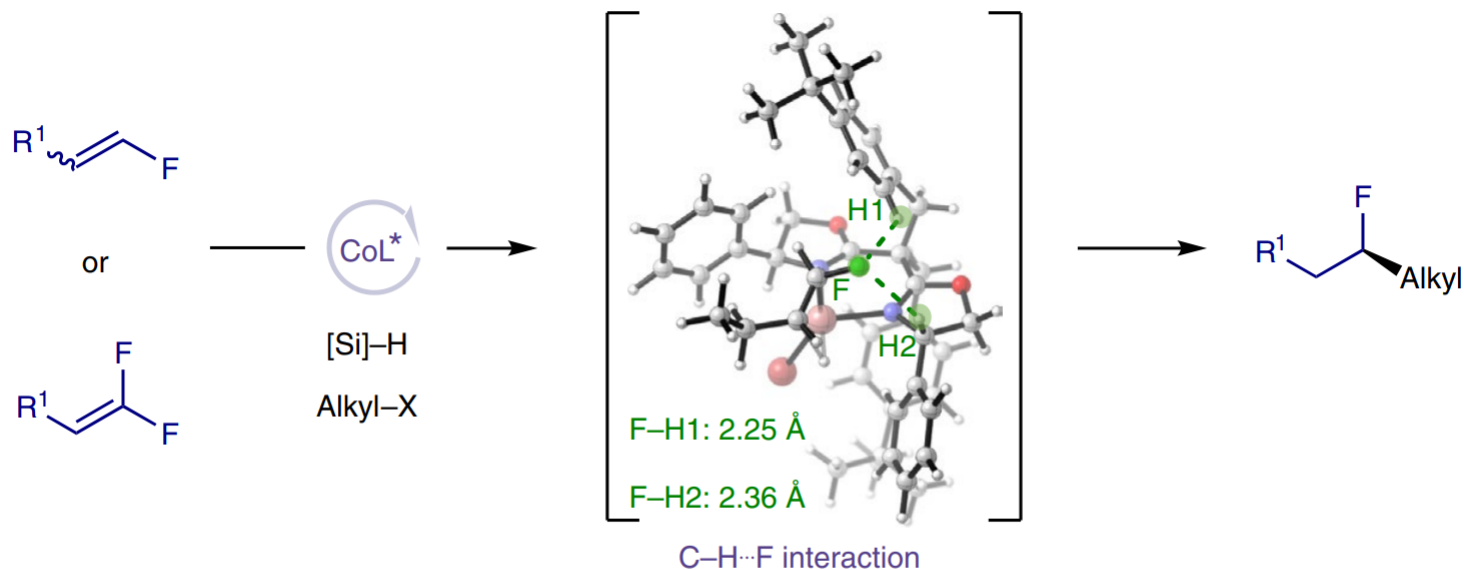


Cobalt-catalysed enantioselective $C(sp^3)-C(sp^3)$ coupling

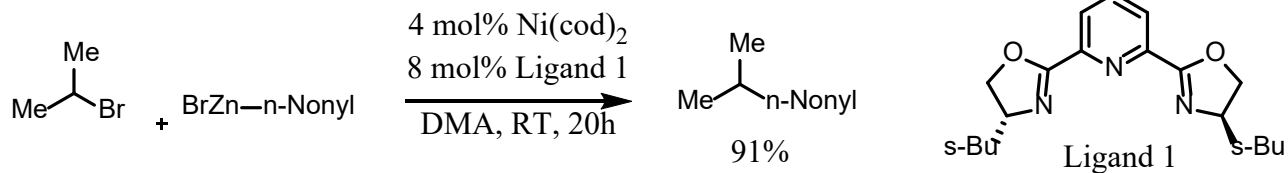
Y. Li, W. Nie, Z. Chang, J.-W. Wang, X. Lu, Y. Fu, **Nature Catalysis** 4(10) (2021) 901-911



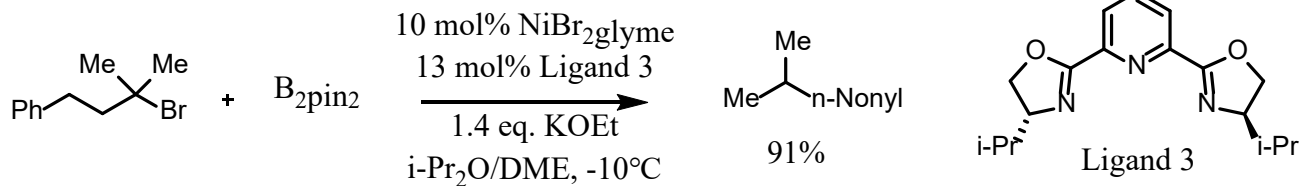
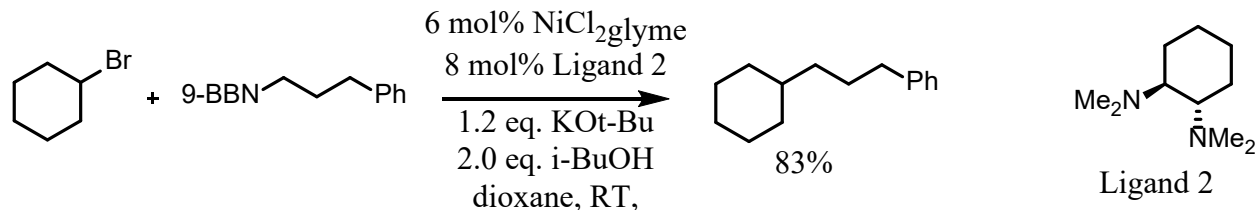
- Cobalt catalytic system enabled enantioselective alkyl-alkyl coupling
- Stereochemical control without a directing group or proximal p/π orbital
- Aliphatic C-F stereogenic centre at the desired position in an alkyl chain

C(sp³)-C(sp³) Cross-coupling reaction

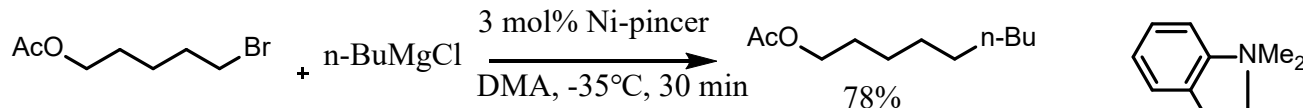
Negishi Reaction



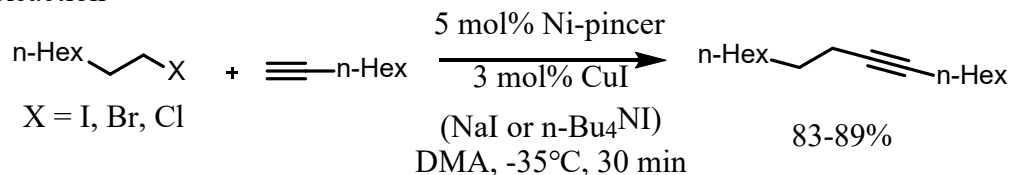
Suzuki Reaction



Kumada Reaction

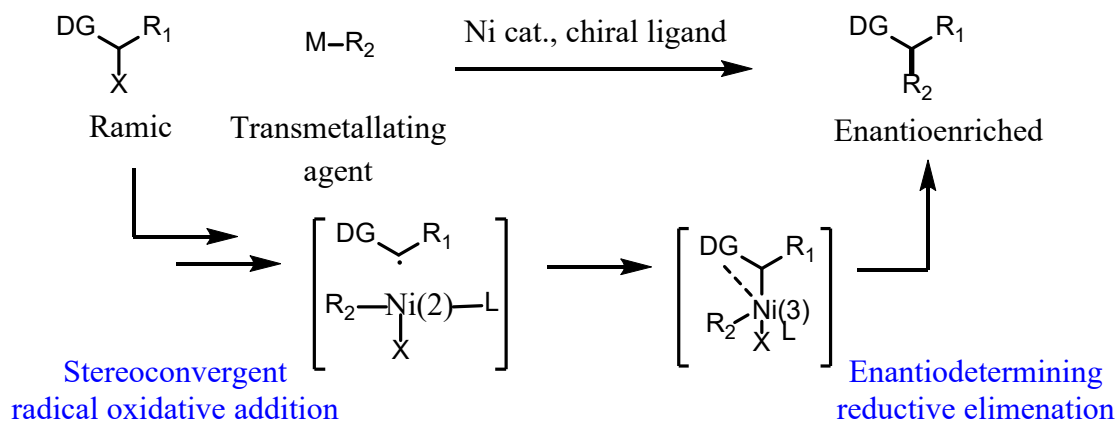
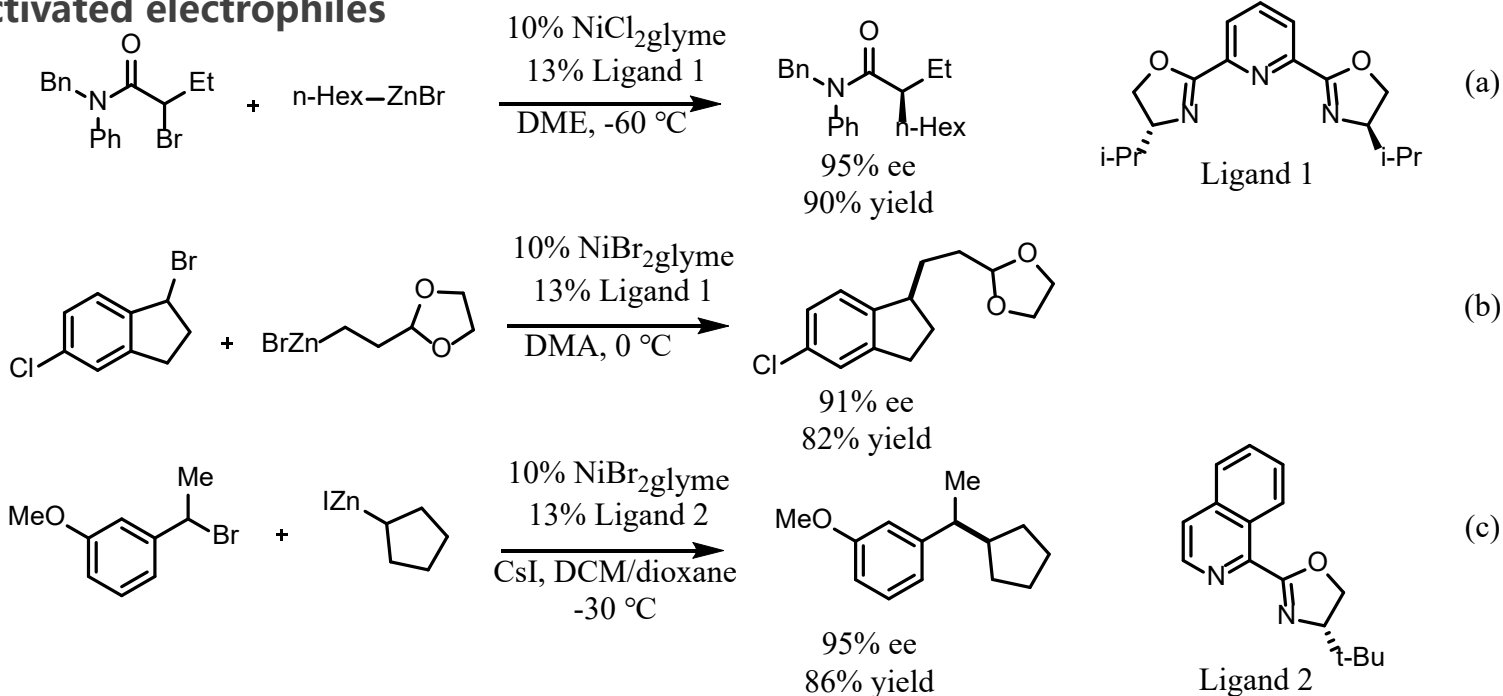


