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Z-Selective Olefin Synthesis via Iron-Catalyzed Reductive Coupling of Alkyl Halides with Terminal Arylalkynes

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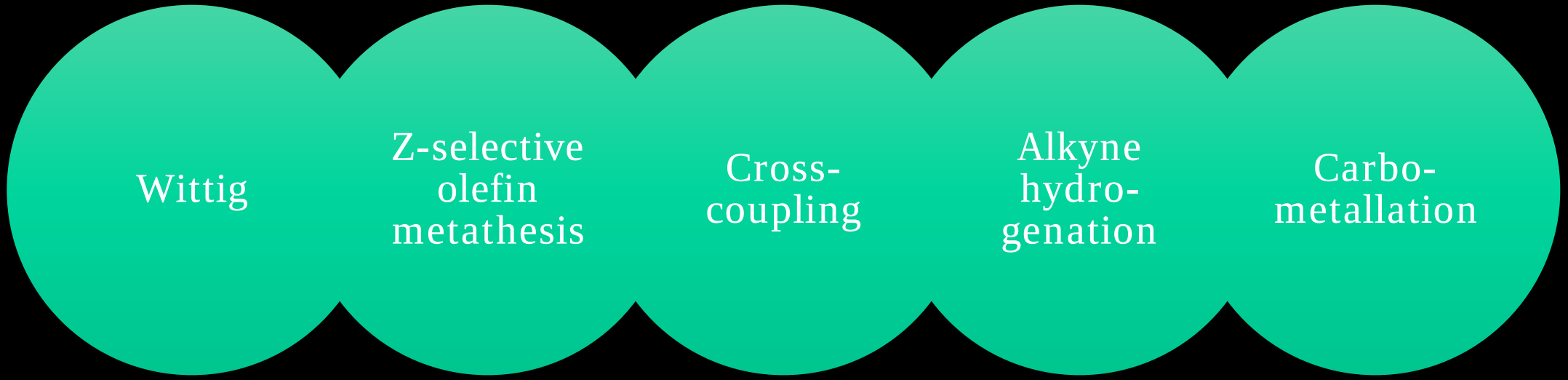
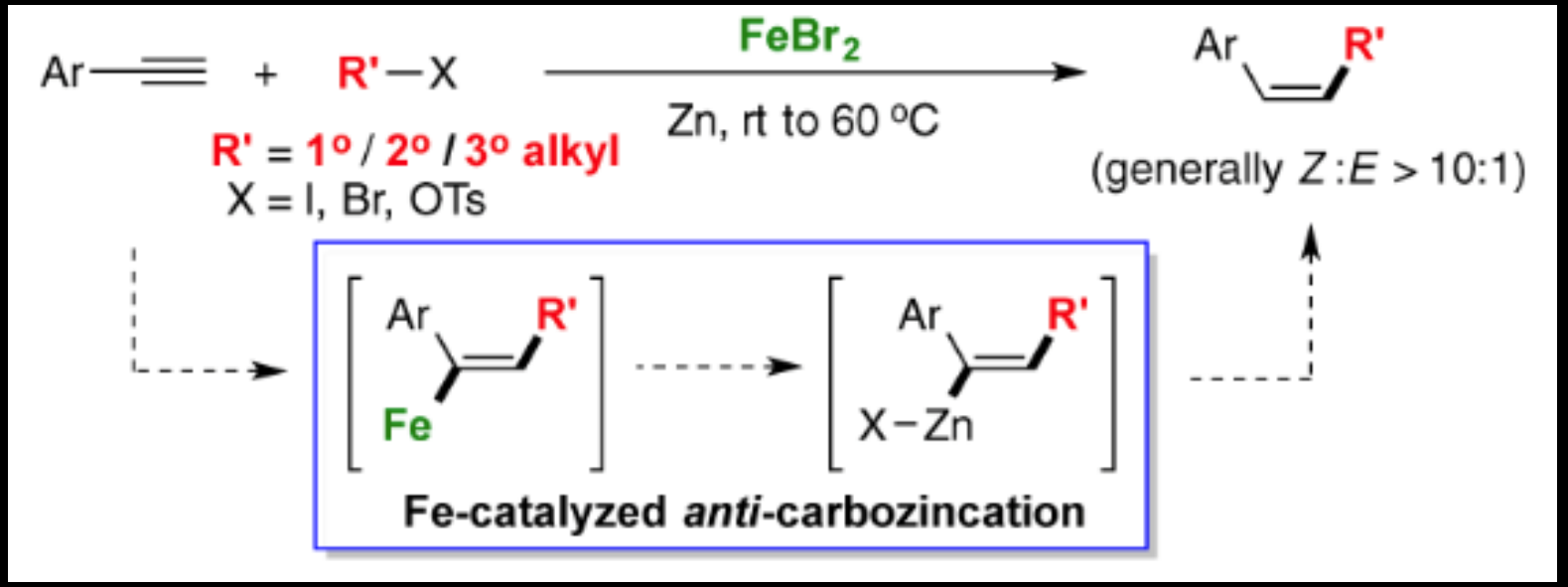
Julien Botton

