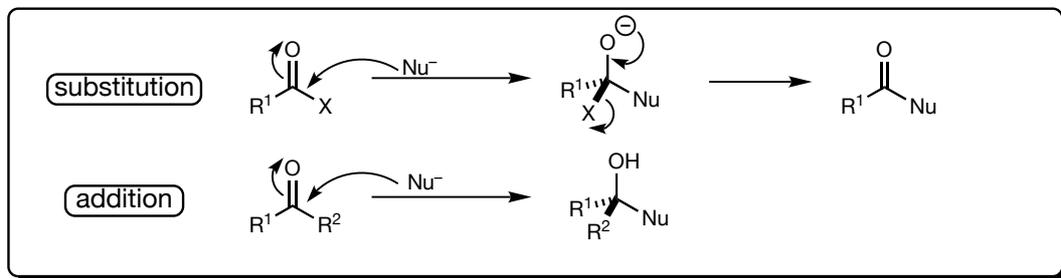


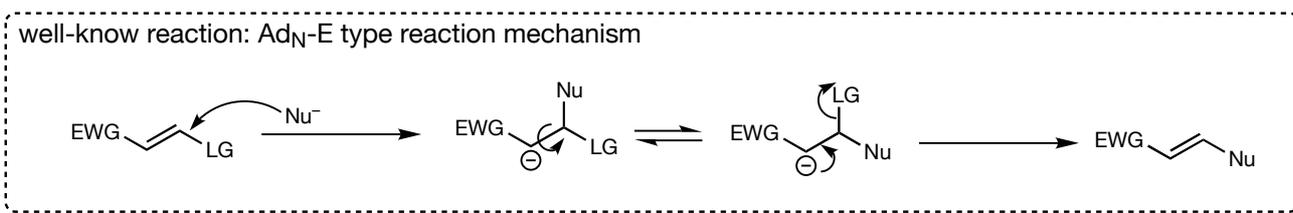
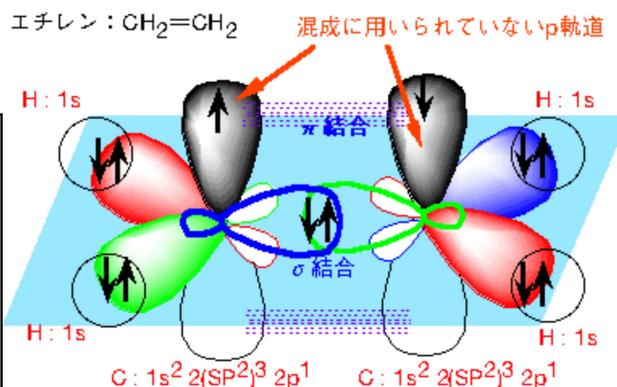
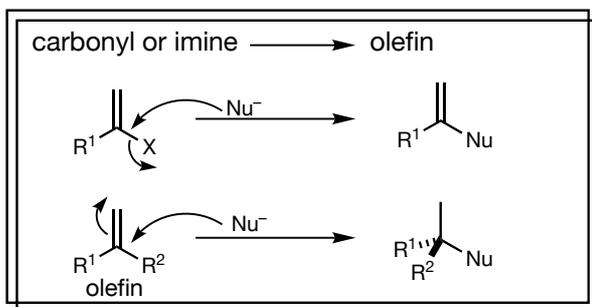


Nucleophilic Substitution & Addition Reaction toward Olefin

0 Introduction



How about simple olefin ??



Other examples (See below)

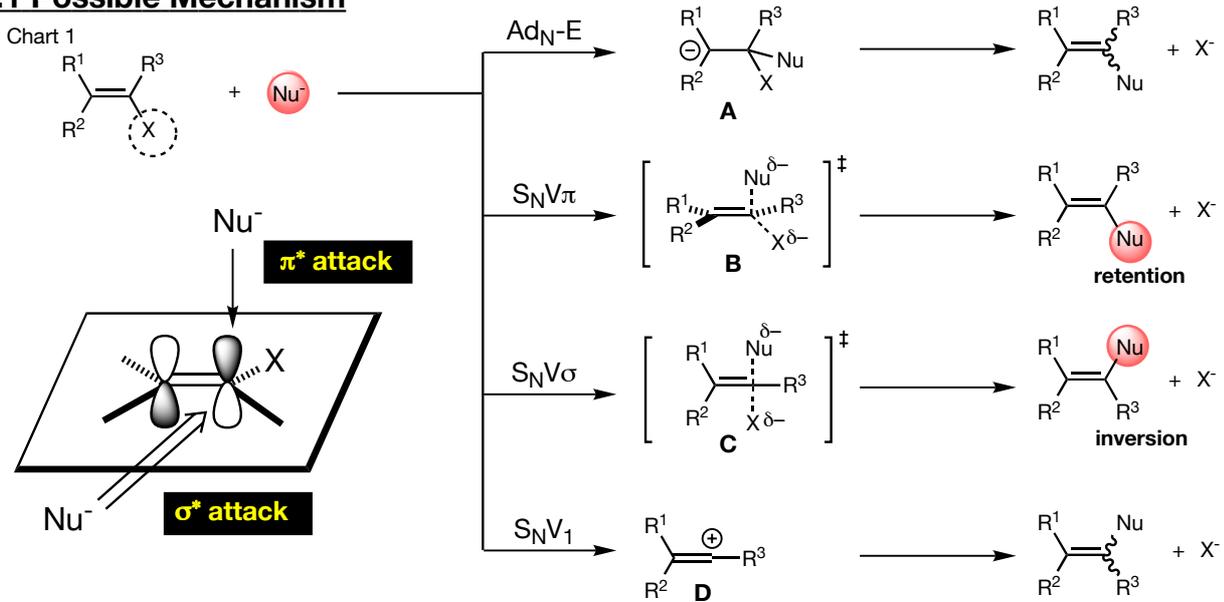
- Qin-san's lit. seminar (2004.11.20); hydroamination
- Fujimori-kun's seminar (2006. 7.19); diamination
- Handa's lit. seminar (2006. 7.15); oxidative amination

Contents

0 Introduction	1	1.3 $S_NV\sigma$ Substitution	3
1 Vinyl Substitution Reaction		1.4 Intramolecular $S_NV\sigma$ Substitution	5
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1.2 $S_NV\pi$ Substitution	2	2.1 Zinc Aza-Enolate	7
1.2.1 Negative Phenomenon for S_NV_1 Substitution		2.2 N-Aryl Zinc-Enamide	9
1.2.2 Neighbouring Participation ($S_NV\pi$ Substitution)		3 Outlook & Remark	10