Sonogashira Reaction



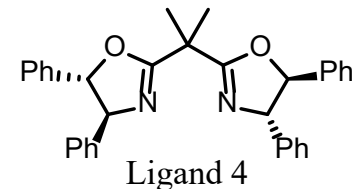
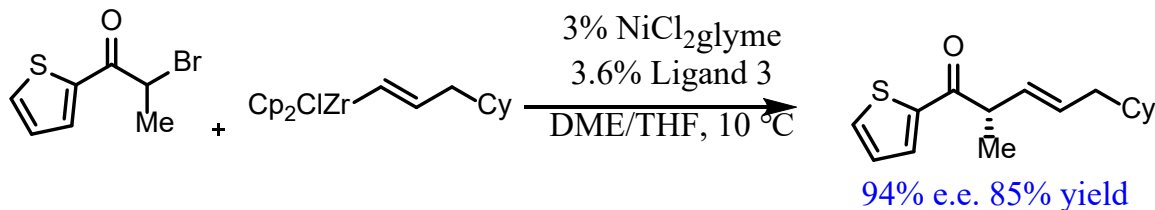
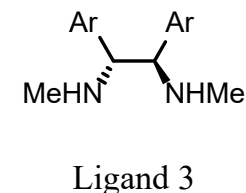
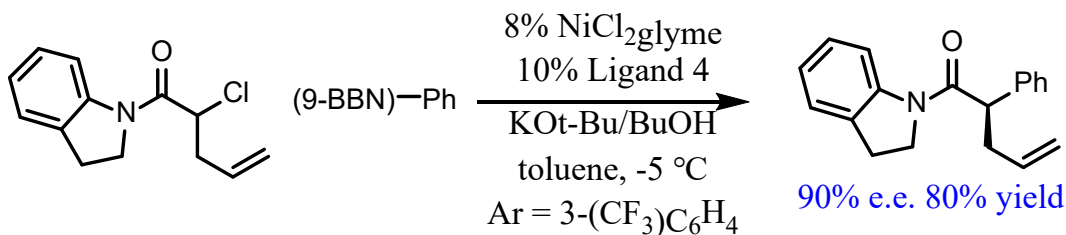
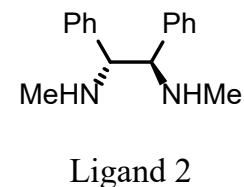
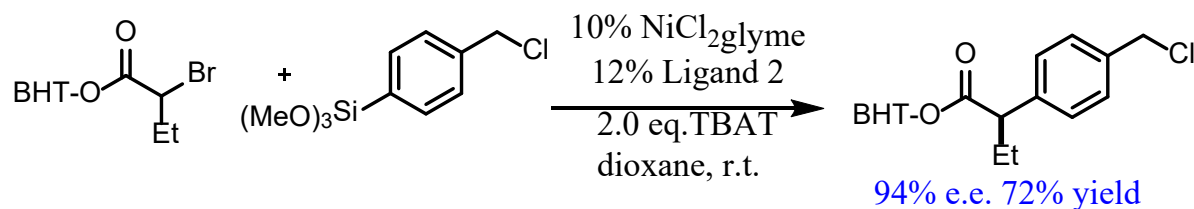
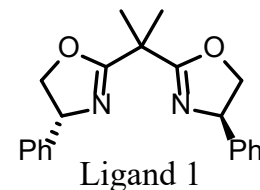
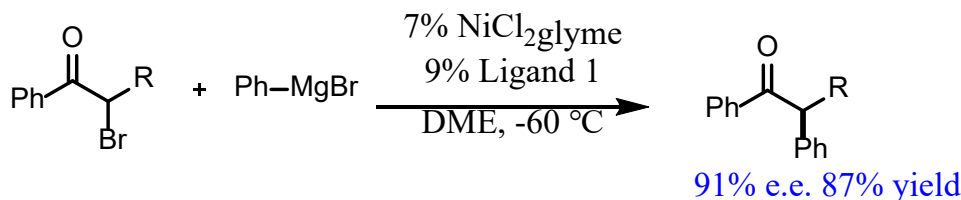
C(sp³)-C(sp³) Cross-coupling reaction

➤ Activated electrophiles



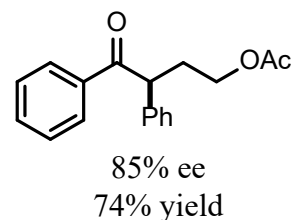
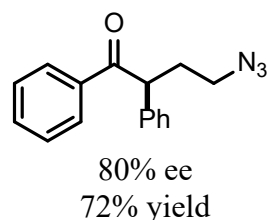
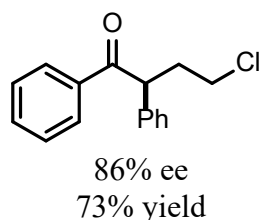
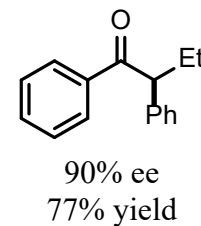
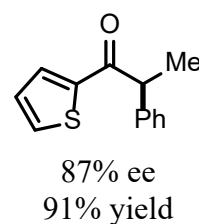
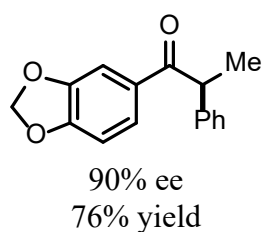
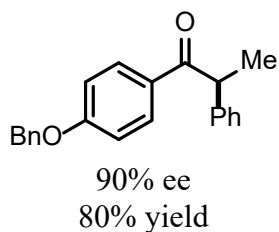
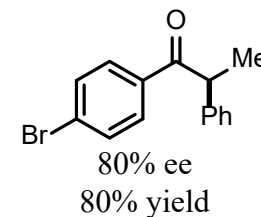
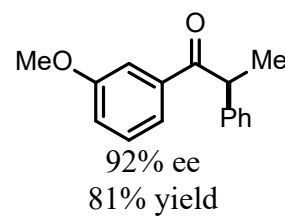
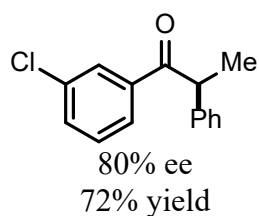
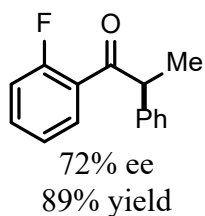
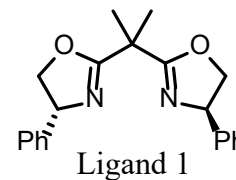
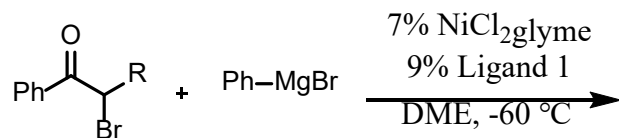
C(sp³)-C(sp³) Cross-coupling reaction

➤ Activated electrophiles



C(sp³)-C(sp³) Cross-coupling reaction

➤ Kumada Reactions of Alkyl Electrophiles

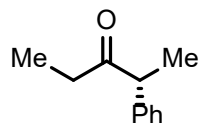
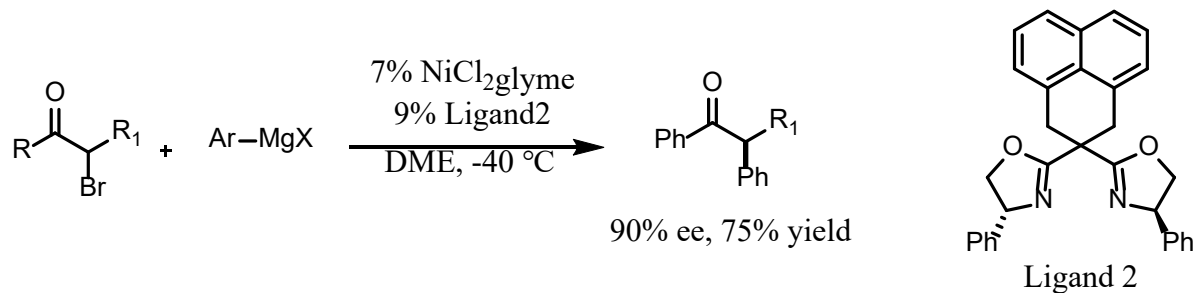


G.C. Fu, J Am Chem Soc 132 (2010) 1264–1266.

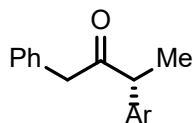
G.C. Fu, J Am Chem Soc 141(38) (2019) 15433-15440

C(sp³)-C(sp³) Cross-coupling reaction

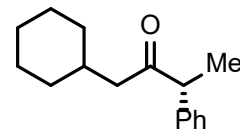
➤ Kumada Reactions of Alkyl Electrophiles



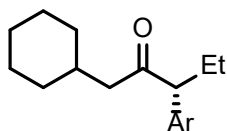
73% ee, 90% yield



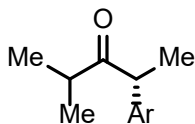
Ar = Ph
4-Cl-C₆H₄
4-CO₂Et-C₆H₄
4-OMe-C₆H₄
81-90% ee, 73-82% yield



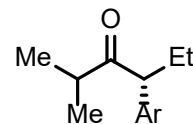
85% ee, 73% yield



Ar = 3-Br-C₆H₄
78% ee, 70% yield



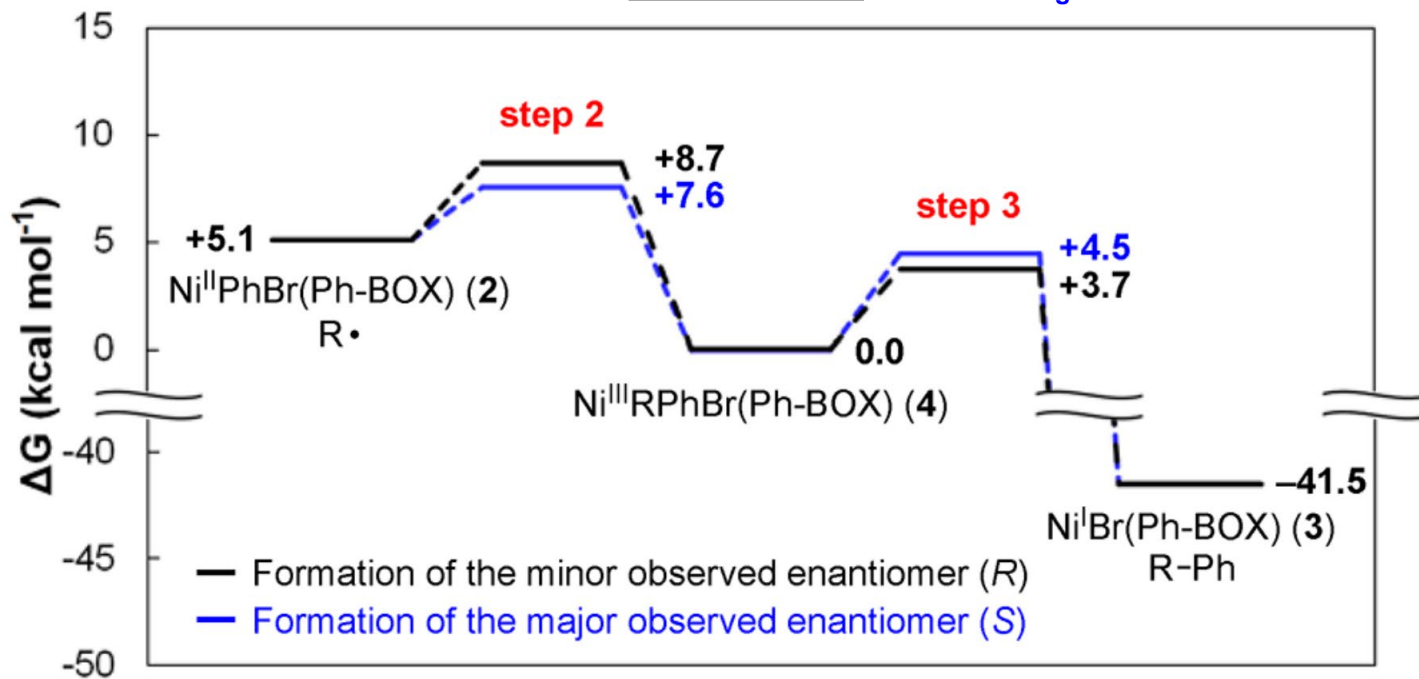
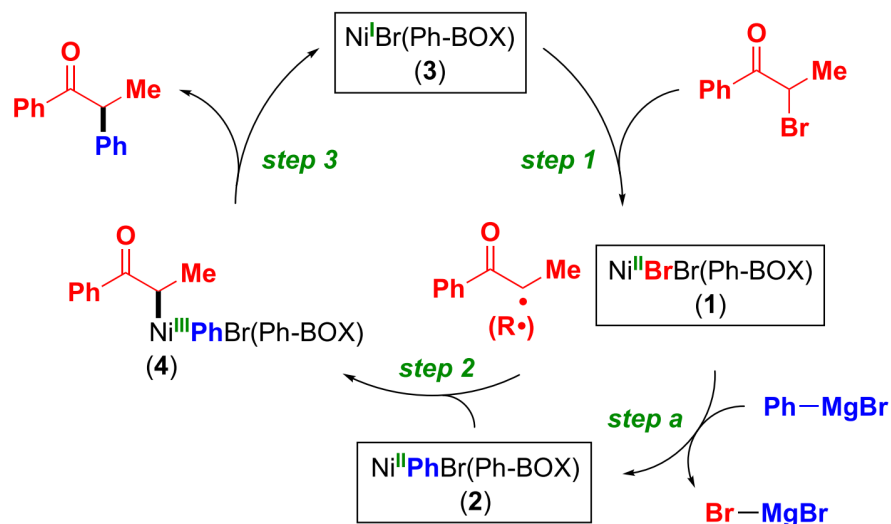
Ar = Ph
3,4-OCH₂O-C₆H₃
83-94% ee, 75-83% yield



