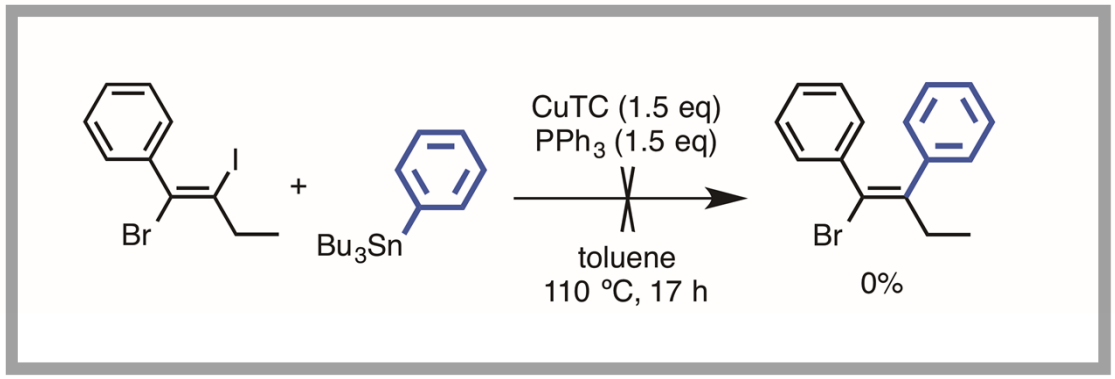
Stereo-defined Synthesis of Tamoxifens those are based on (*E*)-1-bromo-2-iodoalkene Templates



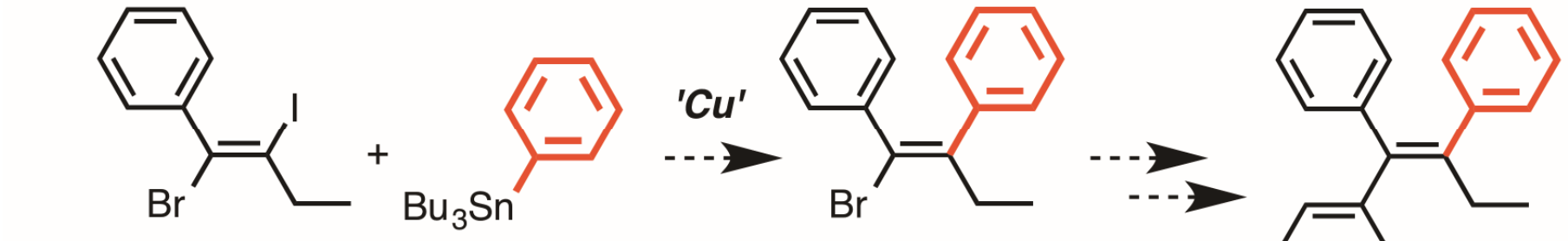
Background: stereo-defined synthesis of differentially all-carbon tetrasubstituted alkenes derived from (*E*)-1-bromo-2-iodoalkenes



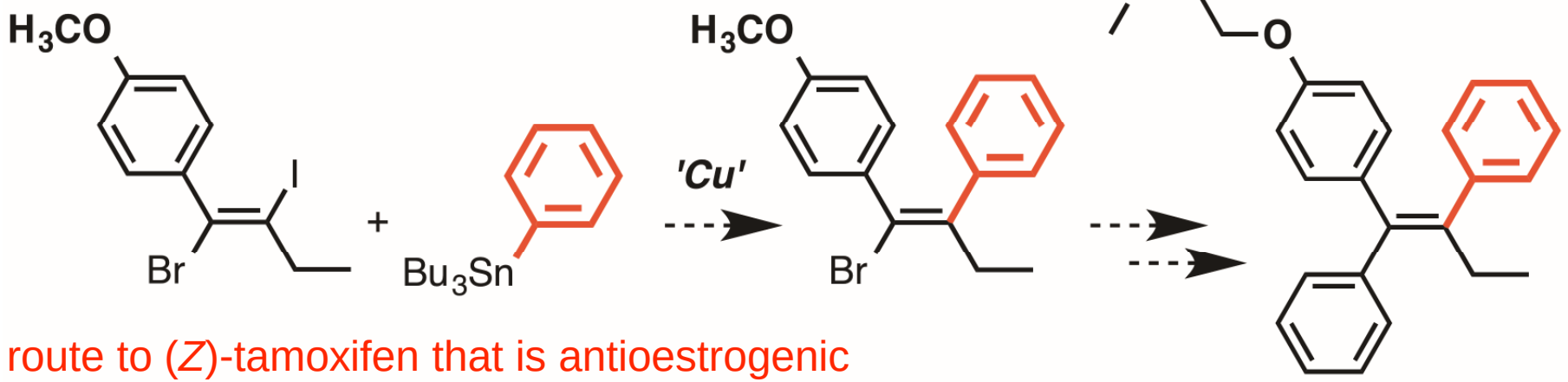


N. Endo, T. Iwasawa, *Tetrahedron* **2017**, *73*, 5833-5840.

Approach: we aim at Cu-based activation of $PhSuBu_3$ and diverse synthesis of Tamoxifen analogues.