1 Vinyl Substitution Reaction

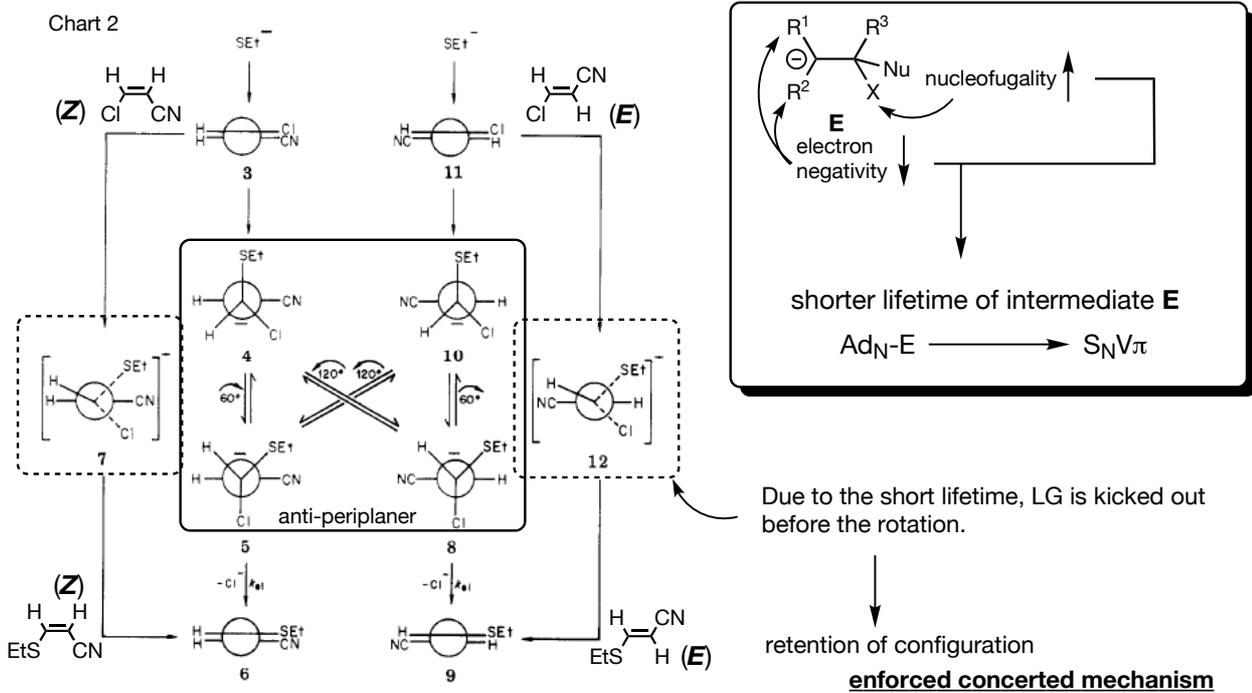
1.1 Possible Mechanism



$\text{Ad}_{\text{N}}\text{-E}$ substitution & $\text{S}_{\text{N}}\text{V}\pi$ substitution

Rappoport, Z. *Acc. Chem. Res.* **1981**, 14, 7.

Rappoport, Z. *Acc. Chem. Res.* **1992**, 25, 474.

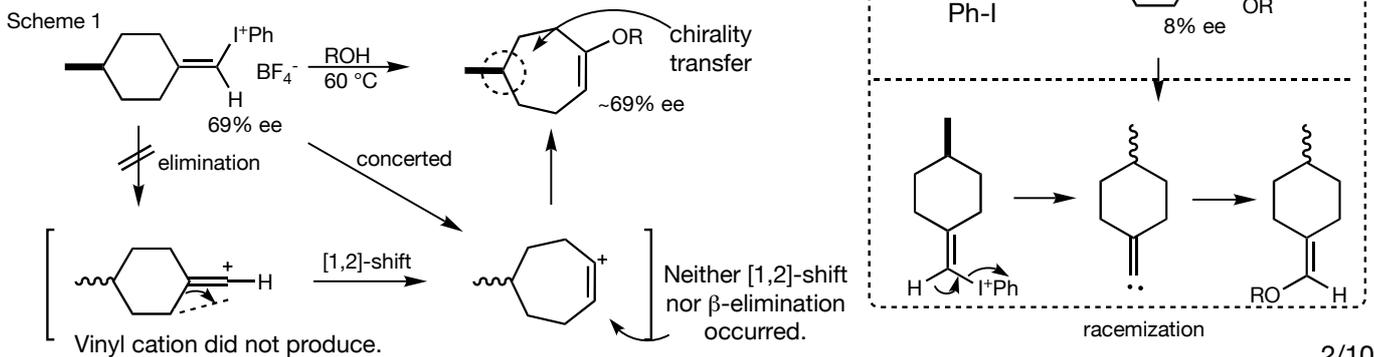


1.2 $\text{S}_{\text{N}}\text{V}\pi$ Substitution

1.2.1 Negative phenomenon for $\text{S}_{\text{N}}\text{V}_1$ Substitution

Fujita, M. and Okuyama, T. et al. *J. Am. Chem. Soc.* **2000**, 122, 8787.

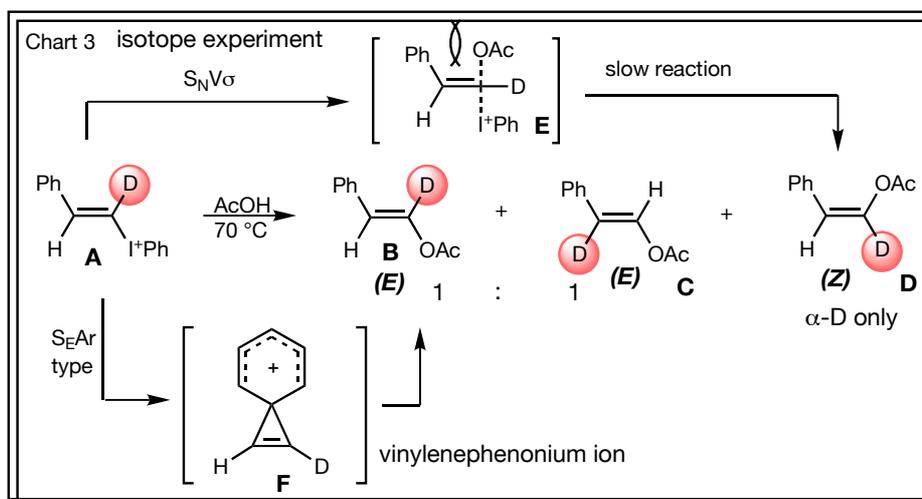
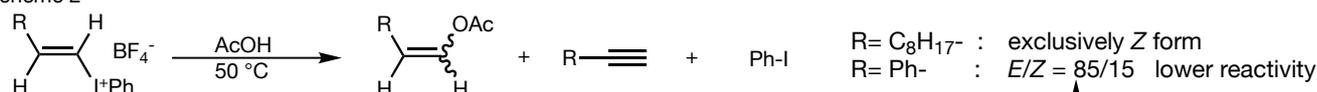
Fujita, M. and Okuyama, T. et al. *J. Org. Chem.* **2002**, 67, 8130.



1.2.2 Neighbouring Participation ($S_NV\pi$ Substitution)

Okuyama, T. and Ochiai, M. *J. Am. Chem. Soc.* **1997**, *119*, 4785.

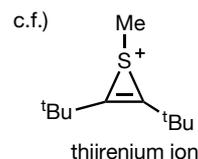
Scheme 2



Discrepancy !!

Considering anion stability, in the case of R=Ph Z isomer should form. \rightarrow not $S_NV\pi$?

Neither $S_NV\sigma$?



Luccihini, V. *J. Org. Chem.* **1982**, *47*, 590.

1.3 $S_NV\sigma$ Substitution

\odot (E)-alkenylvinylidonium salt ; Ochiai, M. et al. *J. Am. Chem. Soc.* **1991**, *113*, 7059.

