Topic

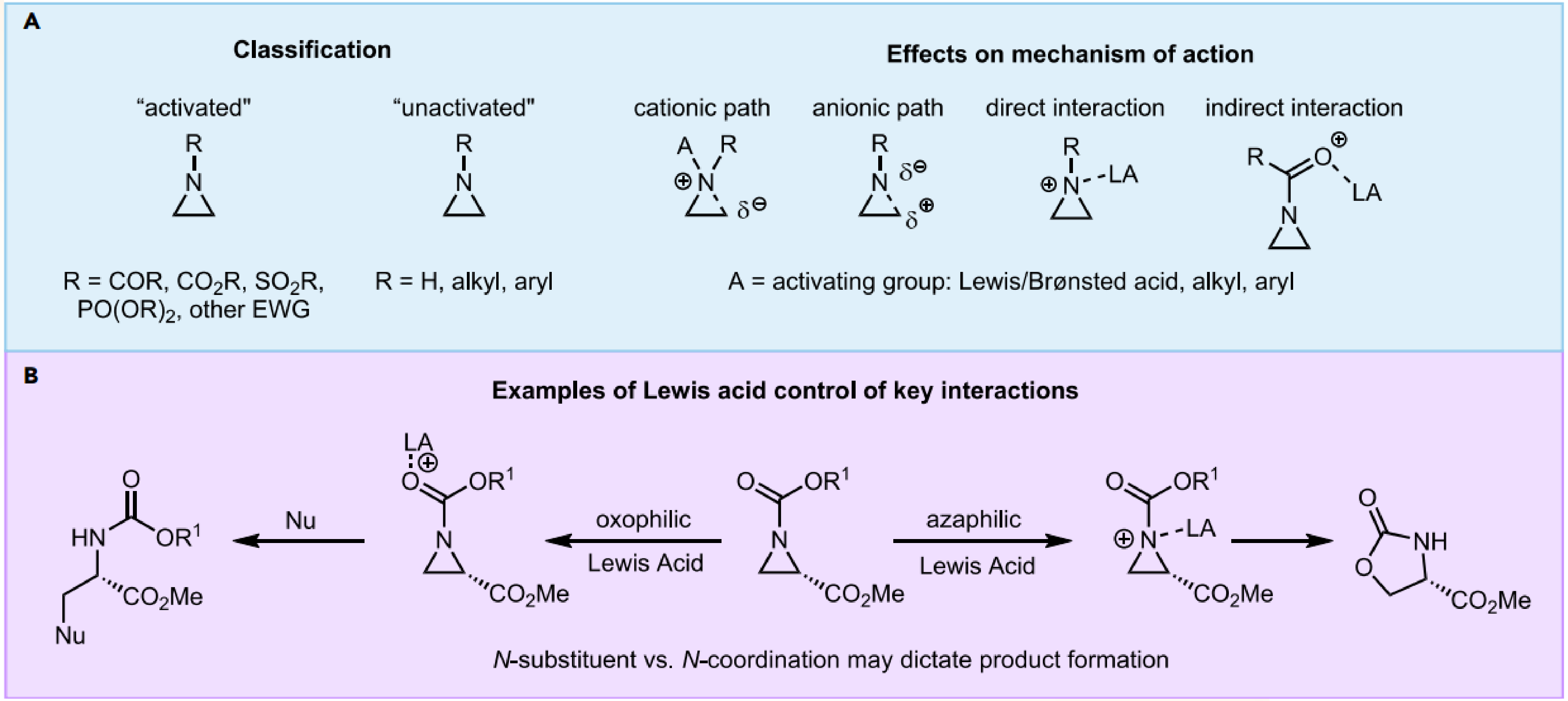
Chemistry Under Strain: Emerging Strategies in Aziridine Reactivity *(2010–Present)*

Lian-Jie Li

2025.03.28

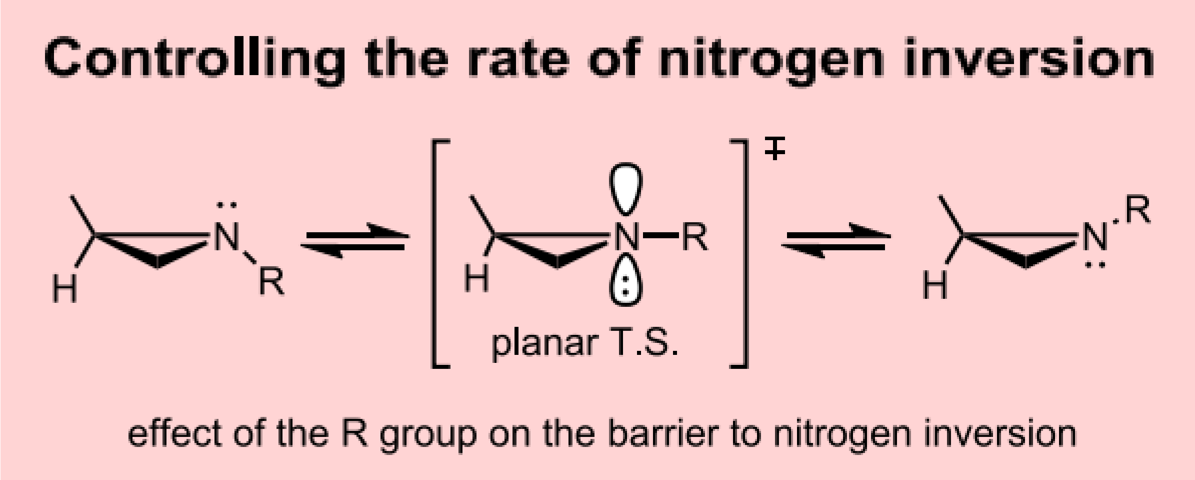
Contents

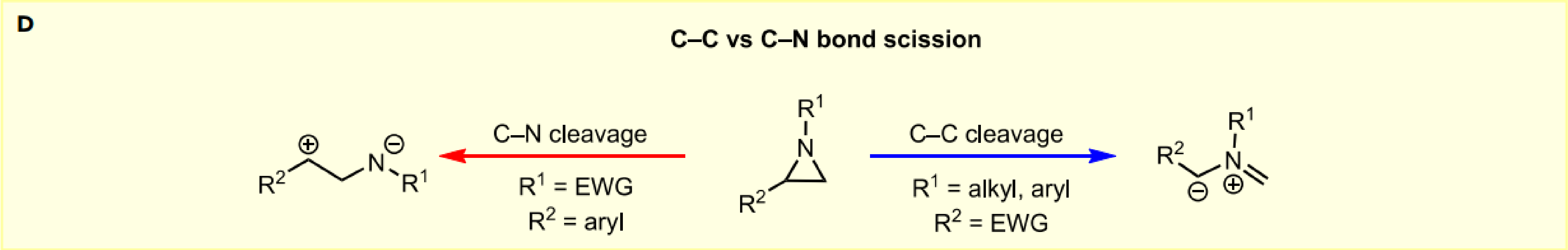
Backgrounds



Schomaker, J. M. *Chem* **2023**, *9*, 1658–1701.

Background





Schomaker, J. M. *Chem* **2023**, *9*, 1658–1701.

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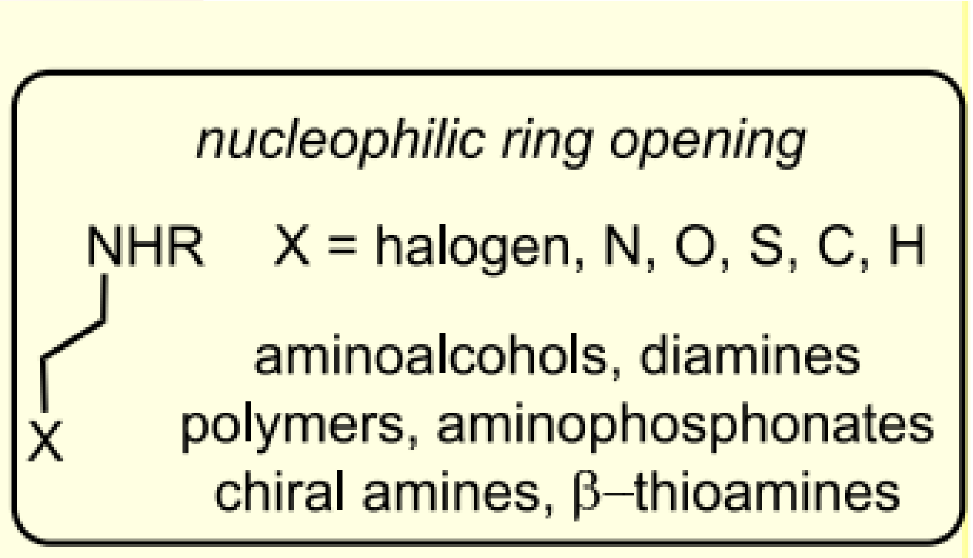
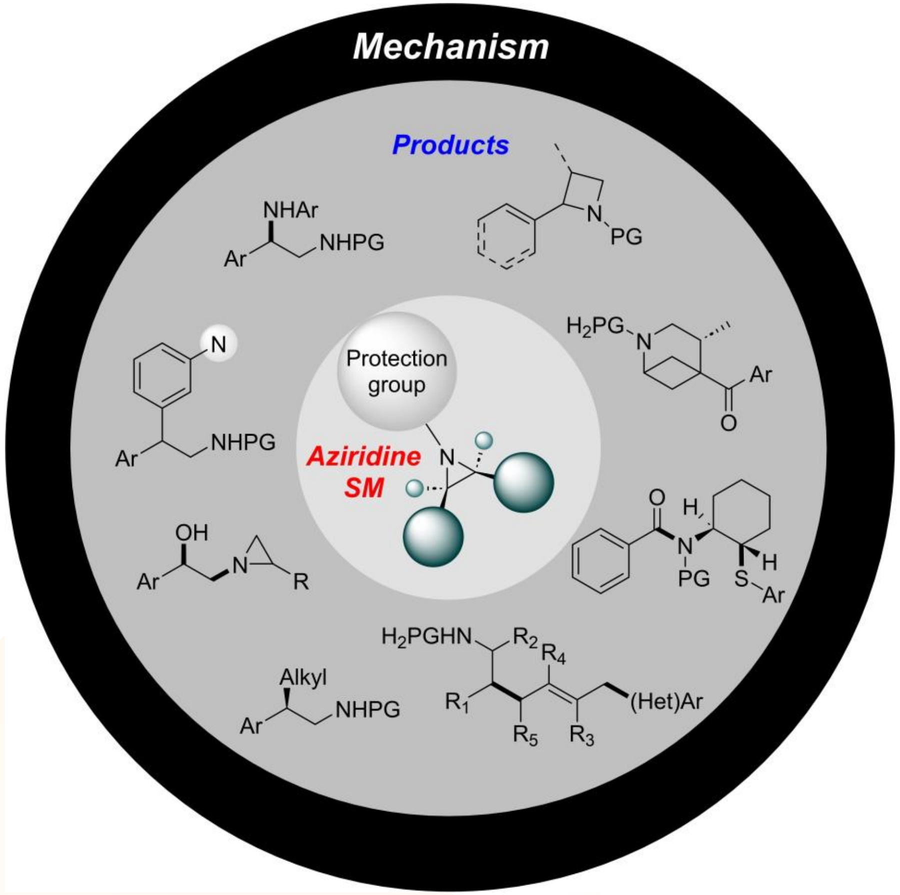
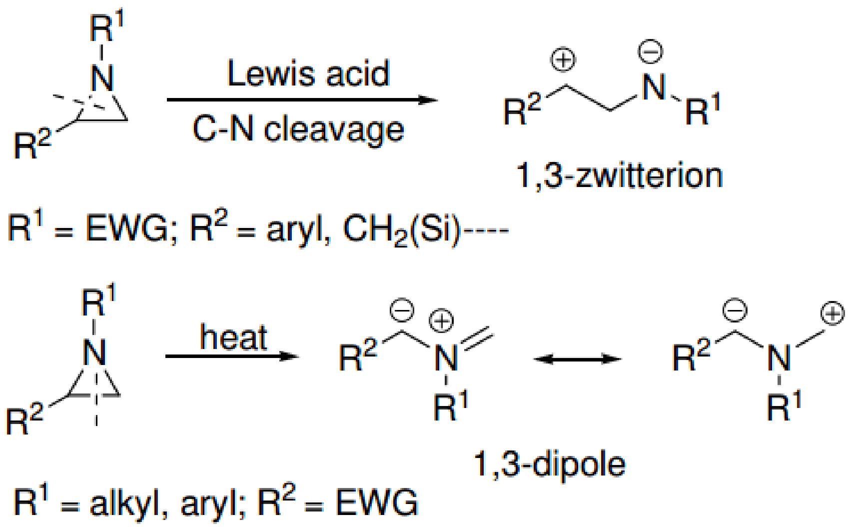
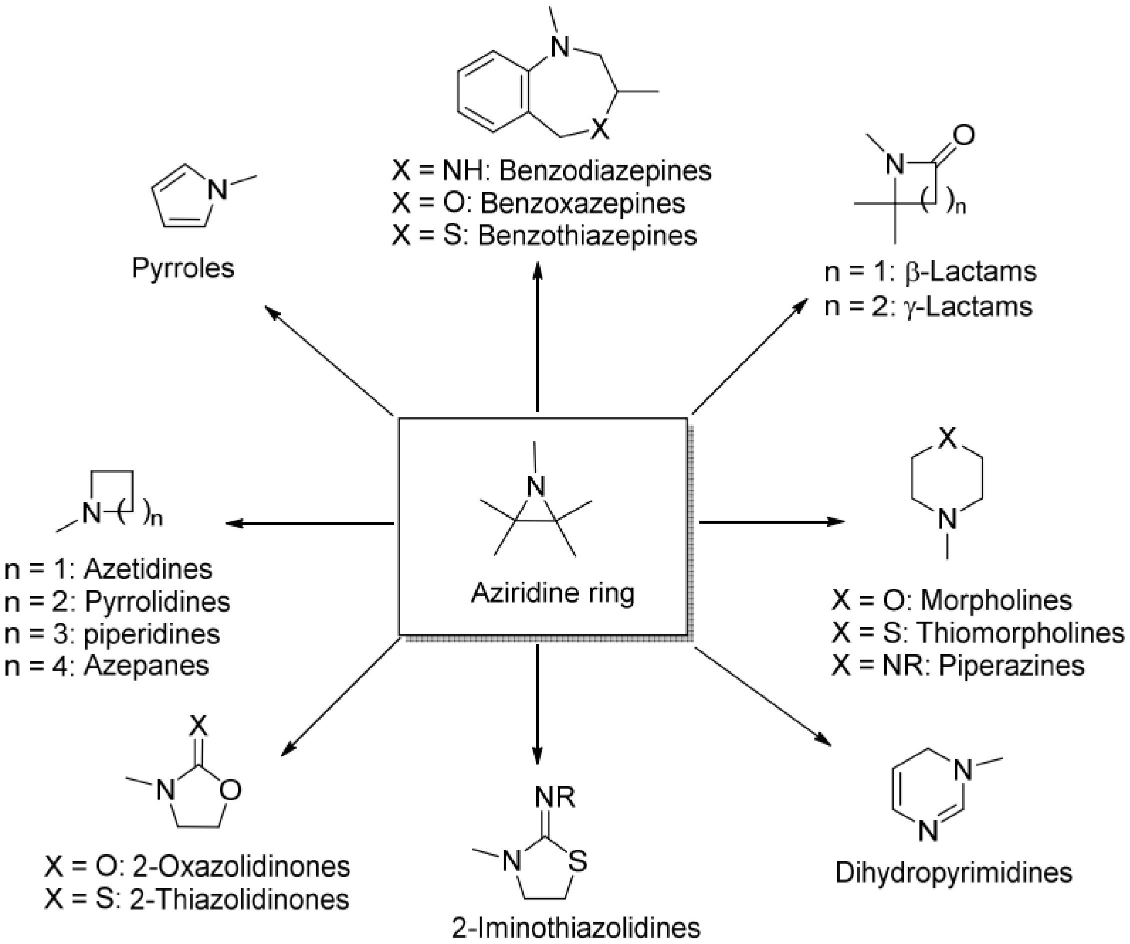




(a) Davis, F. *Synthesis* **2000**, 10, 1347–1365. (b) Hu, X. E. *Tetrahedron* **2004**, *60* , 2701–2743. (c) Ha, H.- J. *Chem. Soc. Rev.* **2012**, *41*, 643–665. (d) Keroletswe, N. *Arkivoc* 2017, 50–113.

Backgrounds





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Ring-Opening Reactions: Pd

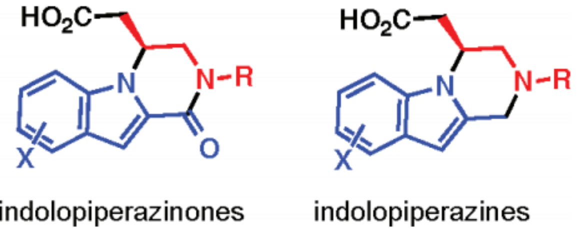


Figure 3. Representative medicinal chemistry lead compounds.

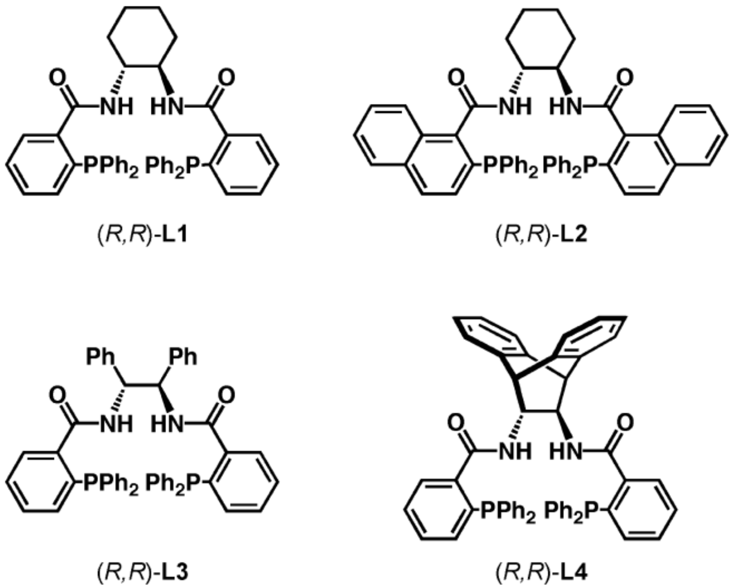
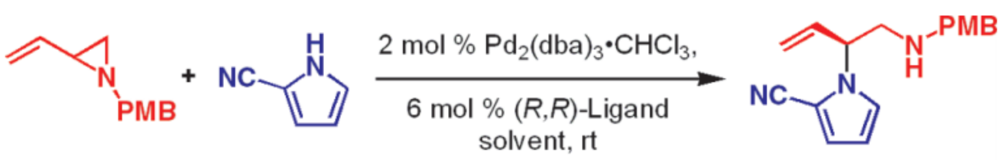


Figure 1. Diphenylphosphino benzoic acid-based ligands.

Table 1. Selected Optimization Conditions[a]



entry	ligand	solvent	% yield[b]	% ee[c]
1	**L1**	DCE	73	61
2	**L2**	DCE	99	89
3	**L3**	DCE	77	72
4	**L4**	DCE	<5	9
5	**L2**	PhMe	50	89
6	**L2**	$PhCF_3$	52	88
7	**L2**	THF	52	89
8	**L2**	DME	44	89
9	**L2**	Dioxane	60	93

[a] All reactions were performed with 1.0 equiv of **2a** and 1.1 equiv of **1a** at ambient temperature at 0.25 M in the designated solvent. [b] Isolated yield. [c] Determined by chiral HPLC.

Trost, B. M.; *J. Am. Chem. Soc.* **2010**, *132* 15800–15807.

Ring-Opening Reactions: Pd

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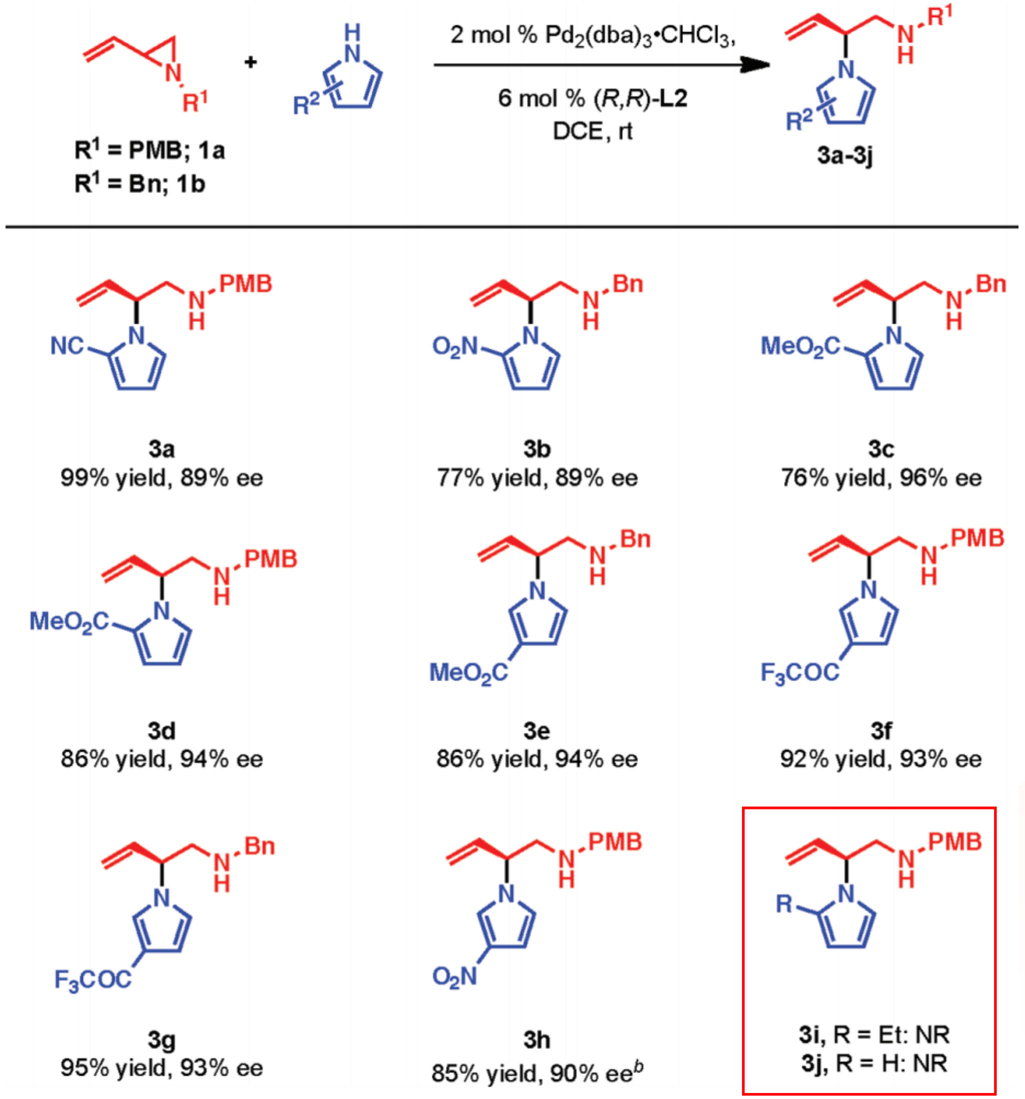
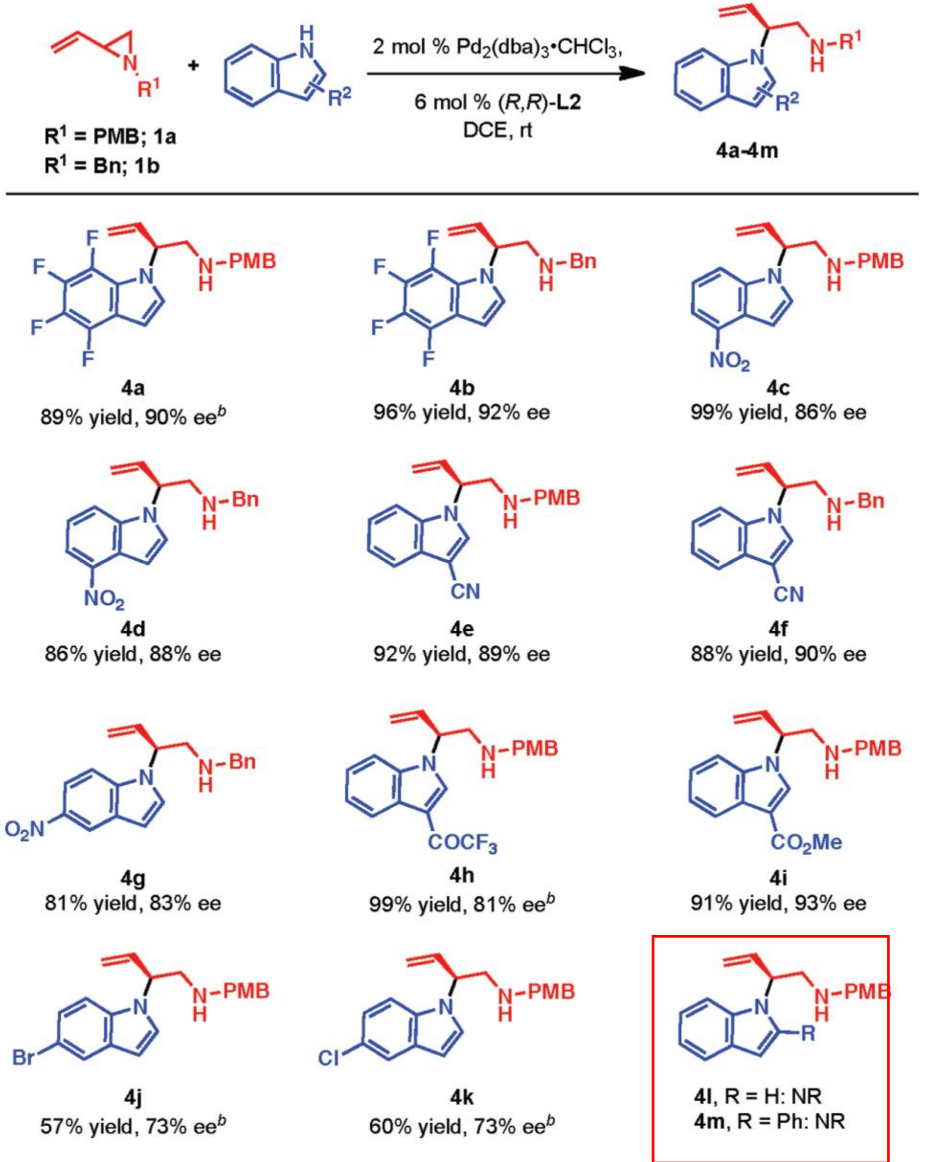
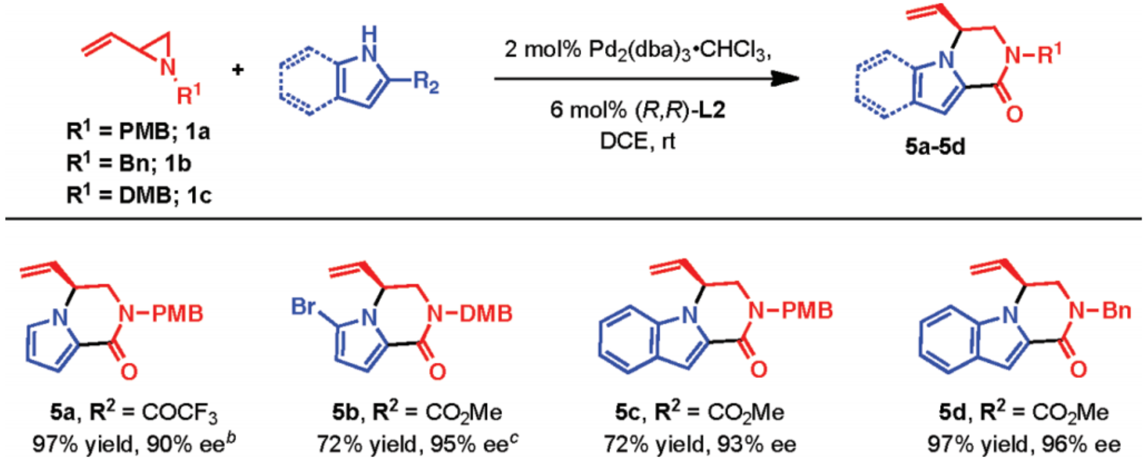
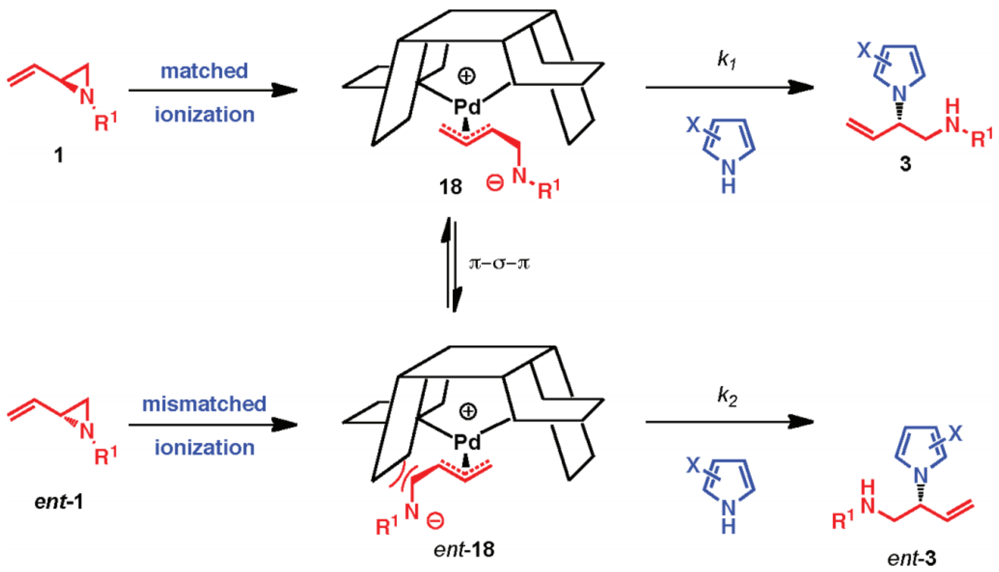




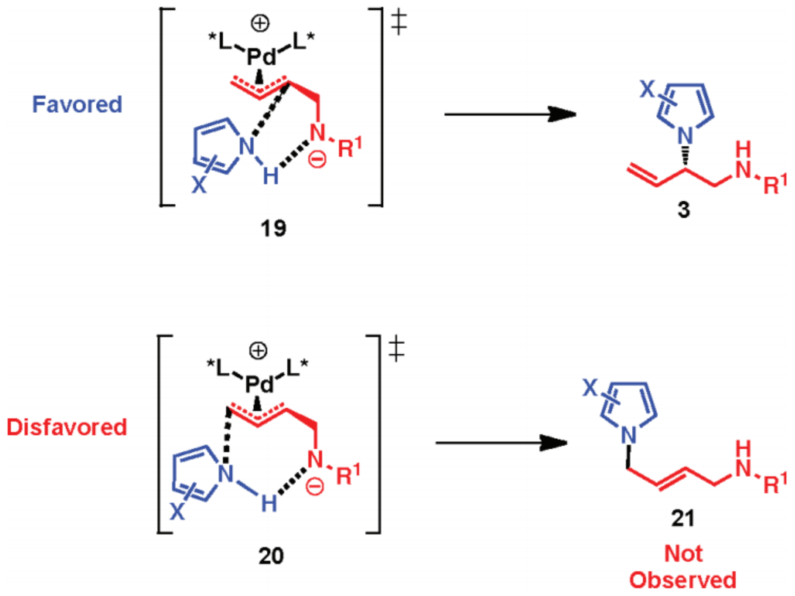
Ring-Opening Reactions: Pd



Scheme 3. Mechanistic Rationale



Scheme 4. Rationale for Observed Regioselectivity



Ring-Opening Reactions: Pd

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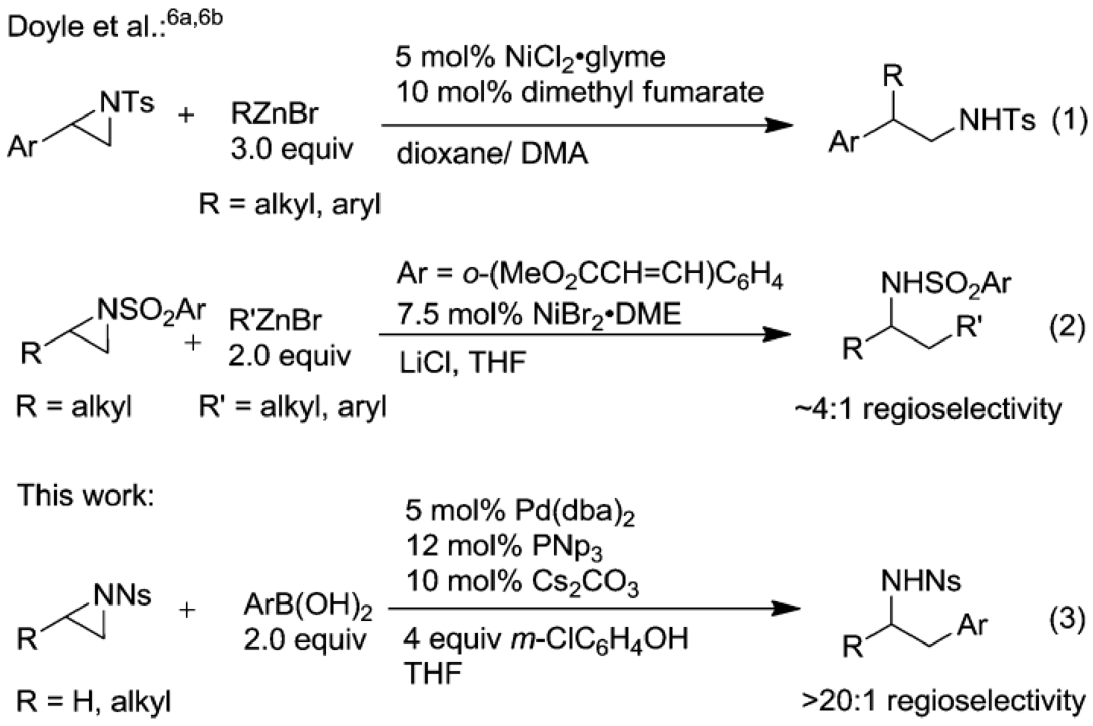
Scheme 1. Previously Reported Aziridine Couplings



Scheme 2. Initial Conditions

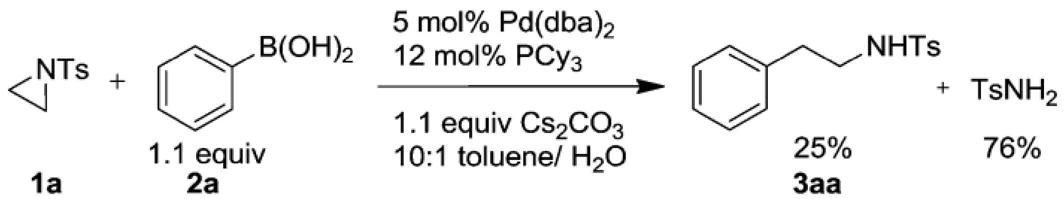
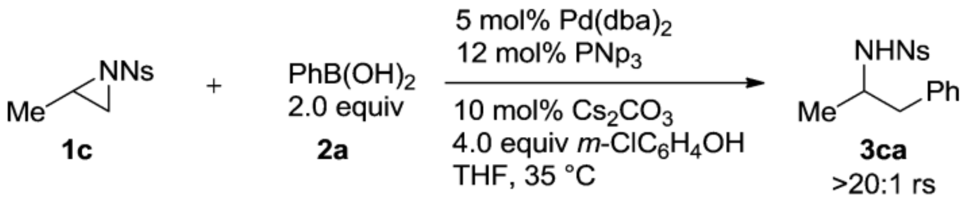


Table 1. Effects of Variation from Optimal Conditions



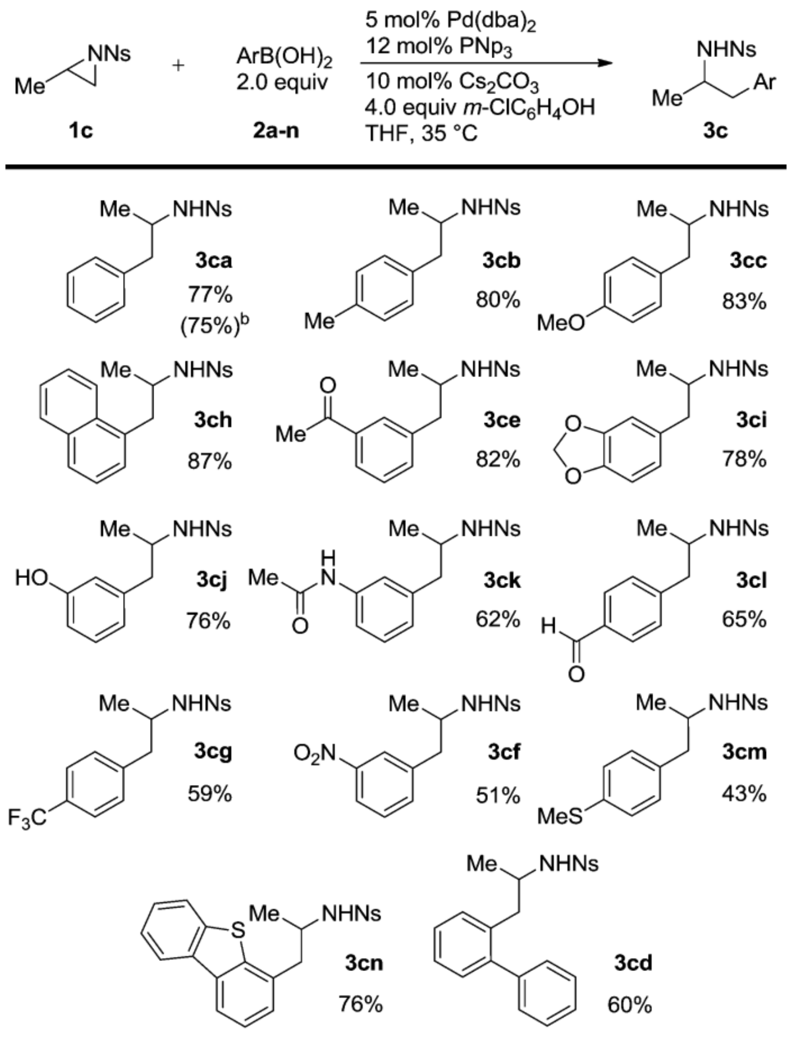
entry	variation from the above conditions	yield, %[a]
1	none	82
2	Ts protecting group on aziridine	32
3	PCy_3 instead of PNp_3	0
4	$P(t\text{-}Bu)_3$ instead of PNp_3	0
5	$P(o\text{-}tol)_3$ instead of PNp_3	44
6	$P(2,4\text{-}Me_2C_6H_3)_3$ instead of PNp_3	63
7	1 equiv of Cs_2CO_3	0
8	no Cs_2CO_3	75
9	K_2CO_3 instead of Cs_2CO_3	24
10	no $m\text{-}ClC_6H_4OH$	19
11	H_2O instead of $m\text{-}ClC_6H_4OH$	53
12	phenol instead of $m\text{-}ClC_6H_4OH$	61

[a] NMR yields using 1,3-dinitrobenzene as internal standard.

Michael, F. E. *J. Am. Chem. Soc.* **2013**, *135*, 18347–18349.

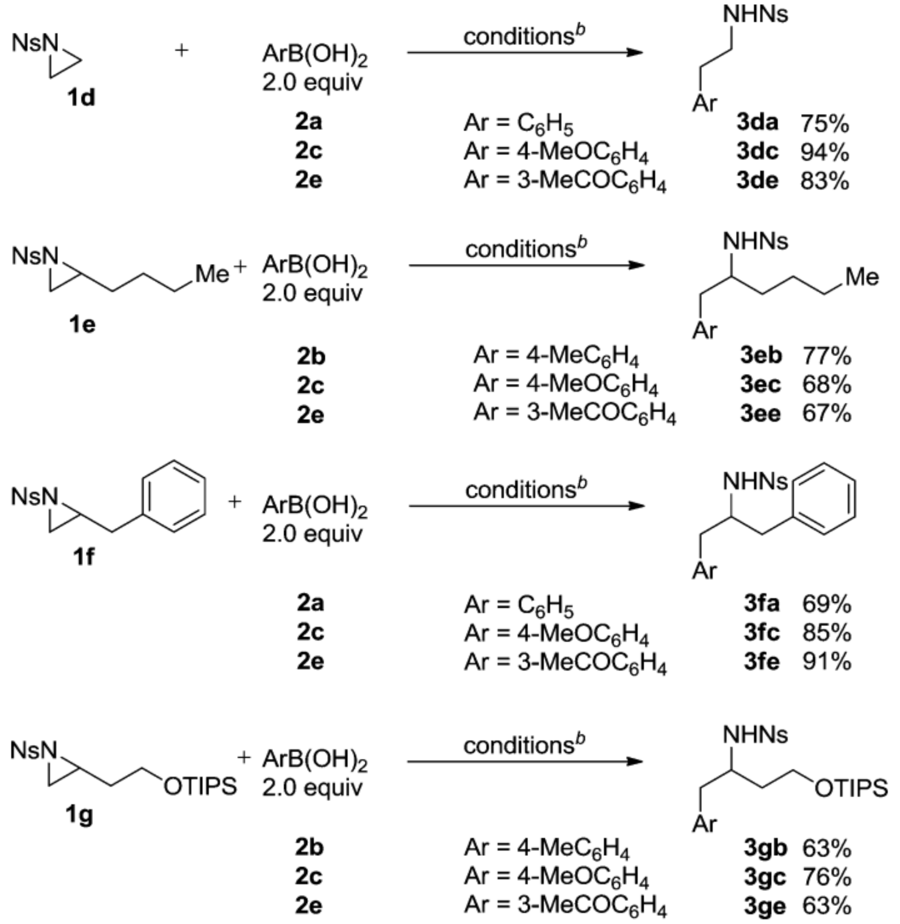
Ring-Opening Reactions: Pd

Table 2. Boronic Acid Scope[a]



[a]Isolated yields. [b]2 mmol scale.

Table 3. Aziridine Scope[a]

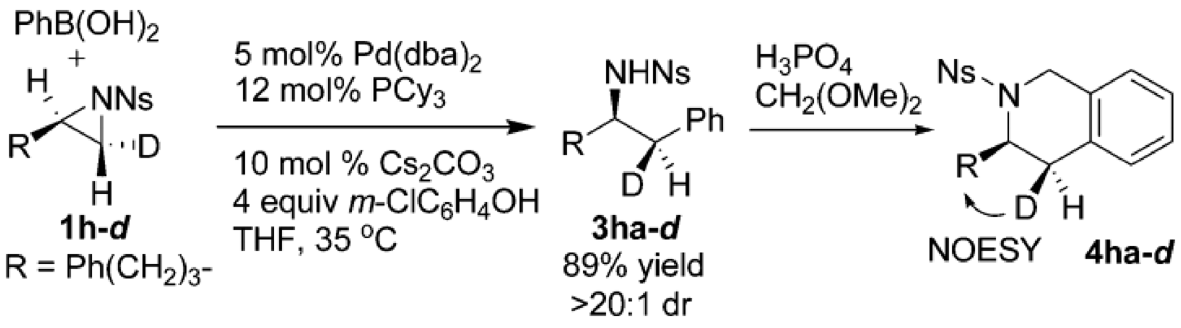


[a]Isolated yields. [b]Conditions: 5 mol % of $Pd(dba)_2$, 12 mol % of PNp_3, 10 mol % of Cs_2CO_3, 4 equiv of *m*-ClC_6H_4OH, THF, 35 °C.