Ar = 4-CO₂Et-C₆H₄
80% ee, 78% yield

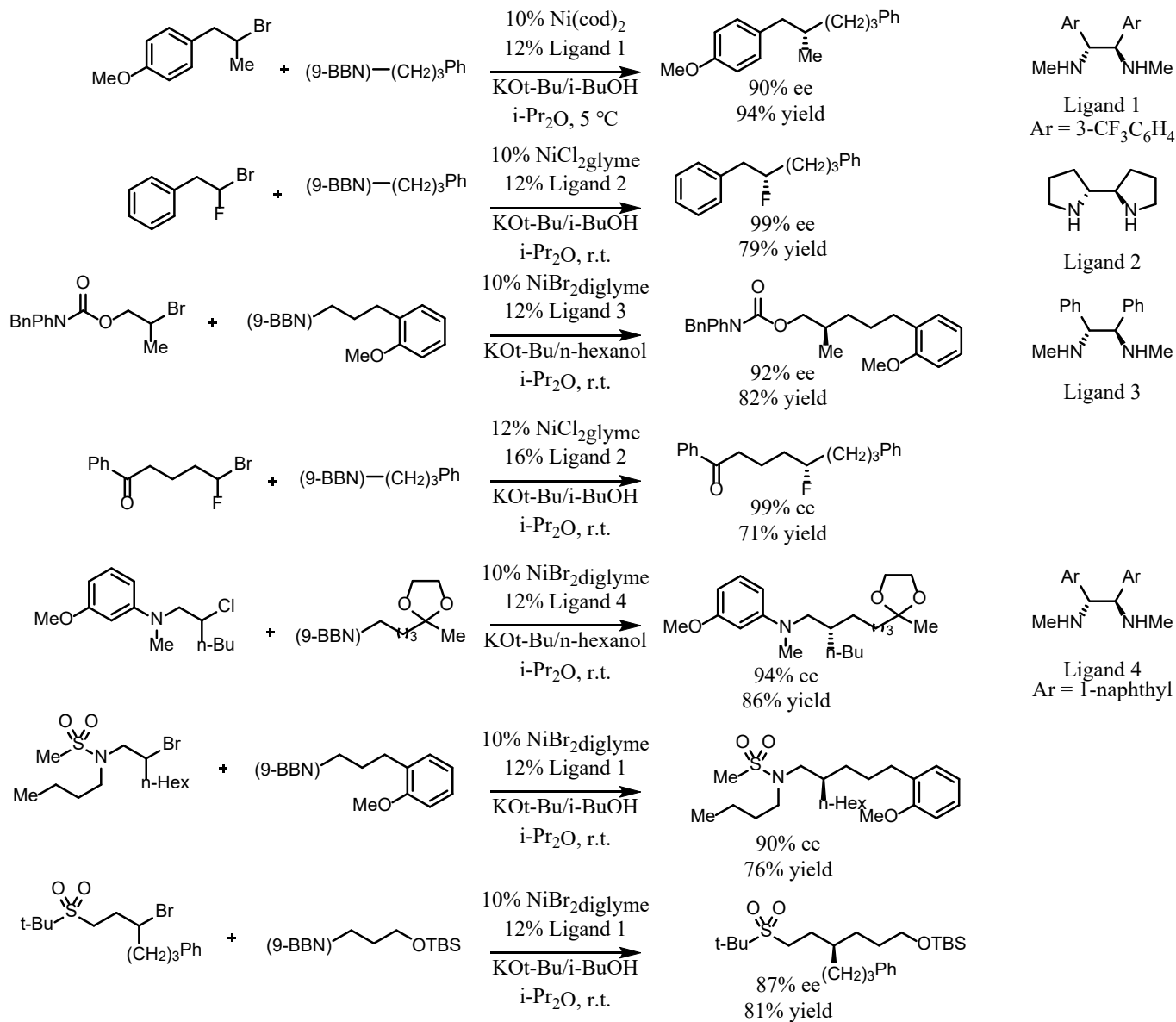
C(sp³)-C(sp³) Cross-coupling reaction

➤ Mechanistic Investigation



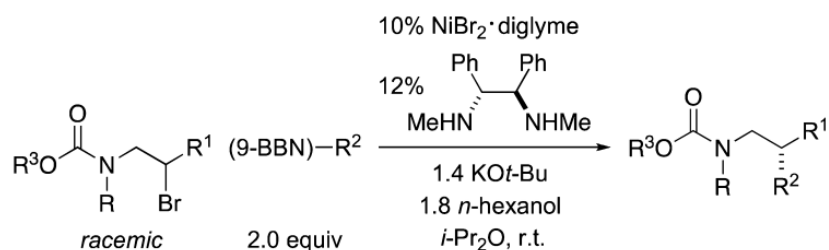
C(sp³)-C(sp³) Cross-coupling reaction

➤ Unactivated electrophiles



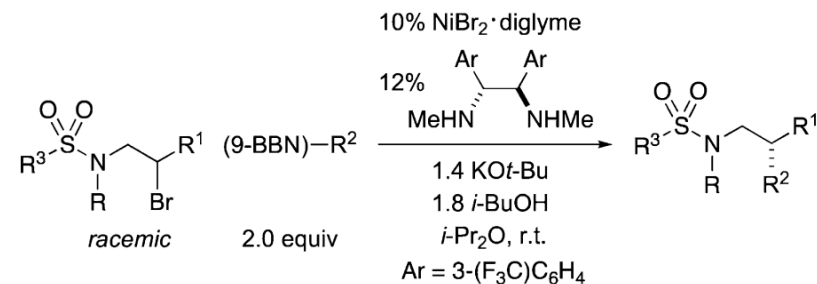
C(sp³)-C(sp³) Cross-coupling reaction

➤ Suzuki Reactions of Alkyl Electrophiles



entry	electrophile	R ²	ee (%)	yield (%) ^b
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1			91	56
2			90	83
3			90	74
4		<i>n</i> -Hex	90	56
5			80	66

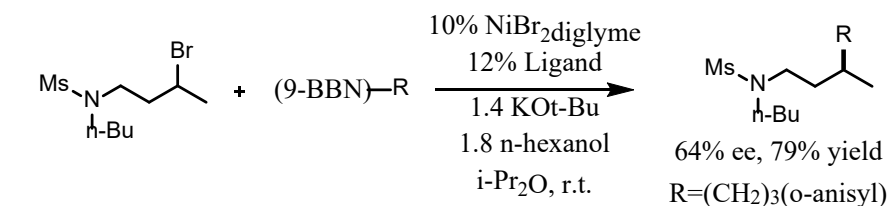
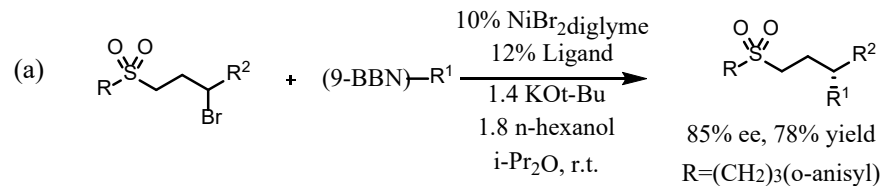
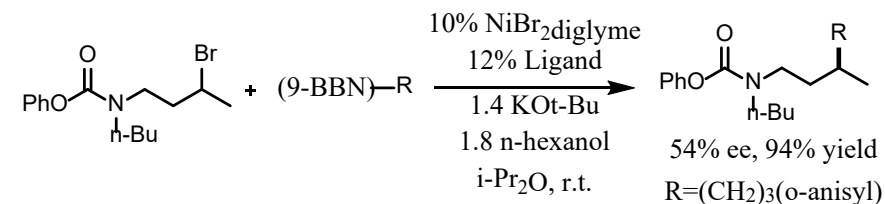


entry	electrophile	R ²	ee (%)	yield (%) ^b
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1			90	58
2			90	54
3			90	76
4			72	68

C(sp³)-C(sp³) Cross-coupling reaction

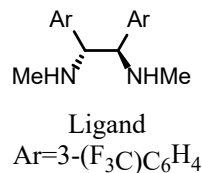
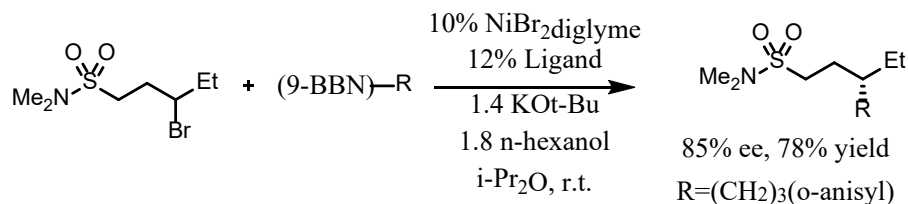
➤ Suzuki Reactions of Alkyl Electrophiles



(a)

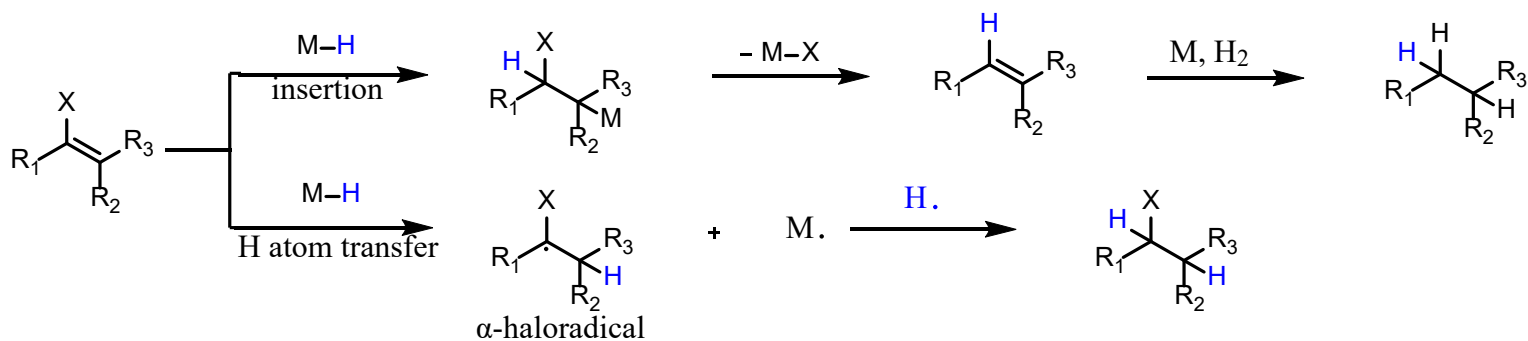
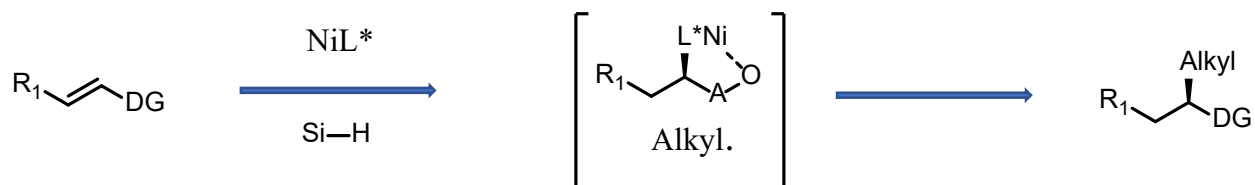
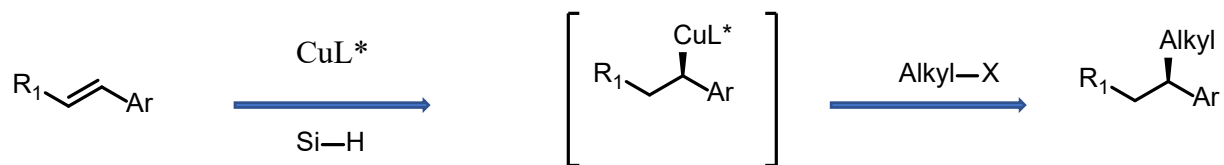
(b)