Ochiai, M. *J. Organomet. Chem.* **2000**, *611*, 494. (Review)

Table 1



Table I. Nucleophilic Vinylic Substitutions of (E)-Alkenyl(phenyl)iodonium tetrafluoroborates 1 with $n\text{-Bu}_4\text{NX}^a$

run no.	substrate	reagent	solvent	reaction time, h	product, % yield ^b			PhI
					alkenyl halide (Z:E ratio)	alkyne	ratio ^c	
1	1a	$n\text{-Bu}_4\text{NF}$	CH ₂ CN	10	—	47	(0:100)	100
2	1a	$n\text{-Bu}_4\text{NCl}$	CH ₂ Cl ₂	10	2a (X = Cl), 83 (100:0)	14	(85:12)	91
3	1a	$n\text{-Bu}_4\text{NCl}$	CH ₂ Cl ₂	10	2a (X = Cl), 91 (100:0)	9	(91:9)	99
4	1a	$n\text{-Bu}_4\text{NBr}$	CH ₂ CN	10	2a (X = Br), 93 (100:0)	5	(95:5)	100
5	1a	$n\text{-Bu}_4\text{NI}$	CH ₂ CN	10	2a (X = I), 88 (100:0)	2	(98:2)	91
6	1b	$n\text{-Bu}_4\text{NCl}$	CH ₂ CN	1	2b (X = Cl), 86 (100:0)	14	(86:14)	100
7	1b	$n\text{-Bu}_4\text{NBr}$	CH ₂ CN	10	2b (X = Br), 96 (100:0)	3	(97:3)	100
8	1b	$n\text{-Bu}_4\text{NI}$	CH ₂ CN	24	2b (X = I), 99 (100:0)	1	(99:1)	100
9	1c	$n\text{-Bu}_4\text{NCl}$	CH ₂ CN	48	2c (X = Cl), 8 (66:34)	36	(18:82)	64
10	1c	$n\text{-Bu}_4\text{NBr}$	CH ₂ CN	48	2c (X = Br), 46 (88:12)	29	(61:39)	89
11	1c	$n\text{-Bu}_4\text{NI}$	CH ₂ CN	48	2c (X = I), 73 (95:5)	17	(81:19)	97

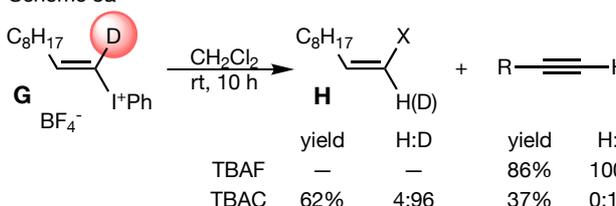
• In the case of X = Cl, Br, I, S_N2 substitution occurred and the product was given with inversion of configuration.

• With TBAF, only terminal alkyne produced.

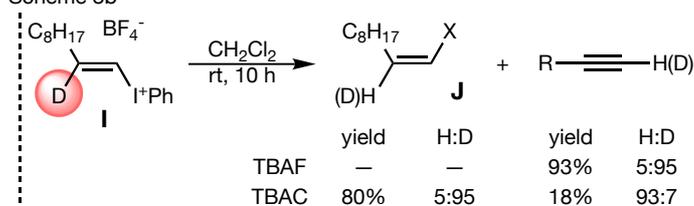
• Styrene derivative gave E/Z mixture due to the vinylene phenonium ion intermediate.

via vinylene phenonium ion ??
see above

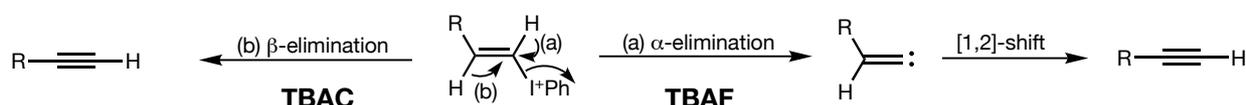
Scheme 3a

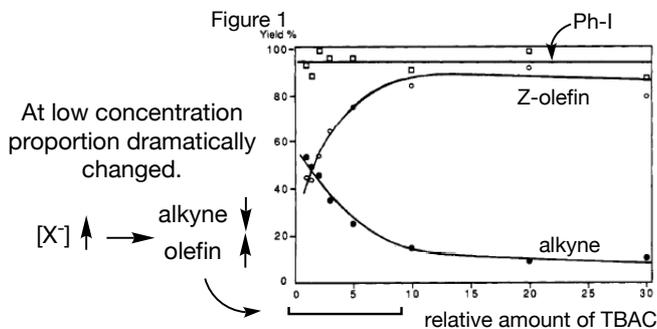


Scheme 3b



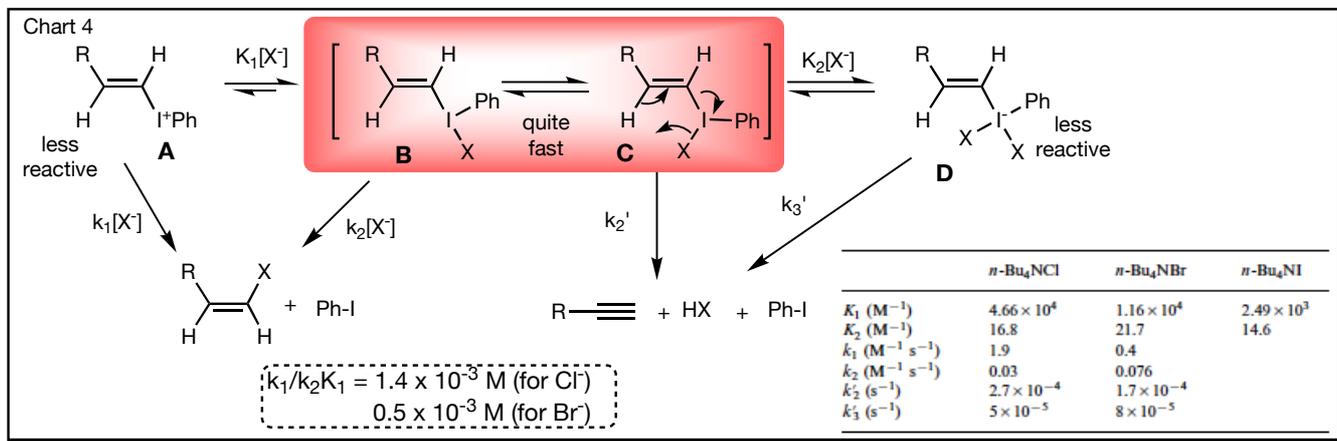
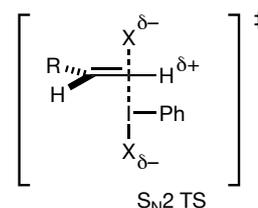
Scheme 4 Mechanism of alkyne formation





SM **A** has UV absorption around 240 nm. By initial addition of X^- , this absorption disappeared.

Generation of another species which quickly forms with X^- .



(Z)-Aroyloxyvinylidonium salt; Ochiai, M. et al. *Tetrahedron Lett.* **2005**, 46, 1863.

