

N-Oxyenamine

N-O cleavage:
Conventional and Recent
application to the Synthesis of
heterocyclic compounds

Literature Talk, 2014, Dec. 10.

Hee Nam Lim

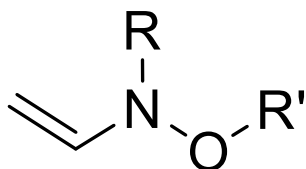
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2. Conventional approaches to the heterocycles by N-O bond cleavage using rearrangement strategy
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Tabolin, A.; Loffe, S. L. *Chem. Rev.* **2014**, *114*, 5426-5476.

Huang, H.; Ji, X.; Wu, W.; Jiang, H. *Chem. Soc. Rev.* **2014**. asap

1. The basic principle of N-O bond cleavage, rearrangement, and some related reactions



Unstable!!

Bond strength

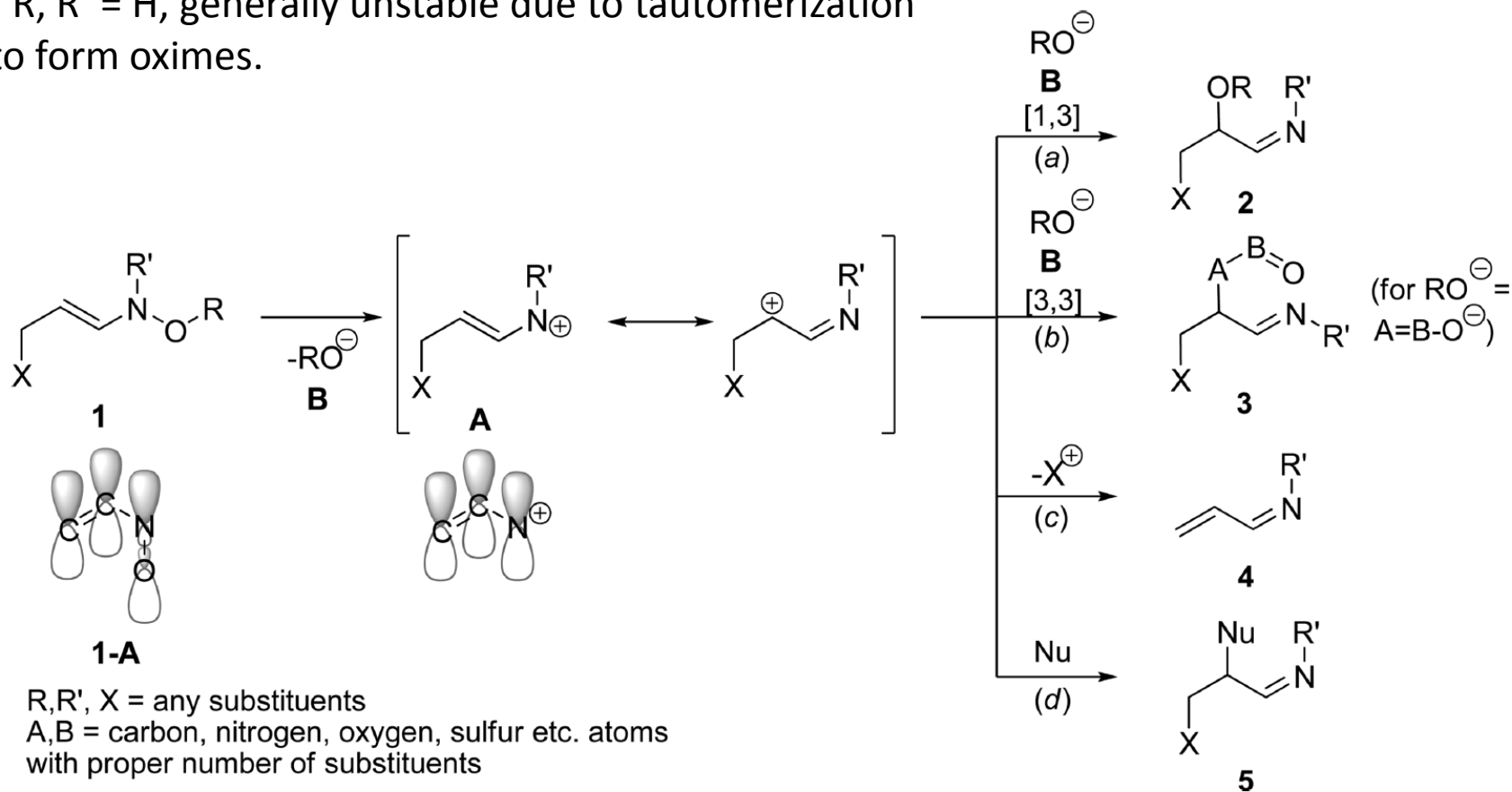
	N-O	π_{C-C}	C-X
Bond energy	~ 57 Kcal/mol	~ 66Kcal/mol	~ 69-91 Kcal

What makes N-O bond weaker? – the repulsion of lone e-pairs on O and N.

1. The basic principle of N-O bond cleavage, rearrangement, and some related reactions

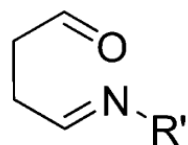
! In situ synthesis

! R, R' = H, generally unstable due to tautomerization to form oximes.

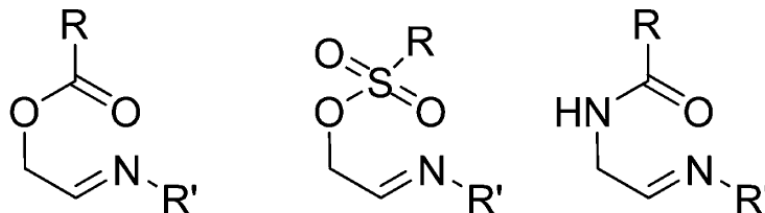


1. The basic principle of N-O bond cleavage, rearrangement, and some related reactions

Common sigmatropic rearrangement



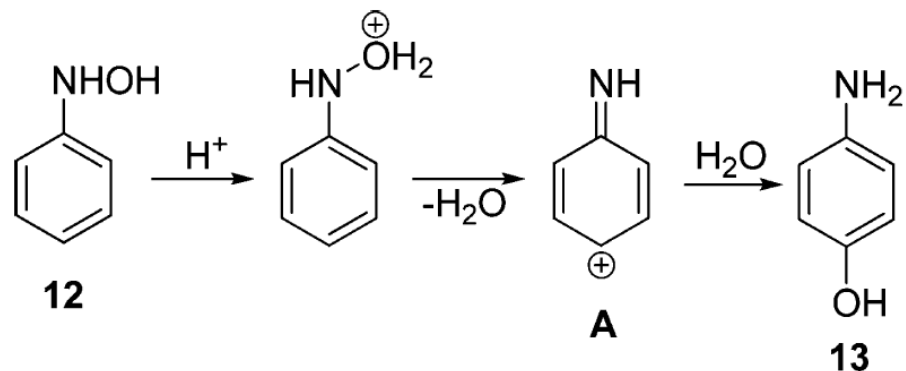
3-(1), if A,B-carbon atoms



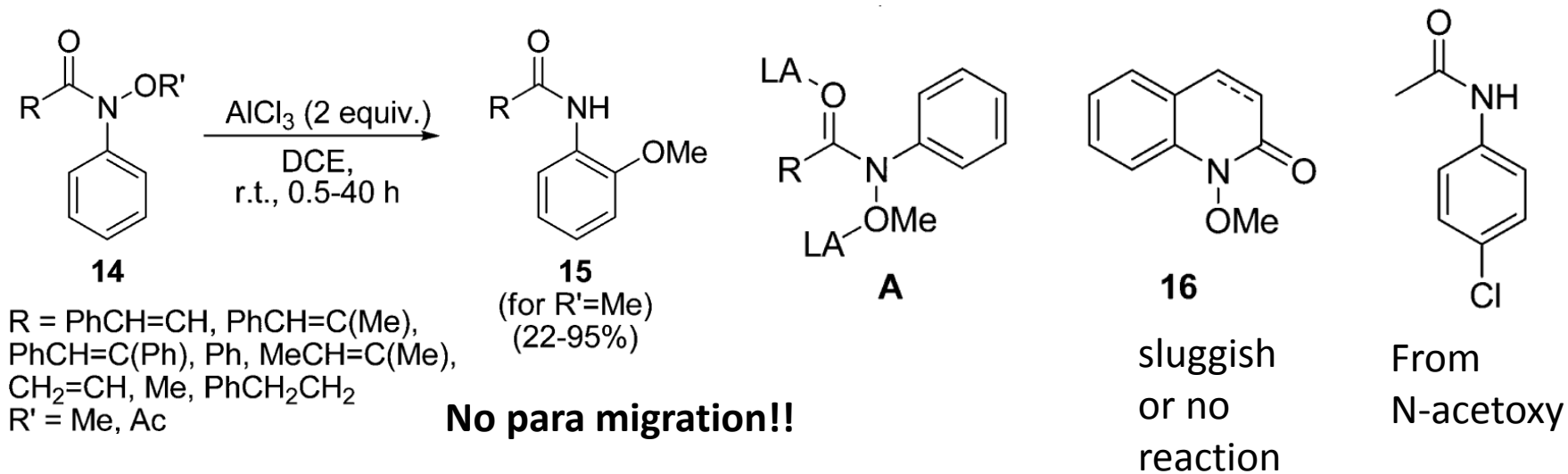
3-(2), if A (and B) - heteroatoms

1. The basic principle of N-O bond cleavage, rearrangement, and some related reactions

Bamberger rearrangement [1,5]



Bamberger-type rearrangement [1,3]

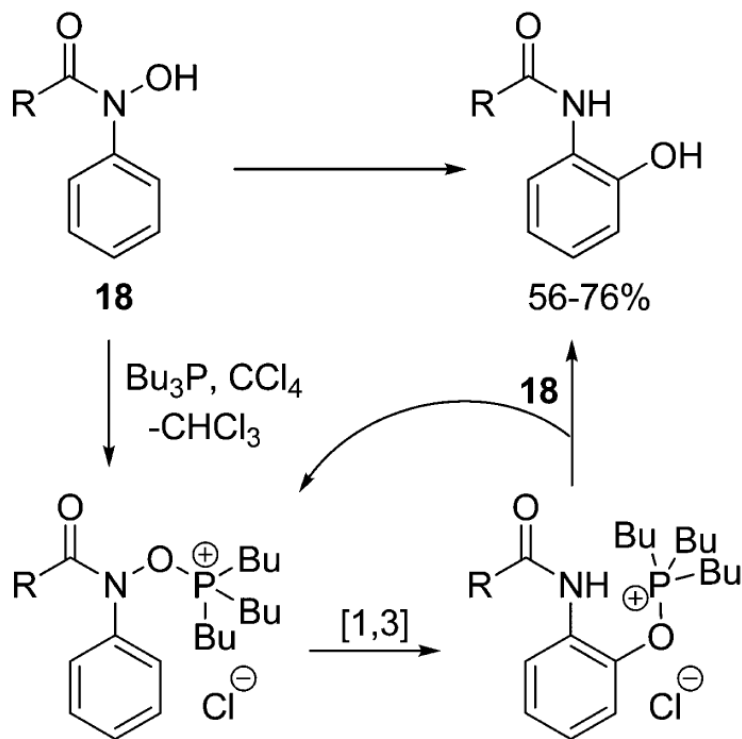


Bamberger, E. *Ber. Dtsch. Chem. Ges.* **1894**, *27*, 1347.

Kikugawa, Y.; Shimada, M. *J. Chem. Soc., Chem. Commun.* **1989**, 1450.

1. The basic principle of N-O bond cleavage, rearrangement, and some related reactions

Bamberger-type rearrangement [1,3]



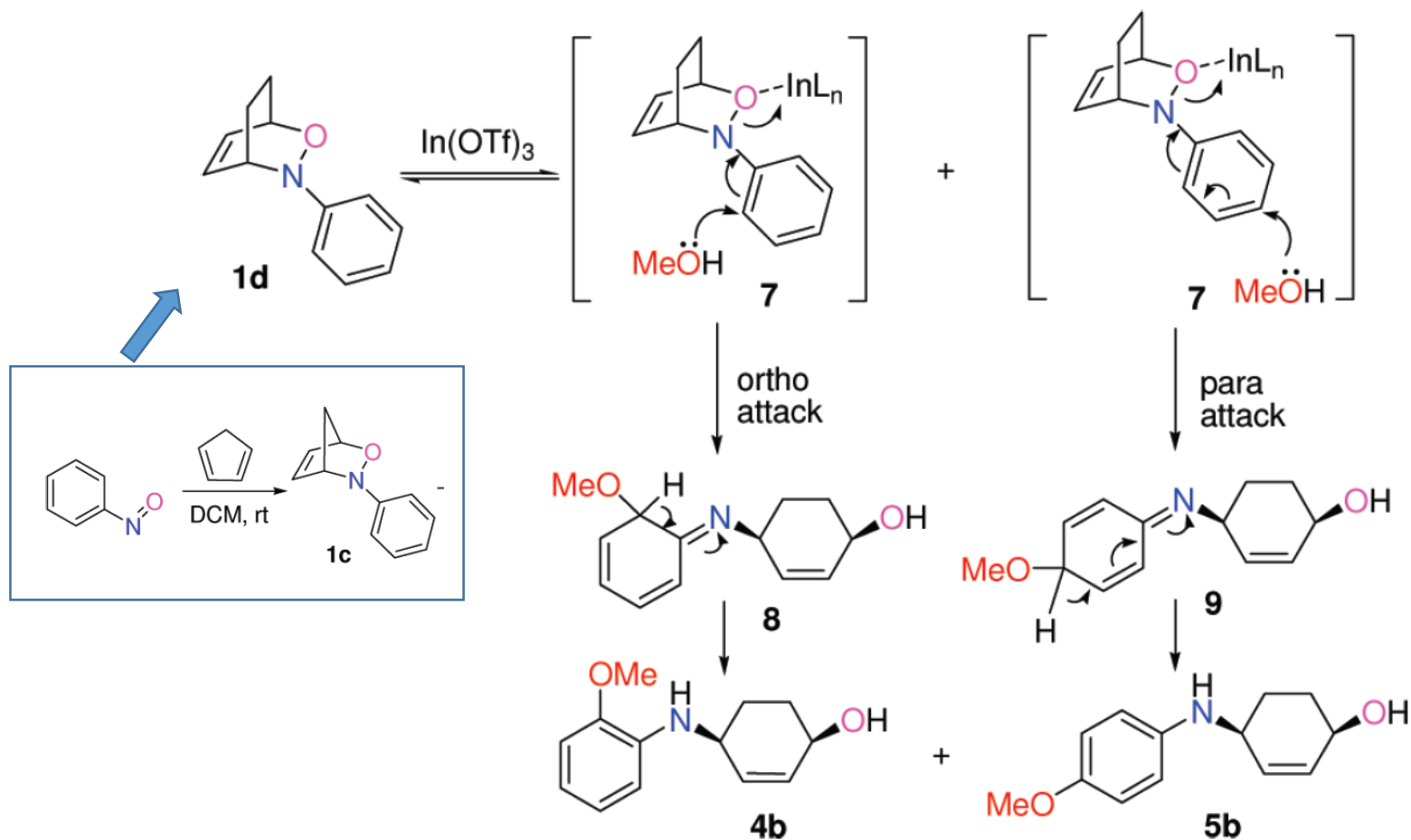
R = Me, Ph, $\text{Ph}(\text{CH}_2)_2$,
(Z)- $\text{PhCH}=\text{C}(\text{Ph})$ -

major byproducts- para hydroxy or chloro

Kikugawa, Y.; Mitsui, K. *Chem. Lett.* **1993**, 1369.

1. The basic principle of N-O bond cleavage, rearrangement, and some related reactions

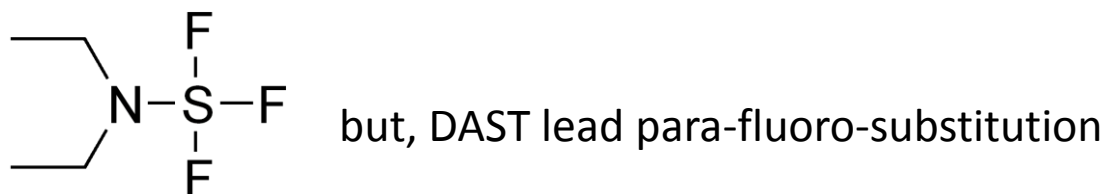
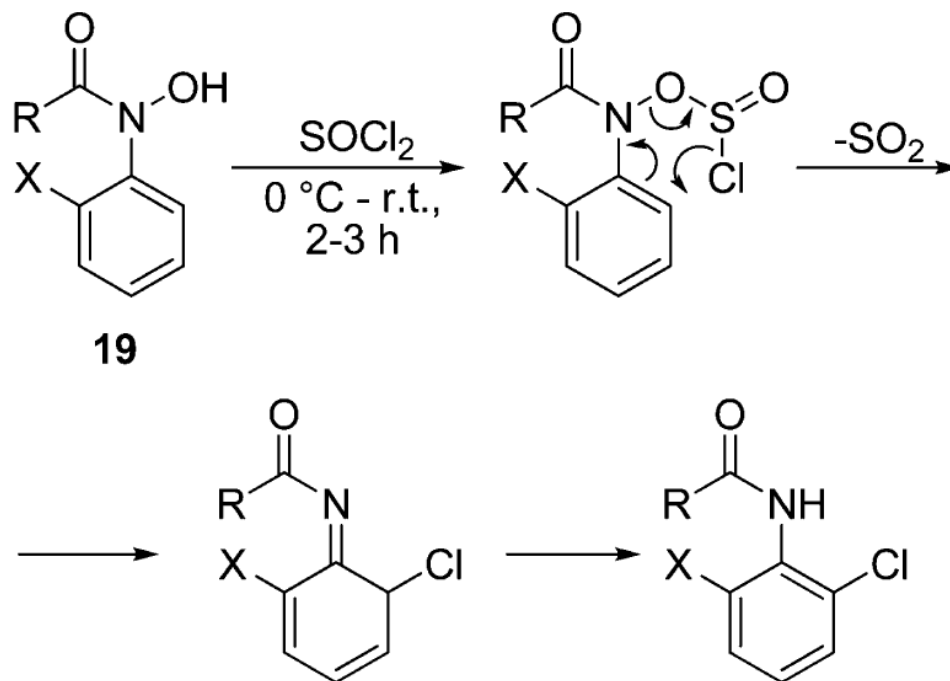
S_NAr



Yang, B.; Miller, M. J. *Org. Lett.* **2010**, *12*, 392.

1. The basic principle of N-O bond cleavage, rearrangement, and some related reactions

Bamberger-type rearrangement [1,3] or [1,5]



Uchida, Y.; Kozuka, S. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 1183.
Kikugawa, Y.; Matsumoto, K.; Mitsui, K.; Sakamoto, T. *J. Chem. Soc., Chem. Commun.* **1992**, 921.

1. The basic principle of N-O bond cleavage, rearrangement, and some related reactions

Fridel-Craft type reaction

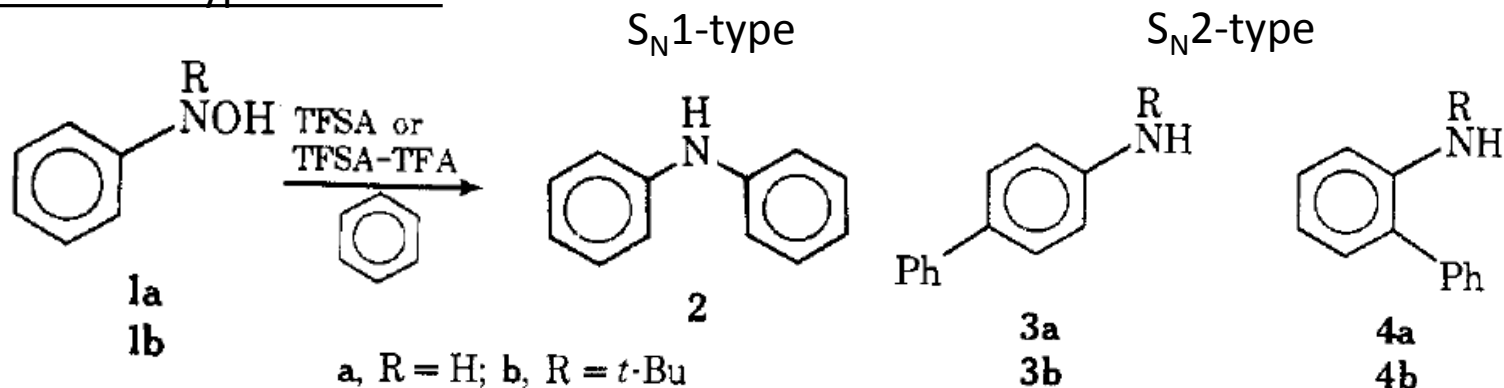
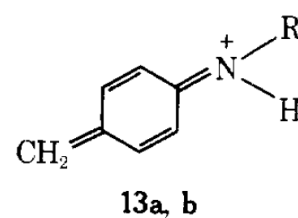
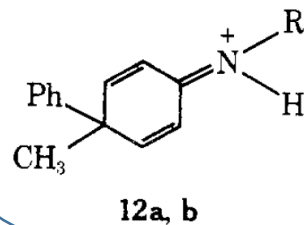
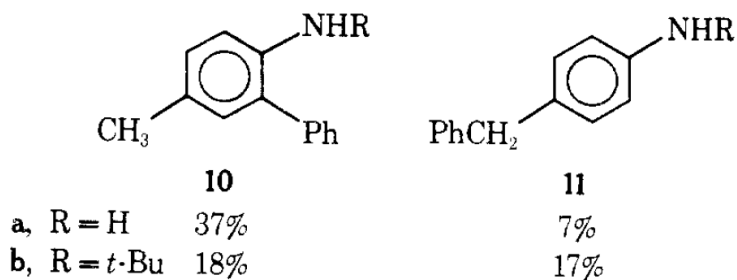
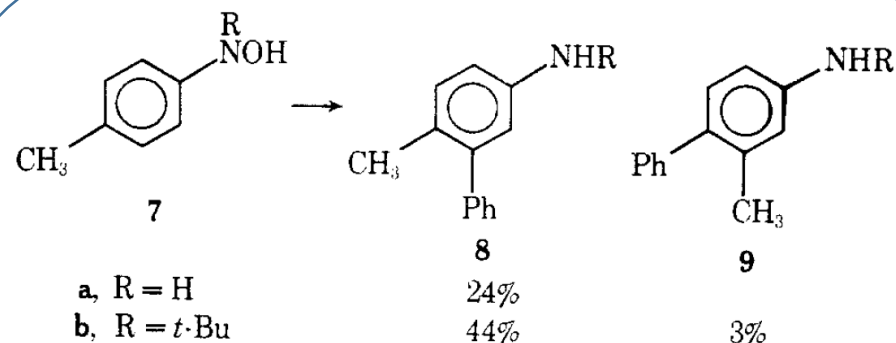
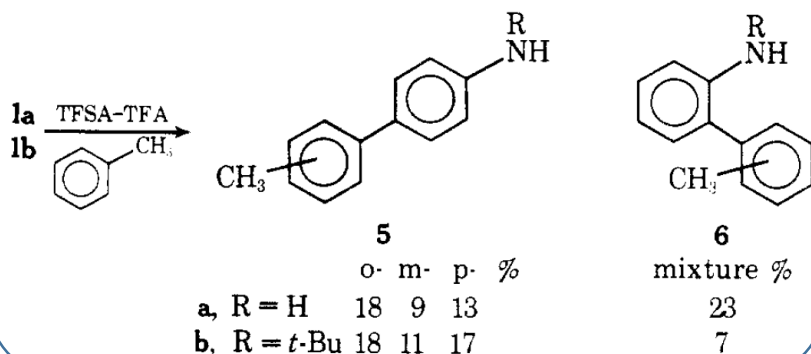
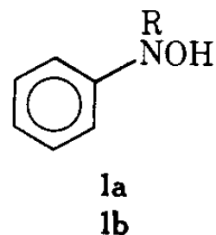