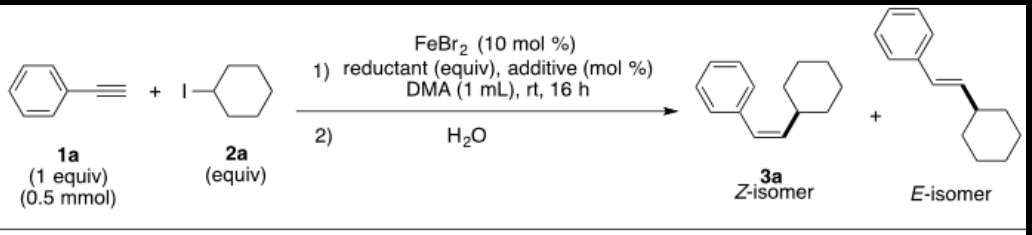
Synthesis of substituted Z-alkenes



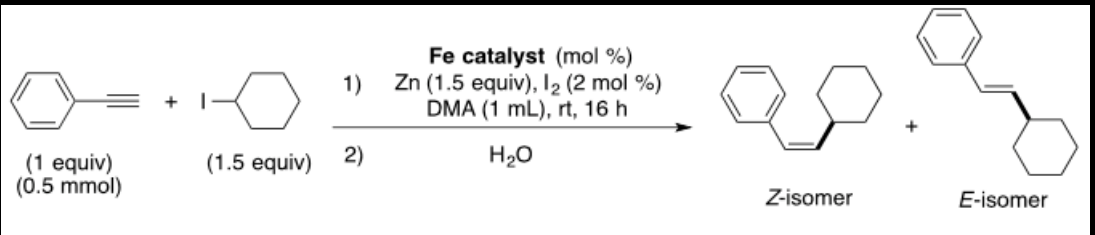
This Work


Ar
+
R'—X
FeBr2
Zn, rt to 60 °C
Ar
R'
(generally Z:E > 10:1)
R' = 1° / 2° / 3° alkyl
X = I, Br, OTs
Ar
R'
Fe
Ar
R'
X—Zn
Fe-catalyzed anti-carbozincation