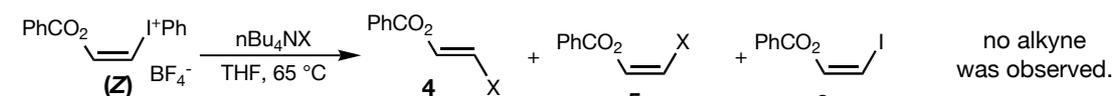


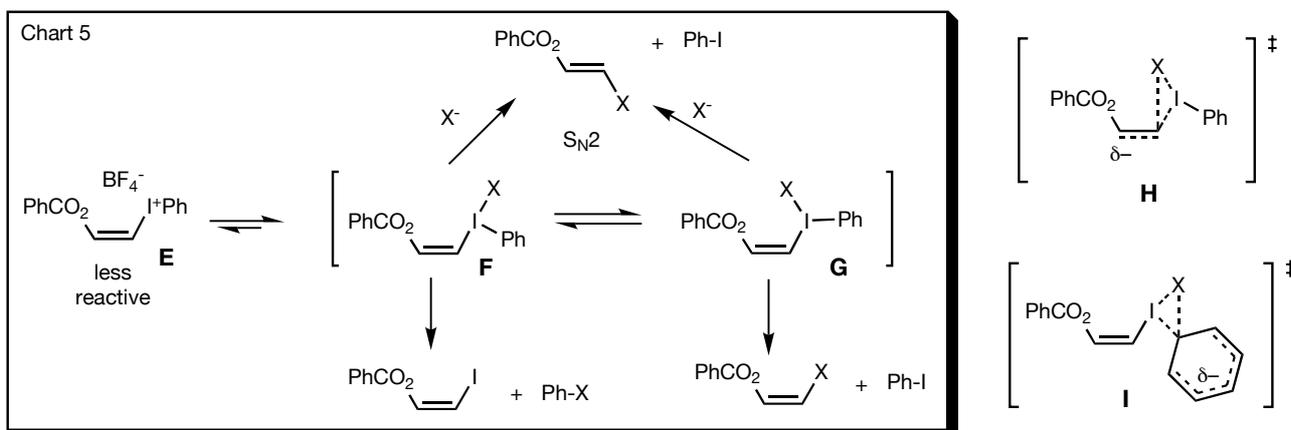
Table 2

Entrt	<i>n</i> -Bu ₄ NX X (M)	Product (yield (%)) ^b			PhI	5:6	Ratio 4:(5+6)
		4	5	6			
1	Cl (0.1)	55.0	—	—	84.6	—	100:0
2	Cl (0.01)	61.1	1.9	4.8	86.5	28:72	90:10
3	Cl (0.001)	42.0	6.2	24.9	64.0 ^c	20:80	57:43
4	Br (0.1)	98.4 ^d	1.0 ^d	0.6 ^d	95.5	62:38	98:2
5	Br (0.01)	95.9 ^d	1.9 ^d	2.2 ^d	94.9 ^e	46:54	96:4
6	Br (0.001)	72.4	10.9	16.7	79.0 ^e	39:61	72:28
7	I (0.1)	77.4	—	6.6	75.4	—	92:8
8	I (0.01)	71.7	—	11.3	77.8	—	86:14

inversion retention

strong dependency on $[X^-]$ conc.

similarity with *E* iodonium isomer



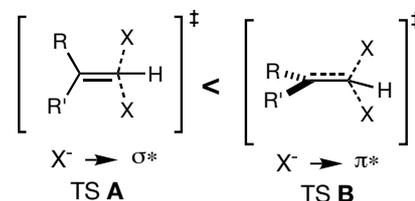
c.f.) Classically, it seemed that S_N2 substitution could not occur.

However, recent computational studies suggested that TS **A** required lower activation energy than TS **B**.

ref) Schelegel, H. et al. *J. Am Chem. Soc.* **2001**, 123, 5787.

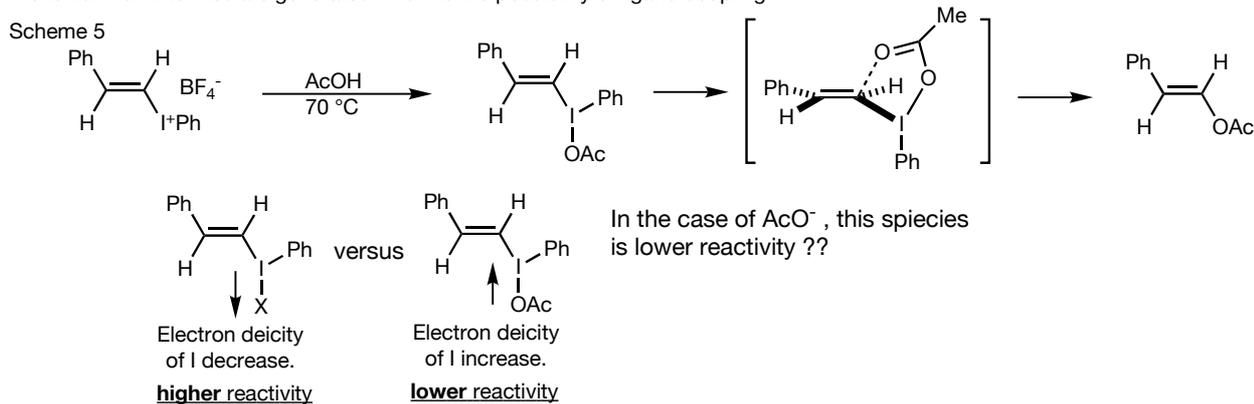
Lucchini, V. et al. *J. Am Chem. Soc.* **1995**, 117, 2297.

Pross, A. et al. *J. Am Chem. Soc.* **1994**, 116, 5961. etc.

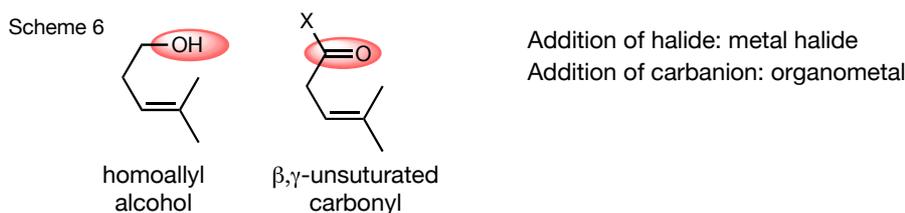


☹️ すこし疑問に思ったことを考えてみる。Now, I will raise a few questions.

Phenonium ion intermediate generated? How is the possibility of ligand coupling ?