Table 1. Reaction of Phenylhydroxylamine with Benzene

Run	Amounts of acids (mol) ^a		Benzene (mol) ^a	Pro-cedure	Product (%) ^b		
	CF ₃ -CO ₂ H	CF ₃ -SO ₃ H			2	3a	4a
1	4	0	3.5	<i>c, e, g</i>	41	3	3
2	10	0	9.0	<i>c, e, g</i>	56	9	8
3	25	0	22.0	<i>c, e, g</i>	46	12	11
4	25	0	22.0	<i>c, e</i>	12	5	5 ^h
5	25	0.2	22.5	<i>c, e</i>	20	4	4
6	25	1.2	22.5	<i>c, f</i>	39	19	17
7	25	2.3	22.5	<i>c, f</i>	14	46	25
8	0	2.0	60.0	<i>d, f</i>	2	25	12
9	0	4.0	60.0	<i>d, f</i>	1	32	16
10	0	20.0	60.0	<i>d, f</i>	<1	48	23

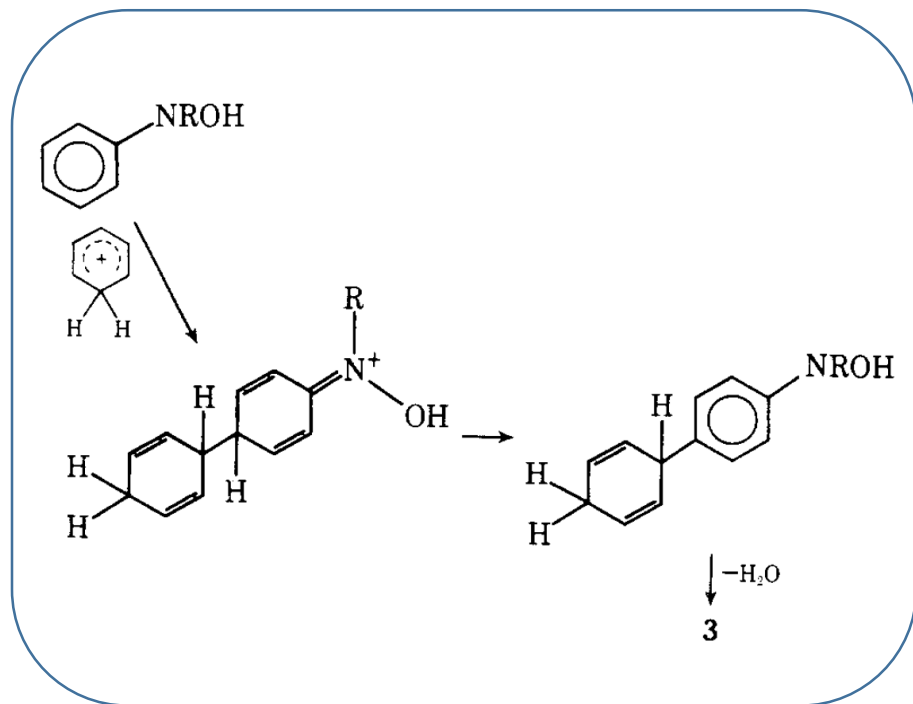
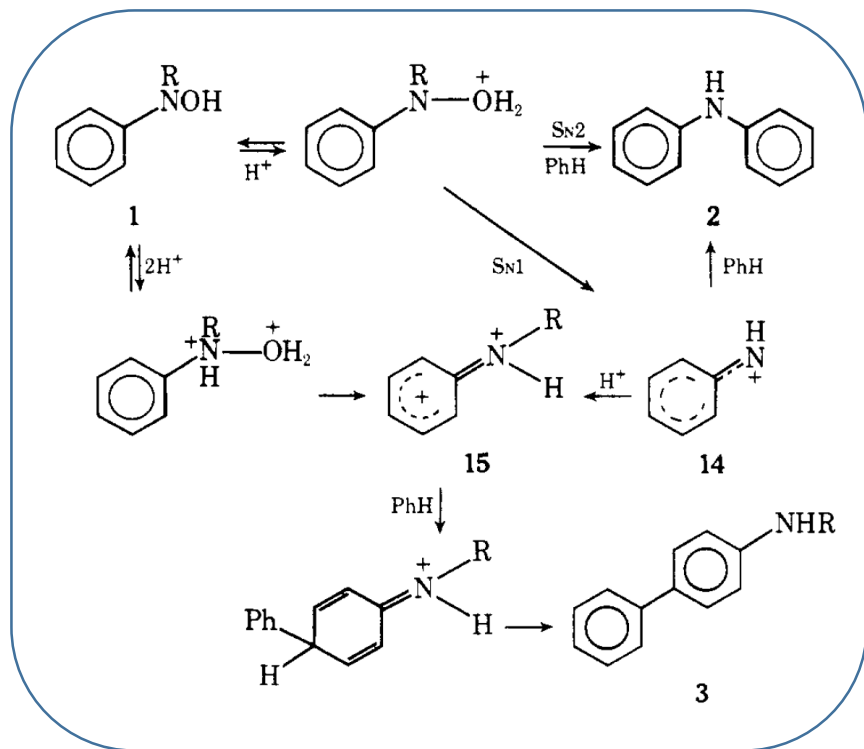
1. The basic principle of N-O bond cleavage, rearrangement, and some related reactions

Fridel-Craft type reaction



1. The basic principle of N-O bond cleavage, rearrangement, and some related reactions

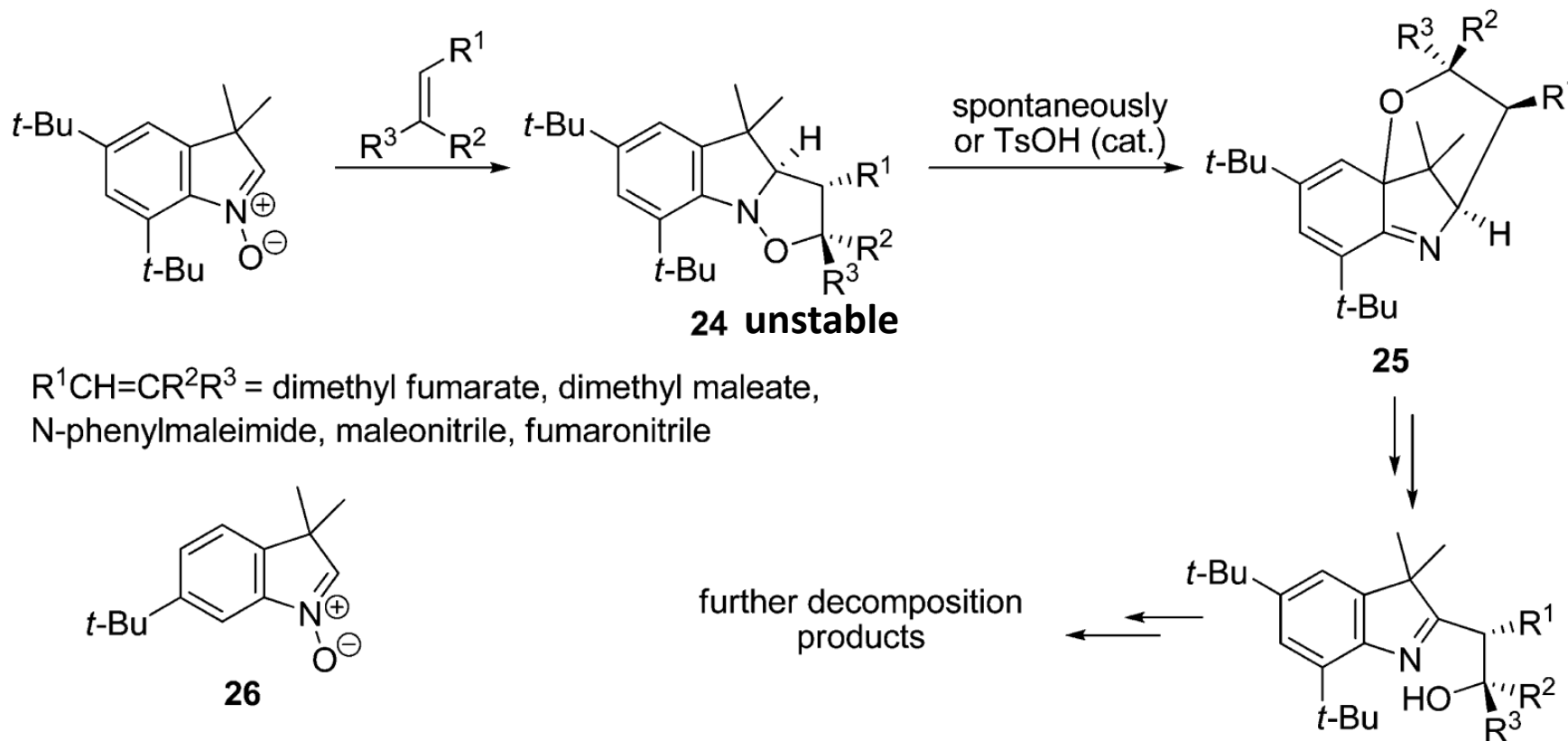
Mechanistic consideration



1. The basic principle of N-O bond cleavage, rearrangement, and some related reactions

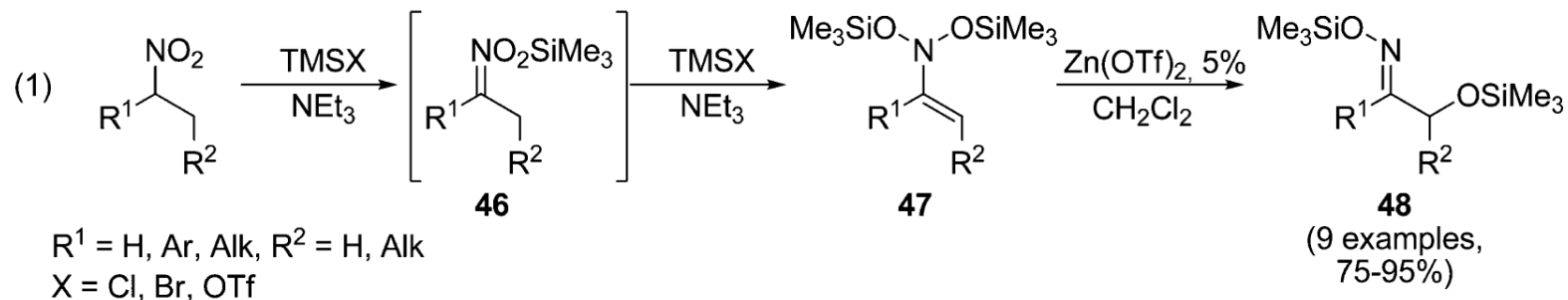
[1,3]-migration

Two of the ortho and para positions are blocked.

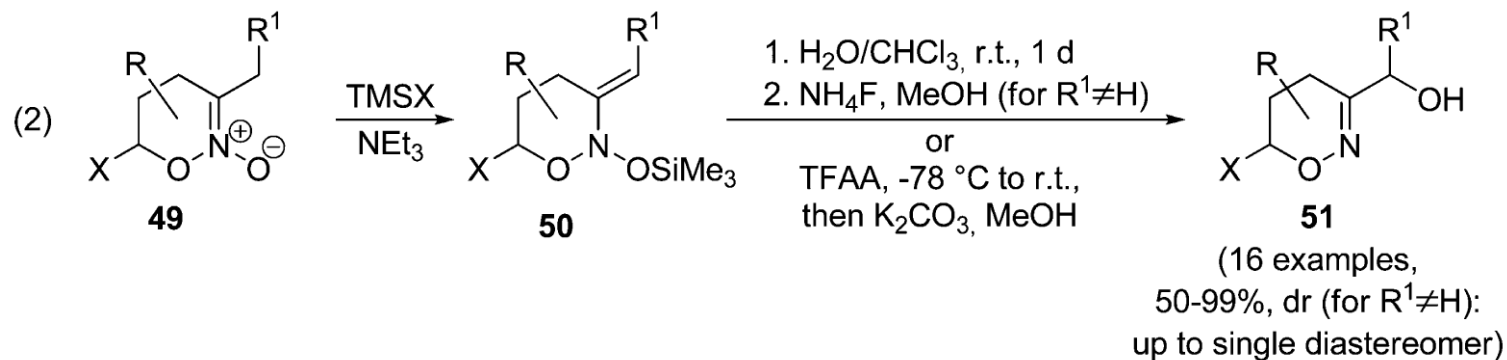


1. The basic principle of N-O bond cleavage, rearrangement, and some related reactions

What's the issue in this chemistry?? – instability of N-oxyenamine limits accessibility
Synthesis of some of the stable silyl nitroso acetals; by distillation or recrystallization



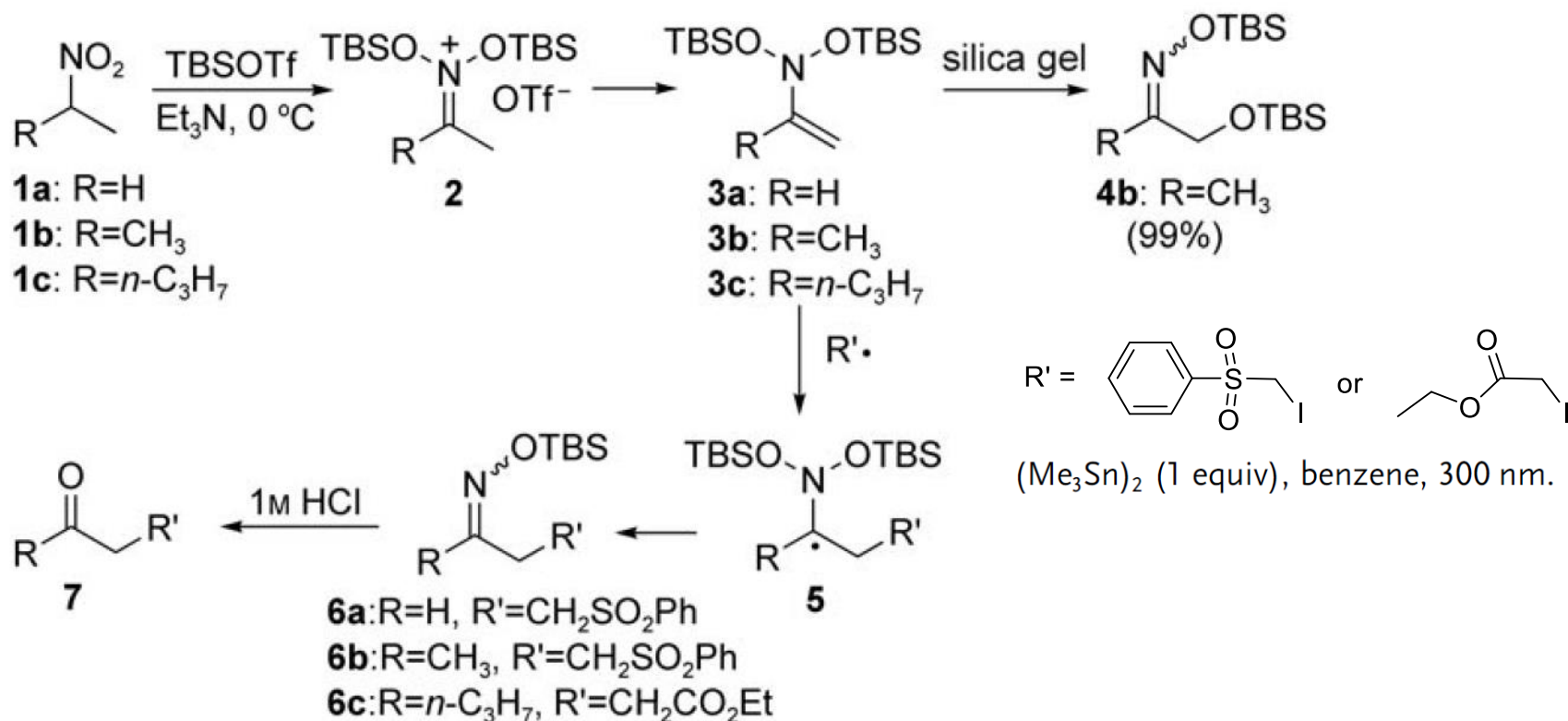
Tishkov, A. A.; Lesiv, A. V.; Khomutova, Yu. A.; Strelenko, Yu. A.; Nesterov, I. D.; Antipin, M. Yu.; Ioffe, S. L.; Denmark, S. E. *J. Org. Chem.* 2003, 68, 9477.



Dilman, A. D.; Tishkov, A. A.; Lyapkalo, I. M.; Ioffe, S. L.; Strelenko, Yu. A.; Tartakovsky, V. A. *Synthesis* 1998, 181

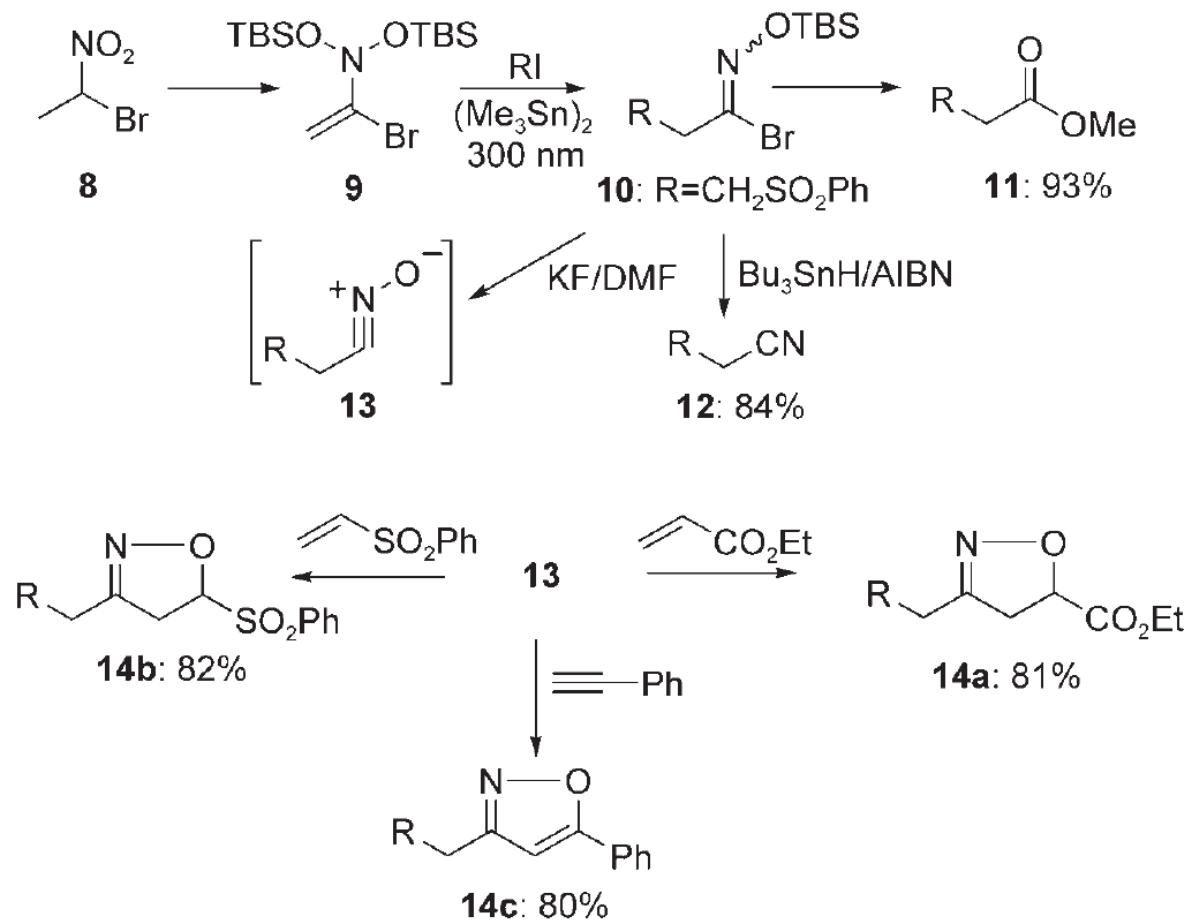
1. The basic principle of N-O bond cleavage, rearrangement, and some related reactions

Alkylation of N-silyloxyenamine



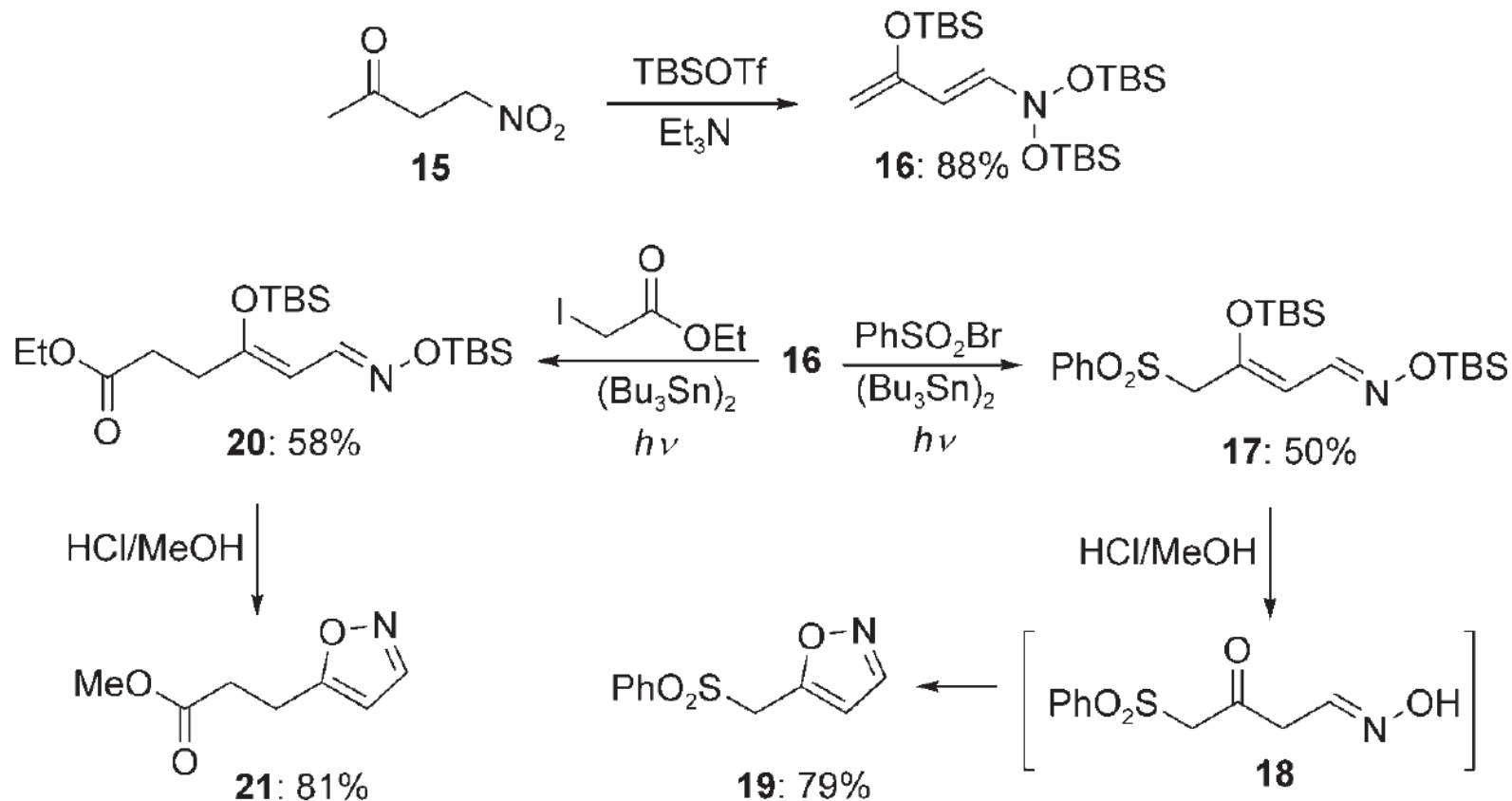
1. The basic principle of N-O bond cleavage, rearrangement, and some related reactions