Optimization Study: Reductants and Iron Salts

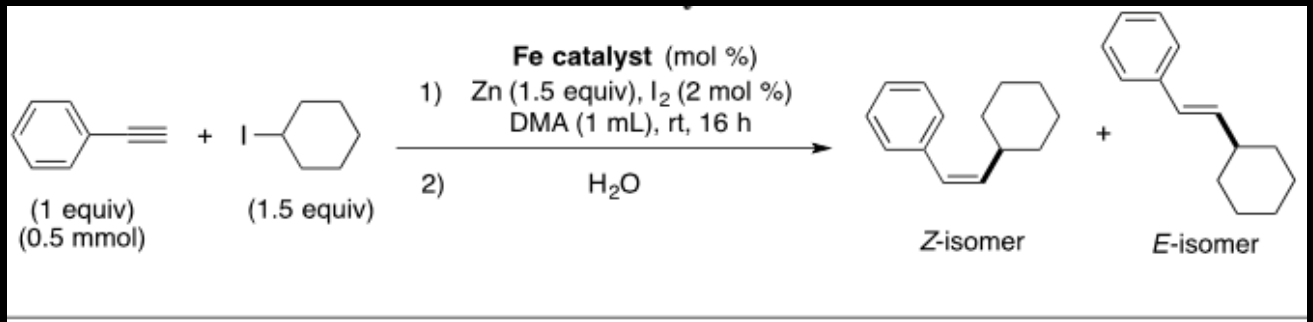


entry	Cyl (equiv)	reductant (equiv)	additive (mol %)	yield of *Z*-product (%)[b]	*Z*: *E*[c]
1	2	Zn (2.5)	---	97	13.8
2	1.5	Zn (2.5)	---	79	13.8
3	1.5	Zn (2.5)	TMSCl (20)	85	15.2
4	1.5	Zn (2.5)	TMSBr (10)	70	17.4
5	1.5	Zn (2.5)	TMSI (10)	85	17.4
6	1.5	Zn (2.5)	I_2 (2)	92	14.0
7	**1.5**	**Zn (1.5)**	**I_2 (2)**	**91**	**13.4**
8	1.5	Zn (1.2)	I_2 (2)	77	12.6
9	1.2	Zn (1.5)	I_2 (2)	77	12.6
10	1.5	Mn (1.5)	I_2 (2)	5	2.9
11	1.5	Mg (1.5)	I_2 (2)	7	1.3



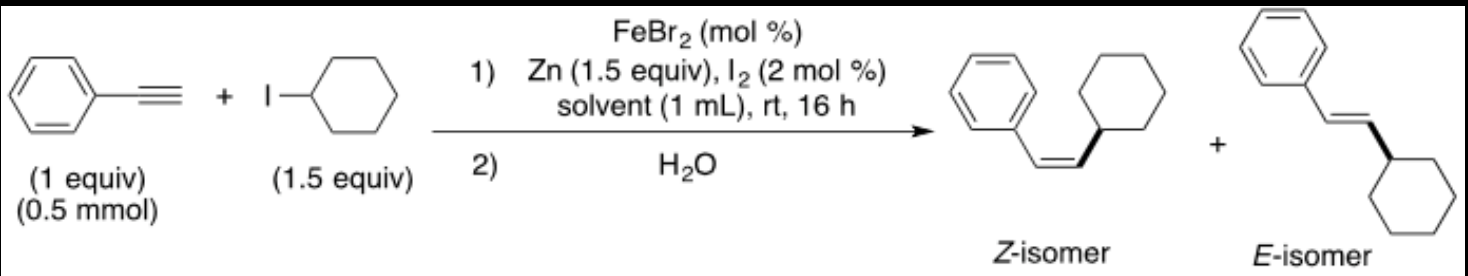
entry	**Fe catalyst (mol %)**	GC yield of *Z*-product (%)[b]	*Z*: *E*[c]
1	**$FeBr_2$ (10)**	**91**	**13.4**
2	$FeBr_2$ (5)	82	14.0
3	$FeBr_2$ (15)	69	12.4
4	$FeBr_2$ (10)[d]	90	12.4
5	$FeBr_2$ (10)[e]	88	13.2
6	$FeBr_3$ (10)	85	12.8
7	$FeCl_2$ (10)	82	13.5
8	FeI_2 (10)	92	14.3
9	$Fe(OTf)_2$ (10)	79	13.6
10	$Fe(acac)_3$ (10)	49	11.2

Optimization Study: Other Metals Sources



entry	**Fe catalyst (mol %)**	GC yield of *Z*-product (%)[b]	*Z*: *E*[c]
1	**$FeBr_2$ (10)**	**91**	**13.4**
2	$NiBr_2$ (10)	1	1.0
3	$CoBr_2$ (10)	2	0.4
4	$CuBr_2$ (10)	73	12.0
5	$AgNO_3$ (10)	7	1.9
6	$Pd(OAc)_2$ (10)	8	7.4
7	$CrCl_2$ (10)	81	17.8
8	$Mn(OAc)_2 \cdot 4H_2O$ (10)	24	21.7

