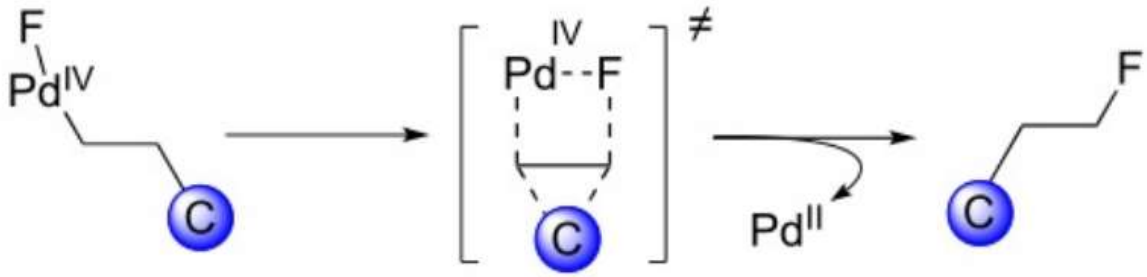
Migrative Carbofluorination of Saturated Amides Enabled by Pd-Based Dyotropic Rearrangement

Guoqiang Yang, Hua Wu, Simone Gallarati, Clémence Corminboeuf, Qian Wang, and Jieping Zhu*



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Ke Yuee 20220914

Prof. Jieping Zhu

◆ Education

1984, B.Sc., Hanzhou Normal University, P. R. China

1987, M.Sc., Lanzhou University (Prof. Y.-L. Li), P. R. China

1991, Ph.D., Université Paris XI (Prof. H.-P. Husson and Prof. J.-C. Quirion), France

1991-1992, Post-doct., Texas A & M University (Prof. Sir D. H. R. Barton), USA

◆ Research Interests

Total synthesis of natural products, Multicomponent reaction, Metal-catalyzed Domino process, Catalytic enantioselective transformation.

◆ Academic Positions

1992-2000, "Chargé de Recherche" at ICSN, CNRS, France

2000-2006, Director of Research, 2nd class, at ICSN CNRS, France

2006-2010, Director of Research, 1st class at ICSN, CNRS, France

2010-present, Professor, ISIC, EPFL

◆ Awards

1996, CNRS bronze medal (1996)

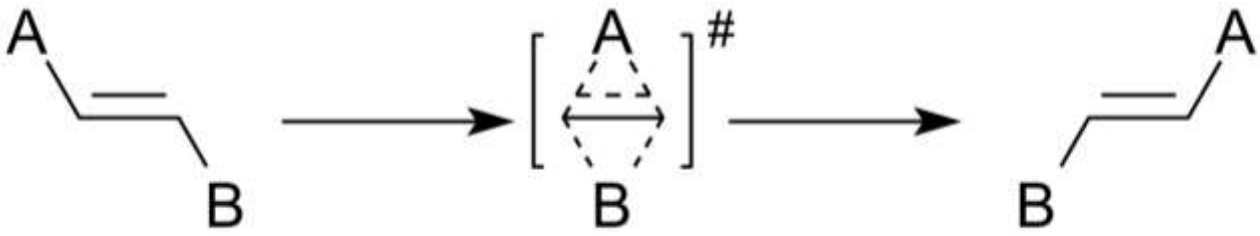
1999, French Chemical Society SCF-Acros award (1999)

2003, Prix Emile Jungfleisch of French Academy of Sciences

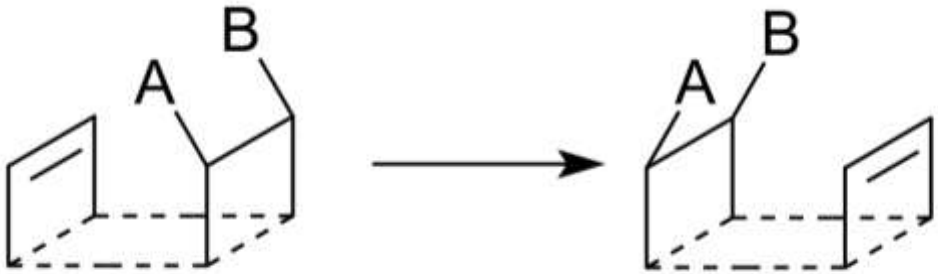
2003, National Science Foundation Outstanding Young Oversea Scientist award (China)

Dyotropic Rearrangement

Type I rearrangements

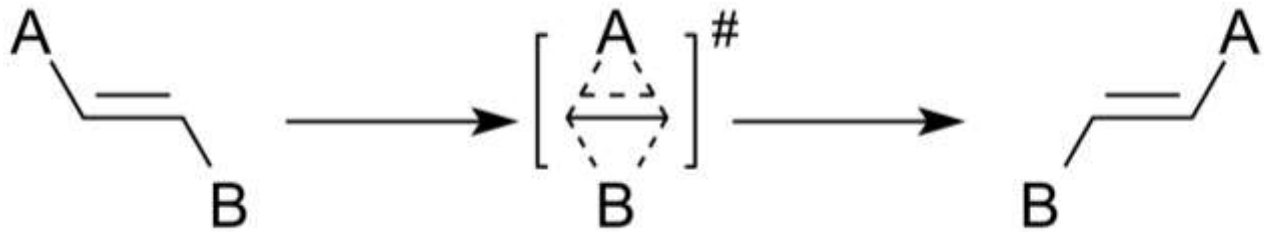


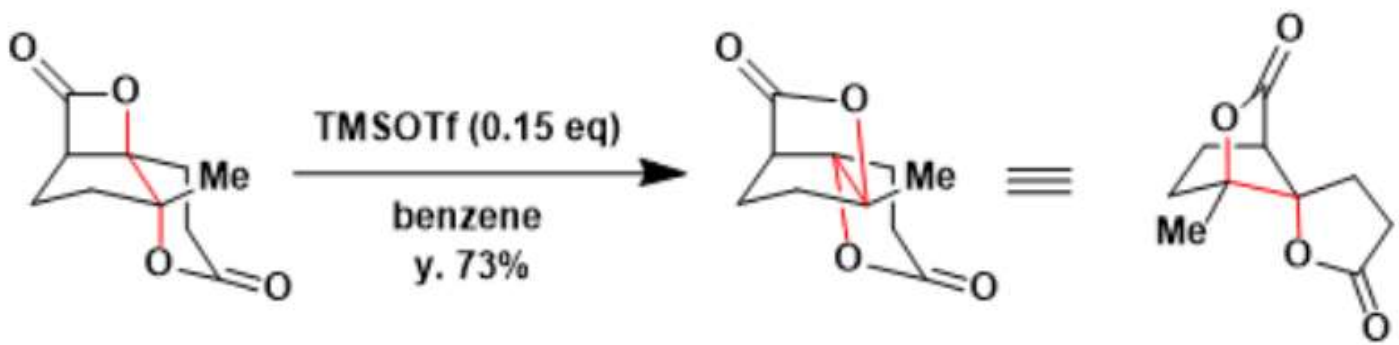
Type II rearrangements



Dyotropic Rearrangement

Type I rearrangements



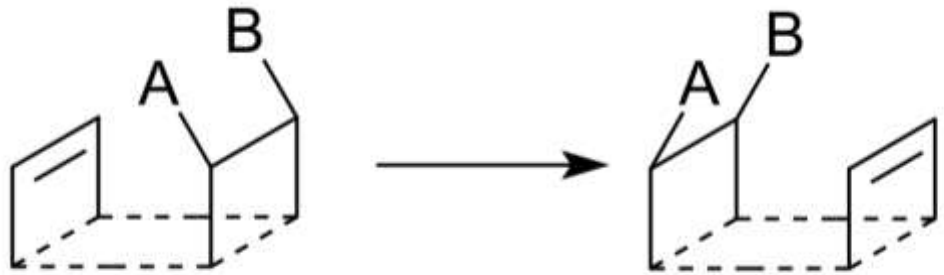


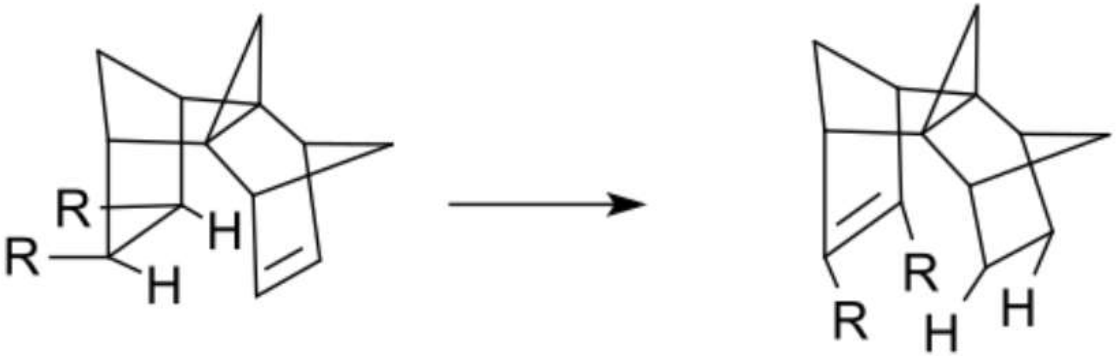
73% yield
98% e.e.

J. Am. Chem. Soc. 2012, 134, 13348

Dyotropic Rearrangement

Type Ⅱ rearrangements



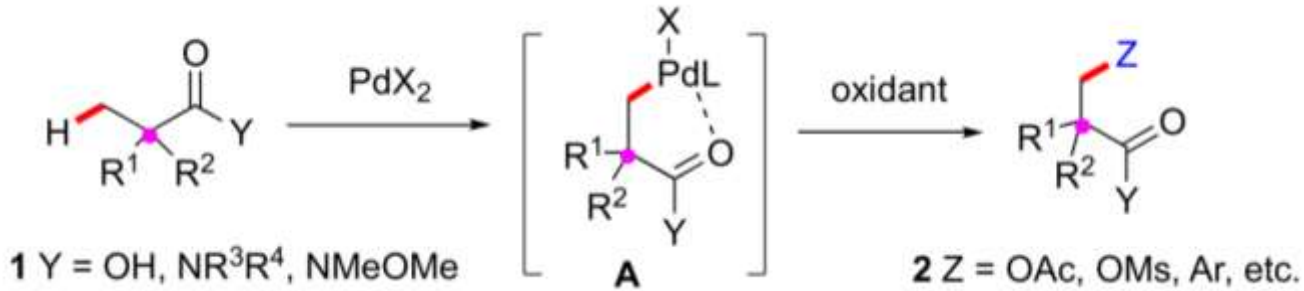


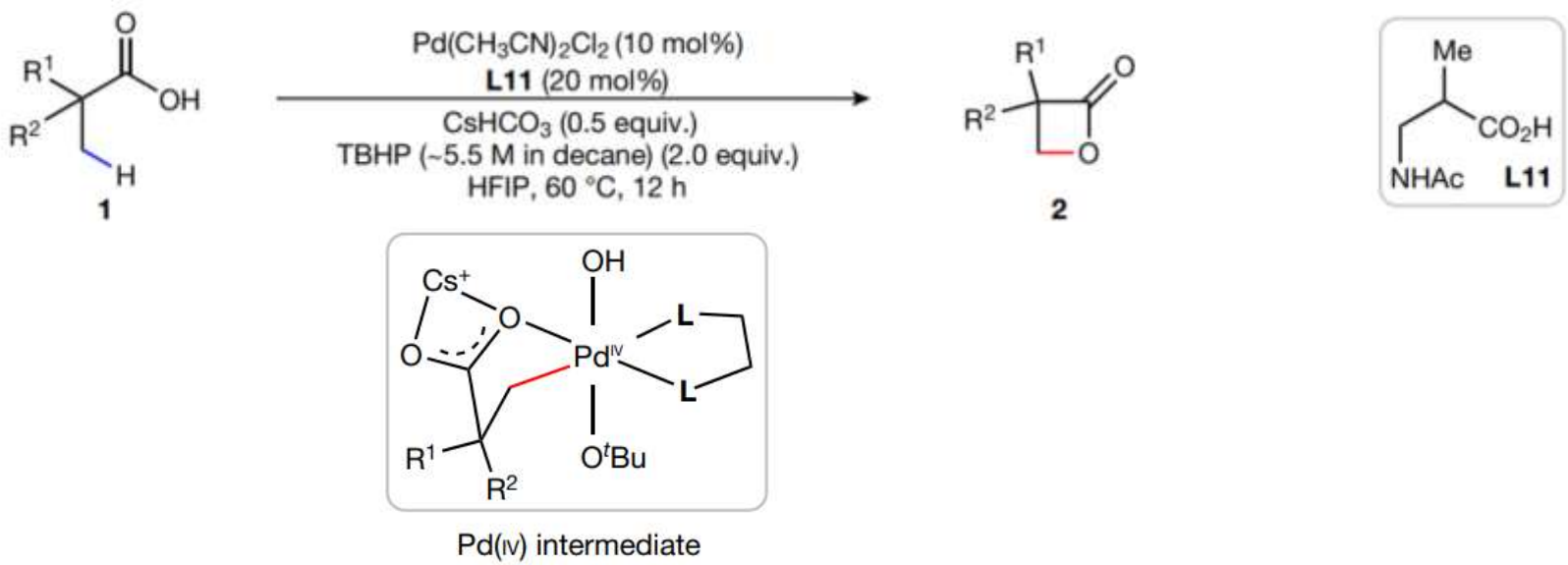
R = SO_2Ph

J. Am. Chem. Soc., 1990, 112 (1), 284–291

Pd-catalyzed C(sp3)–H functionalization

◆ **Pd-catalyzed β-C(sp3)–H functionalization**

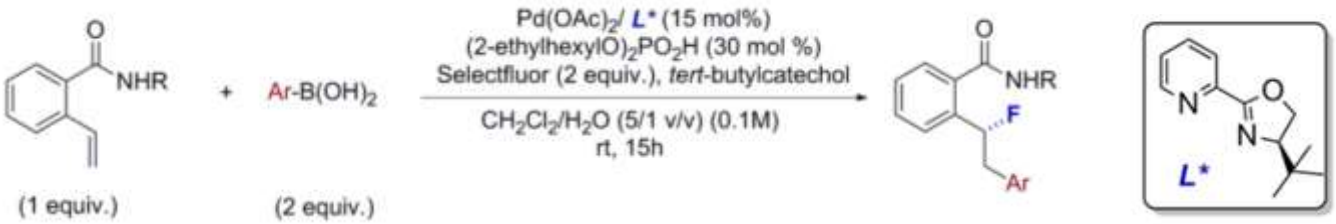


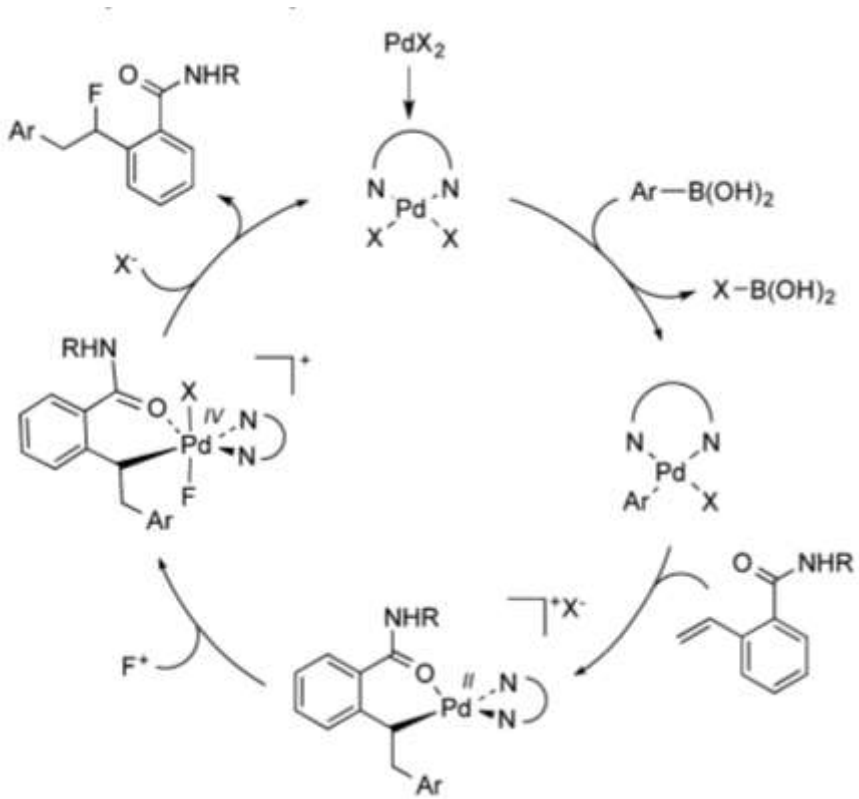


Yu, J.-Q. Lactonization as a general route to β-C(sp3)–H functionalization. Nature 2020, 577, 656–659

Pd-catalyzed C(sp3)–H functionalization

◆ **Pd-catalyzed 1,2-arylative fluorinations**

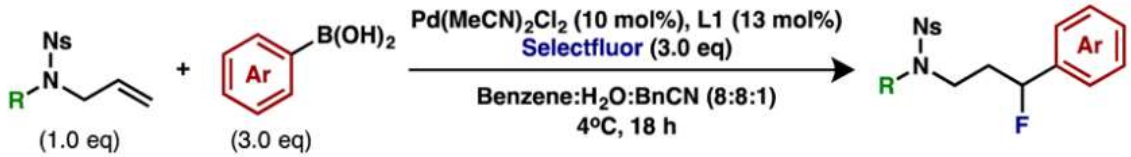


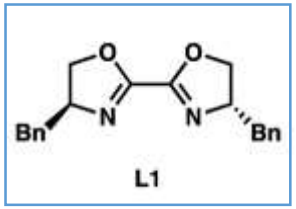


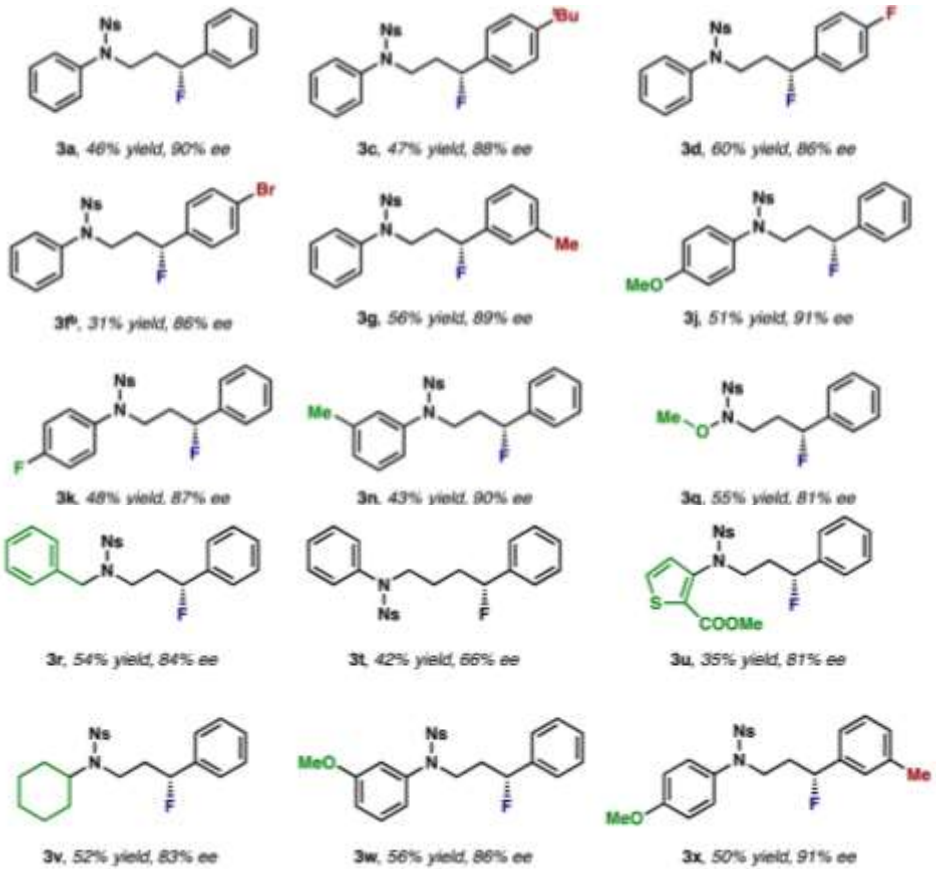
Toste, F. D. Asymmetric palladium-catalyzed directed intermolecular fuoroarylation of styrenes. J. Am. Chem. Soc. 136, 4101–4104 (2014)