Application to show the versatility



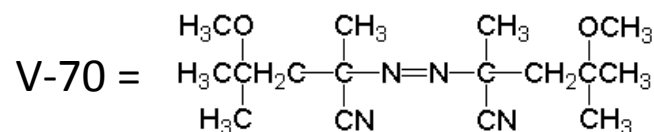
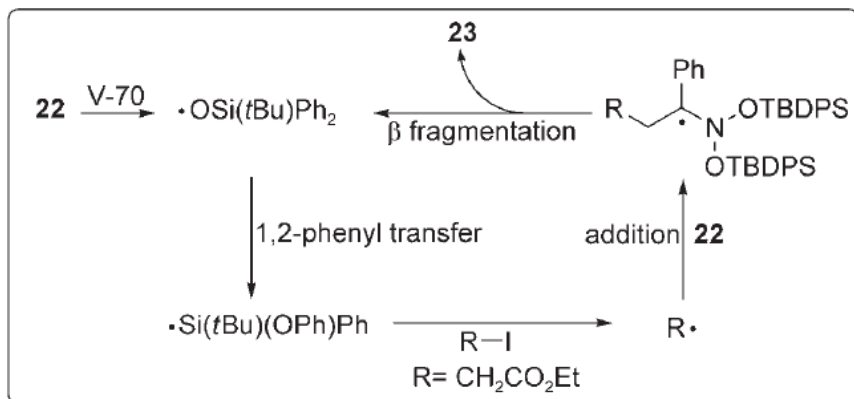
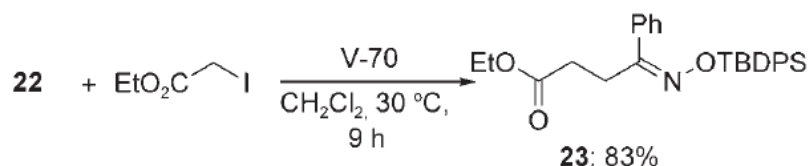
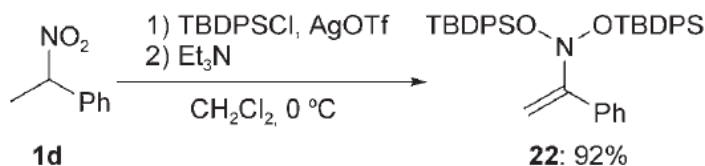
1. The basic principle of N-O bond cleavage, rearrangement, and some related reactions

Application to show the versatility



1. The basic principle of N-O bond cleavage, rearrangement, and some related reactions

Tin-free alkylation

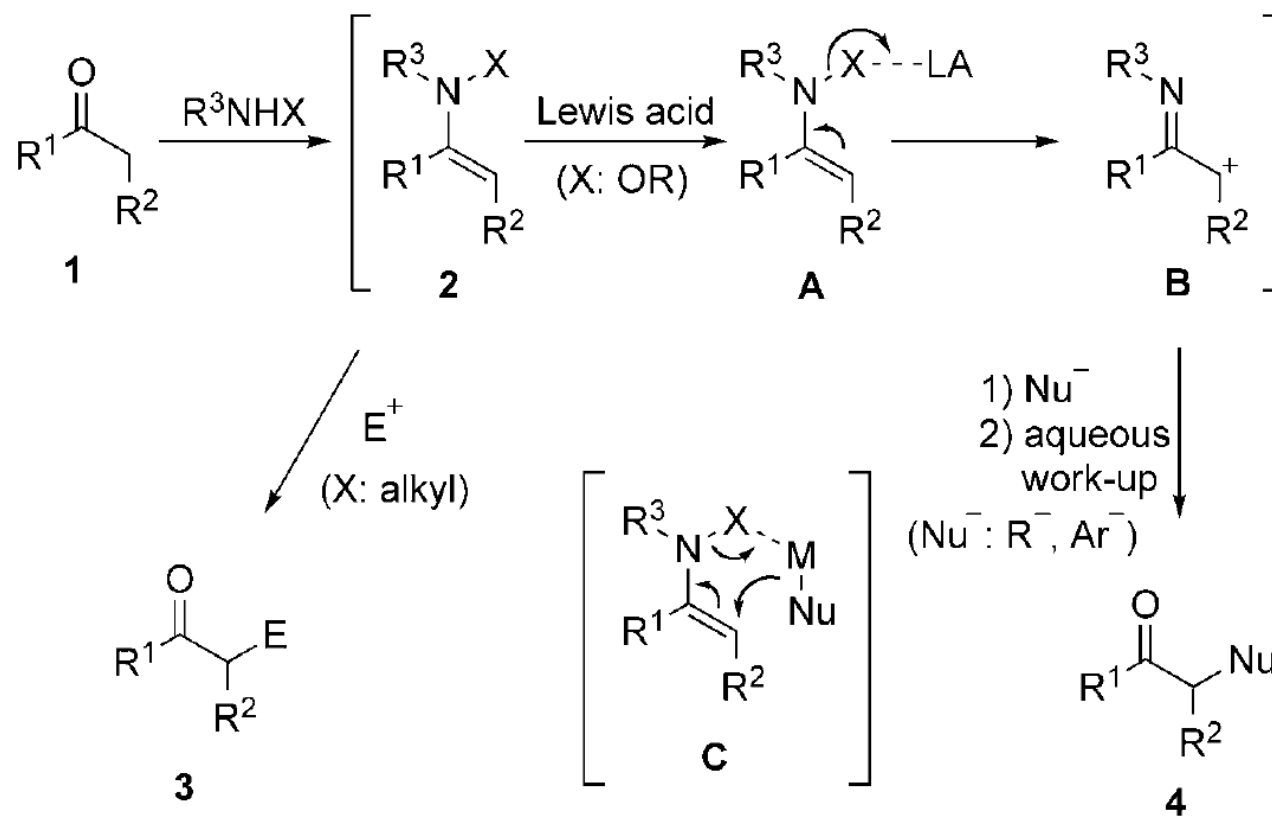


Entry	Substrate	Product	Yield [%]
1	<chem>PhO_2S-CH_2-I</chem>	<chem>PhO_2S-CH_2-CH_2-C(=O)-N(OTBDPS)Ph</chem>	61
2	<chem>Et_2NOC-CH_2-I</chem>	<chem>Et_2NOC-CH_2-CH_2-C(=O)-N(OTBDPS)Ph</chem>	63
3	<chem>NC-CH_2-I</chem>	<chem>NC-CH_2-CH_2-C(=O)-N(OTBDPS)Ph</chem>	68
4	<chem>EtO_2C-CH(CH_3)-I</chem>	<chem>EtO_2C-CH(CH_3)-CH_2-C(=O)-N(OTBDPS)Ph</chem>	72
5	<chem>EtO_2C-CH(CH_3)-Br</chem>	<chem>EtO_2C-CH(CH_3)-CH_2-C(=O)-N(OTBDPS)Ph</chem>	75

[a] Reaction conditions: V-70, CH₂Cl₂, 30 °C, 9 h.

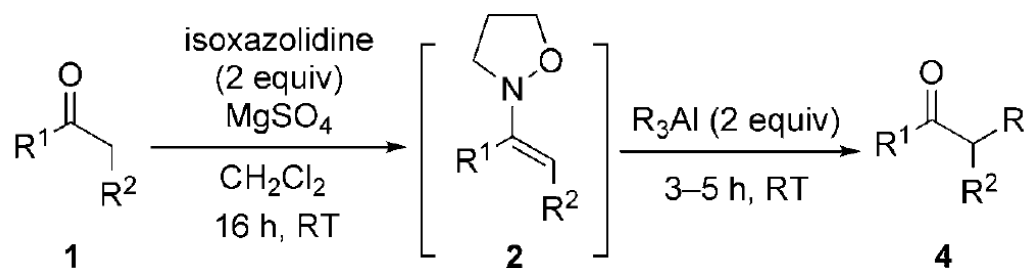
1. The basic principle of N-O bond cleavage, rearrangement, and some related reactions

Umpolung strategy; concept



1. The basic principle of N-O bond cleavage, rearrangement, and some related reactions

Umpolung strategy; alpha alkylation of ketones

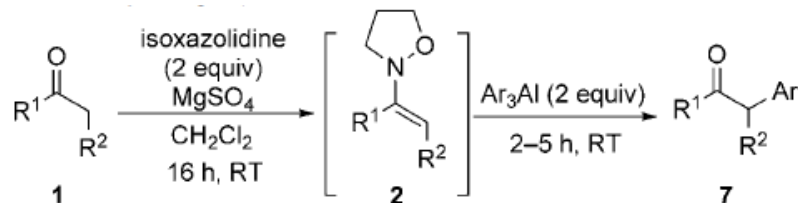


Entry	Substrate	Product: R	Yield [%] ^[a]
1			76
2			69
3			72 (<i>trans/cis</i> = 1:1) ^[b]
4			71 (<i>trans/cis</i> = 1:1) ^[b]
5			70 (<i>trans/cis</i> = 1:3) ^[b]

6			74 (<i>trans/cis</i> = 5:2) ^[b]
7			78
8			51
9			44
10			61

1. The basic principle of N-O bond cleavage, rearrangement, and some related reactions

Umpolung strategy; alpha arylation of ketones

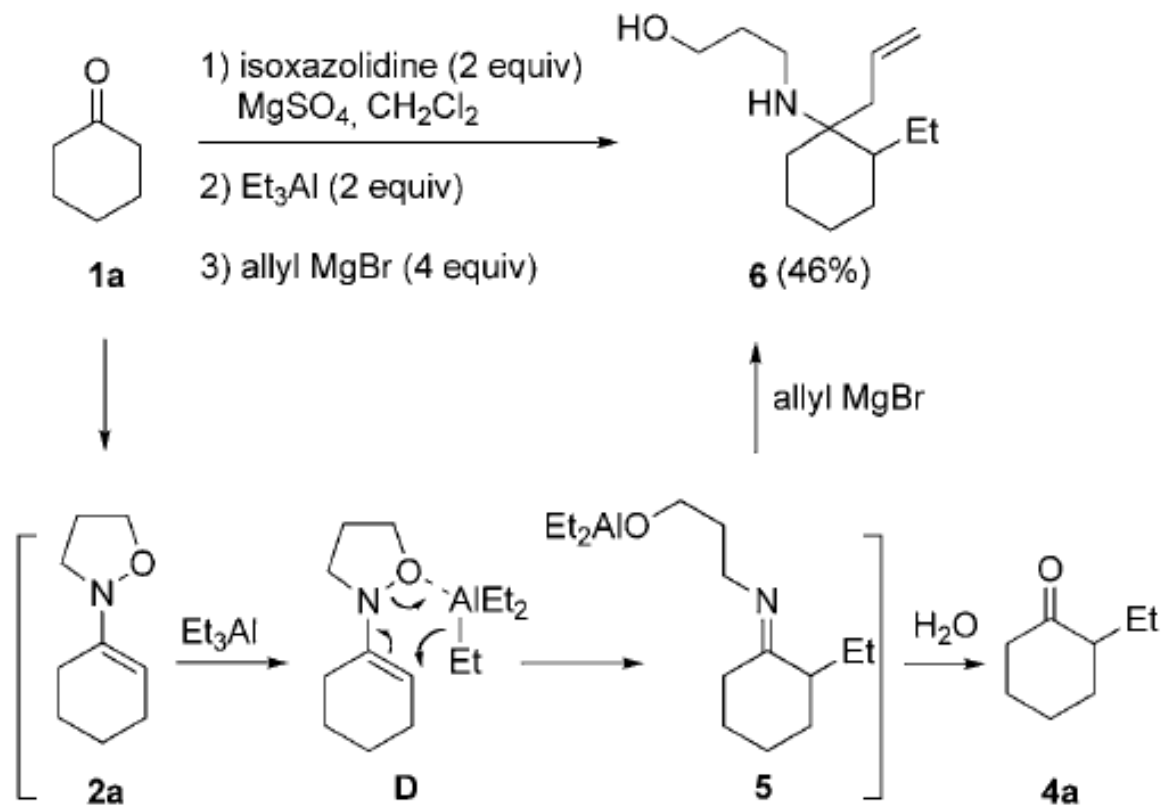


Entry	Substrate	Product: Ar	Yield [%] ^[a]
1		7a: Ph	60
2		7b: <i>p</i> -tolyl	64
3		7c: 4-MeOC ₆ H ₄	68
4		7d: 4-FC ₆ H ₄	60
5		7e: 4-ClC ₆ H ₄	61
6		7f: Ph	83
7		7g: <i>p</i> -tolyl	74
8		7h: 4-MeOC ₆ H ₄	83
9		7i: 4-FC ₆ H ₄	75
10		7j: 4- <i>t</i> BuC ₆ H ₄	85
11		7k: 4-MeOC ₆ H ₄	68
12		7l: 4-MeOC ₆ H ₄	60
13		7m: 4-MeOC ₆ H ₄	86

14		1i		7n: 4-MeOC ₆ H ₄	71
15		1e		7o: 4-MeOC ₆ H ₄	29
16 ^[b]		1g		7p: 4-MeOC ₆ H ₄	47
17		1j		7q: 4-MeOC ₆ H ₄	81
18		1k		7r: 4-MeOC ₆ H ₄	75
19		1l		7s: 4-MeOC ₆ H ₄	80

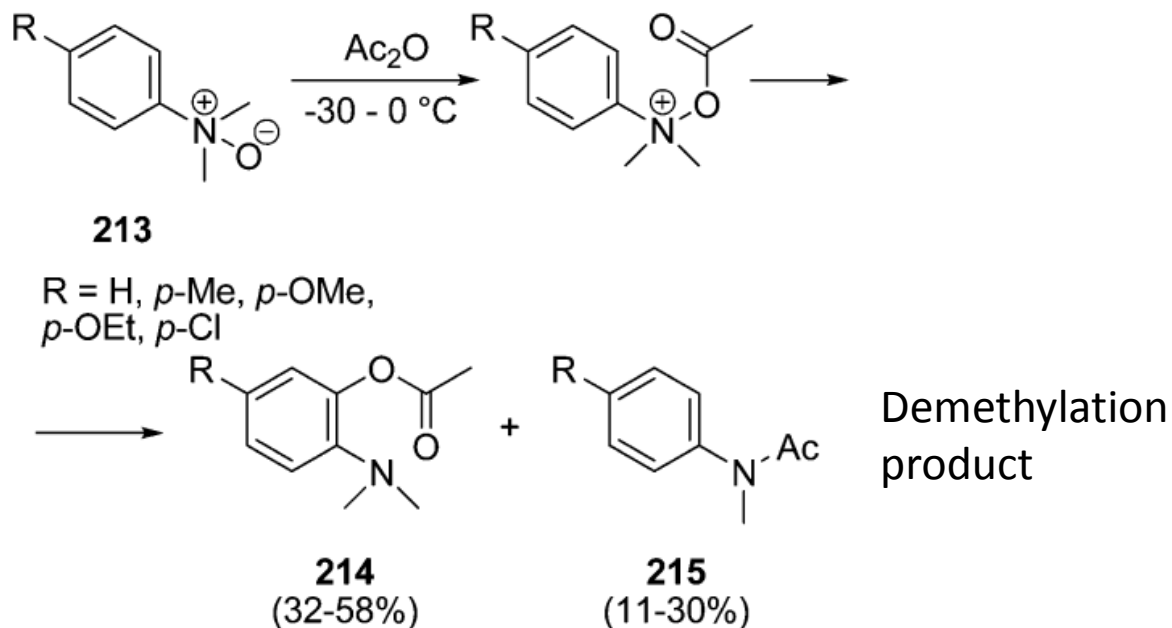
1. The basic principle of N-O bond cleavage, rearrangement, and some related reactions

One pot dinucleophilic addition



1. The basic principle of N-O bond cleavage, rearrangement, and some related reactions

ortho acetoxy transfer from N-oxide

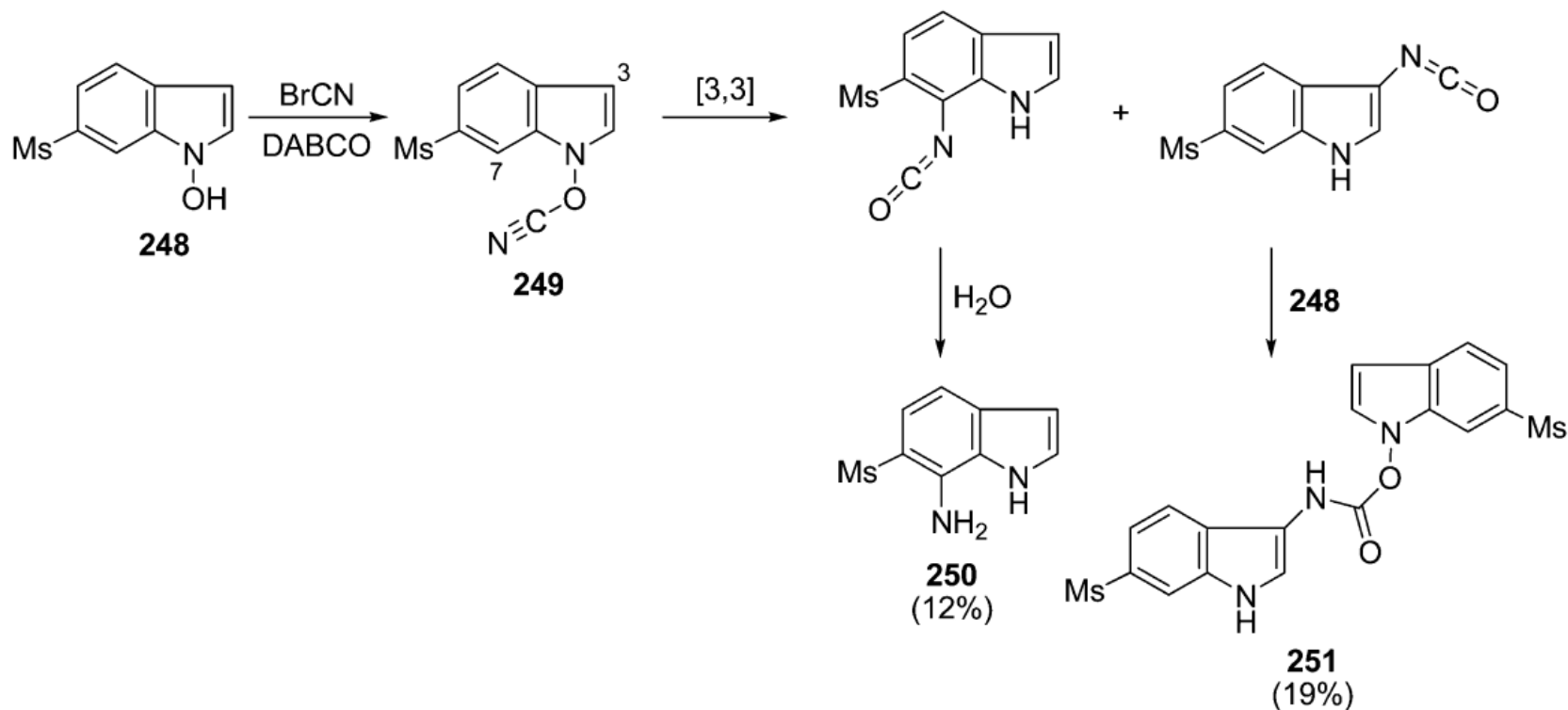


Mechanism -> demonstrated by ¹⁸O-labeling experiment.

Only two research articles cited this paper.

1. The basic principle of N-O bond cleavage, rearrangement, and some related reactions

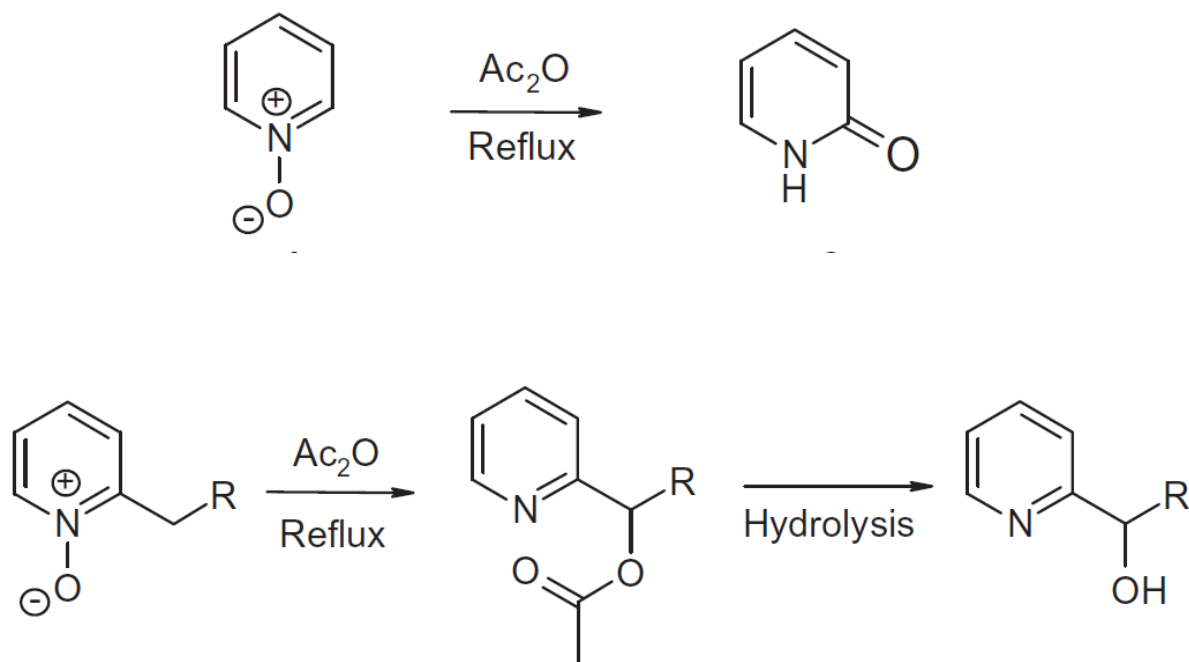
BrCN as electrophile



Other electrophiles such as activated alkynes only gave the rearranged product at C3.

1. The basic principle of N-O bond cleavage, rearrangement, and some related reactions

Pyridine N-oxide; Enantioselective Boekelheide rearrangement

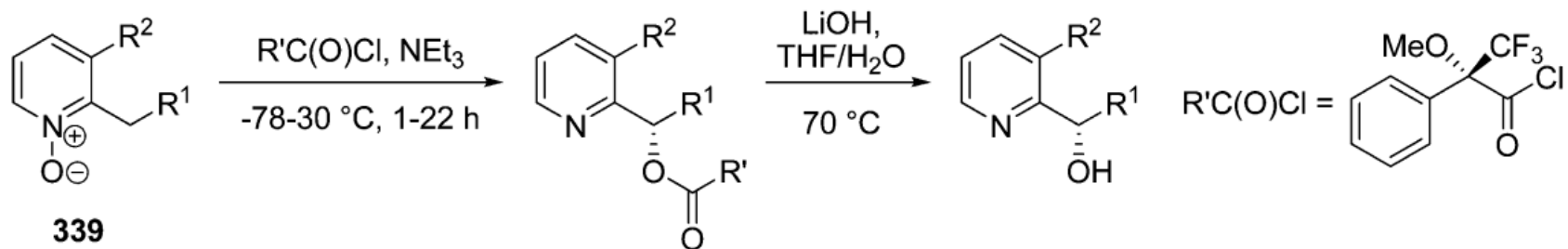


Concerted? or Ion Pair?