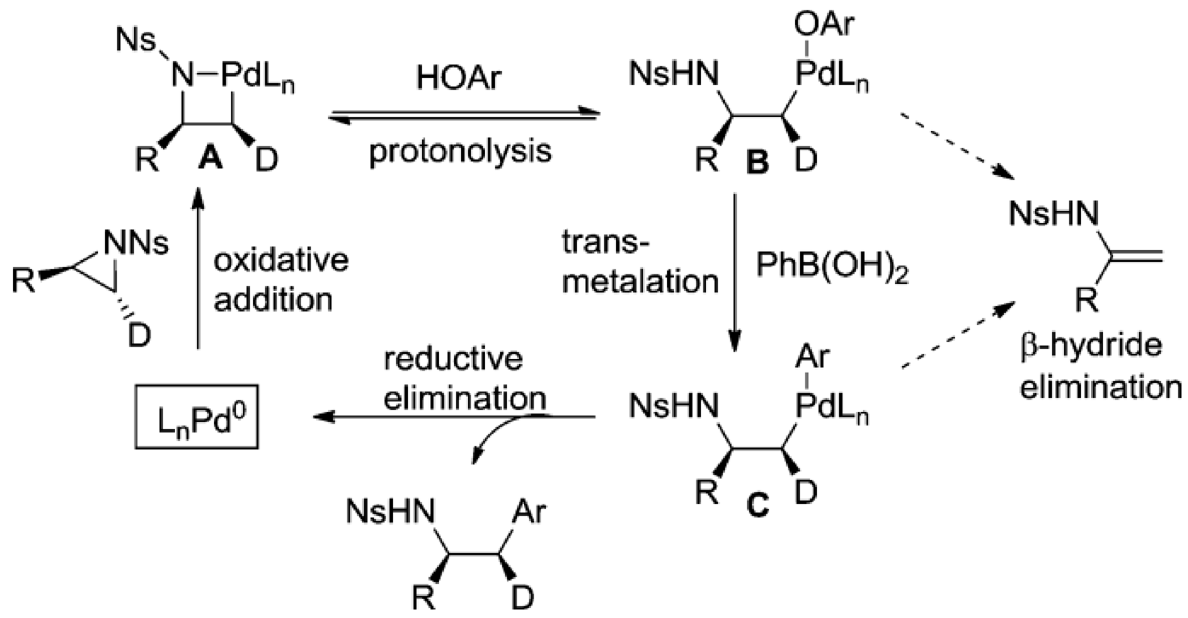
烷基硼酸，2,2-二取代和2,3-二取代氮丙啶均不能反应。

Ring-Opening Reactions: Pd

Scheme 3. Deuterium-Labeled Substrate Coupling

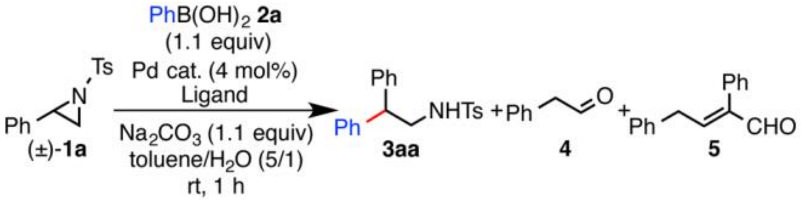


Scheme 4. Proposed Catalytic Cycle

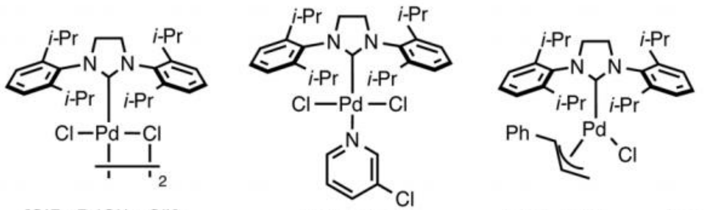


Ring-Opening Reactions: Pd

Table 1. Effect of Pd Catalysts in the Cross-Coupling[a]



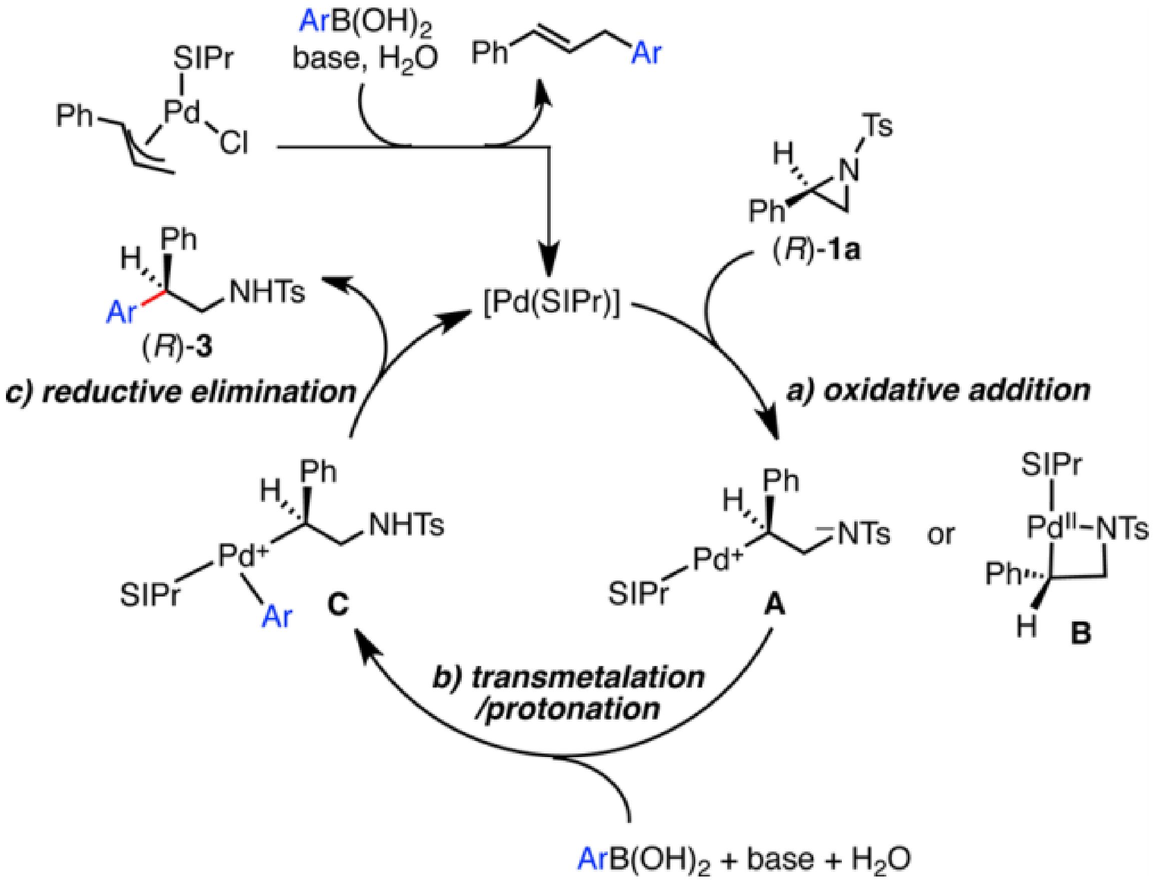
entry	Pd cat.	ligand (mol%)	yield (%)[b]		
			3aa	4	5
1	$Pd(PPh_3)_4$	–	0	28	1
2	$Pd(PCy_3)_2$	–	6	35	2
3	$Pd(dba)_2$	$P(t\text{-}Bu)_3$ (8)	0	24	1
4	$Pd(dba)_2$	IPr (4)	17	0	0
5	$Pd(dba)_2$	SIPr (4)	21	0	0
6	$Pd(dba)_2$	SIMes (4)	3	0	0
7	$[SIPr\text{-}PdCl(\mu\text{-}Cl)]_2$	–	81	0	0
8	PEPPSI-SIPr	–	23	0	0
9	[SIPr-Pd(cinnamyl)Cl]	–	96 (93)[c]	0	0



$[SIPr\text{-}PdCl(\mu\text{-}Cl)]_2$ PEPPSI-SIPr [SIPr-Pd(cinnamyl)Cl]

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.22 mmol), Pd catalyst (8 μmol), ligand, and Na_2CO_3 (0.22 mmol) in toluene/H_2O (1.2 mL, v/v 5:1) at room temperature under N_2 atmosphere for 1 h. [b]Determined with GC. [c]Isolated yield.

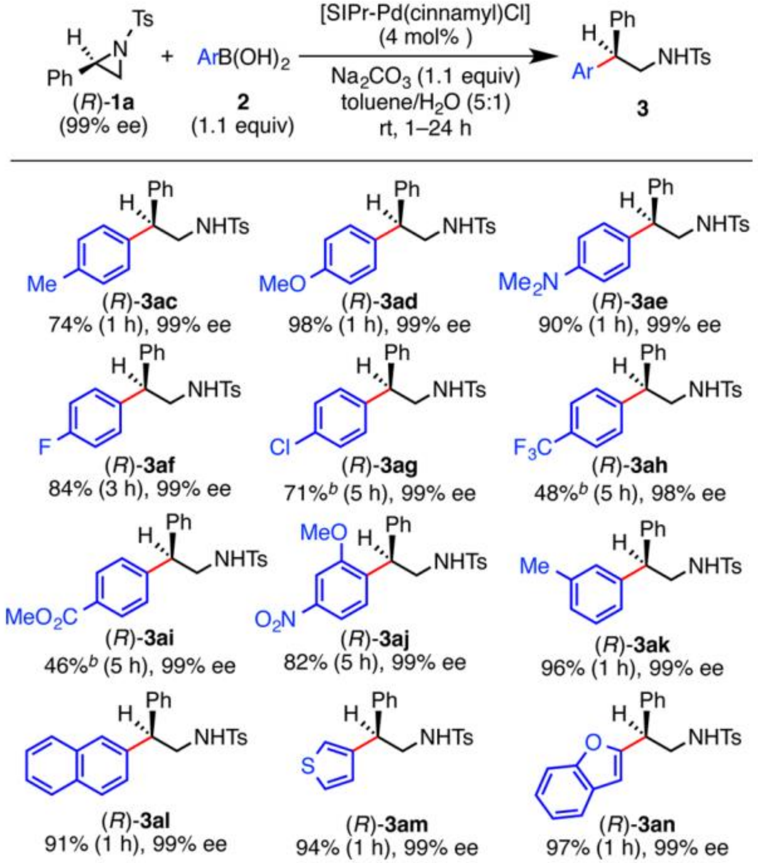
Scheme 3. A Plausible Catalytic Cycle



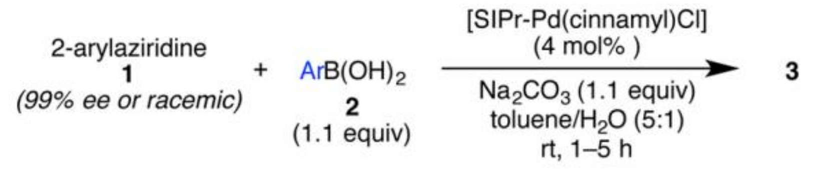
Minakata, S. *J. Am. Chem. Soc.* **2014**, *136*, 8544–8547.

Ring-Opening Reactions: Pd

Table 2. Pd-Catalyzed Enantiospecific Cross-Coupling of (*R*)-1a with $ArB(OH)_2$[a]

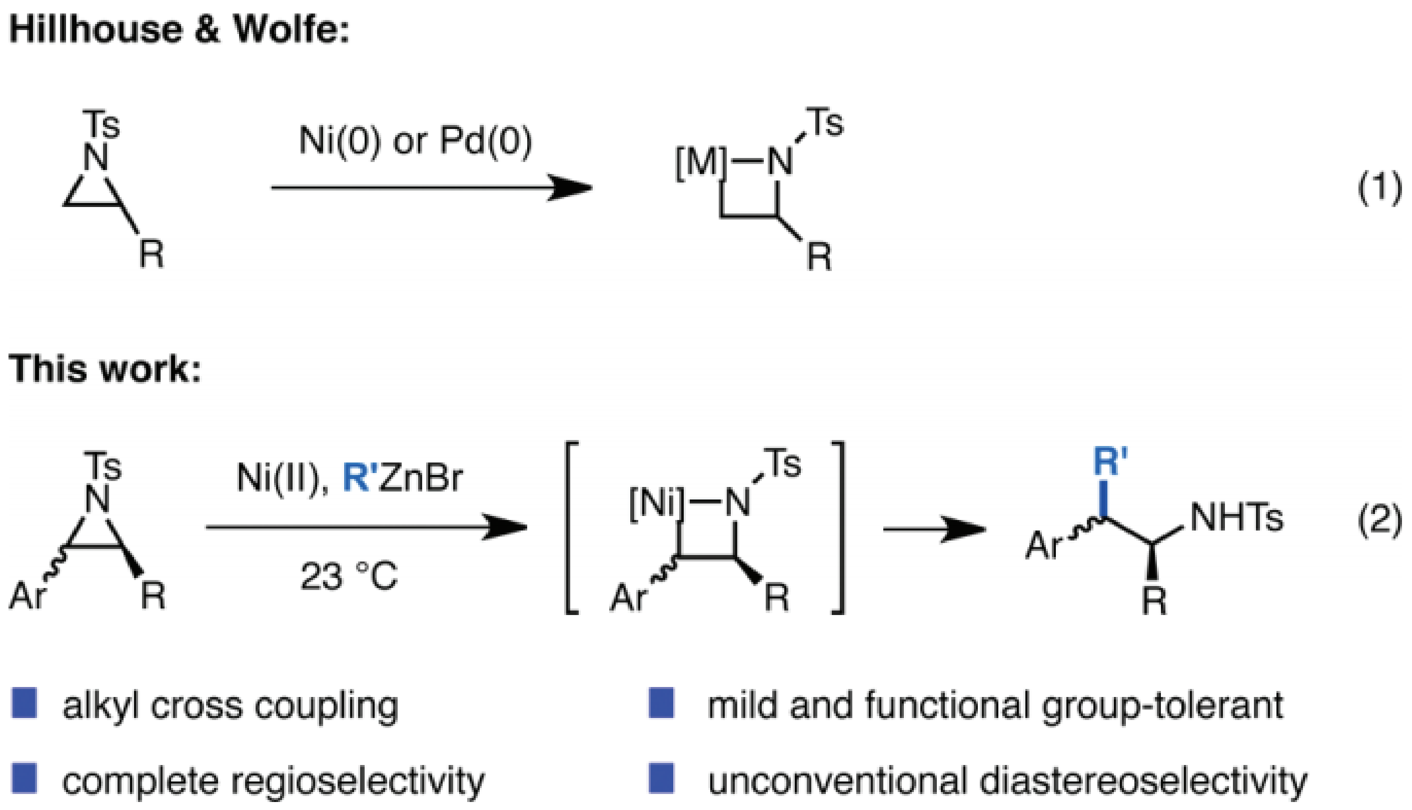


[a]Reaction Conditions: (*R*)-**1a** (1.0 mmol), **2** (1.1 mmol), and Na_2CO_3 (1.1 mmol) in toluene/H_2O (6 mL, *v*/*v* 5:1) at room temperature; enantiomeric excess (ee) was determined by chiral HPLC analysis. [b][SIPr-Pd(allyl)Cl] was used as an alternative catalyst.



entry	aziridine **1**	product **3**	time (h)	yield (%)	ee (%)
1	(*R*)-**1i** (99% ee)	(*S*)-**3ai**	2	91	99
2	(*S*)-**1g** (99% ee)	(*R*)-**3ag**	3	75	99
3	(*S*)-**1o** (99% ee)	(*R*)-**3ao**	1	85	99
4	(*S*)-**1c** (99% ee)	(*R*)-**3ac**	1	87	99

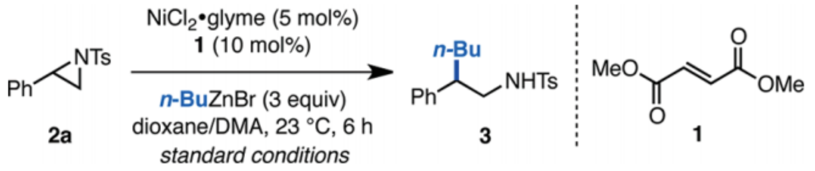
Ring-Opening Reactions: Ni



Doyle, A. G. *J. Am. Chem. Soc.* **2012**, *134*, 9541–9544.

Ring-Opening Reactions: Ni

Table 1. Evaluation of Reaction Conditions



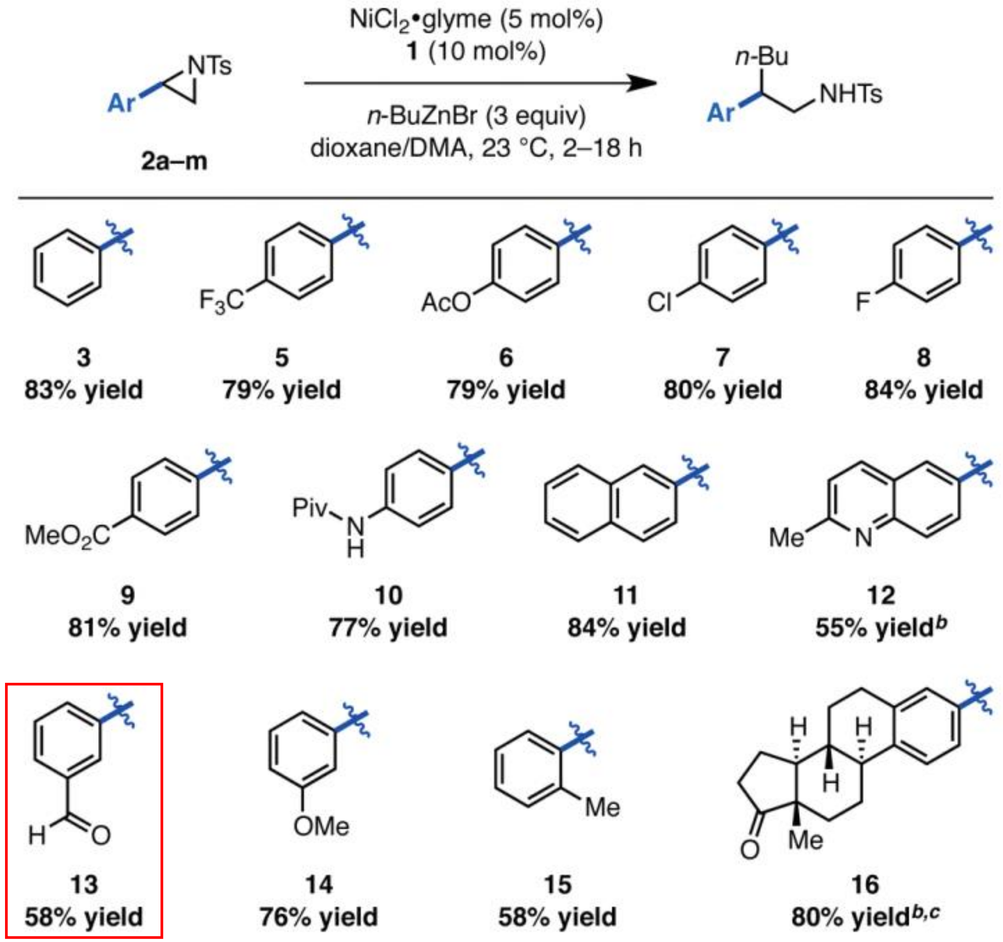
entry	conditions	yield[a] (%)	conv[a,b] (%)
1	standard conditions	71	>99
2	no $NiCl_2$·glyme	<2	7
3	$Ni(cod)_2$ instead of $NiCl_2$·glyme	46	>99
4	no dimethyl fumarate (**1**)	4	26
5	10% PPh_3, PCy_3, BINAP, or bpy instead of **1**	<2	12–25
6	10% 4-fluorostyrene instead of **1**	5	47
7	10% maleic anhydride instead of **1**	8	62
8	10% dimethyl maleate instead of **1**	69	>99
9	with 10% bipyridine and 10% **1**	<2	10

[a]Determined by HPLC, 0.05 mmol scale. [b]*N*-Tosyl-2-phenylethylamine (reduced product) was the major byproduct.

富马酸二甲酯强吸电子配体加速二烷基Ni中间体的还原消除。

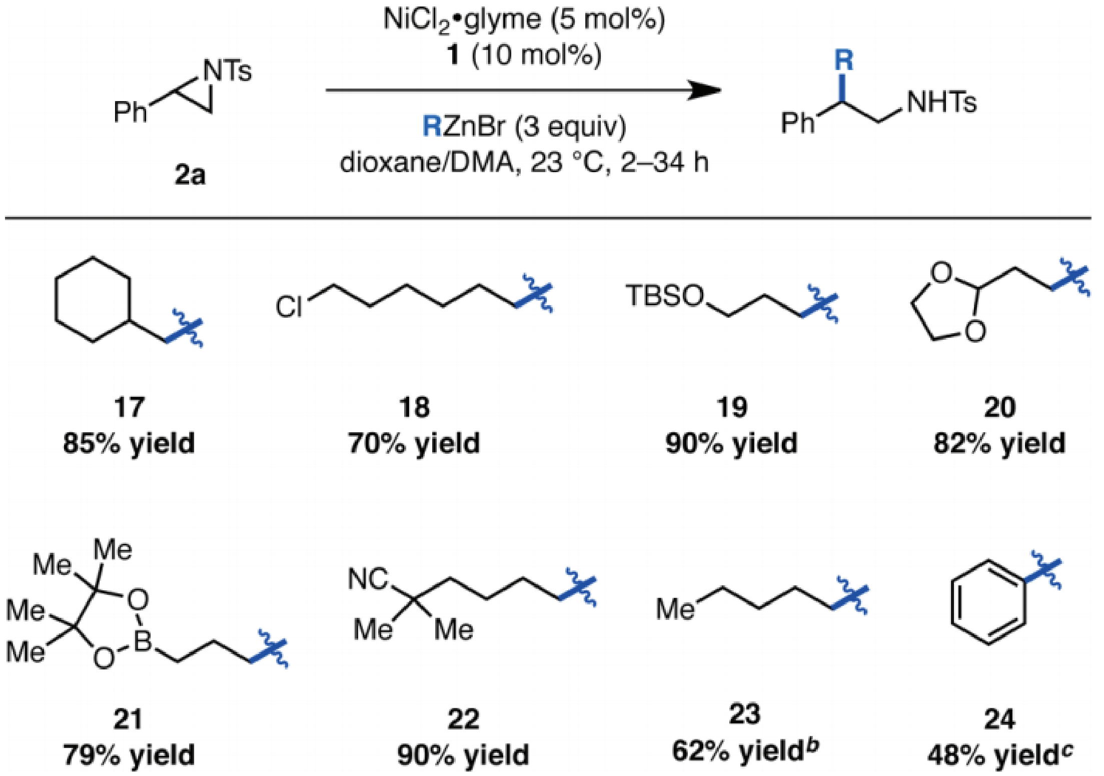
Ring-Opening Reactions: Ni

Table 2. Scope of Styrenyl Aziridines[a]



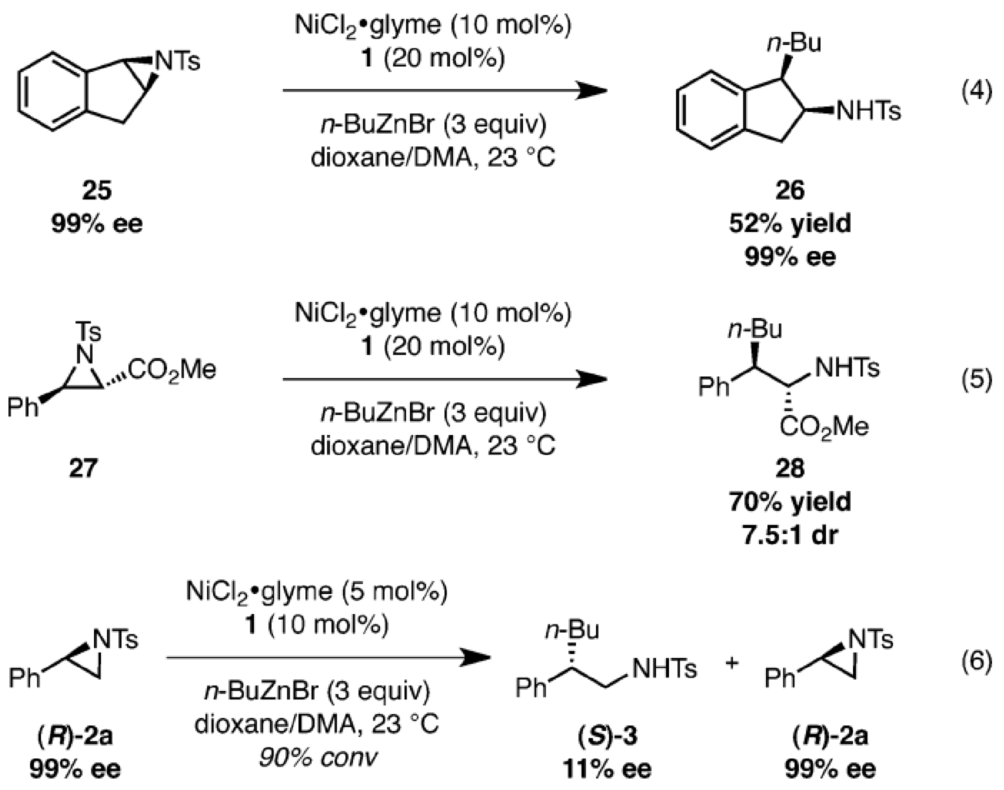
[a]Yields are the average of two runs, 0.50 mmol scale. [b]One run, 0.15 mmol scale. [c]5.3:1 dr (unassigned), see SI for details.

Table 3. Scope of Organozinc Reagents[a]

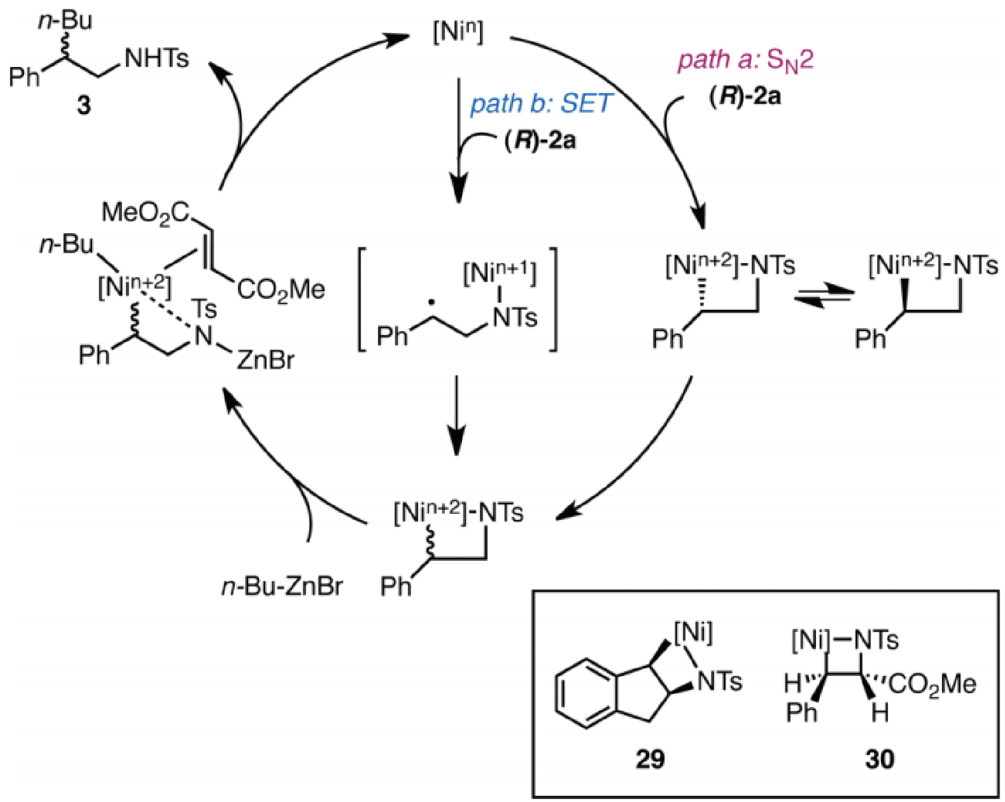


[a]Yields are the average of two runs, 0.50 mmol scale. [b]n-PentylZnI. [c]PhZnBr inTHF.

Ring-Opening Reactions: Ni



Scheme 1. Proposed Catalytic Cycle



Ring-Opening Reactions: Ni

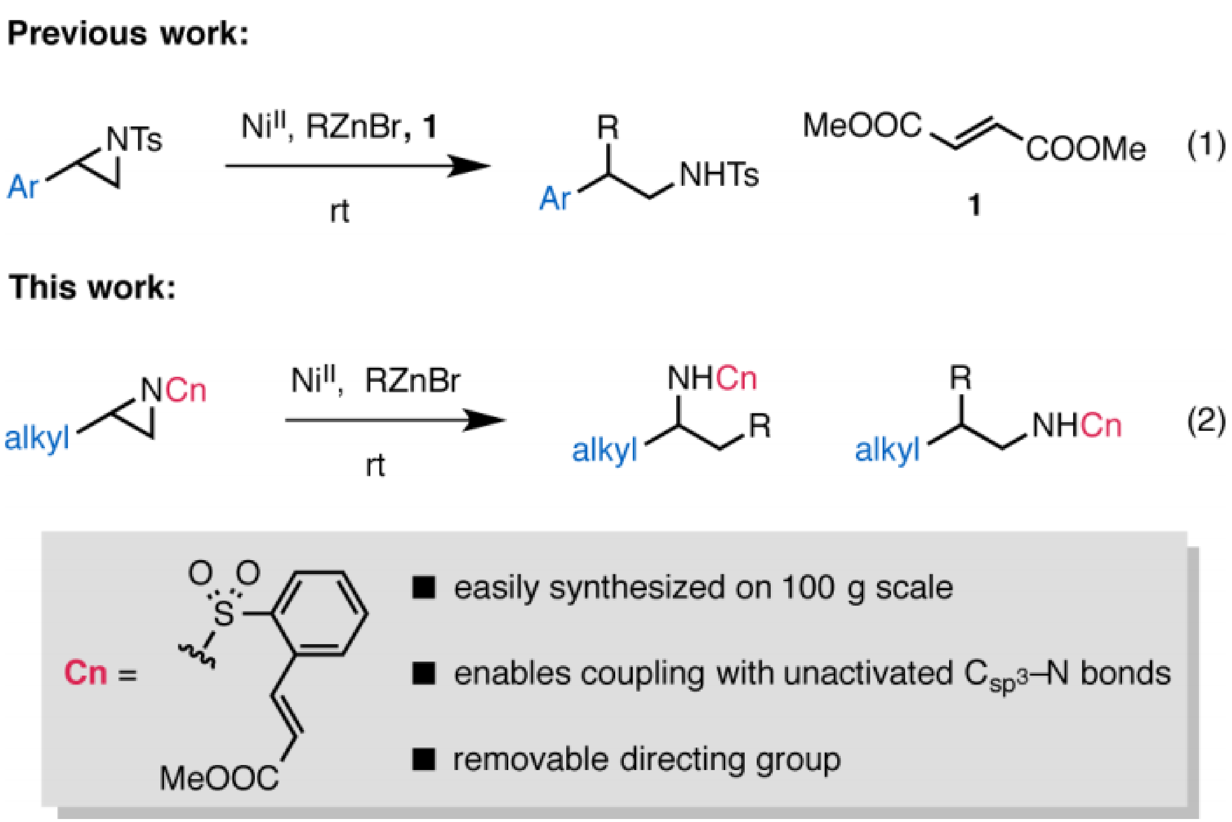
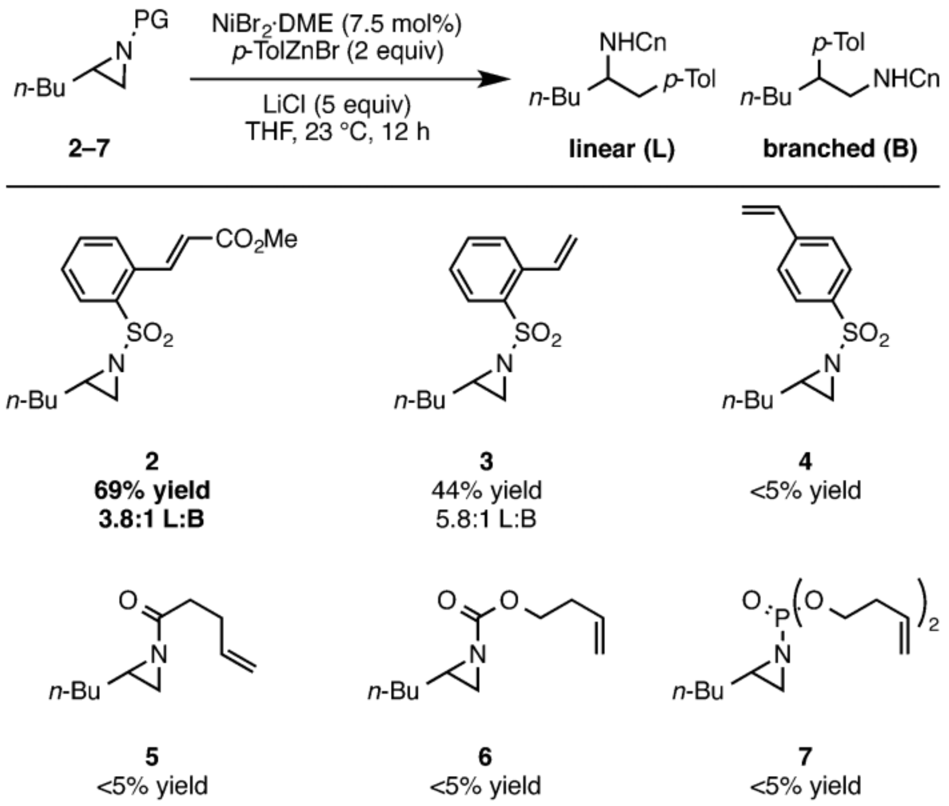
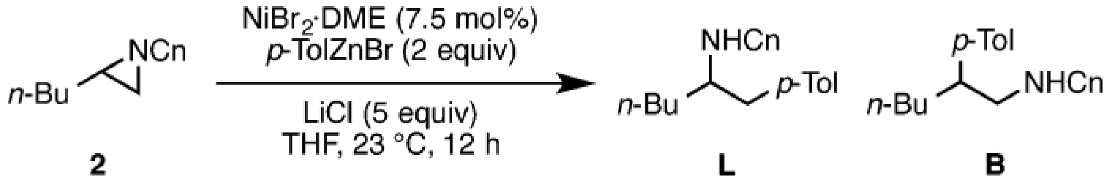


Table 1. Evaluation of Alkene-Containing Protecting Groups[a]



Ring-Opening Reactions: Ni

Table 2. Evaluation of Reaction Conditions



entry	conditions	conv (%)	yield (%)[a]	L:B
1	standard conditions	100	69	3.8:1
2	no LiCl	100	44	1.9:1
3	3.0 equiv of LiCl	85	54	3.5:1
4	$MgCl_2$ instead of LiCl	99	42	5.0:1
5	no $NiBr_2$·DME	7	<2	N/A
6	$Ni(cod)_2$ instead of $NiBr_2$·DME	100	56	3.8:1
7	DMA instead of THF	100	<2	N/A
8	15% dimethyl fumarate **1**	100	30	3.0:1

[a]Yields and regioselectivity determined by ^1H NMR using triphenylene as a quantitative internal standard.

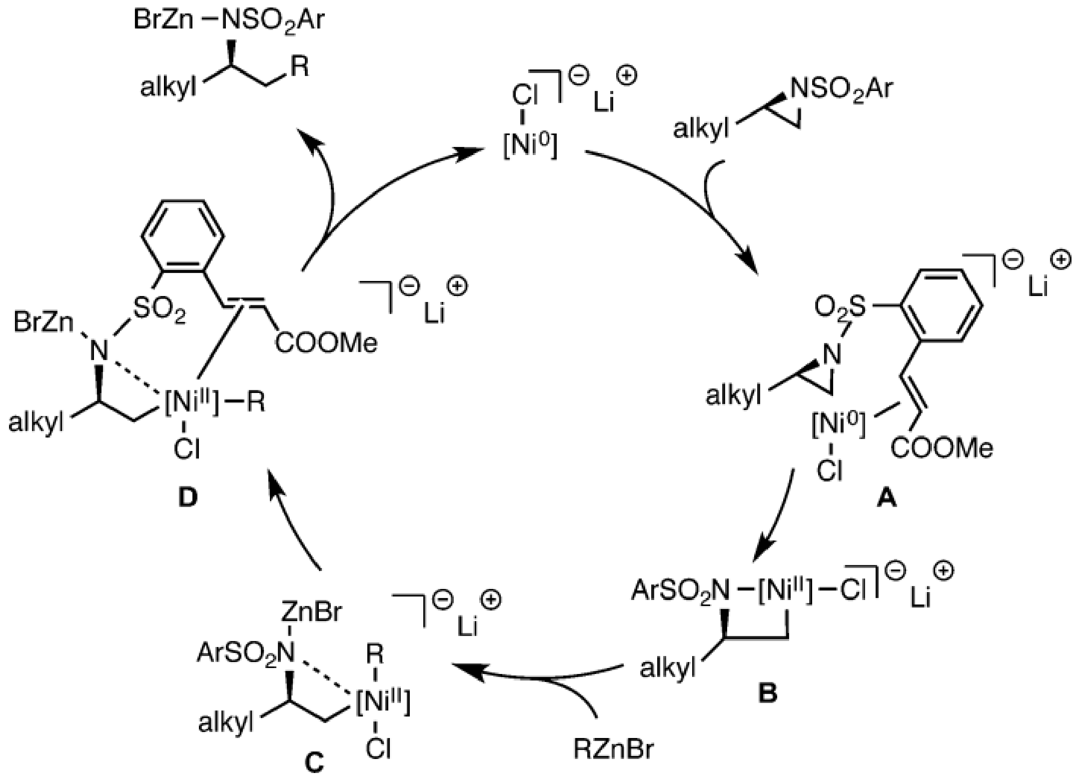
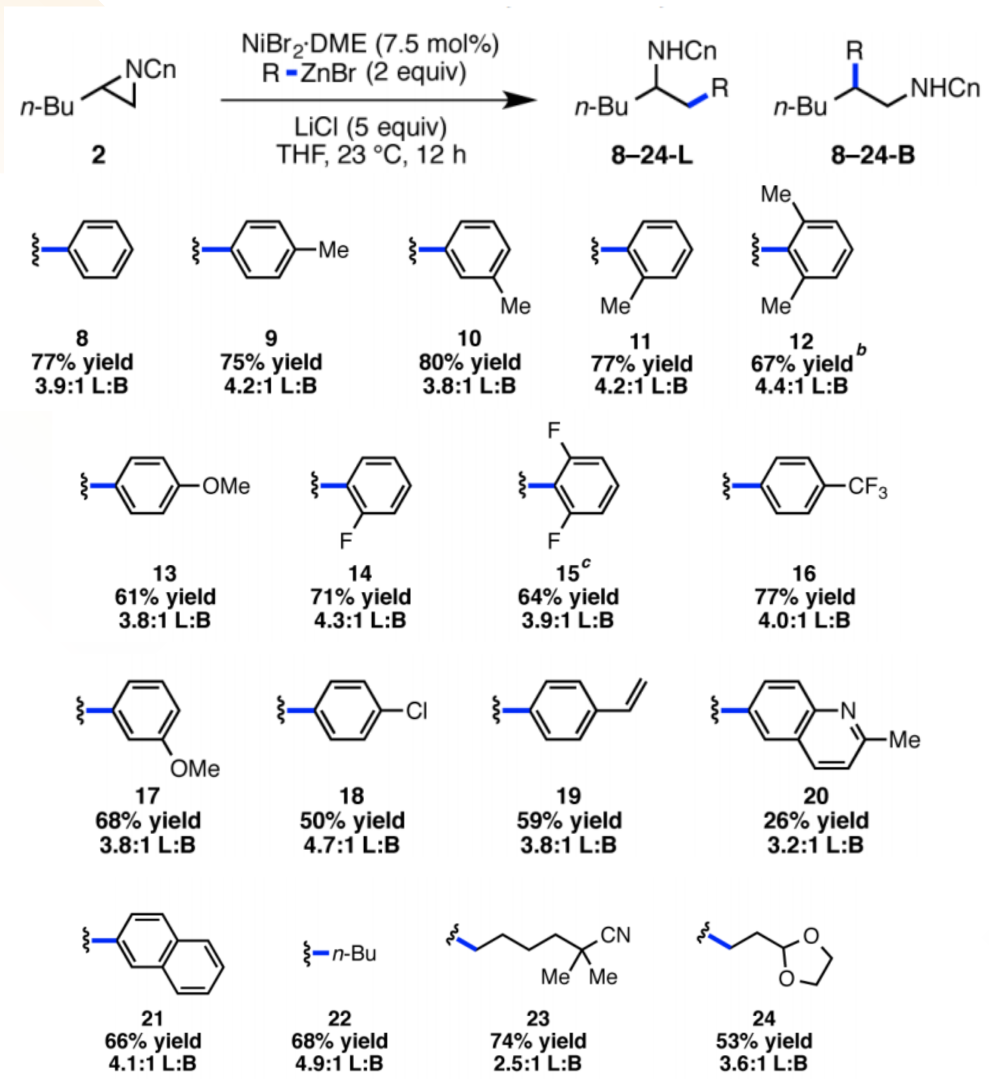
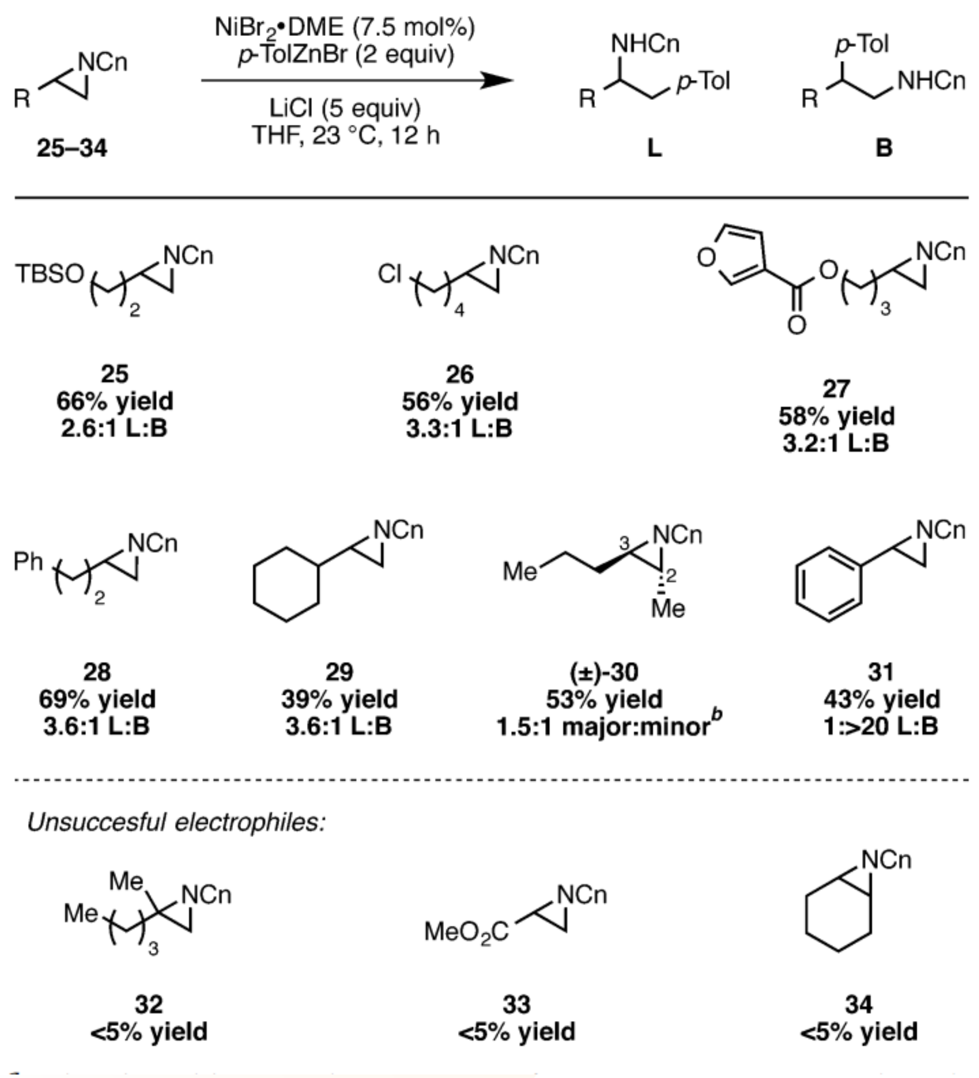


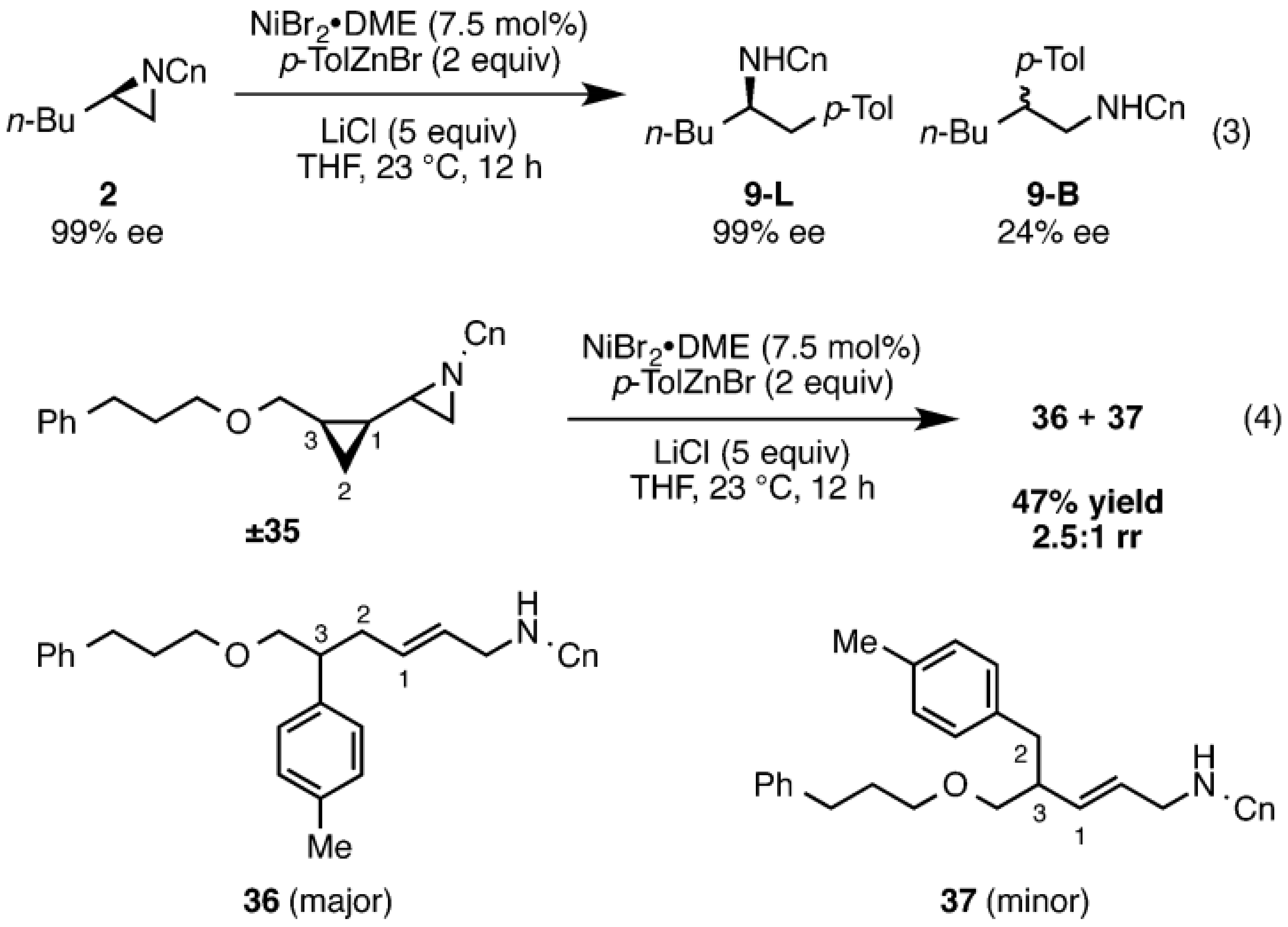
Figure 1. Proposed catalytic cycle.