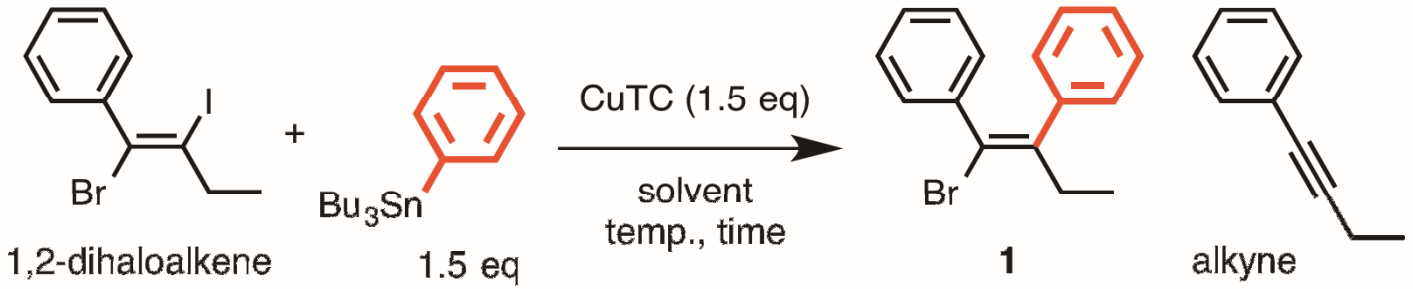


A route to (*E*)-tamoxifen that is oestrogenic



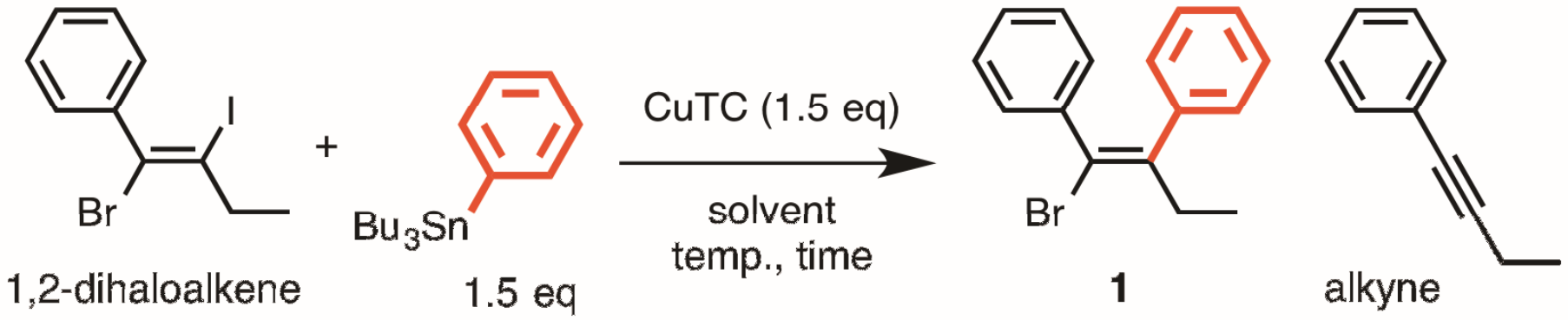
A route to (*Z*)-tamoxifen that is antioestrogenic

Unexpectedly, the CuTC-mediated substitution reaction proceeded even in the absence of PPh_3.



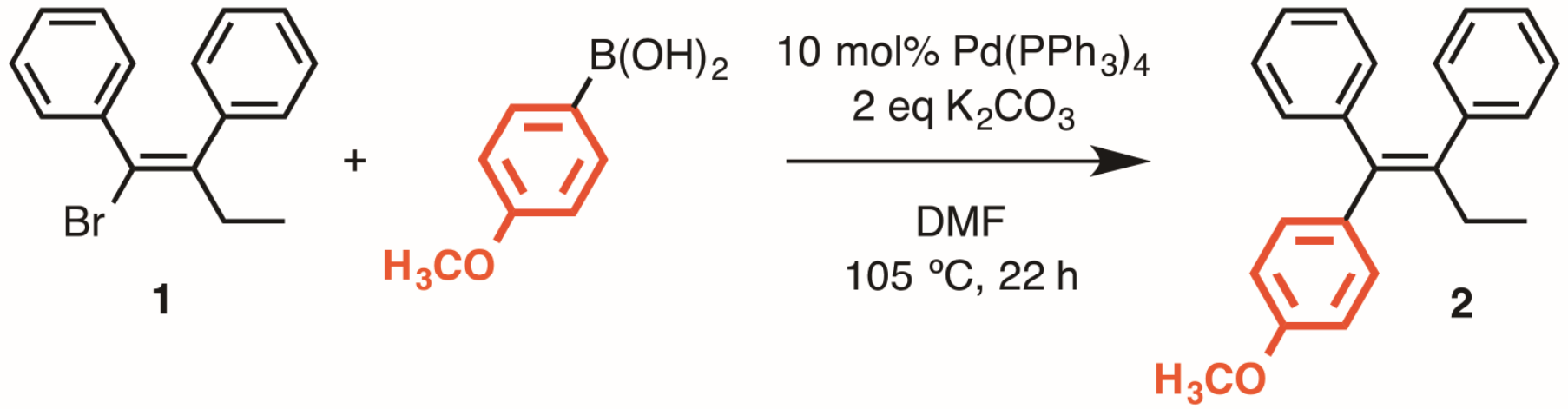
solvent	temp./°C	time/h	scale of the starting	Isolated Yield/%		
				1	alkyne	1,2-dihaloalkene
toluene	90	6	0.3	20	20	37
dioxane	90	2	0.3	<7	-	-
toluene	105	6	0.3	38	13	7
toluene	105	18	1	44	11	8
o-xylene	135	6	1	35	11	3

The protocol was amenable to scale-up.