Andreotti, D.; Miserazzi, E.; Nalin, A.; Pozzan, A.; Profeta, R.; Spada, S. *Tetrahedron Lett.* **2010**, *51*, 6526.

1. The basic principle of N-O bond cleavage, rearrangement, and some related reactions

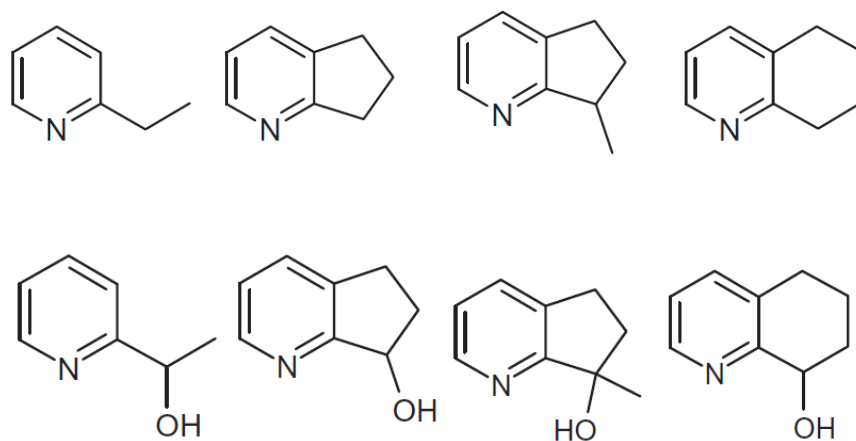
Pyridine N-oxide; Enantioselective Boekelheide rearrangement



- a: $R^1 = \text{Me}$, $R^2 = \text{H}$
- b: $R^1, R^2 = -(\text{CH}_2)_2-$
- c: $R^1, R^2 = -(\text{CH}_2)_3-$

61-70%
dr: 70:30 - 88:12

Tert-alcohol
Is dehydrated.

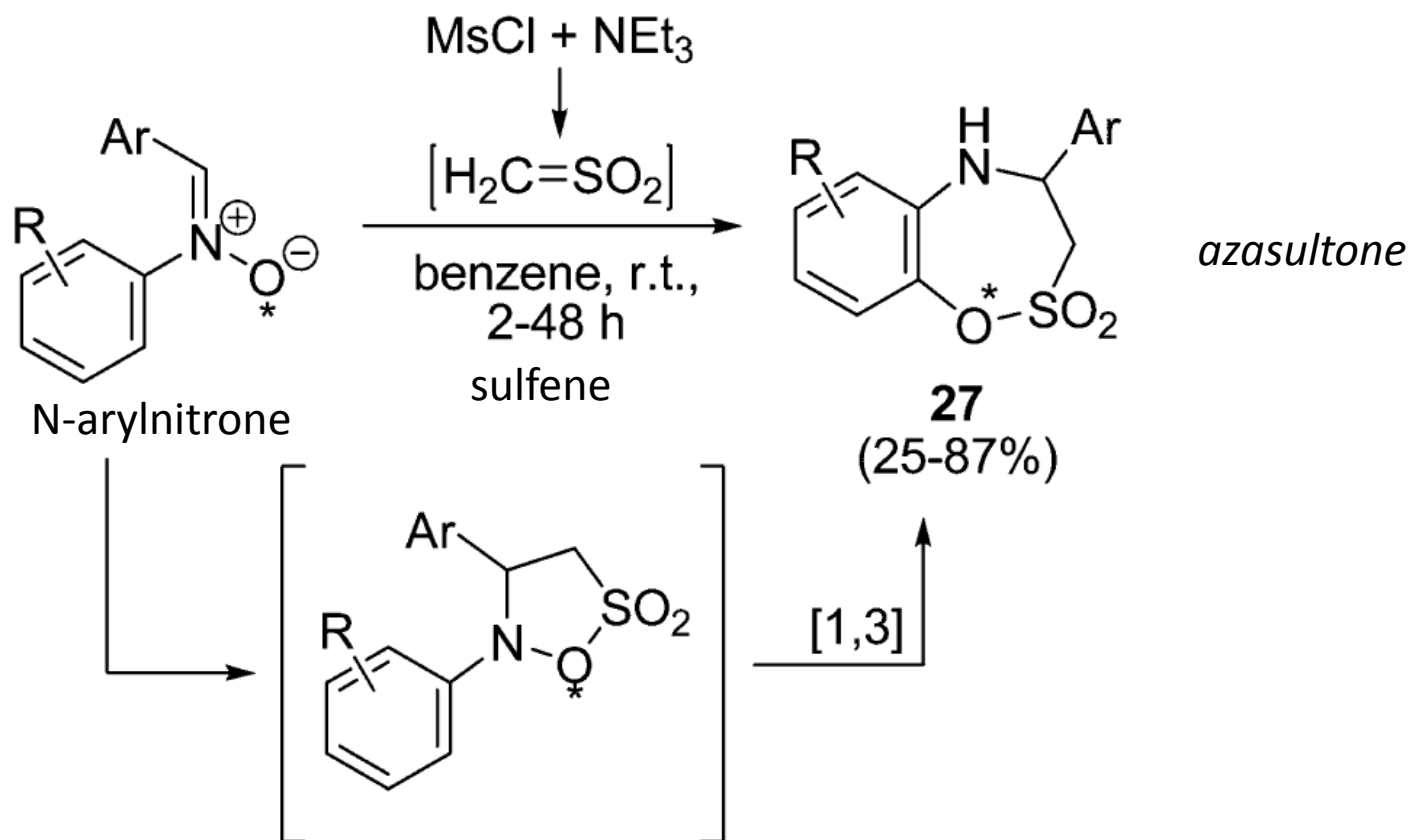


Solvent
= ethyl acetate
Or isopropanol

Andreotti, D.; Miserazzi, E.; Nalin, A.; Pozzan, A.; Profeta, R.; Spada, S. *Tetrahedron Lett.* **2010**, *51*, 6526.

2. Conventional approaches to the heterocycles by N-O bond cleavage

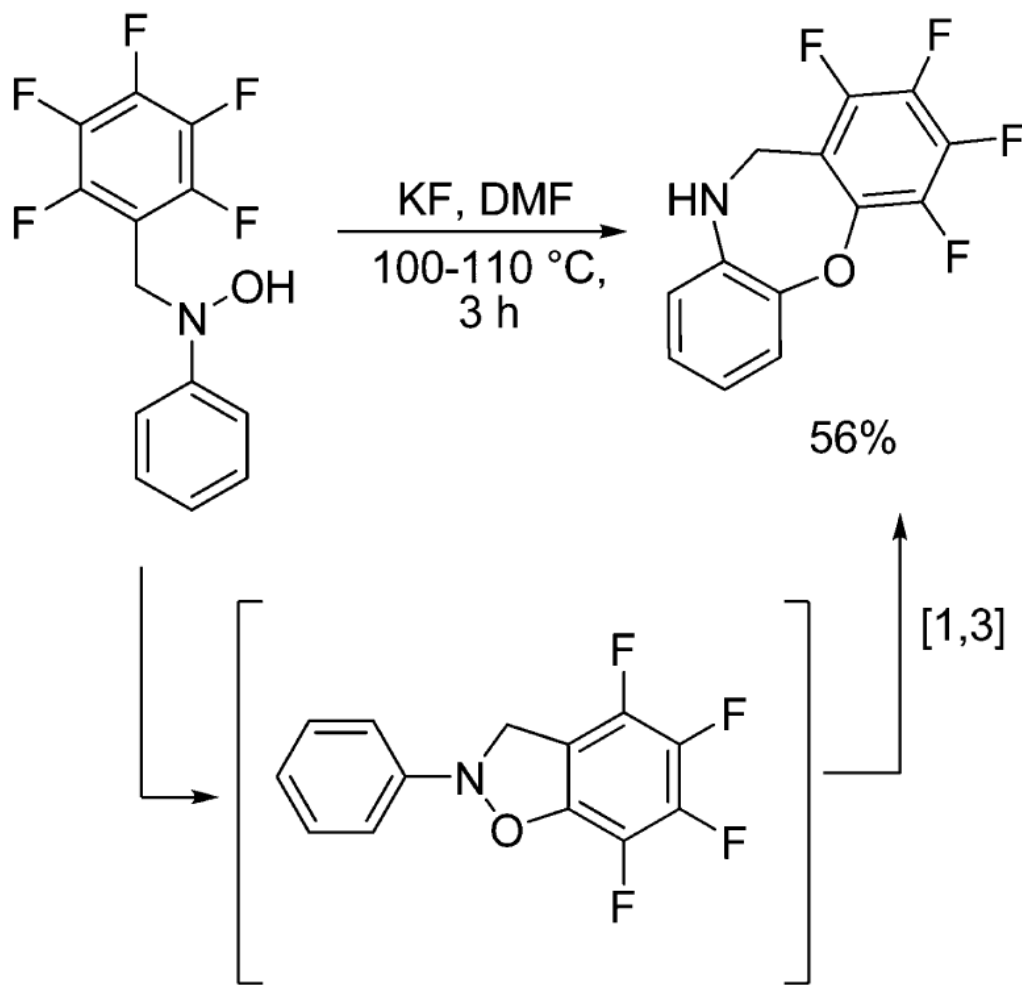
[3+2]-[1,3] cascade



Truce, W. E.; Fieldhouse, J. W.; Vrencur, D. J.; Norell, J. R.;
Campbell, R. W.; Brady, D. G. *J. Org. Chem.* **1969**, *34*, 3097.

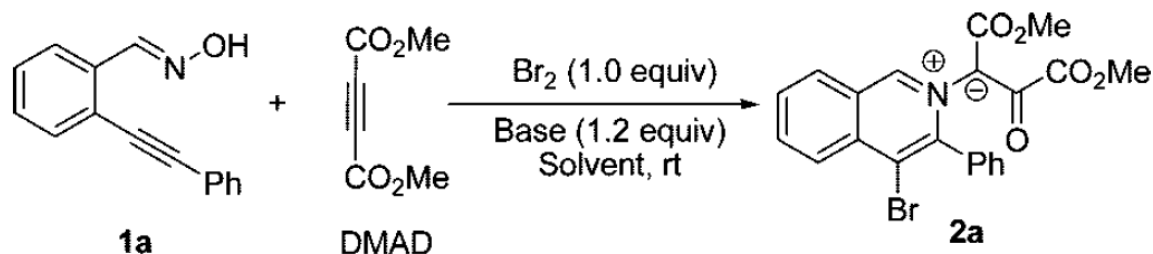
2. Conventional approaches to the heterocycles by N-O bond cleavage

SnAr-[1,3] cascade



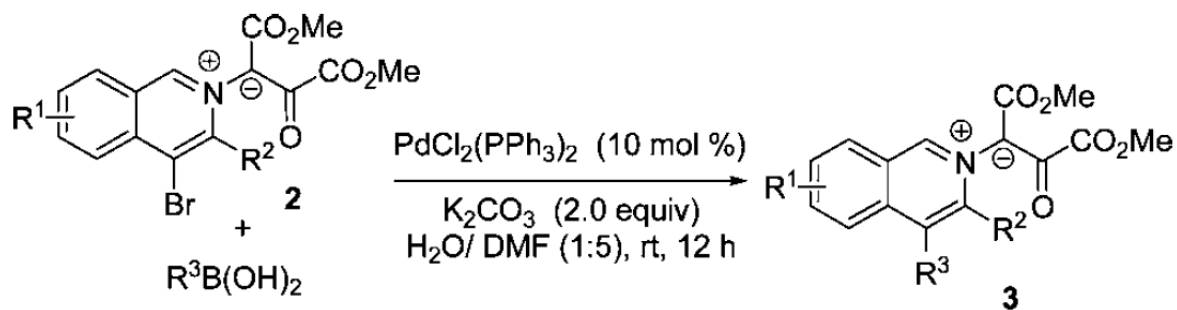
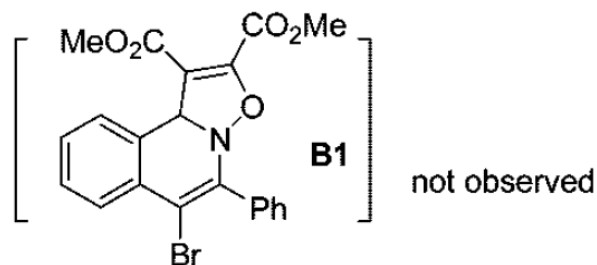
2. Conventional approaches to the heterocycles by N-O bond cleavage

Cycloimerization-cycloaddition; synthesis of azomethine ylide



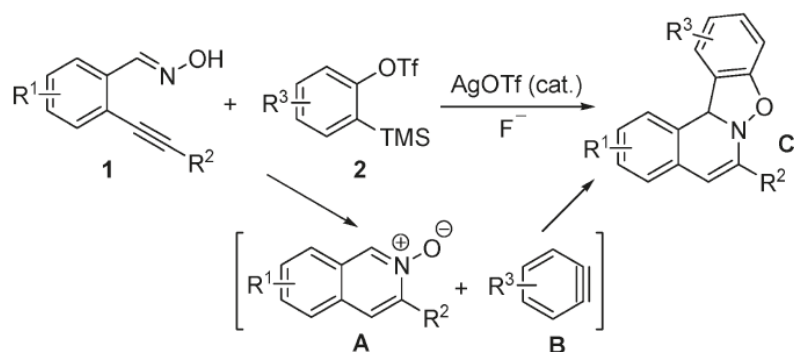
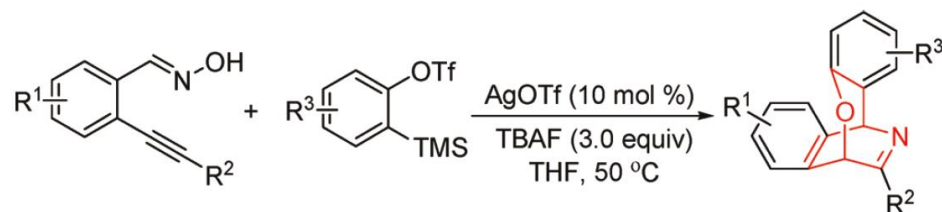
unexpected

Best conditions –
 Br_2 , NaOAc, CH_2Cl_2



2. Conventional approaches to the heterocycles by N-O bond cleavage

[6-endo-cycl]-[3+2]-[1,3] cascade



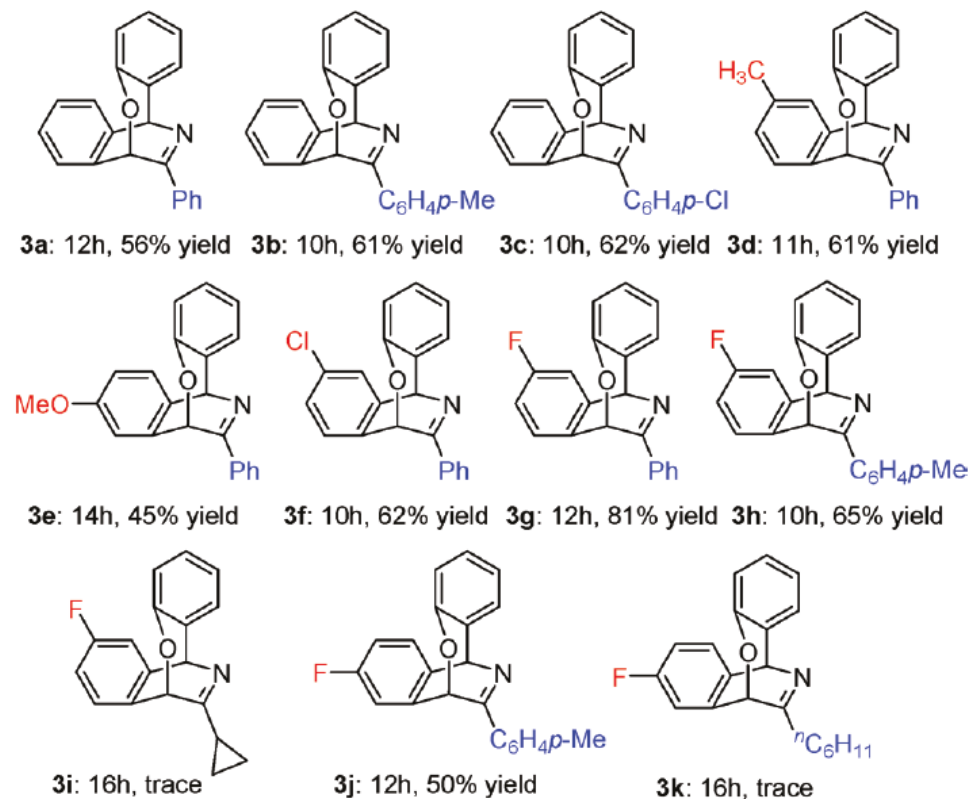
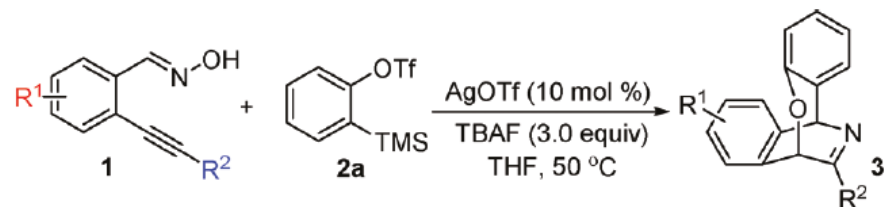
entry	fluoride source	solvent	yield (%) ^a
1	KF	MeCN	trace
2	NaF	MeCN	trace
3	LiF	MeCN	trace
4	CsF	MeCN	30
5	AgF	MeCN	complex
6	ZnF ₂	MeCN	trace
7	MgF ₂	MeCN	trace
8	TBAF	MeCN	37
9	TBAF	toluene	47
10 ^b	TBAF	toluene	48
11	TBAF	THF	56
12 ^c	TBAF	THF	51
13	TBAF	DCE	51
14	TBAF	DMF	17
15	TBAF	DMSO	17

^a Isolated yield based on 2-alkynylbenzaldoxime 1a. ^b The reaction was performed at 70 °C. ^c The reaction occurred at 30 °C.

2. Conventional approaches to the heterocycles by N-O bond cleavage

[3+2]-[1,3] cascade

; scope

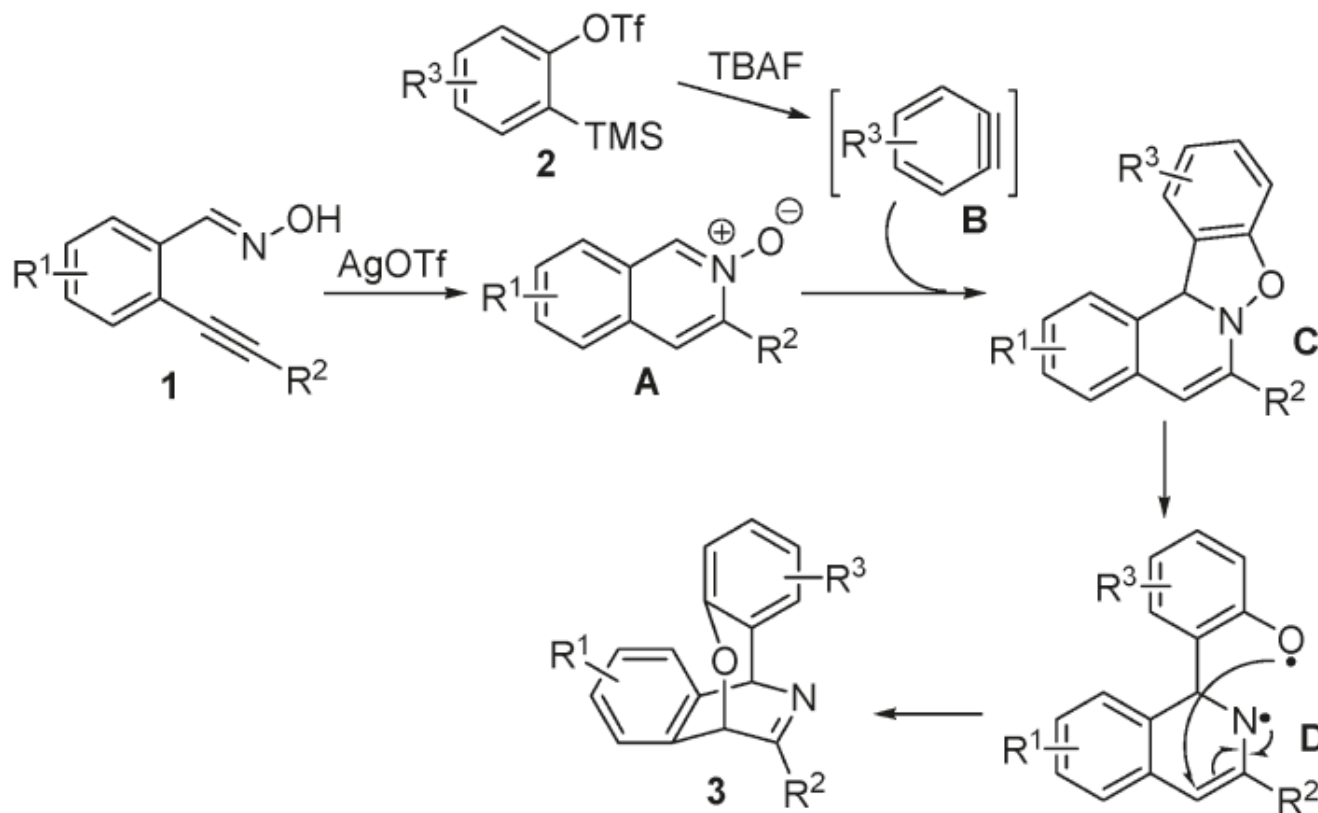


^a Isolated yield based on 2-alkynylbenzaldoxime **1**.

Ren, H.; Luo, Y.; Ye, S.; Wu, J. *Org. Lett.* 2011, 13, 2552.

2. Conventional approaches to the heterocycles by N-O bond cleavage

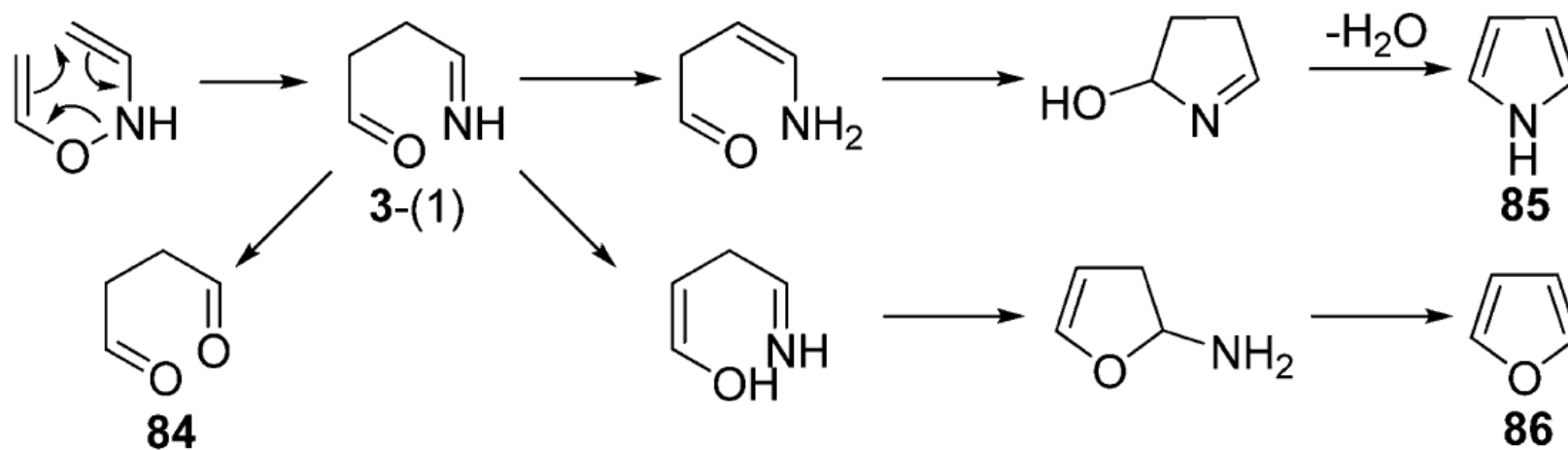
[3+2]-[1,3] cascade
; proposed mechanism



Ren, H.; Luo, Y.; Ye, S.; Wu, J. *Org. Lett.* 2011, 13, 2552.