Pd-catalyzed C(sp3)–H functionalization

◆ **Pd-catalyzed 1,1-arylative fluorinations**



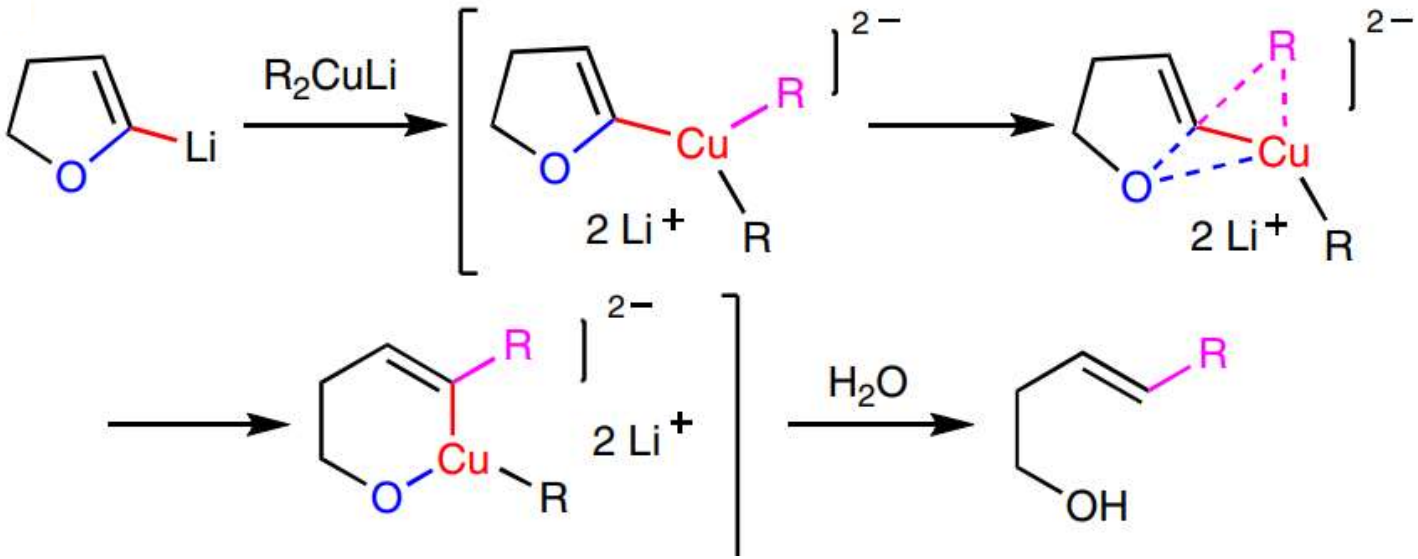




Toste, F. D. Palladium-catalyzed enantioselective 1,1-fuoroarylation of aminoalkenes. J. Am. Chem. Soc. 137, 12207–12210 (2015)

Dyotropic Rearrangement of Vicinal C–C and C–Pd(IV) bonds

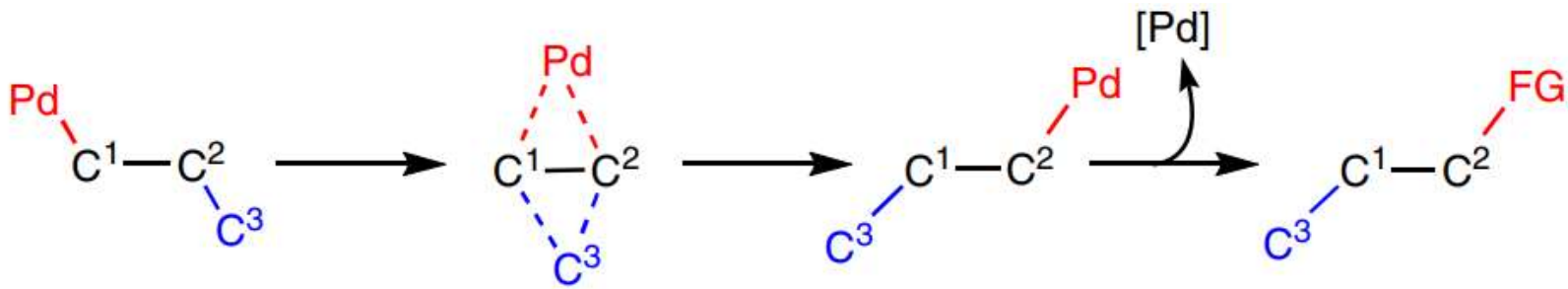
- **Dyotropic rearrangement involving metals**



Kocieński, P. & Barber, C. Synthetic applications of metallate rearrangements. Pure Appl. Chem. 62, 1933–1940 (1990).

Dyotropic Rearrangement

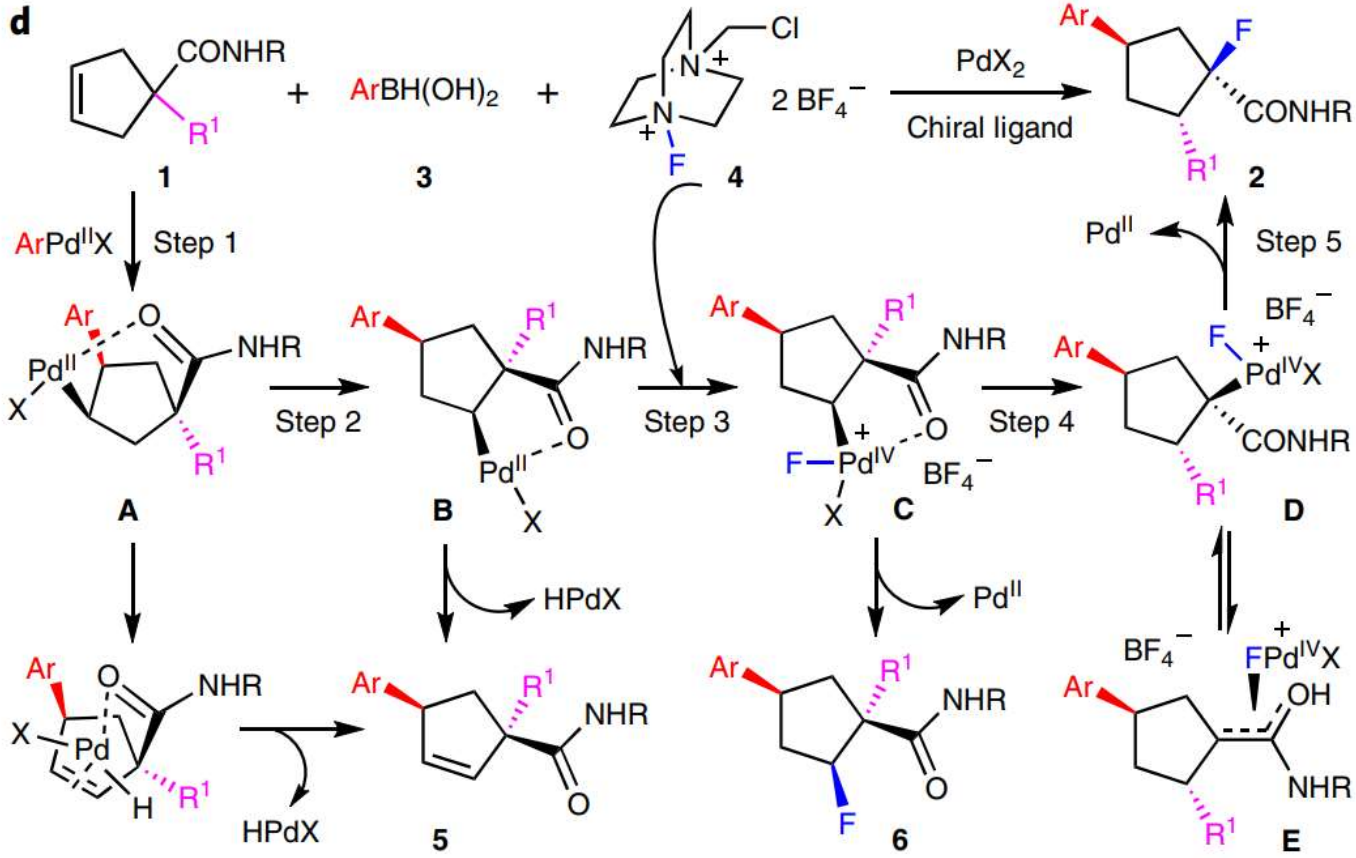
Proposed 1,2-aryl(alkyl)/Pd dyotropic rearrangement



β-Carbon elimination/syn-carbopalladation sequence

Dyotropic Rearrangement of Vicinal C–C and C–Pd(IV) bonds

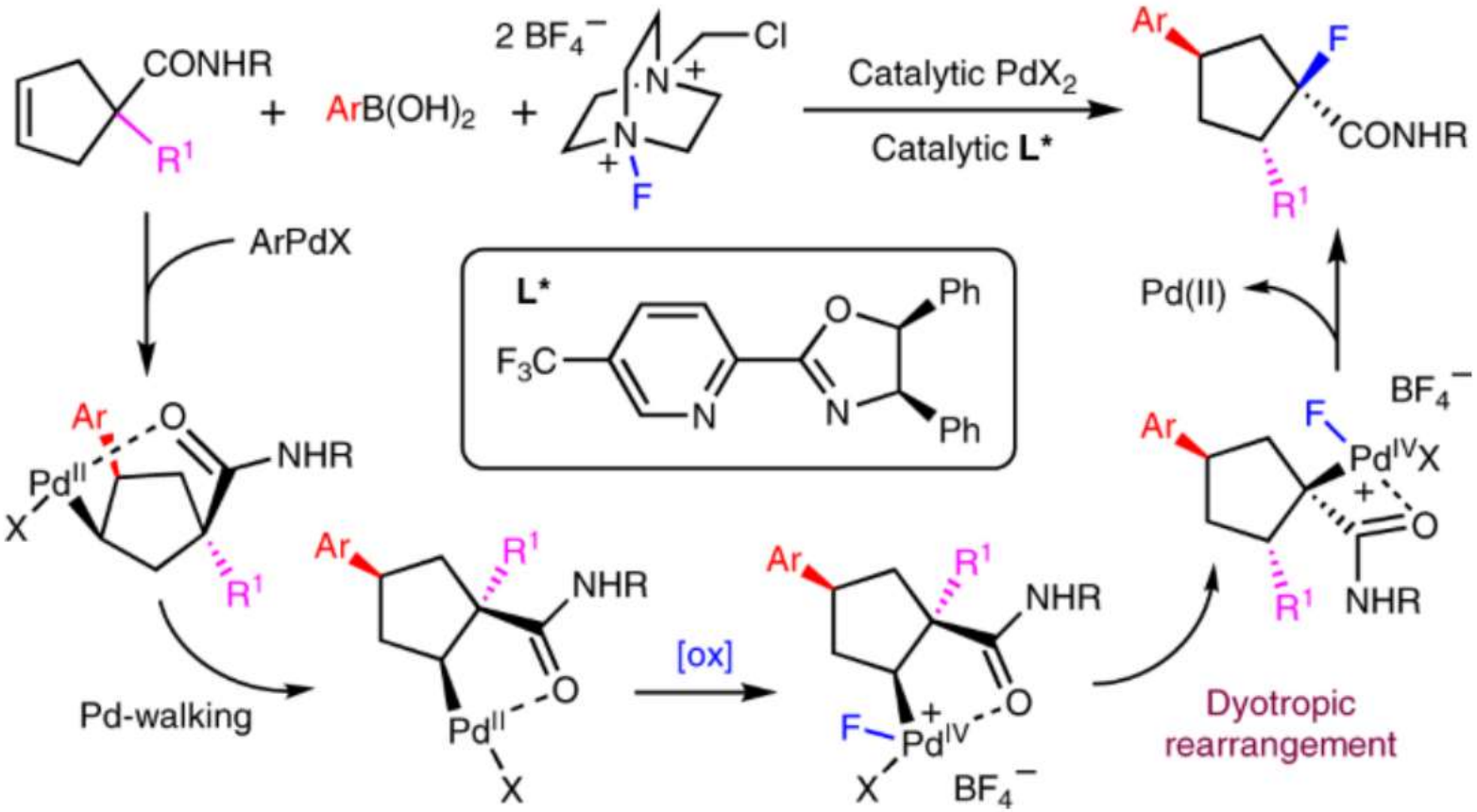
- **Reaction Design**



Zhu, J. Nature chemistry, 13(7), 671-676

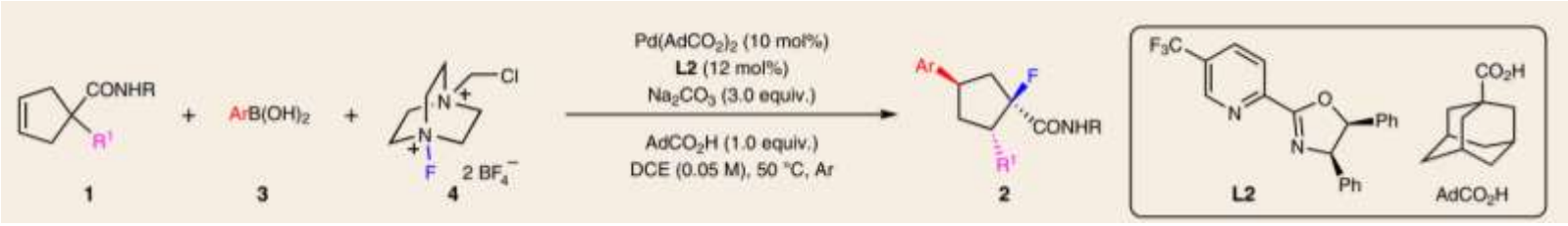
Dyotropic Rearrangement of Vicinal C–C and C–Pd(IV) bonds