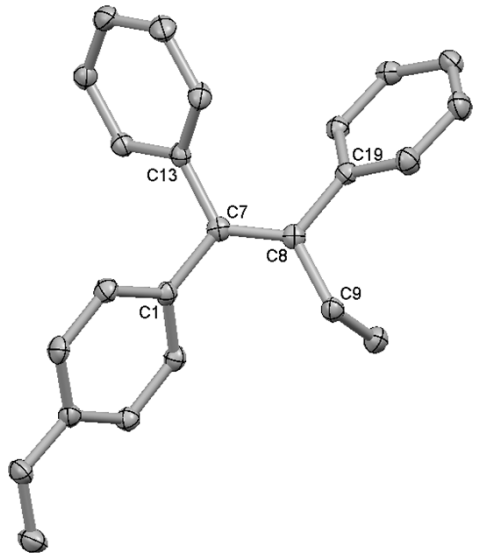


Scale of 1,2-dihaloalkene mmol (g)	time/h	%Yield		
		1	**alkyne**	1,2-dihaloalkene
1.5 (0.51)	18	53	16	5
4.0 (1.3)	6	60	18	13
8.0 (2.7)	22	62	17	6
16 (5.4)	**19**	**63**	**21**	**6**

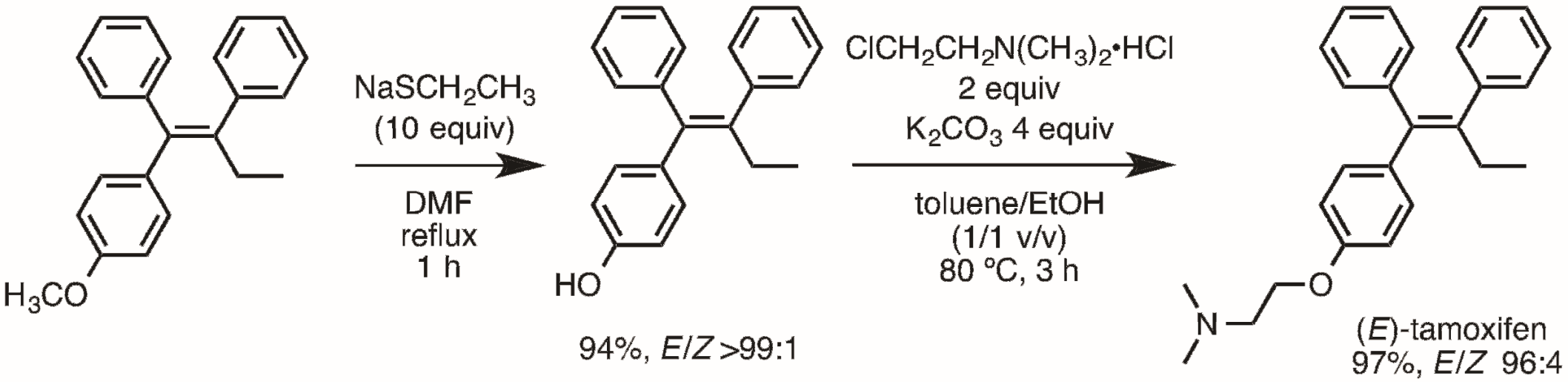
The resultant vinyl bromide undertook the Pd-catalyzed Suzuki reaction to give an all-carbon tetrasubstituted alkene.



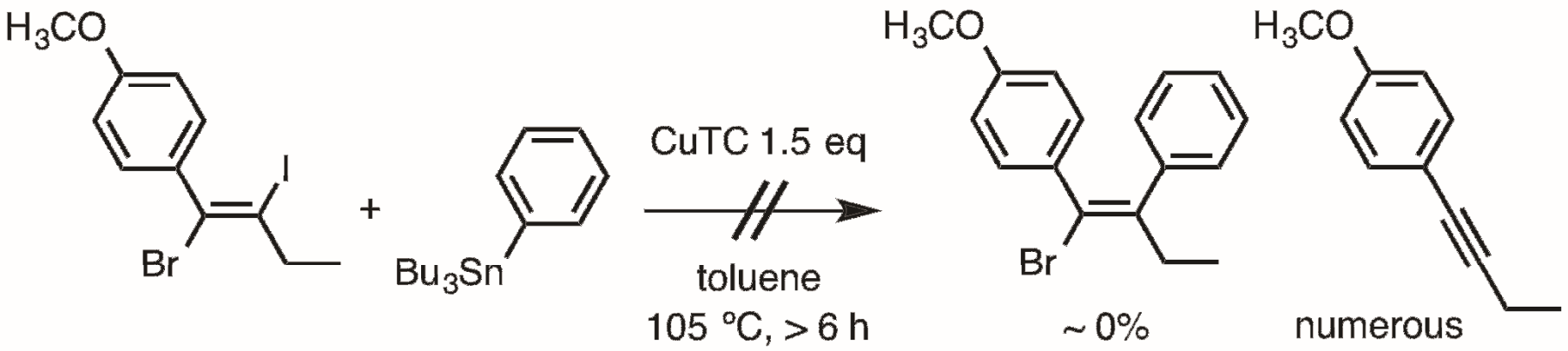
mmol of **1**	%Yield	Purity/%
1.6	77	95 (recryst. from MeOH, 99%)
4.0	90	97
11.3	**77**	**>99**



Synthesis of (*E*)-Tamoxifen



Unfortunately, lots of efforts were unsuccessful.