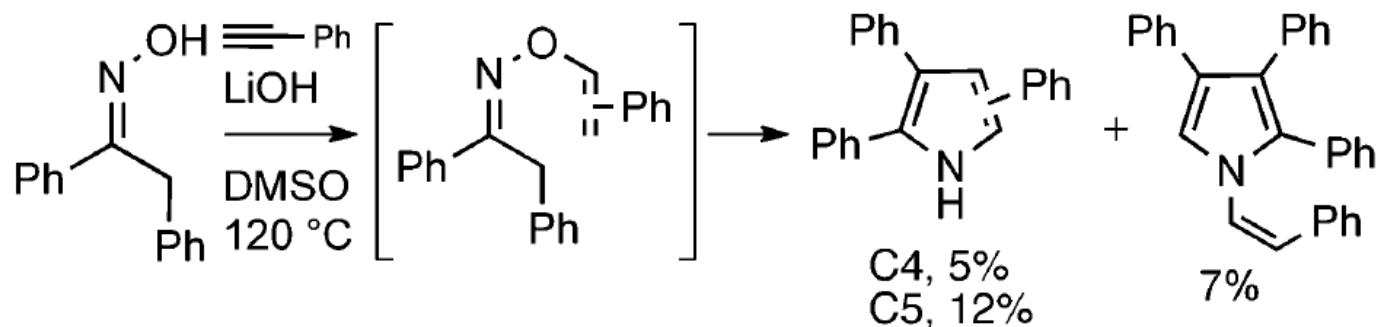
2. Conventional approaches to the heterocycles by N-O bond cleavage

General strategy for [3,3]-sigmatropic rearrangement and cyclization



2. Conventional approaches to the heterocycles by N-O bond cleavage

Trofimov pyrrole synthesis; [3,3]-[condensation]

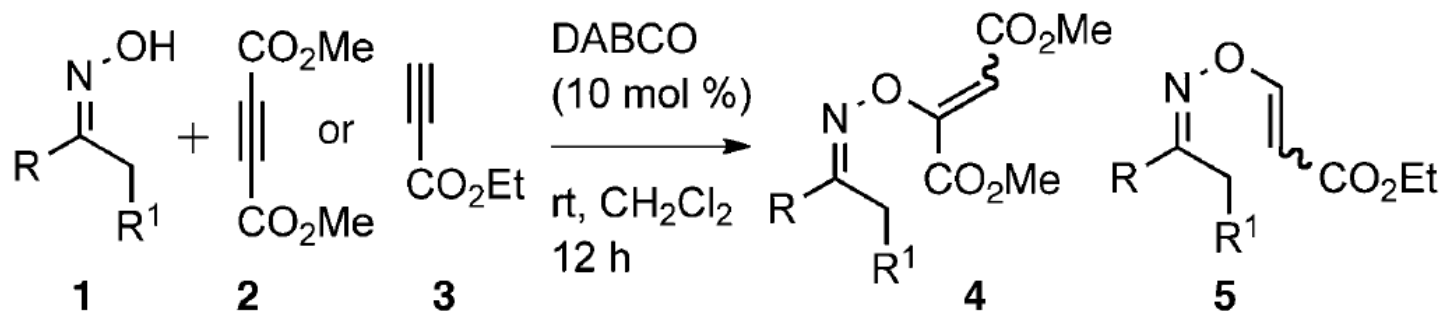
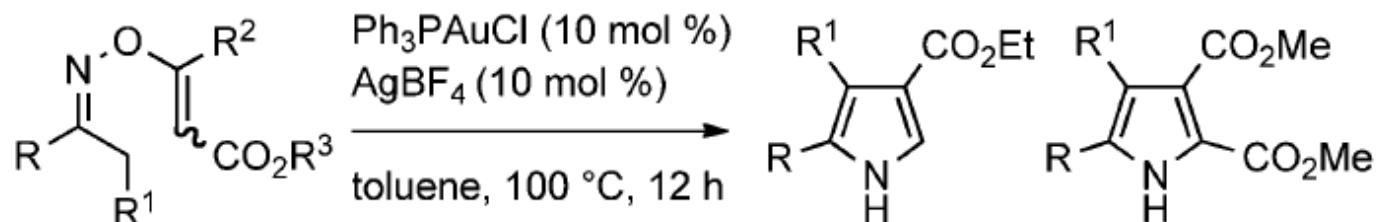


Trofimov, B. A.; Mikhaleva, A. I. *Heterocycles* **1994**, *37*, 1193.

Trofimov, B. A.; Mikhaleva, A. I. *Zh. Org. Khim.* **1996**, *32*, 1127–1141

2. Conventional approaches to the heterocycles by N-O bond cleavage

Au catalyzed Trofimov reaction

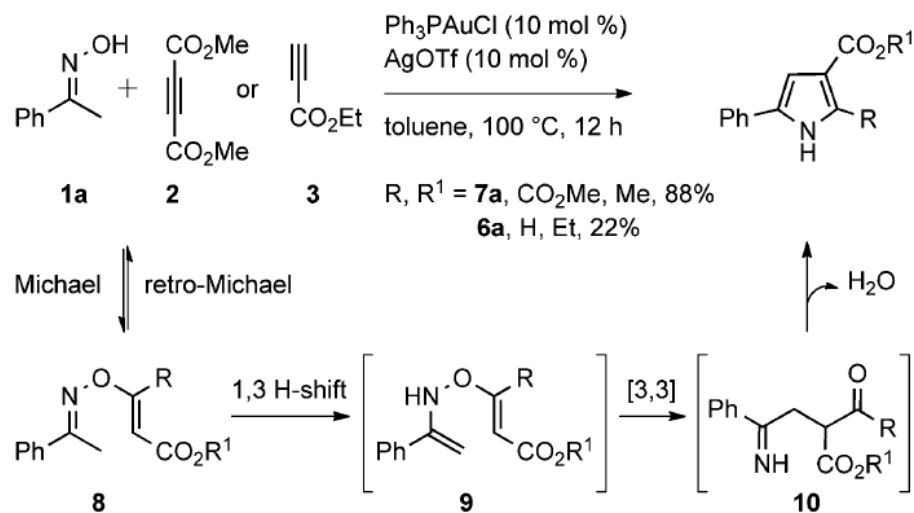
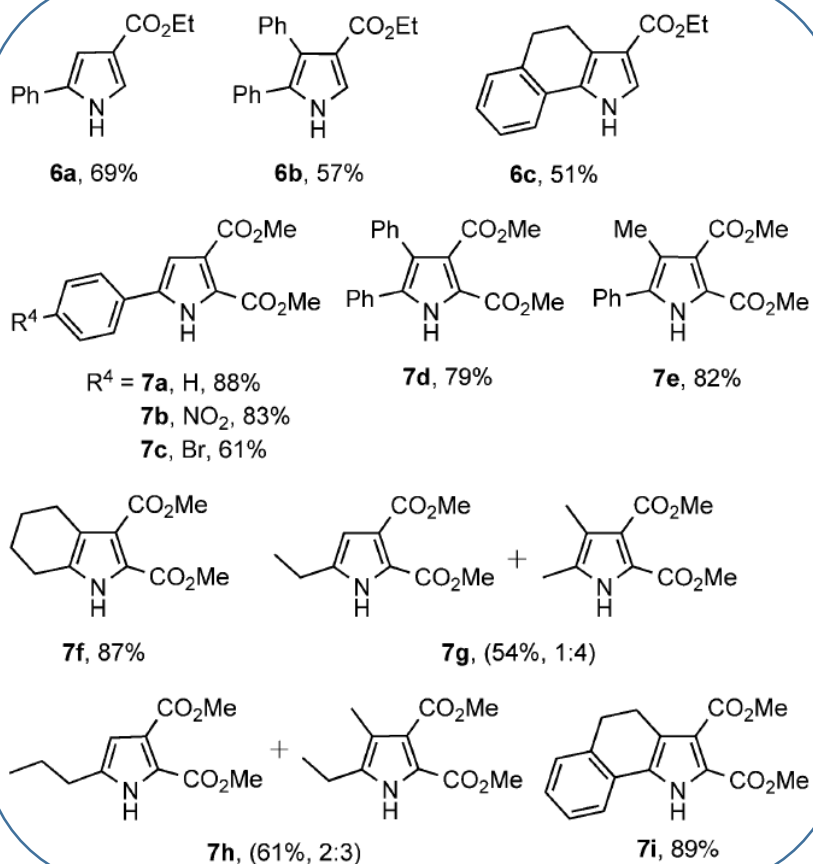


Usually require higher temp.!, but Au catalyst allow relatively low temperature.

Ngwerume, S.; Camp, J. E. *Chem. Commun.* **2011**, 47, 1857.

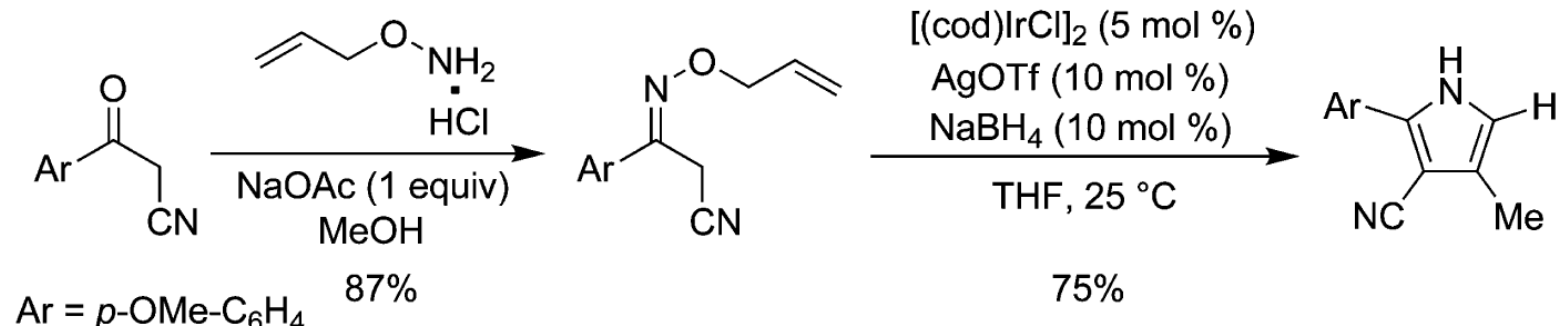
2. Conventional approaches to the heterocycles by N-O bond cleavage

[3,3]-[condensation] scope



2. Conventional approaches to the heterocycles by N-O bond cleavage

Ir-catalyzed Trofimov reaction

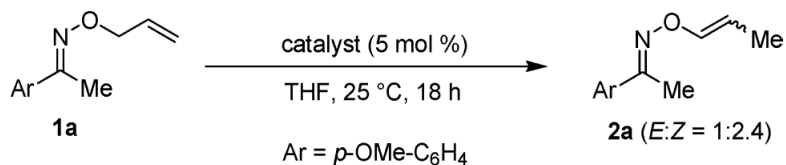


Wang, H.-Y.; Mueller, D. S.; Sachwani, R. M.; Londino, H. N.; Anderson, L. L. *Org. Lett.* **2010**, *12*, 2290.

2. Conventional approaches to the heterocycles by N-O bond cleavage

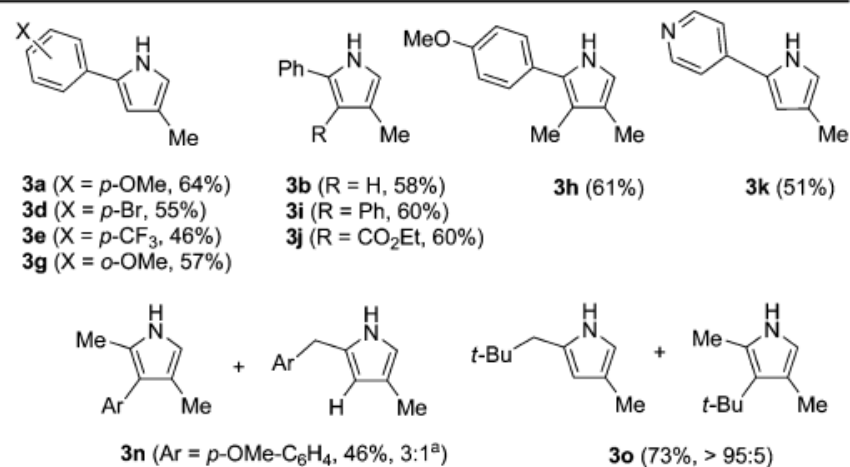
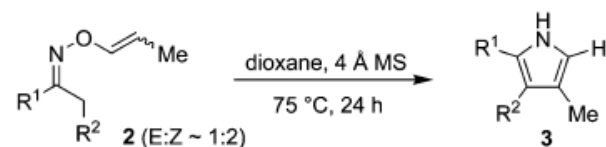
Ir-catalyzed Trofimov reaction; optimization and scope

Table 1. Optimization of the *O*-Allyl Oxime Isomerization Catalyst



entry	catalyst	yield (%) ^a
1	(Ph ₃ P) ₃ RhCl/ <i>n</i> -BuLi	NR
2	[(coe) ₂ IrCl] ₂ /2PCy ₃ /2AgPF ₆	NR ^b
3	[(cod)IrCl] ₂ /2NaBH ₄ /2AgOTf	85
4	[(coe) ₂ IrCl] ₂ /2NaBH ₄ /2AgOTf	53
5	(cod) ₂ Rh(BF ₄)/NaBH ₄ /AgOTf	30
6	[(coe) ₂ RhCl] ₂ /2NaBH ₄ /2AgOTf	NR
7	[(cod)IrCl] ₂ /2LiAlH ₄ /2AgOTf	89

^a Determined by using ¹H NMR spectroscopy with CH₂Br₂ as a reference. ^b The reaction was done in THF and in 50:1 DCE:acetone.



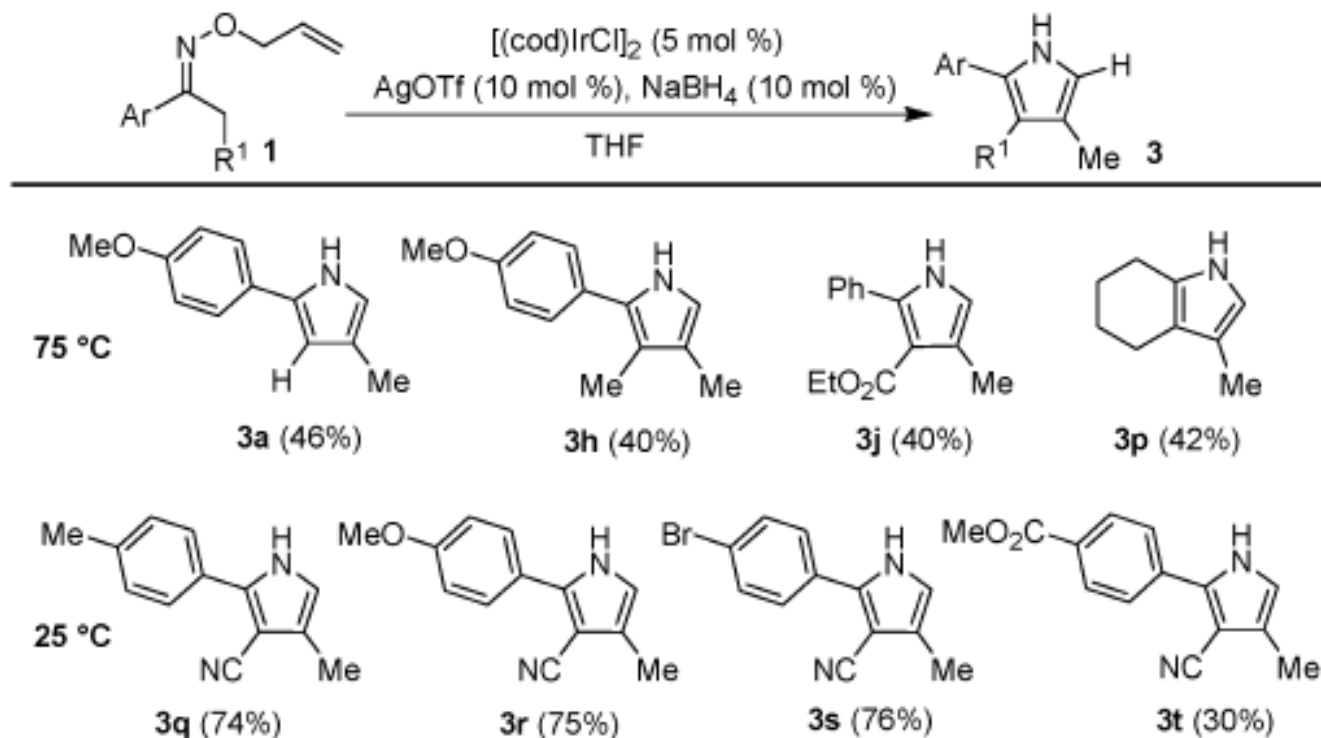
^a Regioselectivity ratio.

Wang, H.-Y.; Mueller, D. S.; Sachwani, R. M.; Londino, H. N.; Anderson, L. L. *Org. Lett.* **2010**, *12*, 2290.

2. Conventional approaches to the heterocycles by N-O bond cleavage

Ir-catalyzed Trofimov reaction; one pot procedure

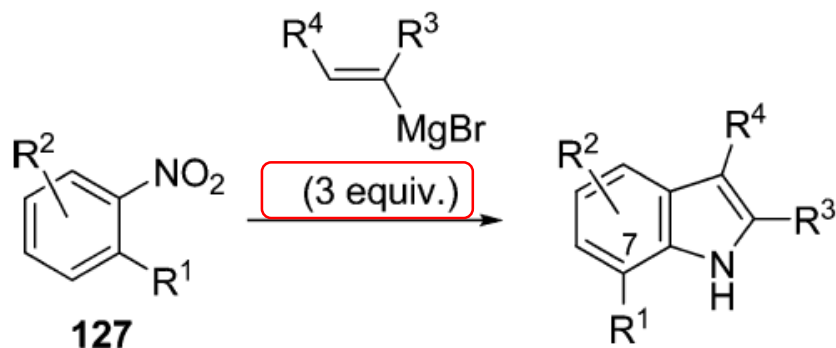
Scheme 5. Conversion of *O*-Allyl Oximes to Pyrroles



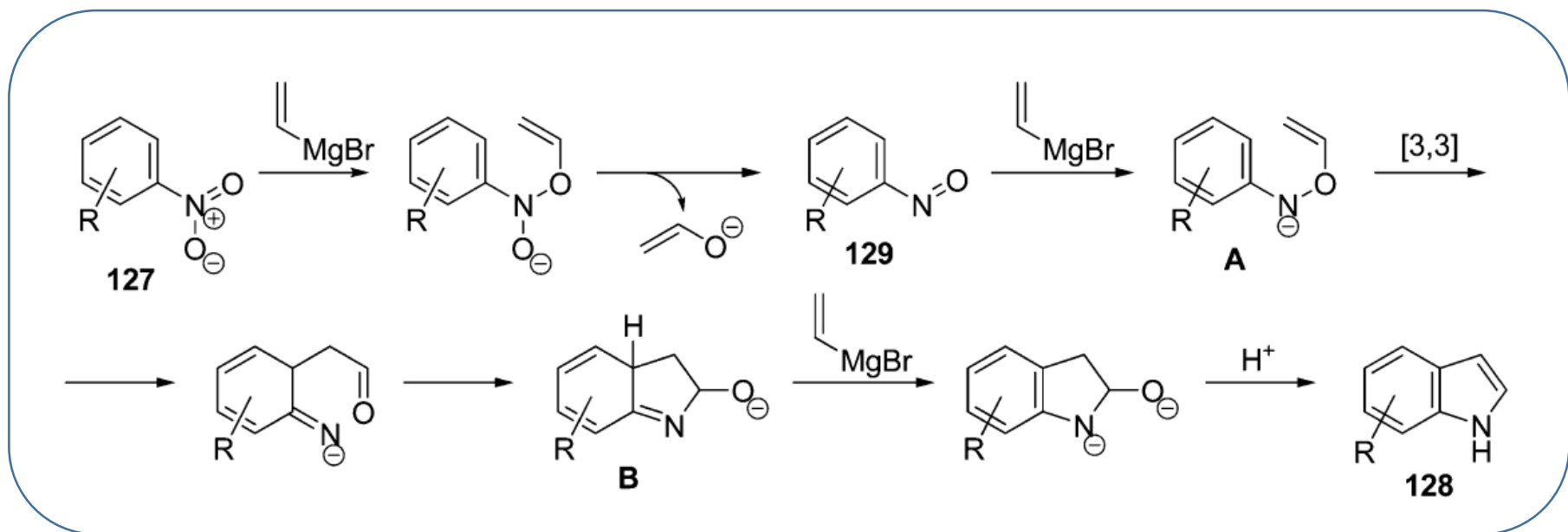
Wang, H.-Y.; Mueller, D. S.; Sachwani, R. M.; Londino, H. N.; Anderson, L. L. *Org. Lett.* **2010**, *12*, 2290.

2. Conventional approaches to the heterocycles by N-O bond cleavage

Bartoli indole synthesis



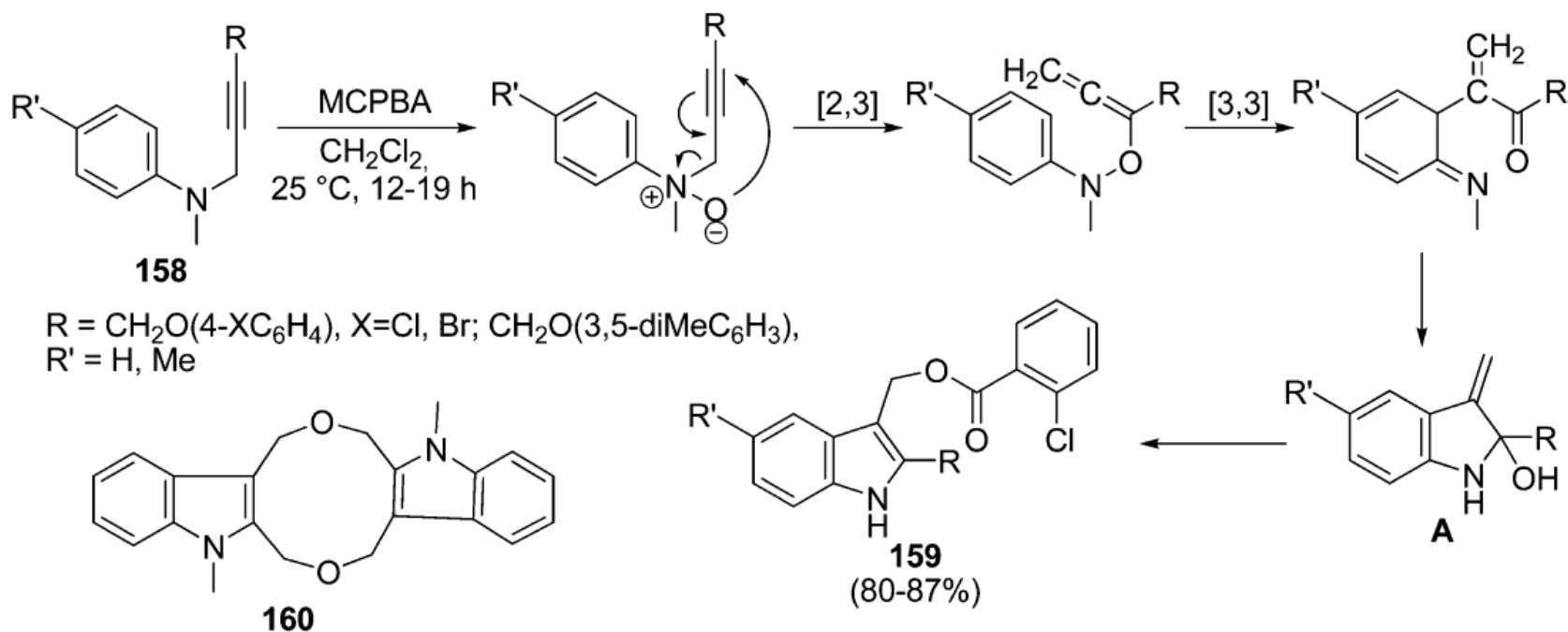
ortho substituent is crucial.