◆ **Reaction Mechanism**

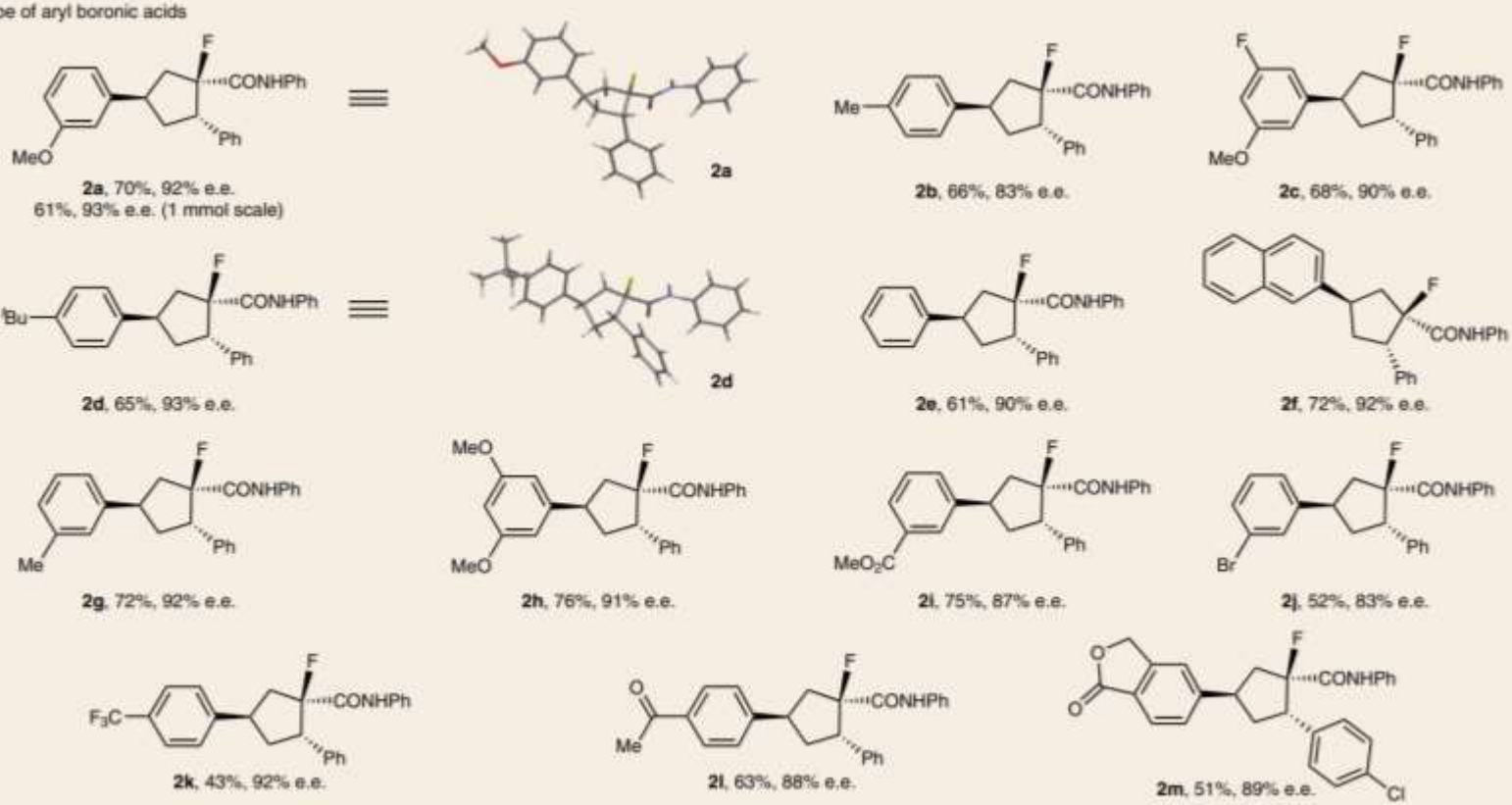


Dyotropic Rearrangement of Vicinal C–C and C–Pd(IV) bonds

◆ Substrate Scope

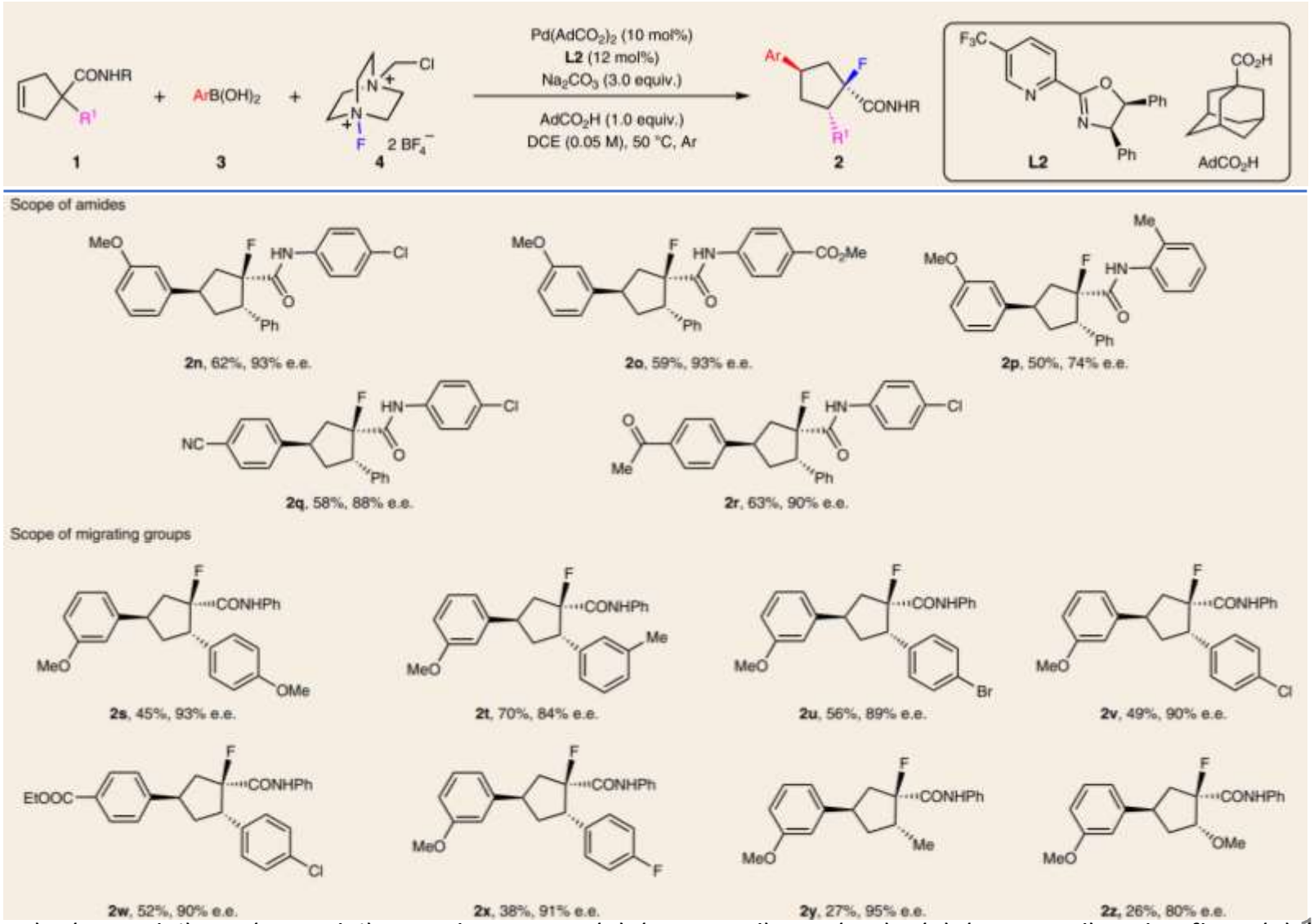


Scope of aryl boronic acids



Dyotropic Rearrangement of Vicinal C–C and C–Pd(IV) bonds

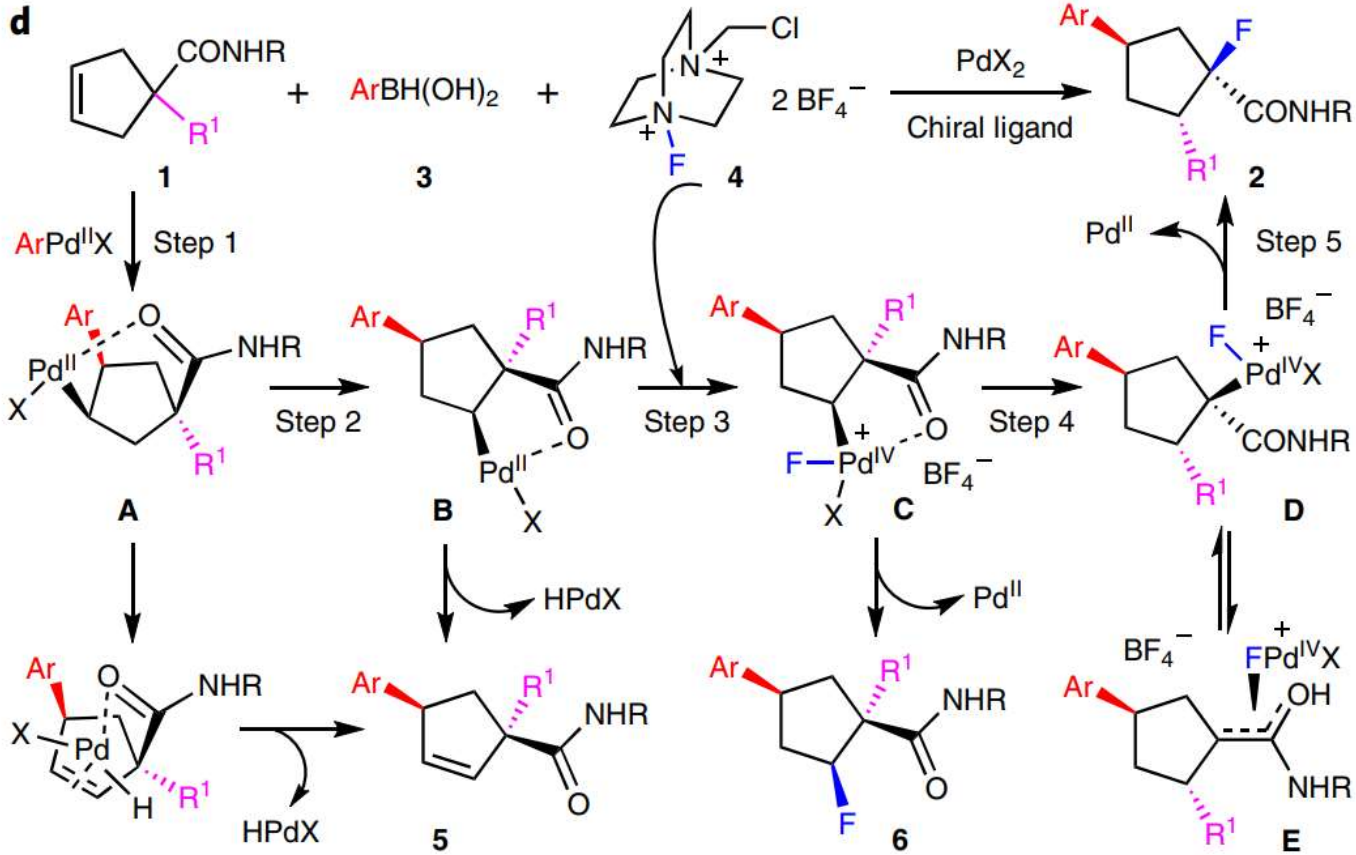
◆ Substrate Scope



Pd(AdCO2)2 (10 mol%), L2 (12 mol%), a cyclopentene (1) (0.1 mmol), ArB(OH)2 (3) (0.2 mmol), Selectfluor (4) (0.2 mmol), Na2CO3 (0.3 mmol), AdCO2H (0.1 mmol) in DCE (2.0 ml) at 50 °C under argon. AdCO2H, adamantane-1-carboxylic acid; Ar,

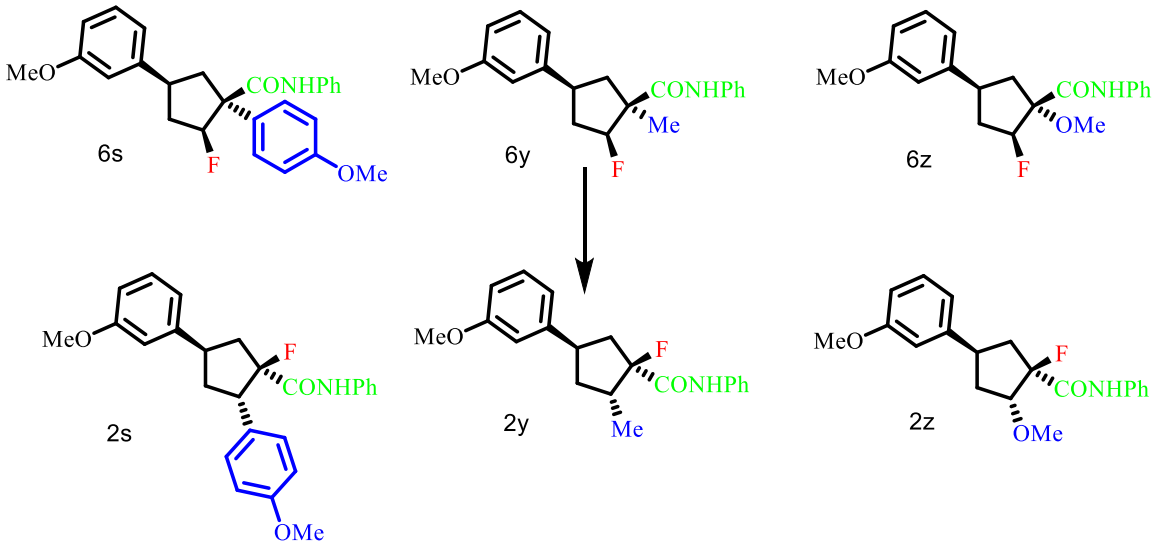
Dyotropic Rearrangement of Vicinal C–C and C–Pd(IV) bonds

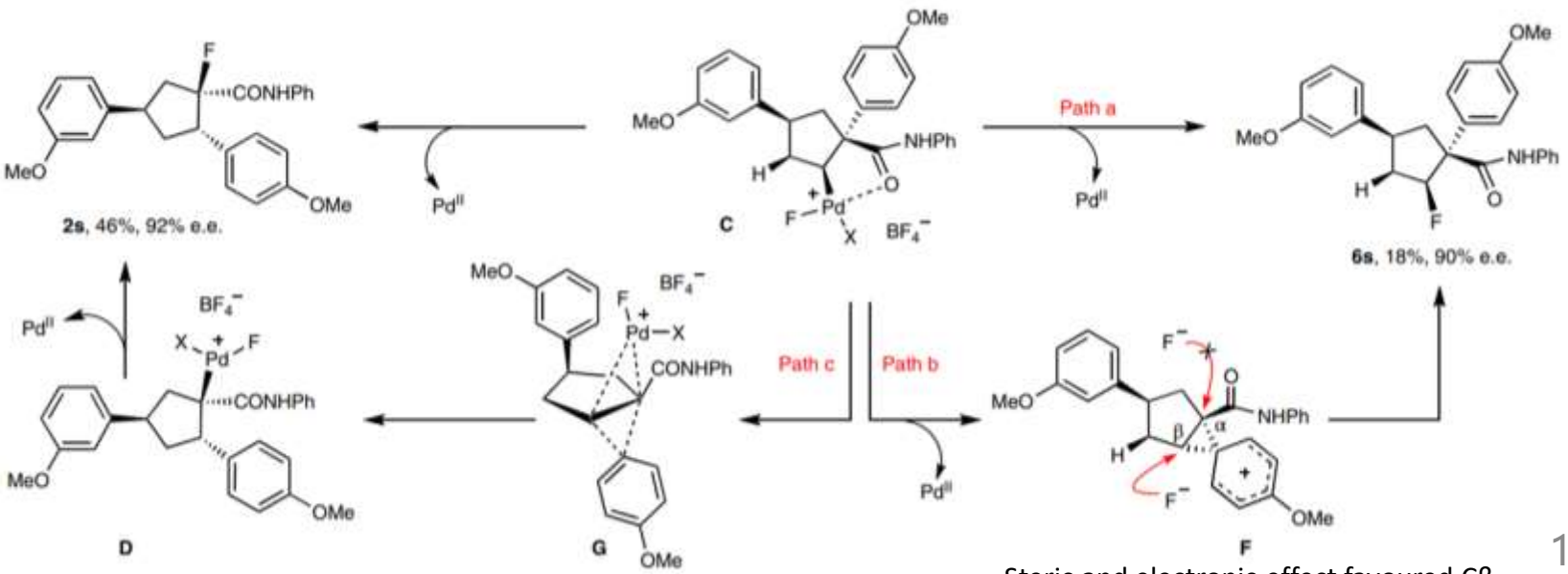
◆ **Reaction Design**



Dyotropic Rearrangement of Vicinal C–C and C–Pd(IV) bonds

◆ Side Products and Mechanistic Implication

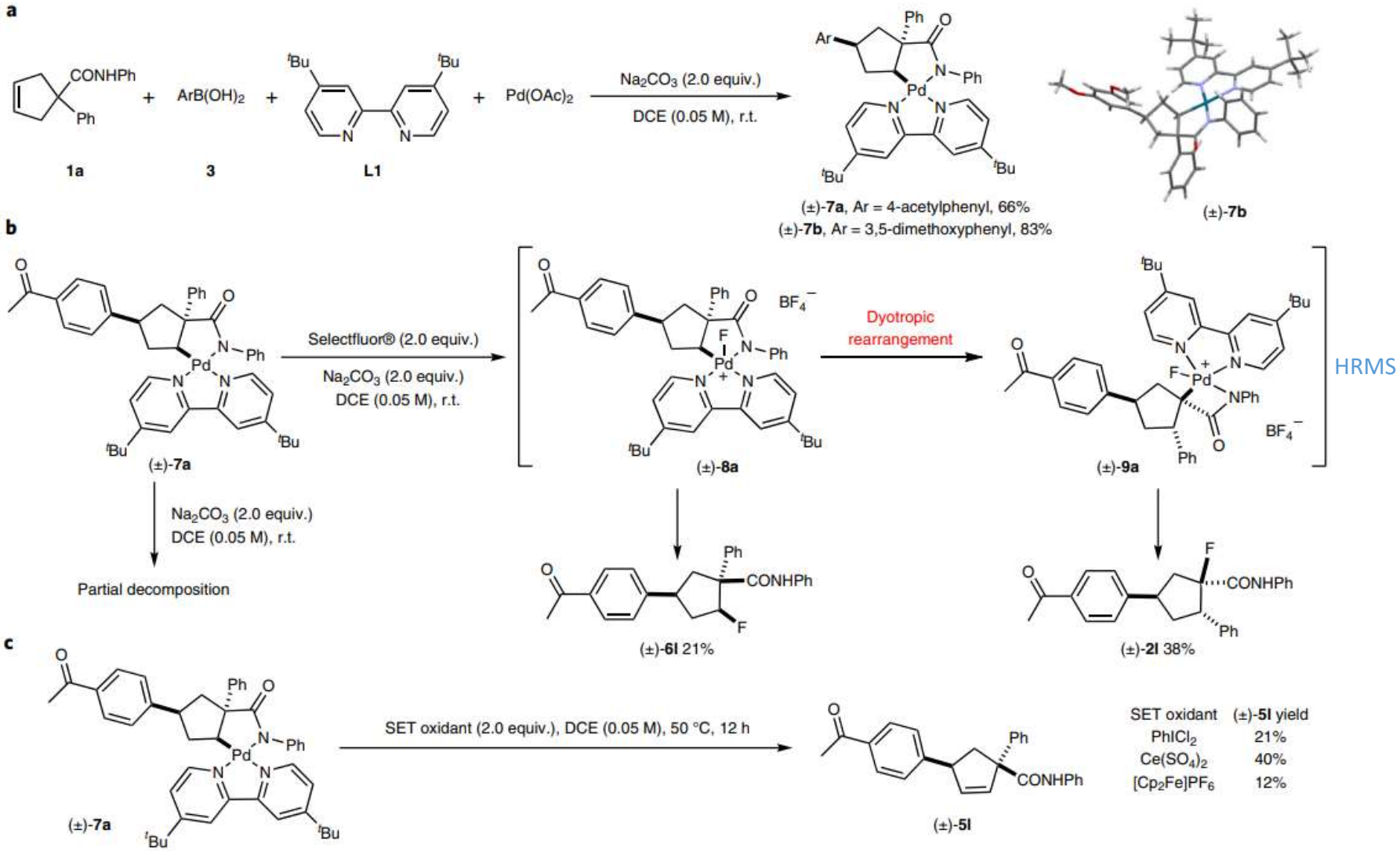




Steric and electronic effect favoured Cβ

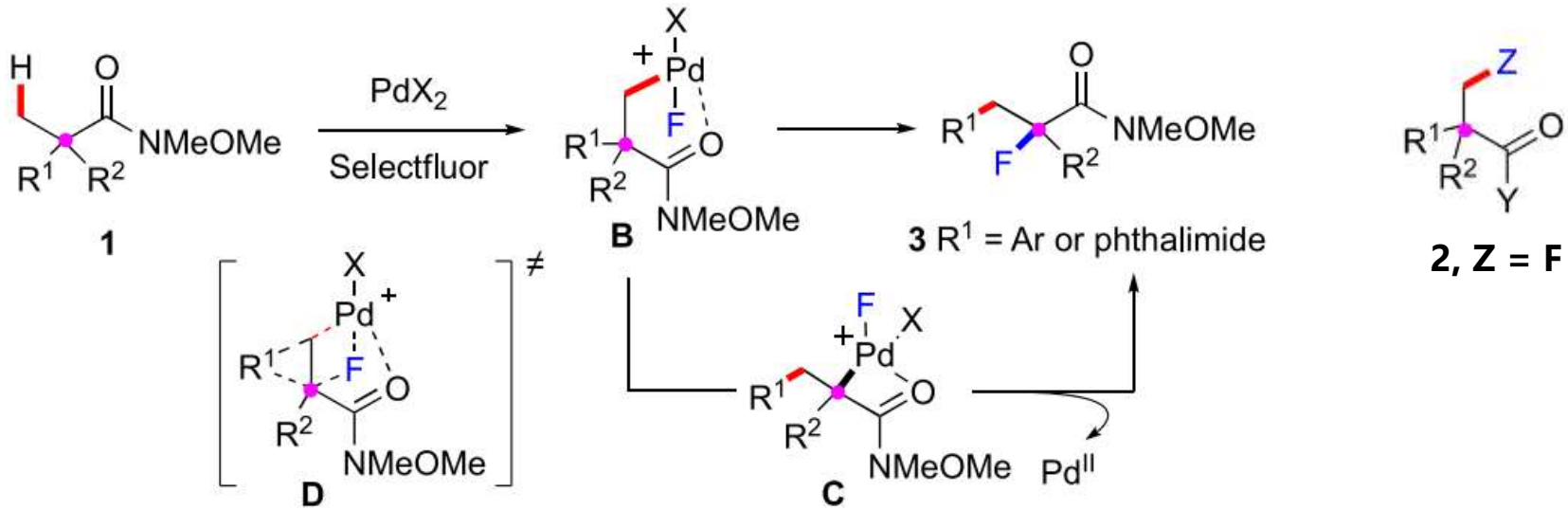
Dyotropic Rearrangement of Vicinal C–C and C–Pd(IV) bonds