Ring-Opening Reactions: Ni

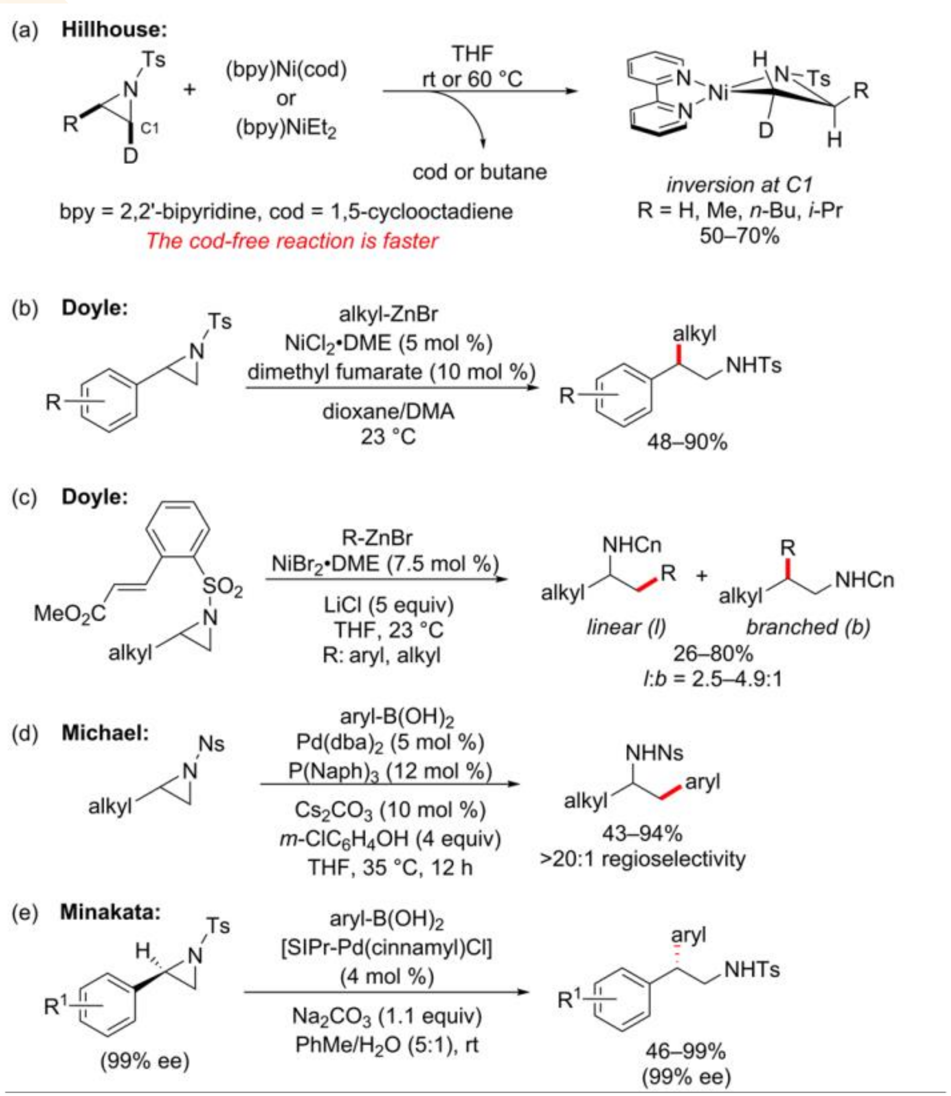




Ring-Opening Reactions: Ni



Ring-Opening Reactions: Ni



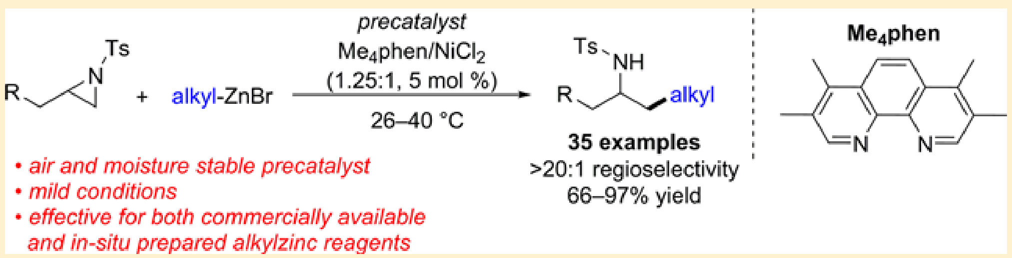
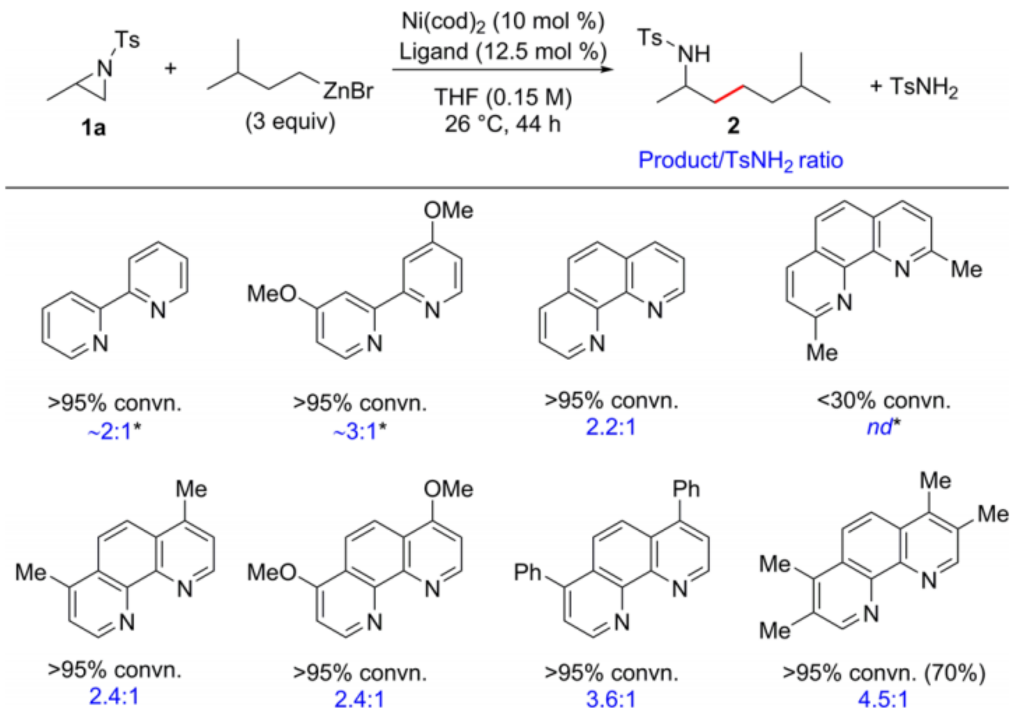
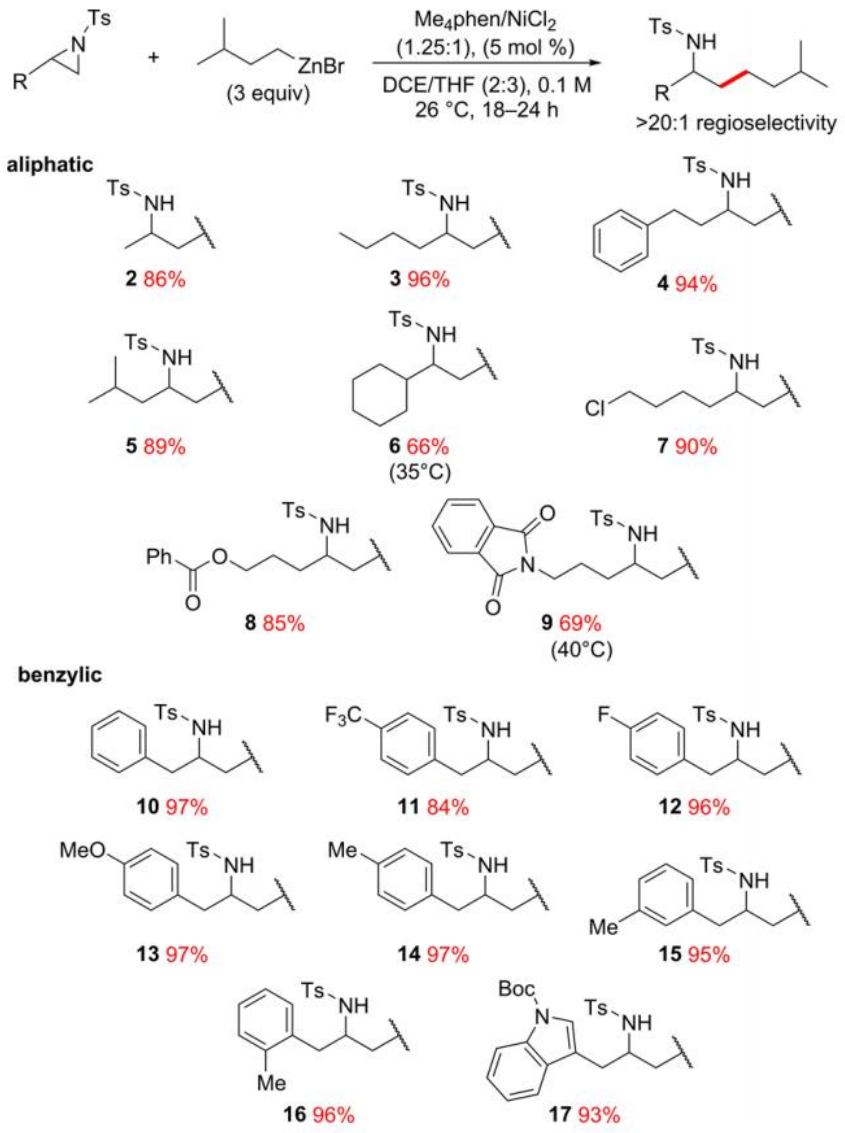


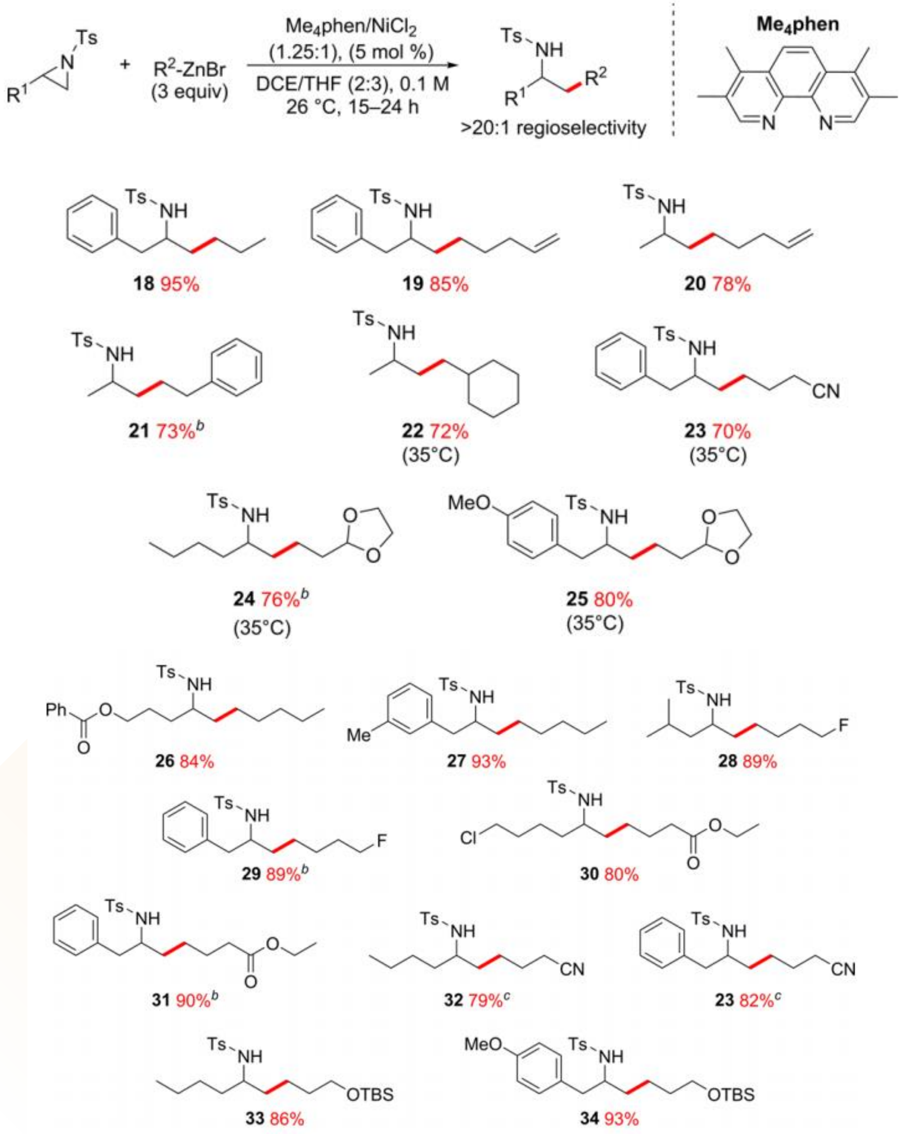
Table 1. Screening of Ligands[a]



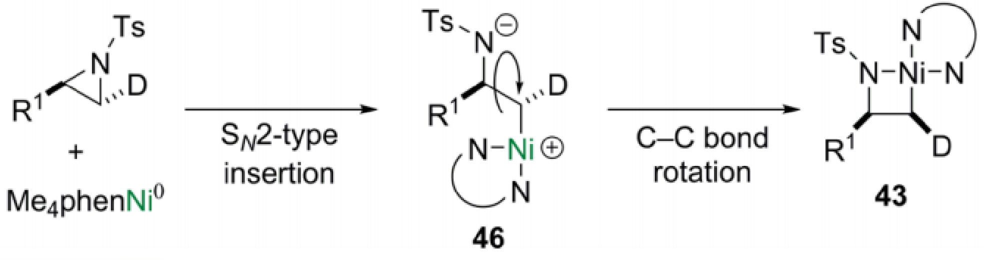
Jamison, T. F. *J. Am. Chem. Soc.* **2014**, *136*, 11145–11152.

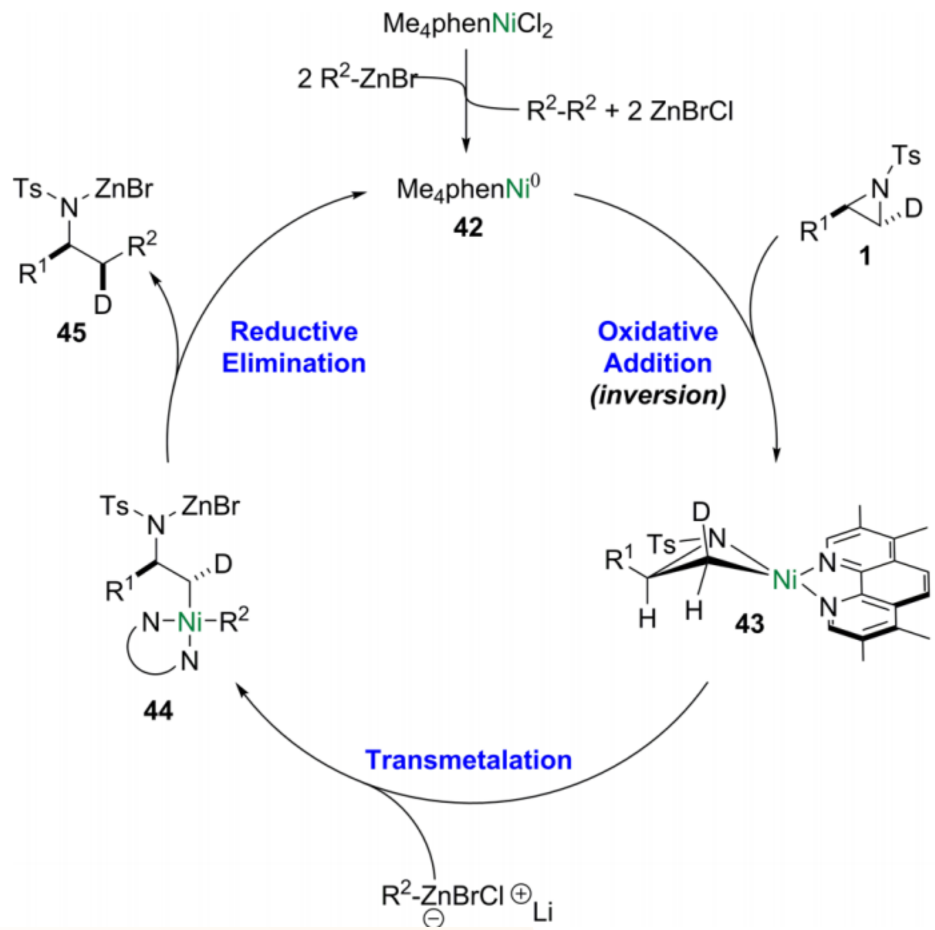
Ring-Opening Reactions: Ni



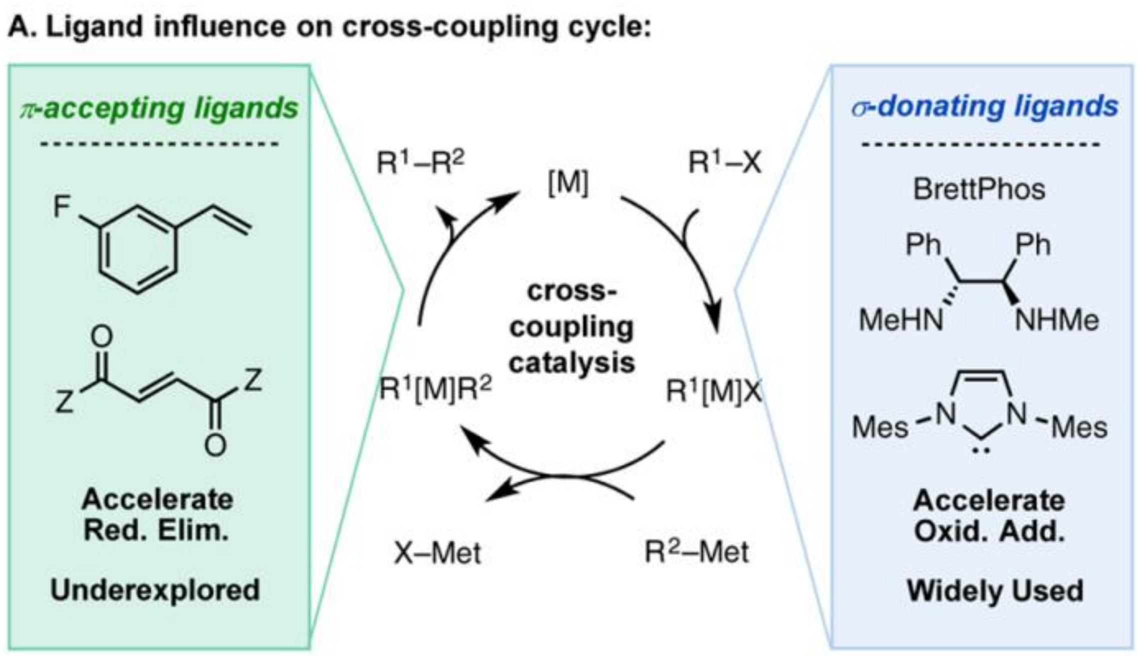


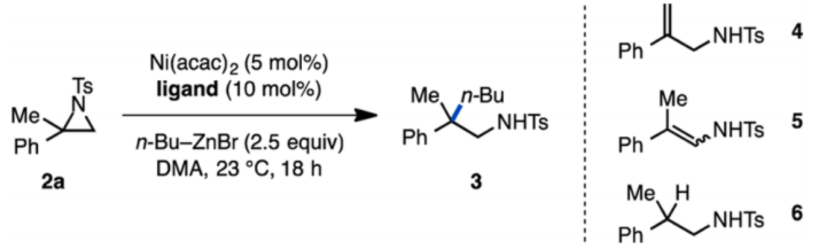
Ring-Opening Reactions: Ni





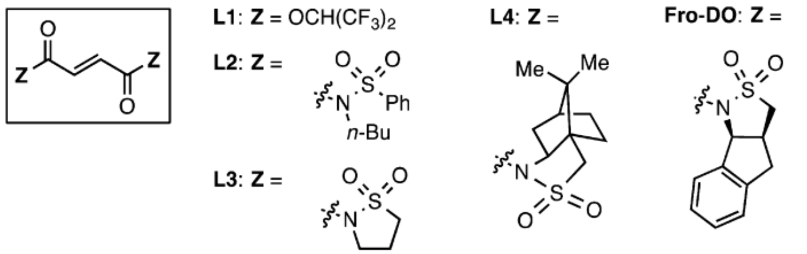
Ring-Opening Reactions: Ni





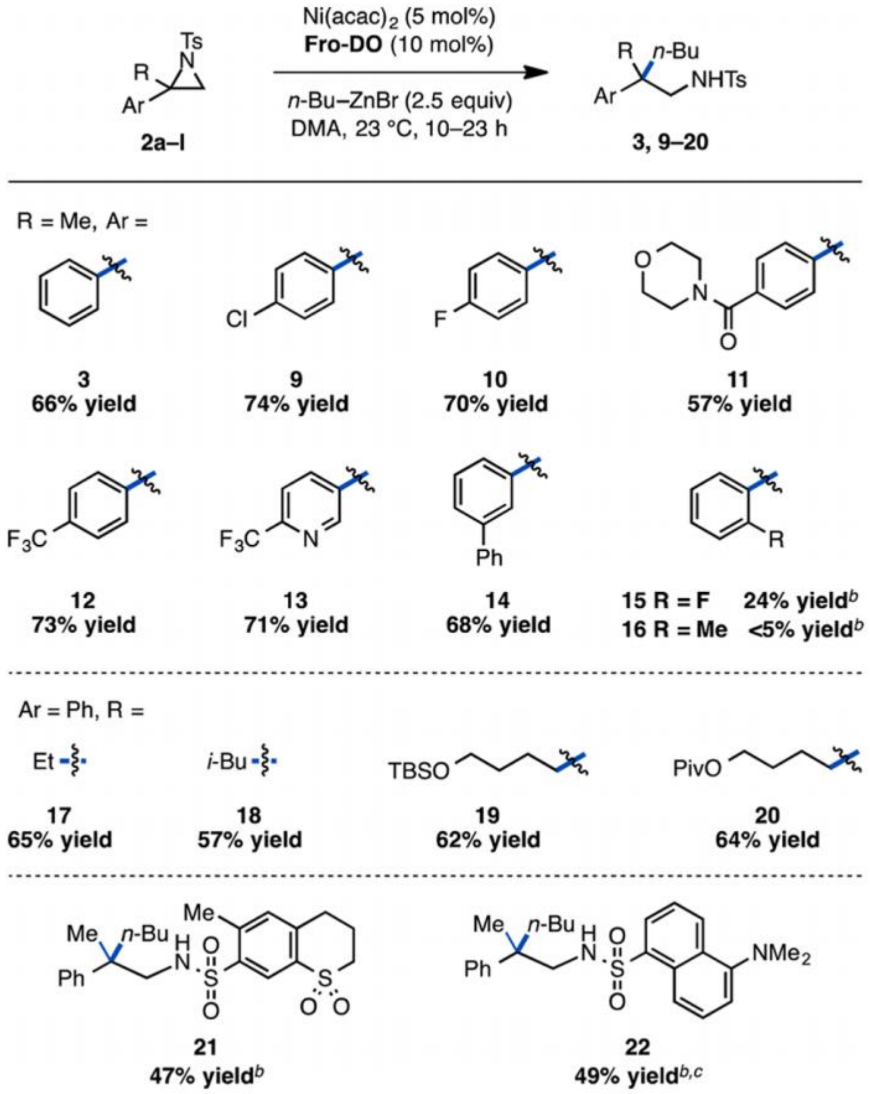
entry	ligand	yield[a]	conv.[a]
1	no ligand	<5%	45%
2	dimethyl fumarate (1)	8%	61%
3	maleic anhydride	<5%	54%
4	*N*-ethylmaleamide	<5%	45%
5	*m*-fluorostyrene	<5%	61%
6	*p*-benzoquinone	<5%	48%
7	**L1**	<5%	44%
8	**L2**	5%	64%
9	**L3**	9%	78%
10	**L4**	48%	73%
11	**Fro-DO**	**68%**	**89%**
12	(±)-**Fro-DO**	71%	91%
13	*meso*-**Fro-DO**	68%	85%
14	10% $Ni(acac)_2$ and 20% **Fro-DO**	77%	92%

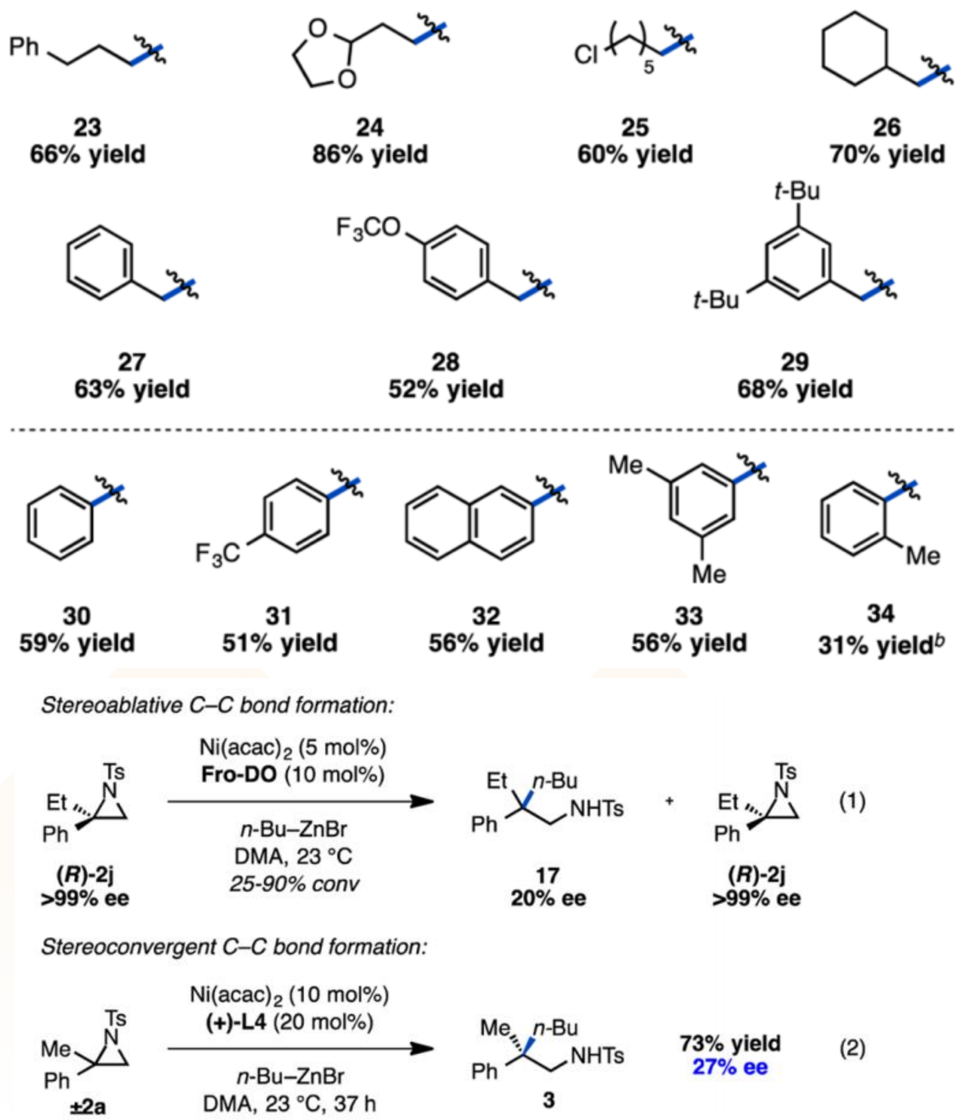
[a]Determined by GC, 0.05 mmol scale with dodecane as internal standard.



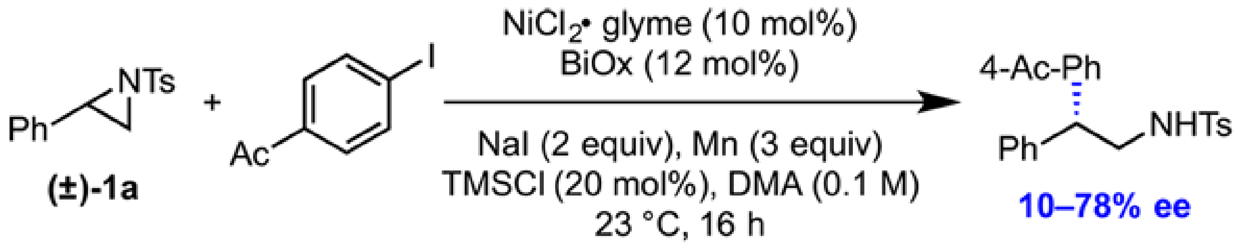
Doyle, A. G. *J. Am. Chem. Soc.* **2015**, *137*, 5638–5641.

Ring-Opening Reactions: Ni

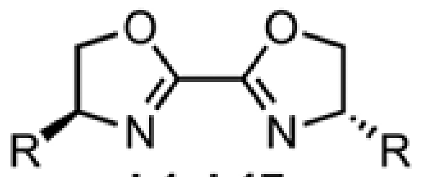




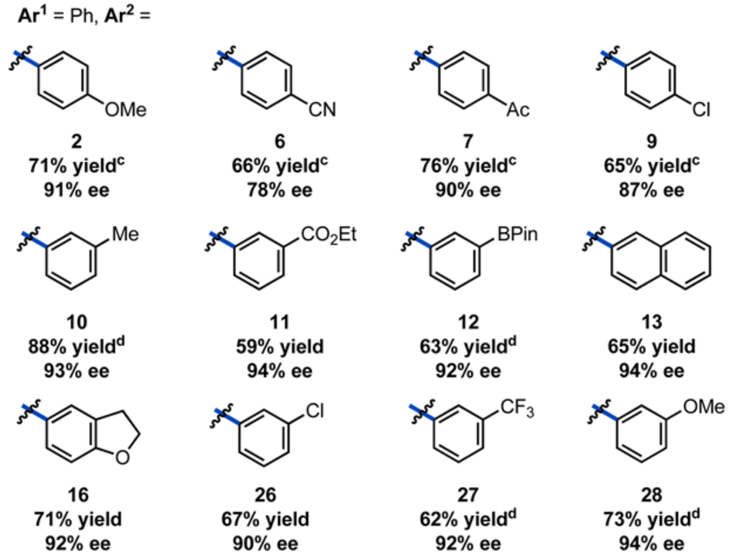
Ring-Opening Reactions: Ni



BiOx	R	ee (%)	BiOx	R	ee (%)	BiOx	R	ee (%)
L1	*i*-Pr	52	L7	4-Heptyl	78	L13	*c*-Pr	52
L2	Cy	72	L8	*n*-Hex	52	L14	*s*-Bu	72
L3	*i*-Bu	43	L9	3-Pentyl	73	L15	*c*-Pentyl	43
L4	Me	52	L10	$(CH_2)_2Ph$	40	L16	Bn	52
L5	$(CH_2)_3Ph$	43	L11	4-F-Bn	43	L17	4-OMe-Bn	43
L6	$CHPh_2$	10	L12	CH_2*t*-Bu	30			



L1–L17



	Ar^1	Ar^2	yield	ee
19	*p*-OAc-Ph	*p*-Ac-Ph	78%	90%
20	*m*-OMe-Ph	*p*-Ac-Ph	61%	78%
29	*p*-CO_2Me-Ph	*p*-OMe-Ph	47%	88%
30	*p*-CO_2Me-Ph	2-naphthyl	70%	78%
31	*p*-CF_3-Ph	*p*-OMe-Ph	67%	85%
32	*p*-CF_3-Ph	2-naphthyl	70%	75%
33	*p*-F-Ph	*m*-CO_2Et-Ph	45%	91%
34	*p*-F-Ph	2-naphthyl	86%	83%
35	*p*-F-Ph	*p*-Cl-Ph	79%	82%

Doyle, A. G. *J. Am. Chem. Soc.* **2017**, *139*, 5688–5691.

Ring-Opening Reactions: Ni

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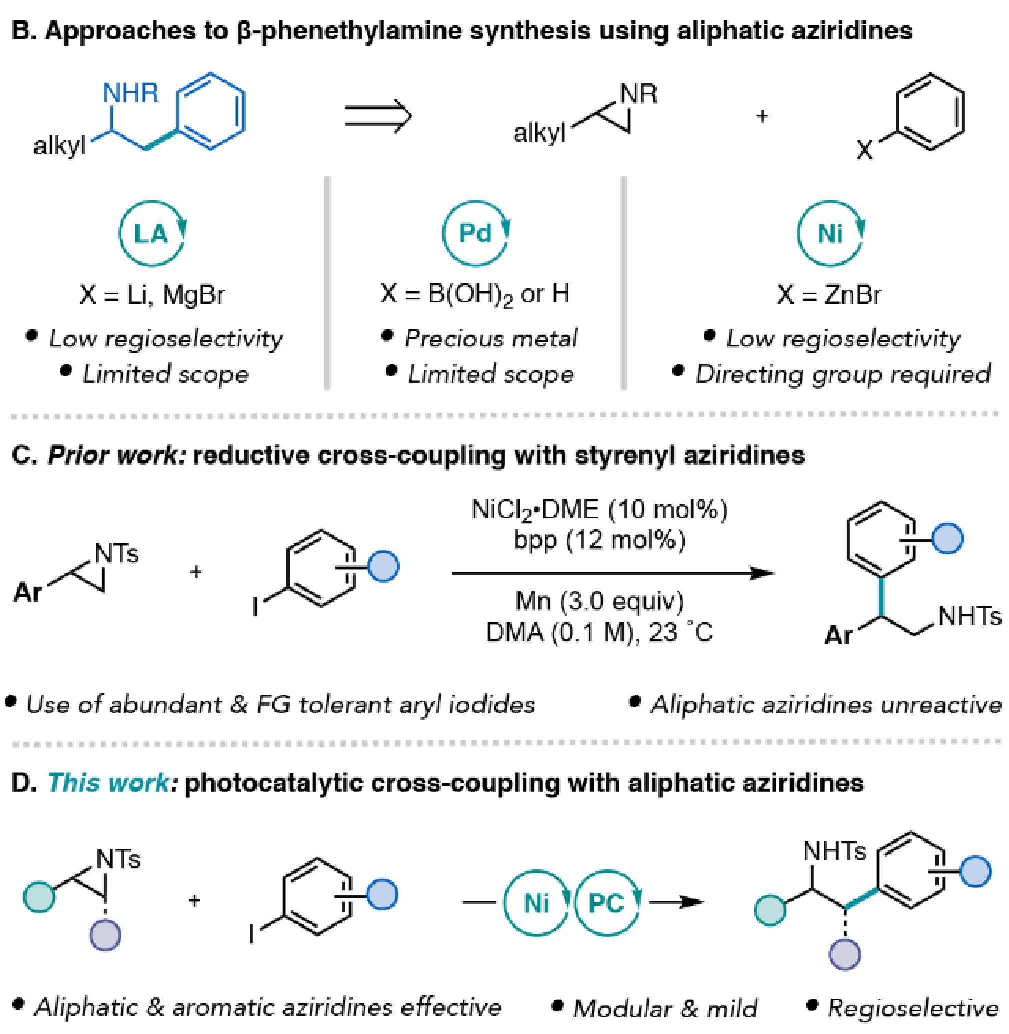
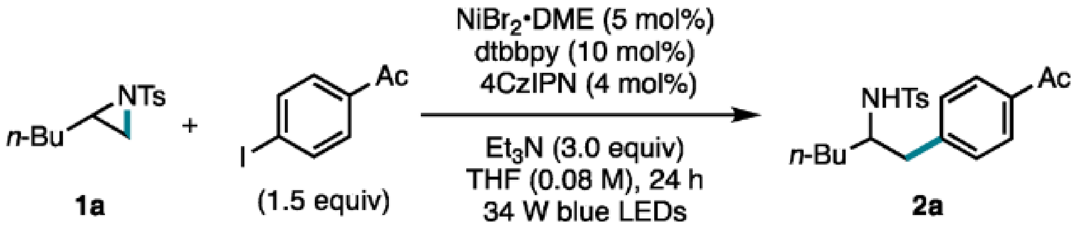


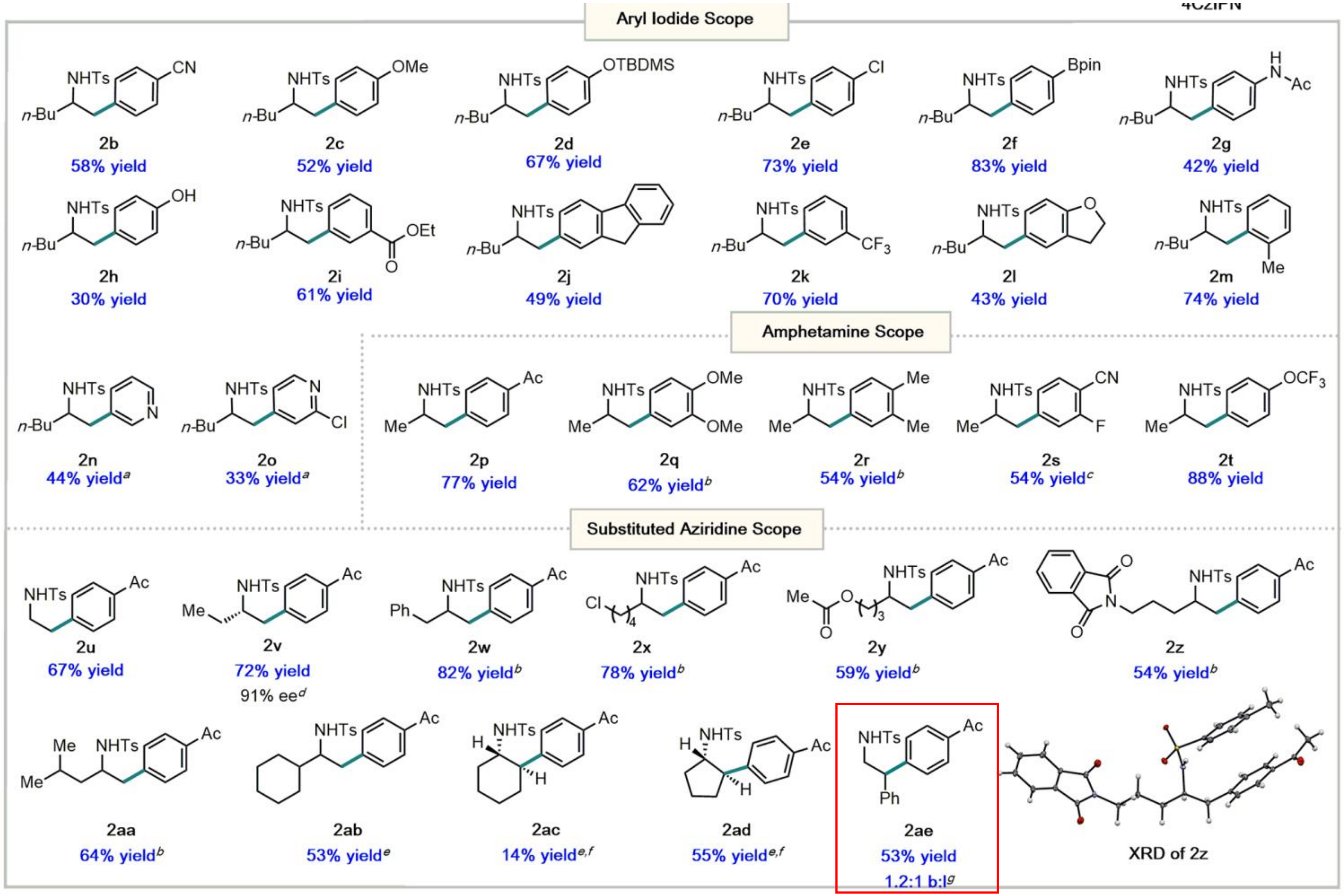


entry	deviation from standard conditions	conversion of **1a** [%]	yield [%][a]
1	none	100	59
2	4′-bromoacetophenone	82	0
3	$Ir(dF\text{-}CF_3\text{-}ppy)_2(dtbbpy)PF_6$	100	57
4	no Et_3N	30	0
5	no dtbbpy	61	0
6	no Ni	100	0
7	no 4CzIPN	11	0
8	no light	0	0[b]
9	0.5 mmol scale	70	46
10	0.5 mmol scale for 48 h	>95	76
11	photoreactor on 0.5 mmol scale	100	82 (72)[c]

[a]Reaction run on 0.1 mmol scale. Yields are the average of two runs and were determined using 1,3,5-trimethoxybenzene (1.0 equiv) as an external standard. [b]Reaction run at 40 °C. [c]Isolated yield.