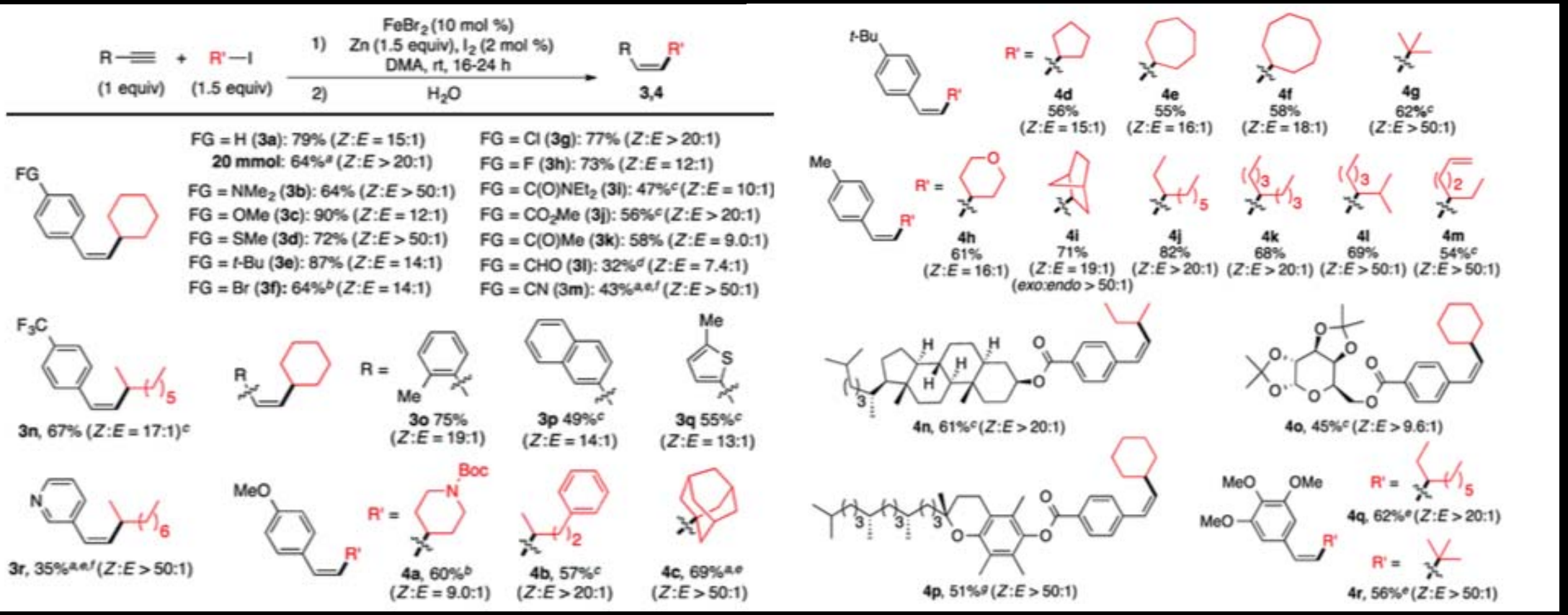
Optimization Study: Solvents and Controls