Bosco, M.; Dalpozzo, R.; Bartoli, G.; Palmieri, G.; Petrini, M. *J. Chem. Soc., Perkin Trans. 2* 1991, 657.

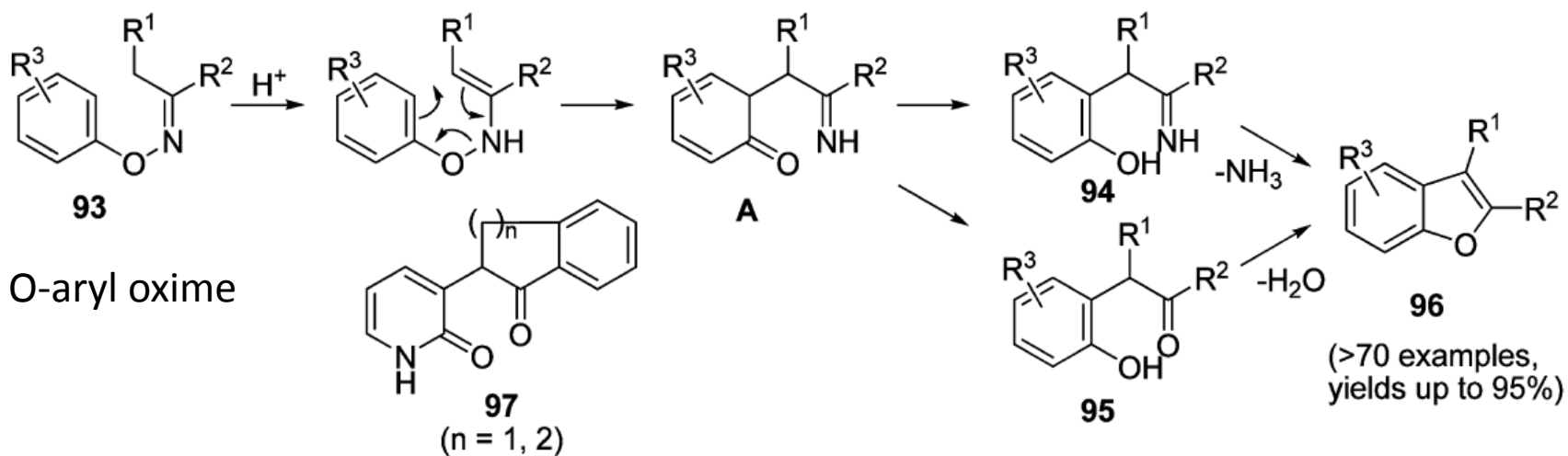
2. Conventional approaches to the heterocycles by N-O bond cleavage

Synthesis of 2,3-disubstituted indole



2. Conventional approaches to the heterocycles by N-O bond cleavage

Benzofuran synthesis; general scheme

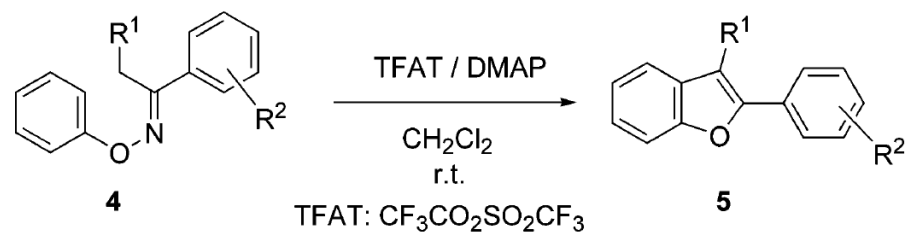


2. Conventional approaches to the heterocycles by N-O bond cleavage

Benzofuran synthesis

TFAT=
trifluoroacetyl
triflate

(strong promoter)

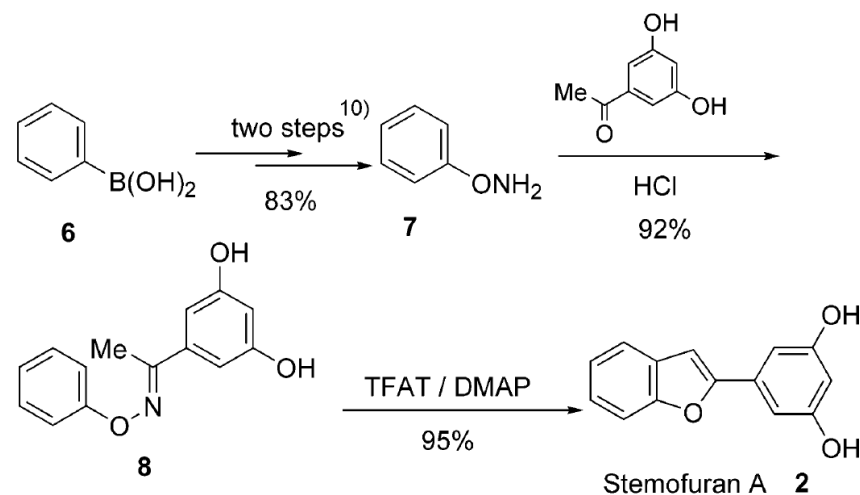
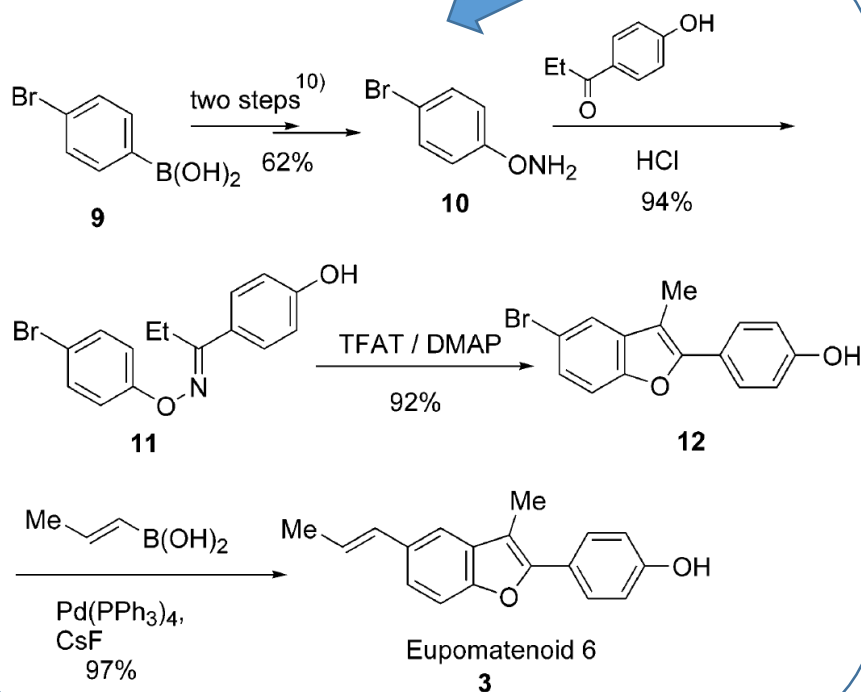
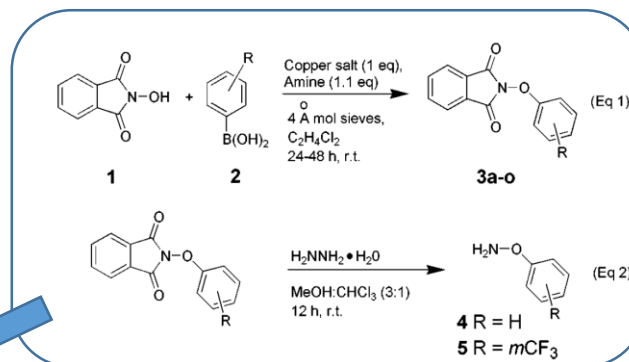


entry	4	R ¹	R ²	time (h)	5	yield ^b (%)
1	4a	H	H	1	5a	99
2	4b	H	<i>p</i> -Br	1.5	5b	96
3	4c	H	<i>p</i> -NO ₂	5	5c	85 (9)
4	4d	H	<i>p</i> -OH	2	5d	84
5	4d	H	<i>p</i> -OH	2	5n^c	92
6	4e	H	<i>p</i> -OMe	2	5e	15 (12)
7	4f	Me	H	2	5f	82
8	4g	Me	<i>p</i> -Br	2	5g	91
9	4h	Me	<i>p</i> -OH	2	5h	86
10	4i	Me	<i>p</i> -OMe	2	5i	26 (13)
11	4j	H	<i>m</i> -Br	2	5j	94
12	4k	H	<i>m</i> -NO ₂	5	5k	95
13	4l	H	<i>m</i> -OH	2	5l	86
14	4m	H	<i>m</i> -OMe	1.5	5m	93

^a TFAT (5 equiv) and DMAP (3 equiv) were used. ^b Yields in parentheses are for the recovered starting material. ^c **5n** (R² = *p*-OCOCF₃).

2. Conventional approaches to the heterocycles by N-O bond cleavage

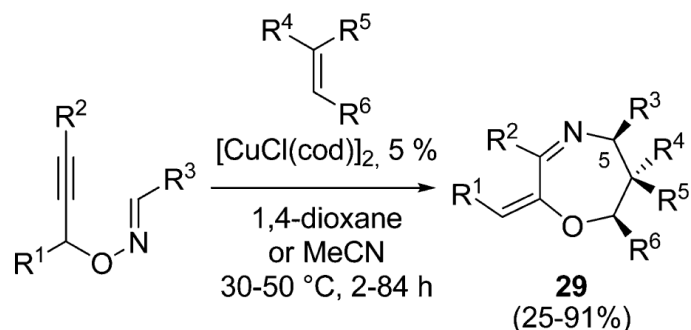
Application to the natural products



3. Recent TM-catalyzed synthesis of heterocycles

[Cu]-catalyzed [2,3]-[3+2]-[1,3] cascade

Olefin: dipolarophile



O-propargylic oxime:
 [1,3]-dipole precursor

CuCl, [CuCl(cod)]₂ - good

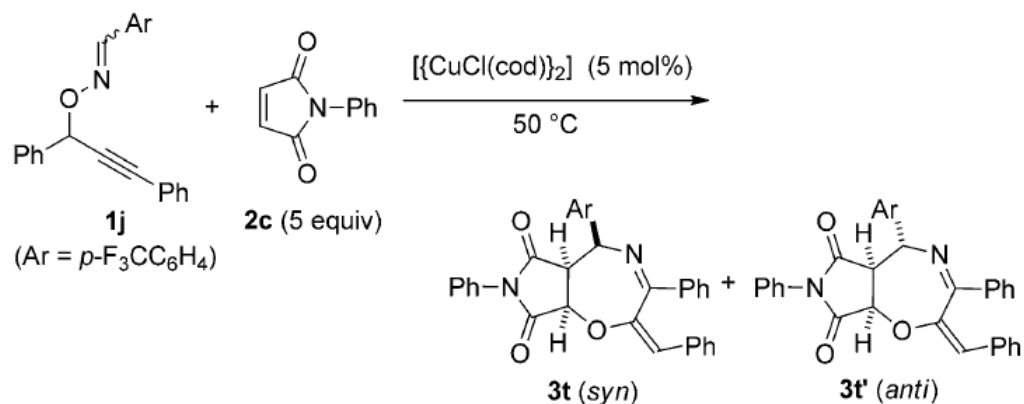
~~CuBr, CuCl₂, Cu(OAc)₂, AuCl, PtCl₂~~

Entry	2	t [h]	3	Yield [%] ^[b]		
				R ⁴	R ⁵	R ⁶
1	2a (R = Me)	20	3a	H	CO ₂ Me	CO ₂ Me
2	2b (R = <i>t</i> Bu)	12	3b	H	CO ₂ <i>i</i> Pr	CO ₂ <i>i</i> Pr
3	2c (R = Ph)	16	3c			
4	2d (R = <i>p</i> -O ₂ NC ₆ H ₄)	12	3d			
5	2e (R = <i>p</i> -MeOC ₆ H ₄)	24	3e	CO ₂ Me	H	CO ₂ Me
6	2f (R = H)	36	3f	H	H	CO ₂ Me
7 ^[c,d]	2g ^[e]	6	3g			
8 ^[c,d]	2h ^[e]	6	3h			
9 ^[c,d]	2i ^[f]	6	3i			
10 ^[c]	2j ^[g]	18	3j			
11 ^[c]	2k ^[e]	84	3k	H	H	CONMe ₂

[a] The reactions of **1a** (0.2 mmol) and **2** (0.3 mmol) were carried out in the presence of [CuCl(cod)]₂ (5 mol%) in 1,4-dioxane (0.2 mL) at 30 °C.
 [b] Yield of isolated product. [c] Acetonitrile was used as solvent. [d] At 50 °C. [e] Used 3 equivalents of **2**. [f] Used 7 equivalents of **2**. [g] Used 5 equivalents of **2**.

3. Recent TM-catalyzed synthesis of heterocycles

Solvent effect for diastereoselectivity



Entry	<i>E/Z</i> ^[b]	Solvent	<i>t</i> [h]	Yield [%] ^[c]	3t/3t' ^[d]
1	<i>Z</i>	CH ₃ CN	2	71	> 99:1
2	<i>Z</i> ^[e]	1,4-dioxane	2.5	76	93:7
3 ^[f,g]	<i>Z</i>	1,4-dioxane	120	0 ^[h]	—
4	<i>E</i> ^[i]	CH ₃ CN	72	63	> 99:1
5	<i>E</i>	1,4-dioxane	24	67	69:31
6	<i>E</i>	toluene	24	55	51:49

[a] The reactions of **1j** (0.2 mmol) and **2c** (1.0 mmol) were carried out in the presence of $[\text{CuCl}(\text{cod})]_2$ (5 mol%) in solvent (0.2 mL) at 50 °C.

[b] *E/Z* stereochemistry at the oxime moiety of **1j**. [c] Combined yields of **3t** and **3t'**. [d] The ratio was determined by ¹H NMR spectroscopy.

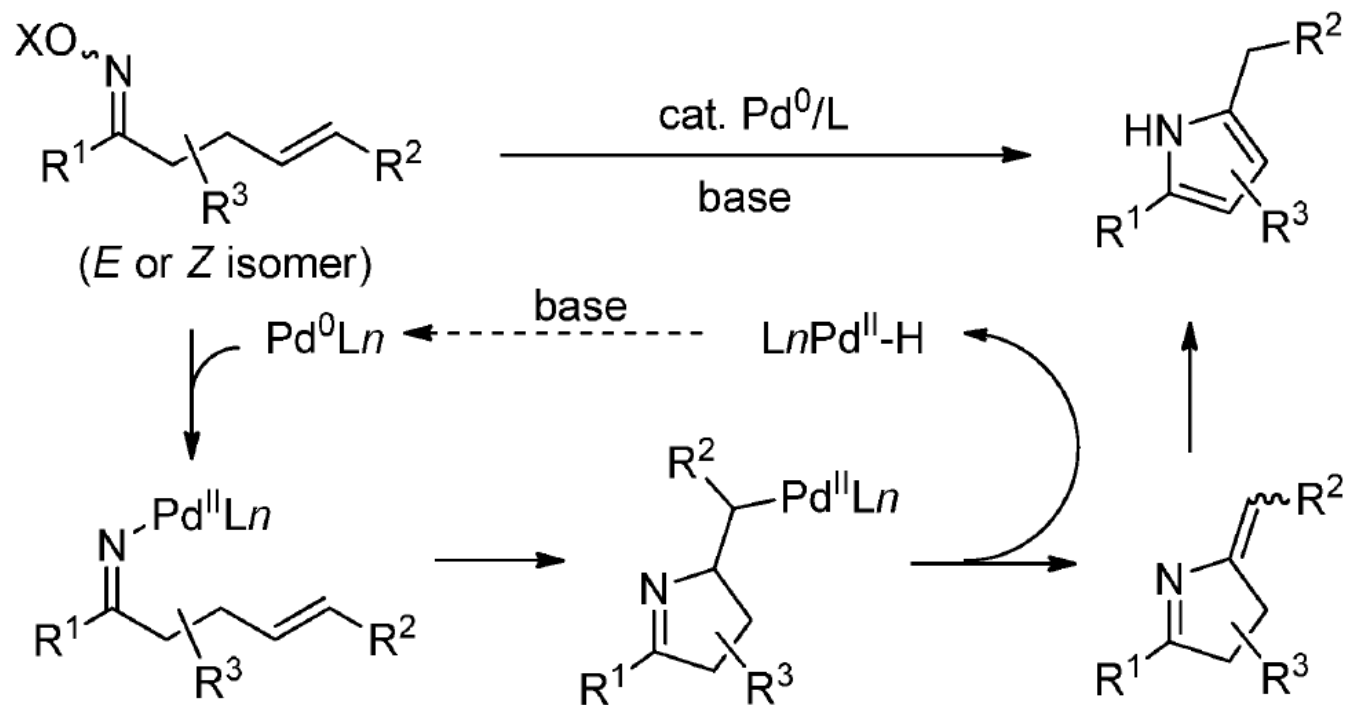
[e] Chiral substrate (*R,Z*)-**1j** (99% *ee*) was used (**3t**: 2% *ee*, **3t'**: 30% *ee*).

[f] The reaction was carried out in the absence of copper catalysts. [g] At 70 °C. [h] Obtained 28% of (*E*)-**1j**. [i] Chiral substrate (*R,E*)-**1j** (99% *ee*) was used (**3t**: < 5% *ee*).

will be discussed in
Quiz 2.

3. Recent TM-catalyzed synthesis of heterocycles

Well-established works; Intramolecular Heck type amination reaction



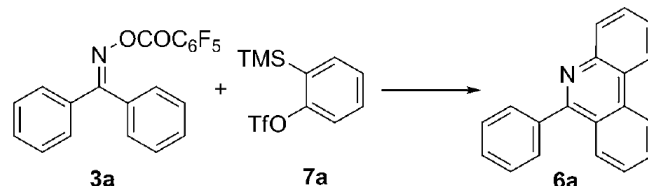
Review papers

M. Kitamura, K. Narasaka, *Chem. Rec.* **2002**, 2, 268–277.

K. Narasaka, M. Kitamura, *Eur. J. Org. Chem.* **2005**, 4505–4519.

3. Recent TM-catalyzed synthesis of heterocycles

Intermolecular Pd-catalyzed annulation; between highly reactive two species



Entry	Pd	Ligand	Pd/ligand	Solvent (ratio)	T [°C]	Yield [%] ^[b]
1	[Pd(dba) ₂]	P(<i>o</i> -tolyl) ₃	1:1	CH ₃ CN/tol (1:9)	110	trace
2	APC	P(<i>o</i> -tolyl) ₃	1:2	CH ₃ CN/tol (1:9)	110	10 ^[g]
3 ^[c]	APC	P(<i>o</i> -tolyl) ₃	1:2	CH ₃ CN/tol (1:9)	110	trace
4	APC	P(<i>o</i> -tolyl) ₃	1:2	CH ₃ CN/tol (1:1)	110	27
5	APC	xphos	1:2	CH ₃ CN/tol (1:1)	110	30
6 ^[c]	APC	dppp		CH ₃ CN	80	trace
7 ^[d]	APC	P(<i>o</i> -tolyl) ₃	1:2	C ₂ H ₅ CN	100	40
8 ^[d]	APC ^[e]	P(<i>o</i> -tolyl) ₃	1:2	C ₃ H ₇ CN	100	40
9 ^[d]	APC	P(<i>o</i> -tolyl) ₃	1:2	C ₃ H ₇ CN	120	67
10 ^[d]	[Pd(PPh ₃) ₄]		–	C ₃ H ₇ CN	120	65
11 ^[d]	APC ^[e]	dppp	1:1	C ₃ H ₇ CN	120	53
12 ^[d]	APC ^[e]	xphos	1:2	C ₃ H ₇ CN	120	53
13 ^[d]	APC ^[e]	–		C ₃ H ₇ CN	120	60
14	APC ^[e]	P(<i>o</i> -tolyl) ₃	1:2	C ₃ H ₇ CN	120	70
15 ^[f]	APC ^[e]	P(<i>o</i> -tolyl) ₃	1:2	C ₃ H ₇ CN	120	74
16	–	–		C ₃ H ₇ CN	120	0

butyronitrile – solubility
is bad for CsF. but high bp

molecular sieve
Improved the yield

No Beckman products

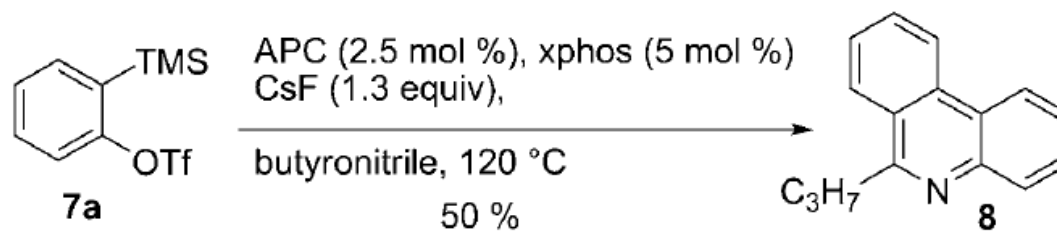
No interference of the
resulting heterocycle

[a] All reactions were carried out under an argon atmosphere using Pd (5 mol%), **7a** (2 equiv), CsF (3 equiv), *c* = 0.42 M for 20 hours. [b] Yield of isolated product. [c] Slow addition of **7a** over 4 h. [d] **7a** (3 equiv) and CsF (4 equiv). [e] 2.5 mol%. [f] *c* = 0.25 M in the presence of M.S. (4 Å). [g] Similar yields were obtained when dppe, P(2-furyl)₃, dppp, and johnphos were used as supporting ligands. dba = *trans,trans*-dibenzylideneacetone, dppe = ethane-1,2-diylbis(diphenylphosphane), dppp = propane-1,3-diylbis(diphenylphosphane), johnphos = 2-(di-*tert*-butylphosphino)biphenyl, Tf = triflate, tol = toluene, TMS = trimethylsilyl, xphos = 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl.

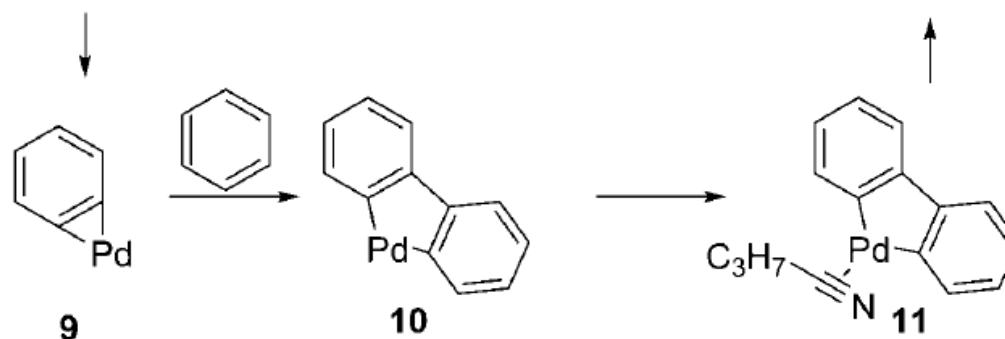
T. Gerfaut, L. Neuville and J. Zhu, *Angew. Chem., Int. Ed.*,
2009, **48**, 572–577.