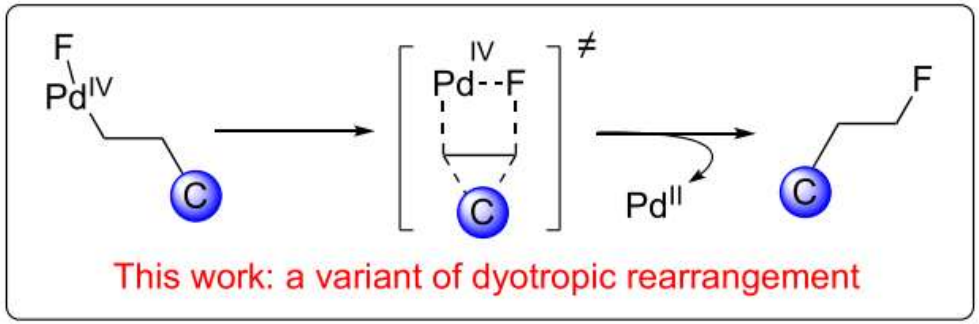
◆ Structure characterization of key reaction intermediates



Dyotropic Rearrangement of Vicinal C–C and C–Pd(IV) bonds

◆ **Pd-catalyzed dual functionalization of α- and β-carbons of saturated carbonyl compounds**

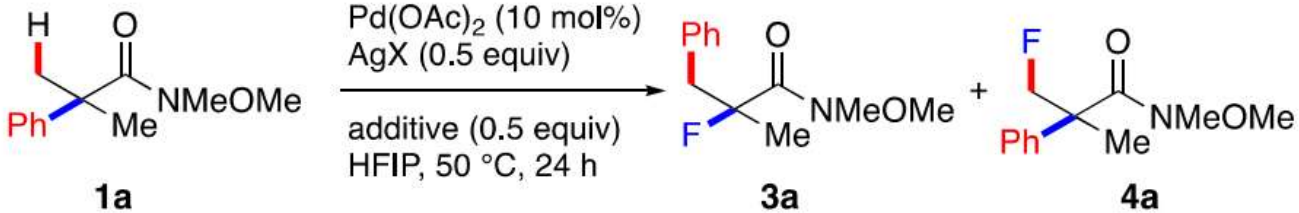




Zhu, J. J. Am. Chem. Soc. 2022, 144, 14047−14052

Dyotropic Rearrangement of Vicinal C–C and C–Pd(IV) bonds

◆ **Reaction Conditions** [a]

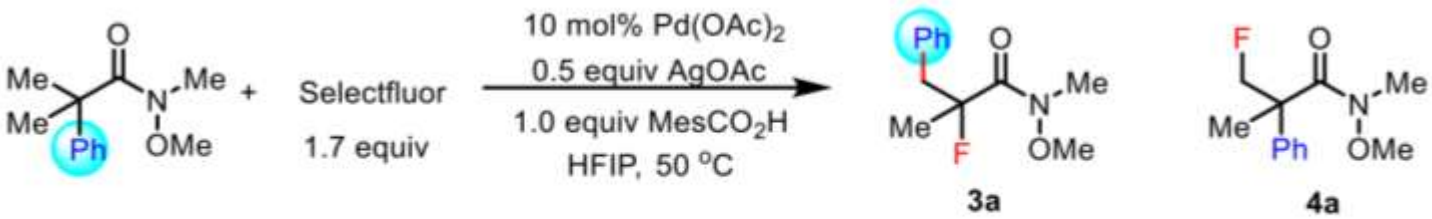


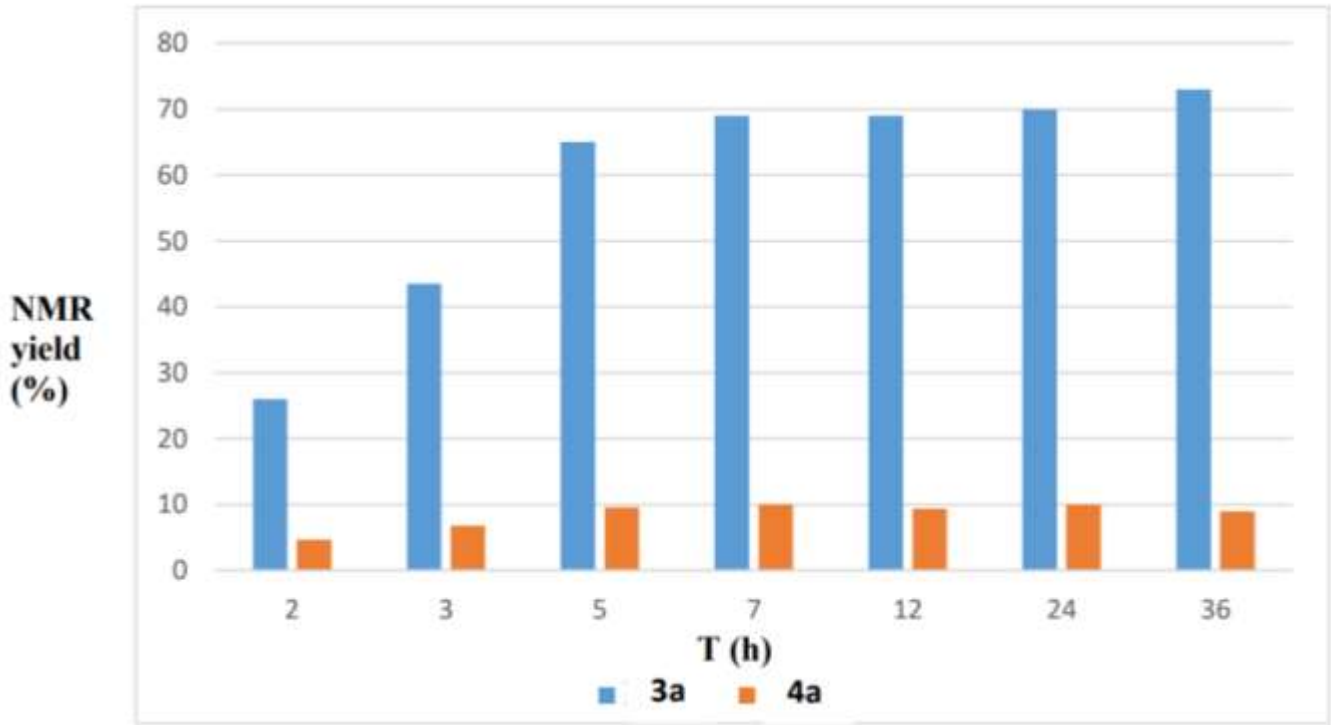
entry	AgX	Additive	3a (%)[b]	4a (%)[b]
1	–	–	43	23
2	CH_3CO_2Ag	–	50	13
3	CF_3CO_2Ag	–	43	12
4	Me_3CCO_2Ag	–	44	17
5	$AdCO_2Ag$	–	49	18
6	$MesCO_2Ag$	–	62	15
7	CH_3CO_2Ag	Me_3CCO_2H	43	15
8	CH_3CO_2Ag	$AdCO_2H$	50	15
9	CH_3CO_2Ag	$MesCO_2H$	72	11
10	CH_3CO_2Ag	$MesCO_2H$	75 (68)[c]	9

[a]Standard conditions: 1a (0.1 mmol), Selectfluor (0.2 mmol),Pd(OAc)2 (10 mol %), additive (0.5 equiv), HFIP (c 0.1 M), 50°C, 24 h. [b]1H NMR yields. [c]1.0 equiv of MesCO2H was used; yield in parentheses refers to isolated product. HFIP = 1,1,1,3,3,3-hexafluoropropan-2-ol, AdCO2H = 1-adamantancarboxylic acid; MesCO2H =2,4,6-trimethylbenzoic acid.

Dyotropic Rearrangement of Vicinal C–C and C–Pd(IV) bonds

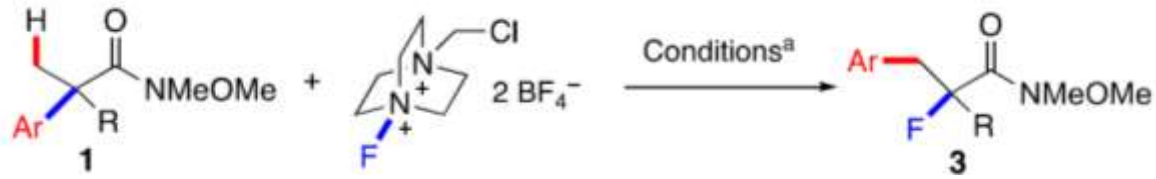
◆ **Reaction Conditions** [a]

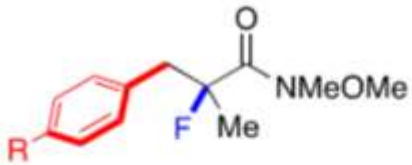




Dyotropic Rearrangement of Vicinal C–C and C–Pd(IV) bonds

◆ **Substrate Scope** [a]



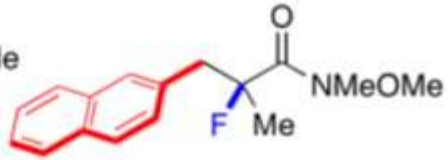


3a R = H, 68%
3b R = Me, 67%
3c R = *t*Bu, 65%
3d R = Ph, 60%
3e R = F, 71%
3f R = Cl, 66%
3g R = Br, 60%
3h R = CF_3, 41% (52%)[b]

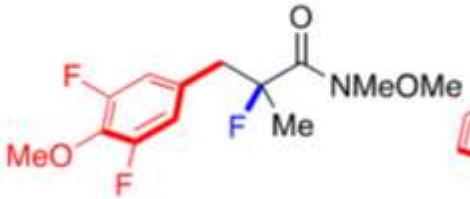
3i R = Me, 65%
3j R = Cl, 58%
3k R = CF_3, 43% (50%)[b]

3l R = F, 54%
3m R = Cl, 48%

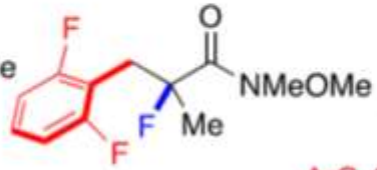
3n 63%



3o 51%



3p 59%

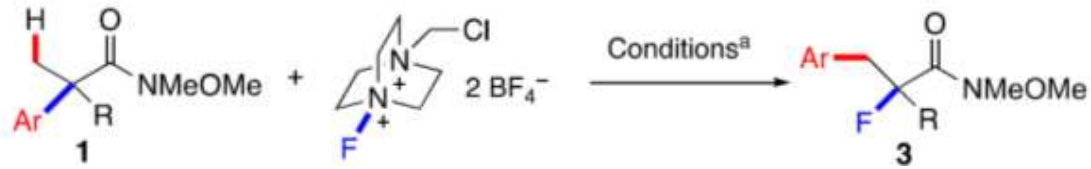


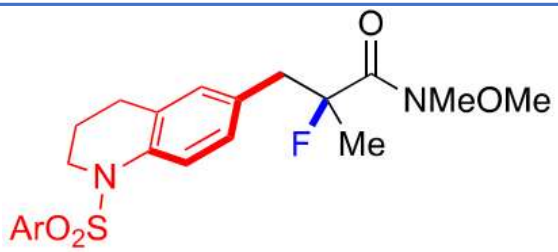
3q 46%

3r Ar = 4-$CF_3C_6H_4$, 50%

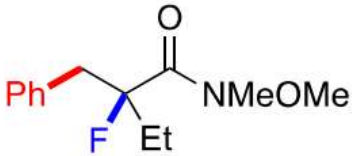
Dyotropic Rearrangement of Vicinal C–C and C–Pd(IV) bonds

◆ **Substrate Scope** [a]

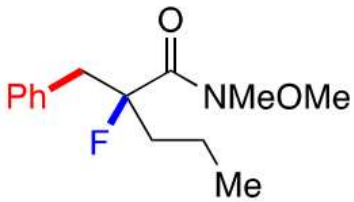




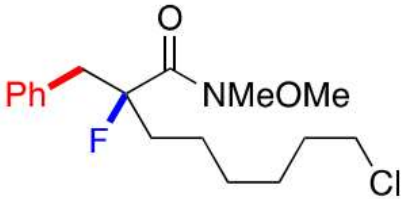
3s Ar = 4-$CF_3C_6H_4$, 62%



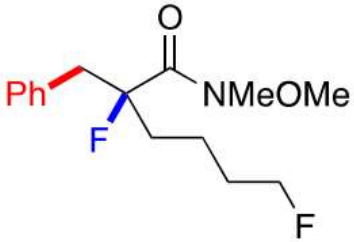
3t 43%[c]



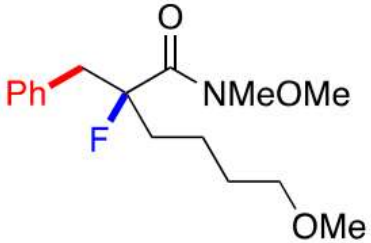
3u 44%[c]



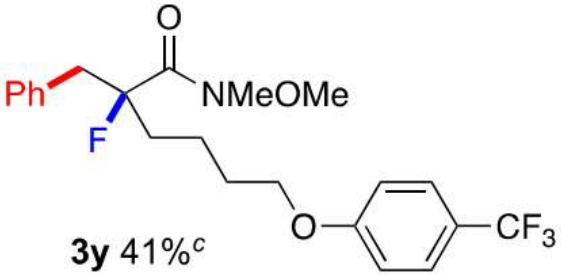
3v 40%[c]



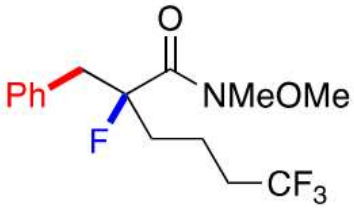
3w 43%[c]



3x 34%[c]



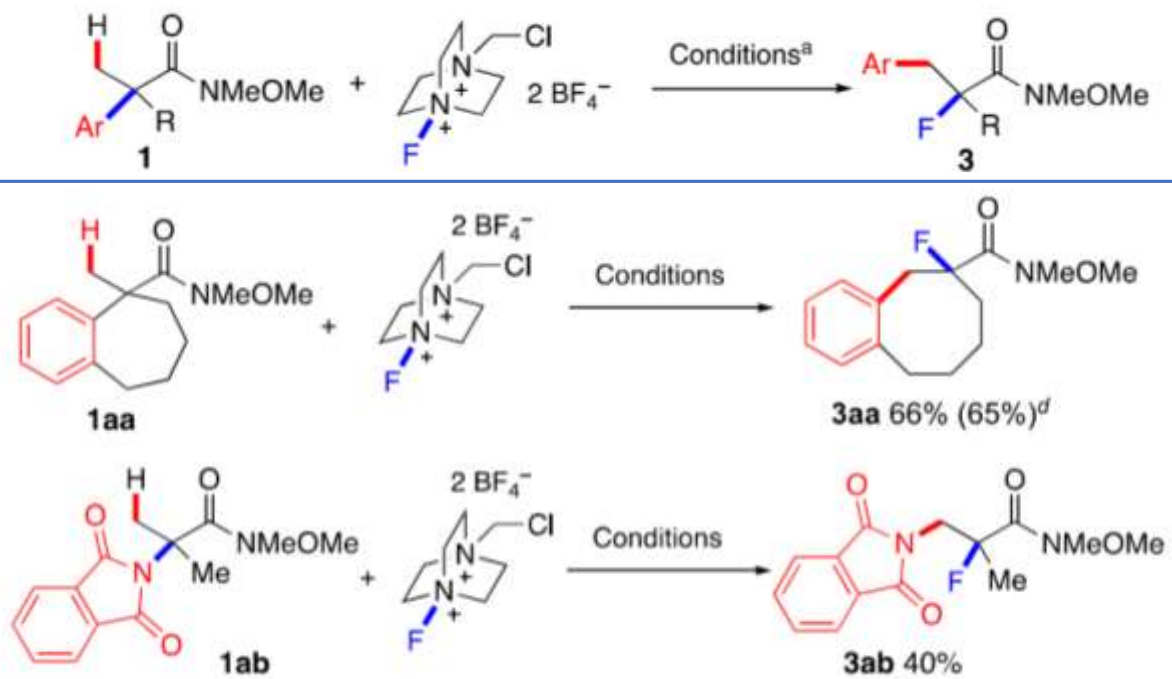
3y 41%[c]



3z 41%[c]

Dyotropic Rearrangement of Vicinal C–C and C–Pd(IV) bonds

◆ **Substrate Scope** [a]

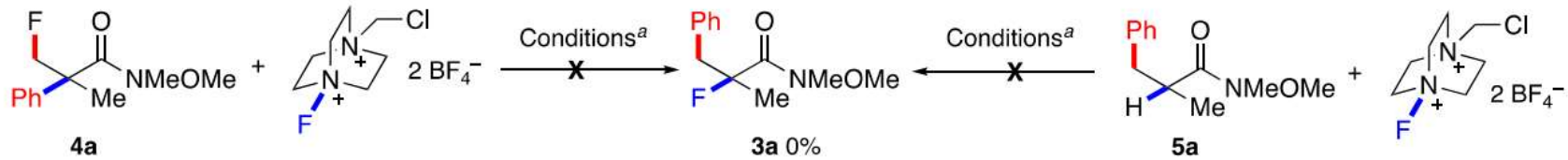


[a]Standard conditions: amides 1 (0.1 mmol), Selectfluor (2.0 equiv),Pd(OAc)2 (10 mol %), AgOAc (0.5 equiv), MesCO2H (1.0 equiv),HFIP (c 0.1 M), 50 °C, under air atmosphere. [b]0.5 equiv of MesCO2H was used under otherwise standard conditions. [c]Pd(OAc)2 (7 mol % × 3), amides 1 (0.1 mmol), Selectfluor (0.8 equiv × 3), AgOAc (0.35 equiv × 3), MesCO2H (1.0 equiv), HFIP (c 0.1 M), 50°C under air atmosphere. [d]Yield in parentheses refers to the reaction performed at 1.0 mmol scale.