Doyle, A. G. *J. Am. Chem. Soc.* **2020**, *142*, 7598–7605.

Ring-Opening Reactions: Ni



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Ring-Opening Reactions: Ni

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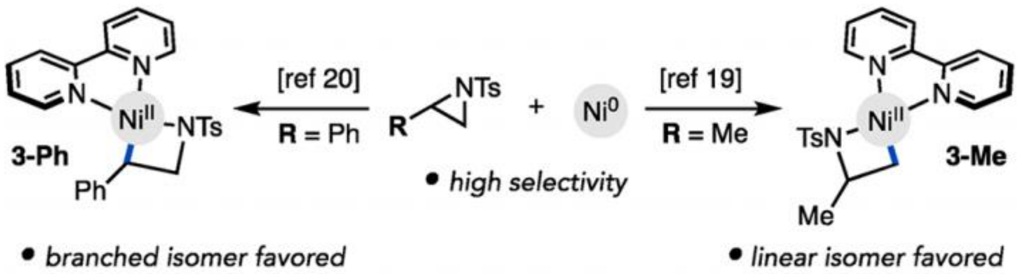
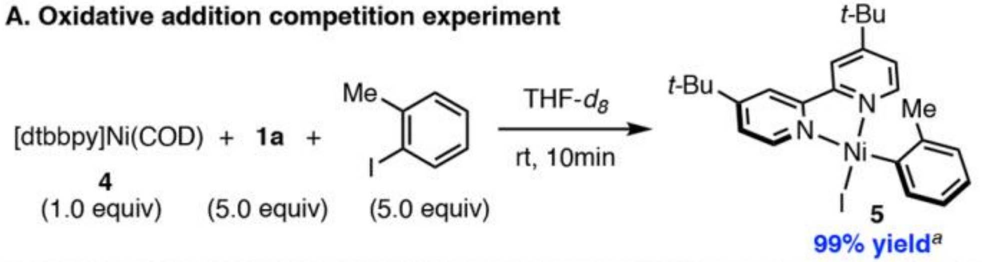
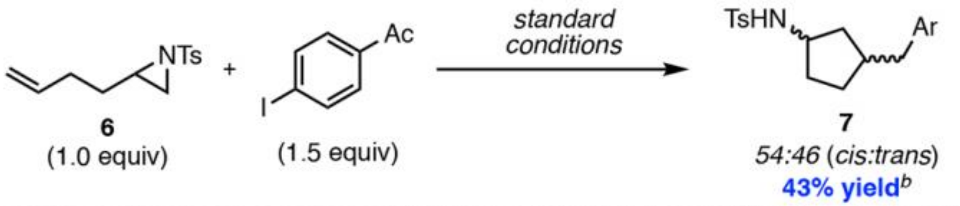
A. Aziridine activation via Ni oxidative addition



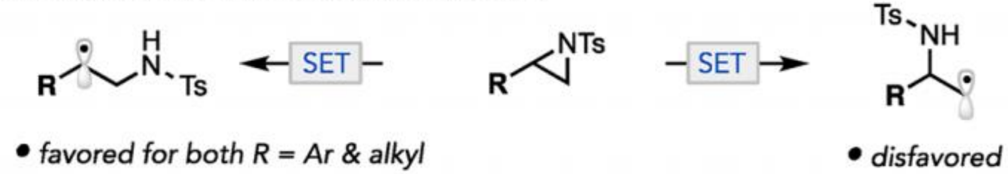
A. Oxidative addition competition experiment



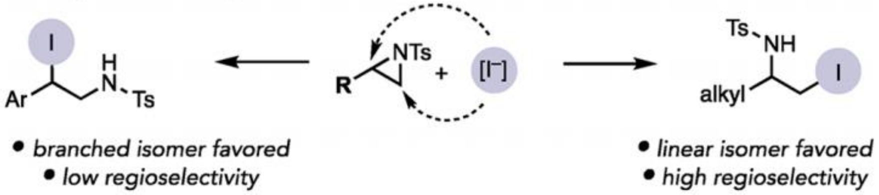
B. Intramolecular radical trap experiment



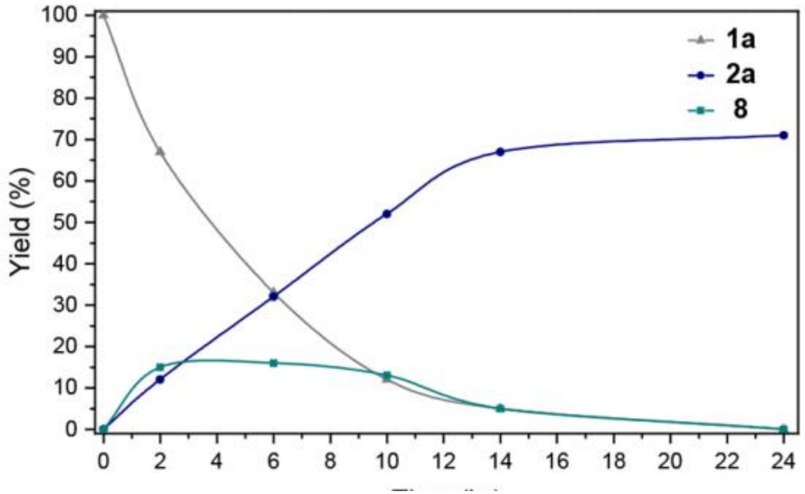
B. Single electron reduction of aziridines



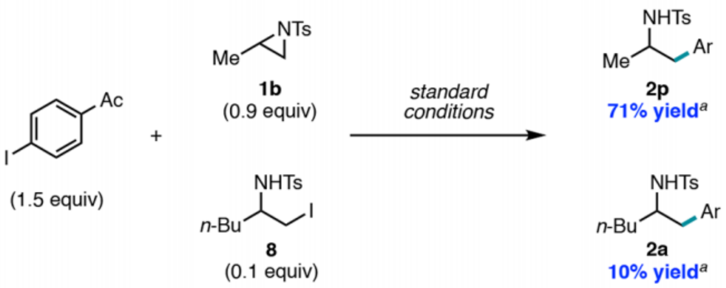
C. *Proposed Pathway*: Aziridine activation with iodide to form iodoamine



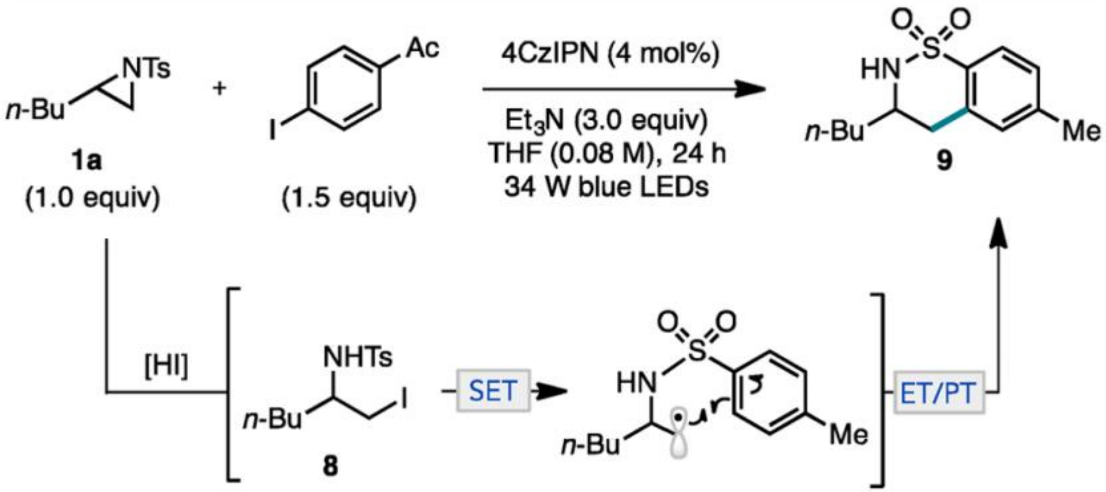
C. Reaction time course



D. Reactivity of β-iodoamine



Ring-Opening Reactions: Ni



Entry	TBAI	Yield of 9 [%][a]
1	none	45
2	10 mol%	60

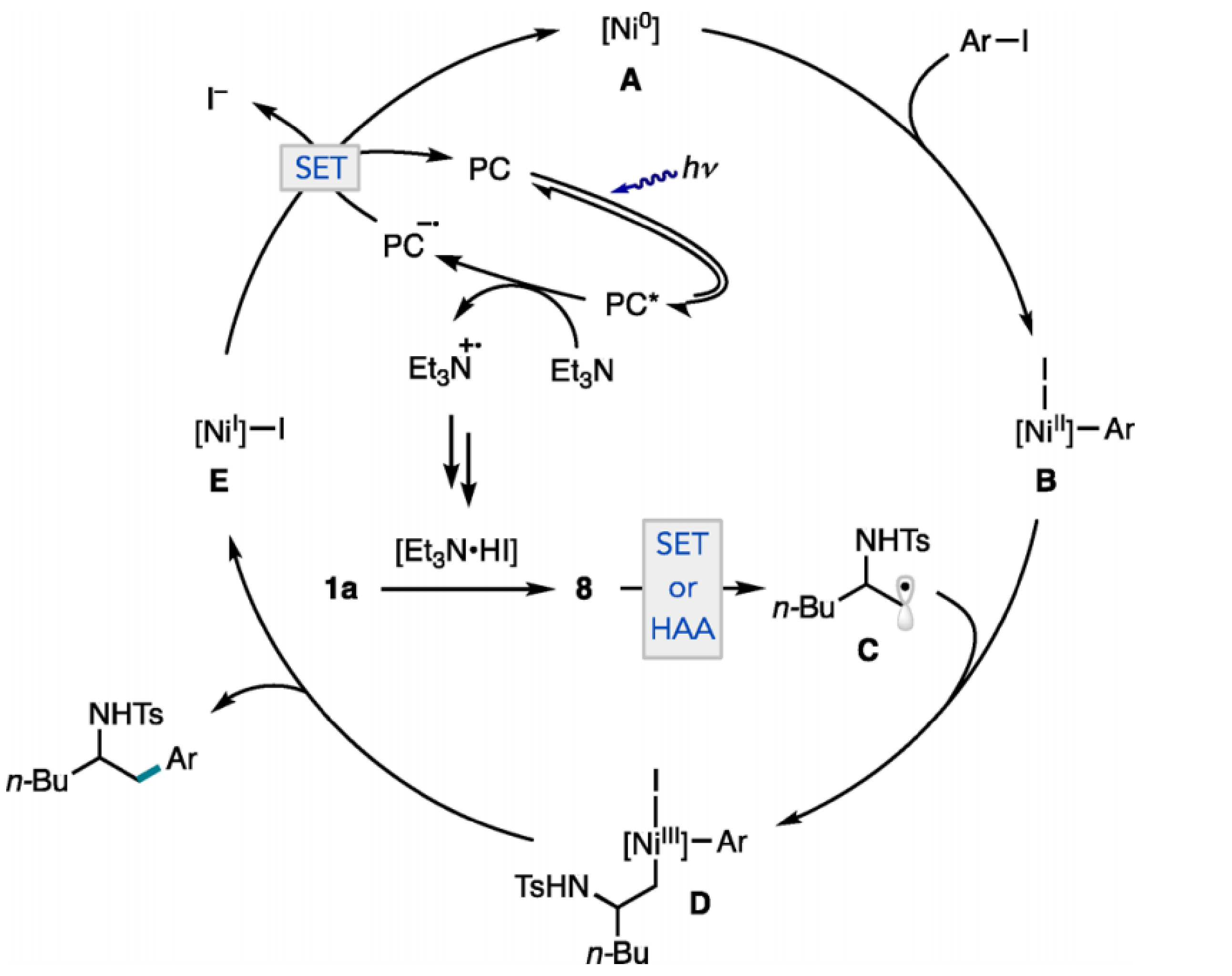


Figure 6. Proposed catalytic cycle. HAA = halogen atom abstraction.

Ring-Opening Reactions: Ni

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Scheme 1. Catalytic Cross-Coupling of Aziridines

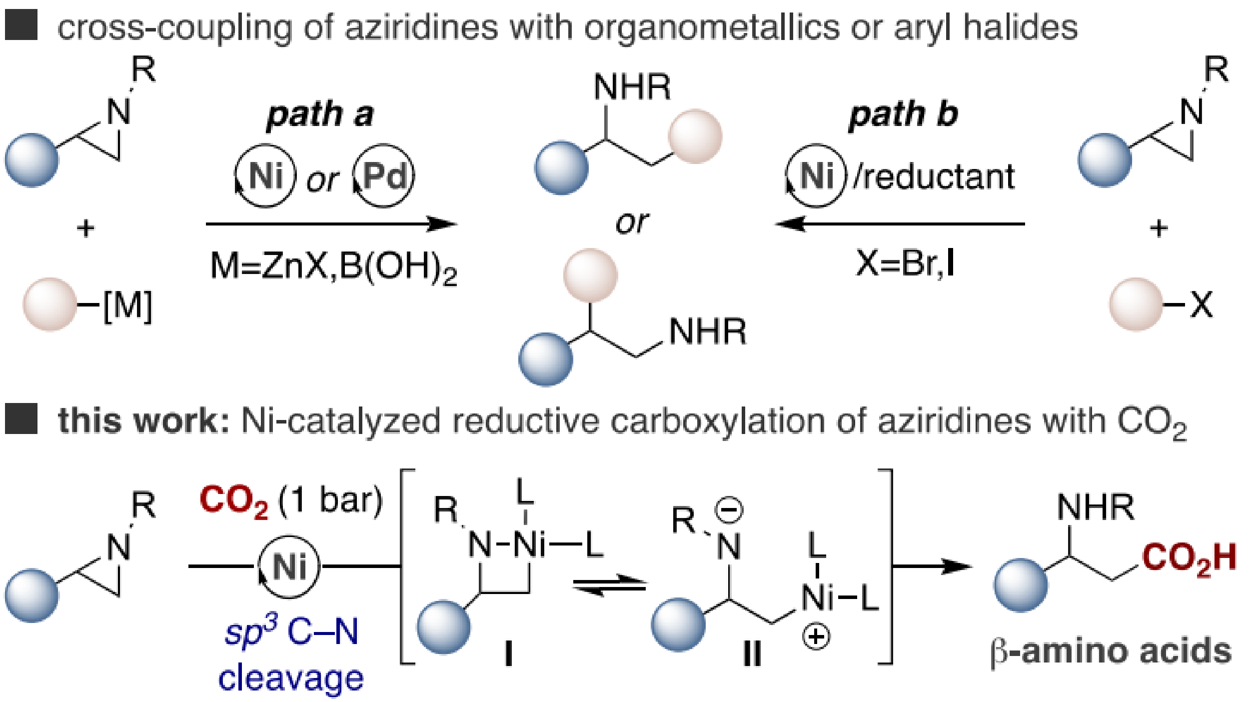
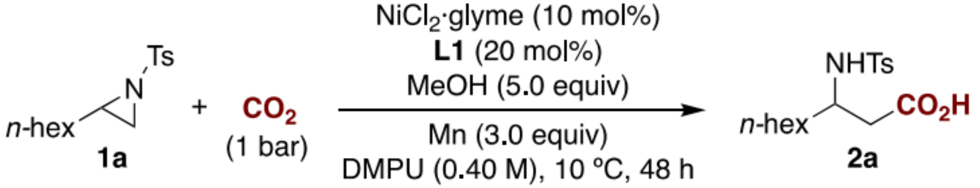
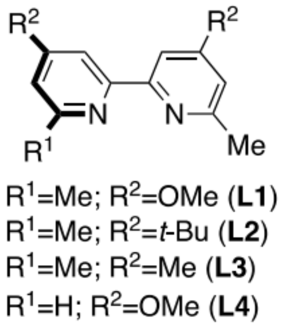
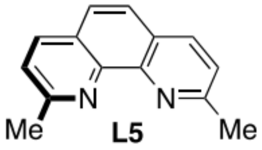


Table 1. Optimization of the Reaction Conditions[a]



entry	deviation standard conditions	2a (%)[b]
1	none	73
2	using $NiCl_2$**L1** as precatalyst	50
3	using **L1** (15 mol%)	61
4	using **L2** instead of **L1**	47
5	using **L3** instead of **L1**	0
6	using **L4** instead of **L1**	trace
7	using **L5** instead of **L1**	56
8	DMA as solvent	62
9	NMP as solvent	67
10	reaction conducted at rt	53
11	reaction time 72h	76 (71)[c]
12	72h, CO_2 (2.5 bar)	65
13	no $NiCl_2$·glyme, **L1** or MeOH	0





[a] **1a** (0.20 mmol), $NiCl_2$·glyme (10 mol %), **L1** (20 mol %), Mn (0.60 mmol). MeOH (1 mmol), CO_2 (1 bar), DMPU (0.50 mL) at 10 °C for 48 h. [b] ^{1}H NMR yields using trimethoxybenzene as internal standard. [c] Isolated yield.

Martin, R. *J. Am. Chem. Soc.* **2021**, *143*, 4949–4954 .

Ring-Opening Reactions: Ni

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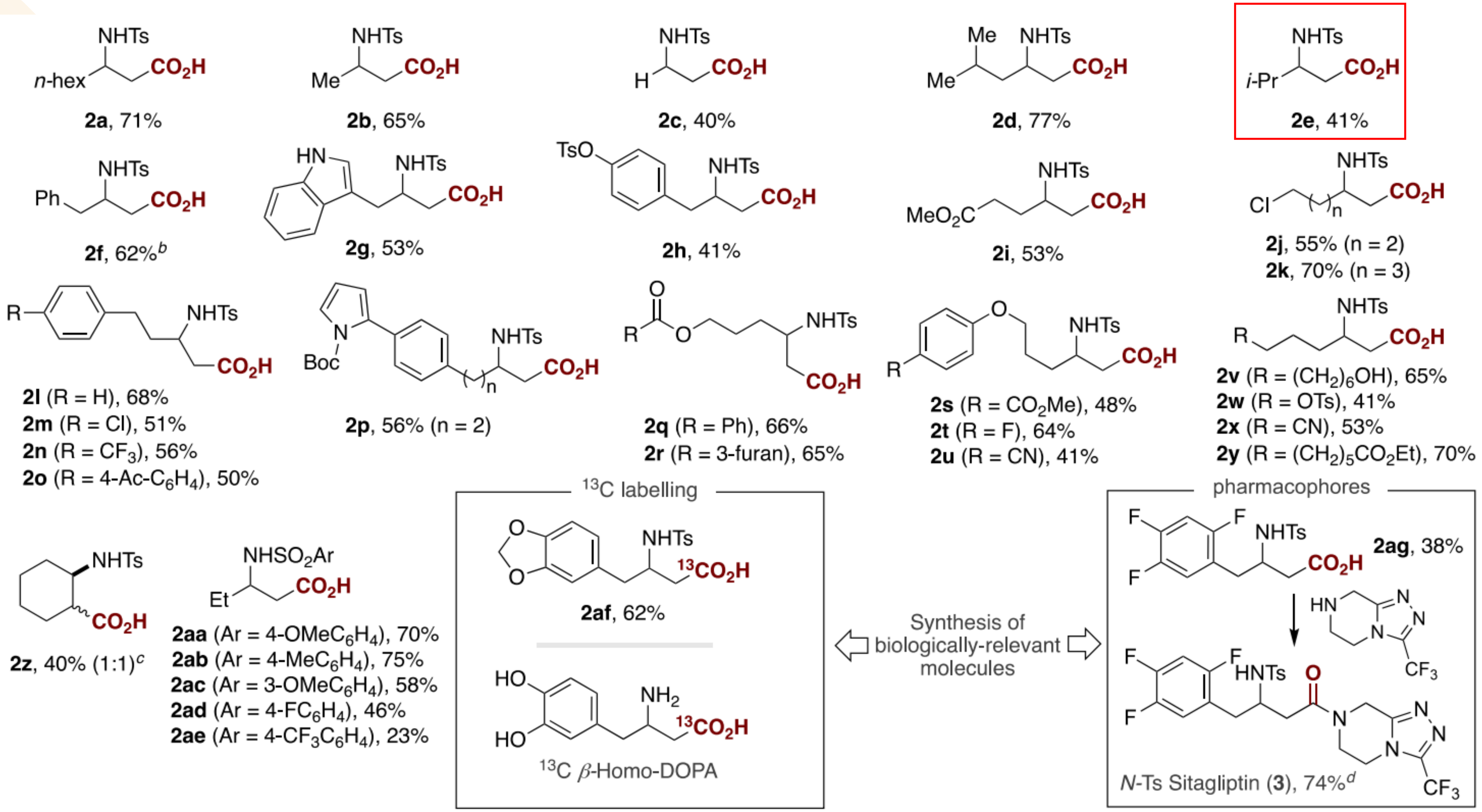

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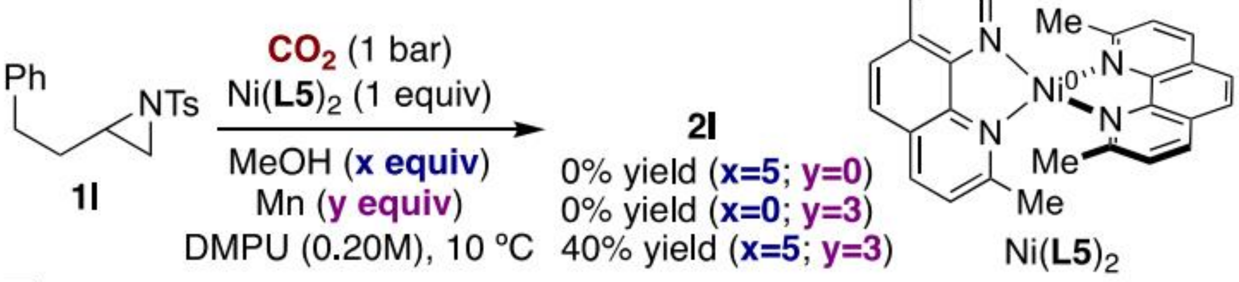
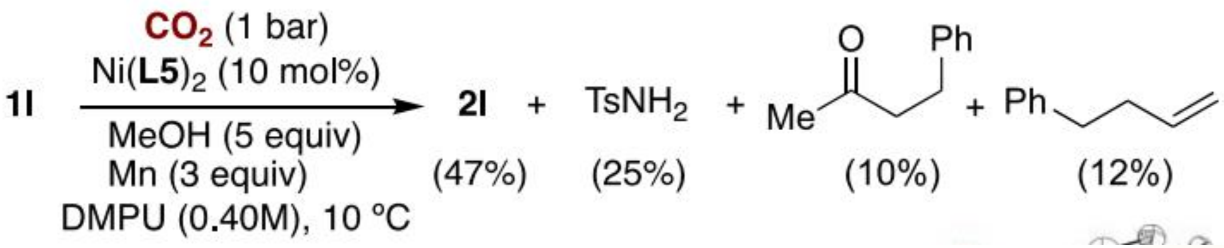
Ring-Opening Reactions: Ni

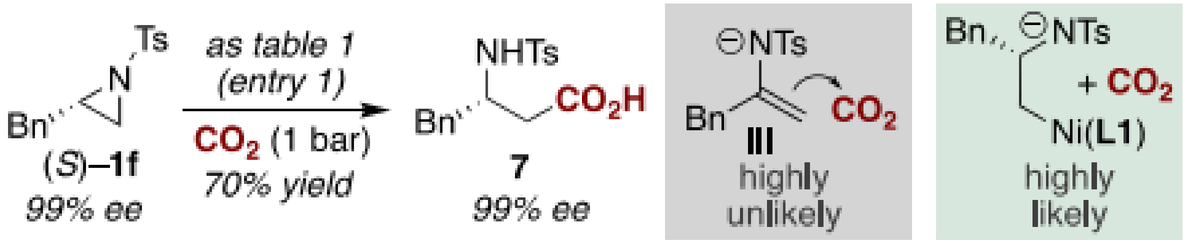
■ stoichiometric studies with $Ni(L5)_2$



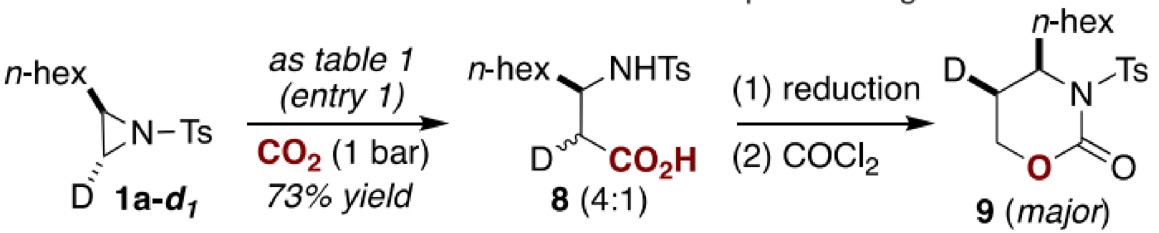
■ catalytic competence of $Ni(L5)_2$



■ preservation of the chiral integrity with enantioenriched aziridines



■ stereochemical course of the reaction via isotope-labelling



Ring-Opening Reactions: Ni

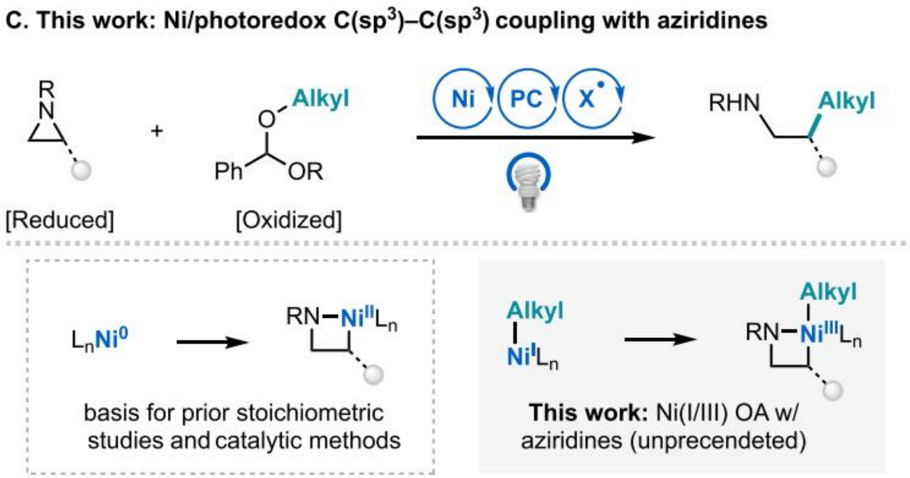
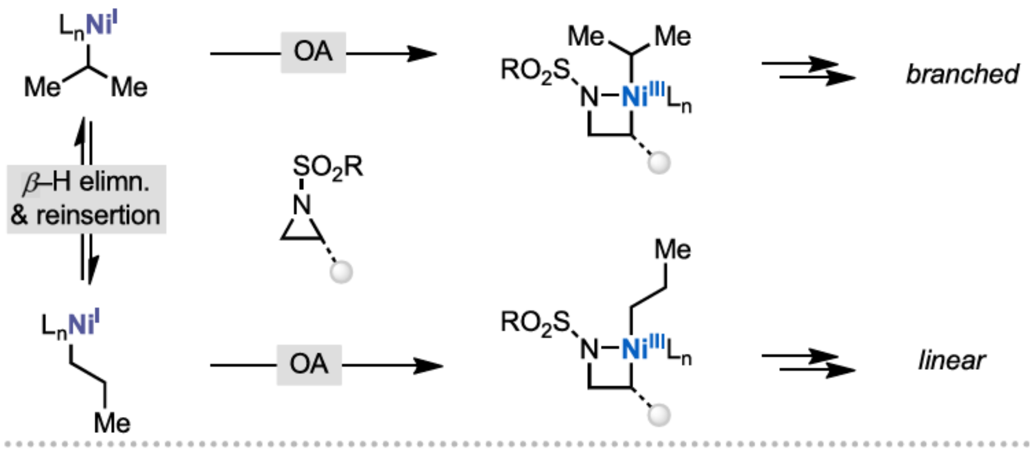
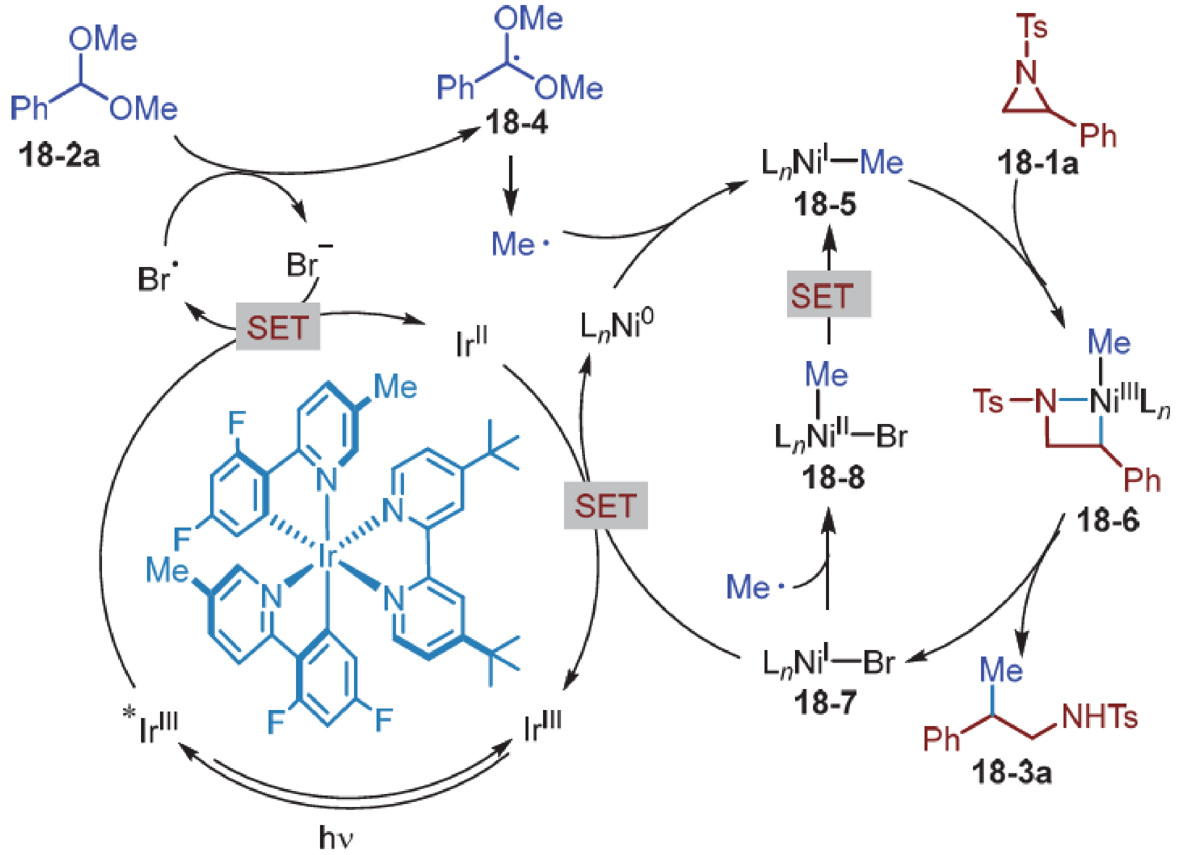


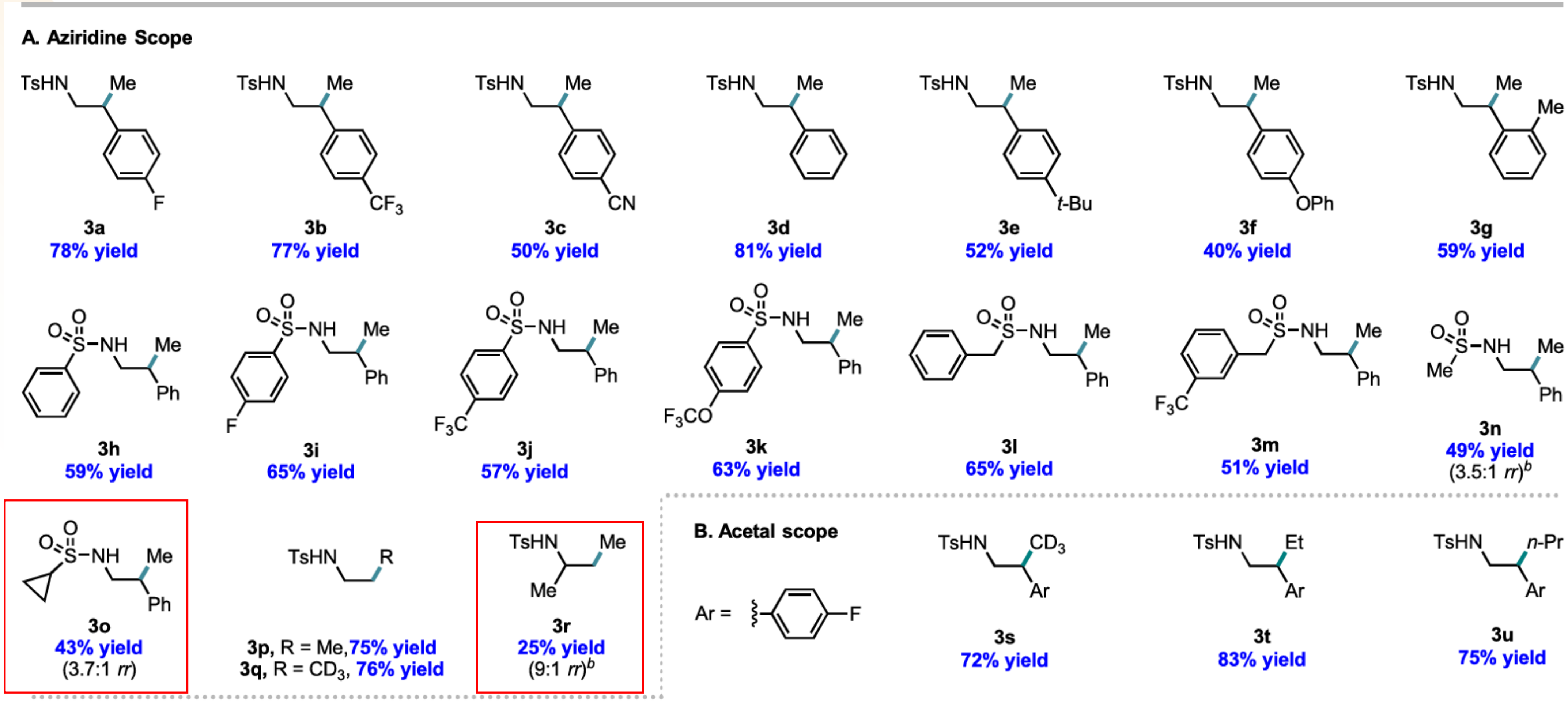
Figure 1. Cross-electrophile and redox-neutral metallaphotoredox coupling with $C(sp^3)$ precursors.



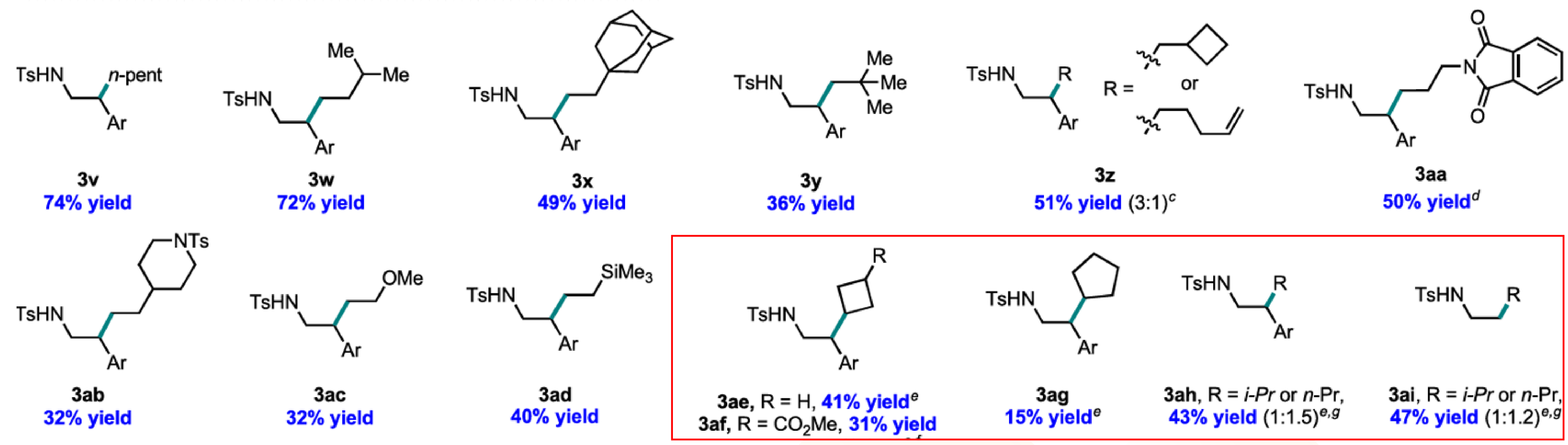


Doyle, A. G. *J. Am. Chem. Soc.* **2022**, *144*, 20067–20077.