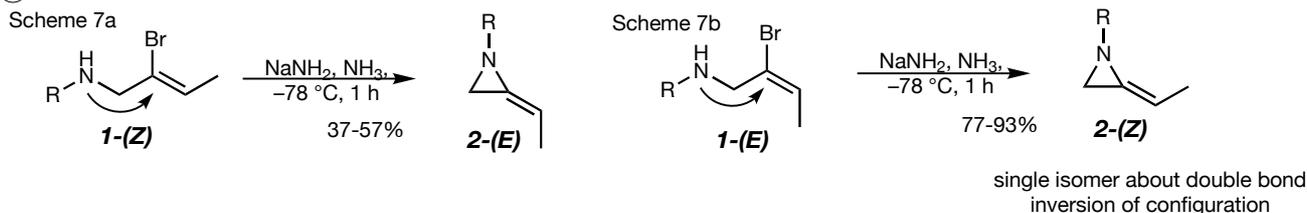


Strategies for improvement of E/Z selectivity → directing group introduction

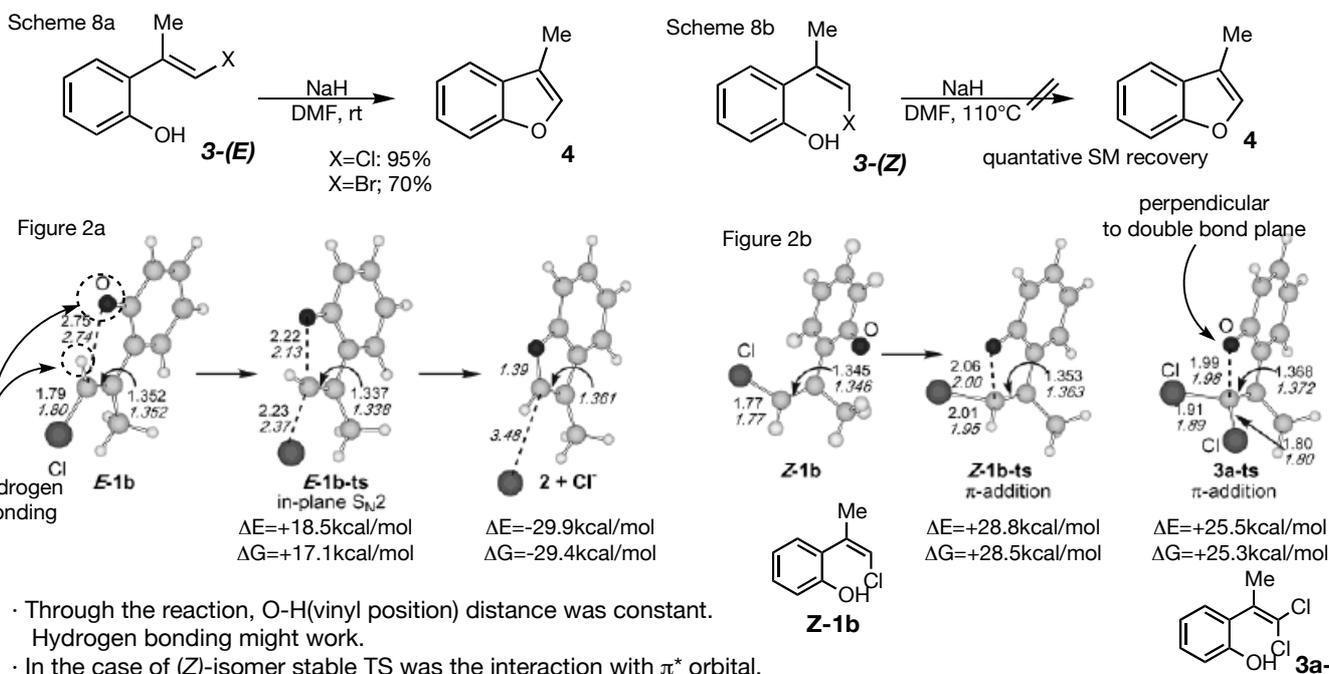


1.4 Intramolecular $\text{S}_{\text{N}}\text{V}\sigma$ Substitution

☹️ stereospecific aziridine formation; Shipman, M. et al. *J. Am. Chem. Soc.* **2004**, 126, 6868.



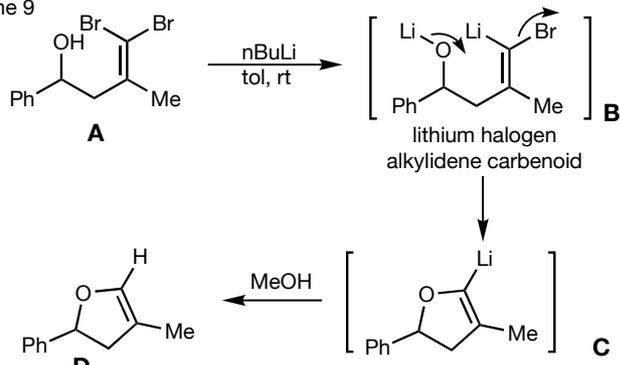
☹️ stereospecific benzofuran formation; Ando, K. and Narasaka, K. et al. *Org. Lett.* **2004**, 6, 2461.



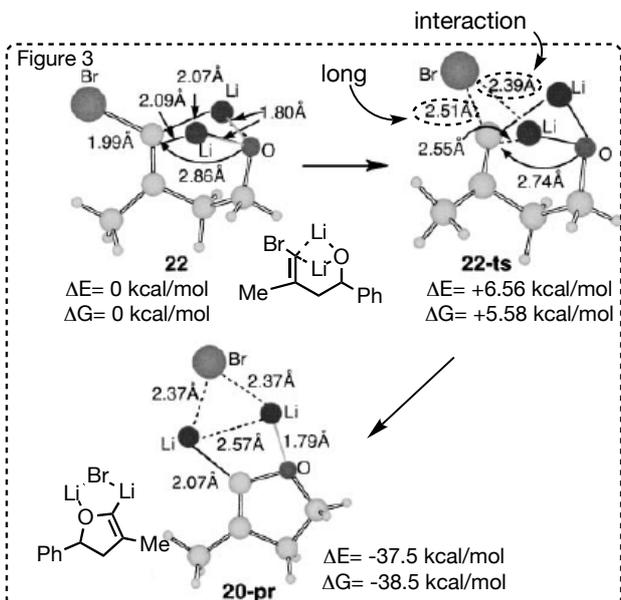
- Through the reaction, O-H(vinyl position) distance was constant. Hydrogen bonding might work.
- In the case of (Z)-isomer stable TS was the interaction with π^* orbital. even though the relatively higher energy was required.
- With dichloro-compound, interaction with σ^* orbital is impossible due to the steric and electronic repulsion by chlorine.

→ These stereospecific substitution reaction suggested $\text{S}_{\text{N}}2$ reaction mechanism.

Scheme 9



This carbenoid easily isomerizes even at -85°C . Then computational study was held to clarify whether $\text{S}_{\text{N}}2$ type or not.