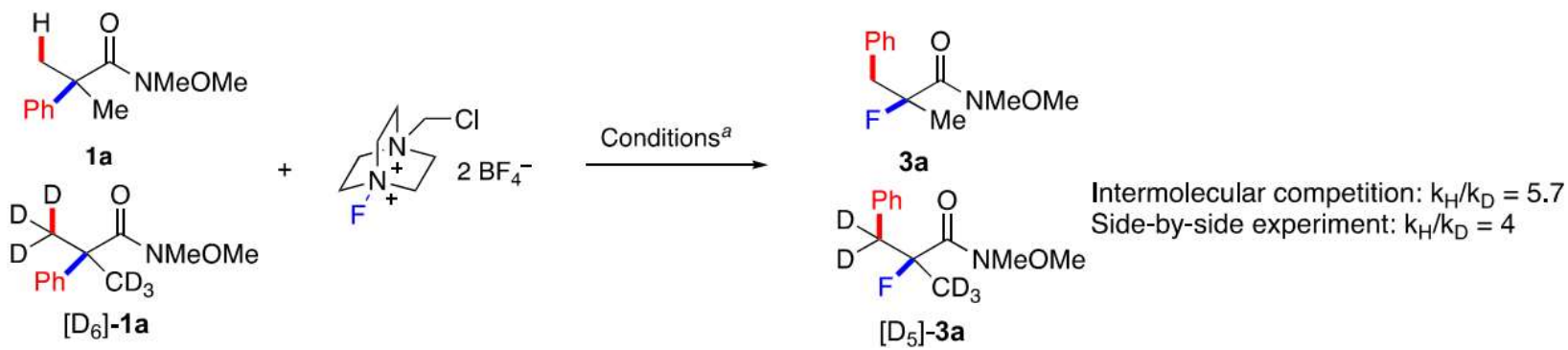
Dyotropic Rearrangement of Vicinal C–C and C–Pd(IV) bonds

◆ Mechanistic Studies

(a) Control experiments



(b) Kinetic isotope effects using **1a** and [D_6]-**1a** as competing substrates

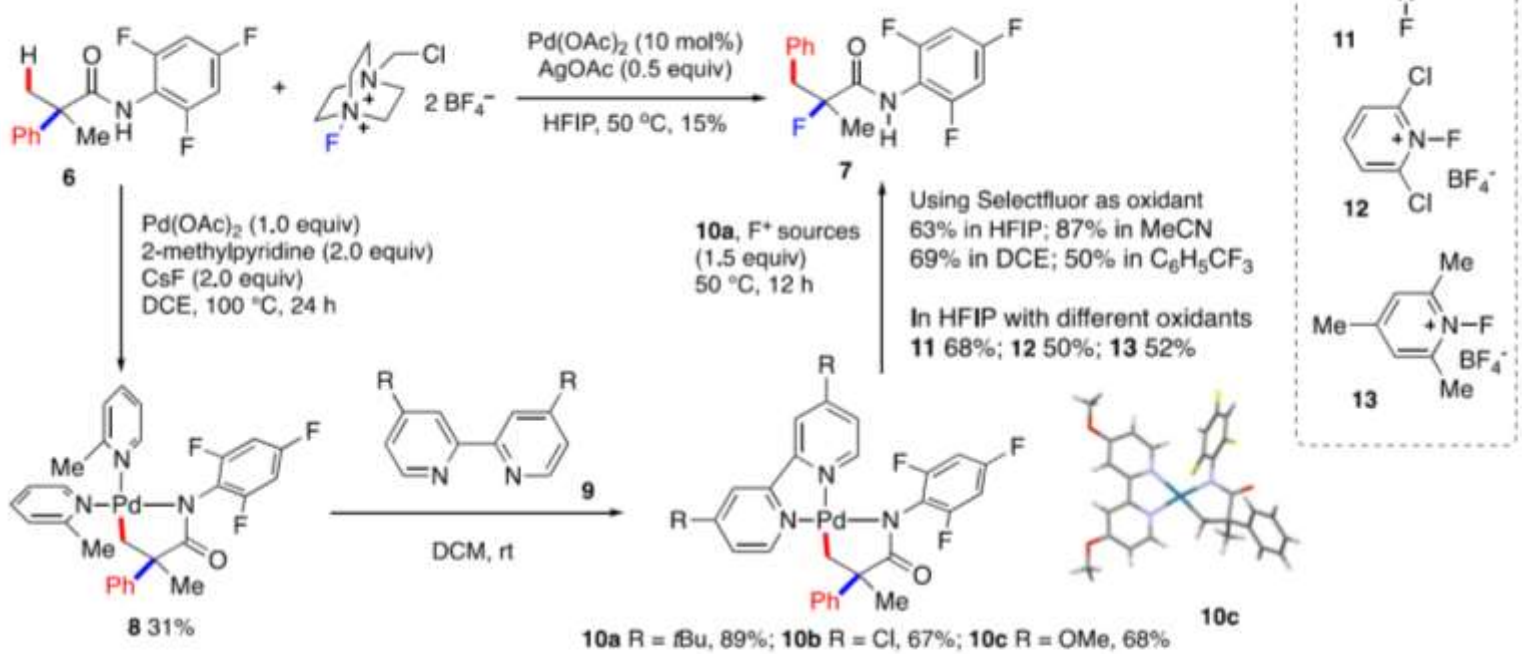


[a]Standard conditions: (a). Control experiments. Conditions: Pd(OAc)2 (10 mol %), amides 4a or 5a (0.1 mmol), Selectfluor (2.0 equiv), AgOAc(0.5 equiv), MesCO2H (1.0 equiv), HFIP (c 0.1 M), 50 °C under air atmosphere. (b). Kinetic isotope effects using 1a and [D6]-1a as competing substrates. (c) Characterization of Pd(II) complexes 10a–10c and conversion of 10a to the rearranged product 7. (d). Stereochemistry of the reaction. Conditions: 0.5 equiv of MesCO2H was used under otherwise standard conditions: Pd(OAc)2 (7 mol % × 3), (R)-1t (0.1 mmol), Selectfluor (0.8 equiv × 3), AgOAc (0.35 equiv × 3), MesCO2H (1.0 equiv), HFIP (c 0.1 M), 50 °C under air atmosphere.

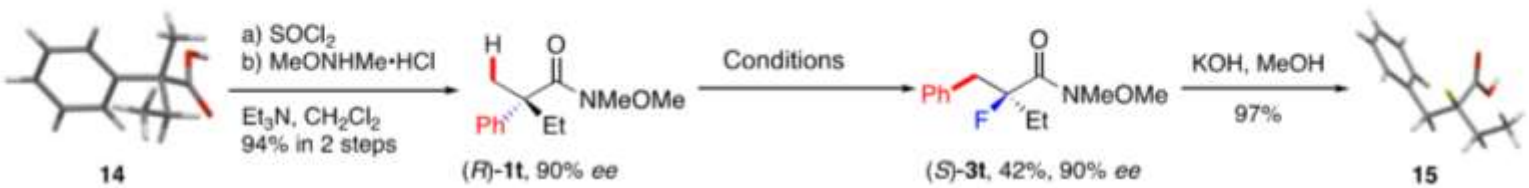
Dyotropic Rearrangement of Vicinal C–C and C–Pd(IV) bonds

◆ Mechanistic Studies

(c) Characterization of Pd(II) complexes **10a-10c** and conversion of **10a** to the rearranged product **7**

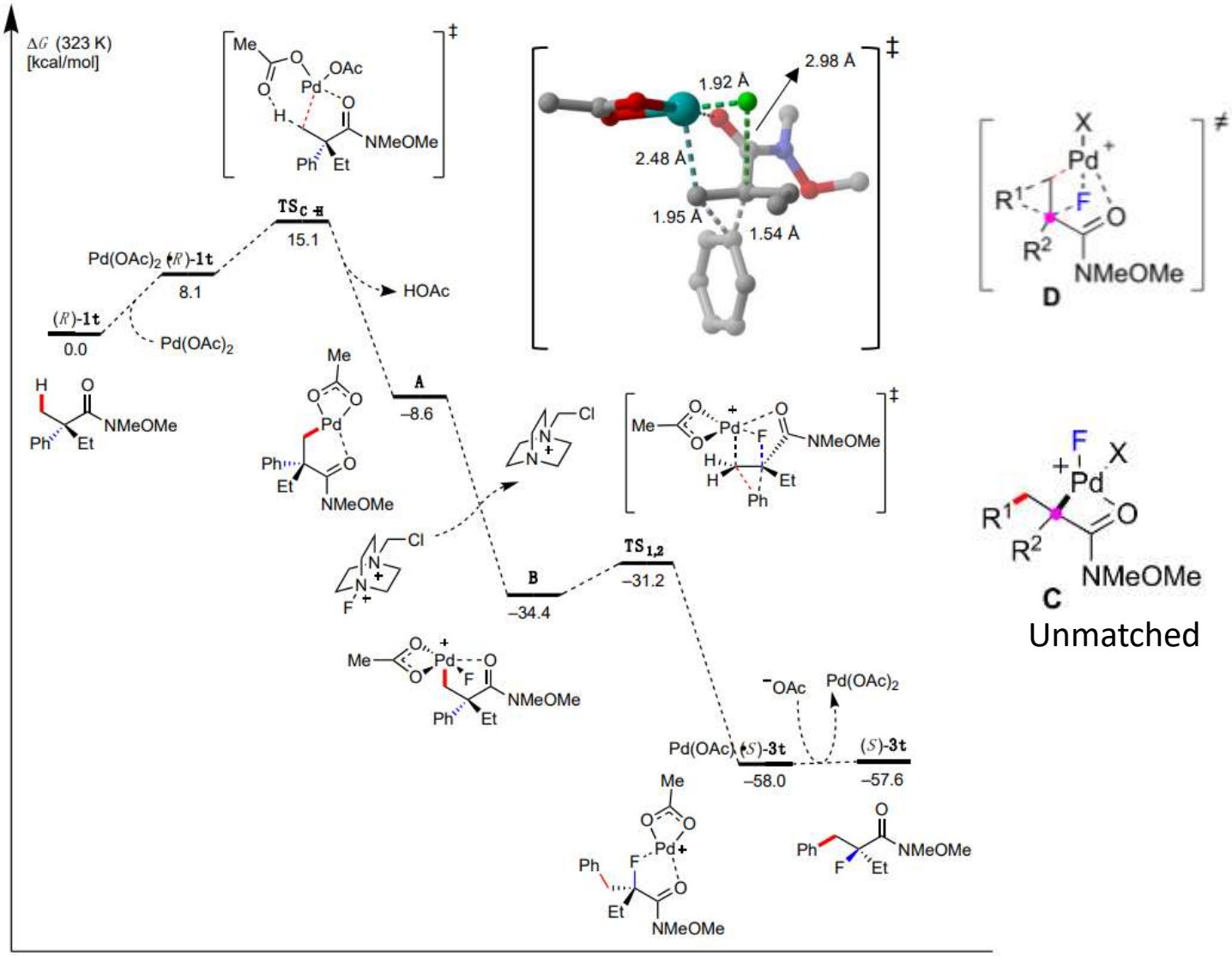


(d) Stereochemistry of the rearrangement reaction: inversion of stereocenter



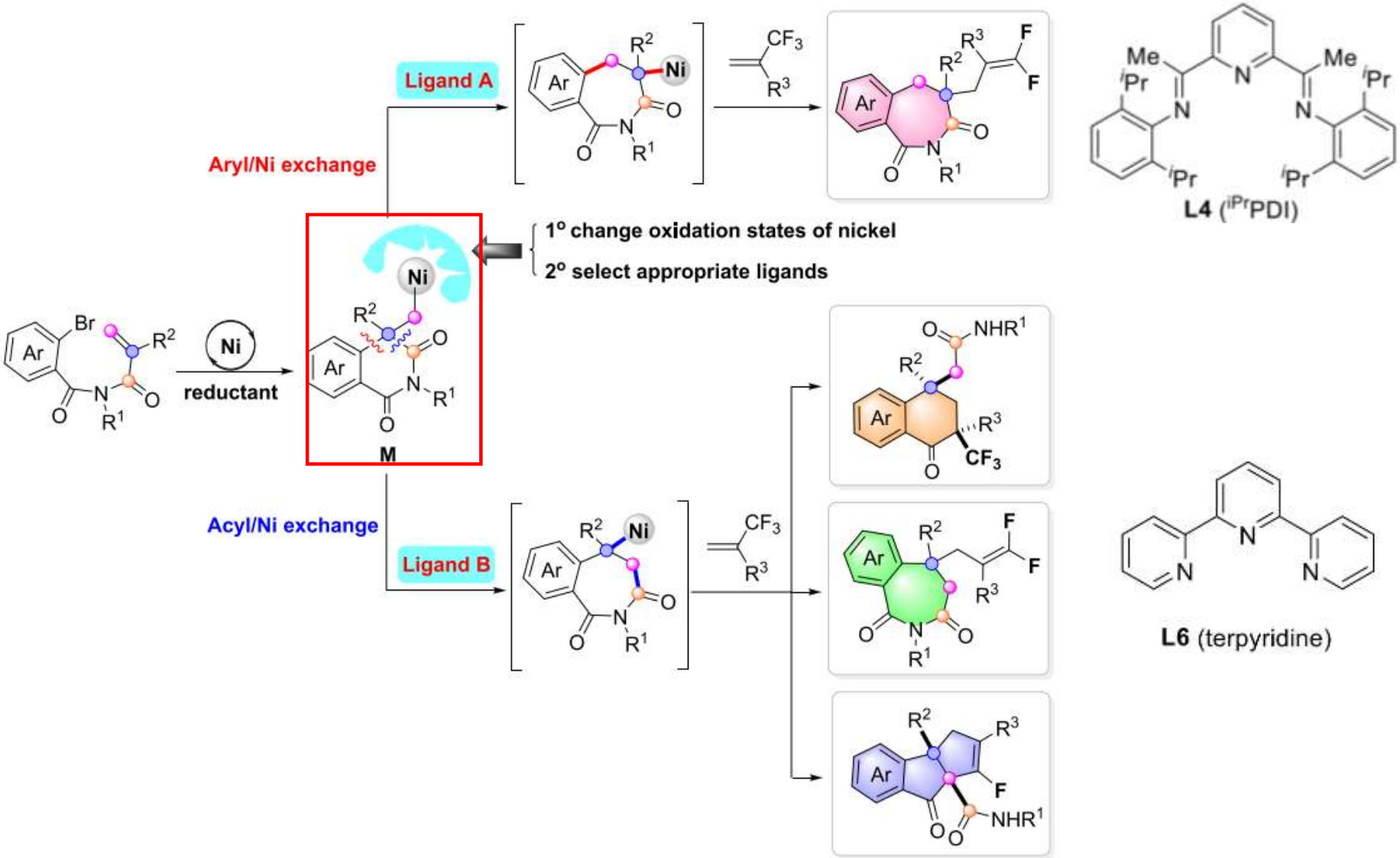
Dyotropic Rearrangement of Vicinal C–C and C–Pd(IV) bonds

◆ **Mechanistic Studies**



C–H cleavage is the turnover-limiting step

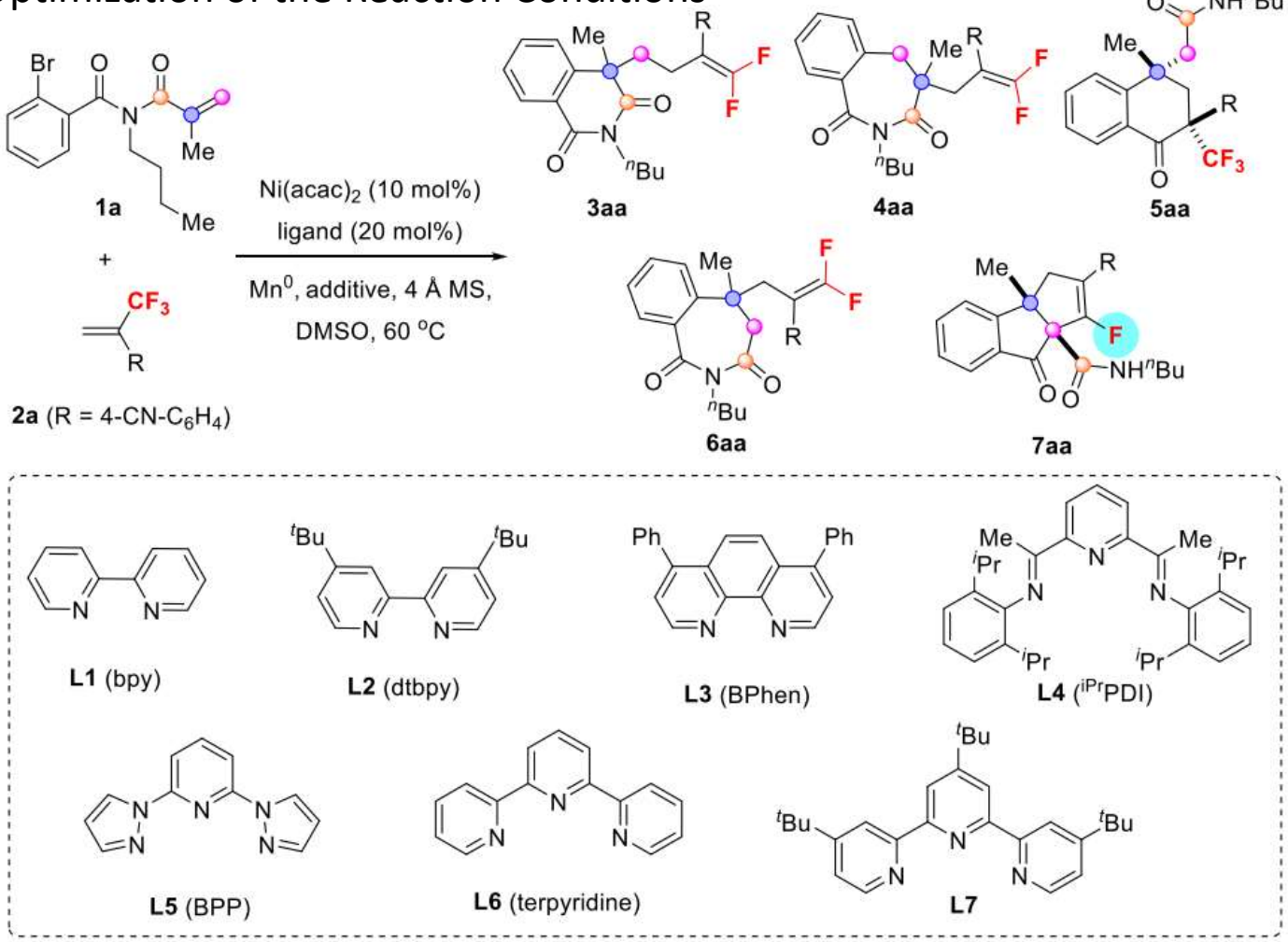
Ni Catalyzed Ligand-Controlled, Switchable 1,2-Rearrangement