Ring-Opening Reactions: Ni

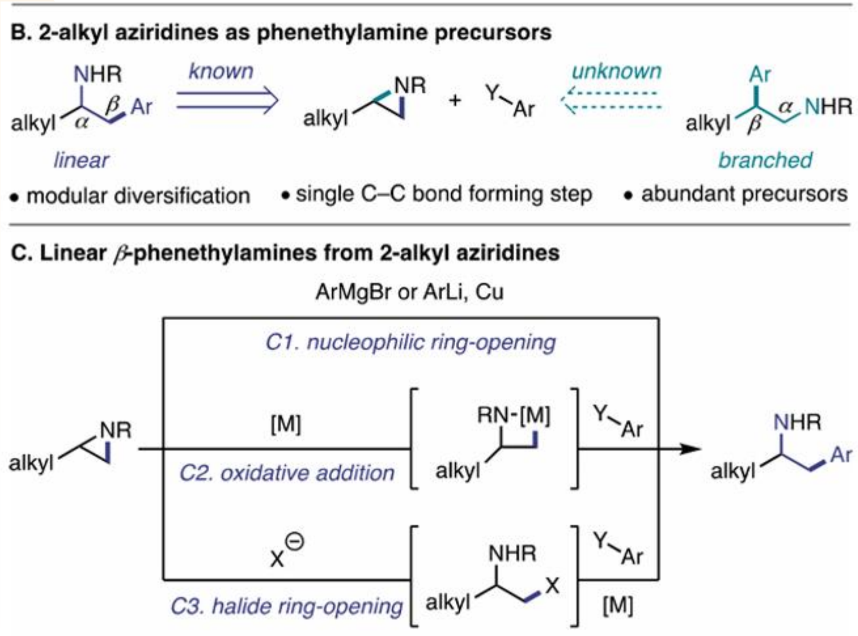


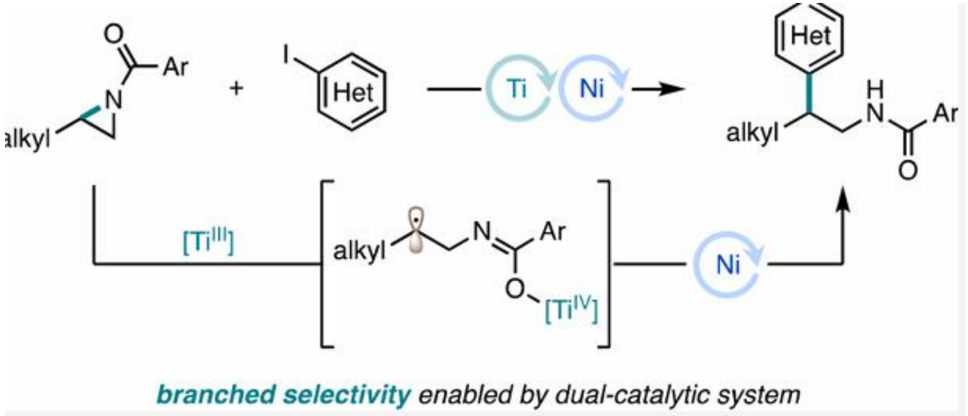
Ring-Opening Reactions: Ni



[g]diisopropyl benzaldehyde acetal was used as the

Ring-Opening Reactions: Ni





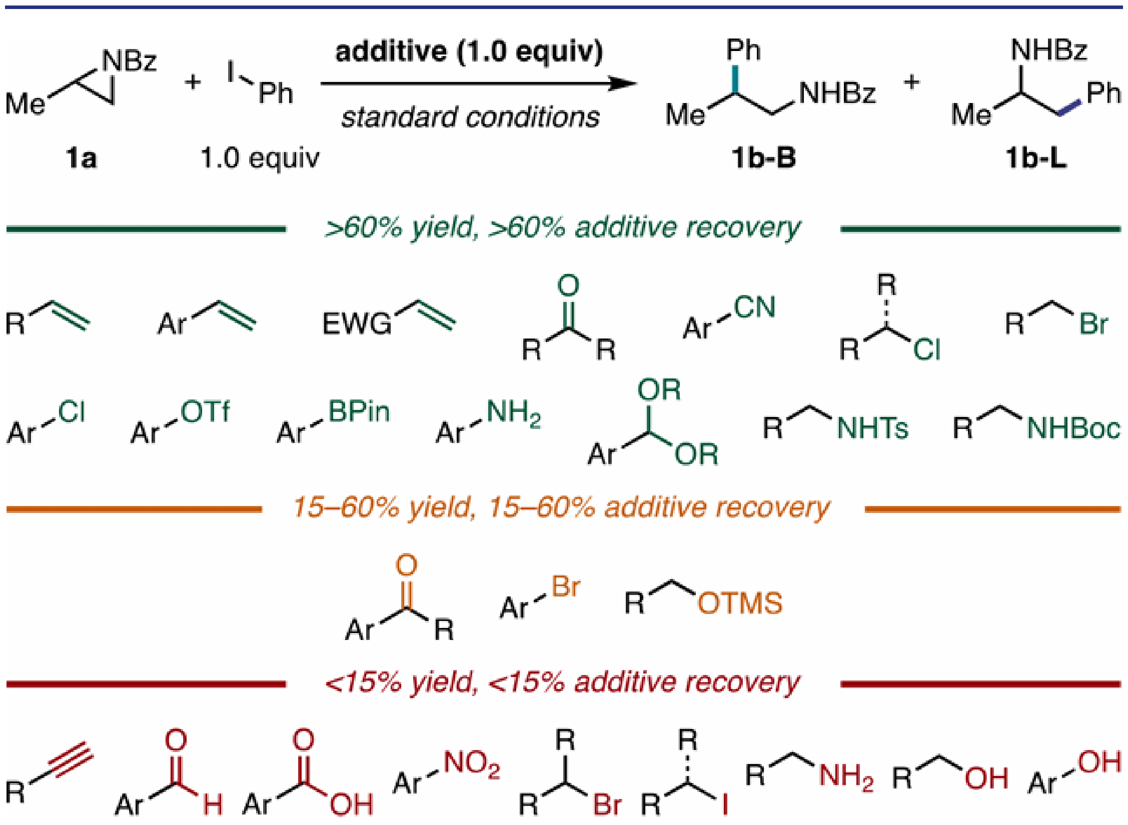
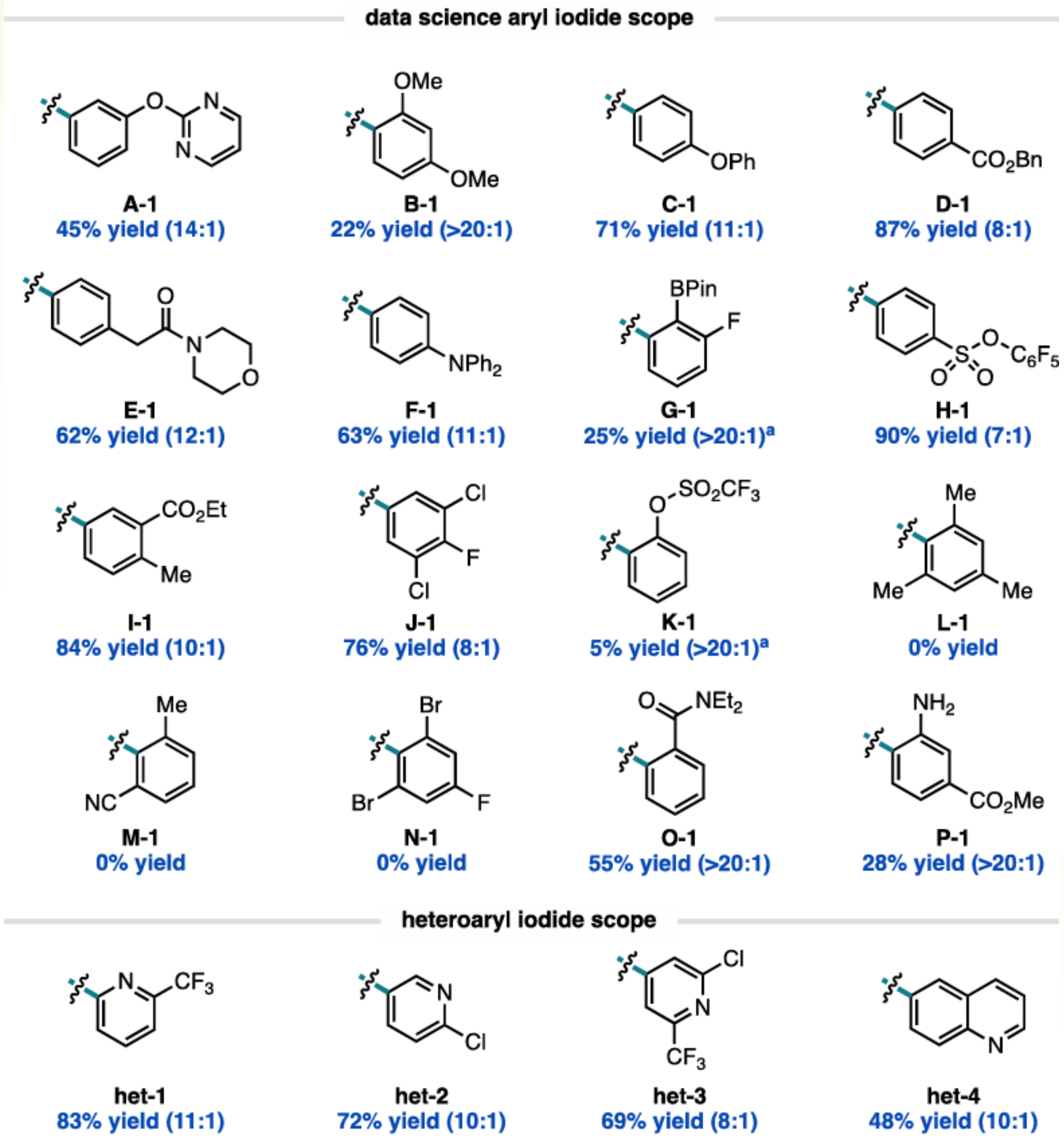
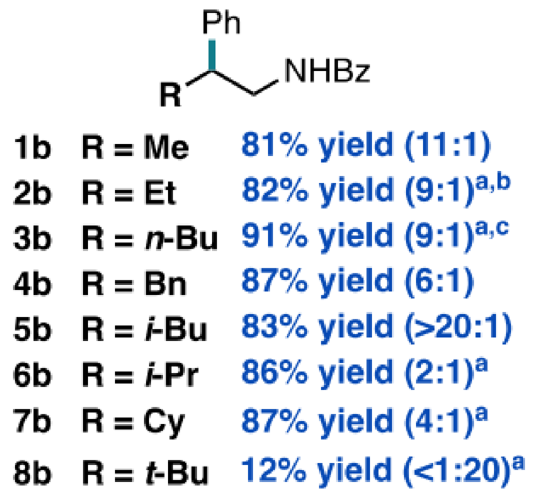


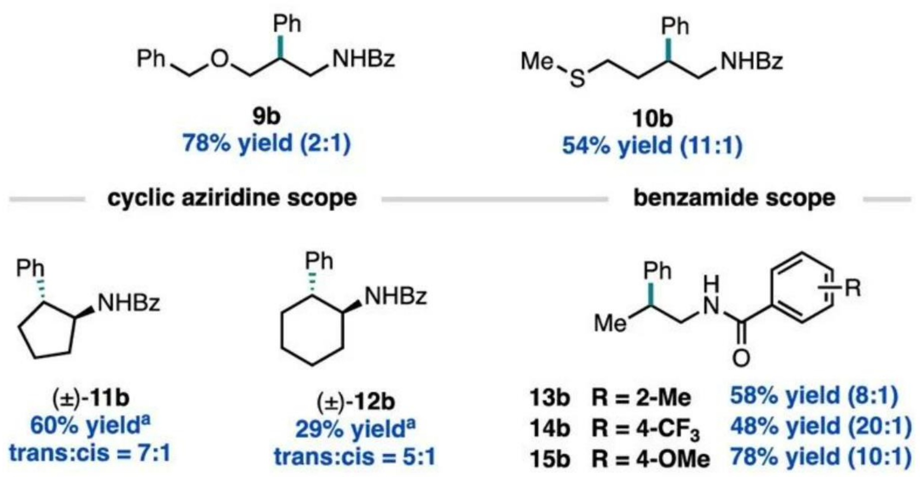
Figure 3. Additive screening campaign. Groupings were determined by the lower value of the yield or additive recovery. Reactions run on 0.075 mmol scale. Yield and additive recovery were determined by GC-FID with dodecane as an internal standard.

Doyle, A. G. *J. Am. Chem. Soc.* **2023**, *145*, 24175–24183.

Ring-Opening Reactions: Ni







Ring-Opening Reactions: Ni

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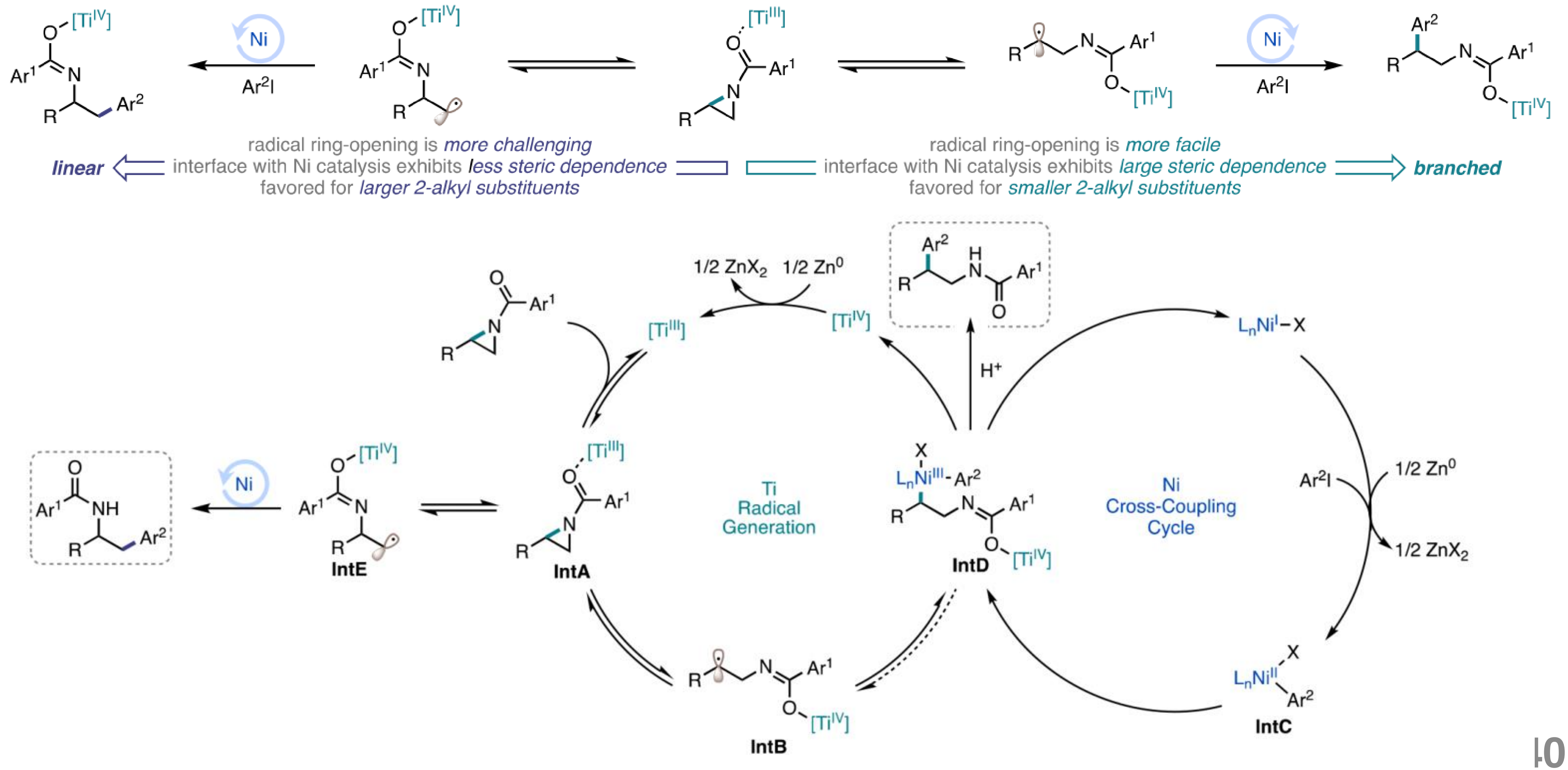
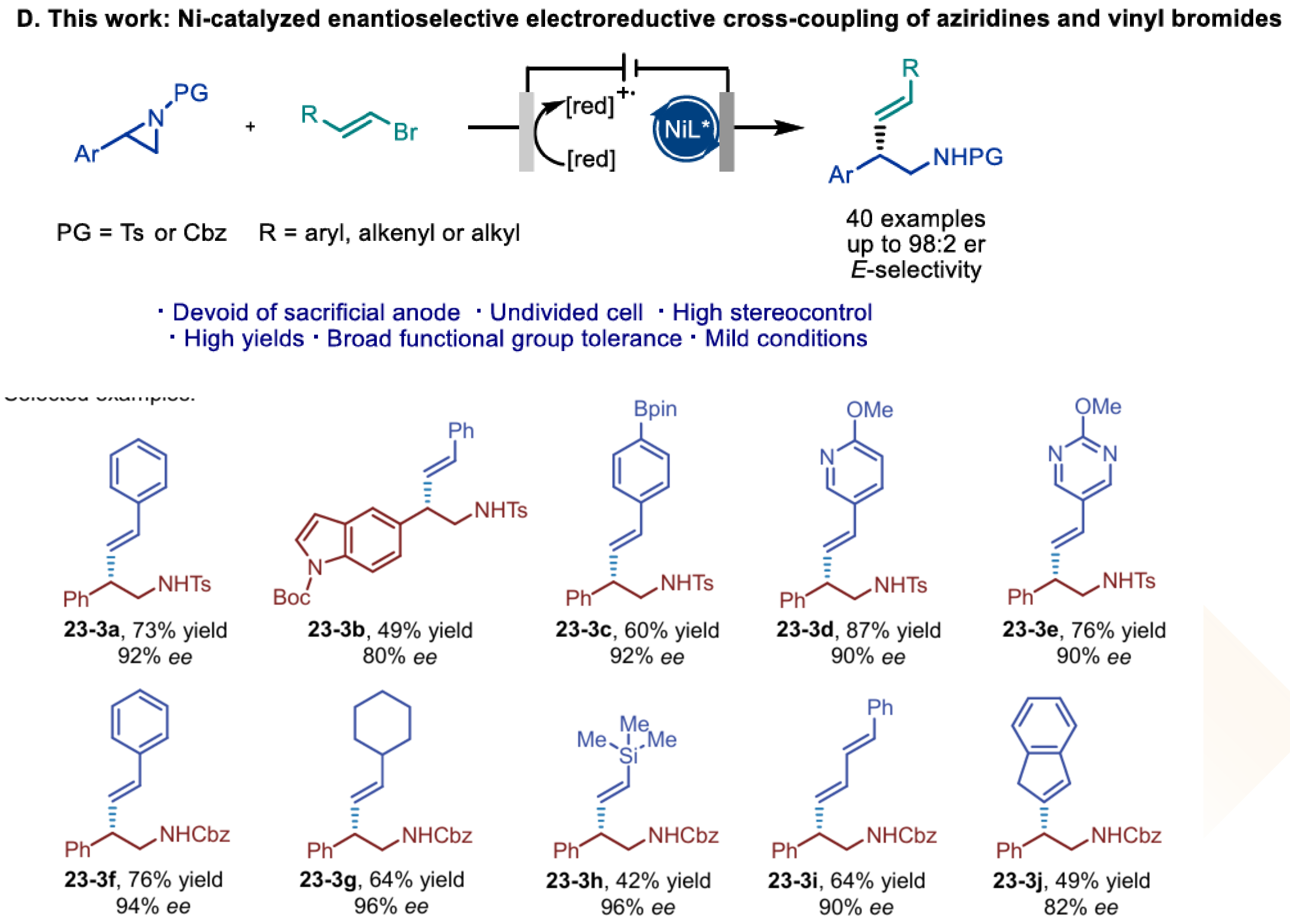


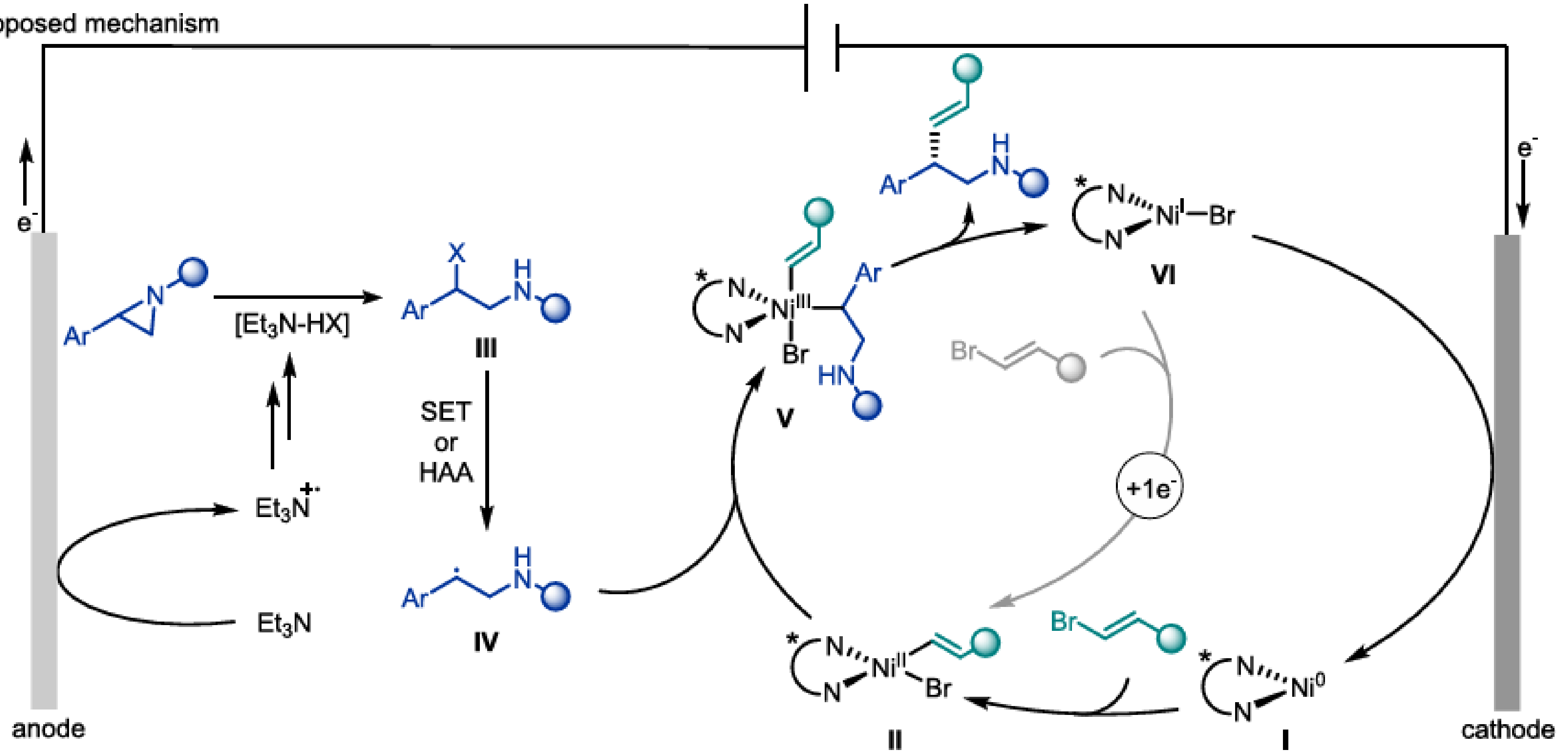
Ring-Opening Reactions: Ni



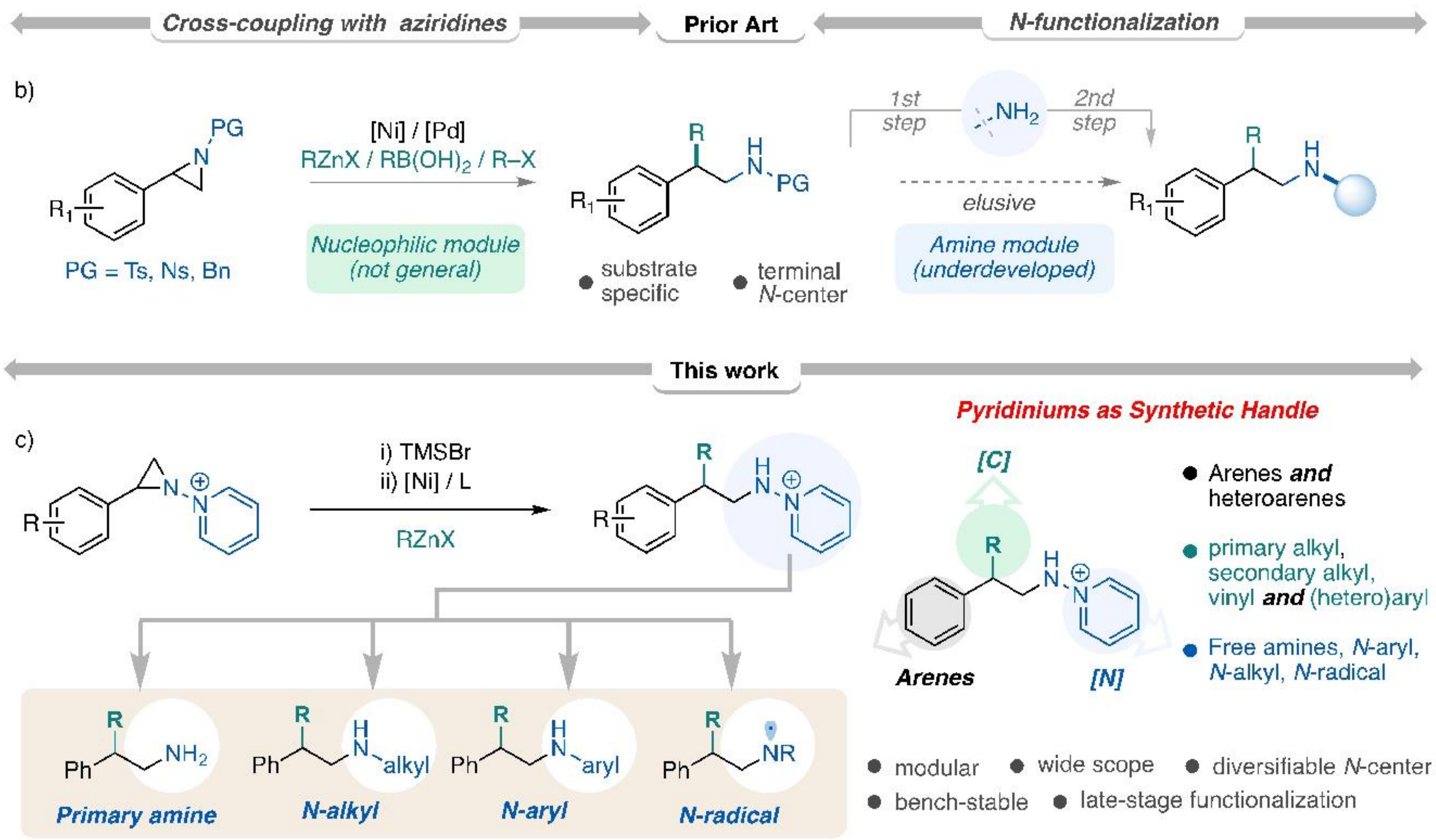
Nevado, C. *J. Am. Chem. Soc.* **2023**, *145*, 6270−6279.

Ring-Opening Reactions: Ni

H. Proposed mechanism



Ring-Opening Reactions: Ni



Powers, D. C. *Angew. Chem. Int. Ed.* **2024**, *63*, e202406335.

Ring-Opening Reactions: Ni

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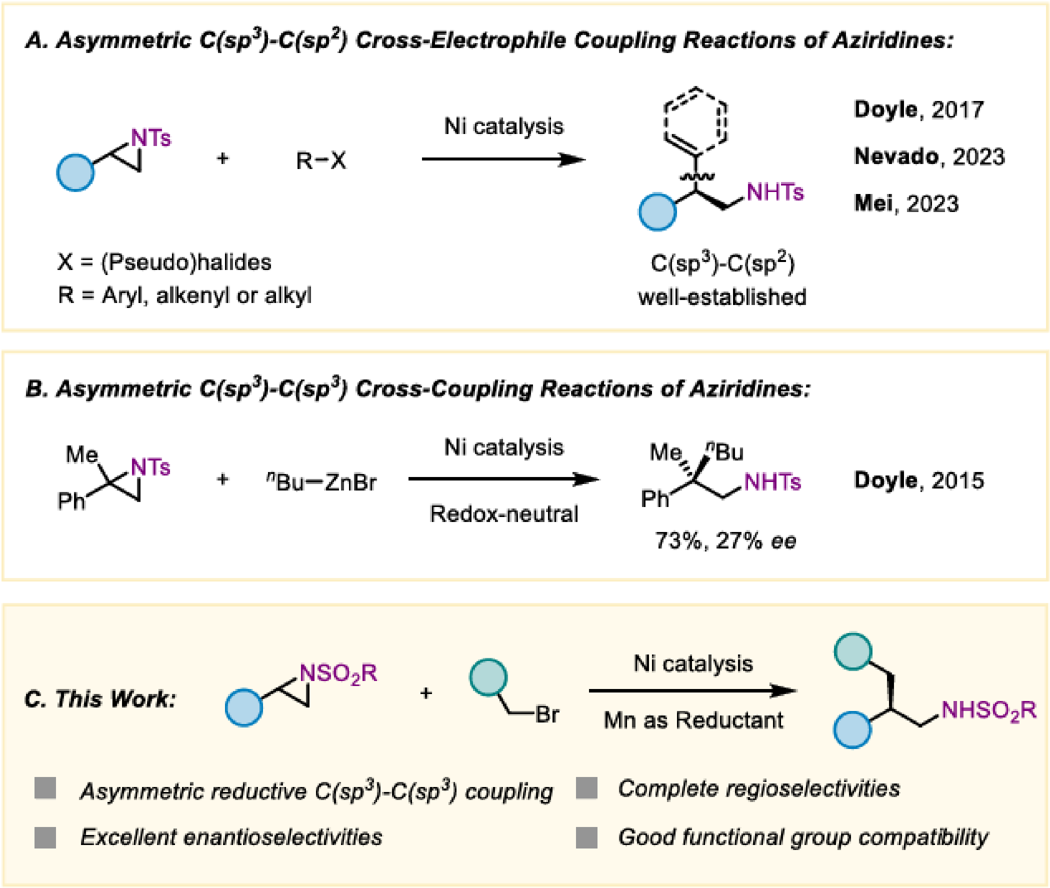
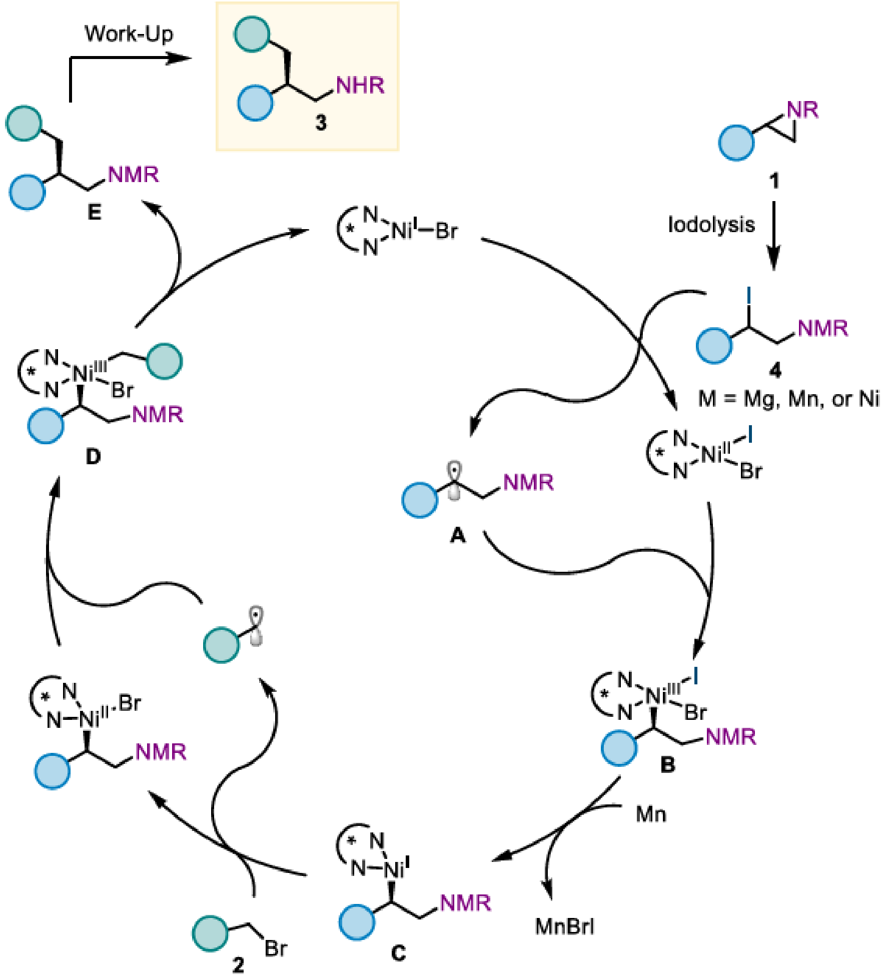
Scheme 1. Nickel-Catalyzed Enantioconvergent Ring-Opening Reactions of Aziridines





Liu, W. *J. Am. Chem. Soc.* **2024**, *1456*, 25426–25432.

Ring-Opening Reactions: Ti

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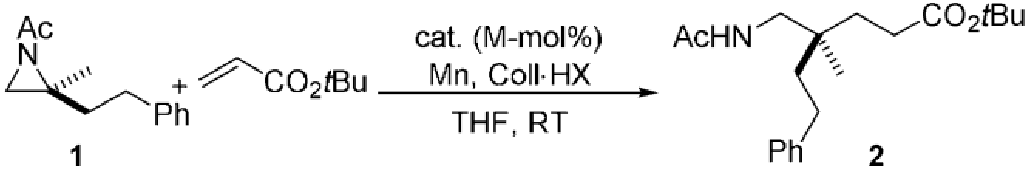
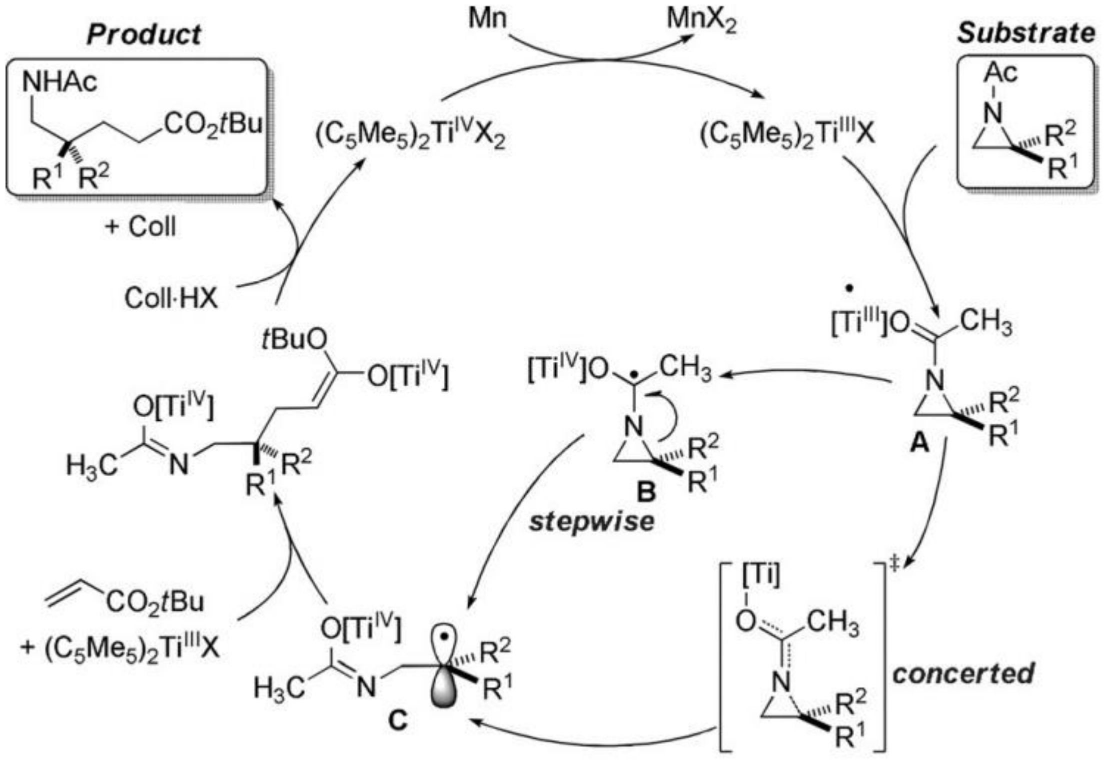
Table 1: Identification of suitable conditions for catalytic radical opening of *N*-acyl aziridines (Coll = 2,4,6-trimethylpyridine).[a]



Entry	Catalyst	mol%	Coll·HX	Yield [%]
1	$[Cp_2TiCl_2]$	10	Coll·HCl	22
2	$[(C_5H_4Me)_2TiCl_2]$	10	Coll·HCl	46
3	$[(C_5Me_5)_2TiCl_2]$	10	Coll·HCl	80
4	***$[(C_5Me_5)_2TiCl_2]$***	***10***	***Coll·HBr***	***82***
5	$[(C_5Me_5)_2TiCl_2]$	5	Coll·HBr	76

[a] Conditions: Catalyst (mol%), Mn (2.0 equiv.), Coll·HX (2.5 equiv.), *tert*-butyl acrylate (5.0 equiv.), **1** (0.125 M in THF), RT.

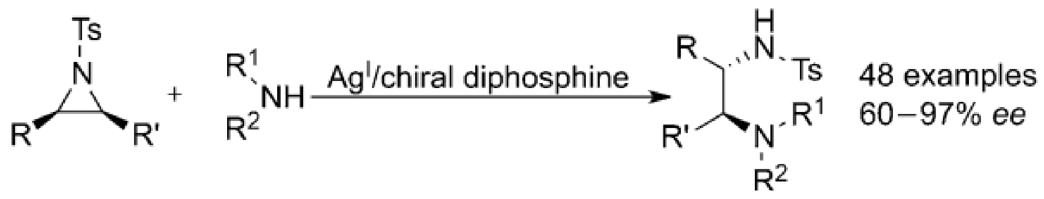


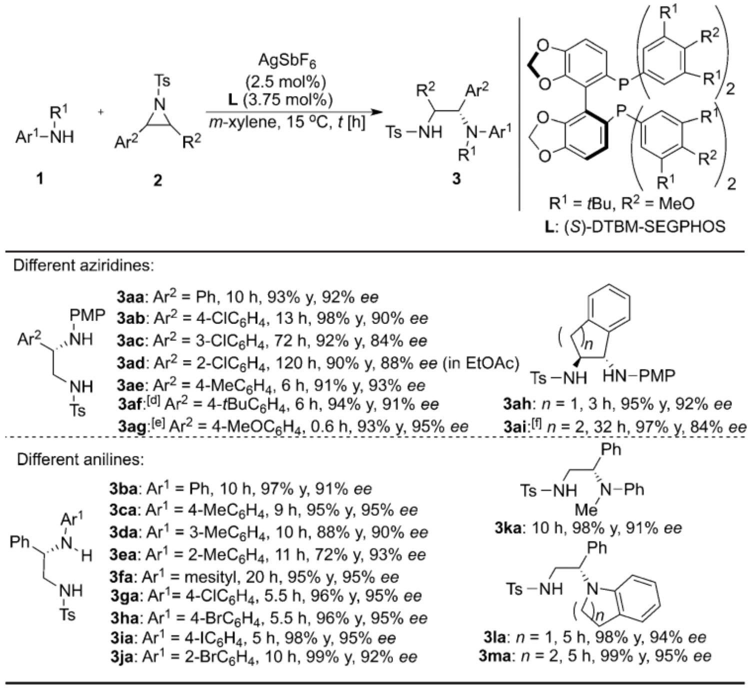
Scheme 1. Proposed catalytic cycle for the trapping of radicals derived from *N*-acyl aziridines ($[Ti^{IV}] = (C_5Me_5)_2TiX$, X = Cl or Br).

Gansäuer, A. *Angew. Chem. Int. Ed.* **2017**, *56*, 12654–12657.

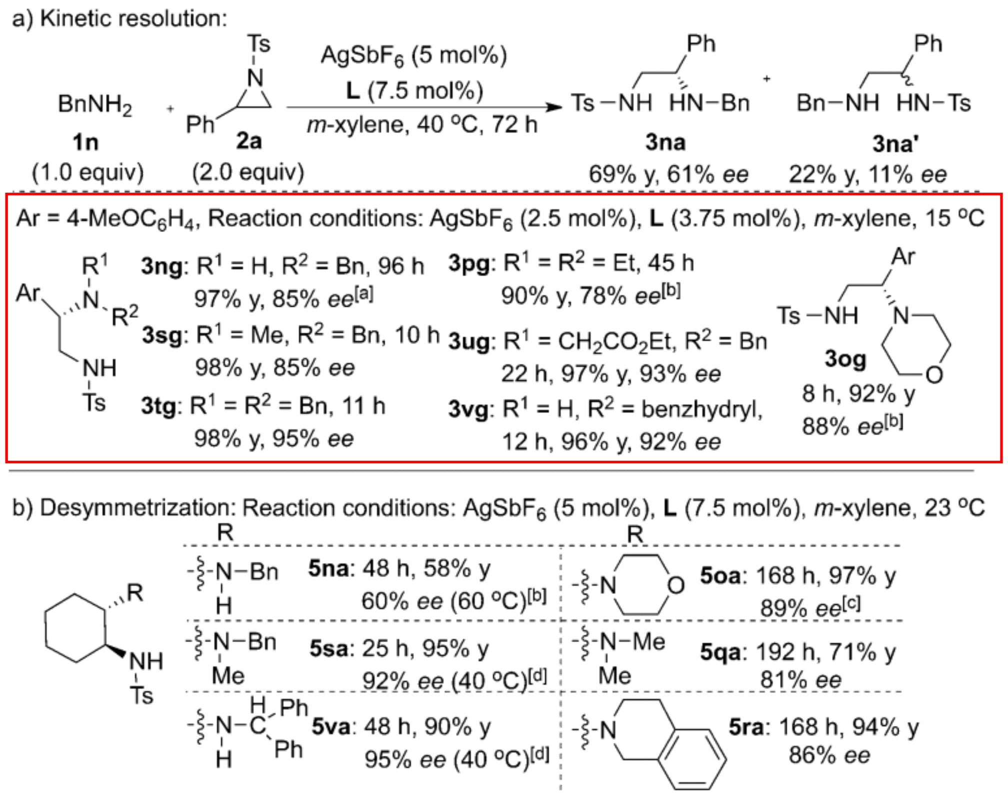
Ring-Opening Reactions: Ag

b) This work: kinetic resolution and desymmetrization with various amines





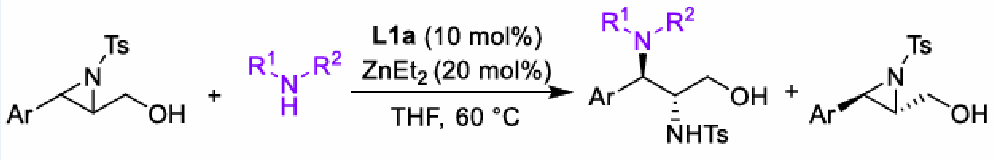
[a] Unless otherwise noted, reactions were run with **1** (0.1 mmol), **2** (0.22 mmol). $[\mathbf{1}]_0 = 0.2$ M. [b] Yield of isolated product. [c] The *ee* values were determined by chiral-phase HPLC. [d] Run with 2.0 equiv of aziridine **2 f**, 49% recovery of **2 f** (92% *ee*), s = 53. [e] Run at 0 °C. [f] Run with 2.0 equiv of aziridine **2 i**, 48% recovery of **2 i** (77% *ee*), s = 14. s = Ln[(1−C/100)(1−*ee*/100)]/Ln[(1−C/100)(1+*ee*/100)]. PMP = *para*-methylphenyl, Ts = 4-toluenesulfonyl.

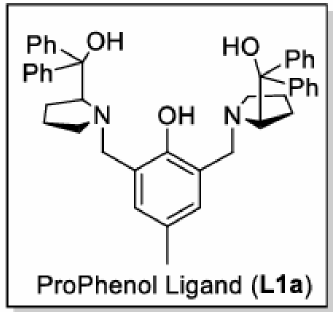


Scheme 2. Reactions with aliphatic amines. [a] Run with 5 mol% of $AgSbF_6$, 7.5 mol% of **L** at 0 °C. [b] Run with 5 mol% of $AgPF_6$, 7.5 mol% of **L**. [c] $[\mathbf{1}]_0 = 0.5$ M. [d] $[\mathbf{1}]_0 = 1.0$ M. The reaction run at $[\mathbf{1}]_0 = 0.2$ M required 120 h (for **5 sa**) and 192 h (for **5 va**), respectively, to provide the almost same results.

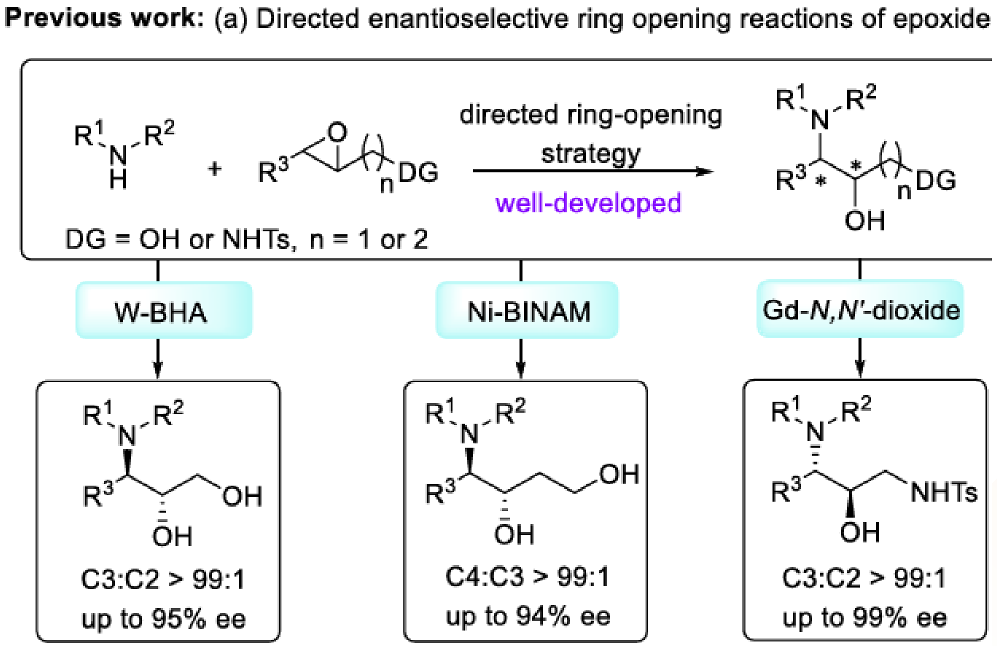
Chai, Z. *Angew. Chem. Int. Ed.* **2017**, *56*, 650–654.