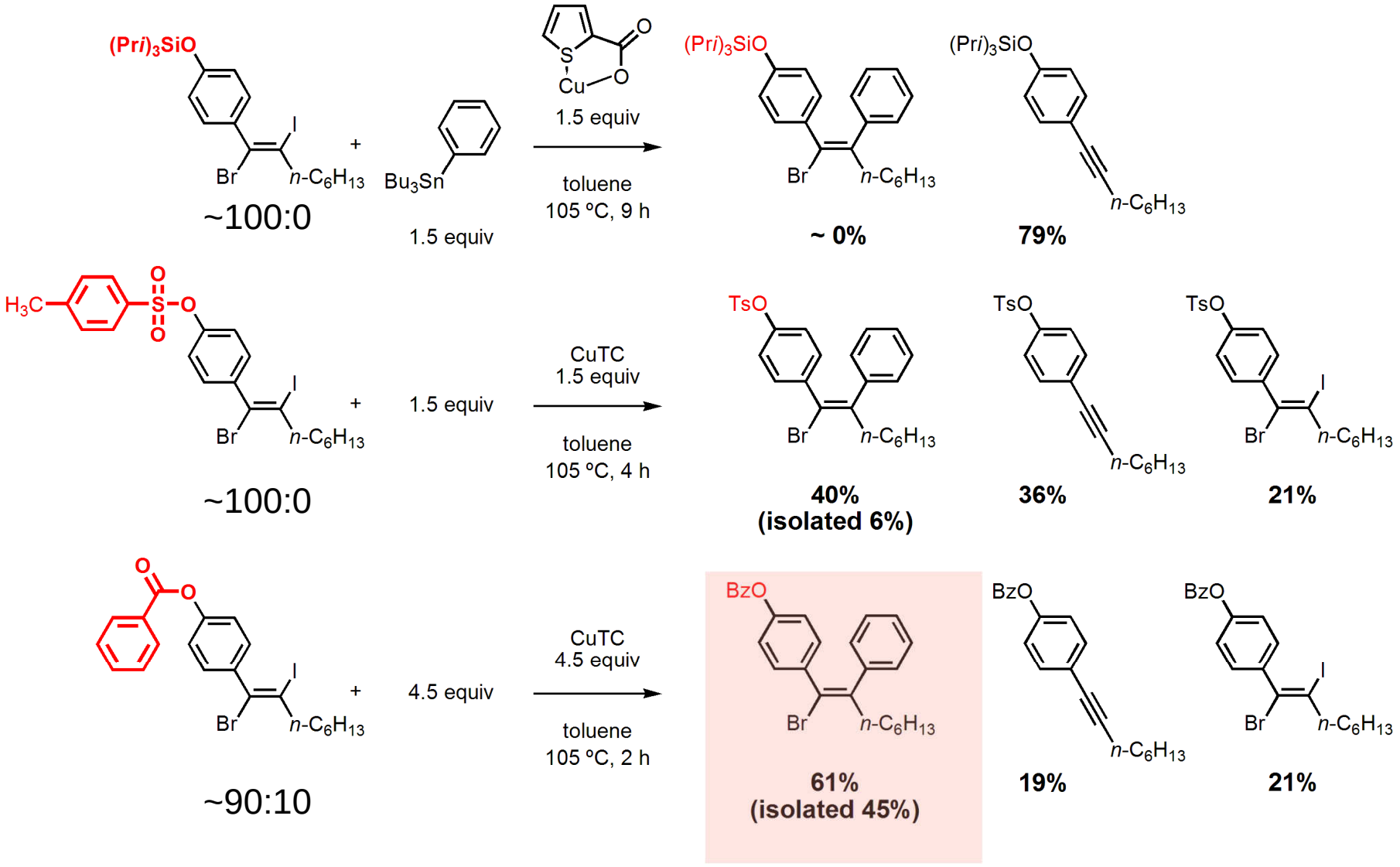


- Conventional copper sources didn't work at all; for example, Cu powder, $Cu(OTf)_2$, $CuOTf•1/2C_6H_6$, $Cu(OAc)_2$, CuOAc, CuI, CuBr, $CuCl_2$, CuCl, Cu_2O, CuO, $CuSO_4•5H_2O$, CuMeSal, $CuBr•SMe_2$, CuI $•P(OEt)_3$, $Cu(MeCN)_4•BF_4$.