Minyan Wang and Wangqing Kong. J. Am. Chem. Soc. 2022, 144, 11626−11637

Ni Catalyzed Ligand-Controlled, Switchable 1,2-Rearrangement

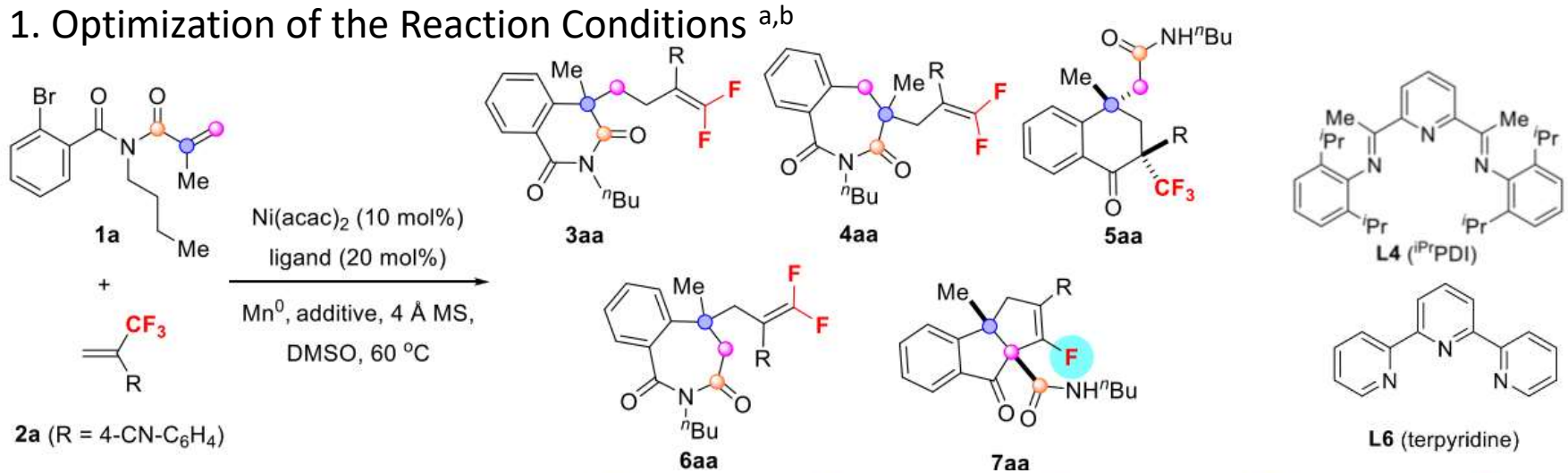
Table 1. Optimization of the Reaction Conditions [a,b]



[a]Reaction conditions: 1a (0.1 mmol), 2a (0.2 mmol), Ni(acac)2 (10.0 mol %), ligand (20.0 mol %), Mn powder (0.3 mmol), MgCl2 (0.2 mmol), 4Å MS (molecular sieves) (20 mg), DMSO (0.05 M), and 60 °C. [b]Isolated yields. [c]NiBr2·DME (10.0 mol %) was used instead of Ni(acac)2. [d]LiOtBu (0.1 mmol) was used instead of MgCl2. [e]MnBr2 (0.1 mmol) was used instead of MgCl2. [f]DMSO/THF (1:1 v/v). [g]DMSO/THF (1:9 v/v), Mn powder (0.2 mmol). [h]KI (0.2 mmol) was used instead of $MgCl_2$

Ni Catalyzed Ligand-Controlled, Switchable 1,2-Rearrangement

Table 1. Optimization of the Reaction Conditions [a,b]



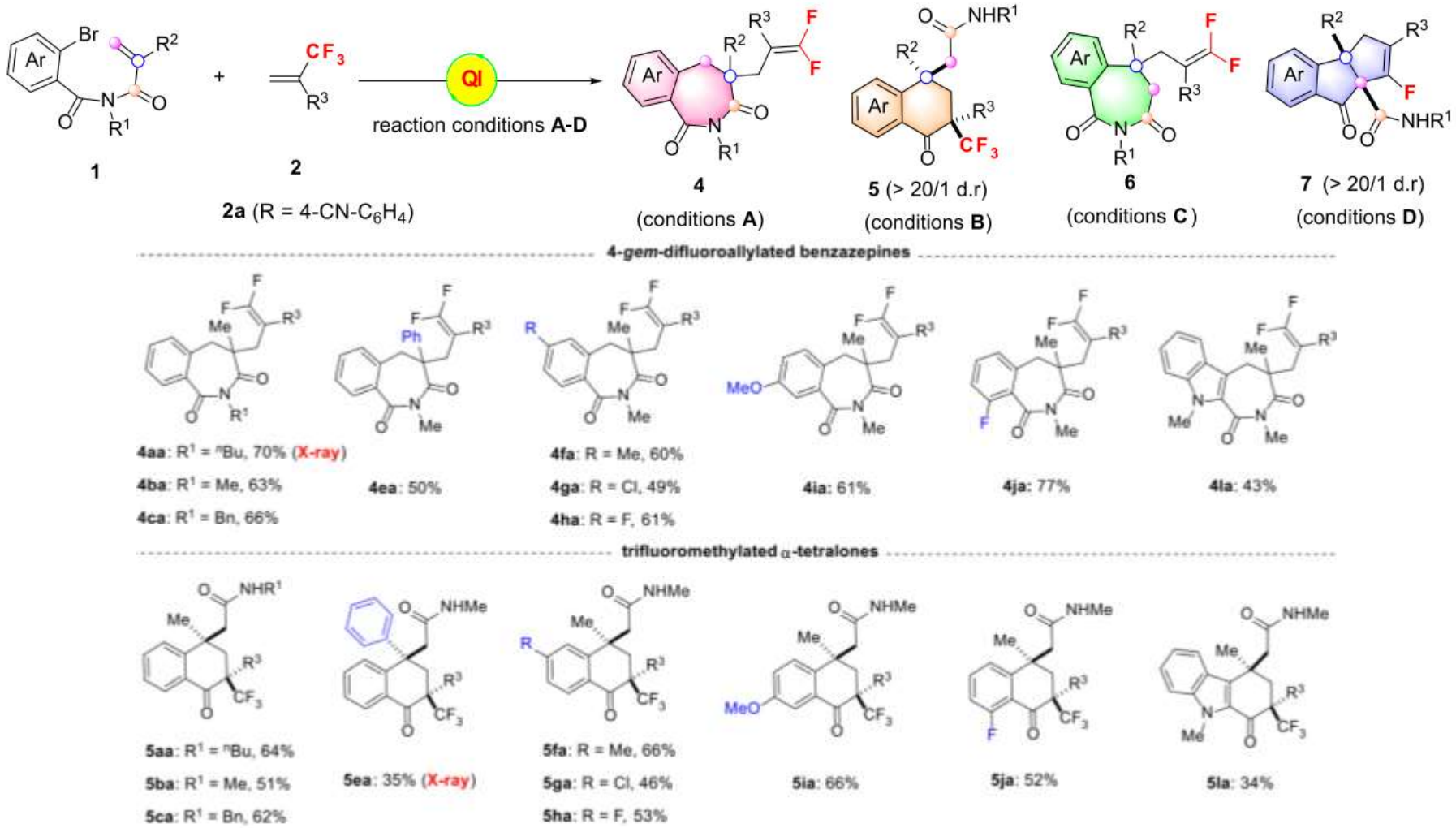
entry	ligand	T (°C)	3aa (%)[b]	4aa (%)[b]	5aa (%)[b]	6aa (%)[b]	7aa (%)[b]
1	L1	60	5	5			
2	L2	60	6	9			
3	L3	60		4			
4	L4	60	7	42			
5[c,d]	L4	80	5	70			
6[c,d]	L5	80	5	46			
7	L6	60	3		8		57
8	L7	60	3		8		54
9[e,f]	L6	80	<2		<2		68
10[e,f]	L6	60		<2	30	5	34
11[e,f]	L6	25	<2	<2	64	5	
12[g,h]	L6	80	<2	<2	21	50	<2

[a]Reaction conditions: 1a (0.1 mmol), 2a (0.2 mmol), Ni(acac)2 (10.0 mol %), ligand (20.0 mol %), Mn powder (0.3 mmol), MgCl2 (0.2 mmol), 4Å MS (molecular sieves) (20 mg), DMSO (0.05 M), and 60 °C. [b]Isolated yields. [c]NiBr2·DME (10.0 mol %) was used instead of Ni(acac)2. [d]LiOtBu (0.1 mmol) was used instead of MgCl2. [e]MnBr2 (0.1 mmol) was used instead of MgCl2. [f]DMSO/THF (1:1 v/v). [g]DMSO/THF (1:9 v/v), Mn powder (0.2 mmol). [h]KI (0.2 mmol) was used instead of $MgCl_2$

Ni Catalyzed Ligand-Controlled, Switchable 1,2-Rearrangement

Scheme 2. Reaction Scope of Ni-Catalyzed Ligand-Directed Divergent Synthesis[a]

◆ **The scope of aryl bromides**

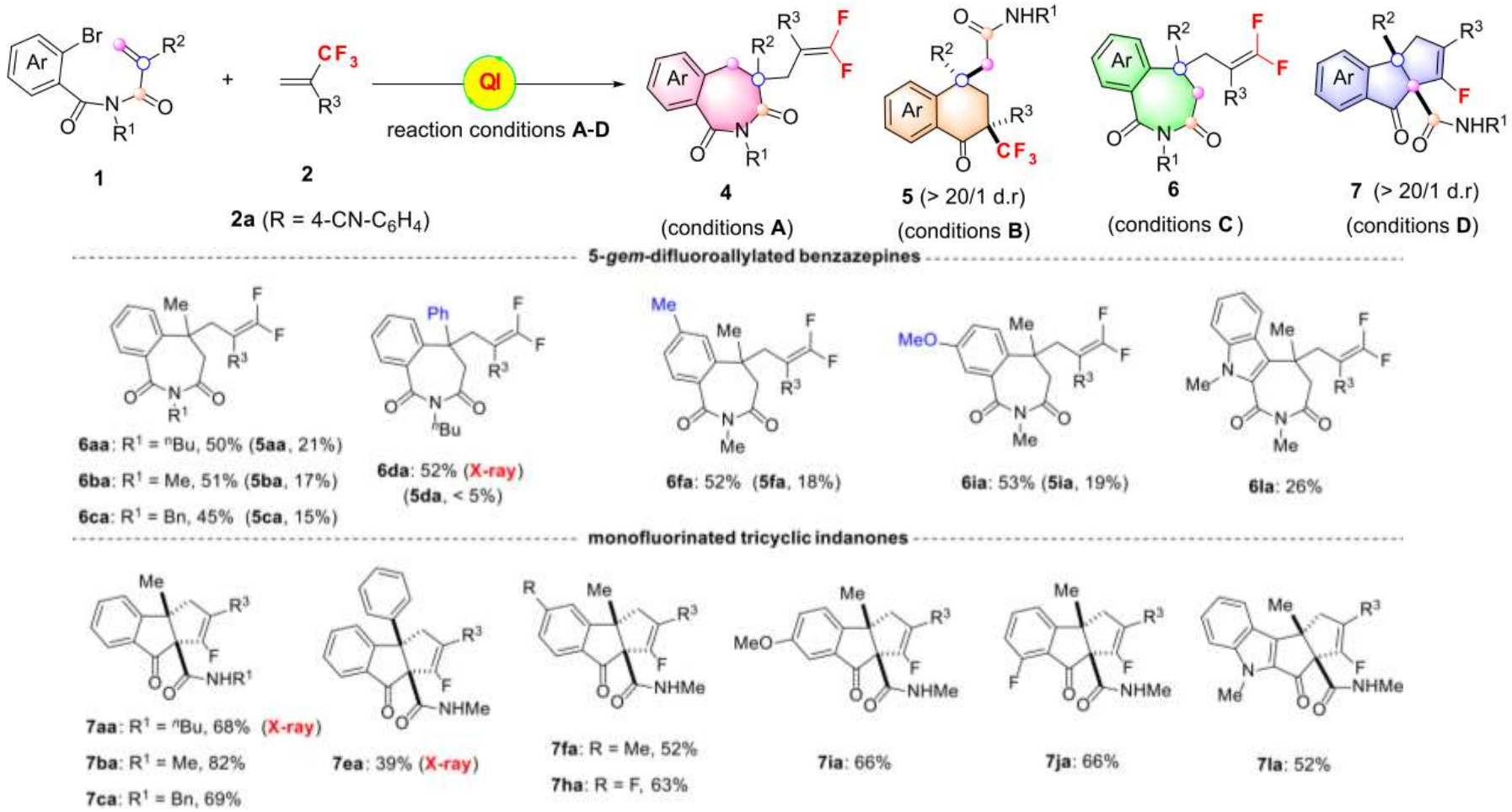


(A) 1 (0.1 mmol), 2 (0.3 mmol), NiBr2(DME) (10.0 mol %), L4 (20.0 mol %), Mn0 (0.3 mmol), LiOtBu (0.1 mmol),DMSO (2 mL), 4 Å MS (20 mg), 80 °C, 48 h; (B) 1 (0.1 mmol), 2 (0.2 mmol), Ni(acac)2 (10.0 mol %), L6 (20.0 mol %), Mn0 (0.3 mmol),MnBr2 (0.1 mmol), 4 Å MS (20 mg), DMSO (1 mL), THF (1 mL), 25 °C, 48−72 h;

Ni Catalyzed Ligand-Controlled, Switchable 1,2-Rearrangement

Scheme 2. Reaction Scope of Ni-Catalyzed Ligand-Directed Divergent Synthesis[a]

◆ **The scope of aryl bromides**

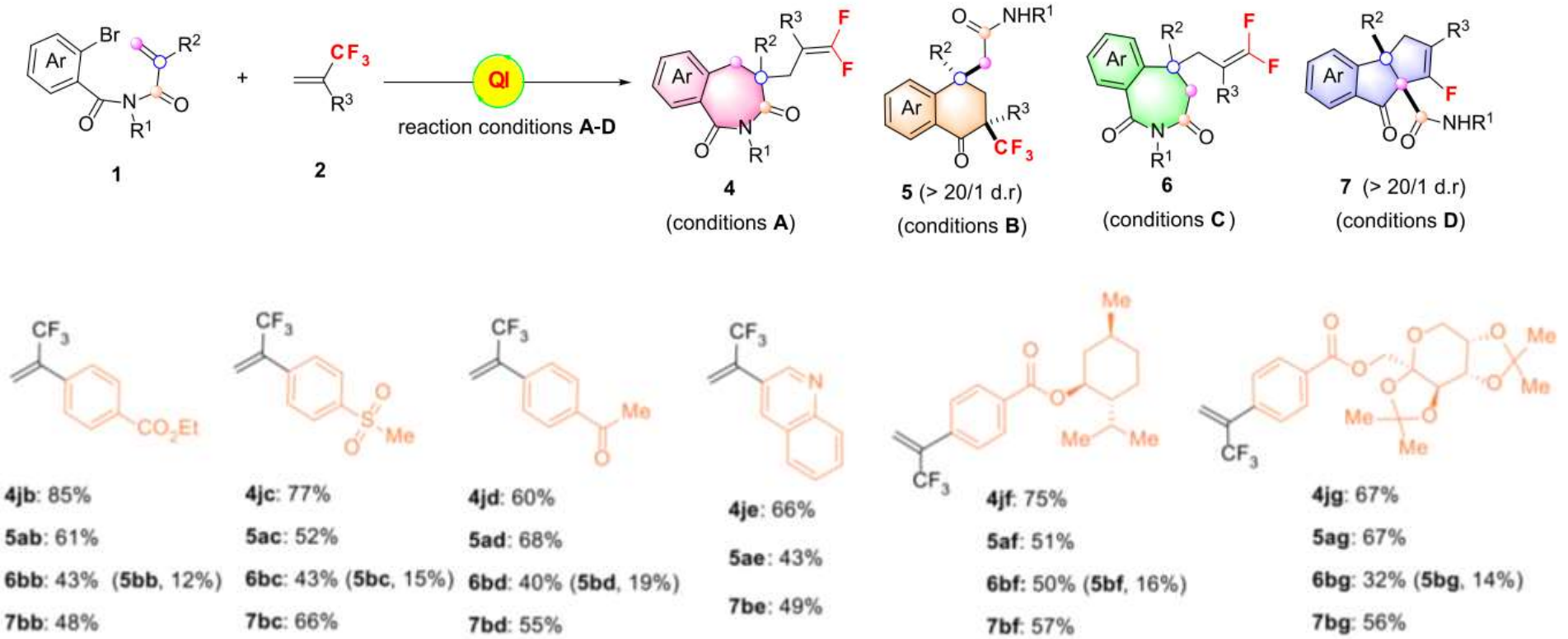


(C) 1 (0.1 mmol), 2 (0.2mmol), Ni(acac)2 (10.0 mol %),L6 (20.0 mol %), Mn0 (0.2 mmol), KI (0.2 mmol),4 Å MS (20 mg), DMSO (0.2 mL), THF (1.8 mL), 80 °C, 36−48 h; (D) 1 (0.1 mmol), 2 (0.2mmol), Ni(acac)2 (10.0 mol %), L6 (20.0 mol %), Mn0 (0.3 mmol), MnBr2 (0.2 mmol), 4 Å MS (20 mg), DMSO (2 mL), THF (2 mL), 80 °C, and 48−96 h. (R3 = 4-CN-C6H4).