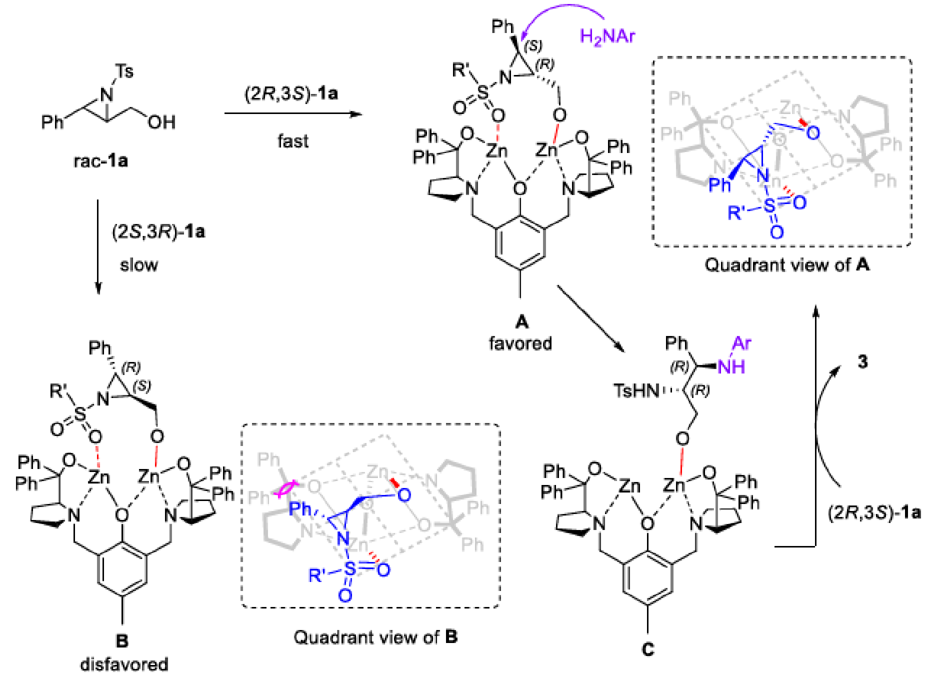
Ring-Opening Reactions: Zn





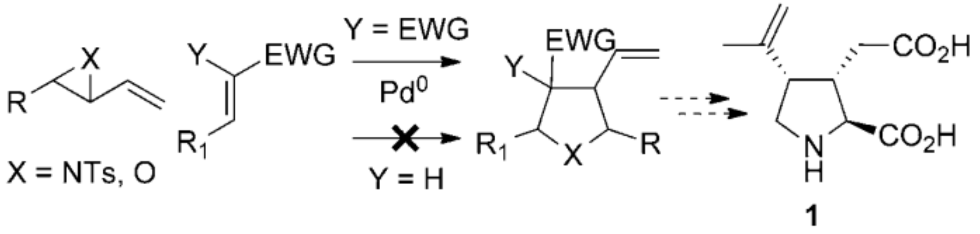
- hydroxyl-directed ring opening strategy
- 35 examples, s factor up to 200
- kinetic resolution of *trans*-2,3-aziridinyl alcohols
- broad scope, gram scale and late-stage functionalization



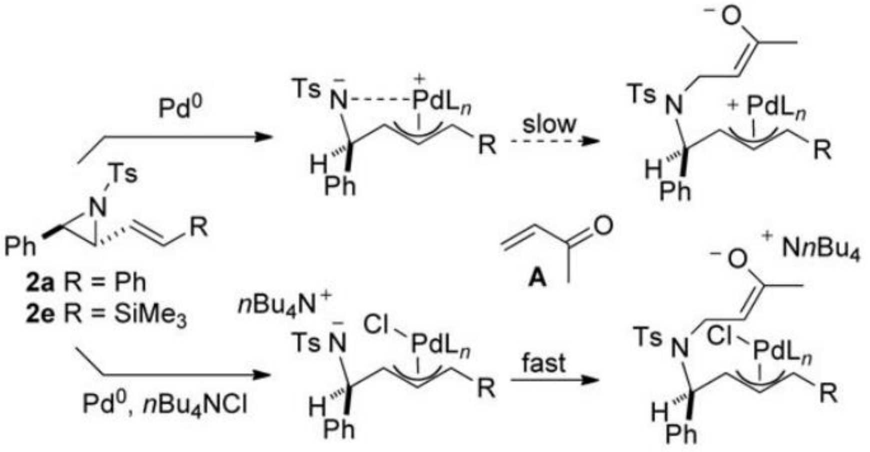


Jia, S.-K. *ACS Catal.* **2023**, *13*, 6873–6878.

Cycloaddition Reaction： Pd

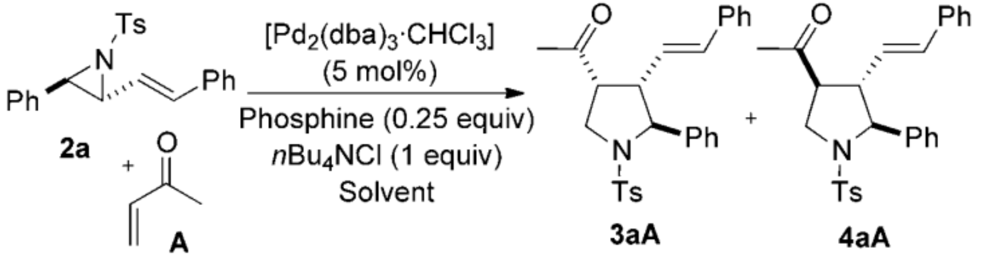


Scheme 1. Palladium-catalyzed annulation reaction of vinyl epoxides/aziridines with Michael acceptors. EWG = electron-withdrawing group, Ts = 4-toluenesulfonyl.



Scheme 2. Possible origin of low reactivity of amide towards MVK.

Table 1: Optimization of the annulation reaction.[a]

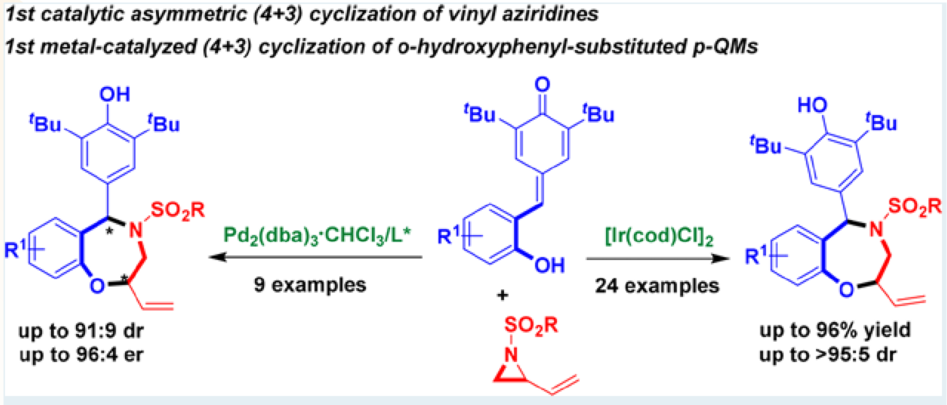


Entry	Phosphine	Solvent	Yield [%][b]	d.r. (3 aA/4 aA)
1[c]	$(4\text{-}FC_6H_4)_3P$	THF	21	50:50
2	$(4\text{-}FC_6H_4)_3P$	THF	38	68:32
3	Ph_3P	THF	36	65:35
4	$(2\text{-furyl})_3P$	THF	56	69:31
5	$(o\text{-tolyl})_3P$	THF	38	83:17
6	$(o\text{-tolyl})_3P$	Et_2O	60	92:8
7	$(o\text{-tolyl})_3P$	Pentane	60	93:7
8	$(o\text{-tolyl})_3P$	Pent/Et_2O[d]	65	93:7
9	$(o\text{-tolyl})_3P$	Pent/TBME[d]	66	93:7

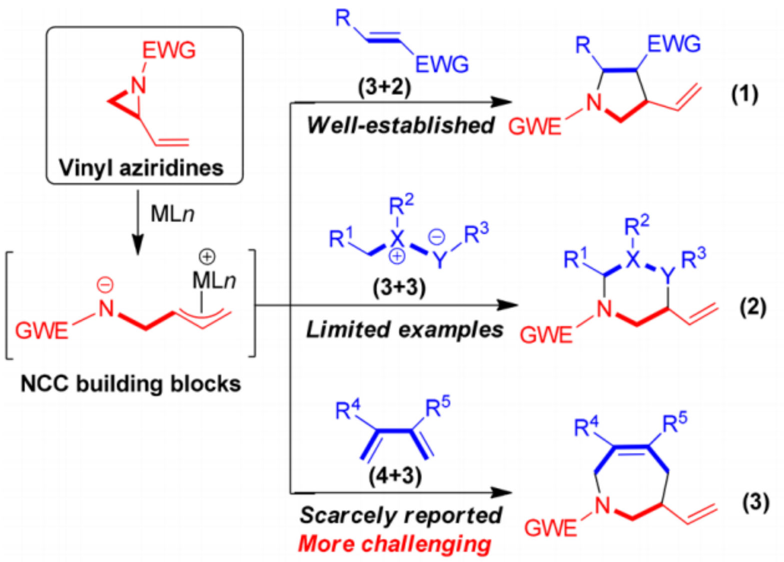
[a] All reactions conducted at 0.1 M, 20 °C, with 10 equivalents of MVK. [b] Yield of isolated product. [c] 2 equivalents of MVK was used. [d] 3:1 mixture of solvents was used. dba = *trans,trans*-dibenzylideneacetone, Pent = pentane, TBME = *t*BuOMe, THF = tetrahydrofuran.

Aggarwal, V. K. *Angew.Chem. Int. Ed.* **2011**, *50*, 6370–6374.

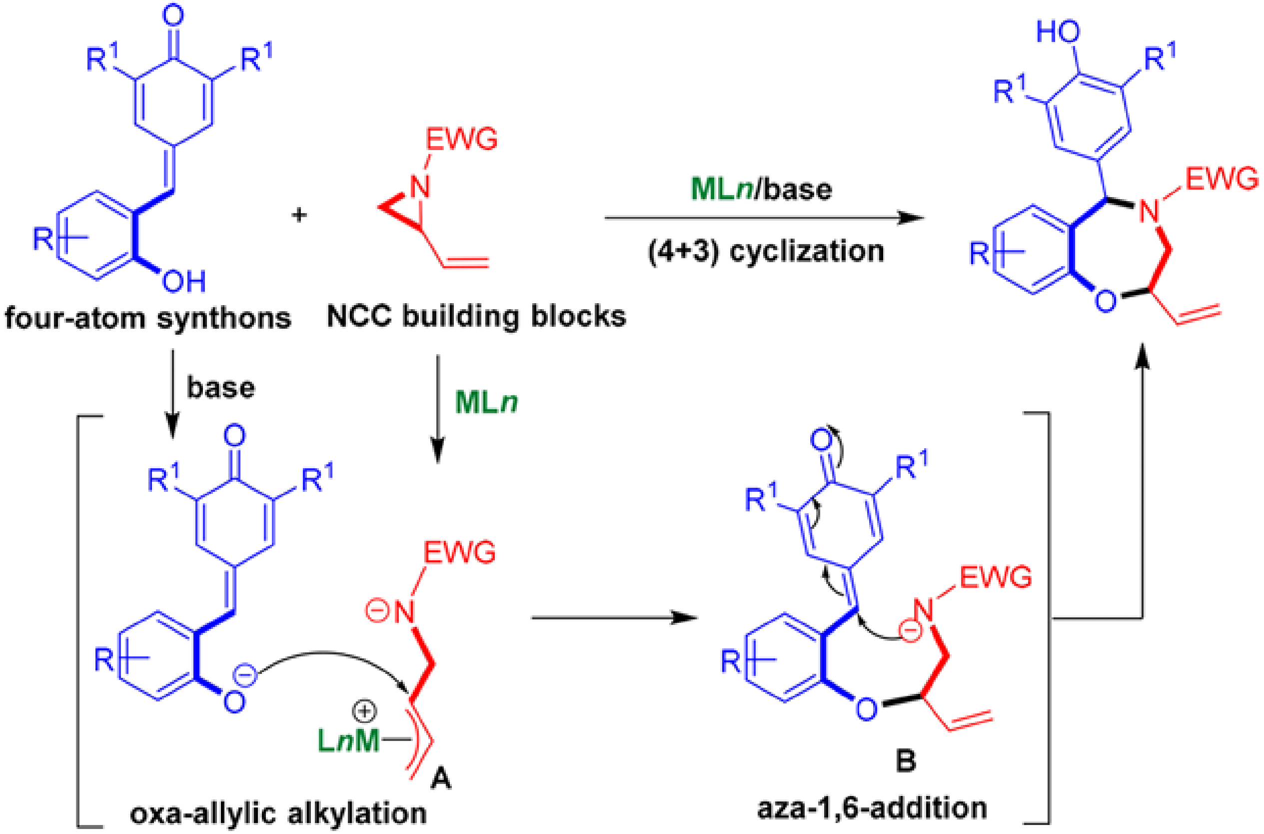
Cycloaddition Reaction： Pd



Scheme 1. Profile of Vinyl Aziridines-Involved Cyclizations Acting as NCC Synthons



1st metal-catalyzed (4+3) cyclization of o-hydroxyphenyl-substituted p-QMs



Shi, F. *ACS Catal.* **2018**, *8*, 10234−10240.

Cycloaddition Reaction： Rh

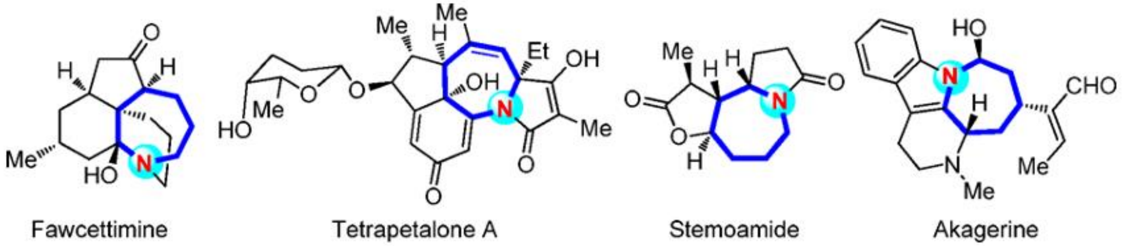


Figure 1. Natural products featuring ring-fused azepines.

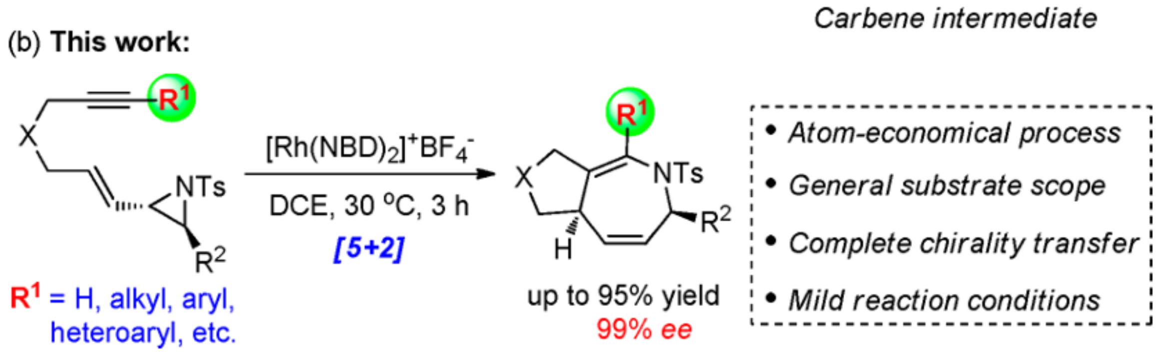
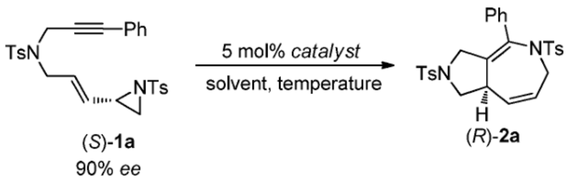


Table 1. Optimization of Reaction Conditions[a]



entry	catalyst	time (h)	yield (%)[b]	ee (%)
1[c]	$[Rh(CO)_2Cl]_2$	15	*f*	
2	$[Rh(\eta^6\text{-}C_{10}H_8)(COD)]\ SbF_6$	15	92	87
3	$[Rh(dnCOT)(MeCN)_2]\ SbF_6$	15	40	83
4	$RhCl(IPr)(COD)/AgSbF_6$	15	92	84
5	$[Rh(NBD)dppe]\ BF_4$	15	56	88
6	$[Rh(NBD)Cl]_2/AgSbF_6$	5	99	90
7	$[Rh(NBD)Cl]_2/AgOTf$	5	99	90
8	$[Rh(NBD)Cl]_2/AgPF_6$	5	92	90
9	$[Rh(NBD)Cl]_2/AgClO_4$	5	88	90
10	$[Rh(NBD)Cl]_2/C_3F_7CO_2Ag$	5	47	70
11[c]	$[Rh(NBD)_2]\ BF_4$	5	99	91
12[d]	$[Rh(NBD)_2]\ BF_4$	3	99	90
13[e]	$[Rh(NBD)_2]\ BF_4$	3	99(90)	90
14[e]	$[Rh(COD)_2]\ BF_4$	3	90	90

[a]All reactions were carried out with 0.2 mmol of **1a** and 5 mol % of catalyst (Rh to $AgSbF_6$ = 1:1) in 3.0 mL of 1,2-dichloroethane (DCE) at 80 °C. [b]NMR yield with CH_2Br_2 as an internal standard; values in the parentheses are isolated yield. [c]Ten mole percent of catalyst was used. [d]Reaction was run at 60 °C. [e]Reaction was run at 30 °C. [f]Complex mixture.

Zhang, J. *J. Am.Chem. Soc.* **2015**, *137*, 3787–3790.

Cycloaddition Reaction： Rh

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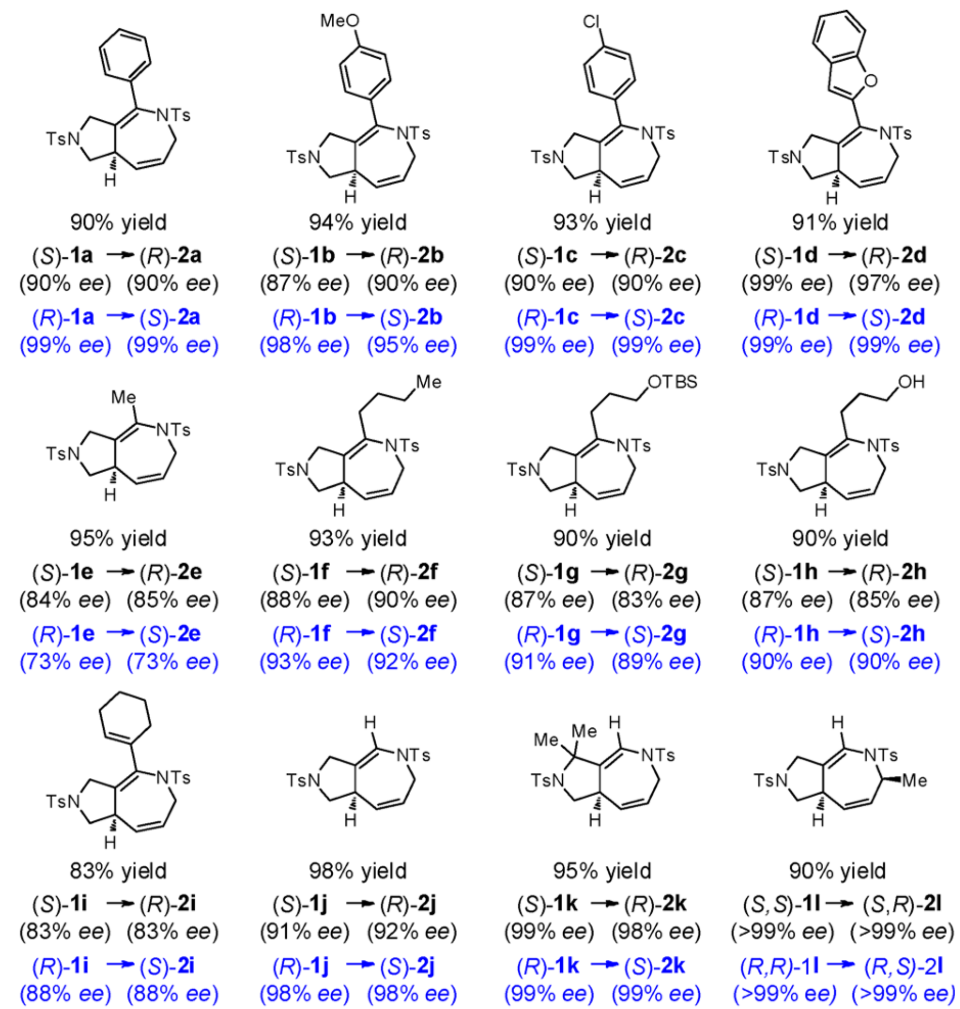
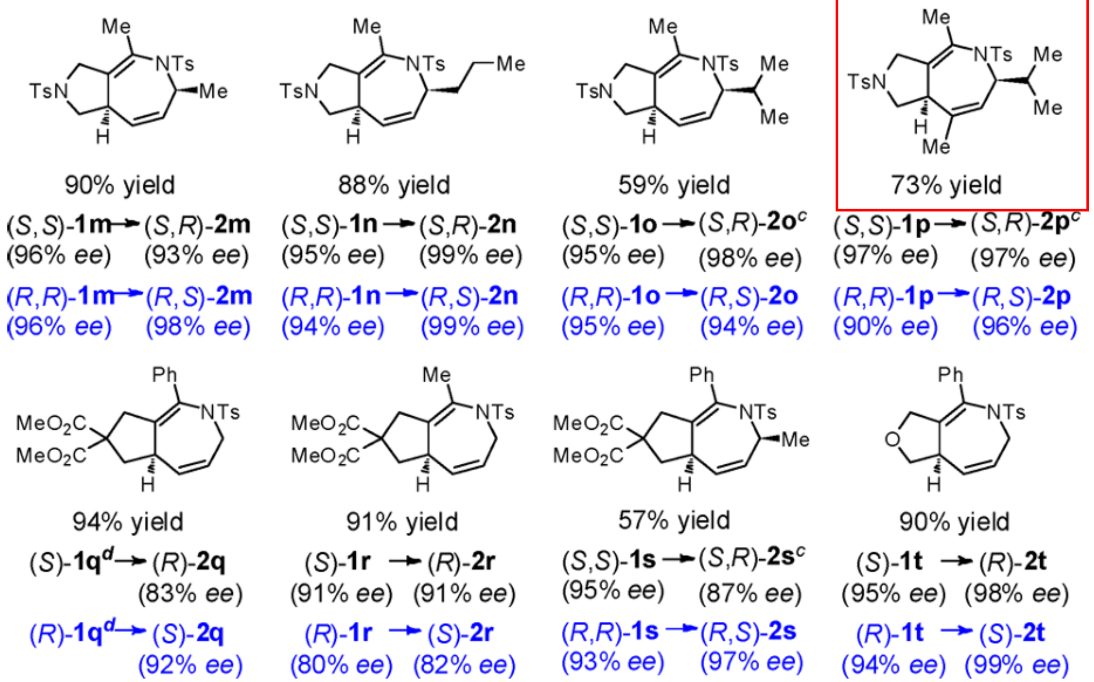
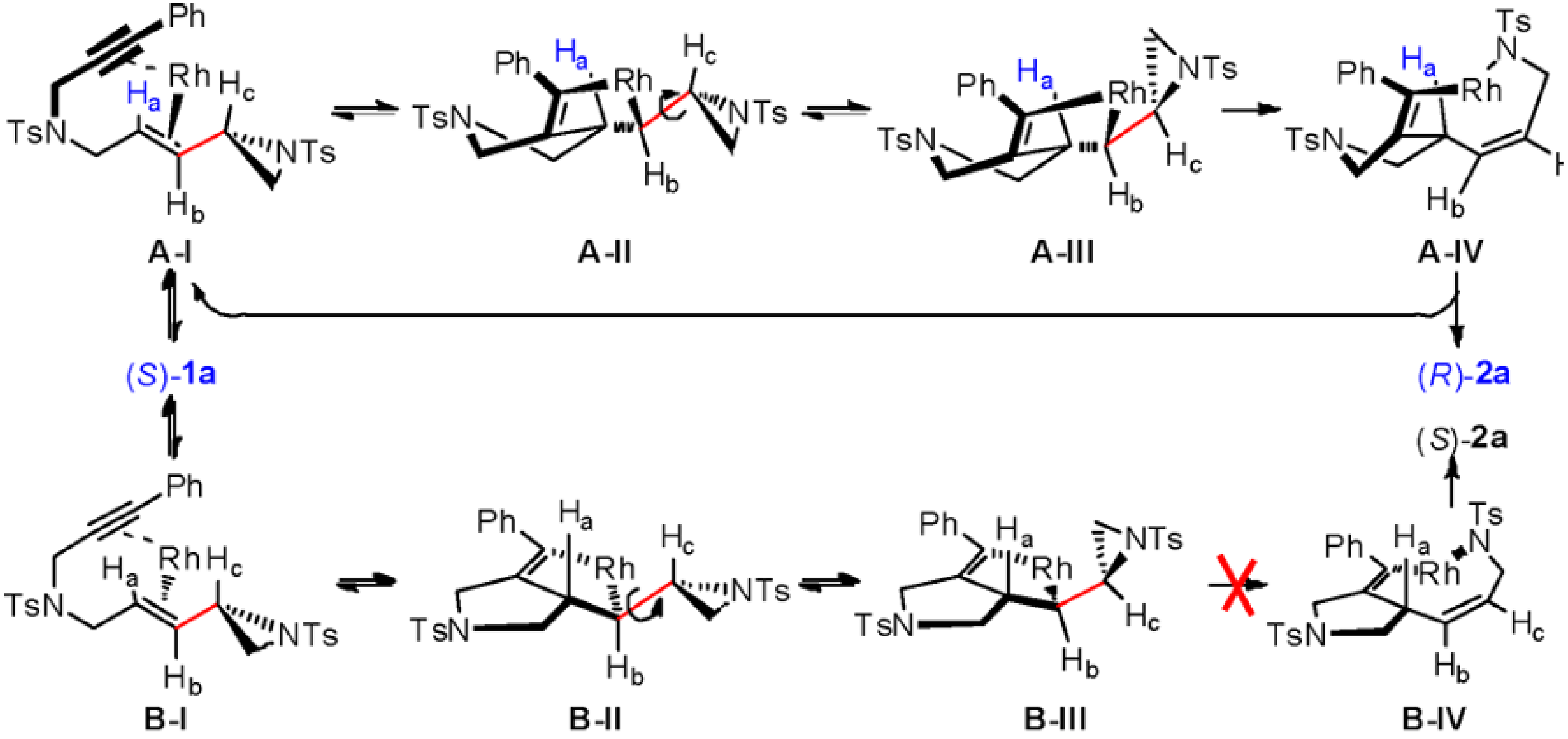
Table 2. Exploration of Substrate Scope[a,b]





[a]Standard conditions: $[Rh(NBD)^2]^+BF_4^-$ (5 mol %), DCE (0.067 M), 30 °C, 3 h. [b]Average isolated yield of the reactions from (*S*)-**1** and its enantiomer. [c]The reaction was run at 80 °C for 4 h with 10 mol % catalyst. [d]The *ee* value of **1q** can not be determined by HPLC analysis using a chiral stationary phase.

Cycloaddition Reaction： Rh



Cycloaddition Reaction： Rh

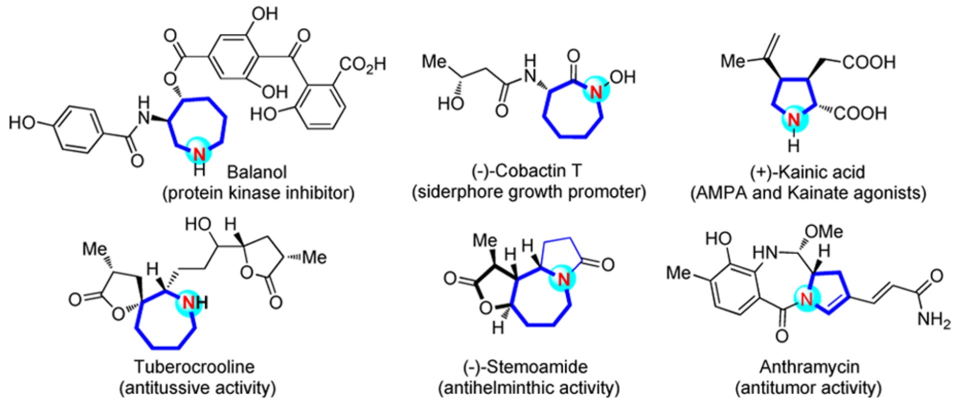
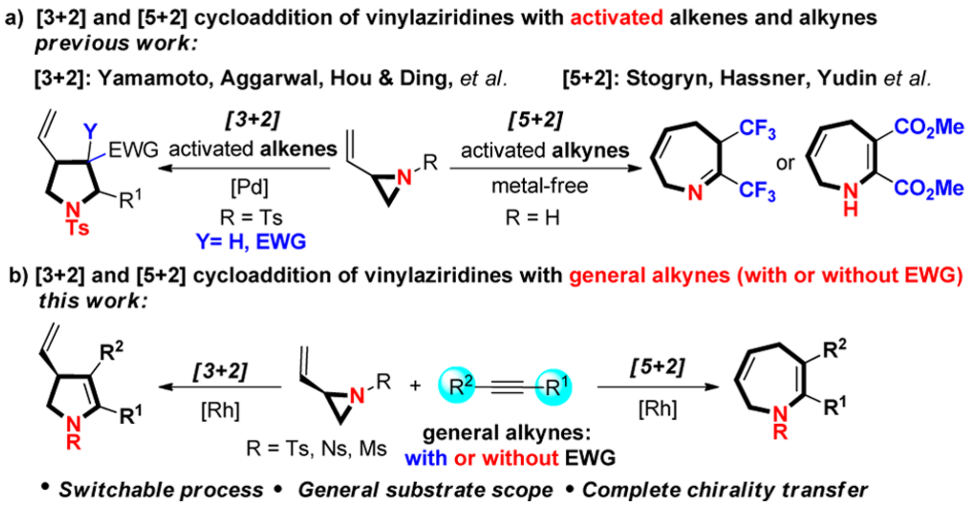
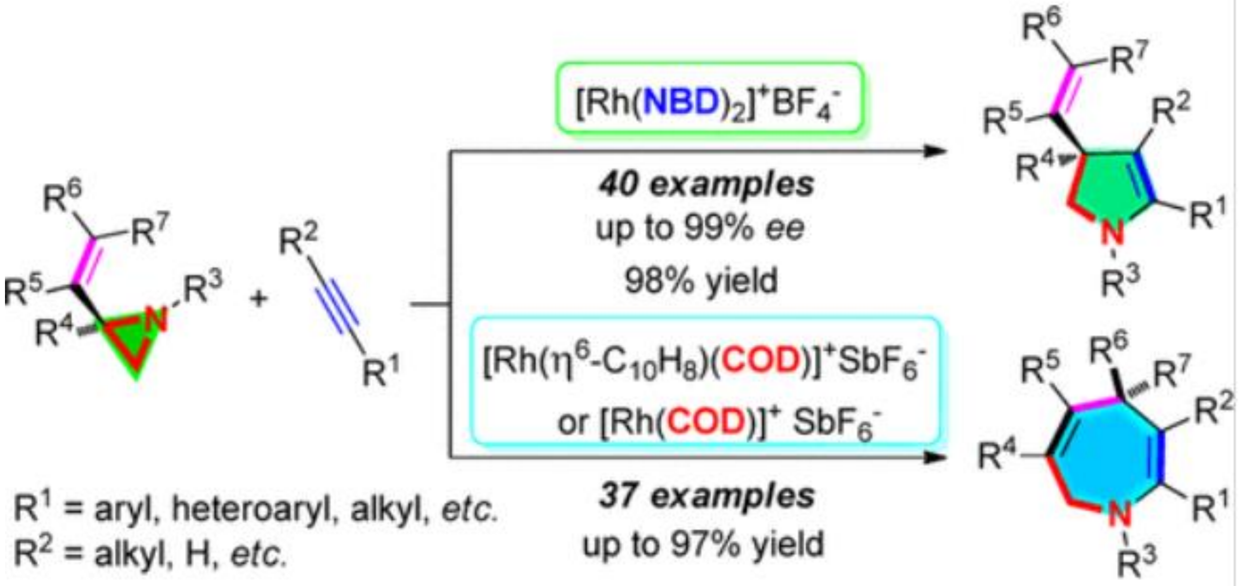


Figure 1. Biologically active natural products containing pyrrolidine anc azepine skeletons.

Scheme 1. Intermolecular [3 + 2] and [5 + 2] Cycloadditions of Vinylaziridines

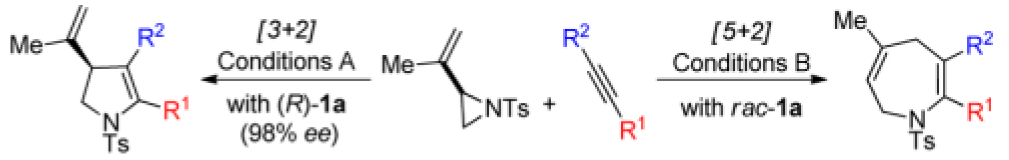




Zhang, J. *J. Am.Chem. Soc.* **2016**, *138*, 2178–2181.

Cycloaddition Reaction： Rh

Table 1. Scope with Respect to Various Alkynes 2



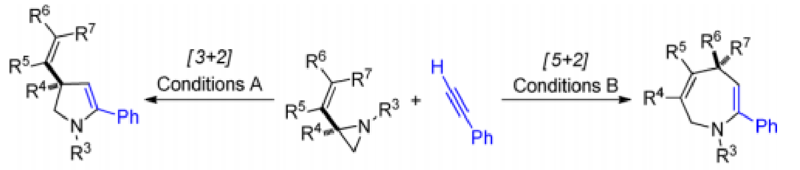
3 1a 2 4

entry	R^1/R^2	Cond. A,[c] Yield (ee) (%)	Cond. B,[c] Yield (%)
1	Ph/H (**2a**)	**3aa**, 80 (97)	**4aa**, 90
2	4-EtOC_6H_4/H (**2b**)	**3ab**, 70 (98)	**4ab**, 94
3	4-*t*-BuC_6H_4/H (**2c**)	**3ac**, 93 (96)	**4ac**, 93
4	4-MeC_6H_4/H (**2d**)	**3ad**, 72 (97)	**4ad**, 90
5	3-MeC_6H_4/H (**2e**)	**3ae**, 78 (98)	**4ae**, 97
6	2-MeC_6H_4/H (**2f**)	**3af**, 90 (98)	**4af**, 97
7	4-FC_6H_4/H (**2g**)	**3ag**, 91 (98)	**4ag**, 91
8	4-ClC_6H_4/H (**2h**)	**3ah**, 82 (96)	**4ah**, 75
9	4-BrC_6H_4/H (**2i**)	**3ai**, 86 (94)	**4ai**, 60
10	4-AcC_6H_4/H (**2j**)	**3aj**, 70 (97)	**4aj**, 17
11	4-Me$CO_2C_6H_4$/H (**2k**)	**3ak**, 65 (98)	**4ak**, 61
12	1-naphthyl/H (**2l**)	**3al**, 87 (94)	**4al**, 30
13	2-naphthyl/H (**2m**)	**3am**, 88 (99)	**4am**,93
14	2-thienyl/H (**2n**)	**3an**, 82 (98)	**4an**, 61
15	2-benzofuranyl/H (**2o**)	**3ao**, 89 (98)	**4ao**, 61
16	cyclohexenyl/H (**2p**)	**3ap**, 66 (97)	**4ap**, 82
17	*n*-C_3H_7/H (**2q**)[i]	**3aq**, 90(97)[d,e]	**4aq**, 90[f]
18	*n*-C_5H_{11}/H (**2r**)	**3ar**, 66(98)[d,e]	**4ar**, 76[f]
19	C_6H_5(CH2)$_2$/H (**2s**)	**3as**, 71(96)	**4as**, 74[j]
20	$(CH_3)_2CHCH_2$/H (**2t**)[i]	**3at**, 85(97)[d,e]	**4at**, 75
21	cyclopropyl/H (**2u**)[i]	**3au**, 98(97)[e]	**4au**, 84
22	$(CH_2)_3$OTBS/H (**2v**)	**3av**, 70(–)[e,g]	**4av**, 69[f]
23	$(CH_2)_3$OBn/H (**2w**)	**3aw**, 65(97)[d,e]	**4aw**, 75[f]
24	$(CH_2)_2CO_2$Me/H (**2x**)	**3ax**, 55(90)[d,e]	**4ax**, 78[f,j]
25	$(CH_2)_3$Phth/H (**2y**)	**3ay**, 77(93)[d]	**4ay**, 67[f]
26	Et/Et (**2z**)[h]	**3az**, 52 (92)	**4az**, 18[a]
27	TMS/Me (**2aa**)	**3aaa**, 64(96)	**3aaa**, 40[e]
28	4-MeOC_6H_4/CH_2OMe (**2bb**)	**3abb**, 69(96)	**3abb**, 30[e]
29	Ph/COMe (**2cc**)	**3acc**, 75(94)	**3acc**, 37

[a]Condition A: 0.25 mmol (*R*)-**1a**, 1.2 equiv **2**, and 5 mol % $[Rh(NBD)_2]BF_4$ in 2.5 mL 1,2-dichloroethane (DCE) at rt for 15 min. [b]Condition B: 0.25 mmol *rac*-**1a**, 1.5 equiv **2**, and 5 mol % $[Rh(\eta^6\text{-}C_{10}H_8)(COD)]SbF_6$ in 2.5 mL DCE at 0 °C for 30 min, then it was stirred at rt for 15 min. [c]Isolated yield. [d]The ee value was determined after conversion of **3** to *γ*-amino ketone **5**. [e]NMR yield. [f]**4aq**:**4aq′** = 14:1, **4ar**: **4ar′** = 10:1, **4av**:**4av′** = 10:1, **4aw**:**4aw′** = 10:1, **4ax**:**4ax′** = 3.3:1, **4ay**:**4ay′** = 6.3:1. [g]The product is very unstable. [h]5.0 equiv of **2**. [i]10.0 equiv of **2**. [j]10 mol % catalyst.

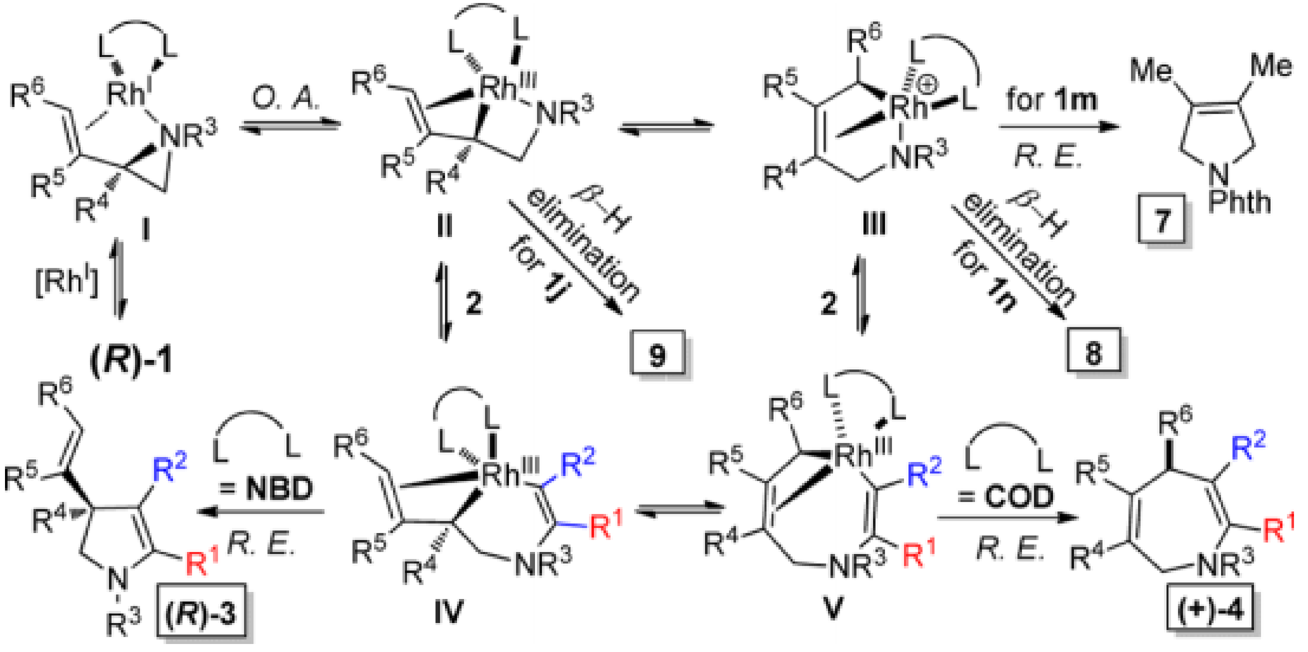
Cycloaddition Reaction： Rh

Table 2. Scope with Respect to Various VAs 1[a]

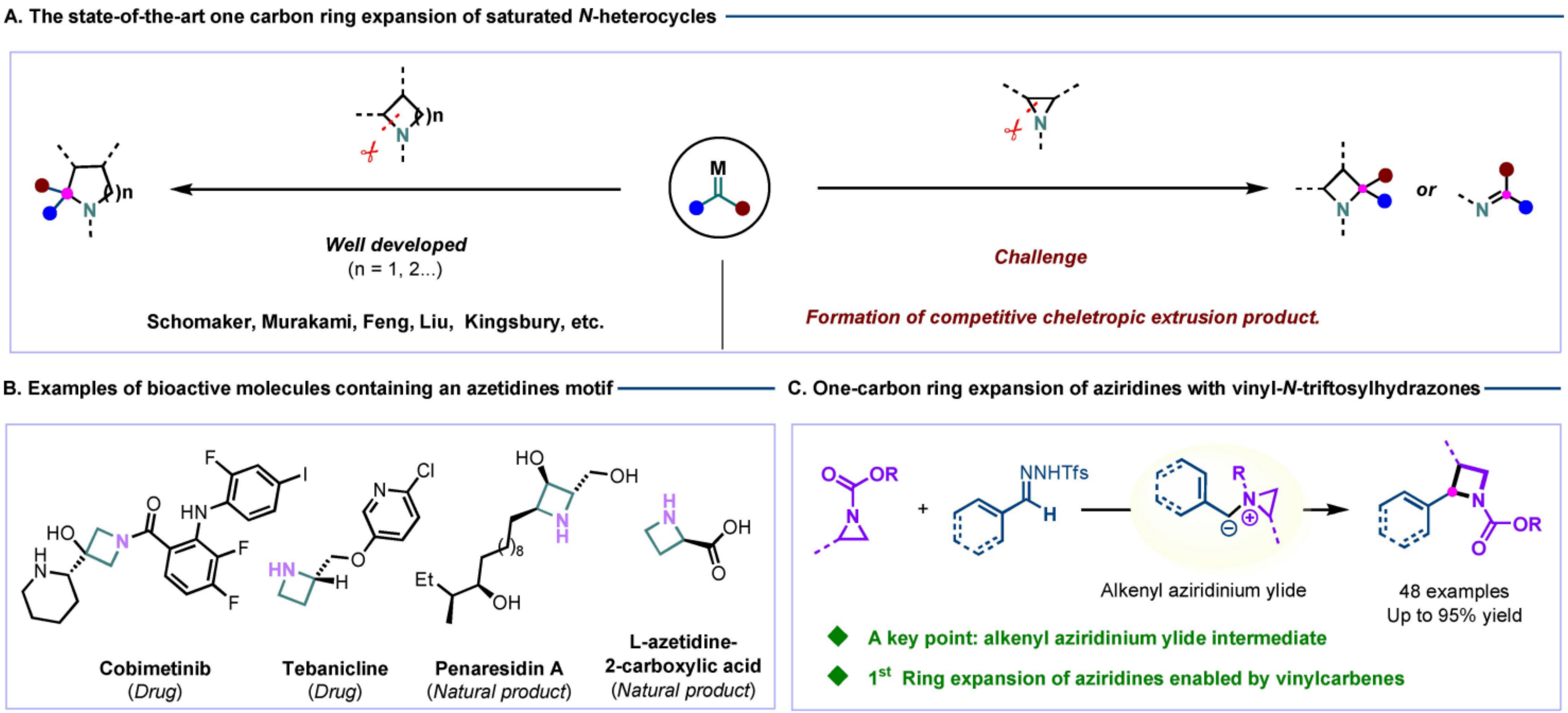


entry	(1)(ee%)	Cond. A Yield(ee)(%)	Cond. B Yield(%)
1	R^3 = Ts(**1b**)(99)	**3ba**, 75 (97)	**4ba**, 40[b]
2	R^3 = Ns(**1c**)(92)	**3ca**, 84 (92)	**4ca**, 70
3	R^3 = Ms(**1d**)(86)	**3da**, 50(86)	**4da**, 62
4	R^5 = *i*-Pr(**1e**)(90)	**3ea**, 72 (90)	**4ea**, 92
5	R^5 = *n*-Bu(**1f**)(88)	**3fa**, 65 (93)	**4fa**, 91
6	R^5 = Ph(**1g**)(97)	**3ga**, 75 (99)	**4ga**, 90
7	R^5 = OTBS(**1h**)(95)	**3ha**,84 (95)	**4ha**, 78
8	R^5 = OTES(**1i**)(94)	**3ia**, 75[c] (-)	**4ia**, 76[c]
9	R^5 = H, R^4 = *i*-Pr ((*R*)-**1j**)(85)	**3ja**, 78 (84)	**4ja**, 48[d]
10	R^5 = Me, R^4 = Me ((*S*)-**1k**)(86)	**3ka**, 55 (85)[e]	**4ka**, 40[f]
11	**1l** (98)	**3la**, 53 (32)[c]	**4la**,40[g]

Scheme 2. Proposed Mechanism



Cycloaddition Reaction： Rh



Bi, X. *Angew. Chem. Int. Ed.* **2024**, *63*, e202318072.