entry	electrophile	R ²	ee (%)	yield (%) ^b
1			88	79
2			87	81
3			90	84

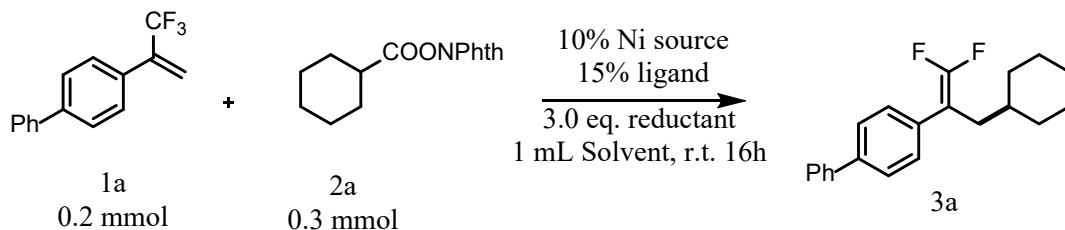


C(sp³)-C(sp³) Cross-coupling reaction

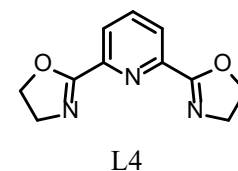
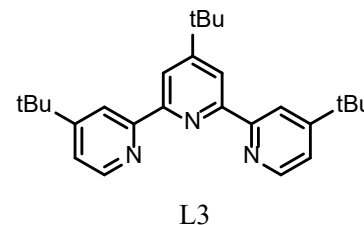
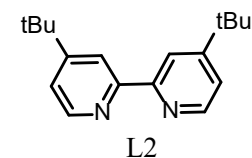
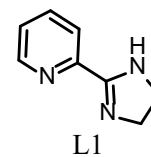
➤ M-H insertion across alkenes



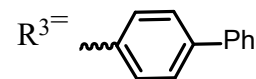
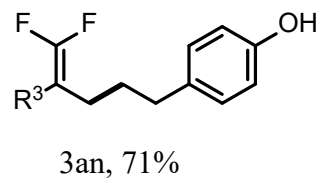
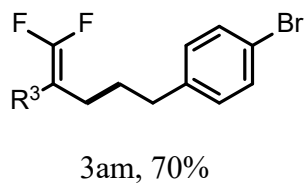
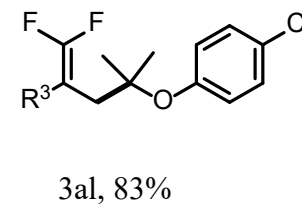
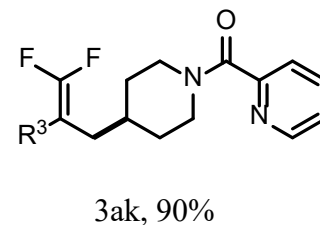
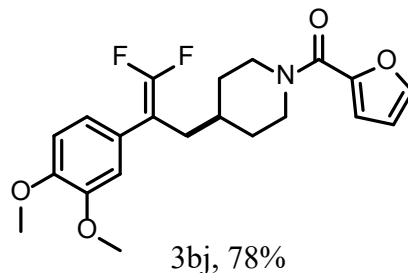
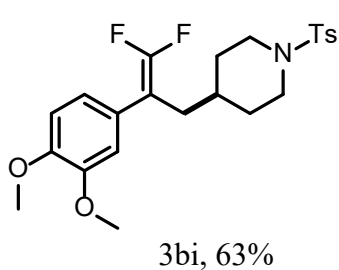
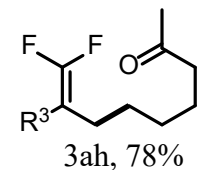
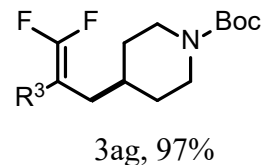
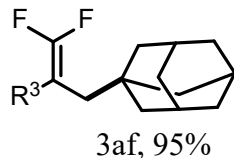
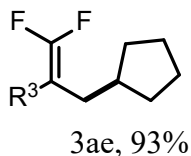
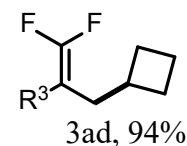
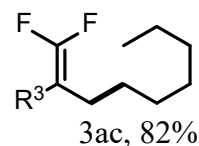
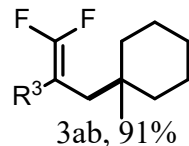
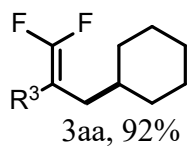
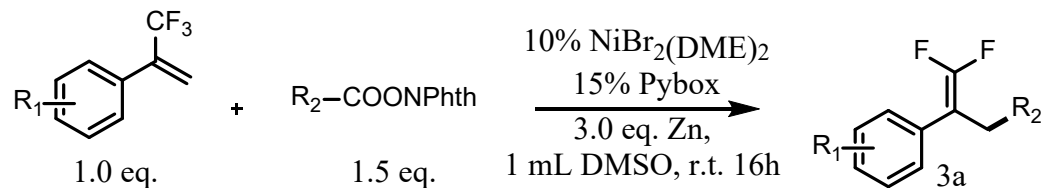
Allylic defluorinative alkylation of trifluoromethyl alkenes



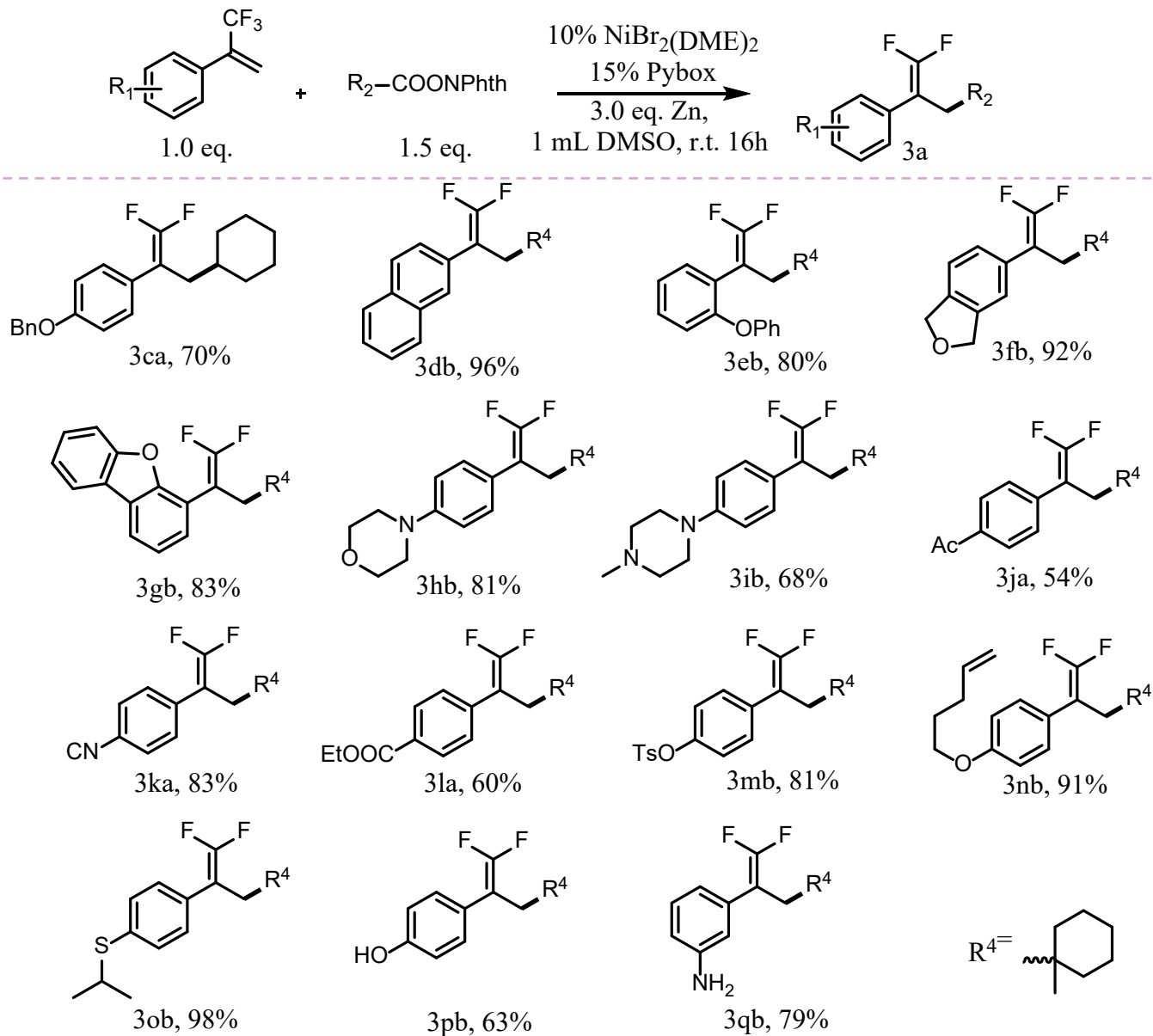
Entry	Nickel source	Ligand	Reductant	Solvent	Yield ^a /%
1	NiBr ₂ (diglyme)	L1	Zn	DMAc	23
2	NiBr ₂ (diglyme)	L2	Zn	DMAc	32
3	NiBr ₂ (diglyme)	L3	Zn	DMAc	47
4	NiBr ₂ (diglyme)	L4	Zn	DMAc	79
5	NiCl ₂	L4	Zn	DMAc	33
6	Ni(NO ₃) ₂	L4	Zn	DMAc	<5
7	Ni(acac) ₂	L4	Zn	DMAc	26
8	NiCl ₂ (Py) ₄	L4	Zn	DMAc	75
9	NiCl ₂ (PPh ₃) ₂	L4	Zn	DMAc	23
10	NiCl ₂ (PCy ₃) ₂	L4	Zn	DMAc	17
11	NiBr ₂ (diglyme)	L4	Zn	Dioxane	<5
12	NiBr ₂ (diglyme)	L4	Zn	DME	22
13	NiBr ₂ (diglyme)	L4	Zn	THF	43
14	NiBr ₂ (diglyme)	L4	Zn	MeCN	<5
15	NiBr ₂ (diglyme)	L4	Zn	NMP	54
16	NiBr ₂ (diglyme)	L4	Zn	DMF	60
17	NiBr₂(diglyme)	L4	Zn	DMSO	95 (92^b)
18	NiBr ₂ (diglyme)	L4	Mn	DMSO	64
19	NiBr ₂ (diglyme)	L4	DEMS/Na ₂ CO ₃	DMSO	18
20	NiBr ₂ (diglyme)	L4	(BPin) ₂ /K ₃ PO ₄	DMSO	22