Ni Catalyzed Ligand-Controlled, Switchable 1,2-Rearrangement

Scheme 2. Reaction Scope of Ni-Catalyzed Ligand-Directed Divergent Synthesis[a]

◆ **The scope of trifluoromethyl alkenes**

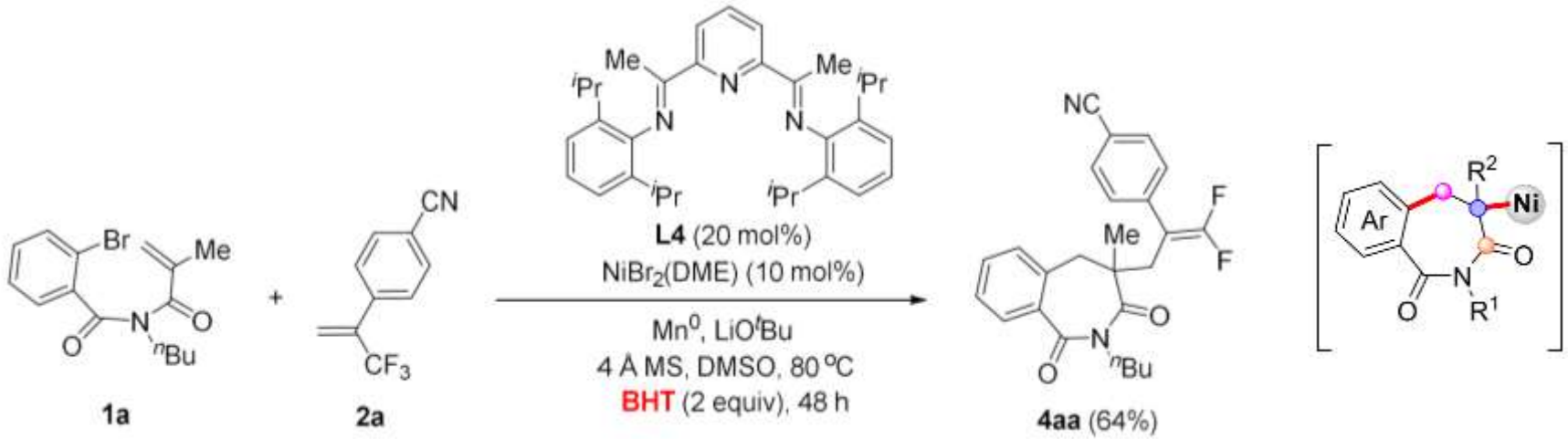


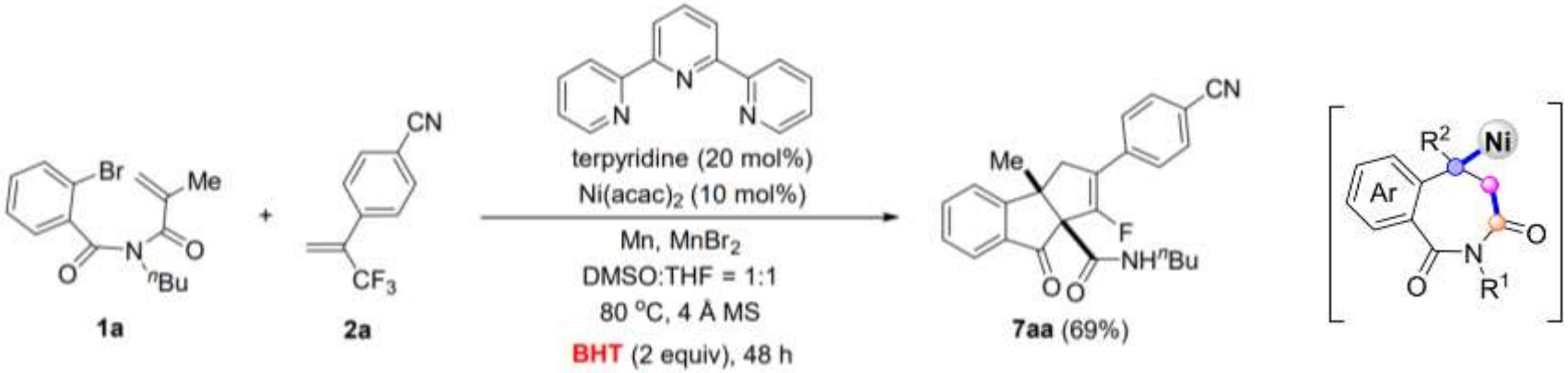
[a]Reaction conditions: (A) 1 (0.1 mmol), 2 (0.3 mmol), NiBr2(DME) (10.0 mol %), L4 (20.0 mol %), Mn0 (0.3 mmol), LiOtBu (0.1 mmol),DMSO (2 mL), 4 Å MS (20 mg), 80 °C, 48 h; (B) 1 (0.1 mmol), 2 (0.2 mmol), Ni(acac)2 (10.0 mol %), L6 (20.0 mol %), Mn0 (0.3 mmol),MnBr2 (0.1 mmol), 4 Å MS (20 mg), DMSO (1 mL), THF (1 mL), 25 °C, 48−72 h; (C) 1 (0.1 mmol), 2 (0.2mmol), Ni(acac)2 (10.0 mol %),L6 (20.0 mol %), Mn0 (0.2 mmol), KI (0.2 mmol),4 Å MS (20 mg), DMSO (0.2 mL), THF (1.8 mL), 80 °C, 36−48 h; (D) 1 (0.1 mmol), 2 (0.2mmol), Ni(acac)2 (10.0 mol %), L6 (20.0 mol %), Mn0 (0.3 mmol), MnBr2 (0.2 mmol), 4 Å MS (20 mg), DMSO (2 mL), THF (2 mL), 80 °C, and 48−96 h. (R3 = 4-CN-C6H4).

Ni Catalyzed Ligand-Controlled, Switchable 1,2-Rearrangement

◆ **Mechanistic Studies**

Radical Trapping experiments



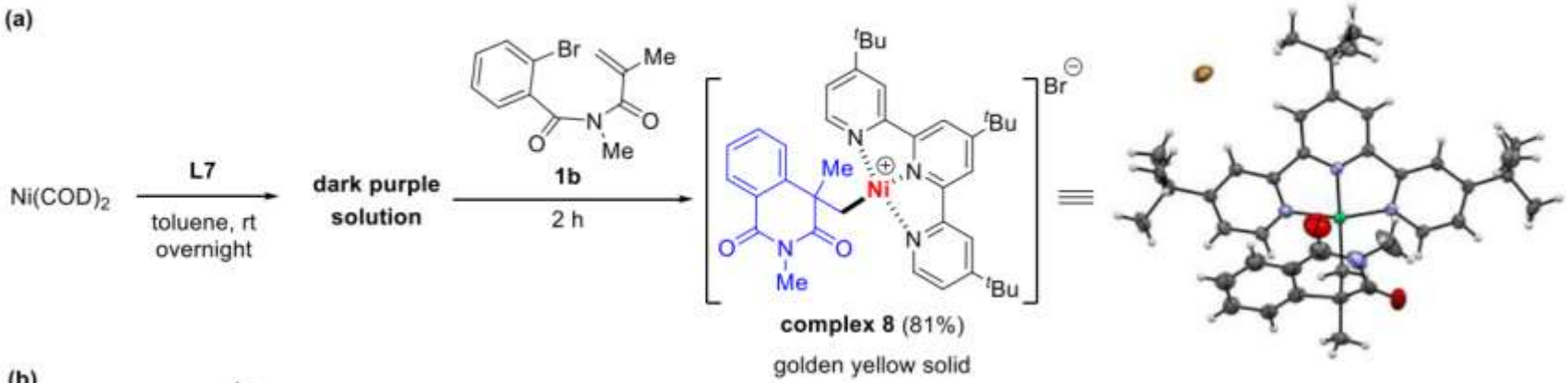


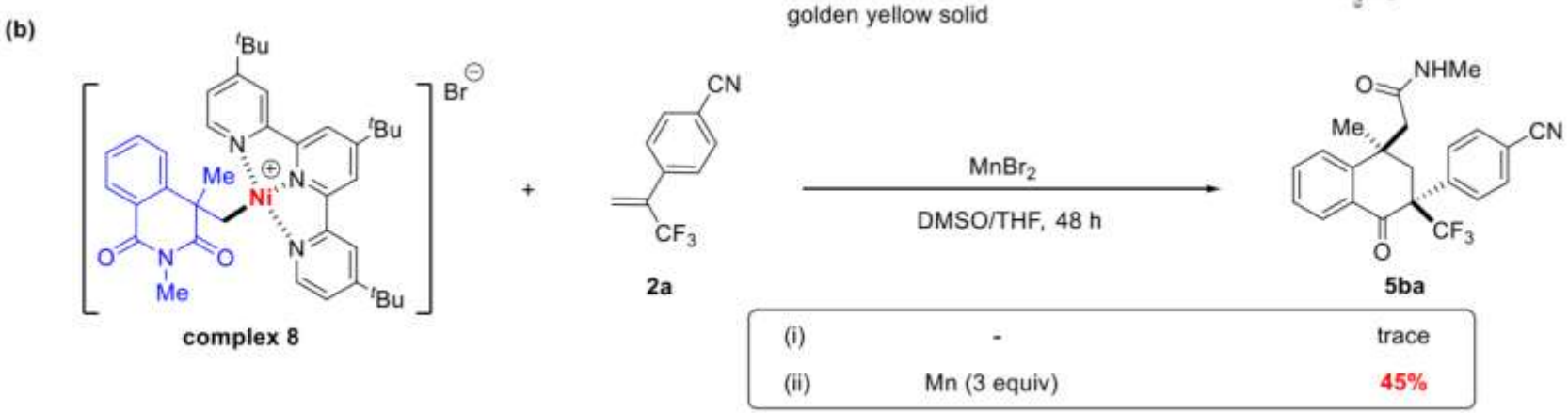
The formation of 4aa and 7aa is not affected by BHT

Ni Catalyzed Ligand-Controlled, Switchable 1,2-Rearrangement

◆ **Mechanistic Studies**

Control experiments



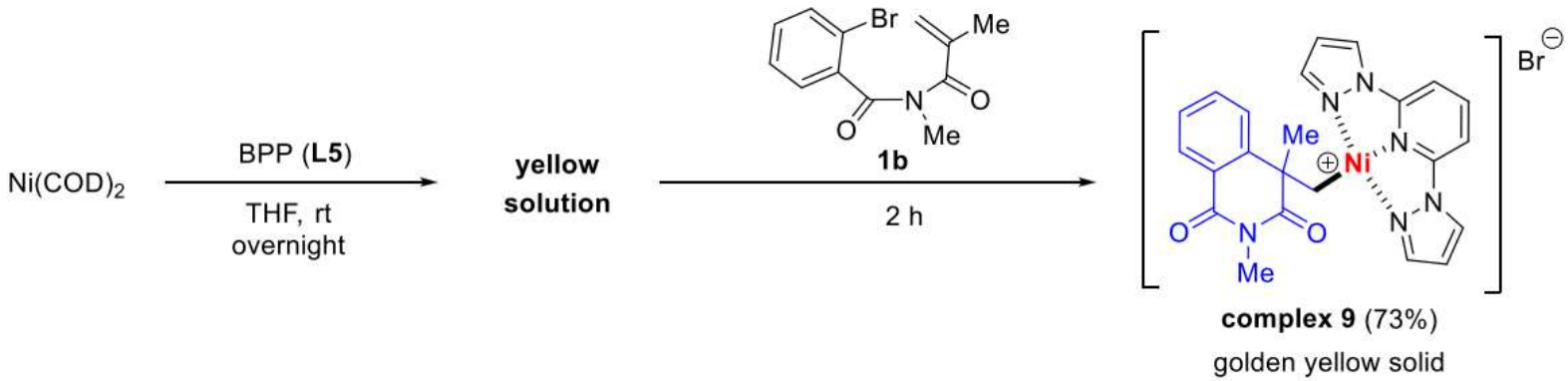


Ni Catalyzed Ligand-Controlled, Switchable 1,2-Rearrangement

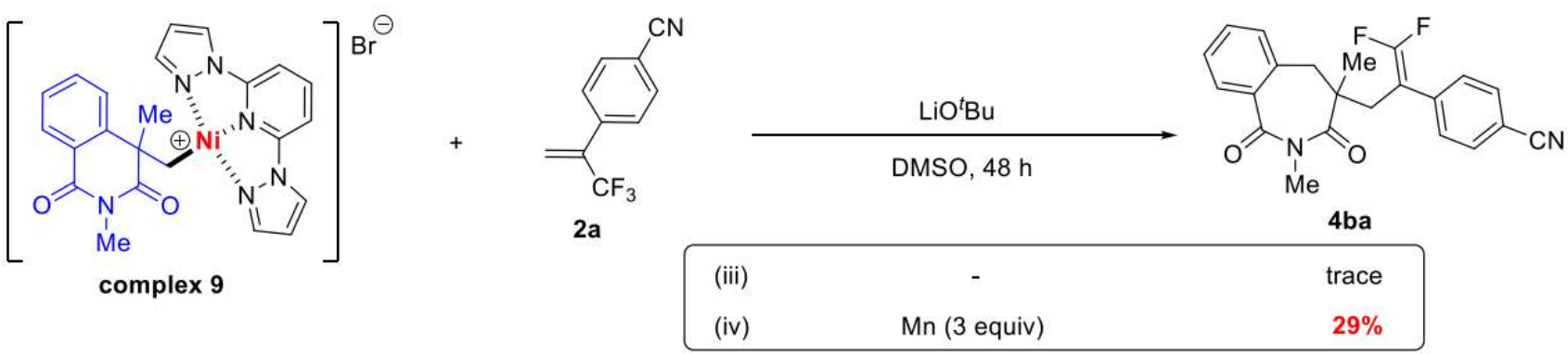
◆ **Mechanistic Studies**

Control experiments

(c)



(d)