Synthesis of indene from dibromoalkene

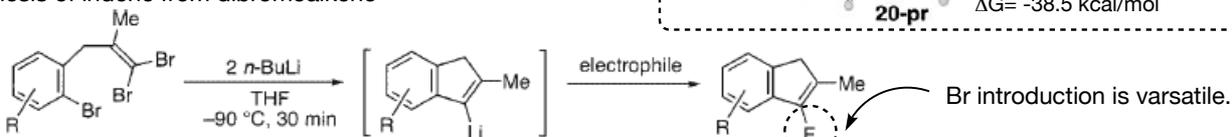


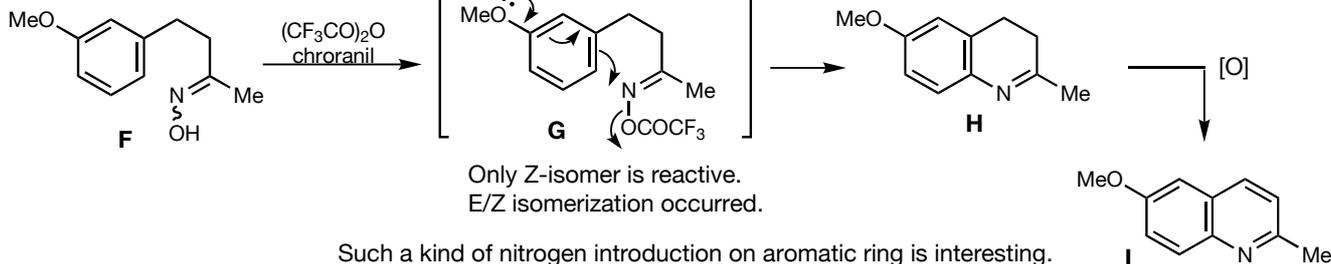
Table 3

Entry	Substrate	Electrophile	Product	E	Yield/%
1		$\text{BrCF}_2\text{CF}_2\text{Br}$		Br	83
2		PhCHO		CH(OH)Ph	84
3		$\text{BrCF}_2\text{CF}_2\text{Br}$		Br	80
4		PhCHO		CH(OH)Ph	87
5		$\text{BrCF}_2\text{CF}_2\text{Br}$		Br	28
6		PhCHO		CH(OH)Ph	49
7		$\text{BrCF}_2\text{CF}_2\text{Br}$		Br	63
8		PhCHO		CH(OH)Ph	87



Due to Lithium bridges, aryl anion can interact with $\text{Br } \sigma^*$??

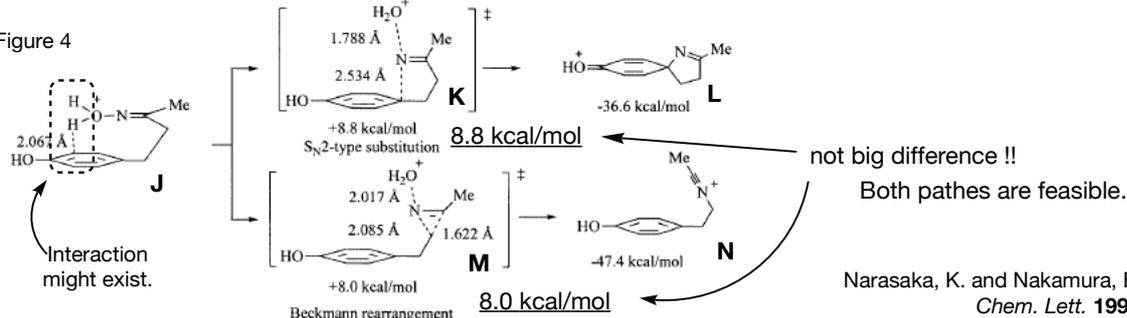
Scheme 10



from anti : 83%
from syn : 81%

Seemingly, such substitution reaction is unfavourable. However...

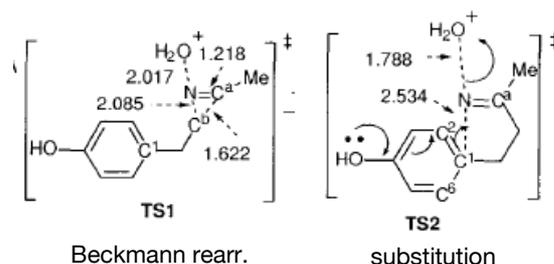
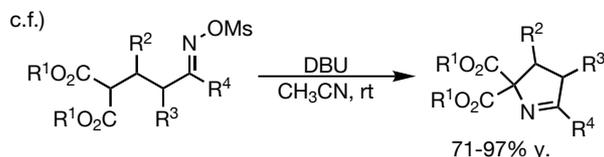
Figure 4



Narasaka, K. and Nakamura, E. et al. *Chem. Lett.* **1998**, 111.

☠ What factor prompts sp² nitrogen substitution predominantly ??

- 1 selection of solvent
polar solvent: Beckmann rearrangement non-polar solvent: substitution
- 2 selection of leaving group
trigger to find this phenomenon: nBu₄NReO₄, TfOH condition
- 3 electron density of aromatic ring
interaction benzene π orbital and leaving group on oxime
- 4 proper length of the tether
to form 5 or 6 membered ring.



2 Addition of Enamide to Olefin

2.1 Zinc aza-enolate (employing alkylzinc)

☠ Nakamura, E. et al. *Angew. Chem., Int. Ed.* **1997**, 36, 2491.

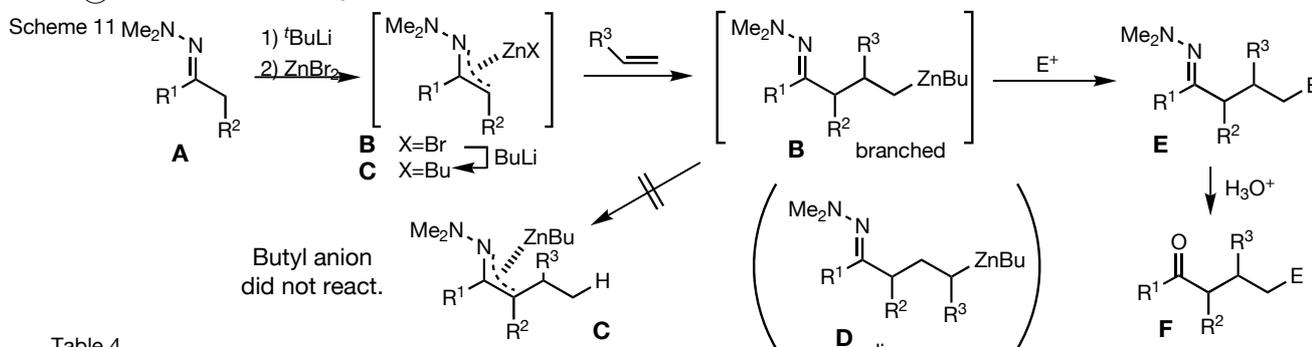


Table 4

Entry	Olefin	Zinc hydrazone[b]	Electrophile[c]	Product	Yield[%] [d]
	CH ₂ =CH ₂	Me ₂ N-N=CH-CH ₂ -Ph	H ₂ O (D ₂ O)	Ph-CH ₂ -CH ₂ -CH ₂ -CH ₂ -NMe ₂ -H(D)	90
	CH ₂ =CH ₂	Me ₂ N-N=CH-CH ₂ -Me	PhCH=CHCH ₂ Br, CuCN	Ph-CH ₂ -CH ₂ -CH ₂ -CH ₂ -NMe ₂ -CH ₂ -Ph	74[e]
	Ar-CH=CH ₂	Me ₂ N-N=CH-CH ₂ -Me	H ₂ O	Ar-CH ₂ -CH ₂ -CH ₂ -CH ₂ -NMe ₂	46[e, f]
			H ₂ O	Ar = <i>p</i> -CH ₃ OC ₆ H ₄	33[e, g]
			H ₂ O	Ar = <i>o</i> -CF ₃ OC ₆ H ₄	69[e, h]

Entry	Olefin	Zinc hydrazone[b]	Electrophile[c]	Product	Yield[%] [d]
	CH ₂ =CH ₂	(SAMP)	H ₂ O	82 : 18	42
	C ₆ H ₁₃	Me ₂ N-N=CH-CH ₂ -Ph	H ₂ O	Ph-CH ₂ -CH ₂ -CH ₂ -CH ₂ -NMe ₂ -C ₆ H ₁₃	30[e, j]

Ligand exchange (Br->Bu) increased the reactivity toward unactivated olefin.
(Toward vinyl Grignard reagent, Br species did work well.)