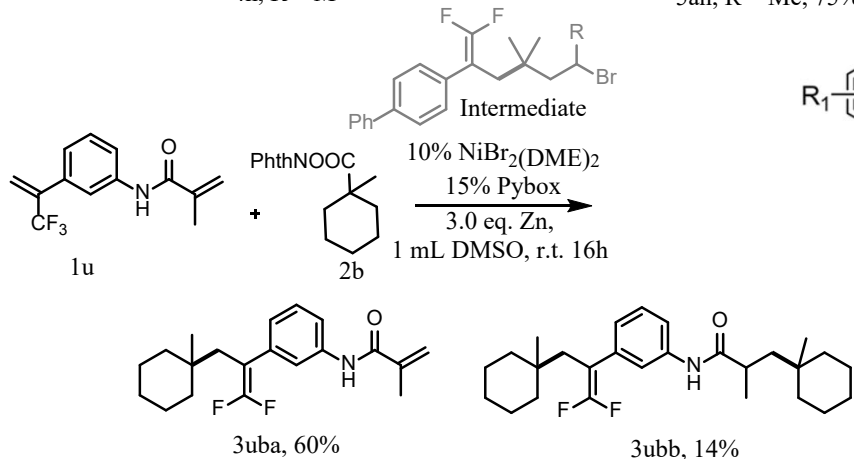
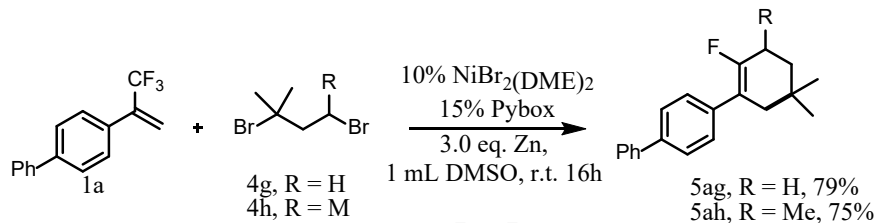
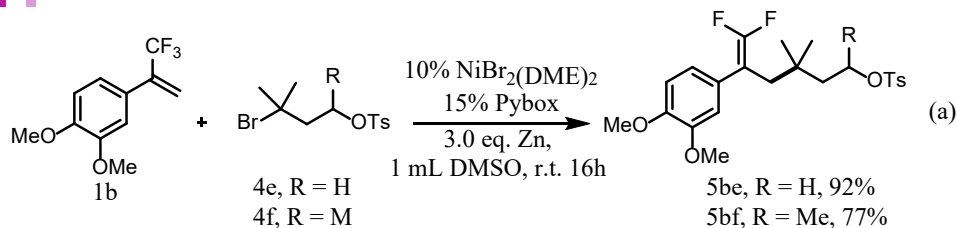
Allylic defluorinative alkylation of trifluoromethyl alkenes



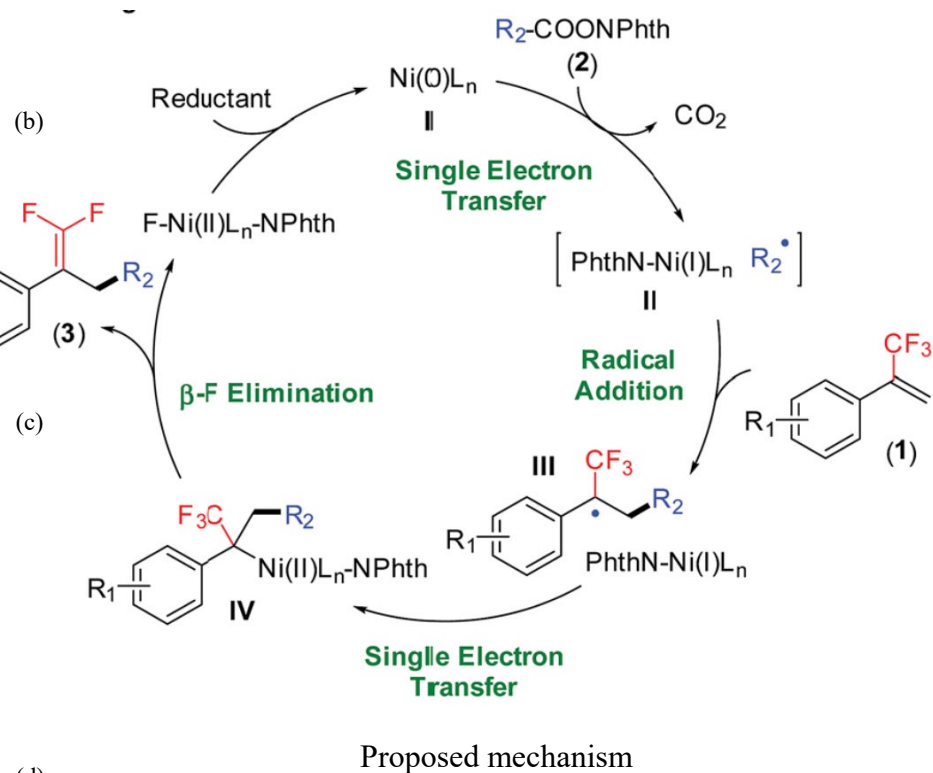
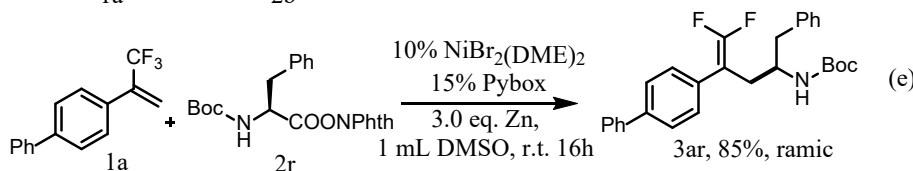
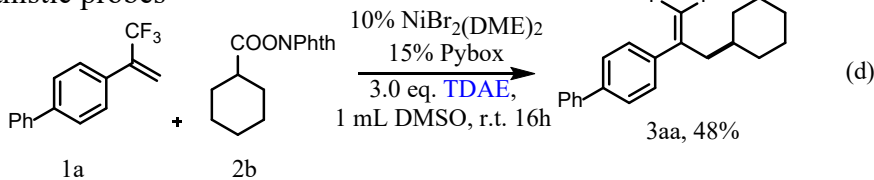
Allylic defluorinative alkylation of trifluoromethyl alkenes



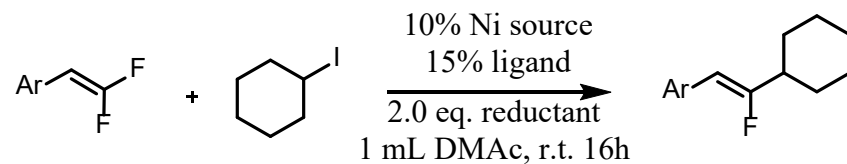
Allylic defluorinative alkylation of trifluoromethyl alkenes



Mechanistic probes

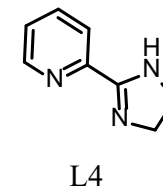
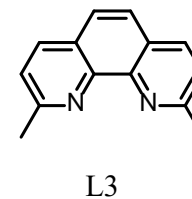
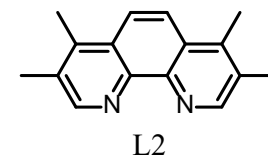
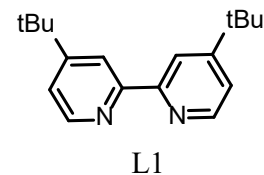


gem-Difluoroalkenes defluorinative reductive cross-coupling

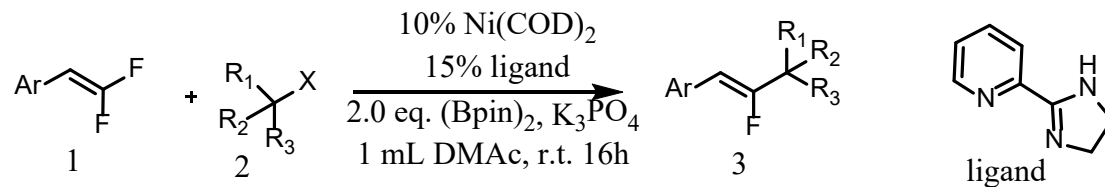


Ar = 3,4-dimethoxy-phenyl

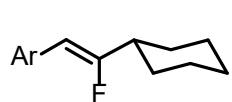
entry	nickel source	ligand	reductant	yield (%) ^b
1	NiBr ₂ ·diglyme	L1	Zn	10
2	NiBr ₂ ·diglyme	L1	Mn	17
3	NiBr ₂ ·diglyme	L1	DEMS/Na ₂ CO ₃	23
4	NiBr ₂ ·diglyme	L1	(Bpin) ₂ /K ₃ PO ₄	37
5	NiBr ₂ ·diglyme	L2	(Bpin) ₂ /K ₃ PO ₄	44
6	NiBr ₂ ·diglyme	L3	(Bpin) ₂ /K ₃ PO ₄	3
7	NiBr ₂ ·diglyme	L4	(BPin) ₂ /K ₃ PO ₄	55
8	Ni(COD) ₂	L4	(Bpin) ₂ /K ₃ PO ₄	64
9 ^d	Ni(COD)₂	L4	(Bpin)₂/K₃PO₄	77 (74)^c
10 ^e	Ni(COD)₂	L4	(Bpin)₂/K₃PO₄	94 (92)^c



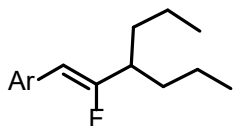
gem-Difluoroalkenes defluorinative reductive cross-coupling