3. Recent TM-catalyzed synthesis of heterocycles

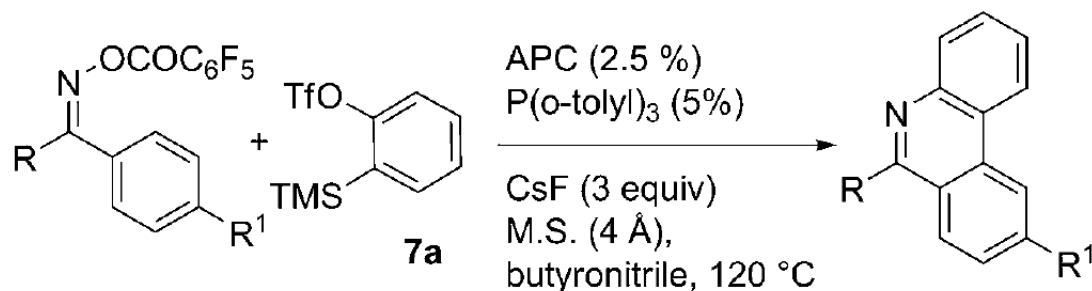
Scope



byproduct



R=alkyl



Keto-enol
tautomerization?

3p: R=Me, R¹=H

3q: R=Me, R¹=NO₂

3r: R=*i*Pr, R¹=H

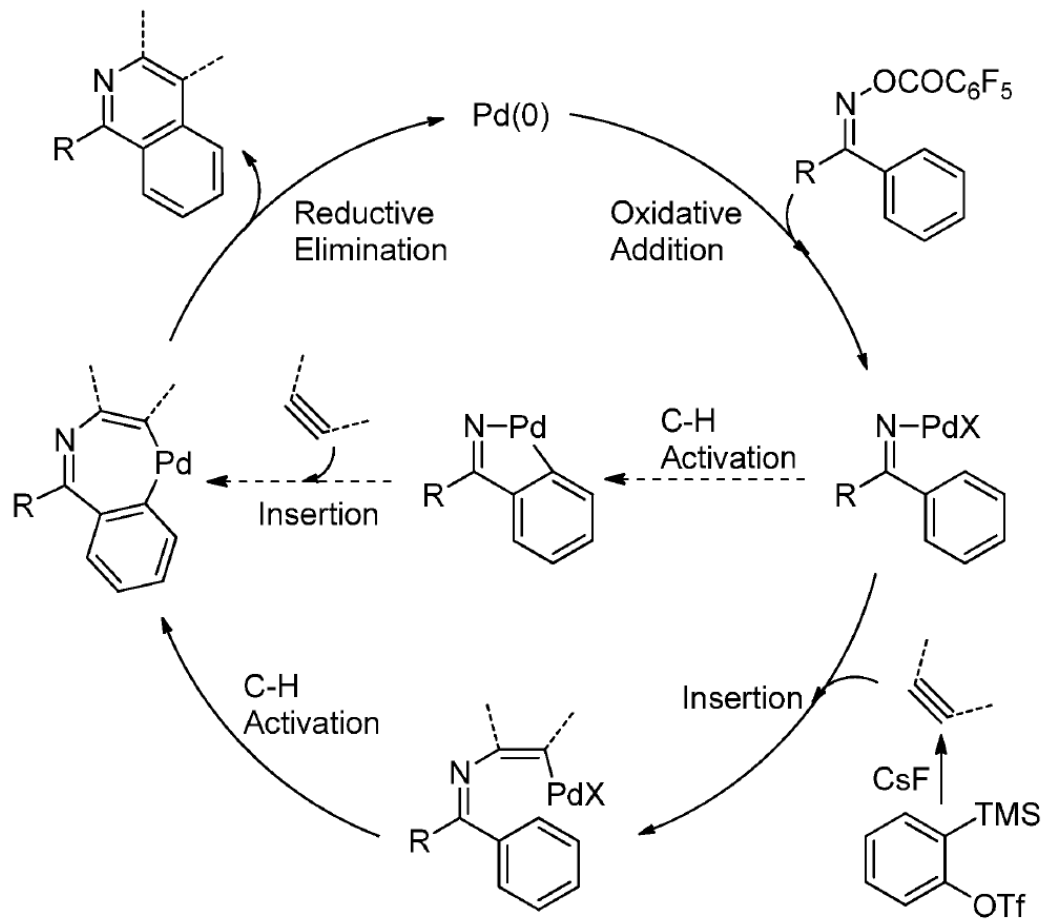
6p: R=Me, R¹=H 24%

6q: R=Me, R¹=NO₂ 19%

6r: R=*i*Pr, R¹=H 29%

3. Recent TM-catalyzed synthesis of heterocycles

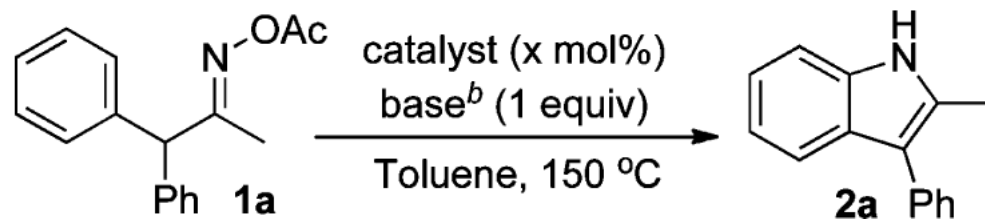
[proposed mechanism]



T. Gerfaut, L. Neuville and J. Zhu, *Angew. Chem., Int. Ed.*, 2009, **48**, 572–577.

3. Recent TM-catalyzed synthesis of heterocycles

Pd-catalyzed intramolecular C-H amination



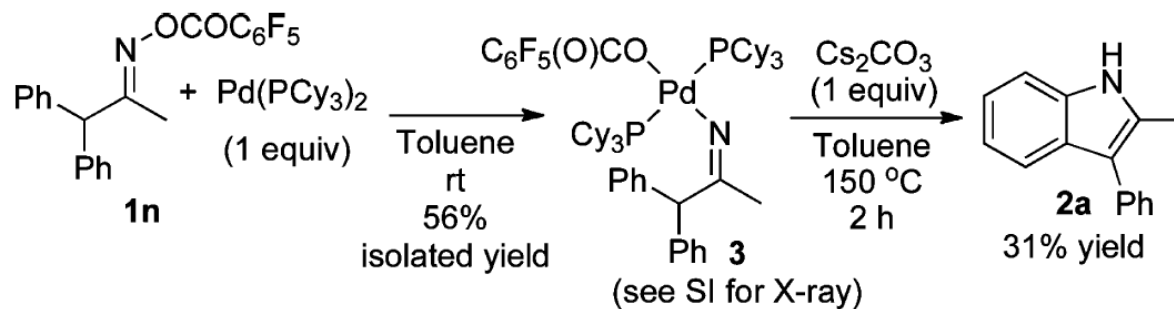
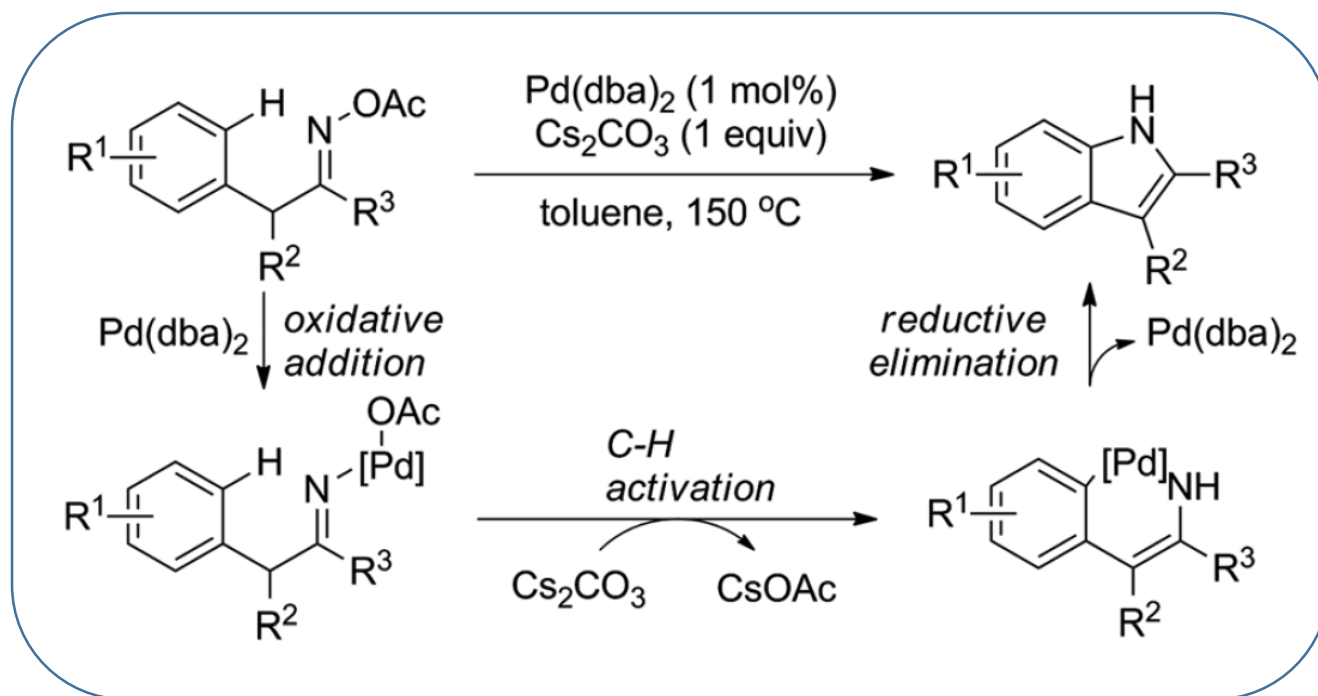
entry	catalyst	base	time (h)	yield (%) ^c
1	Pd(dba) ₂ (100 mol %)	—	4	70
2	Pd(dba) ₂ (10 mol %)	K ₃ PO ₄	24	74
3	Pd(dba) ₂ (1 mol %)	Cs ₂ CO ₃	24	72
4	Pd(PCy ₃) ₂ (1 mol %)	Cs ₂ CO ₃	24	56

^a The reactions were conducted on 0.05 mmol scale in 1 mL of toluene. ^b Dried in a furnace at 500 °C. ^c GC yields.

Y. Tan and J. F. Hartwig, *J. Am. Chem. Soc.*, 2010, **132**, 3676–3677.

3. Recent TM-catalyzed synthesis of heterocycles

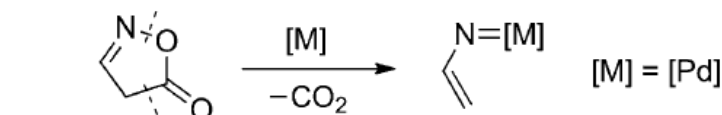
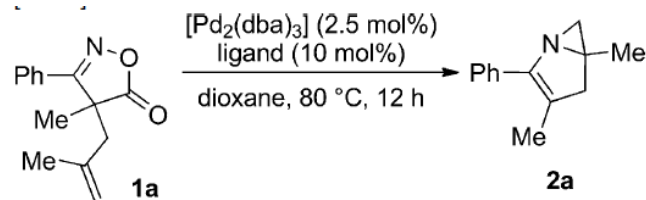
[proposed mechanism]



Y. Tan and J. F. Hartwig, *J. Am. Chem. Soc.*, 2010, **132**, 3676–3677.

3. Recent TM-catalyzed synthesis of heterocycles

Pd-catalyzed decarboxylative alkylation



4H-isoxazol-5-ones

- N–O activation
- decarboxylation

vinylnitrene complex

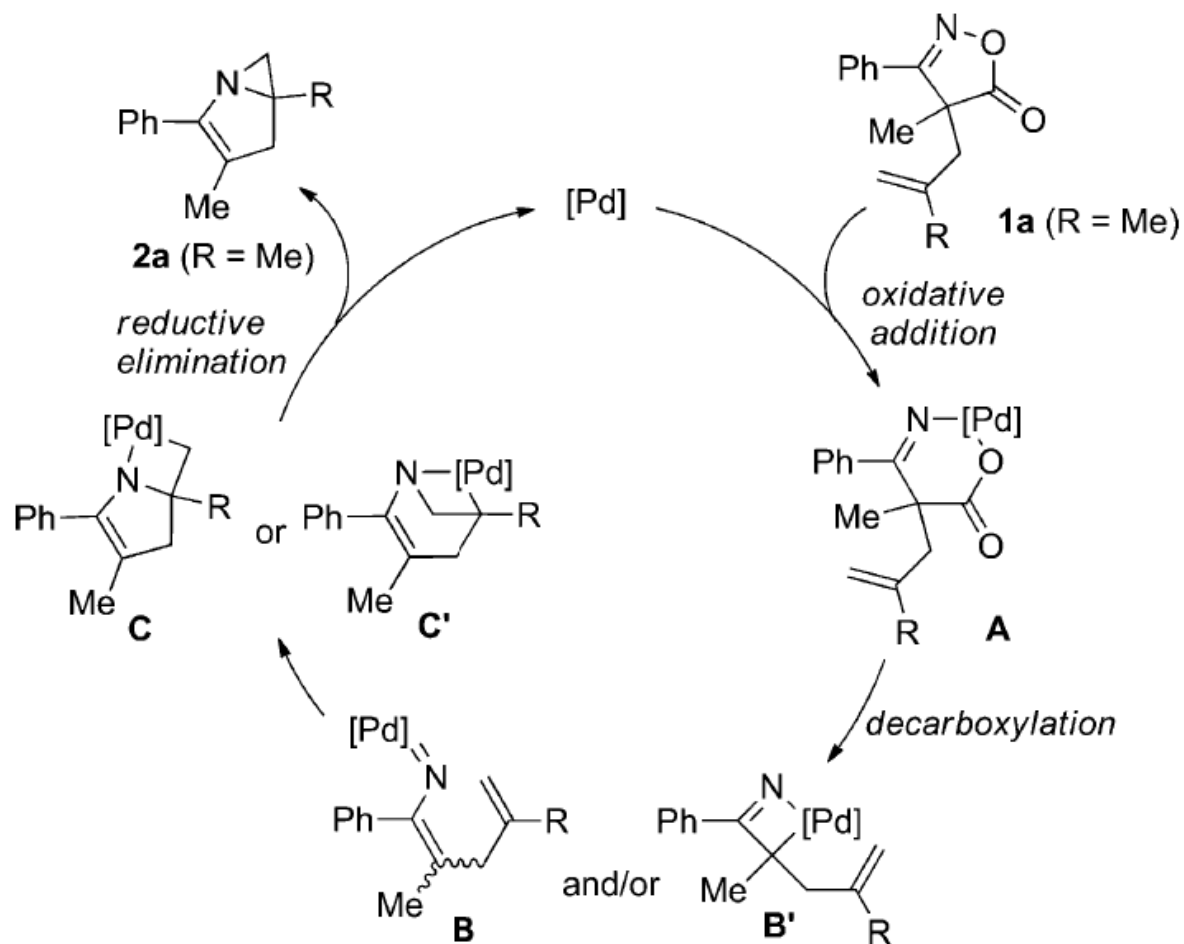
Entry	Ligand	Conversion [%] ^[b]	Yield [%] ^[b]
1	PPh_3	98	84
2	$\text{P}(4\text{-MeC}_6\text{H}_4)_3$	91	76
3	$\text{P}(4\text{-MeOC}_6\text{H}_4)_3$	98	83
4	$\text{P}(2\text{-furyl})_3$	81	69
5	$\text{P}(4\text{-FC}_6\text{H}_4)_3$	100	92
6	$\text{P}(4\text{-FC}_3\text{C}_6\text{H}_4)_3$	100	95 (87 ^[c])
7	$\text{P}(\text{C}_6\text{F}_5)_3$	0	0
8	$\text{P}(2\text{-MeC}_6\text{H}_4)_3$	14	11
9	$\text{P}(2\text{-MeOC}_6\text{H}_4)_3$	9	0
10	PBU_3	0	0
11	PCy_3	3	0
12	$\text{P}(t\text{Bu})_3$	7	6
13 ^[d]	dppb	11	0
14 ^[d]	<i>rac</i> -binap	15	0

[a] The reaction was carried out with isoxazolone **1a** (0.20 mmol), $[\text{Pd}_2(\text{dba})_3]$ (2.5 mol%), and ligand (10 mol%) in 1,4-dioxane (1.3 mL).
 [b] The yields were determined by ^1H NMR spectroscopy of the crude products (see the Supporting Information). [c] Yield of the isolated product. [d] 5 mol % of ligand was used. binap = 2,2'-bis(diphenylphosphanyl)-1,1'-binaphthyl, Cy = cyclohexyl, dba = dibenzylideneacetone, dppb = bis(diphenylphosphanyl)butane.

K. Okamoto, T. Oda, S. Kohigashi and K. Ohe, *Angew. Chem., Int. Ed.*, 2011, **50**, 11470–11473.

3. Recent TM-catalyzed synthesis of heterocycles

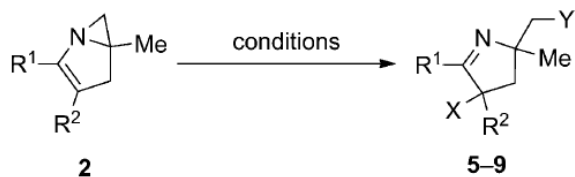
[proposed mechanism]



K. Okamoto, T. Oda, S. Kohigashi and K. Ohe, *Angew. Chem., Int. Ed.*, 2011, **50**, 11470–11473.

3. Recent TM-catalyzed synthesis of heterocycles

Further functionalization of aziridines



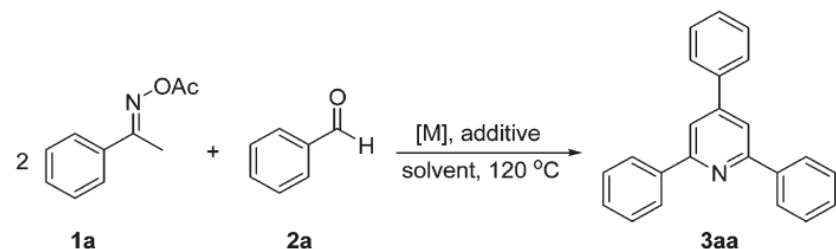
Entry	Aziridine	Pyrroline	Conditions	Yield [%] ^[b]	d.r. ^[c]
1	2a		AcOH	79	1:1
2	2a		Me ₃ SiN ₃ , H ₂ O	62	1:1
3	2a		Br ₂	73	2:1

4	2i		Br ₂	63	> 20:1
5	2a		I ₂	67	3:1
6	2a		H ₂ , 5% Pd/C	54	–
7	2d		H ₂ , 5% Pd/C	61	–

K. Okamoto, T. Oda, S. Kohigashi and K. Ohe, *Angew. Chem., Int. Ed.*, 2011, **50**, 11470–11473.

3. Recent TM-catalyzed synthesis of heterocycles

Cu-catalyzed coupling reaction; oxime acetate and aldehyde



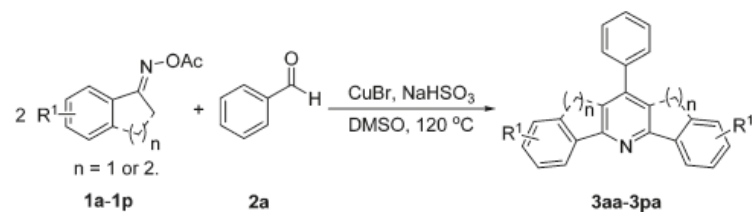
entry	catalyst	additive	solvent	yield (%)
1	CuI	—	DMSO	30
2	CuI	NaHSO ₃	DMSO	79
3	CuBr	NaHSO₃	DMSO	89
4	CuCl	NaHSO ₃	DMSO	77
5	Cu ₂ O	NaHSO ₃	DMSO	61
6	Cu(OAc) ₂	NaHSO ₃	DMSO	60
7	CuBr	NaHSO ₃	NMP	78
8	CuBr	NaHSO ₃	1,4-Dioxane	42
9	CuBr	NaHSO ₃	Toluene	35
10	CuBr	Na ₂ SO ₃	DMSO	32
11	—	NaHSO ₃	DMSO	0
12	Pd ₂ (dba) ₃	NaHSO ₃	DMSO	0

^a Reaction conditions: acetophenone oxime acetate **1a** (0.9 mmol), benzaldehyde **2a** (0.3 mmol), catalyst (10 mol %), and additive (0.9 mmol) in solvent (5 mL) under Ar at 120 °C for 2.5 h.

Z.-H. Ren, Z.-Y. Zhang, B.-Q. Yang, Y.-Y. Wang and Z.-H. Guan, *Org. Lett.*, 2011, **13**, 5394–5397.

3. Recent TM-catalyzed synthesis of heterocycles

Scope



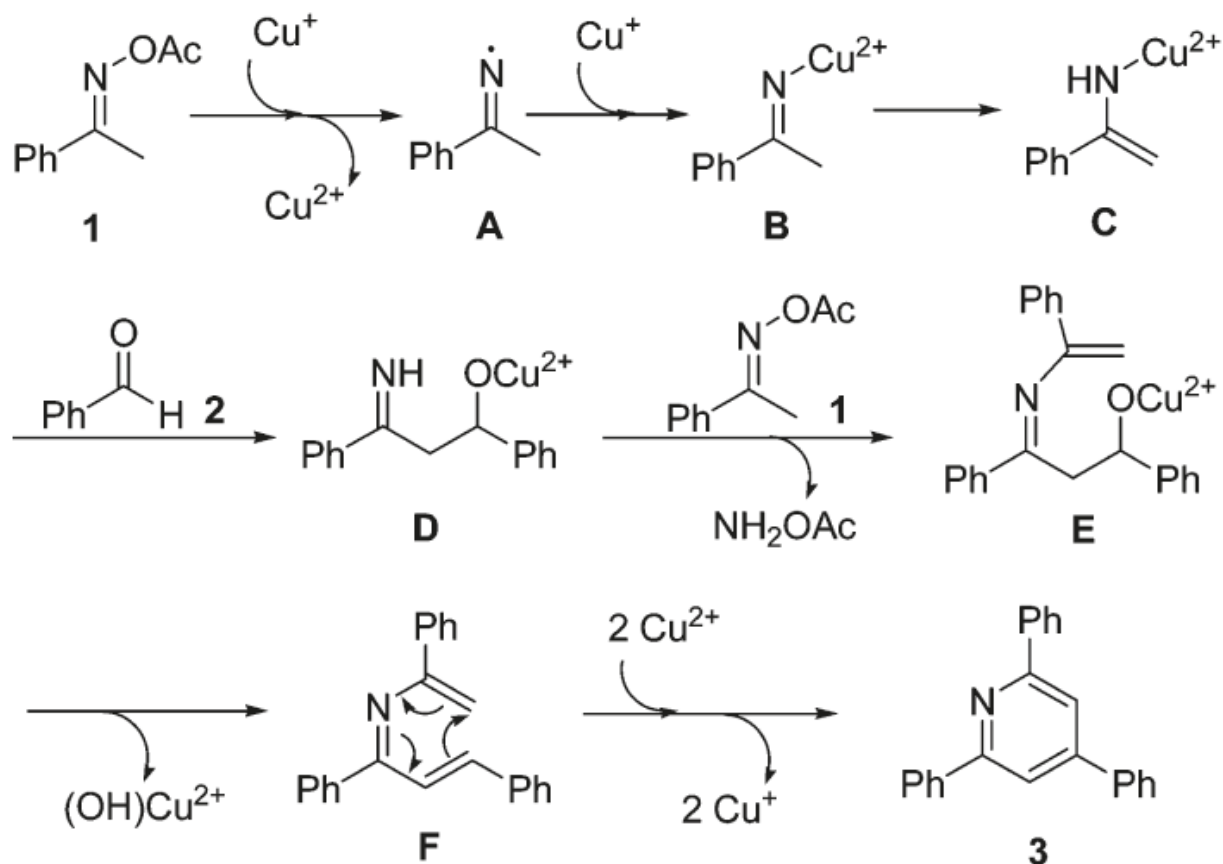
entry	1	product	R ¹	yield (%)
1			H, 3aa	89
2			Me, 3ba	88
3			OMe, 3ca	90
4			F, 3da	80
5			Cl, 3ea	80
6			Br, 3fa	85
7			3ga	90
8			3ha	90
9			3ia	91

10			3ja	89
11			3ka	90
12			3la	78
13			H, 3ma	61
14			OMe, 3na	68
15			H, 3oa	63
16			Cl, 3pa	56

^a Reaction conditions: oxime acetate **1** (0.9 mmol), benzaldehyde **2a** (0.3 mmol), CuBr (10 mol %), and NaHSO₃ (0.9 mmol) in DMSO (5 mL) under Ar at 120 °C for 2.5 h.