☠ Nakamura, E. et al. *J. Am. Chem. Soc.* **2003**, 125, 6362.

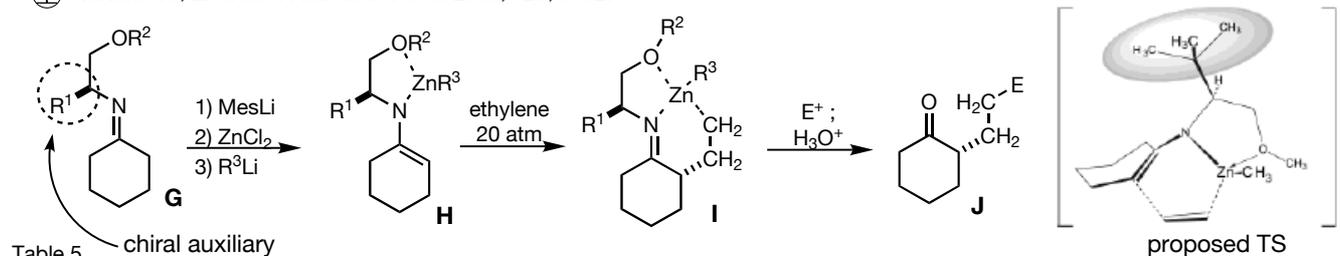
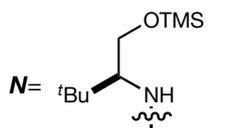


Table 5

R ¹	R ²	R ³	yield	ee
<i>i</i> Pr	Me	Me	85	92
<i>i</i> Pr	Me ₃ Si	Me	81	94
<i>t</i> Bu	Me	Me	87	94
<i>t</i> Bu	Me ₃ Si	Me	91	95

R ¹	R ²	R ³	yield	ee
<i>t</i> Bu	Me	<i>t</i> Bu	73	88
<i>t</i> Bu	<i>t</i> BuMe ₂ Si	Bu	14	55
Ph	Me ₃ Si	Me	86	76



ethylene 20-30 atm
propylene 8 atm

Table 5

entry	zinc enamide ^a	product ^b	ee(%) ^c , yield(%)
2			91% ee, 98% yield
3			89% ee, 90% yield
4			82% ee, 96% yield
5			93% ee, 96% yield

entry	zinc enamide ^a	product ^b	ee(%) ^c , yield(%)
6			84% ee, 18% yield
7			47% ee, 93% yield
8			71% ee, 78% yield

linear product

- Branched product selectively generated.
1° zinc anion is electronically and sterically favourable.
(with styrene: linear adduct < electronic effect?)
- When the reaction between Li enamide and alkyl iodide, alkyl group was introduced from β-face.
Transition state is different?
- Adequate soft character is suitable for the olefin?
Toward alkyl halide, Mg enamide is better. (Nakamura, E. et al. *J. Am. Chem. Soc.* **2005**, 127, 14192.)

E/Z ratio affect the ee.

To give E enamide exclusively, Mesityl was used as the ligand on zinc. → 81% y. 58% ee

☹️ Toward vinylborane; Nakamura, E. et al. *J. Am. Chem. Soc.* **2004**, 126, 14344.

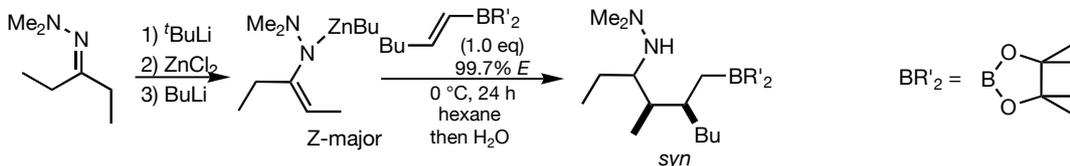
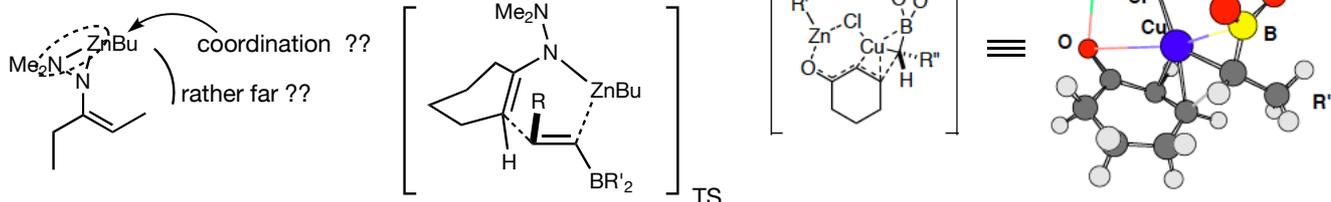
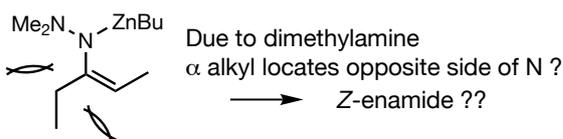


Table 6 should be Z isomer

entry ^a	zincated hydrazone ^{b,c}	alkenyl -boronate ^d	electro -phile ^e	major diastereomer yield ^f , dr ^g
1			H ₂ O	9: 93%, 99.2:0.8 <i>syn</i>
2			H ₂ O	10: 87%, 99.5:0.5 <i>syn</i>
3			H ₂ O	11: 80%, 99.6:0.4 <i>syn</i>
4			H ₂ O	9: 86%, 18.0:82.0 <i>anti</i>
5 ^h			H ₂ O	14: 48%, 19.0:81.0 <i>anti</i>
6			H ₂ O	14: 75%, 98.5:1.5 <i>syn</i>

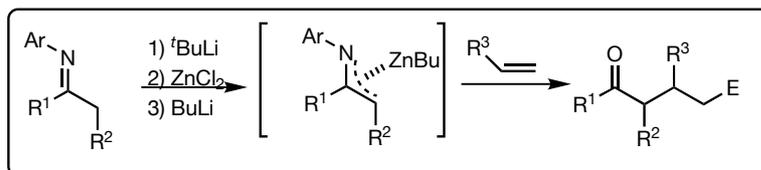
entry ^a	zincated hydrazone ^{b,c}	alkenyl -boronate ^d	electro -phile ^e	major diastereomer yield ^f , dr ^g
7				15: 86%, 99.2:0.5:0.2:<0.1 <i>total</i> 99.2dr
8				16: 69%, >95% <i>ds</i>
9				17: 70%, >94.7:3.5:1.7:<0.1
10				19: 80%, 97.6:1.0:1.0:0.4

successive Michael addition (diastereoselective)



2.2 N-aryl Zinc-Enamide

Nakamura, E. et al. *J. Am. Chem. Soc.* **2004**, *126*, 11820.