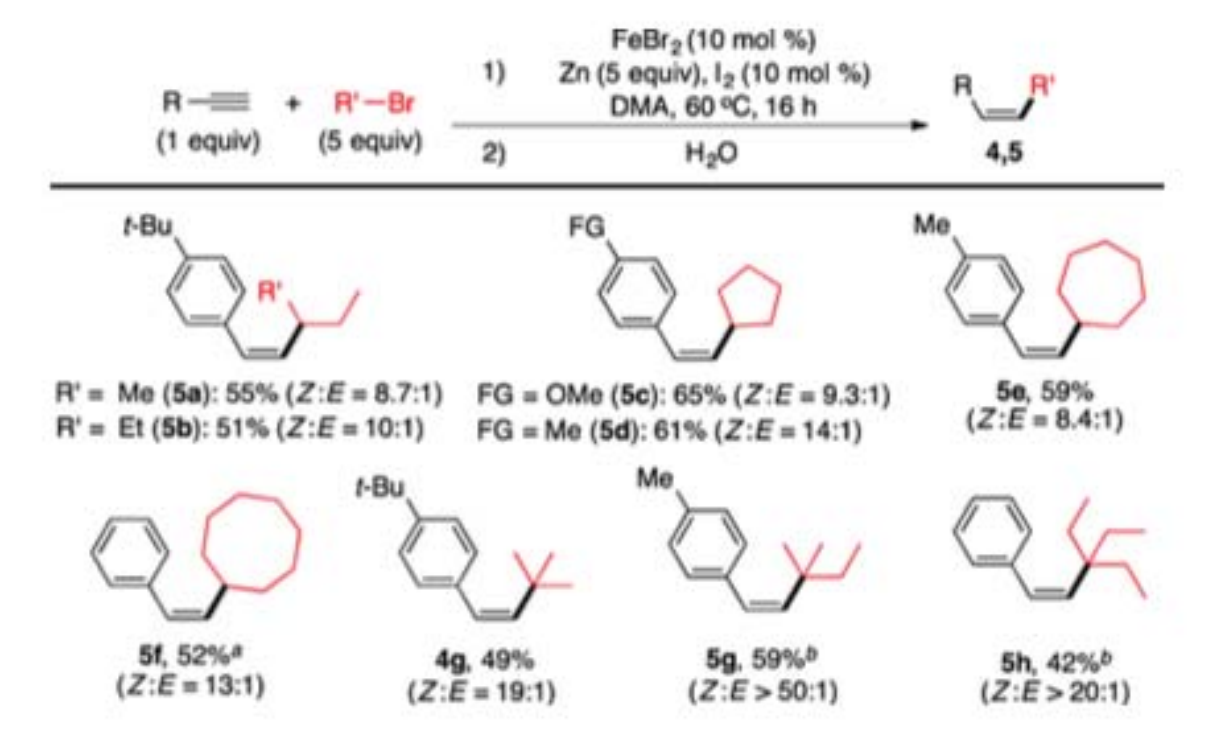
entry	**solvent (mL)**	concentration of alkyne (M)	GC yield of Z-product (%)[b]	*Z*: *E*[c]
1	**DMA (1)**	0.5	**91**	**13.4**
2	DMA (2)	0.25	87	12.0
3	DMA (0.5)	1	80	14.6
4	NMP (1)	0.5	81	11.2
5	DMF (1)	0.5	62	14.1
6	THF (1)	0.5	5	3.7

entry	$FeBr_2$ (mol%)	Zn (equiv)	GC yield of Z-product (%)[b]	*Z*: *E*[c]
1	**10**	**1.5**	**91**	**13.4**
2	0	1.5	34	14.3
3	10	0	0	---

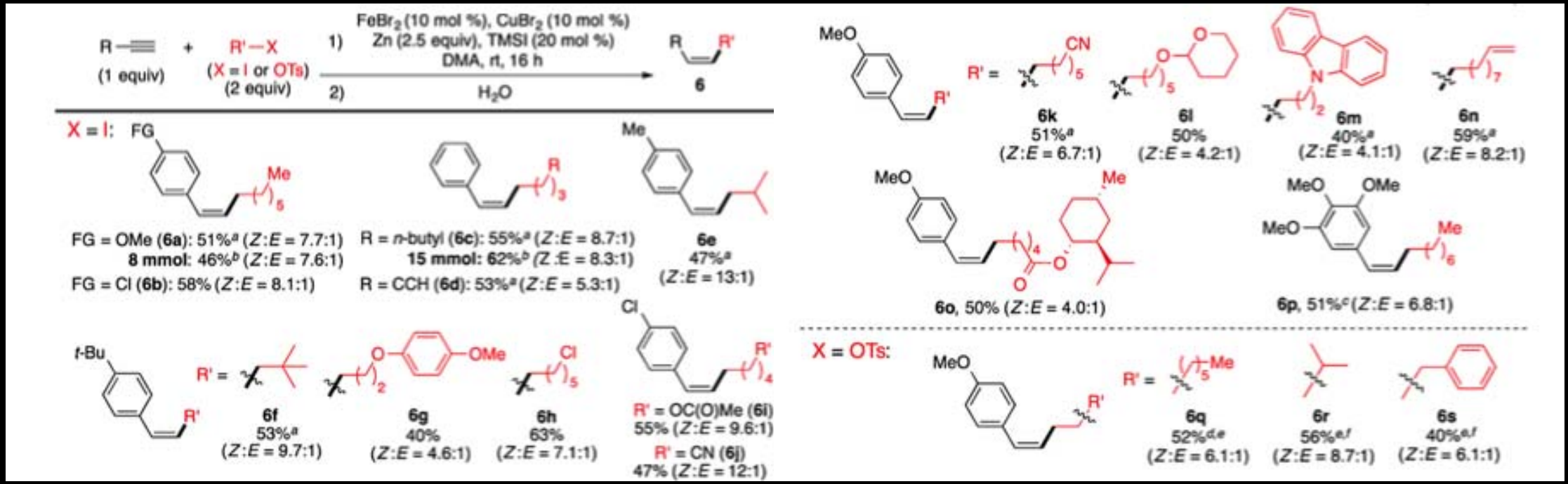
Screening of Secondary and Tertiary Iodides