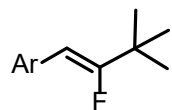
Ar = 3,4-dimethoxy-phenyl



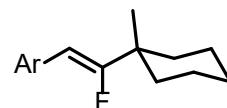
3aa, 74% (X=I)
Z/E > 20:1



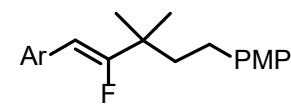
3ab, 58% (X=I)
Z/E > 17:1



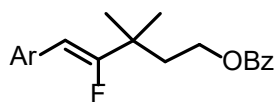
3ac, 92% (X=Br)
Z/E > 50:1



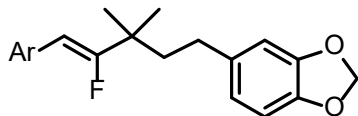
3ad, 56% (X=Br)
Z/E > 50:1



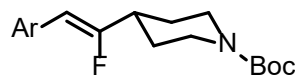
3ae, 81% (X=Br)
Z/E > 20:1



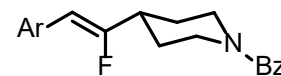
3af, 81% (X=Br)
Z/E > 50:1



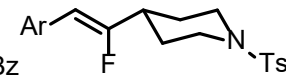
3ag, 81% (X=Br)
Z/E > 50:1



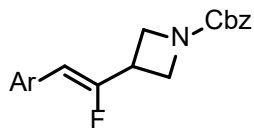
3ah, 68% (X=I)
Z/E > 18:1



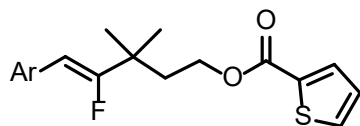
3ai, 81% (X=I)
Z/E > 20:1



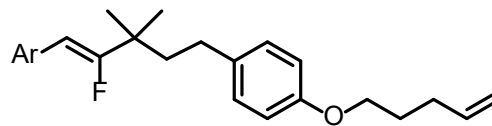
3aj, 62% (X=I)
Z/E > 20:1



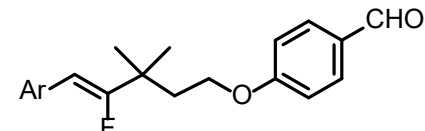
3ak, 44% (X=I)
Z/E > 11:1



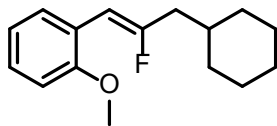
3al, 48% (X=I)
Z/E > 14:1



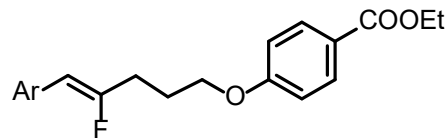
3am, 52% (X=Br)
Z/E > 50:1



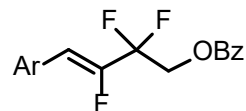
3an, 56% (X=Br)
Z/E > 50:1



3ao, 44% (X=I)
Z/E > 20:1

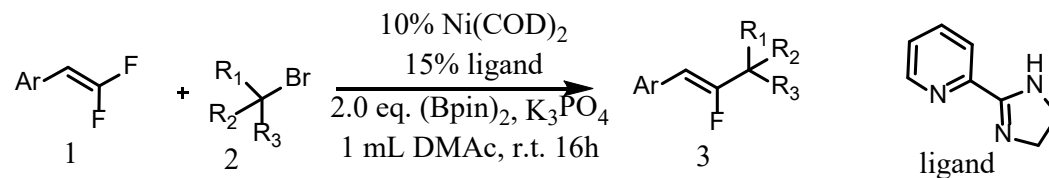


3ap, 53% (X=I)
Z/E > 8:1

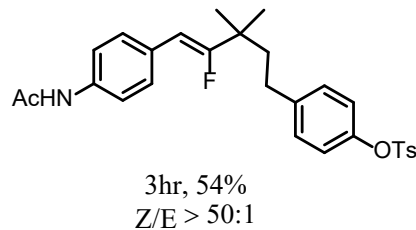
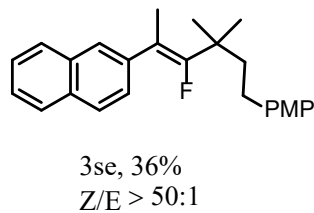
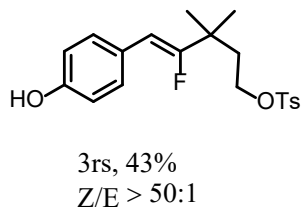
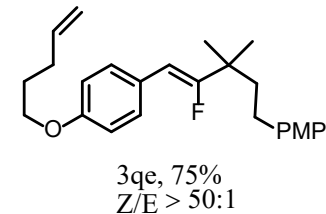
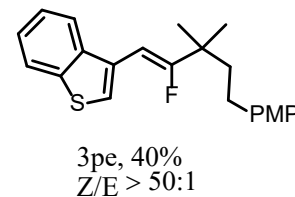
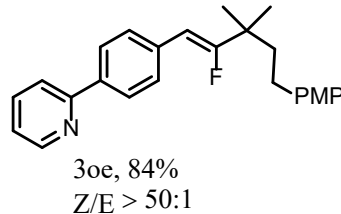
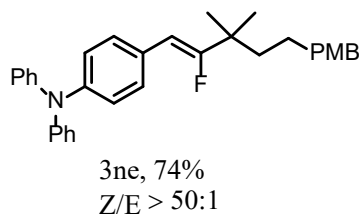
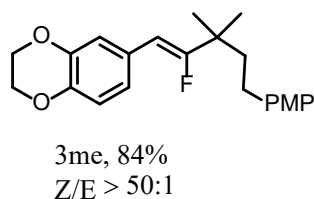
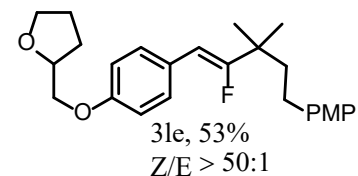
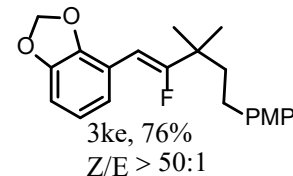
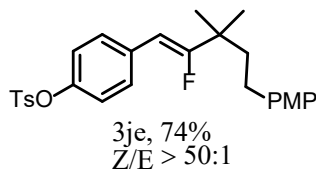
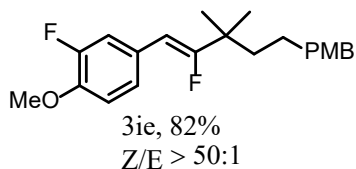
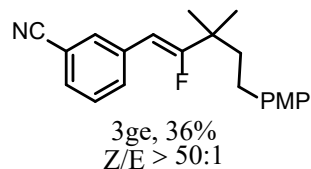
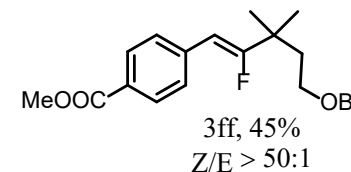
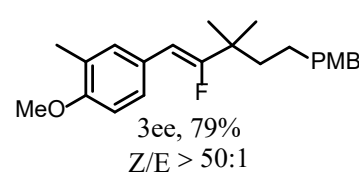
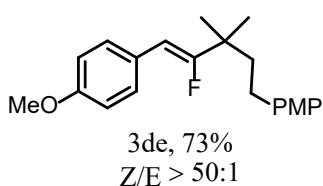
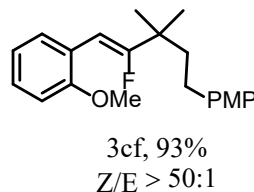
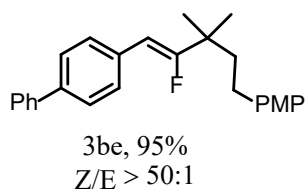


3aq, 40% (X=Br)
Z/E > 20:1

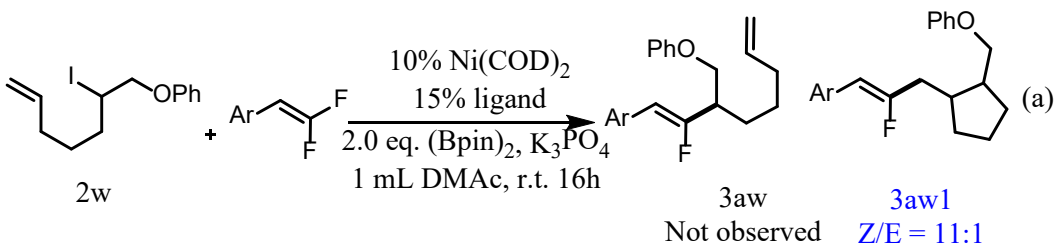
gem-Difluoroalkenes defluorinative reductive cross-coupling



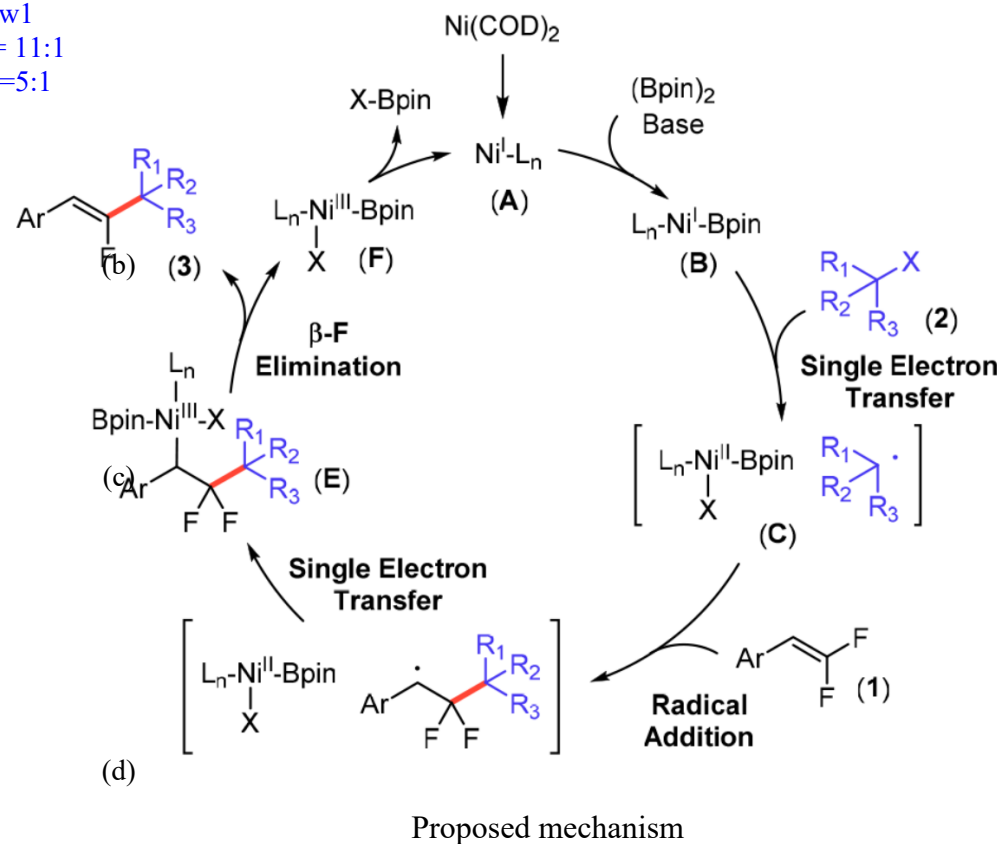
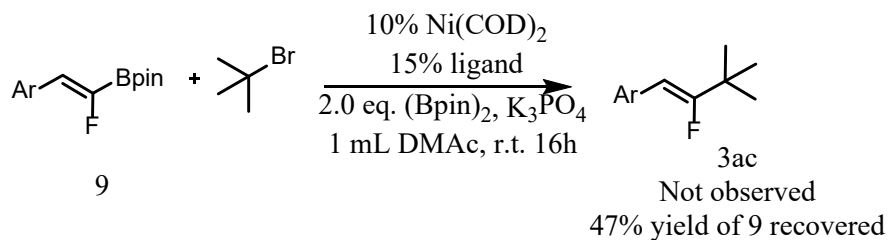
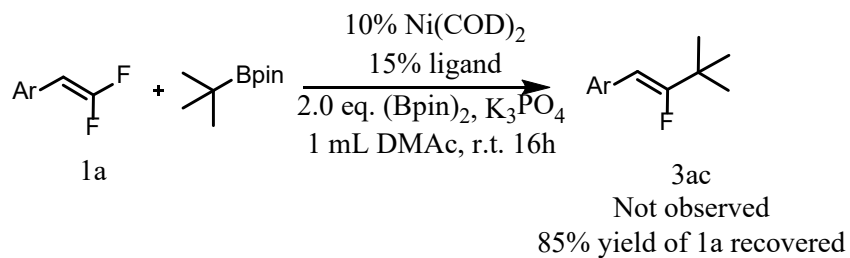
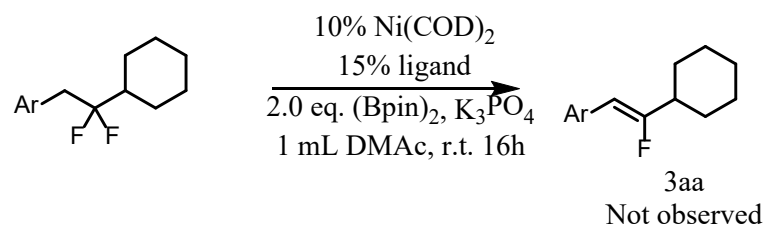
Ar = 3,4-dimethoxy-phenyl



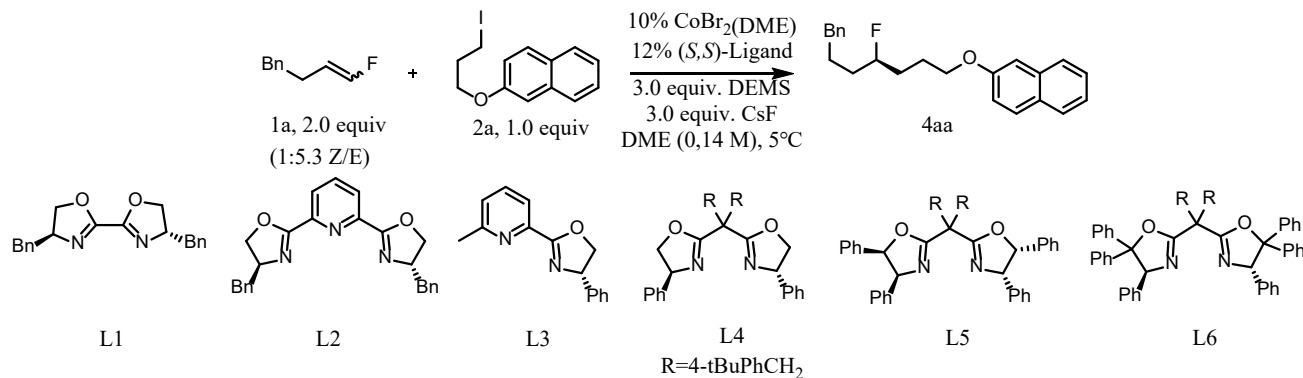
gem-Difluoroalkenes defluorinative reductive cross-coupling



$3aw1$
 $Z/E = 11:1$
 $d.r. = 5:1$



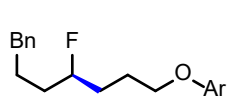
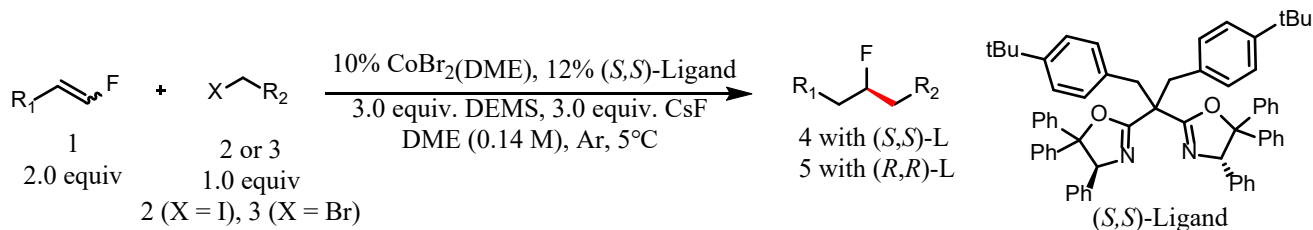
Cobalt-catalysed enantioselective hydroalkylation