3. Recent TM-catalyzed synthesis of heterocycles

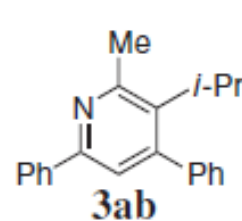
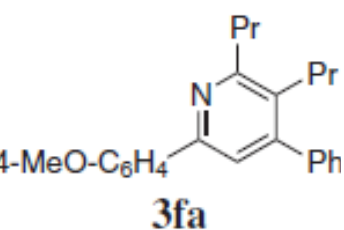
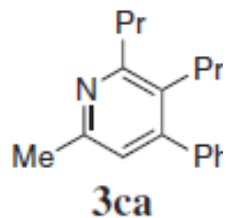
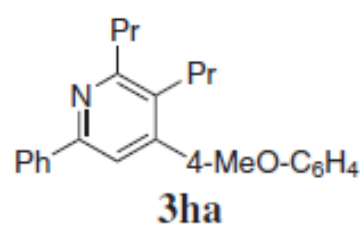
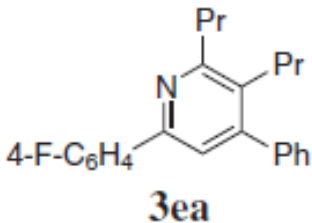
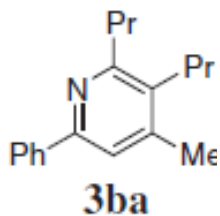
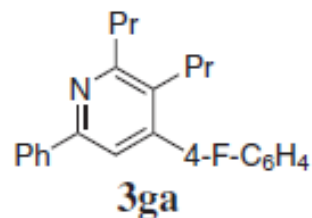
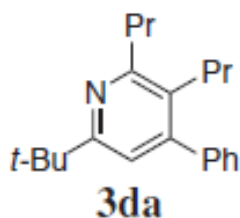
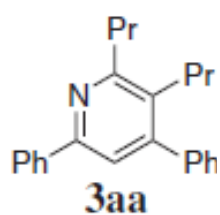
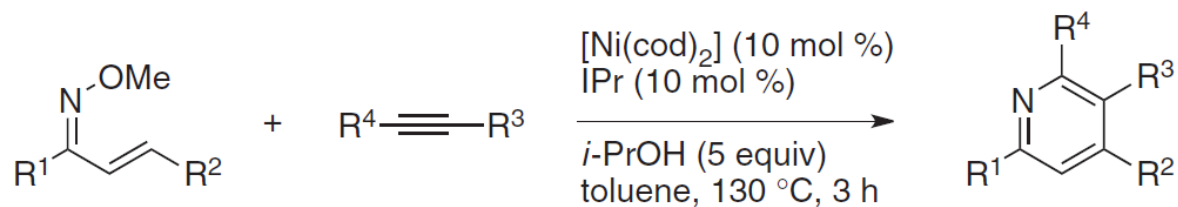
Proposed mechanism



Z.-H. Ren, Z.-Y. Zhang, B.-Q. Yang, Y.-Y. Wang and Z.-H. Guan, *Org. Lett.*, 2011, **13**, 5394–5397.

3. Recent TM-catalyzed synthesis of heterocycles

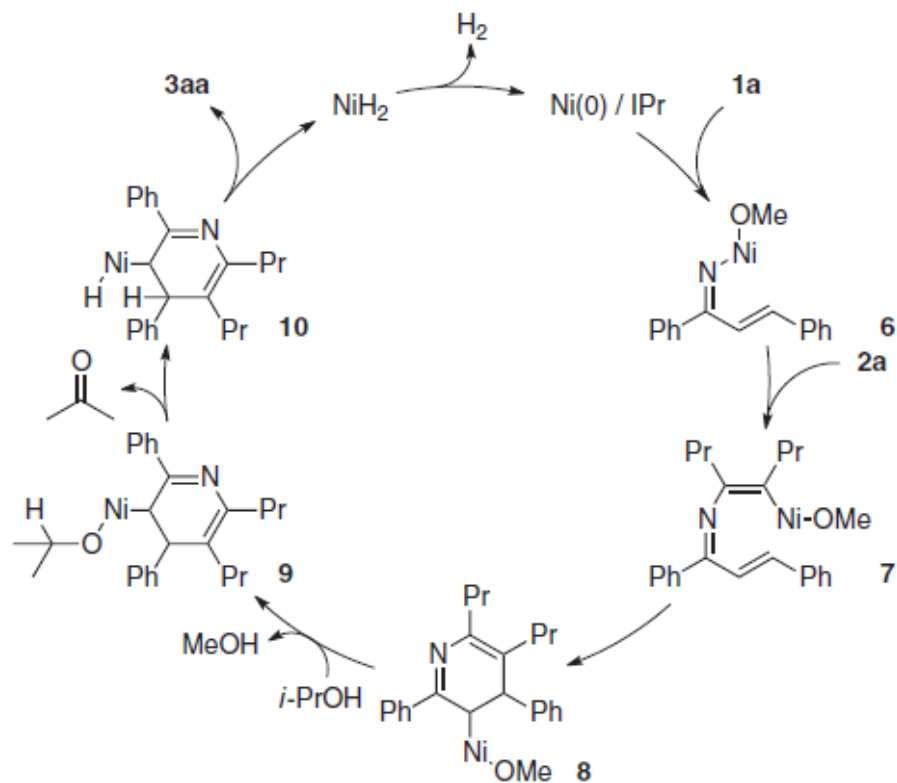
Ni-catalyzed synthesis of pyridines; [4+2]



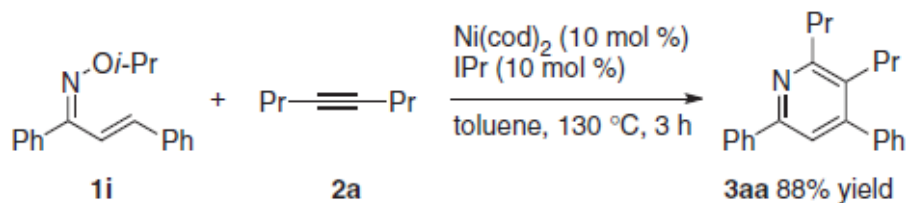
Y. Yoshida, T. Kurahashi and S. Matsubara, *Chem. Lett.*, 2012, **41**, 1498–1499.

3. Recent TM-catalyzed synthesis of heterocycles

Proposed mechanism



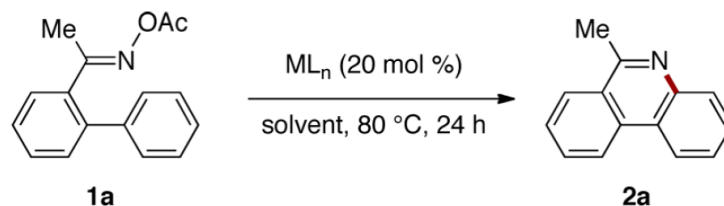
Scheme 1. Plausible reaction pathway.



Y. Yoshida, T. Kurahashi and S. Matsubara, *Chem. Lett.*, 2012, **41**, 1498–1499.

3. Recent TM-catalyzed synthesis of heterocycles

Fe-catalyzed synthesis of phenanthridine



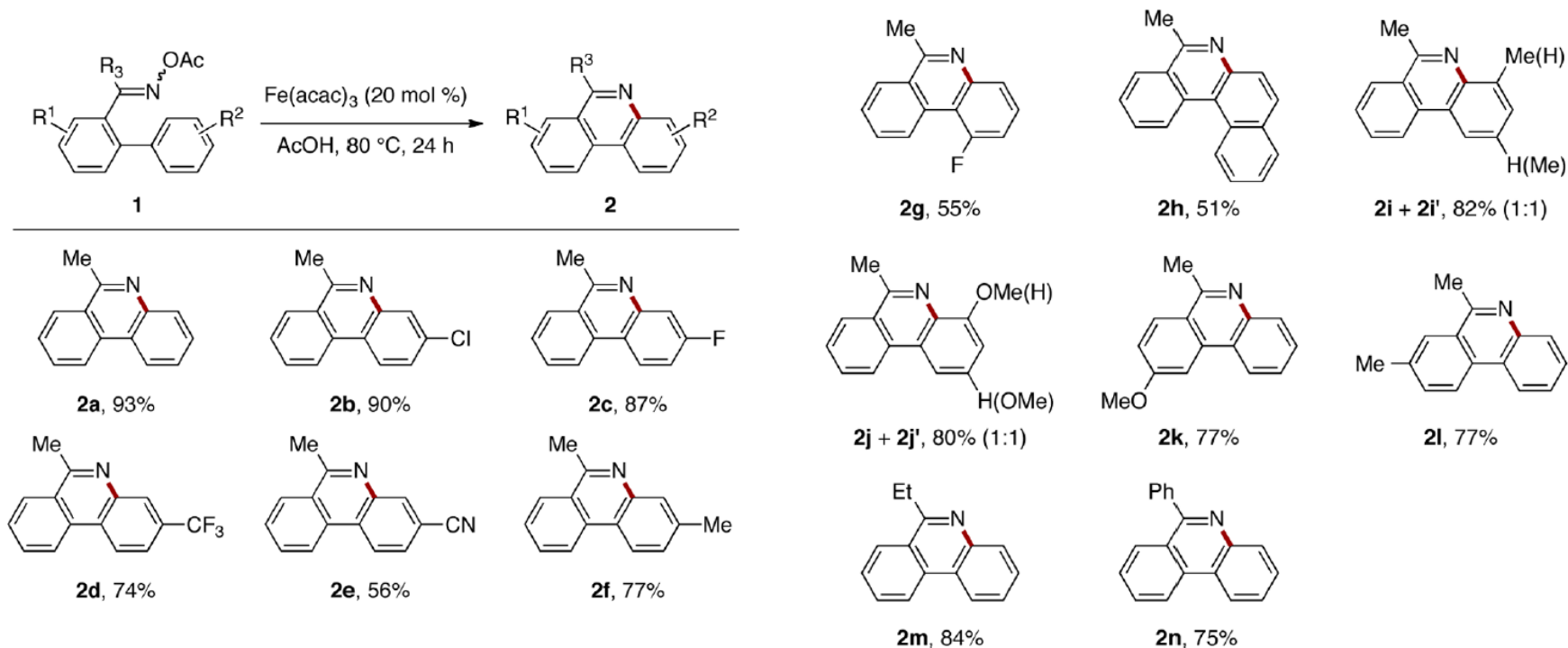
entry	ML_n (mol %)	solvent	temp (°C)	yield (%) ^b
1 ^c	CuI (20)	DMSO	80	40
2	Cu(OAc) ₂ (20)	DMSO	80	55
3	Cu(OAc) ₂ (20)	AcOH	80	70
4	Fe(acac) ₃ (20)	AcOH	80	96 (93) ^c
5	Fe(acac) ₃ (10)	AcOH	80	90
6	Fe(acac) ₃ (20)	AcOH	60	92
7	Fe(acac) ₃ (10)	AcOH	60	51
8	Fe(acac) ₃ (5)	AcOH	60	8
9	FeCl ₃ (20)	AcOH	60	48
10	Mn(acac) ₃ (20)	AcOH	60	0 ^d
11	Co(acac) ₃ (20)	AcOH	60	0 ^d
12	Ni(acac) ₂ (20)	AcOH	60	0 ^d
13	Fe(acac) ₃ (20)	DMSO	60	5
14	Fe(acac) ₃ (20)	dioxane	60	5
15	Fe(acac) ₃ (20)	toluene	60	8

^aThe reaction was performed on a 0.2 mmol scale in 1.2 mL of the solvent. ^bDetermined by ¹H NMR using 1,1,2,2-tetrachloroethane as an internal standard. ^cIsolated yield is shown in the parentheses. ^dDetermined by GC.

3. Recent TM-catalyzed synthesis of heterocycles

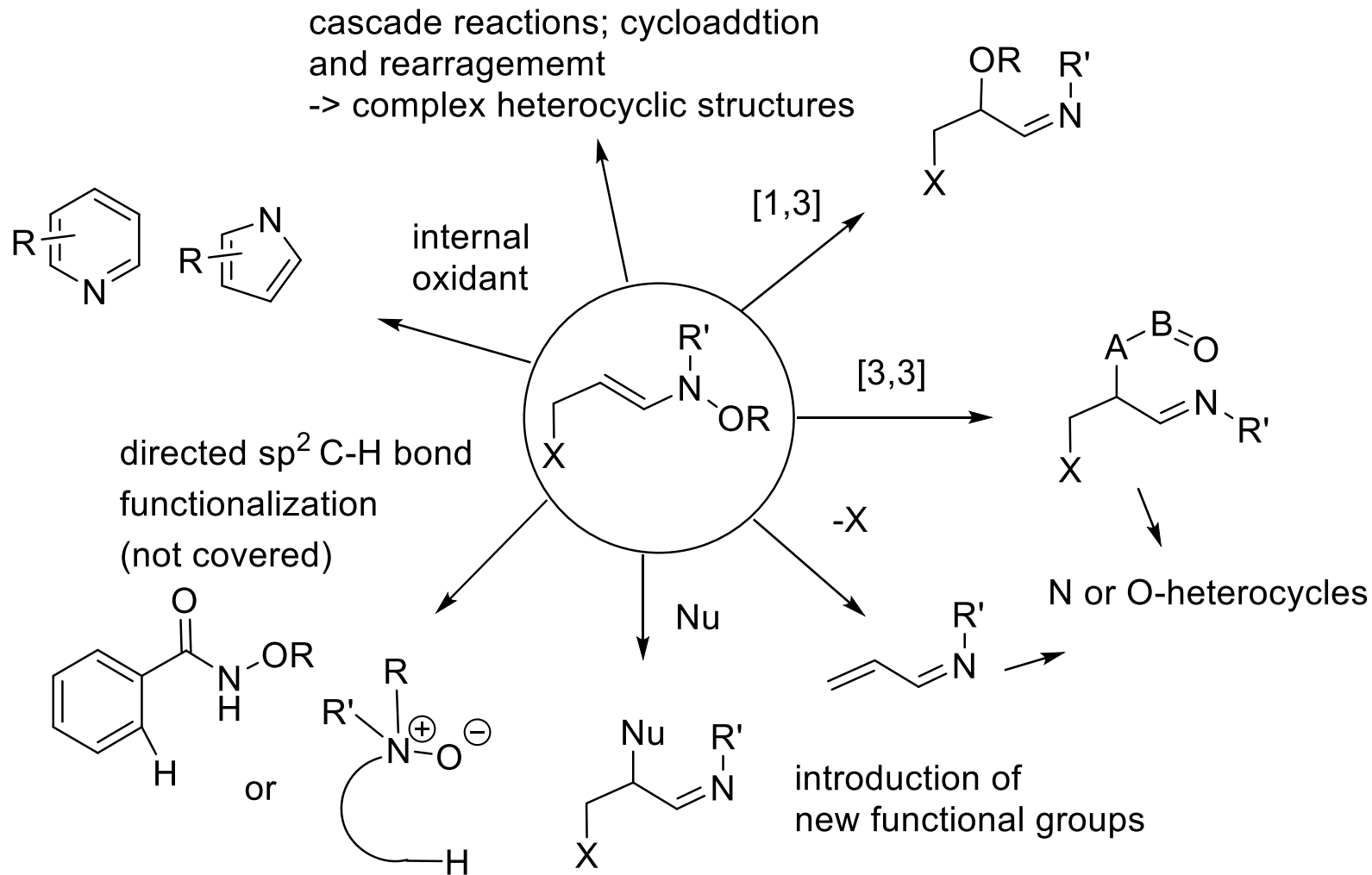
Scope

“aldoxime acetate – unstable in this reaction conditions”



^a Unless otherwise noted, the reaction was performed on a 0.2 mmol scale in 1.2 mL of AcOH. Yields refer to isolated yields.

SUMMARY

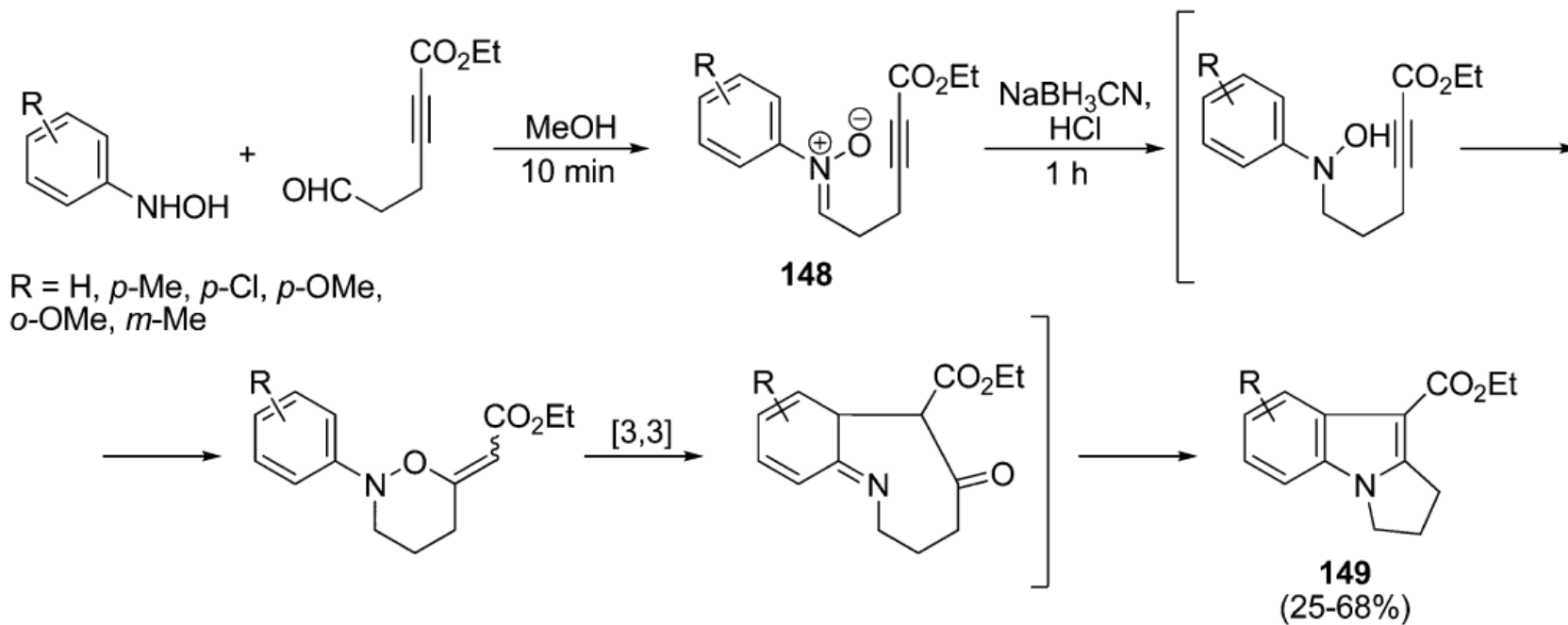


Thank You!

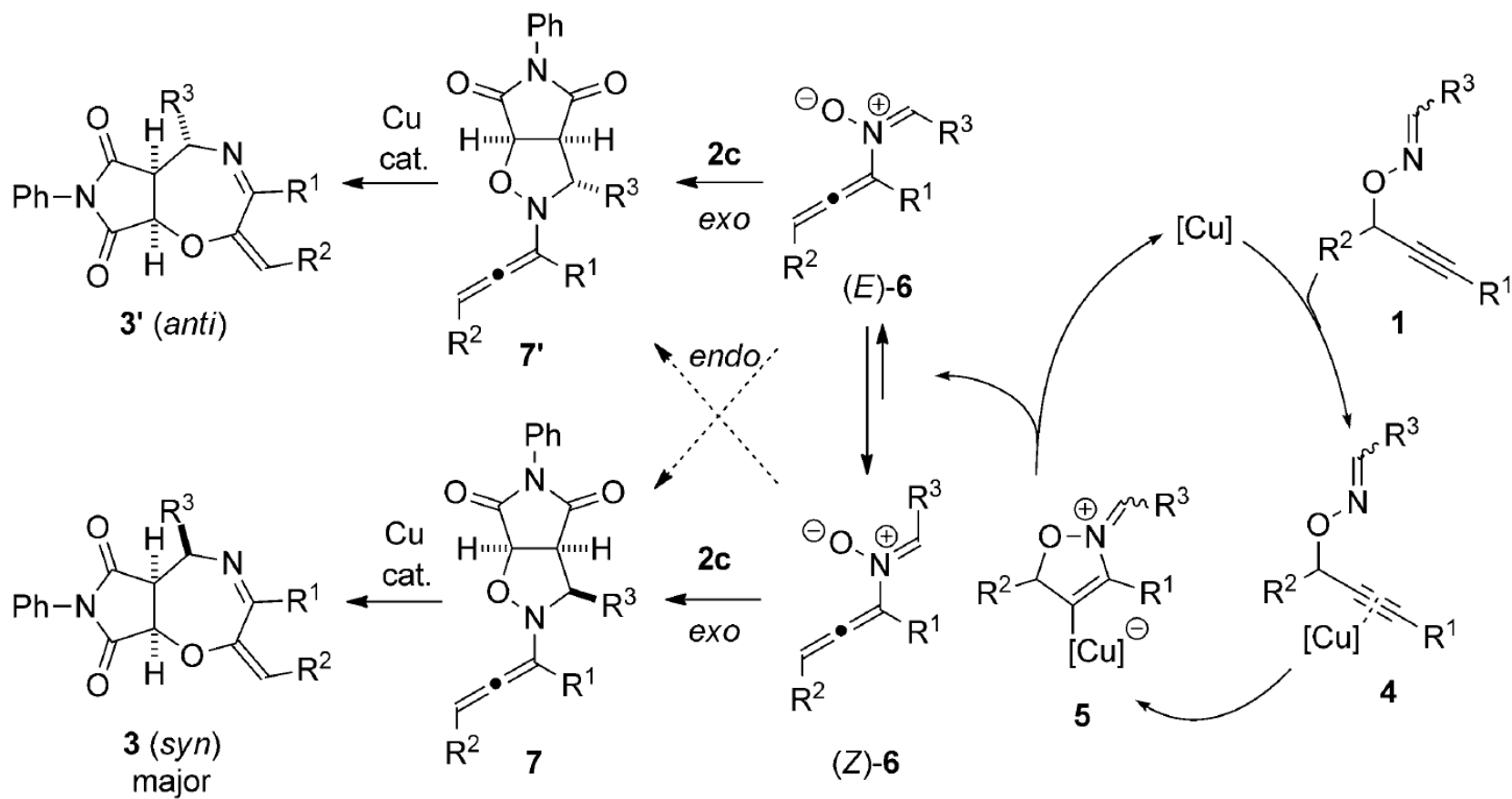
Q&A
You have
Questions
We have
Answers



Quiz 1.



Quiz 2.



exo selective [3+2] cycloaddition is preferred..

Quiz 3.