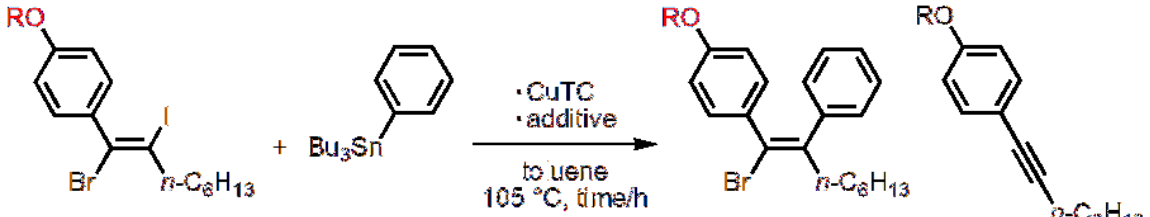
- Cross-coupling protocols of Suzuki, Negishi, and Stille put the starting dihaloalkene back to the corresponding alkyne.

- Alternative ways using C-H activation, Bismuth and so on were ineffective.

Designed to replace the *para*-positioned MeO-moiety with (*i*Pr)$_3$SiO-, TsO-, and BzO- substructures.



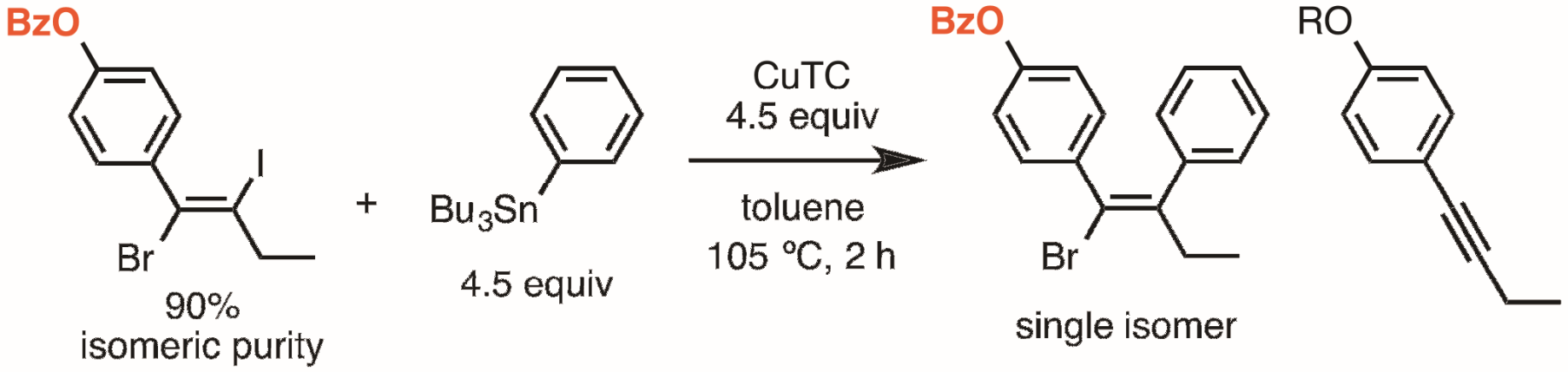
para-Substituent-induced activation of the vinylic iodines was found, barely…



~90:10 Single

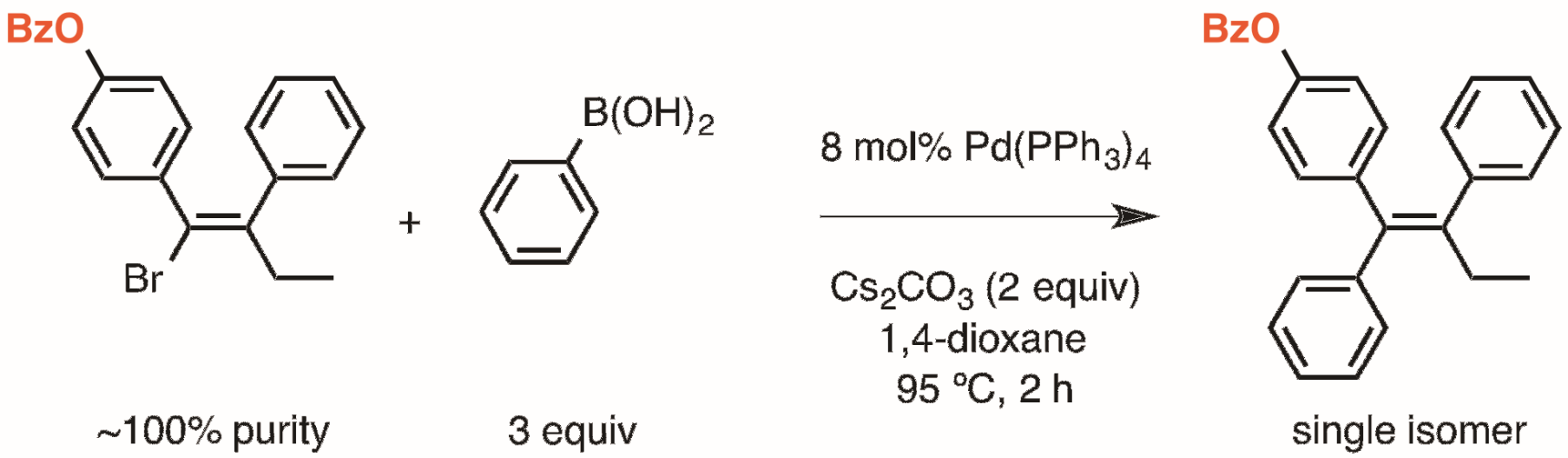
R	equiv. of CuTC	additive	*t* [h]	%Yield[c]		
				Target	**Alkyne**	**Starting**
PhCO	1.5	-	3	28	24	24
	4.5	**-**	**2**	**61 (45)**	**19**	**19**
	1.5	PPh_3	2	<10	-	-
	1.5	$O=PPh_3$	2	<6	-	-
CF_3	4.5	-	16	44 (33)	16	4
C_6F_5CO	4.5	-	4	54 (6)	32	6
2-Naph-CO	4.5	-	2	47	13	10
4-CF_3PhCO	4.5	-	4	43	15	9
CH_3CO	4.5	-	3	46	28	12