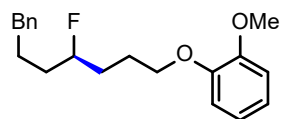
1	None	90 (85) ^a	97
2	L1, L2 or L3	Trace	–
3	L4	37	91
4	L5	52	91
5	CoCl ₂	64	96
6	CoI ₂	35	96
7	Co(acac) ₂	Trace	–
8	CoCl(PPh ₃) ₃ or CoF ₃	Trace	–
9	PMHS	71	97
10	MeEt ₂ SiH	Trace	–
11	Cs ₂ CO ₃	40	98
12	KF	76	98
13	LiO ^t Bu	17	85
14	1,4-Dioxane ^b	23	91
15	Diglyme	86	96
16	DMAc	8	59
17	CH ₃ CN, DCE or ^t Pr ₂ O	Trace	–

Cobalt-catalysed enantioselective hydroalkylation

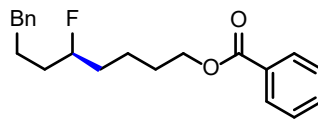
➤ Scope of alkyl halides in hydroalkylation



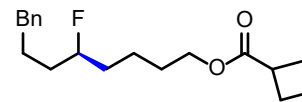
4aa, 85%, **97% e.e.**
 1a (1:5.3 Z/E) and 2a
 83%, **92% e.e.**
 1a (>20:1 Z/E) and 2a
 68%, **97% e.e.**
 1a (1:5.3 Z/E) and 3a



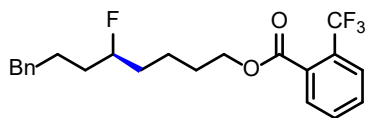
4ab, 86%, **97% e.e.**
 1a (1:5.3 Z/E) and 2b
 83%, **92% e.e.**
 1a (1:5.3 Z/E) and 3b



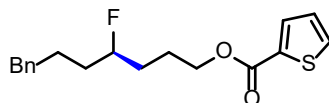
4ac, 82%, **97% e.e.**
 1a (1:5.3 Z/E) and 2c
 57%, **97% e.e.**
 1a (1:5.3 Z/E) and 3c



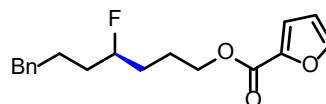
4ad, 72%, **96% e.e.**
 1a (1:5.3 Z/E) and 2d
 70%, **93% e.e.**
 1a (>20:1 Z/E) and 2d



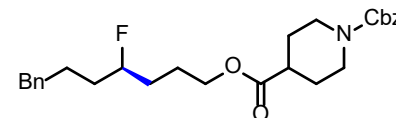
4ae, 80%, **97% e.e.**
 1a (1:5.3 Z/E) and 2e



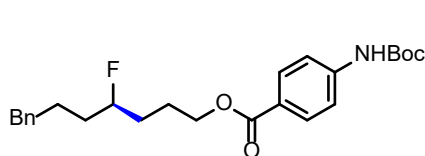
4af, 60%, **93% e.e.**
 1a (1:5.3 Z/E) and 2f
 40%, **96% e.e.**
 1a (1:5.3 Z/E) and 3f



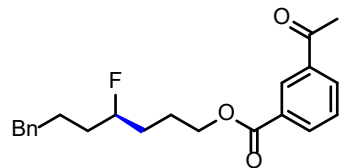
4ak, 85%, **96% e.e.**
 1a (1:5.3 Z/E) and 2g



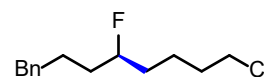
4ah, 82%, **97% e.e.**
 1a (1:5.3 Z/E) and 2h



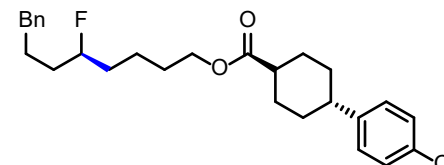
4ai, 84%, **97% e.e.**
 1a (1:5.3 Z/E) and 2i
 90%, **93% e.e.**
 1a (>20:1 Z/E) and 2i



4aj, 68%, **99% e.e.**
 1a (1:5.3 Z/E) and 2j



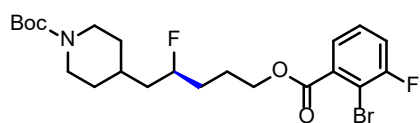
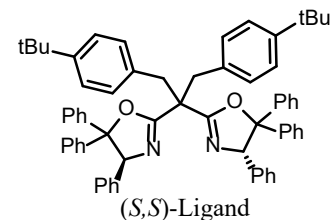
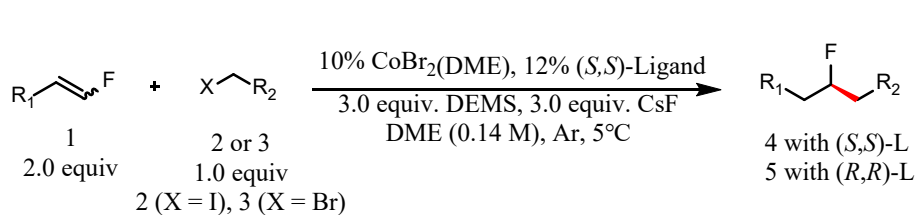
4ak, 85%, **96% e.e.**
 1a (1:5.3 Z/E) and 2k
 80%, **92% e.e.**
 1a (>20:1 Z/E) and 2k



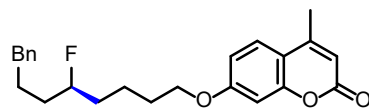
4al, 84%, **97% e.e.**
 1a (1:5.3 Z/E) and 2l

Cobalt-catalysed enantioselective hydroalkylation

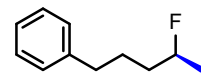
➤ Scope of alkyl halides in hydroalkylation



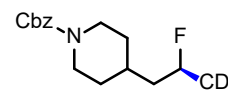
4km, 76%, 95% e.e.
1a (>20:1 Z/E) and 2m



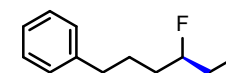
4an, 86%, 97% e.e.
1a (1:5.3 Z/E) and 2n



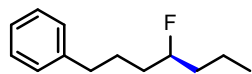
4ao, 70%, 96% e.e.
1a (1:5.3 Z/E) and 2o



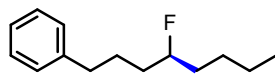
4lp, 78%, 94% e.e.
1l (>20:1 Z/E) and 2p



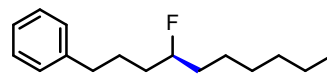
4aq, 68%, 96% e.e.
1a (1:5.3 Z/E) and 2q



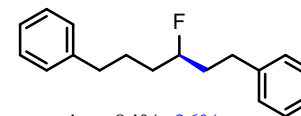
4ar, 83%, 96% e.e.
1a (1:5.3 Z/E) and 2r



4as, 83%, 93% e.e.
1a (>20:1 Z/E) and 2s

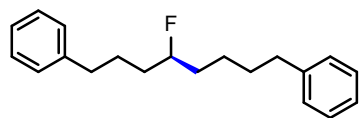


4at, 81%, 97% e.e.
1a (1:5.3 Z/E) and 2t

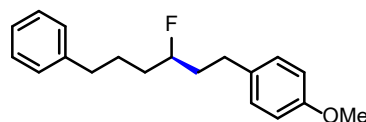


4au, 84%, 96% e.e.
1a (1:5.3 Z/E) and 2u

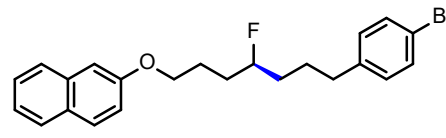
4au
This work: 2 steps
50%, 96% e.e.
Previous literature: 7steps
67% yield for 7th steps, 44% e.e.



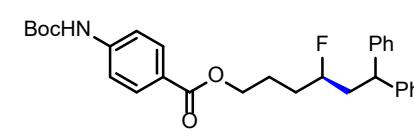
4av, 76%, 96% e.e.
1a (1:5.3 Z/E) and 2v



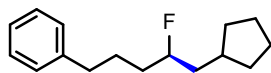
4aw, 82%, 96% e.e.
1a (1:5.3 Z/E) and 2w



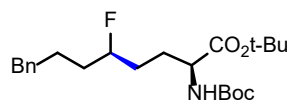
4Cx, 72%, 93% e.e.
1c (>20:1 Z/E) and 2x



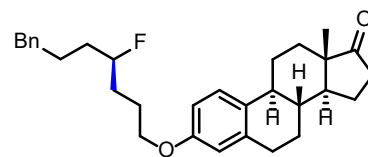
4Dy, 58%, 88% e.e.
1D (>20:1 Z/E) and 2y



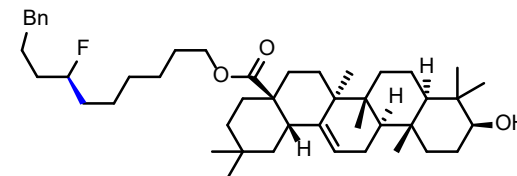
4az, n = 1, 68%, 96% e.e.
1a (1:5.3 Z/E) and 2z
4aA, n = 2, 72%, 94% e.e.
1a (>20:1 Z/E) and 2A



4aB, (S,S)-L, 54%, 99:1 d.r.
5aB, (R,R)-L, 53%, 3:97 d.r.
1a (1:5.3 Z/E) and 2B



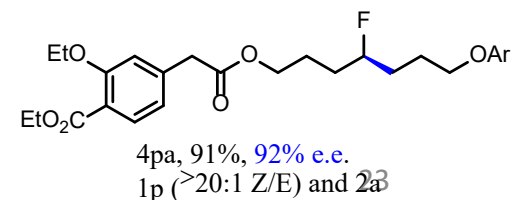
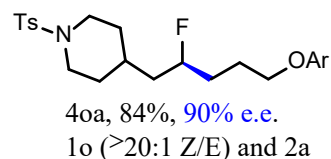
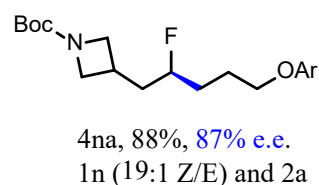
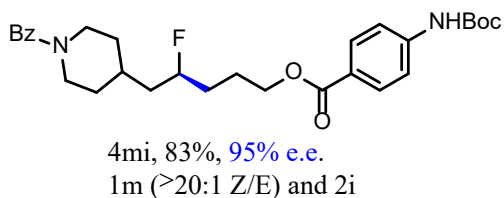
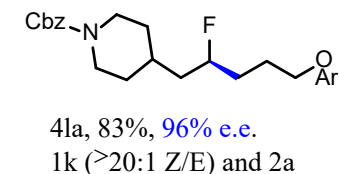
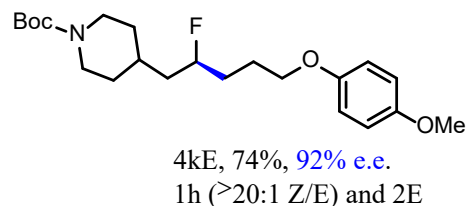
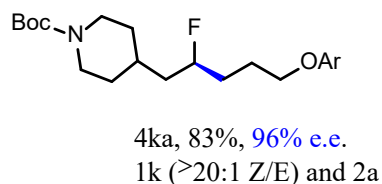
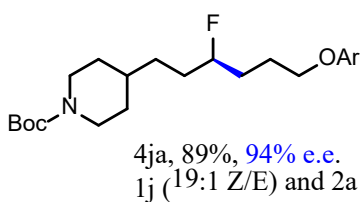
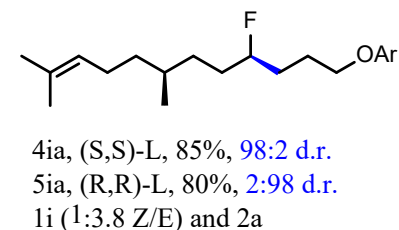
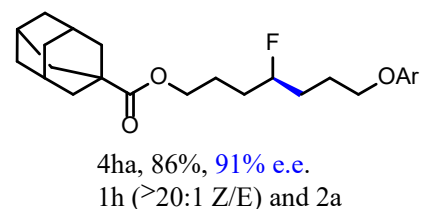
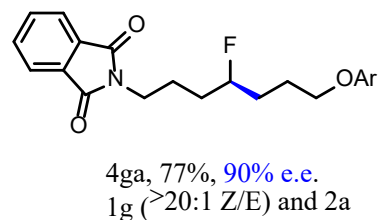
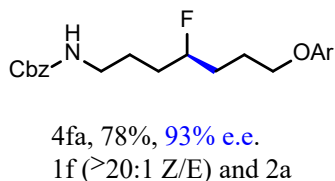
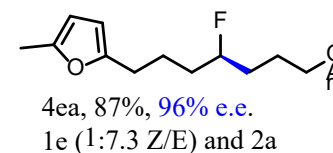
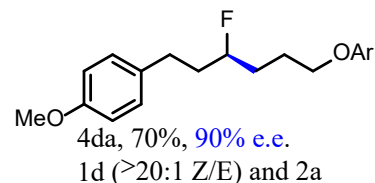
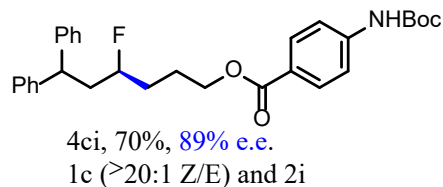
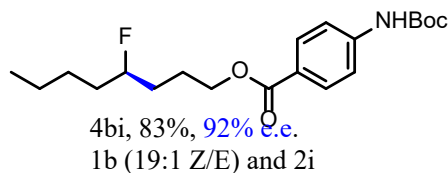
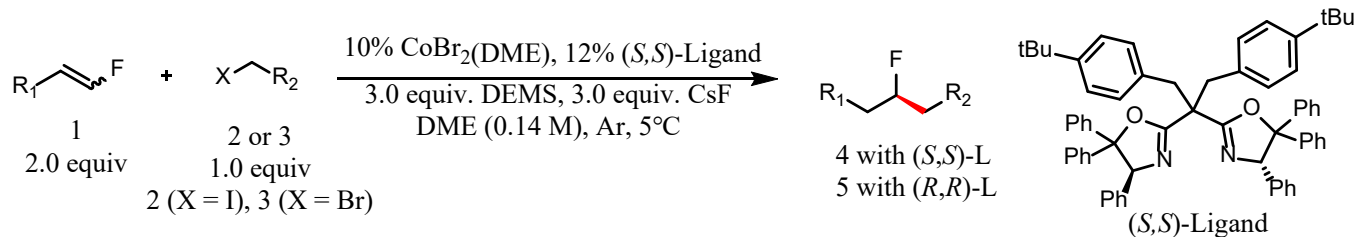
4aC, (S,S)-L, 81%, 98:2 d.r.
5aC, (R,R)-L, 53%, 2:98 d.r.
1a (1:5.3 Z/E) and 2C