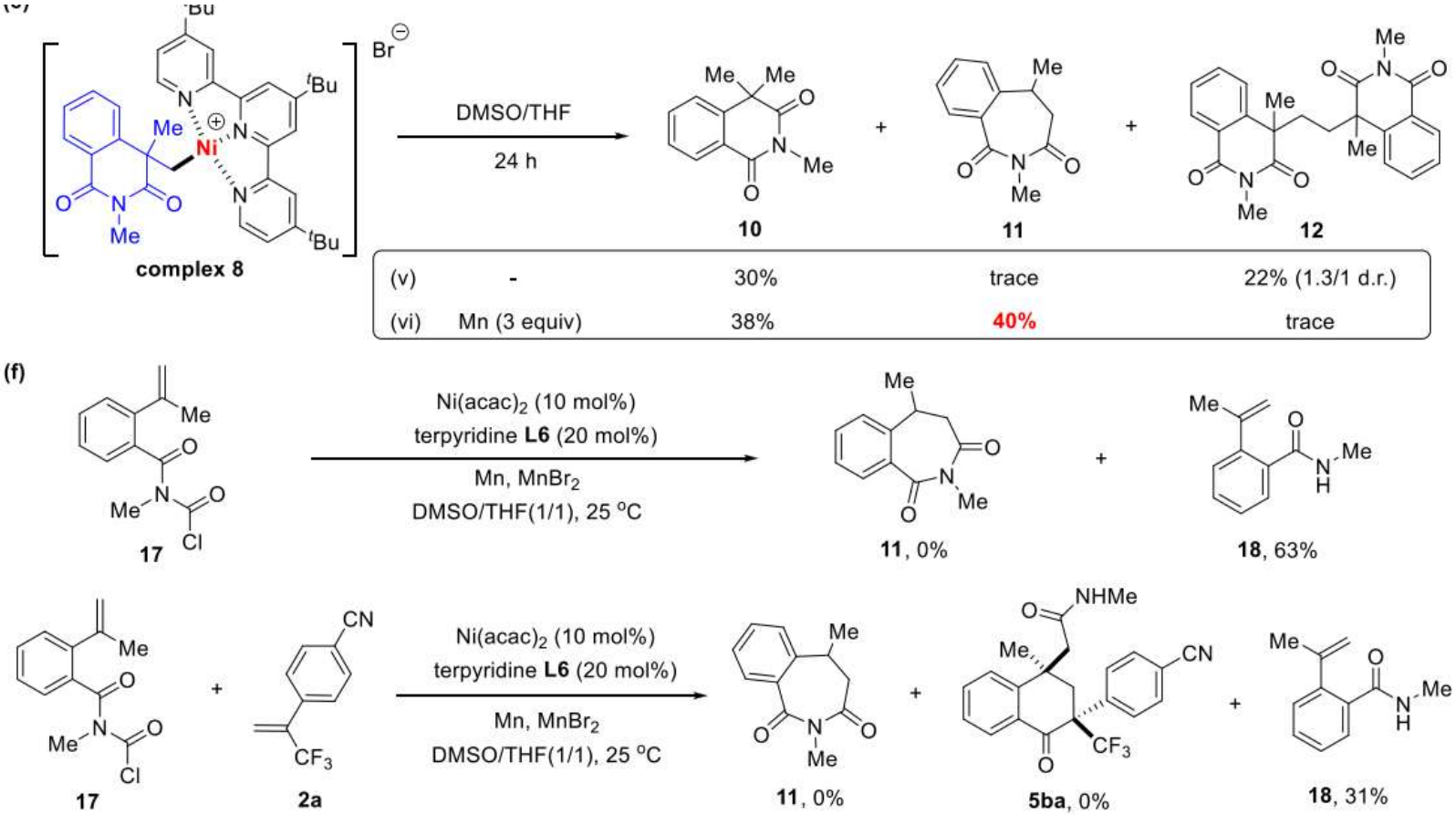


(iii)	-	trace
(iv)	Mn (3 equiv)	**29%**

Ni Catalyzed Ligand-Controlled, Switchable 1,2-Rearrangement

◆ **Mechanistic Studies**

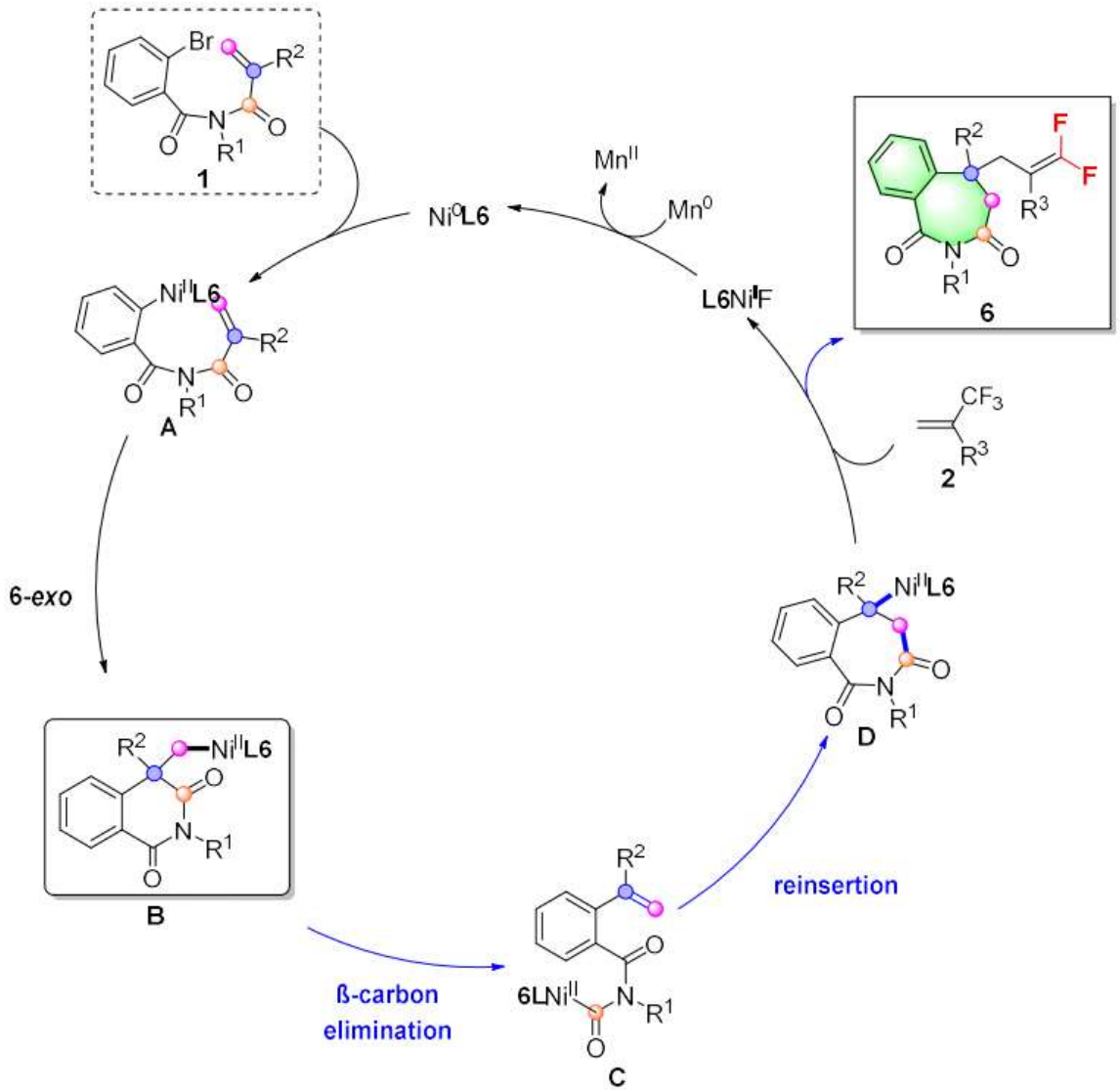
Control experiments



Ni Catalyzed Ligand-Controlled, Switchable 1,2-Rearrangement

◆ **Mechanistic Studies**

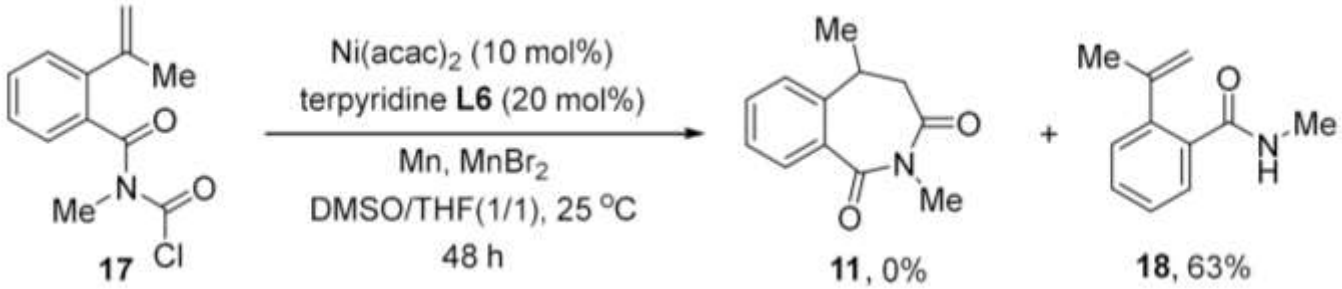
Possible Mechanism via β-carbon elimination followed by reinsertion

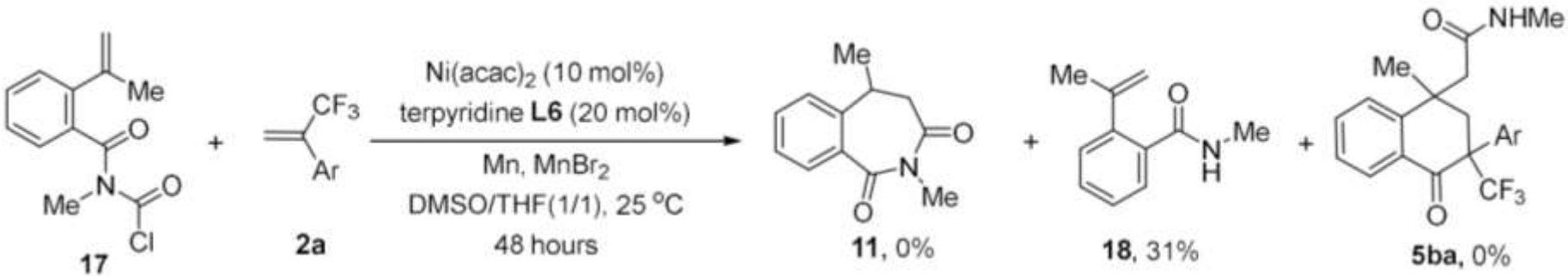


Ni Catalyzed Ligand-Controlled, Switchable 1,2-Rearrangement

◆ **Mechanistic Studies**

Possible Mechanism via β-carbon elimination followed by reinsertion



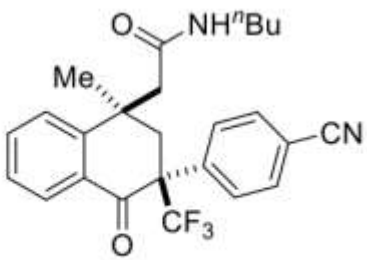


Ni Catalyzed Ligand-Controlled, Switchable 1,2-Rearrangement

◆ **Mechanistic Studies**

Control experiments

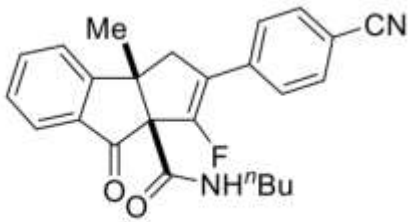
(g)



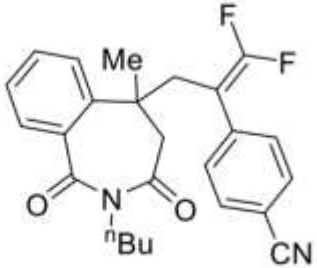
5aa

$Ni(acac)_2$ (10 mol%)
terpyridine **L6** (20 mol%)

Mn, $MnBr_2$, 4 Å MS,
DMSO/THF = 1/1, 80 °C, 48 h



7aa, 60%



6aa

$Ni(acac)_2$ (10 mol%)
terpyridine **L6** (20 mol%)

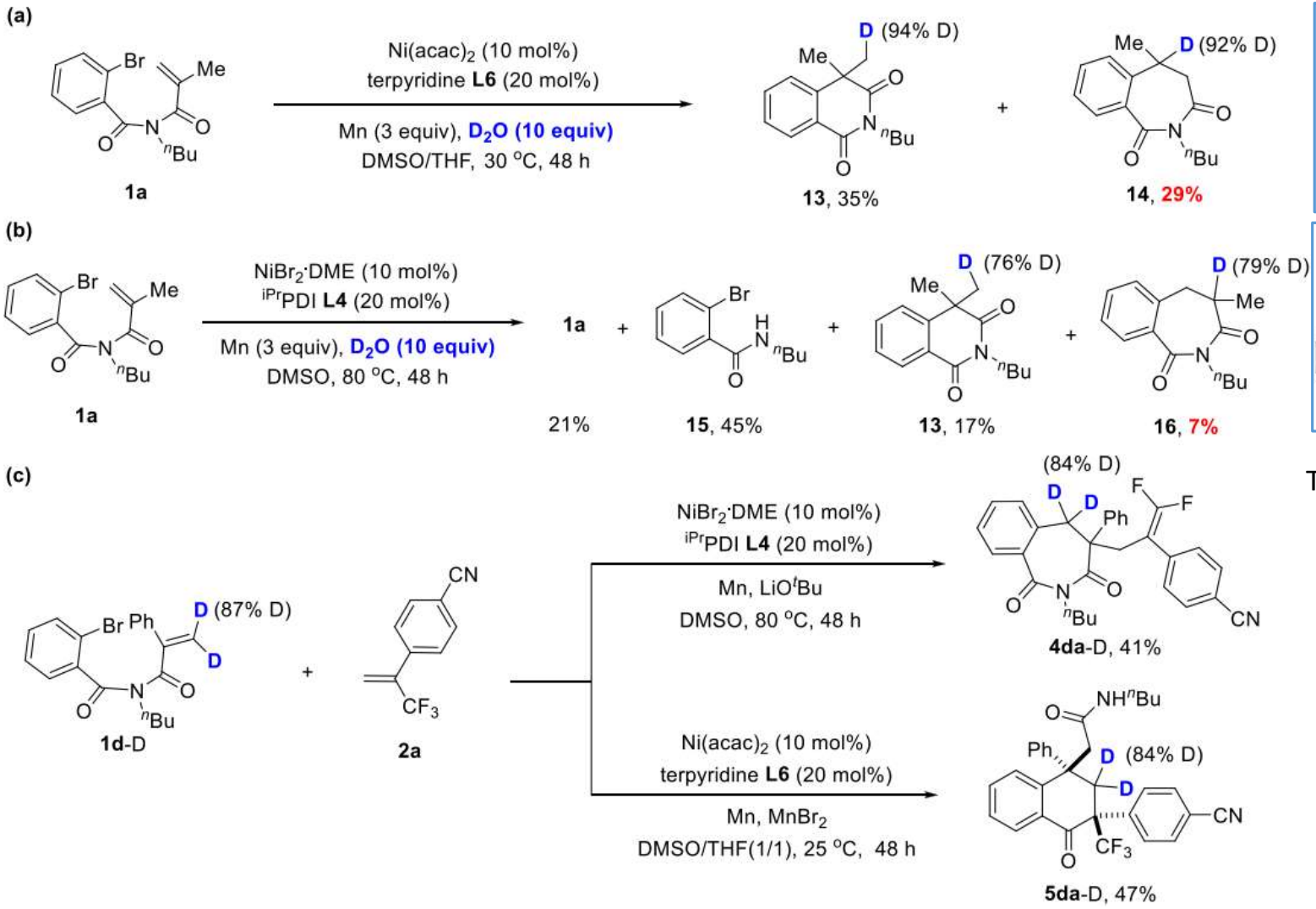
Mn (3 equiv), $MnBr_2$ (2 equiv), 4 Å MS
DMSO:THF = 1:1, 80 °C, 90 h

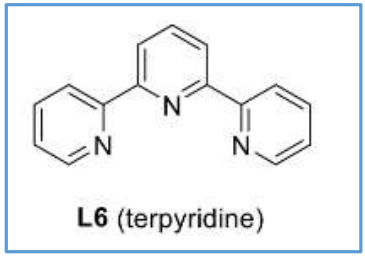
7aa, 53%

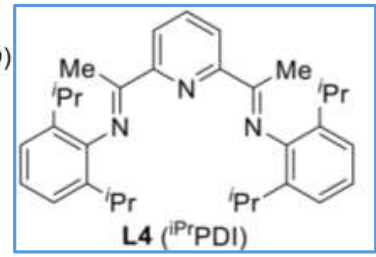
Ni Catalyzed Ligand-Controlled, Switchable 1,2-Rearrangement

◆ Mechanistic Studies

Deuterium Labeling Experiments





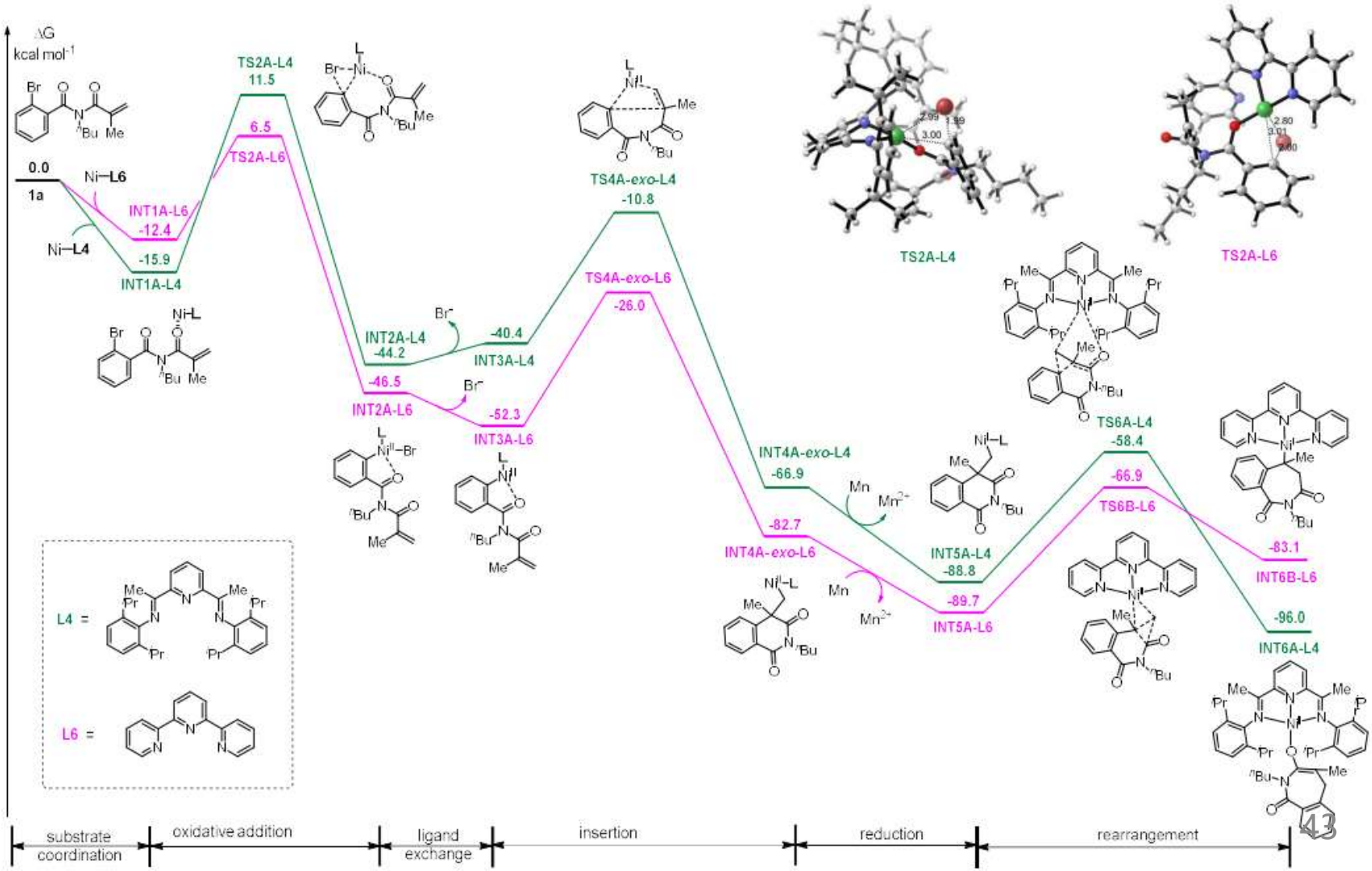


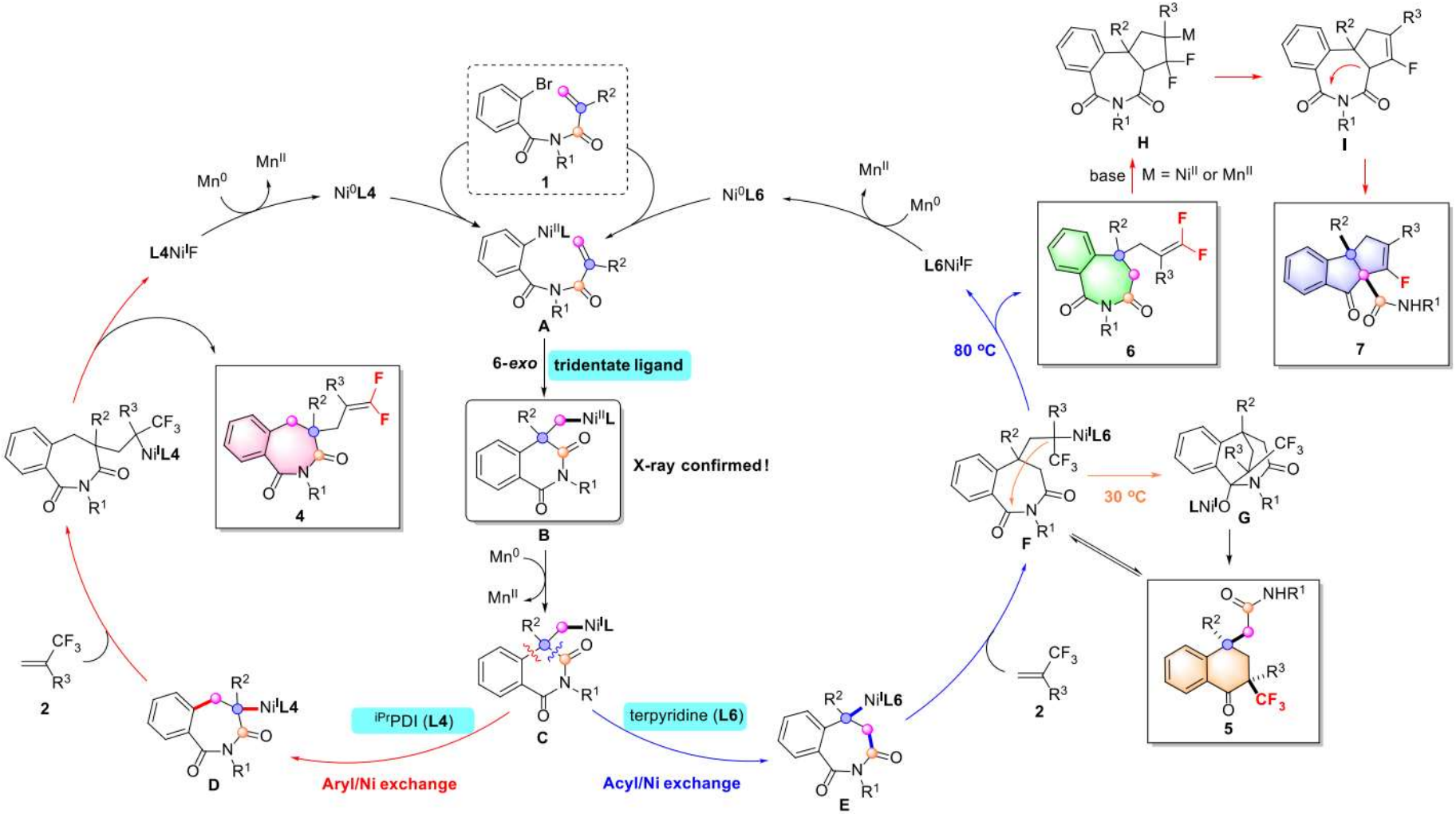
The isolated yield in red

Ni Catalyzed Ligand-Controlled, Switchable 1,2-Rearrangement

◆ Mechanistic Studies

DFT calculations



Ni Catalyzed Ligand-Controlled, Switchable 1,2-Rearrangement

◆ Mechanistic Proposal