Scalable synthesis of phenyl-substituted benzoate-protected one.

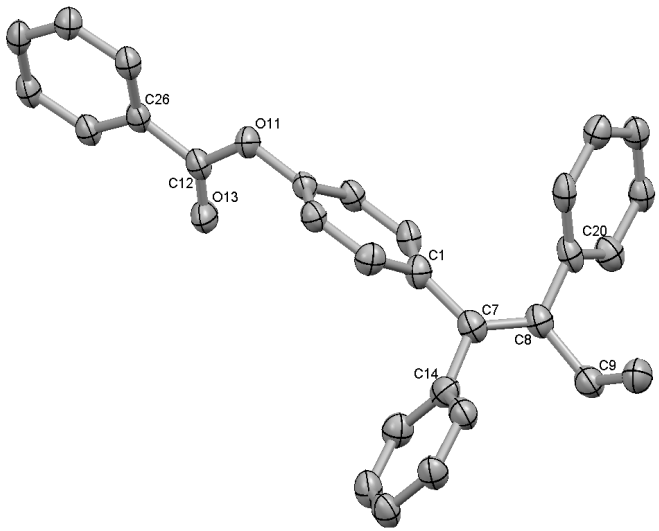


Scale of **the starting** mmol (g)	%Yield		
	Target	**Alkyne**	**Starting**
0.5 (0.23)	41 (19)	11	15
1.5 (0.69)	60 (40)	12	16
4.0 (1.8)	60 (45)	13	13
8.0 (3.7)	60 (47)	14	25
16 (7.4)	61 (45)	15	9

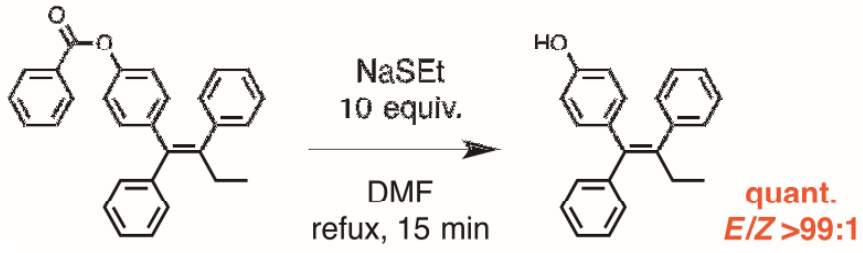
The following activation of the vinylic bromine was successful without erosion of the geometry.



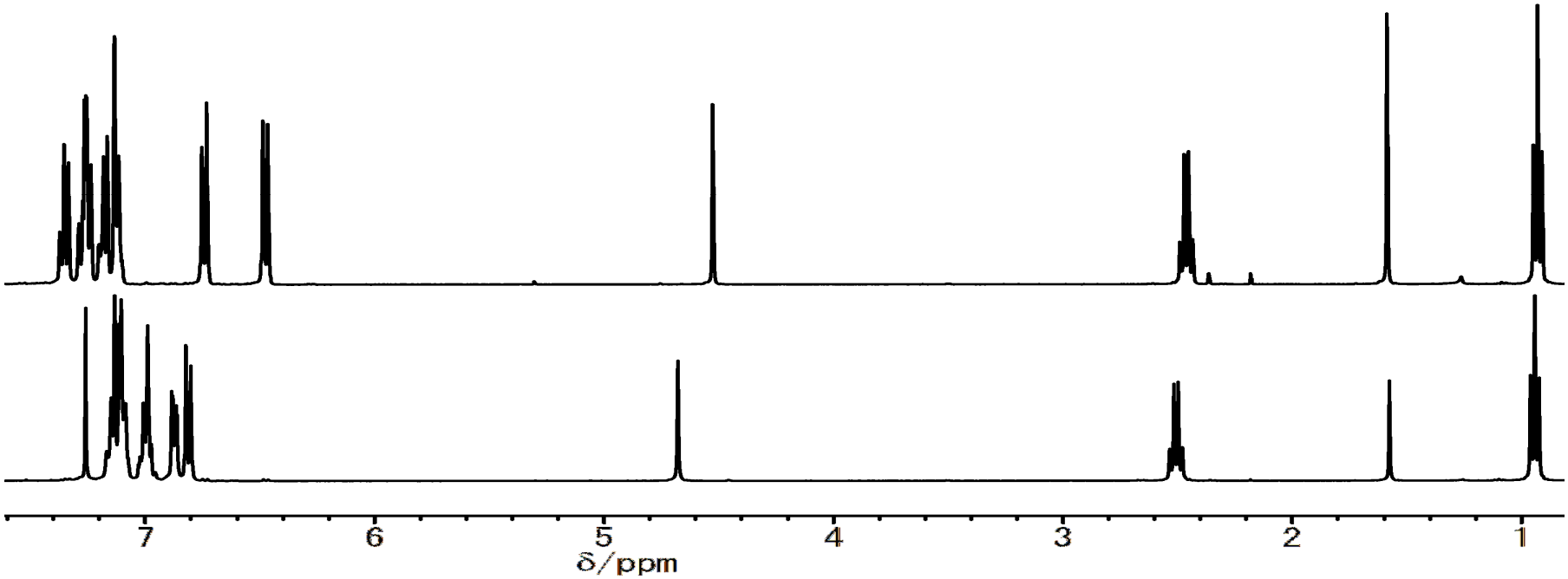
Starting BzO-mmol (g)	%Yield	Ratios
1.5 (0.62)	75	98/2
5.0 (2.0)	82	99/1
11 (4.5)	**89**	**99/1**