Cycloaddition Reaction： Rh

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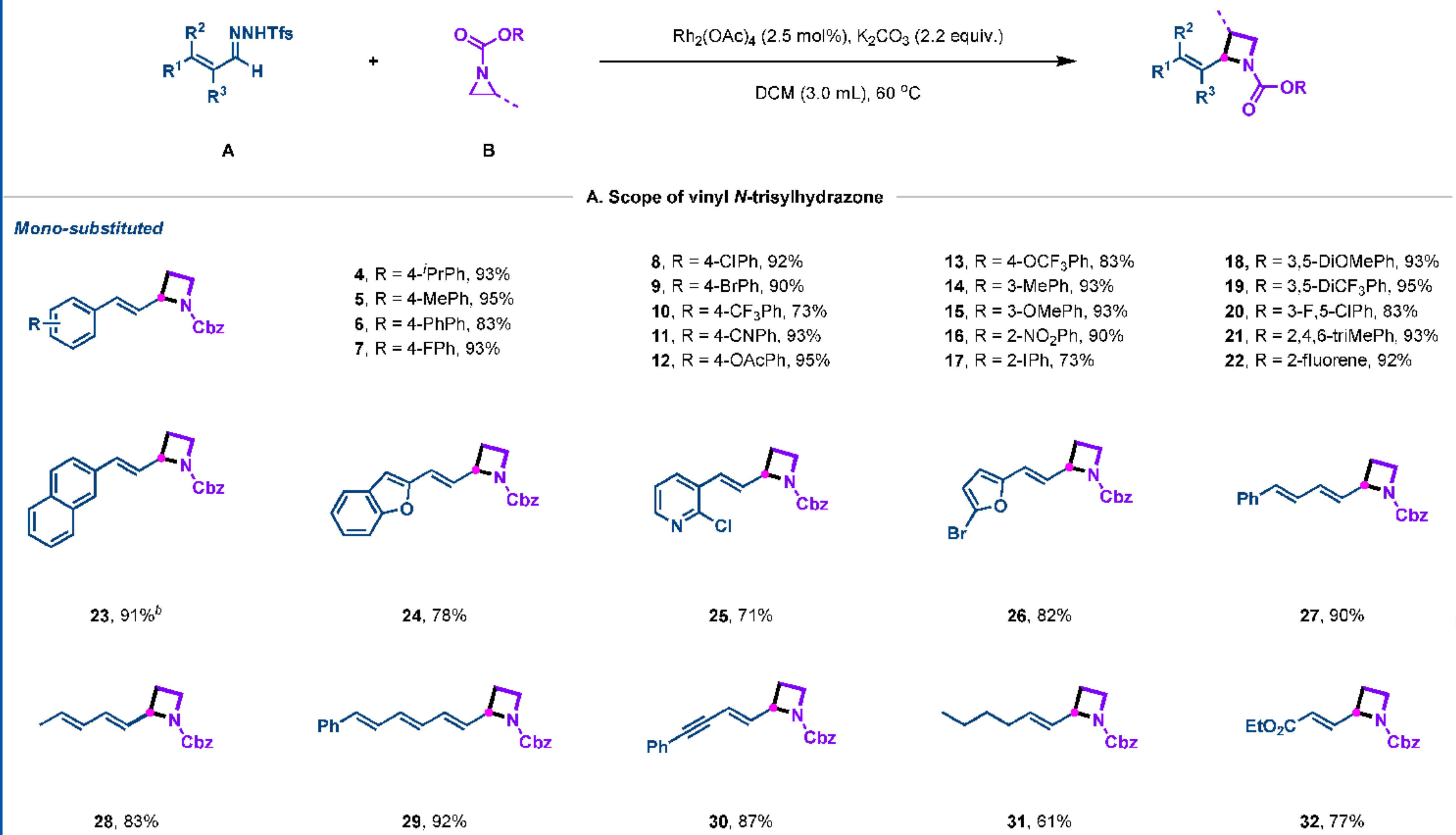

Cycloaddition Reaction： Rh

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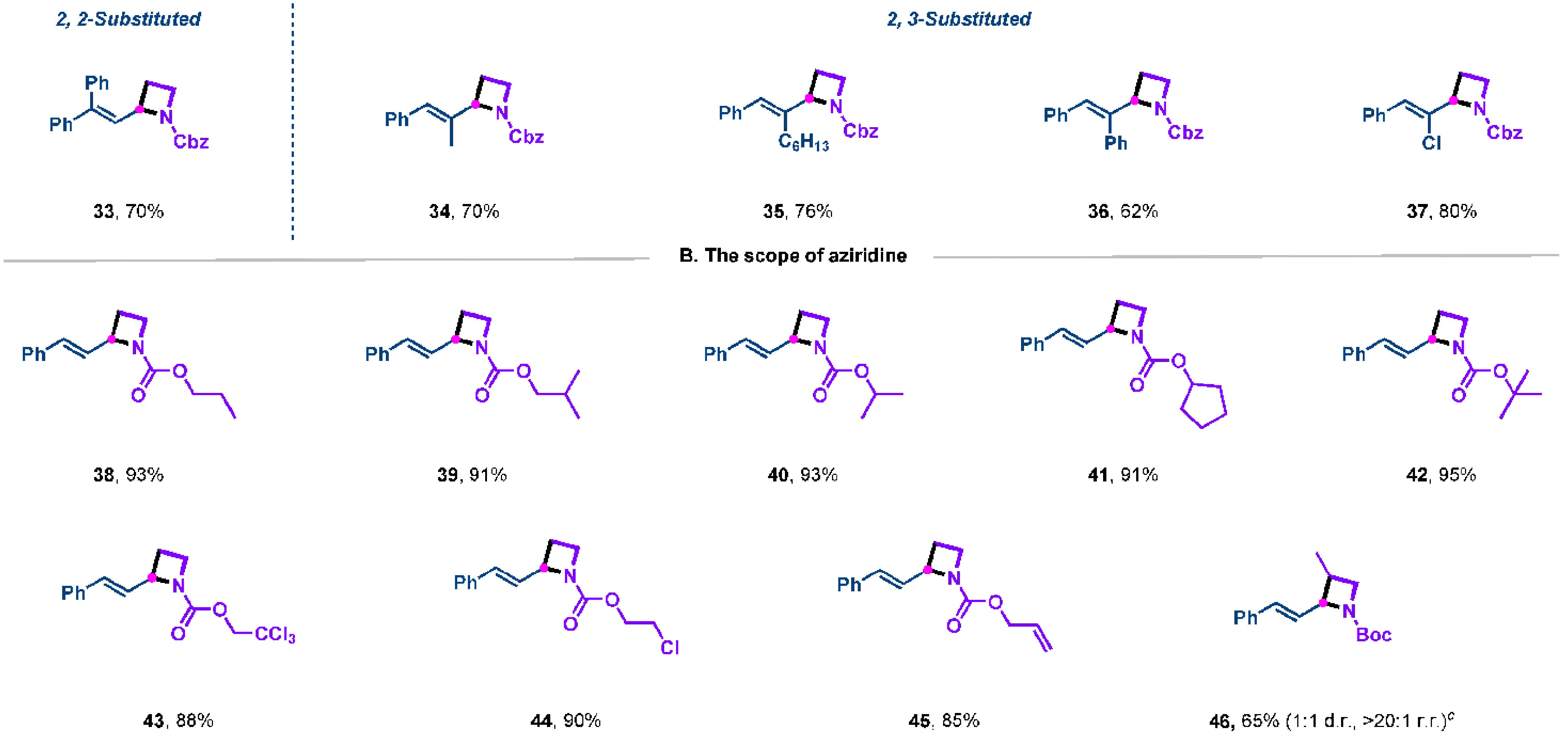

Cycloaddition Reaction： Rh

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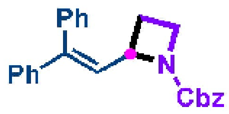
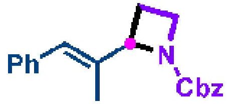
2, 2-Substituted

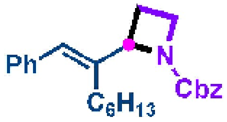


33, 70%

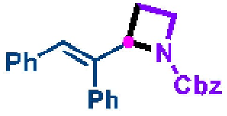
2, 3-Substituted



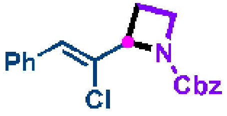
34, 70%



35, 76%

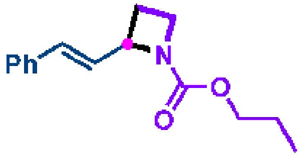


36, 62%

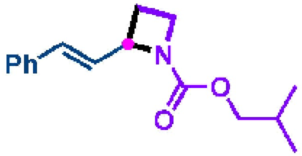


37, 80%

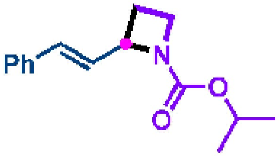
B. The scope of aziridine



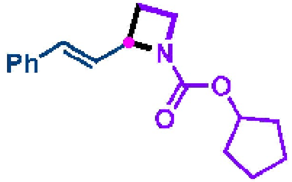
38, 93%



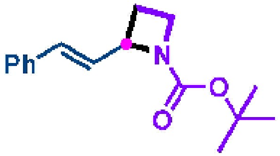
39, 91%



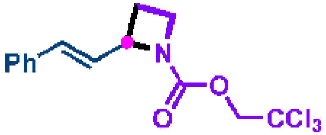
40, 93%



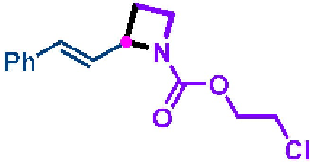
41, 91%



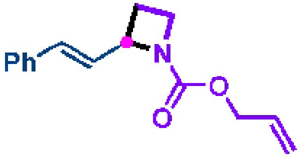
42, 95%



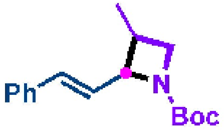
43, 88%



44, 90%



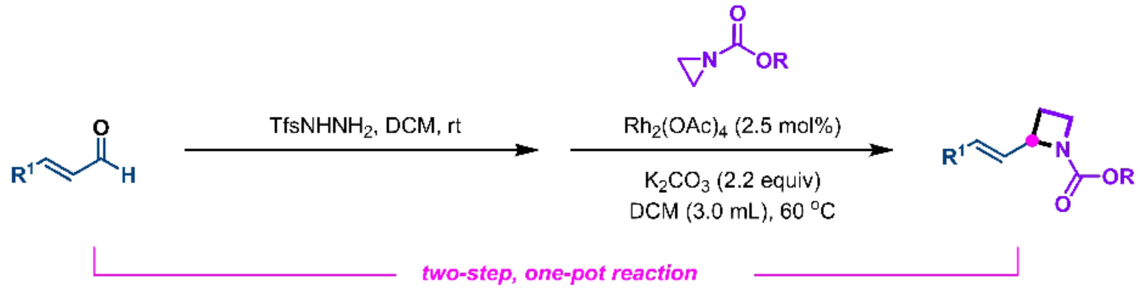
45, 85%

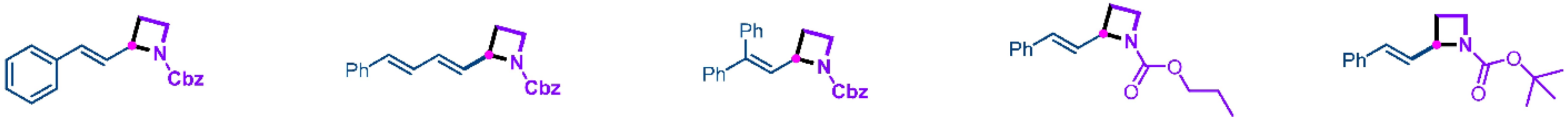


46, 65% (1:1 d.r., >20:1 r.r.)[c]

Cycloaddition Reaction： Rh

A. One-Pot tandem hydrazone synthesis/ ring expansion of aziridines





3, 91% | 27, 87% | 30, 63% | 38, 88% | 42, 92%

B. Late-stage modification of molecules bearing an alylaldehyde moiety

47, 67%
From Fluvastain

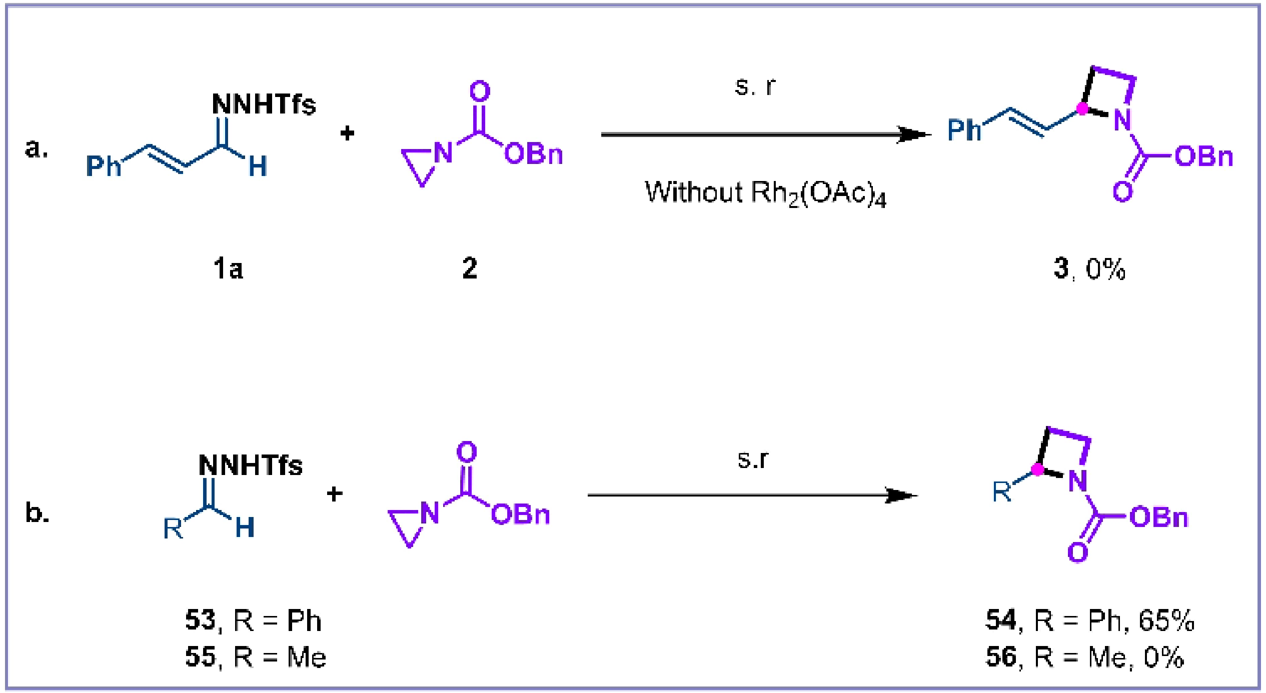
48, 64%
From Crotonaldehyde

49, 62% (dr = 1:1)
From Perillyl aldehyde

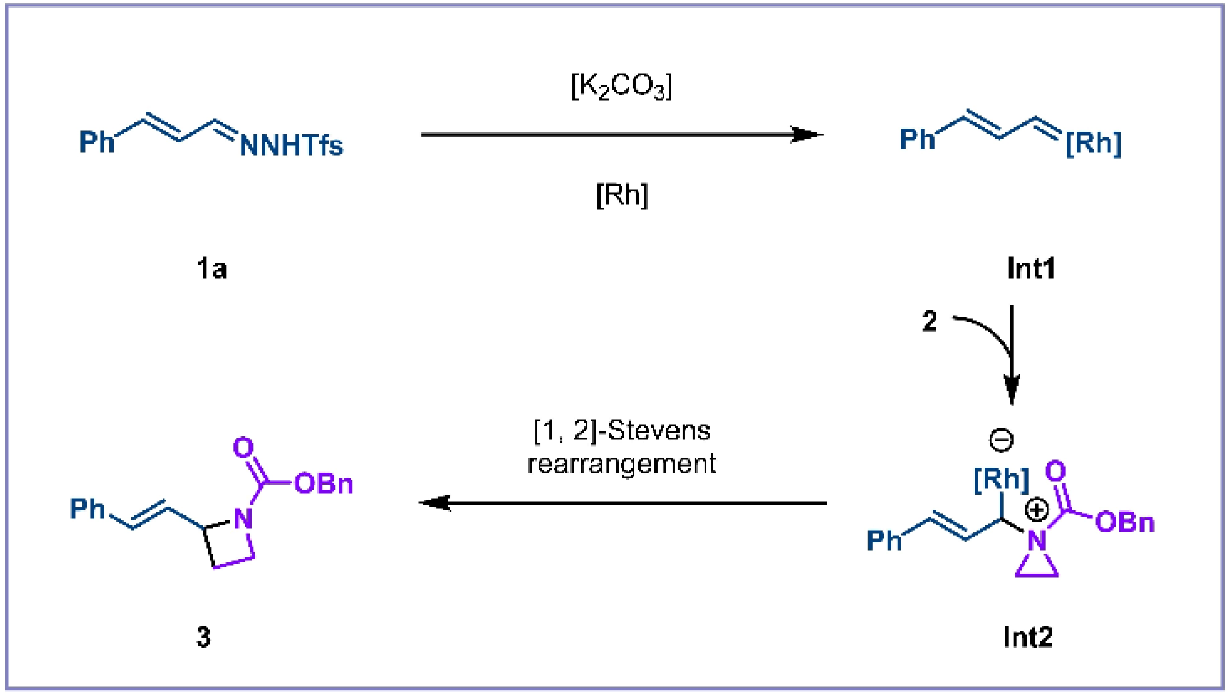
50, 82% (dr = 1:1)
From(-)-Menthyl ChloroforMate

Cycloaddition Reaction： Rh

A. Controlled experiments

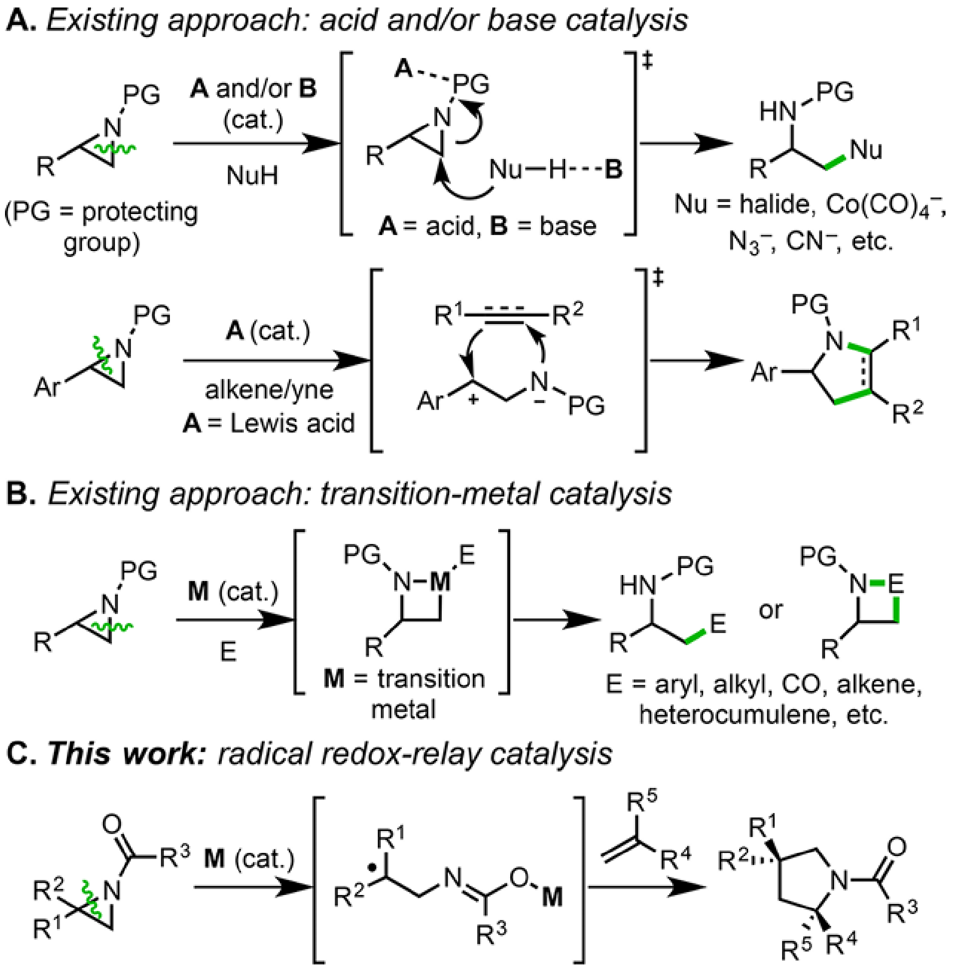


B. Proposed mechanism

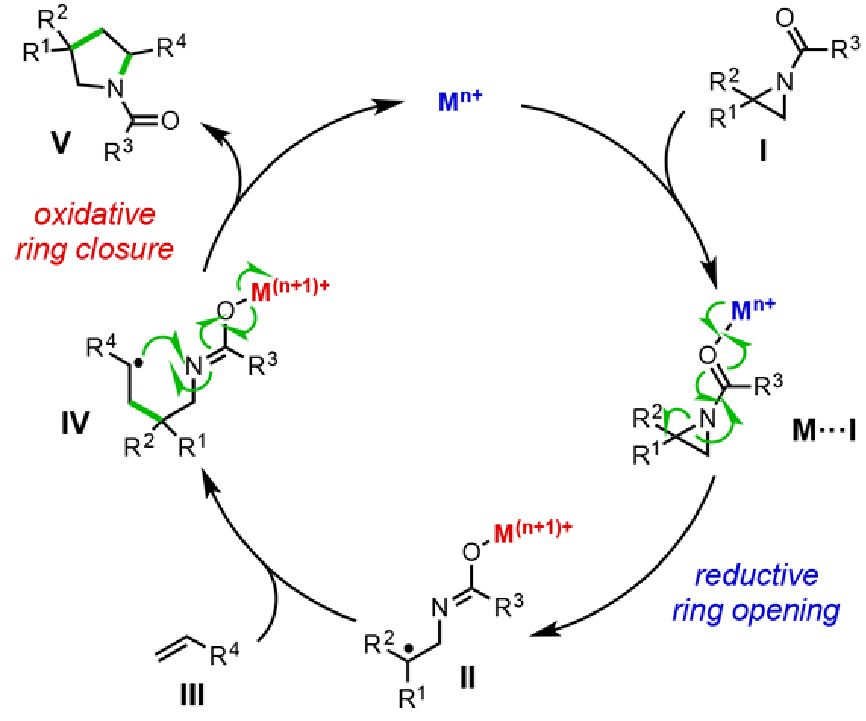


Cycloaddition Reaction： Ti

Scheme 1. Ring Opening of Aziridines: Two-Electron versus Radical Redox-Relay Approach



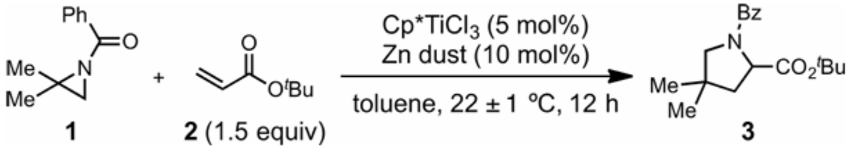
Scheme 2. Proposed Catalytic Cycle



Lin, S. *J. Am. Chem. Soc.* **2017**, *139*, 12141−12144.

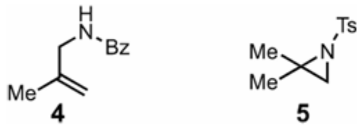
Cycloaddition Reaction： Ti

Table 1. Ti-Catalyzed [3+2] Cycloaddition under Various Reaction Conditions

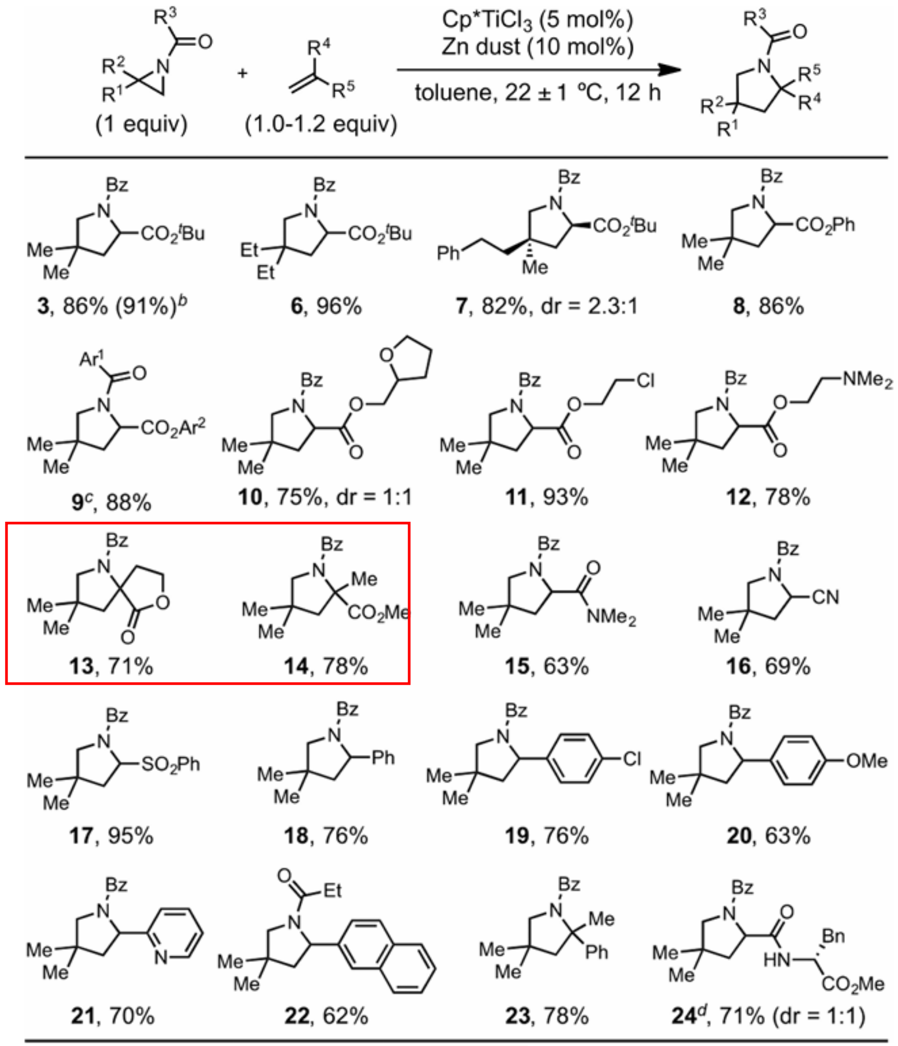


entry	variation from standard conditions	yield (%)[a]
1	none	94
2	$CpTiCl_3$ instead of Cp^*TiCl_3	20[b]
3	Cp_2TiCl_2 instead of Cp^*TiCl_3	<5[b]
4	$TiCl_4$ instead of Cp^*TiCl_3	<5[b](11% **4**)
5	without Zn dust	<5 (>99% **4**)
6	Mn dust instead of Zn dust	82%
7	$ZnCl_2$ instead of Cp^*TiCl_3 and Zn dust	<5[b]
8	DCM instead of toluene	82%
9	THF or MeCN instead of toluene	<5[b]
10	1.0 equiv **2**	92
11	**4** or **5** instead of **1**	<5[b]

[a]Determined with ^{1}H NMR. [b]Unreacted starting material observed.

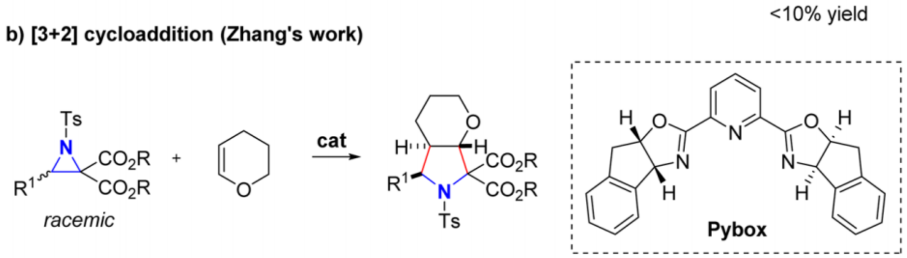


Scheme 3. Substrate Scope[a]

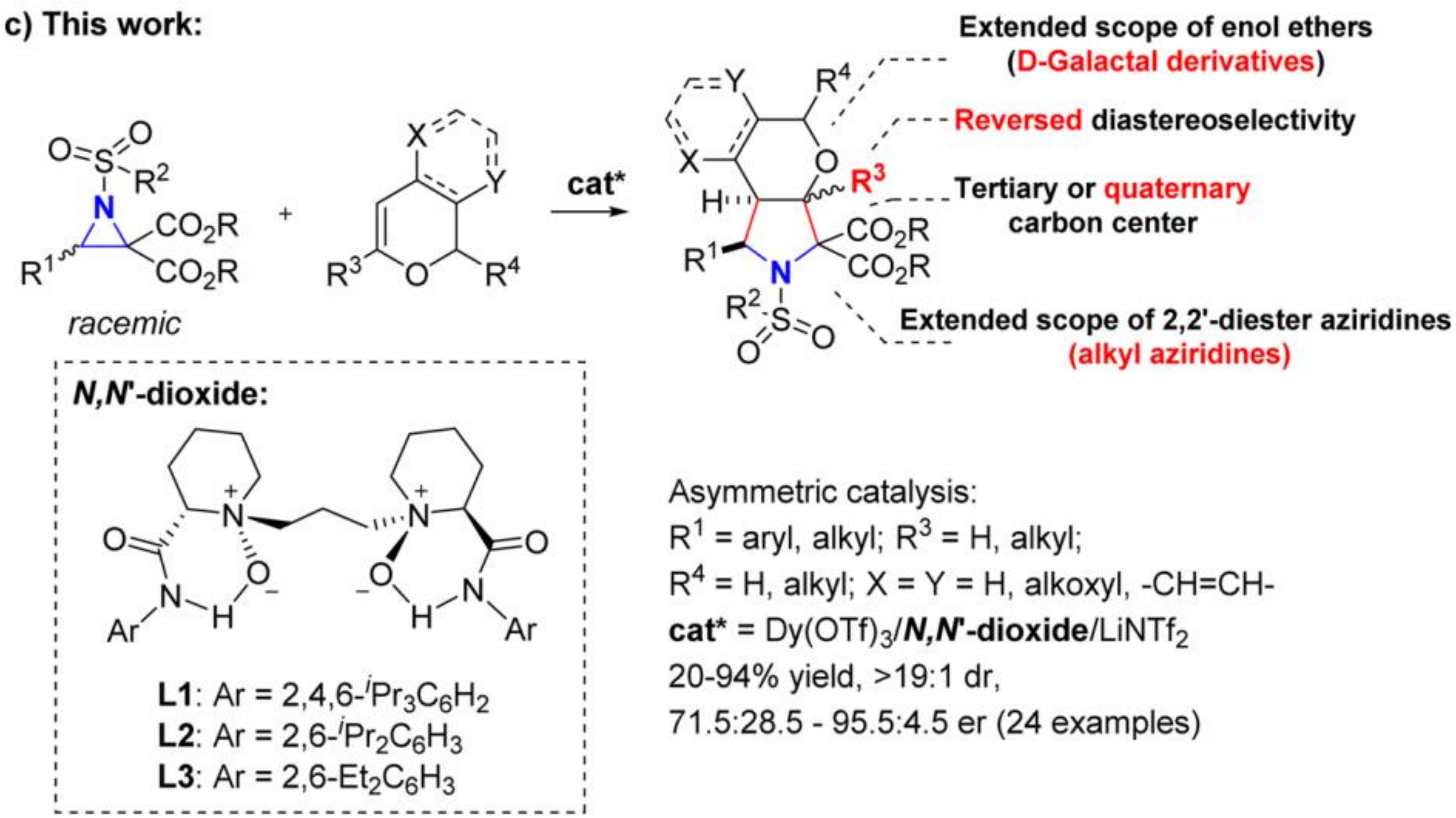


单取代N丙啶不反应，二取代烯烃能够反应。

Cycloaddition Reaction： Dy

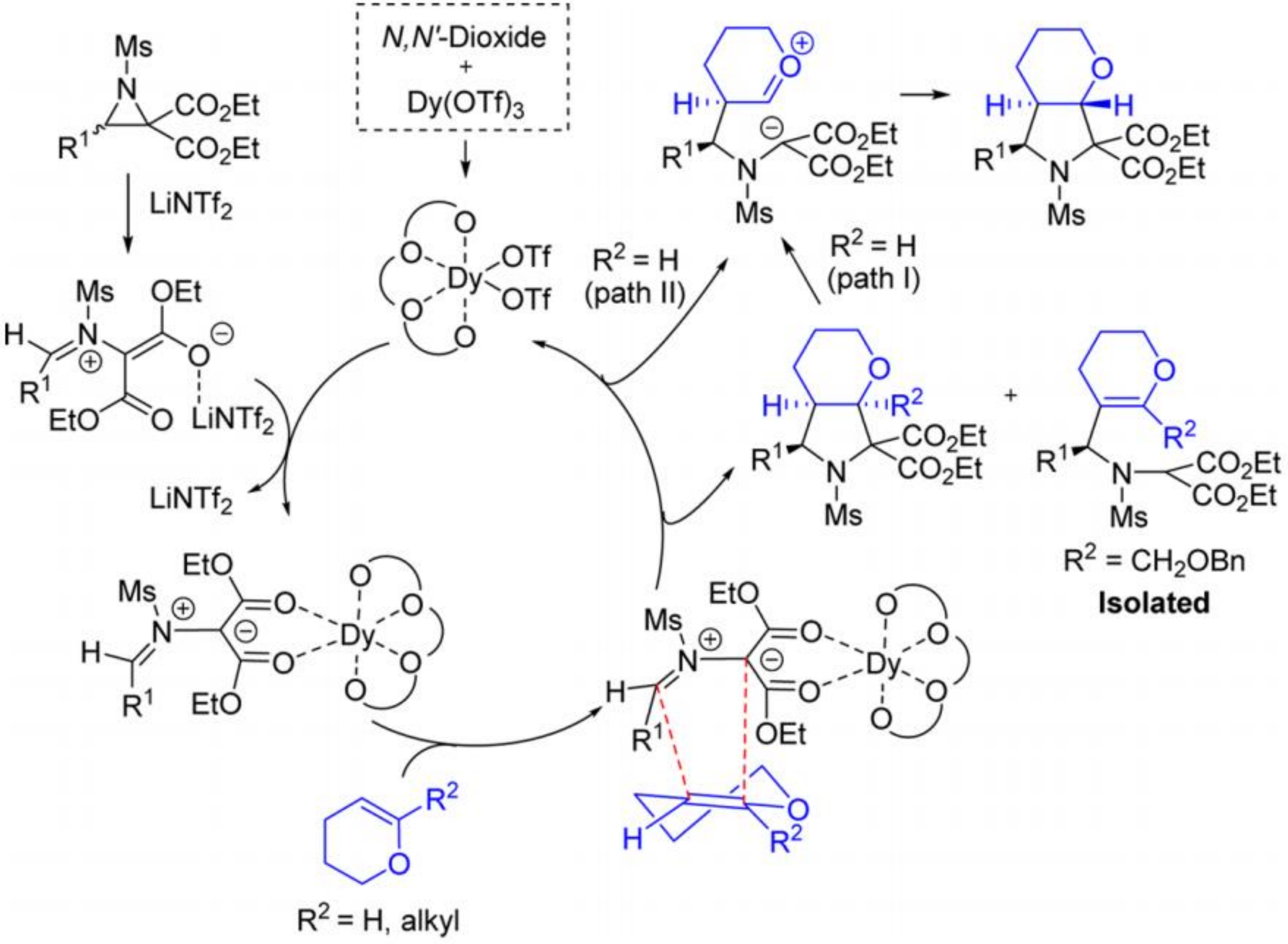


Racemic synthesis: R^1 = aryl, **cat** = $Y(OTf)_3$, 68-85% yield
Asymmetric catalysis: R^1 = 4-MeC_6H_4, **cat*** = **Pybox**/$Y(OTf)_3$
75% yield, >19:1 dr, 79.5:20.5 er (one case)



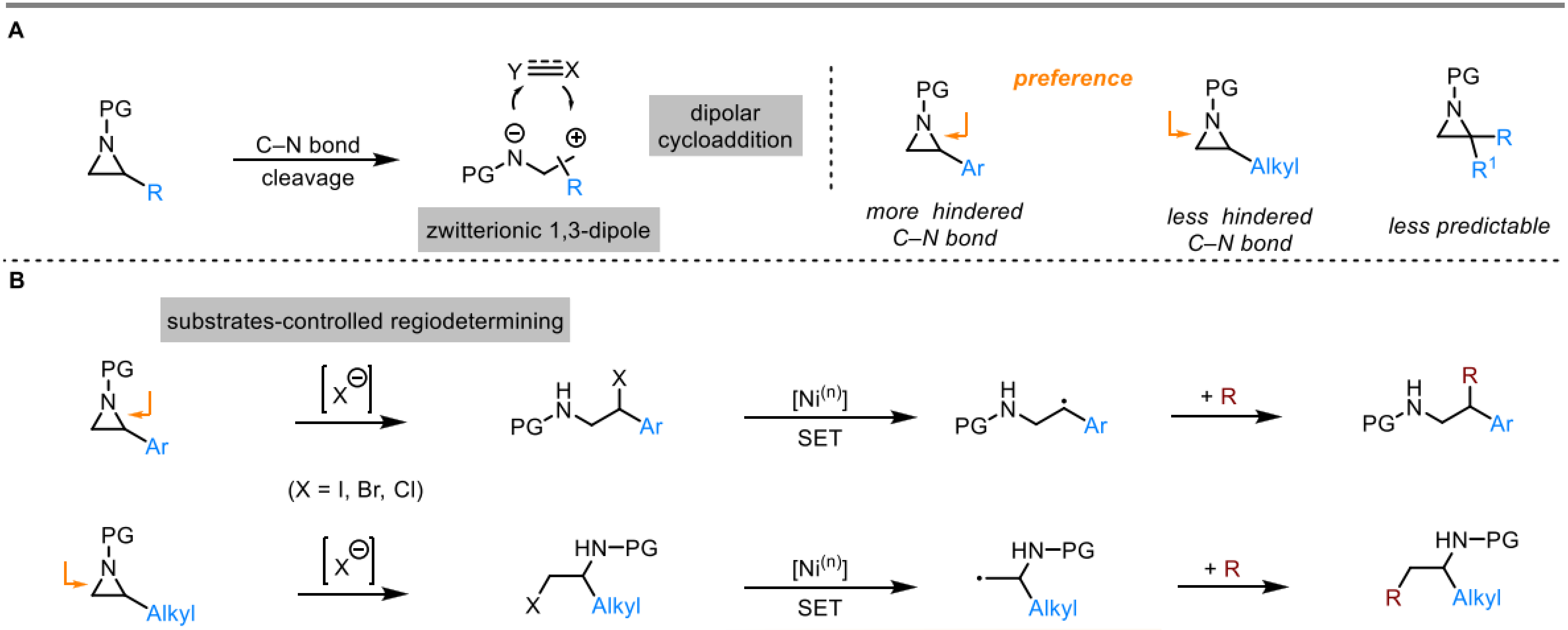
Feng, X. *ACS Catal*. **2017**, *7*, 3934–3939.

Cycloaddition Reaction： Dy



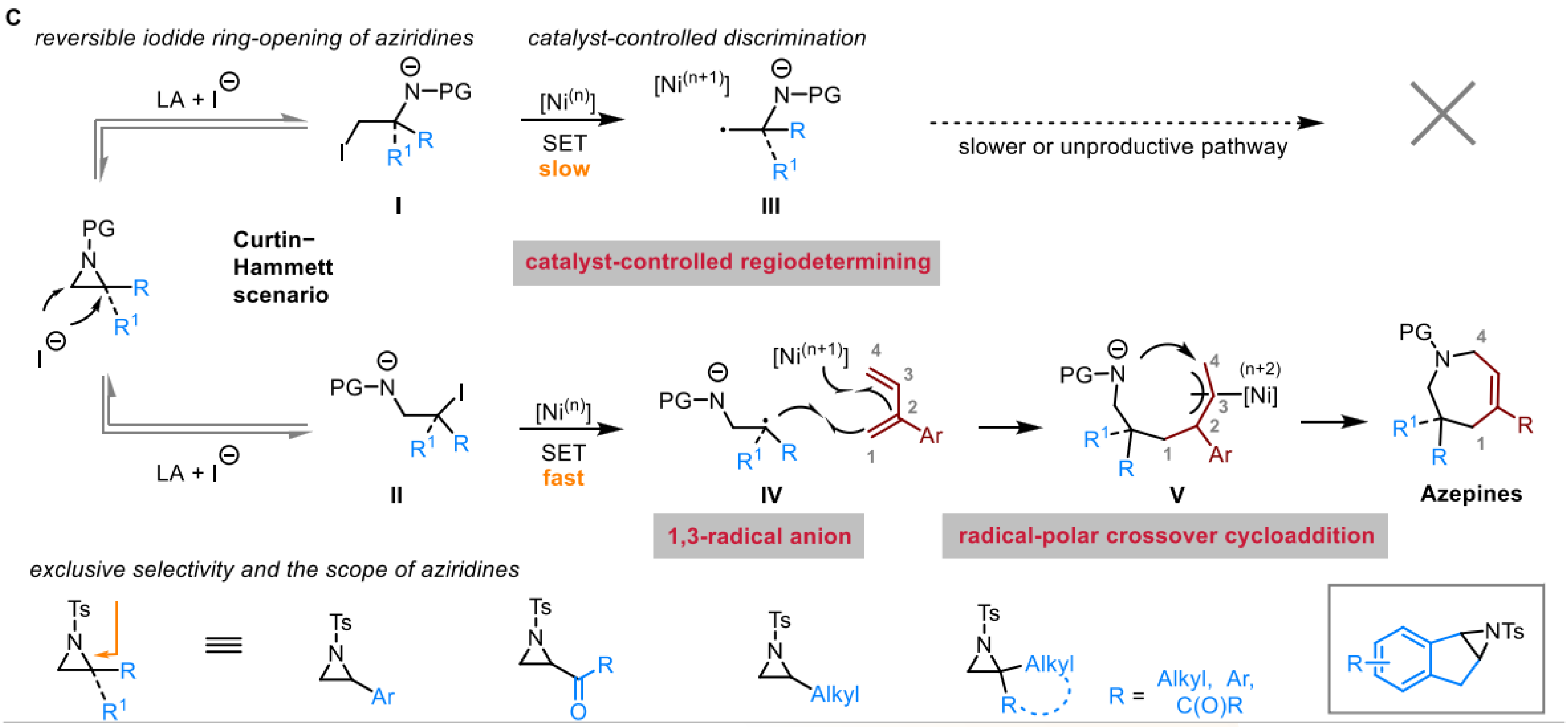
Cycloaddition Reaction： Ni

Scheme 1. Aziridines Involved Cycloaddition and the Strategy of Halide Ring-Opening[a]



Wang, G. –W. *J. Am. Chem. Soc.* **2025**, *147*, 2675–2688.