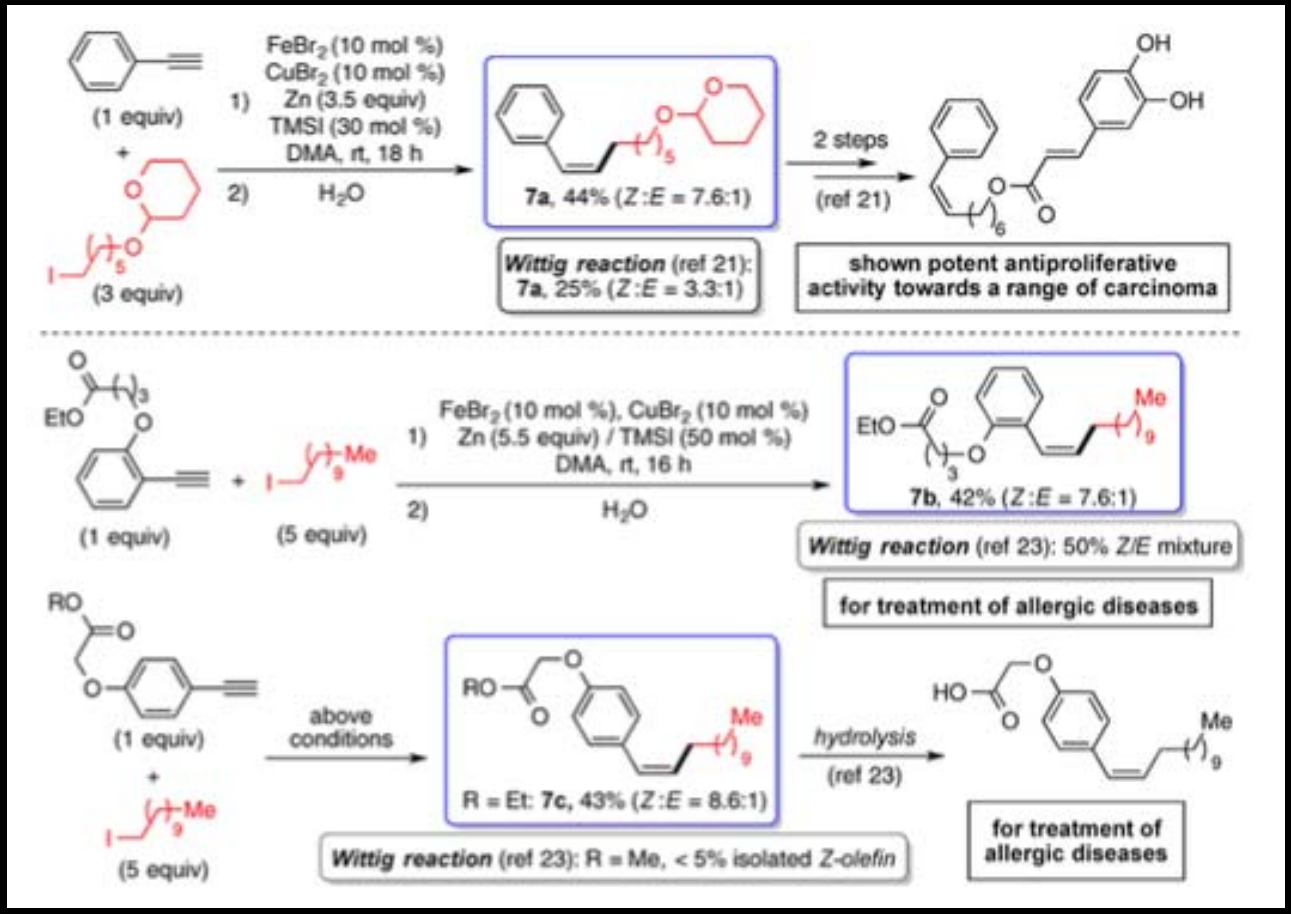
Screening of Secondary and Tertiary Bromides