NaSEt cleanly cleaved the ester bond without erosion of the stereo-chemistry, which relieved us!

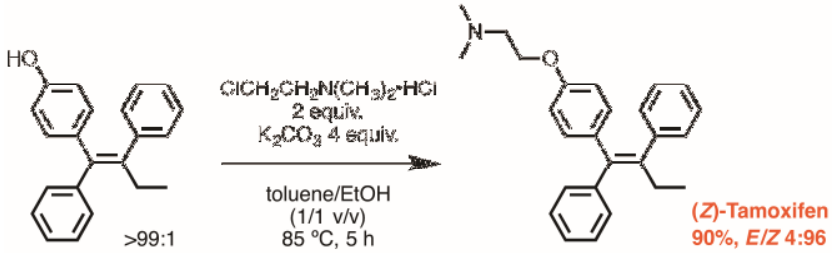


The ester	The phenol	Ratio
0.5 mmol	67%	>99:1
1.0 mmol	79%	>99:1
1.5 mmol	88%	>99:1

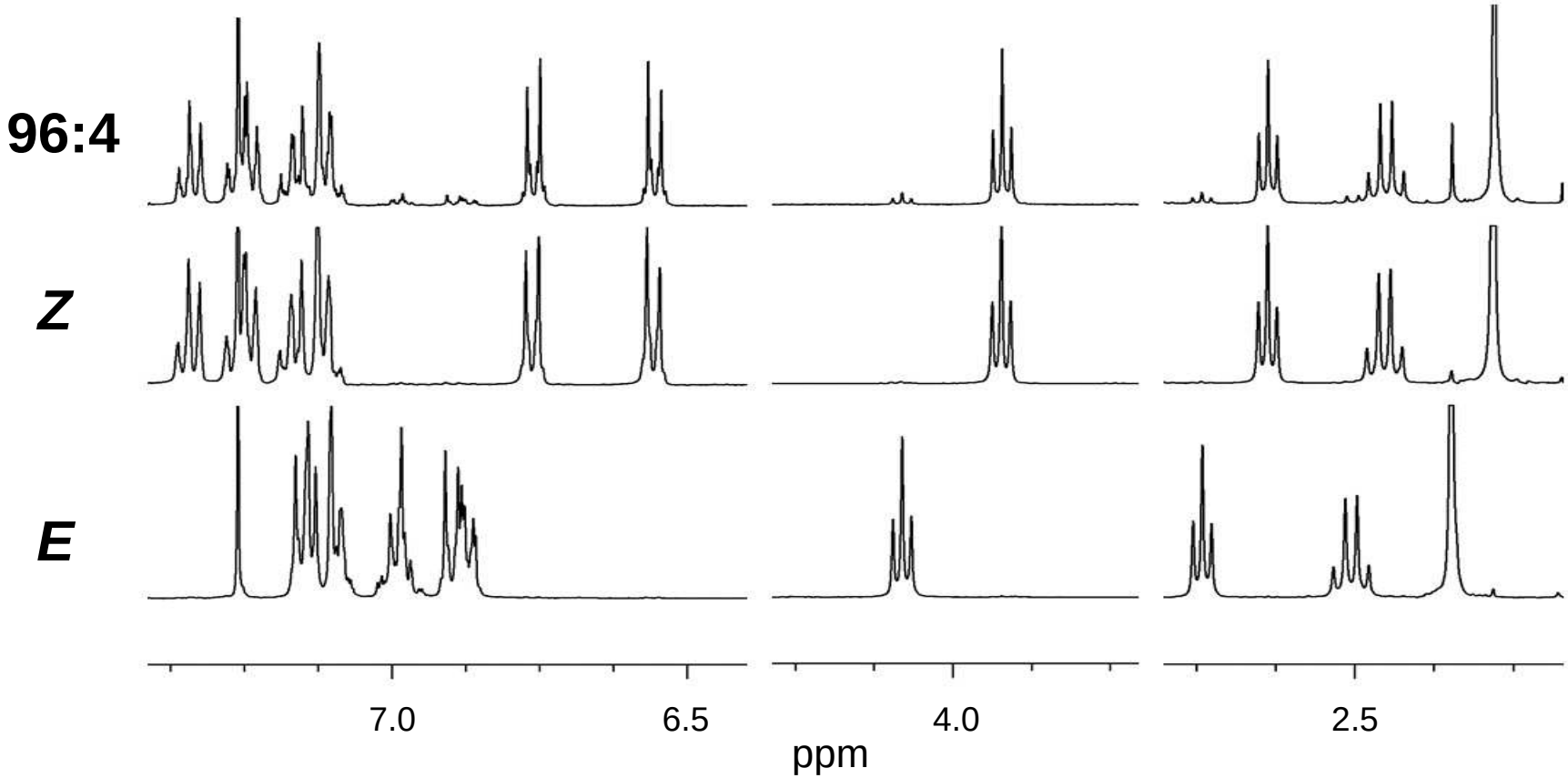


- A. K. Chakraborti, M. K. Nayak, L. Sharma, *J. Org. Chem.* **2002**, *67*, 1776-1780.