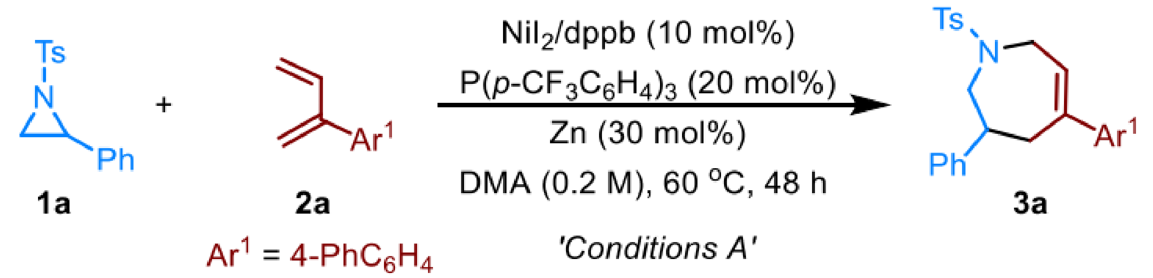
Cycloaddition Reaction： Ni



Wang, G. –W. *J. Am. Chem. Soc.* **2025**, *147*, 2675–2688.

Cycloaddition Reaction： Ni

Table 1. Reaction Optimization[a]



entry	deviation from "Conditions A"	yield of 3a[b]
1	none	82%[c]
2	without NiI_2 *or* Zn or dppb	0%
3	without $P(p\text{-}CF_3C_6H_4)_3$	65%[c]
4	Mn (30 mol %) instead of Zn	64%
5	Zn (10 mol %) used	46%
6	Zn (1.0 equiv) used	52%
7	$NiBr_2$ as a catalyst	54%
8	$NiCl_2$ as a catalyst	42%
9	$Ni(OTf)_2$ *or* $Ni(acac)_2$ as a catalyst	0%
10	$Ni(OTf)_2$ as a catalyst + NaI (20 mol %) as a additive	38%
11	$Ni(acac)_2$ as a catalyst + NaI (20 mol %) as a additive	24%
12	$Ni(cod)_2$ as a catalyst without Zn	0%
13	$Ni(cod)_2$ as a catalyst	13%
14	$Ni(cod)_2$ as a catalyst + NaI (20 mol %) as a additive	60%

[a]Reaction details: **1a** (0.1 mmol) and **2a** (0.2 mmol) were used. [b]Yield measured by NMR with CH_2Br_2 as internal standard. [c]Isolated yield.

Cycloaddition Reaction： Ni

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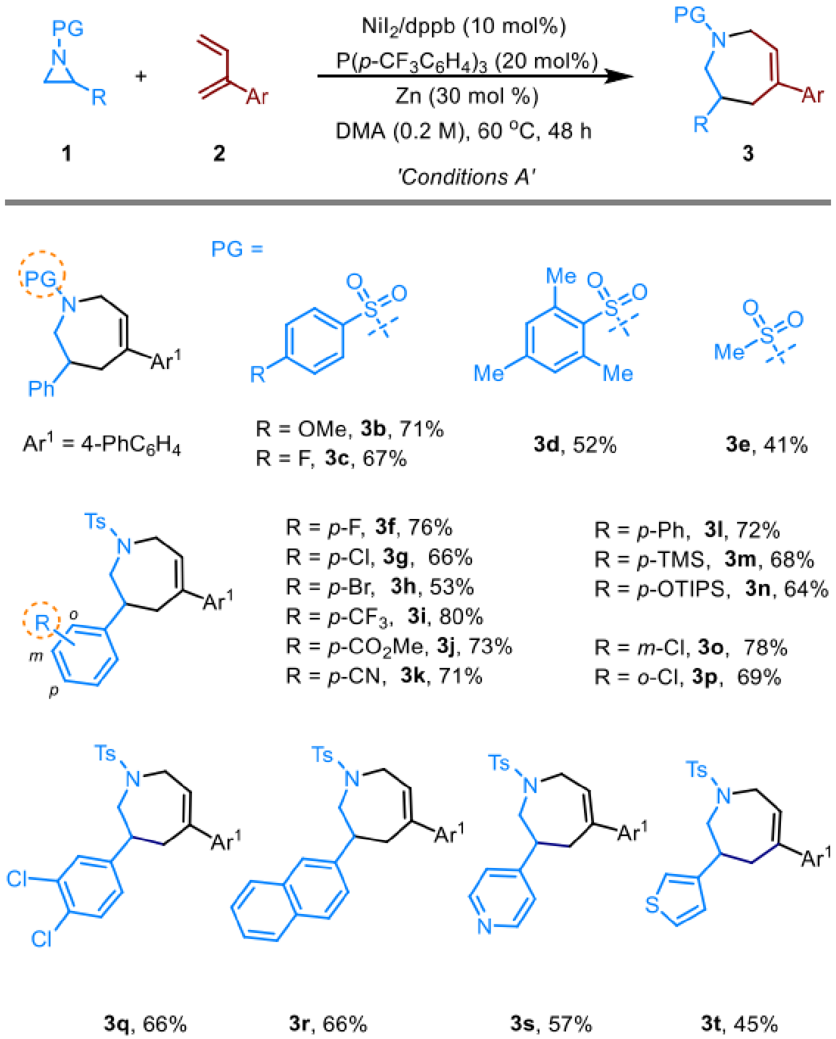
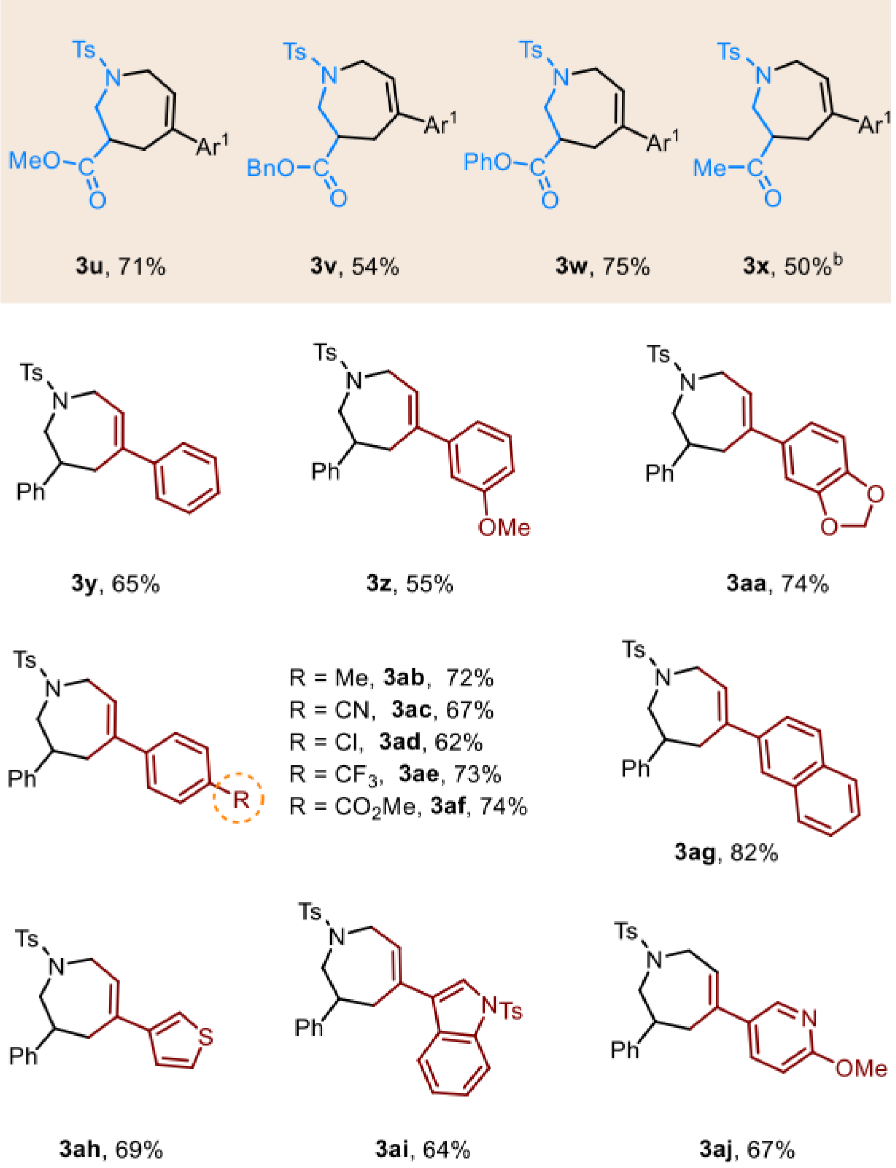
Scheme 2. Scope of Aziridines and 1,3-Dienes[a]

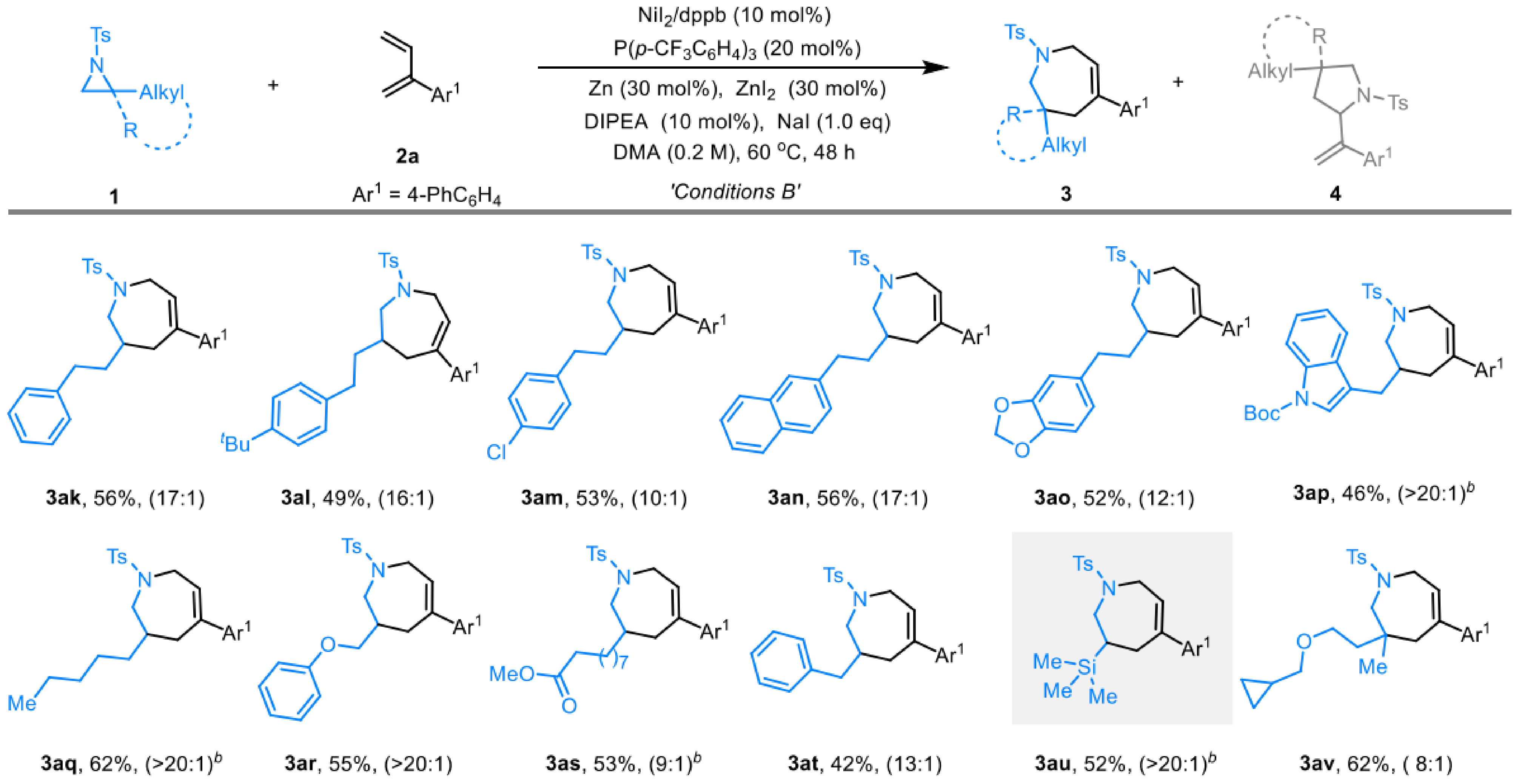




2-酯基的氮丙啶通常发生C-C断裂。同时，这类底物首次在卤素辅助开环中被报道。

Cycloaddition Reaction： Ni

Scheme 3. Scope of 2-Alkyl and Disubstituted Aziridines[a]



单烷基的自由基环加成还未被报道。

Cycloaddition Reaction： Ni

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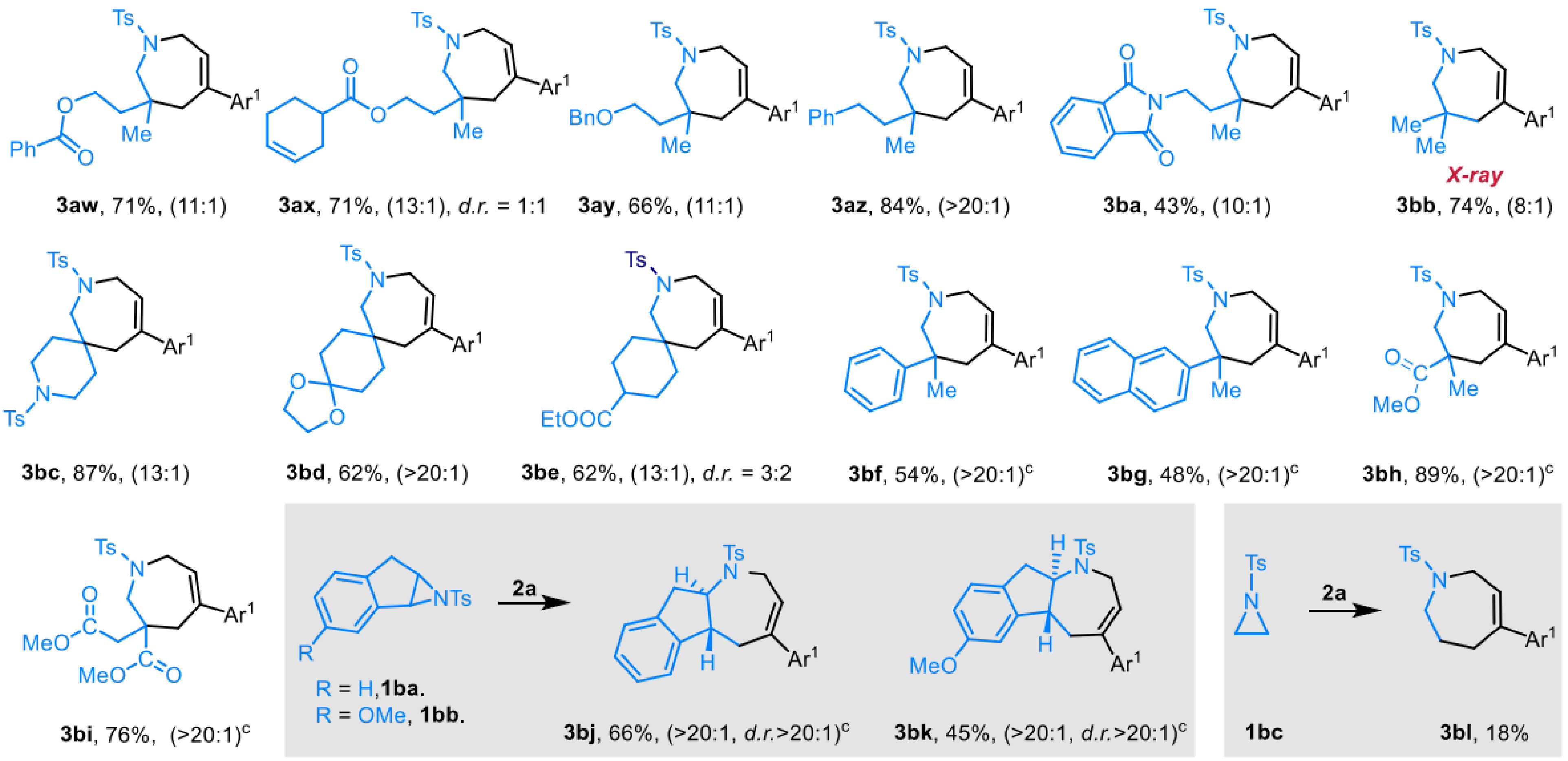
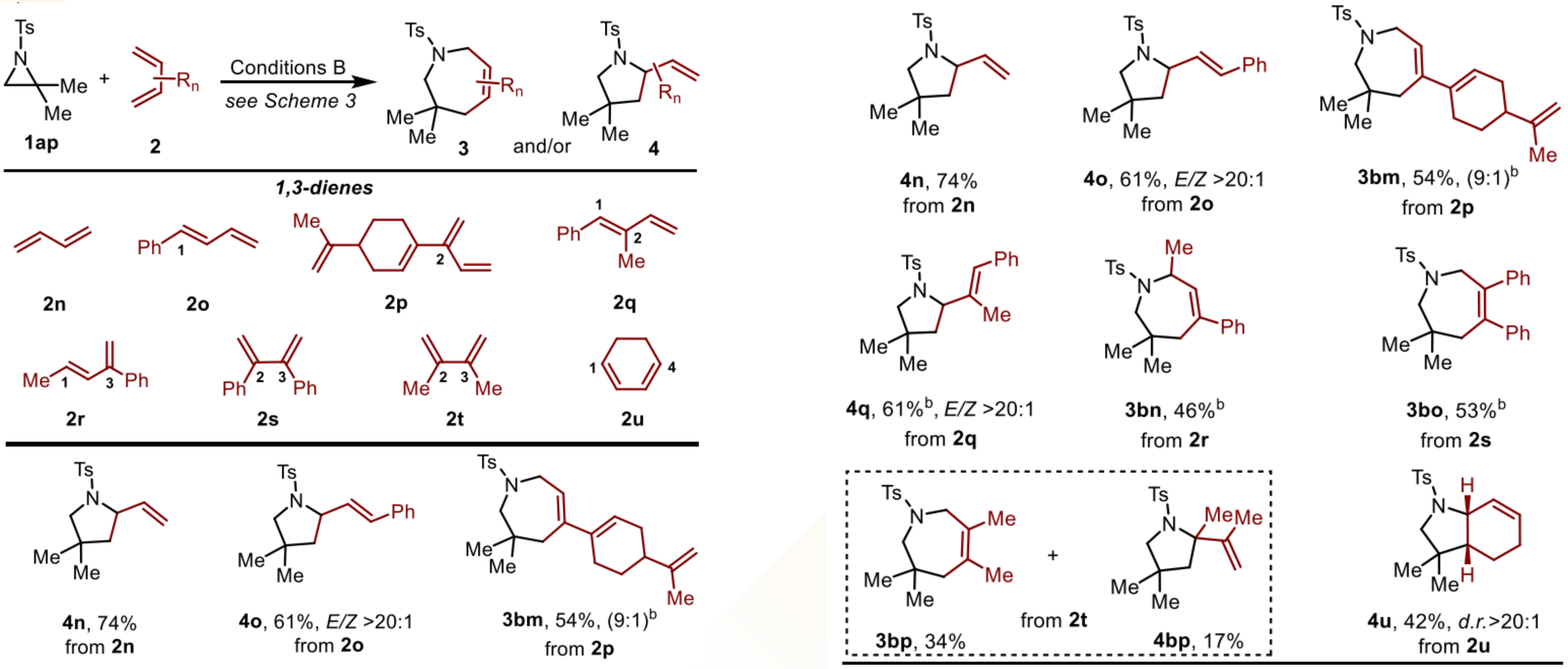


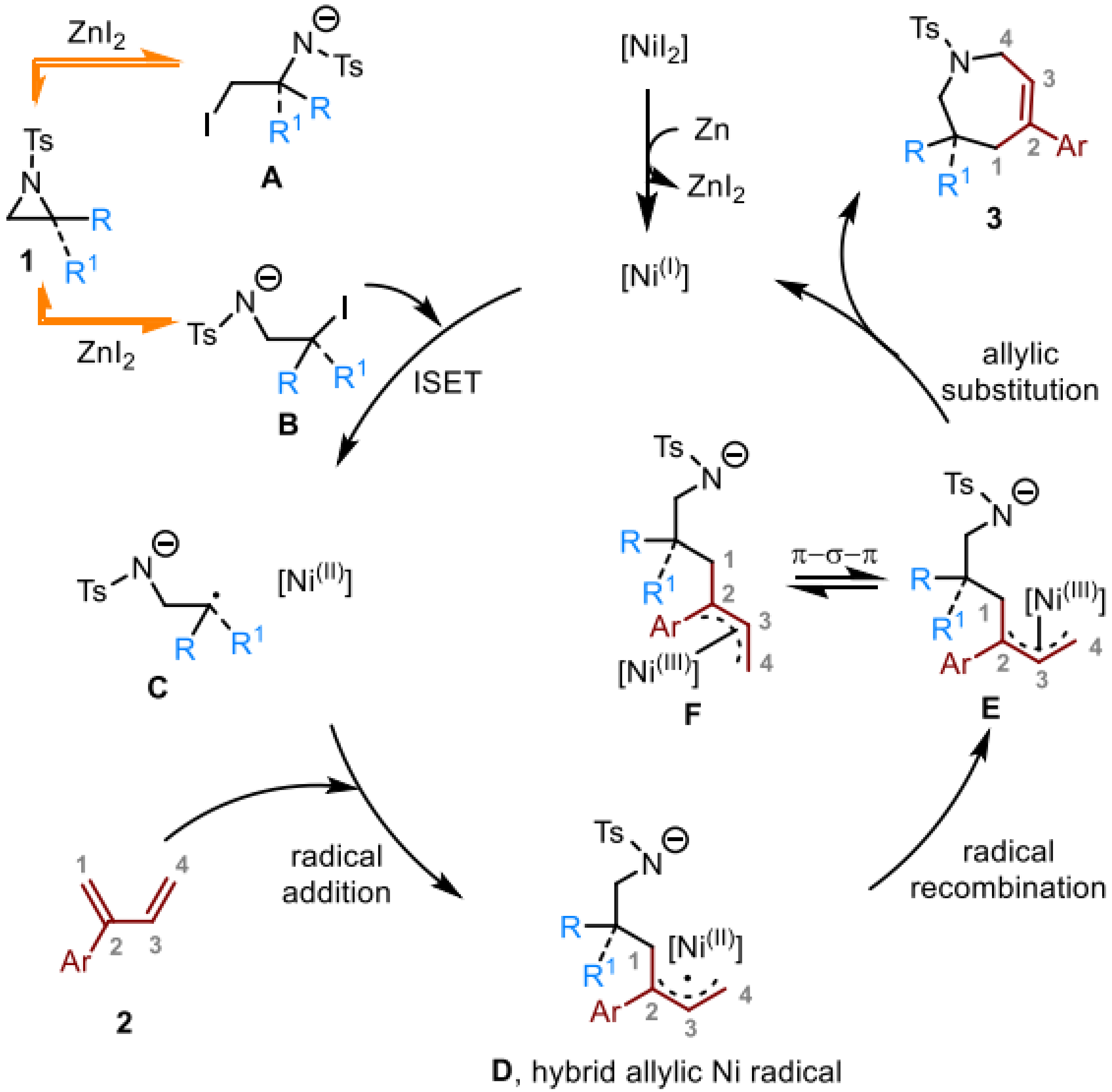
[a]Reaction details: **1** (0.1 mmol) and **2** (0.2 mmol) were used, and isolated yields of the mixture of isomers were reported. The ratios in parentheses are regioisomeric ratios (**3**:**4**). [b]NiI_2 (20 mol %), dppb (20 mol %), $P(p\text{-}CF_3C_6H_4)_3$ (40 mol %), Zn (60 mol %) were used instead. [c]"Conditions A" was used, see Table 1.

Cycloaddition Reaction： Ni



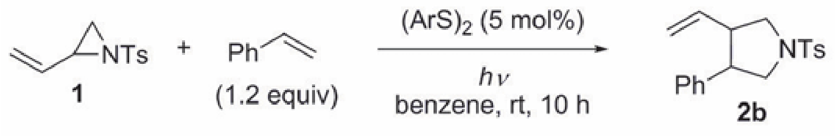
三取代、杂原子或高位阻二烯不反应

Cycloaddition Reaction： Ni



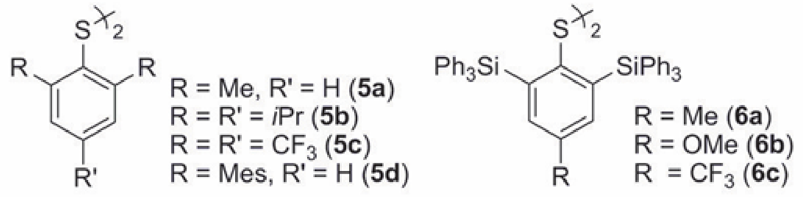
Cycloaddition Reaction：$(ArS)_2$

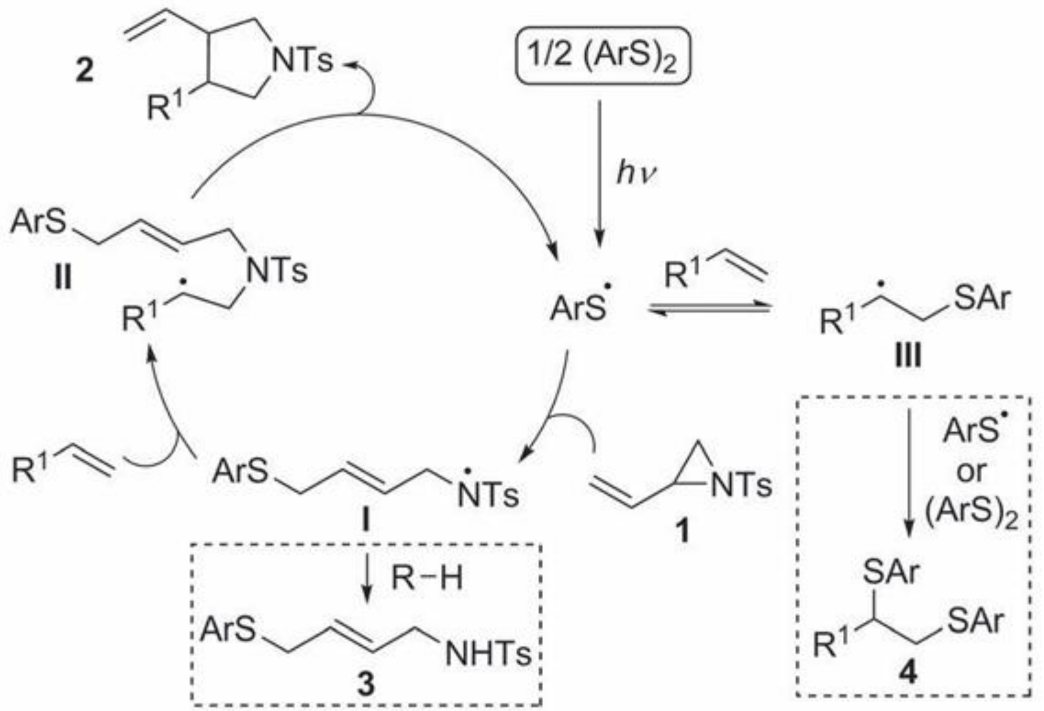
Table 1: Optimization of the reaction conditions.[a]



Entry	$(ArS)_2$	Yield [%][b]	d.r.[c]
1	**5a**	10	67:33
2	**5b**	13	72:28
3	**5c**	48	69:31
4	**5d**	7	64:36
5	**6a**	80	72:28
6	**6b**	71	72:28
7	**6c**	88	72:28
8[d,e]	**6c**	87	72:28

[a] Reaction conditions: *N*-tosyl vinylaziridine (**1**, 0.10 mmol), styrene (0.12 mmol), disulfide (0.005 mmol). [b] Combined yield of the diastereomers, as determined by ^{1}H NMR spectroscopy with mesitylene as an internal standard. [c] The diastereomeric ratio (*trans*/*cis*) was determined by ^{1}H NMR analysis of the crude material. [d] The reaction was carried out for 2 h with 6 mol% of the disulfide. [e] Isolated yield.





Scheme 3. Proposed catalytic cycle and catalyst-decomposition pathways.

Maruoka, *K. Angew.Chem. Int.Ed.* **2016**, *55*, 8081–8085.

Cycloaddition Reaction： BCF

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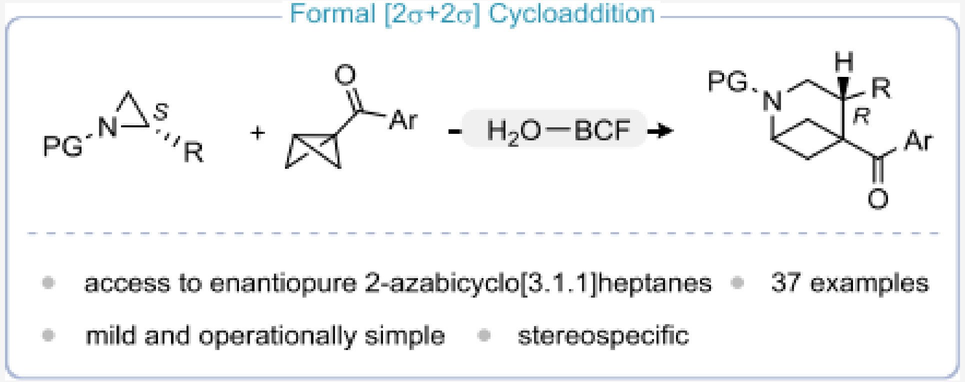
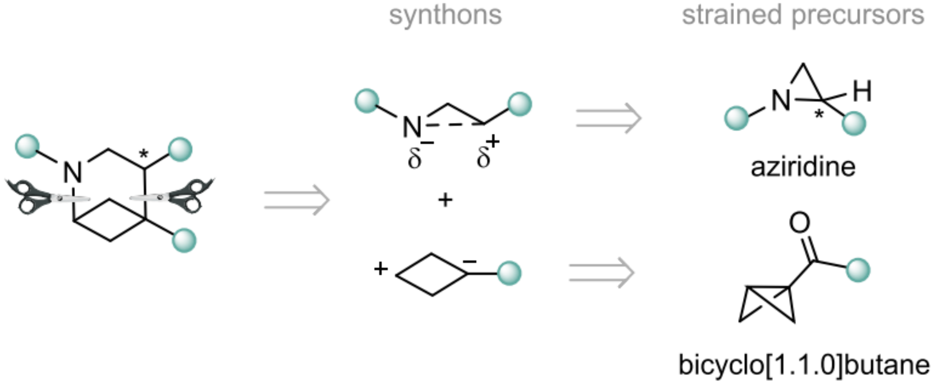
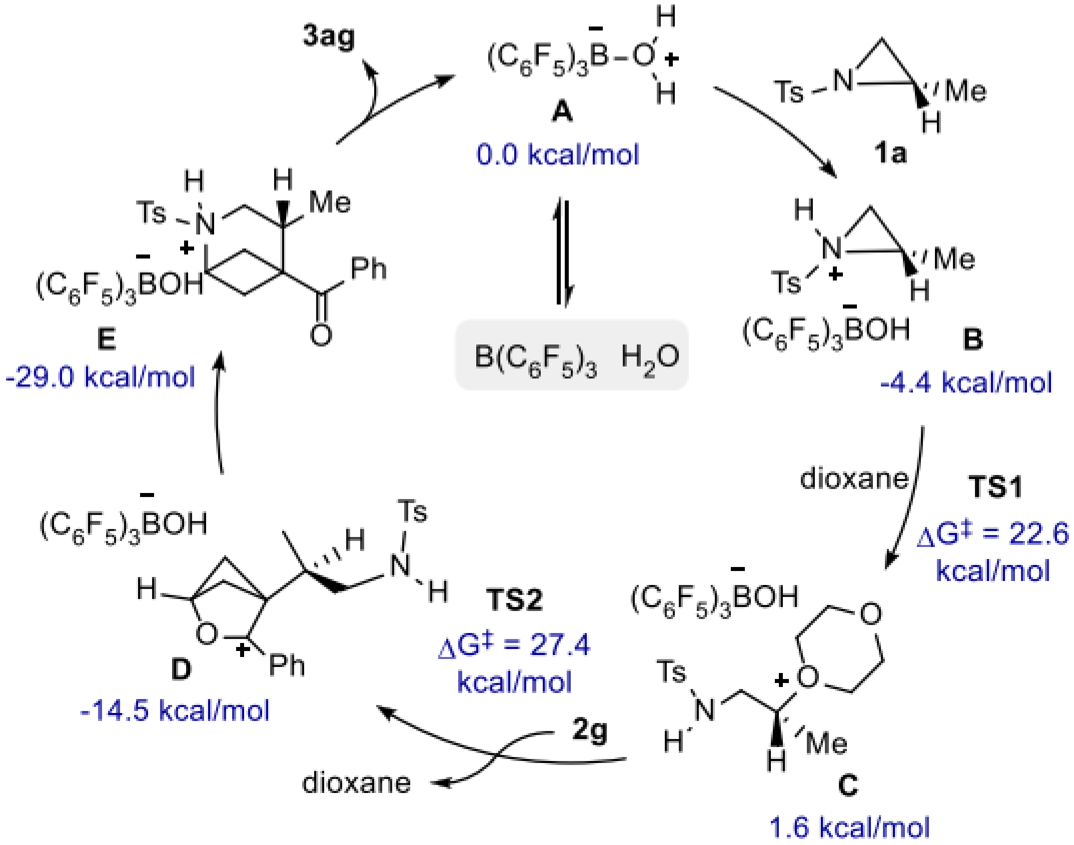


(C) Access to enantiopure 2-azabicyclo[3.1.1]heptanes through stereospecific intermolecular formal [2σ+2σ] cycloaddition – retrosynthesis (*this work*)





Studer, A. *J. Am. Chem. Soc.* **2024**, *146*, 27204–27212.

N-aziridine radical reaction

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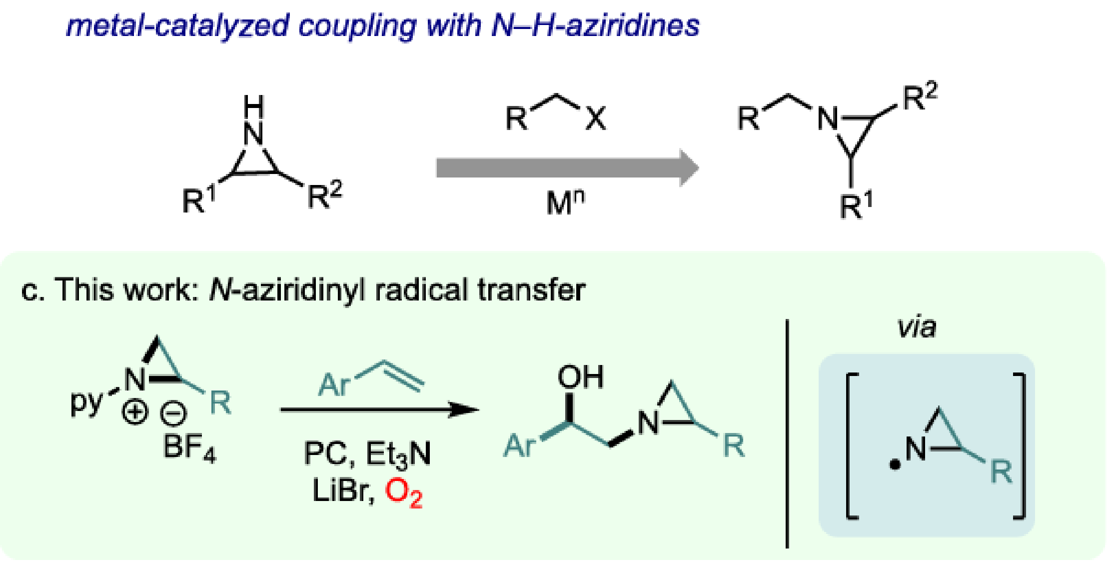


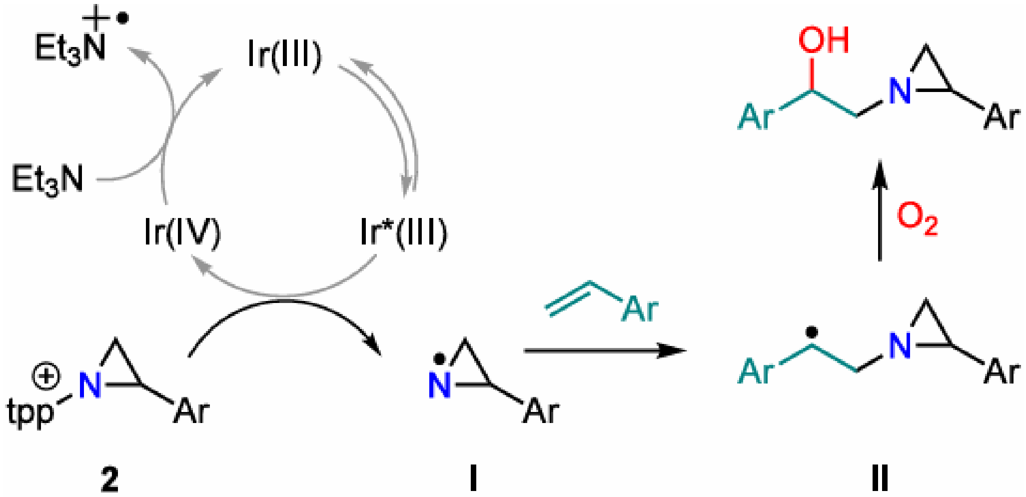
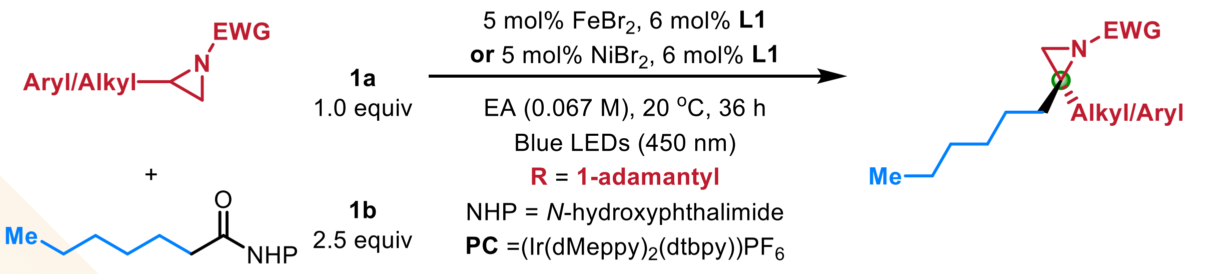
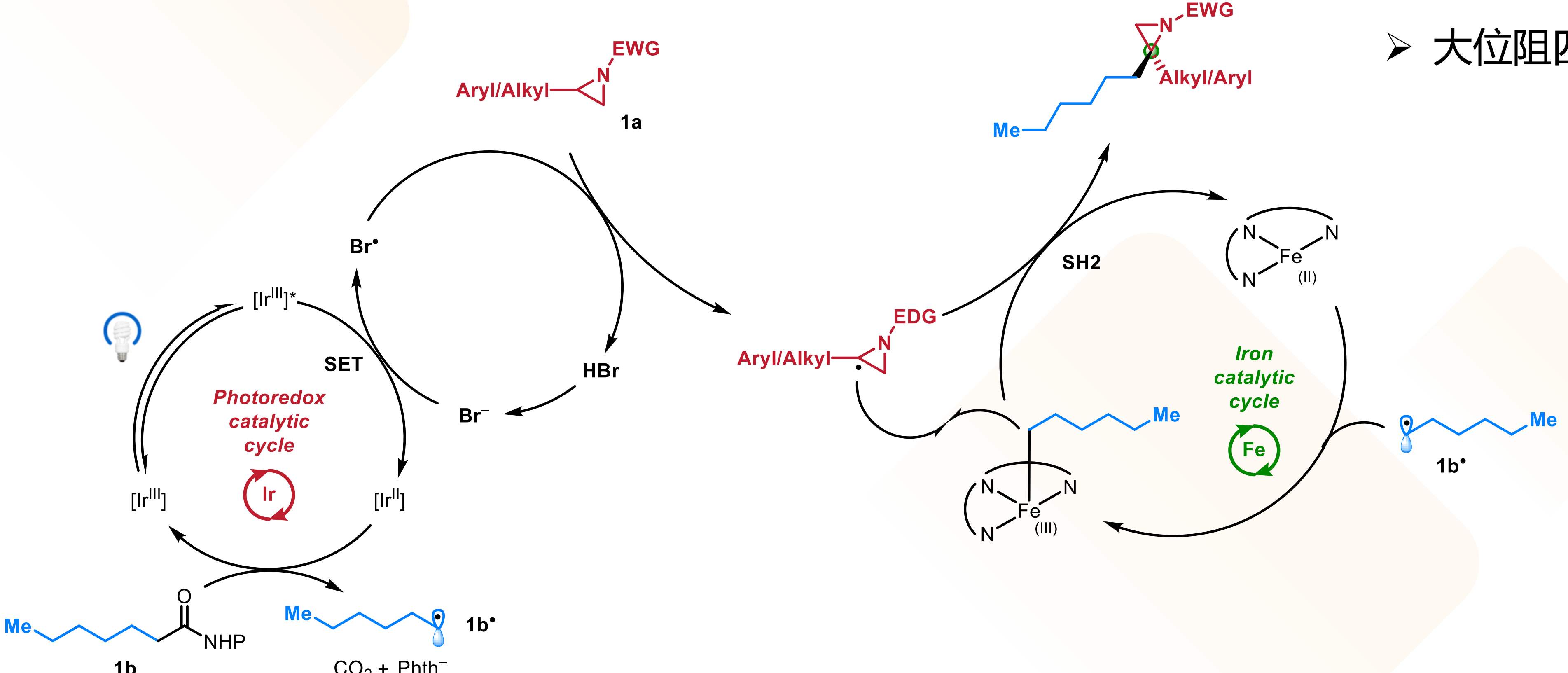


Figure 5. Potential photocatalytic mechanism for the *N*-aziridinyl radical generation and transfer.

Powers, D. C. *J. Am. Chem. Soc.* **2024**, *146*, 30796–30801.

Proposal





- 一种新型氮丙啶自由基催化机制
- 高区域选择性生成三级自由基
- 大位阻四级含氮碳手性中心构筑

THANKS!