N-substituent effect

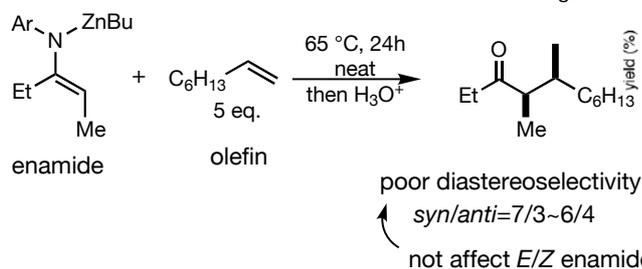
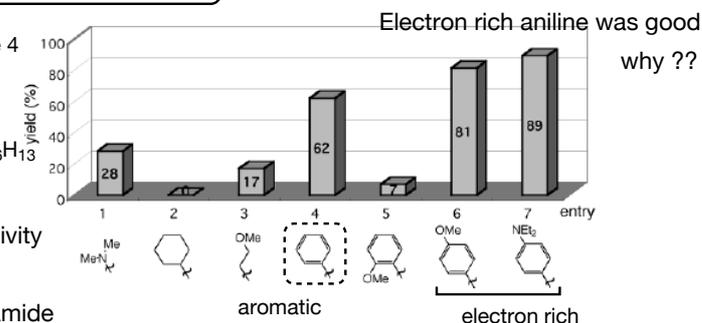


Figure 4



N-substituent effect

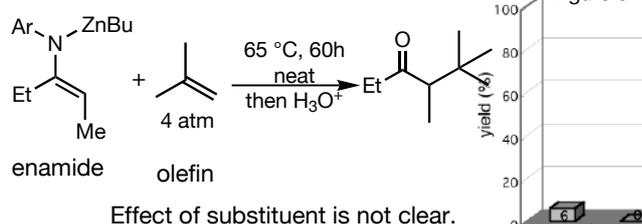


Figure 5

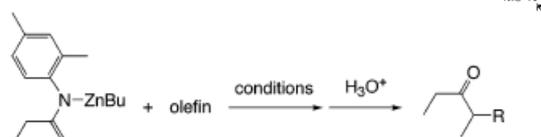
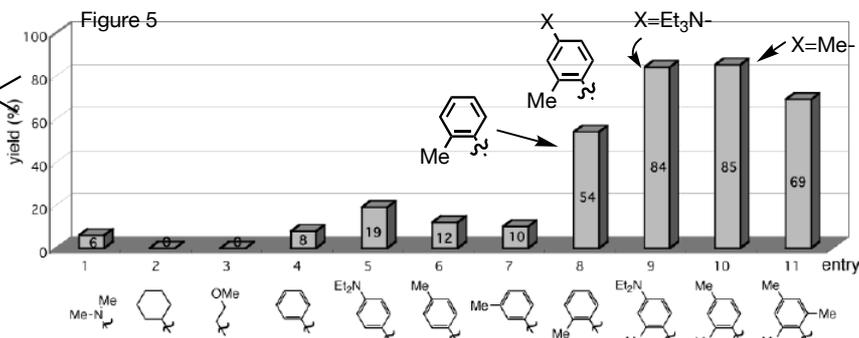


Table 7

entry	olefin	conditions	product ^a	% yield
1		1 atm, hexane 50 °C, 12 h		94 ^b
2		1 atm, hexane 65 °C, 60 h		86 ^b
3		1.2 eq, hexane 65 °C, 12 h		92 ^{b,d}
4		1.2 eq, hexane 30 °C, 12 h		90 ^{c,e}
5		3.0 eq, neat 65 °C, 72 h		77 ^c
6		4 atm, neat 65 °C, 60 h		85 ^b
7		5 atm, neat 80 °C, 36 h		84 ^b

Table 8

entry	Zn enamide ^a	olefin	conditions	product ^b	% yield
1			5 atm, neat 80 °C, 72 h		76 ^c
2			1 atm, hexane 65 °C, 24 h		90 ^d
3	18		8 atm, neat 65 °C, 24 h		88 ^d
4	18		2 eq, hexane 50 °C, 12 h		87 ^{c,e}
5	18		5 atm, neat 80 °C, 72 h		24 ^d
6			10 atm, neat 80 °C, 72 h		74 ^c

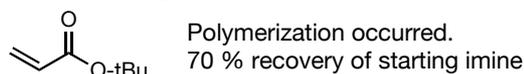
high yield

The *E/Z* geometry of enamide did not affect the *syn/anti* selective production.

→ not 6-membered boat form TS

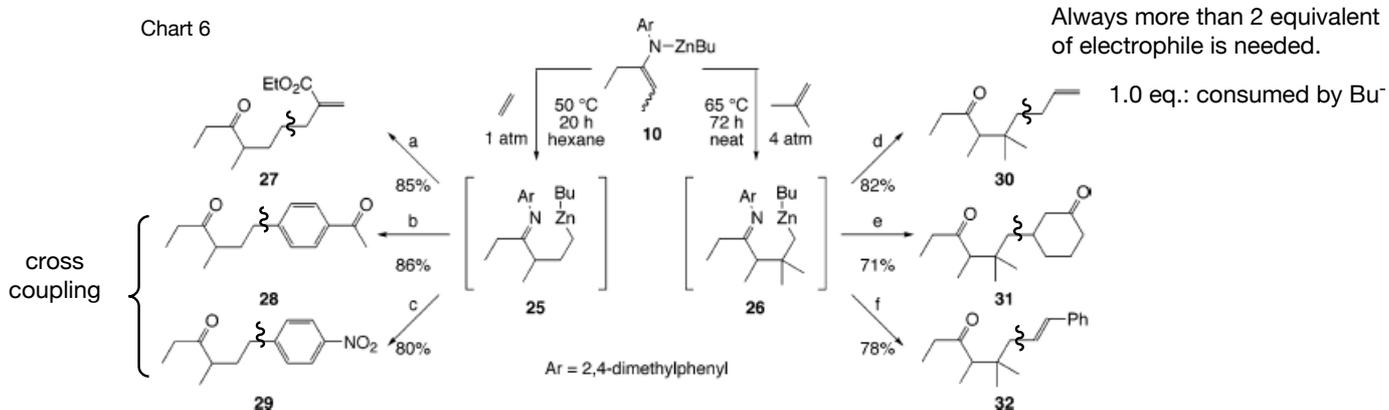
o-methylsubstituent on benzene ring gave better reactivity.

Zinc enamide had poor reactivity with Michael acceptor.



linear adduct only
stability of benzyl anion
(prior to steric effect)

Chart 6



^a Reagents and conditions: (a) ethyl 2-bromomethylacrylate (2.2 equiv), 0 °C, 4 h then H₃O⁺; (b) 4-iodoacetylbenzene (2.2 equiv)/TMEDA (2.0 equiv)/PdCl₂(PPh₃)₂ (5 mol %), 25 °C, 8 h then H₃O⁺; (c) 4-iodonitrobenzene (2.2 equiv)/TMEDA (2.0 equiv)/PdCl₂(PPh₃)₂ (5 mol %), 25 °C, 8 h then H₃O⁺; (d) allyl bromide (2.4 equiv), 25 °C, 3 h then H₃O⁺; (e) iodomethane (0.2 equiv) then in vacuo, 2-cyclohexen-1-one (2.4 equiv)/Me₃SiCl (2.4 equiv)/TMEDA (2.0 equiv)/CuCN (0.3 equiv), 0 °C, 6 h then H₃O⁺; (f) iodomethane (0.2 equiv) then in vacuo, β-bromostyrene (>99.9% E, 2.4 equiv)/TMEDA (2.0 equiv)/CuCN (1.0 equiv), 0 °C, 8 h then H₃O⁺.

Unreacted enamide which interfere the coupling reaction was trapped.

3 Outlook & Remark