- A. K. Chakraborti, M. K. Nayak, L. Sharma, *J. Org. Chem.* **1999**, *64*, 8027-8030.

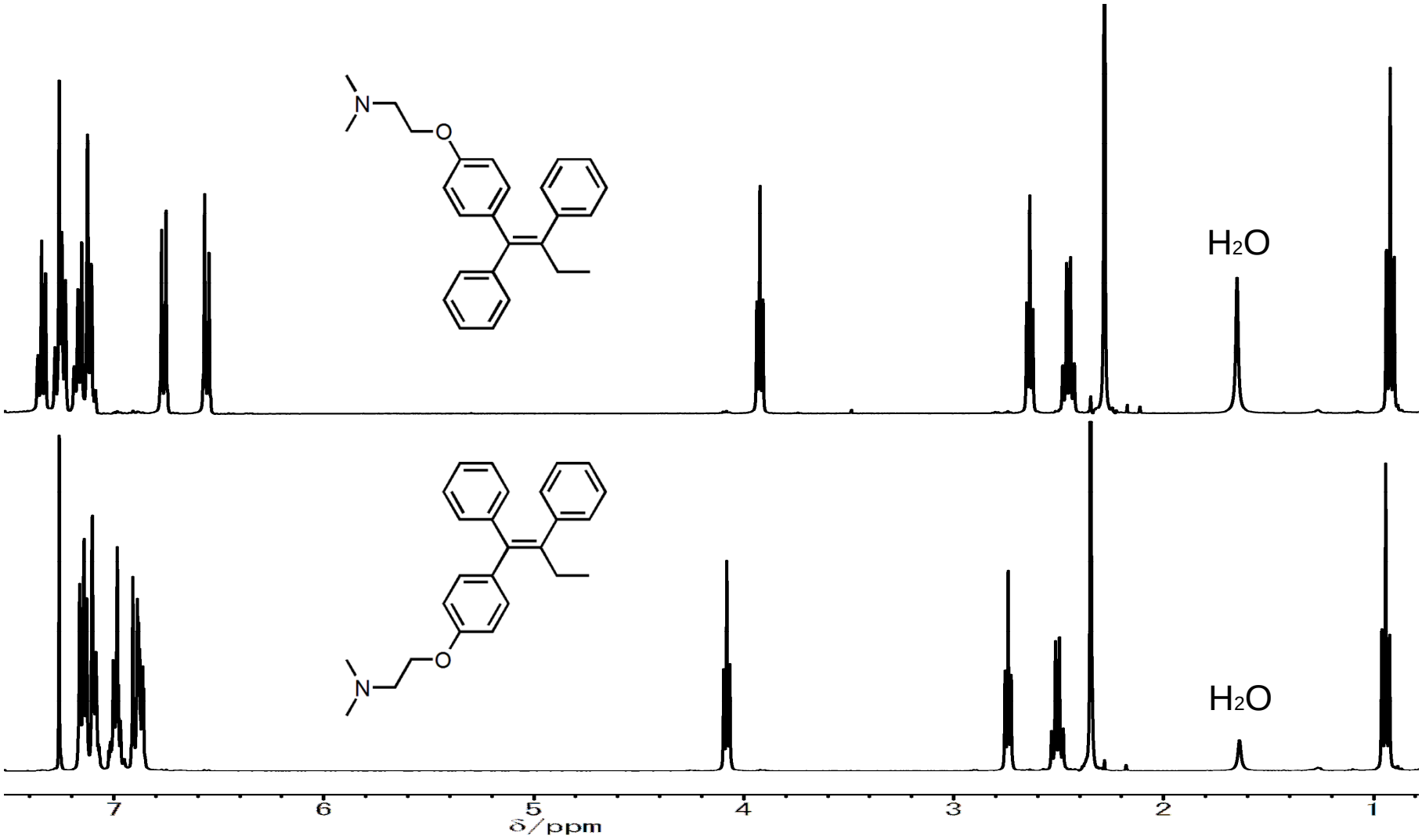
The phenol undertook the final alkylaiton.



The phenol	Product	Ratio
0.25 mmol	90%	96:4
0.58 mmol	83%	96:4



Here, the spectra of (*E*)- and (*Z*)-Tamoxifen those we are longing for…



Summary: finally, we've got both of them!