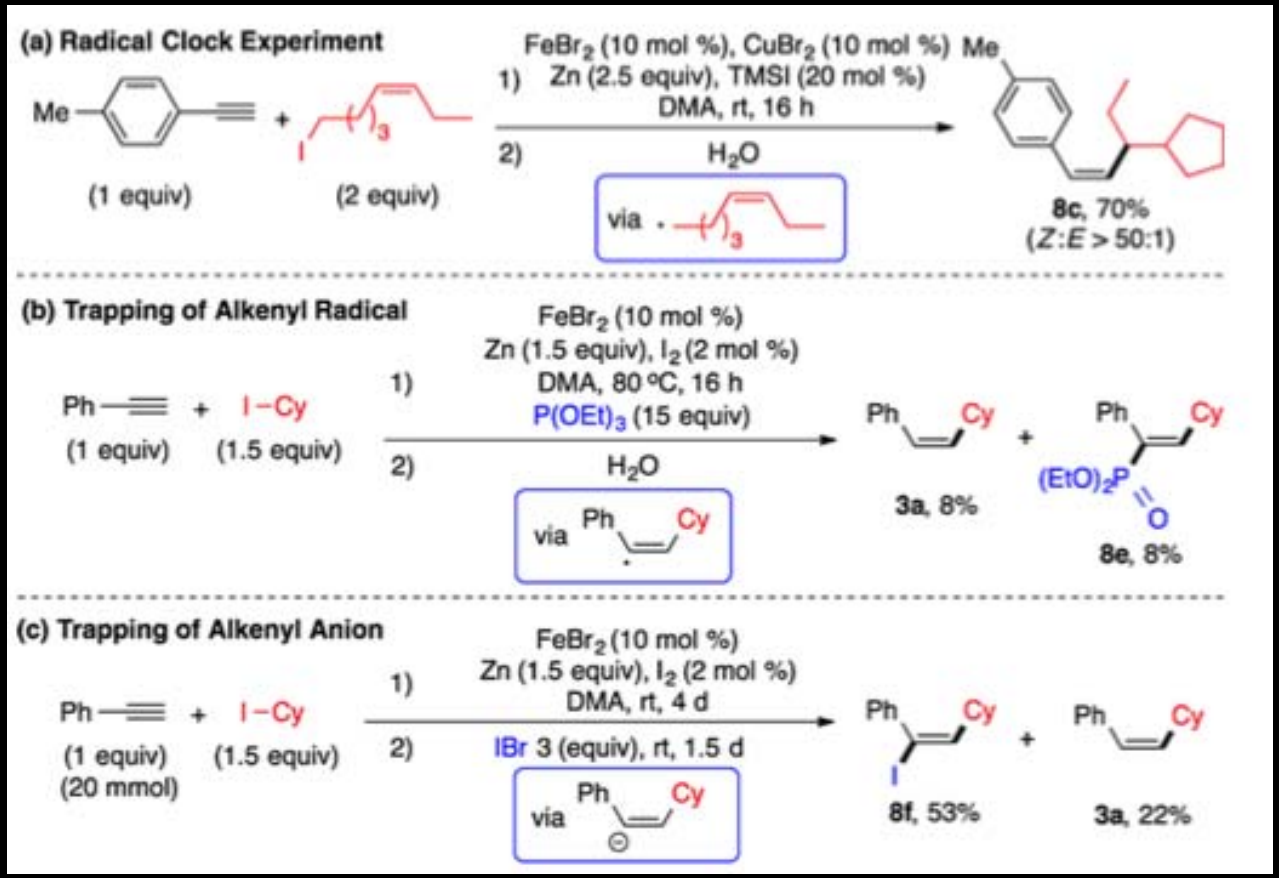
Screening of Primary Alkyls



Synthetic Applications

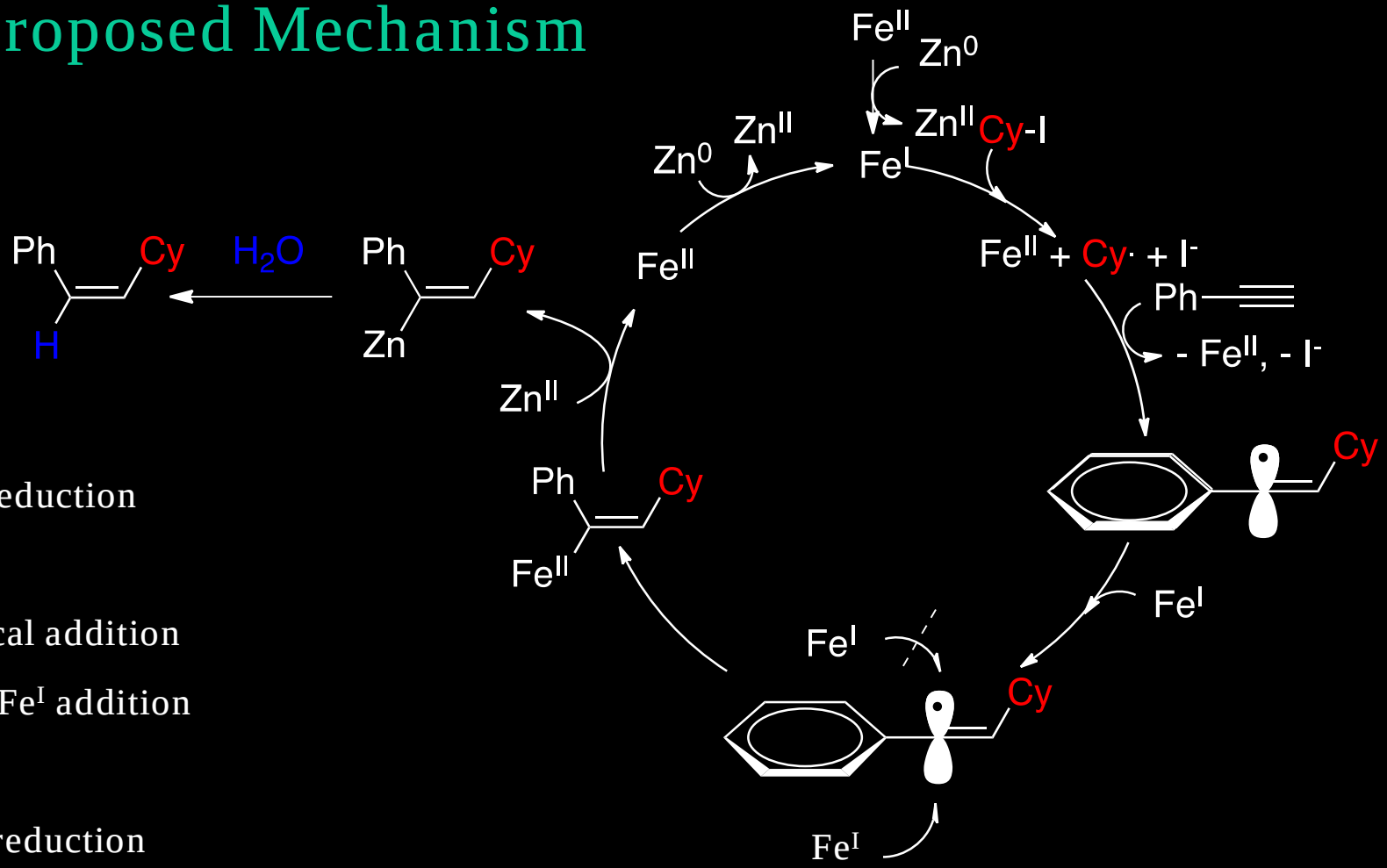


Mechanistic Studies



- **Use of TEMPO**:
  alkyl-TEMPO adduct + No desired product
- **Use of D2O and DMA-d9:**
  olefinic Hydrogen comes from aqueous work-up
- **Use of alkyl-zinc reagents:**
  No desired product

Proposed Mechanism



1) Fe^{II} reduction
2) SET
3) Radical addition
4) Anti-Fe^{I} addition
5) TM
6) Fe^{II} reduction
7) Hydrolysis

Conclusion

Alternative access to Z-olefin

Wide range of alkyls partners

Limited to terminal arylalkynes

Synthesis of complex structures with biological activities