4aD, (S,S)-L, 63%, 98.5:1.5 d.r.
5aD, (R,R)-L, 68%, 3:97 d.r.
1a (1:5.3 Z/E) and 2D

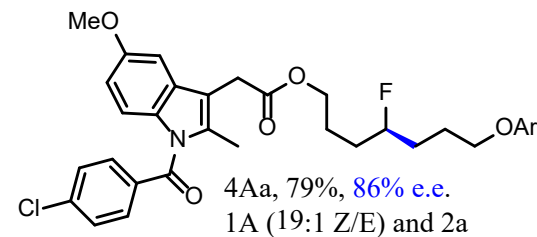
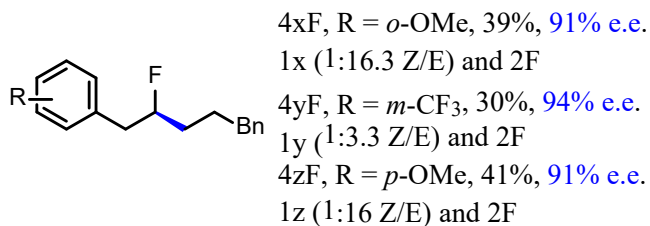
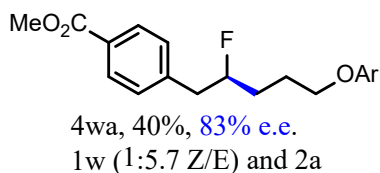
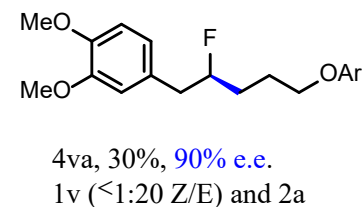
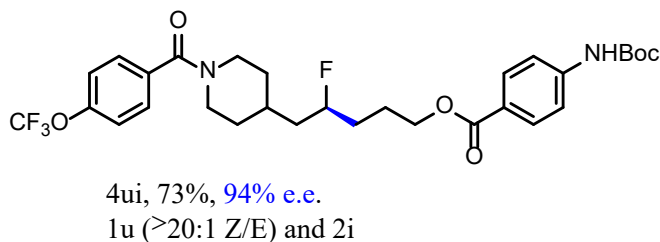
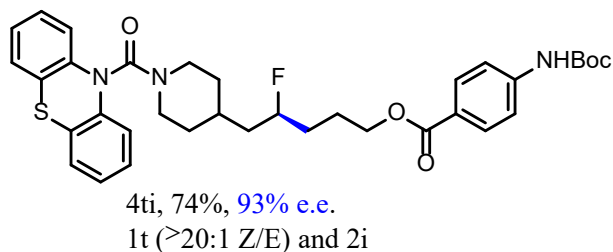
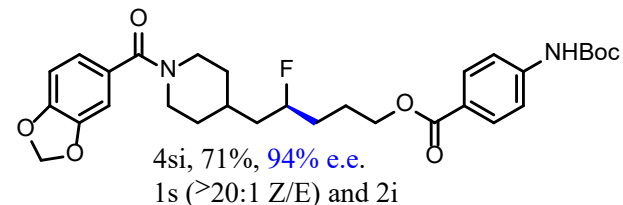
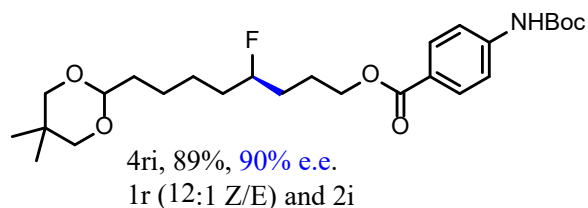
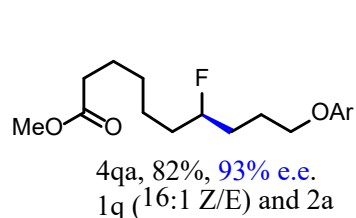
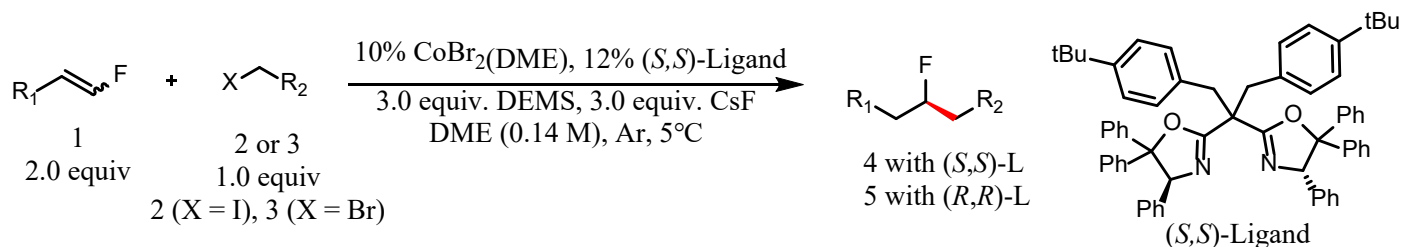
Cobalt-catalysed enantioselective hydroalkylation

➤ Scope of monofluoroalkenes in hydroalkylation



Cobalt-catalysed enantioselective hydroalkylation

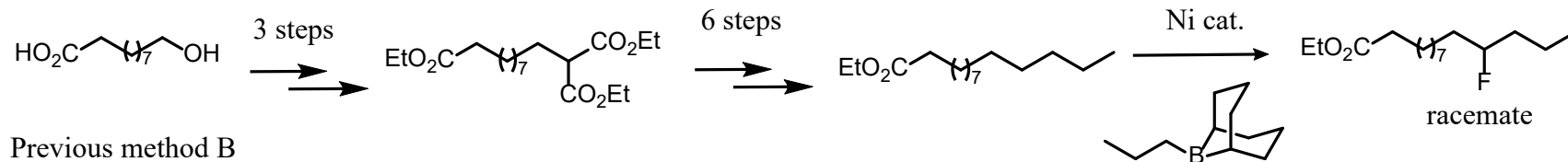
➤ Scope of monofluoroalkenes in hydroalkylation



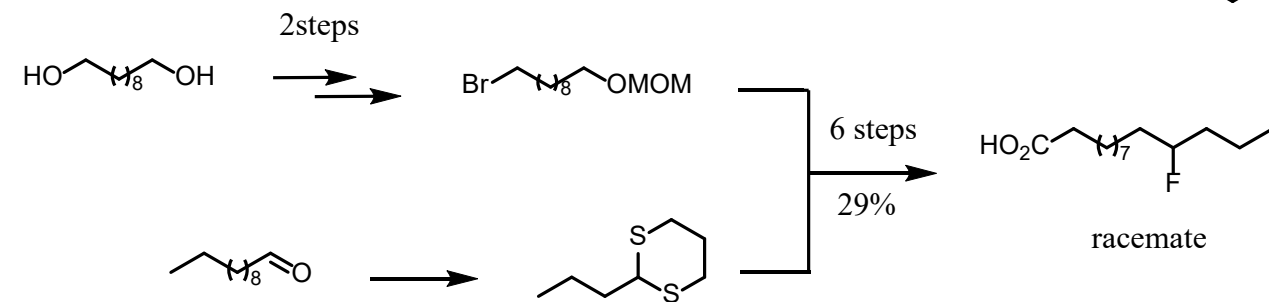
Cobalt-catalysed enantioselective hydroalkylation

➤ Synthesis application

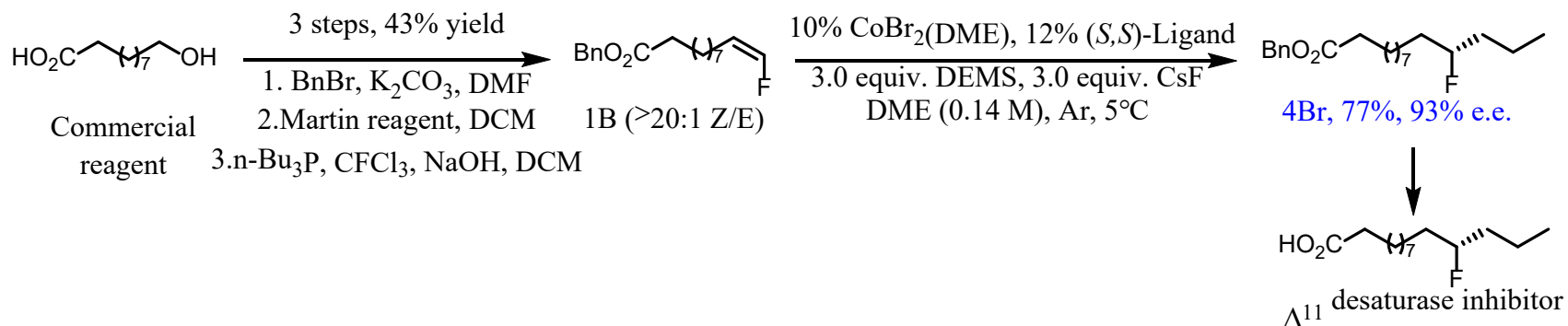
Previous method A



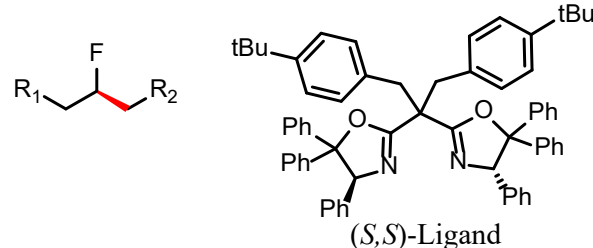
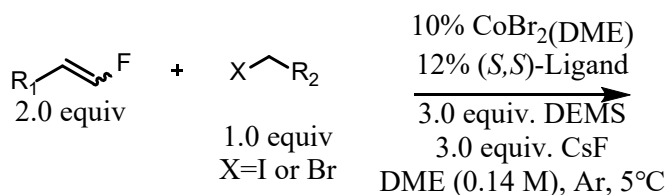
Previous method B



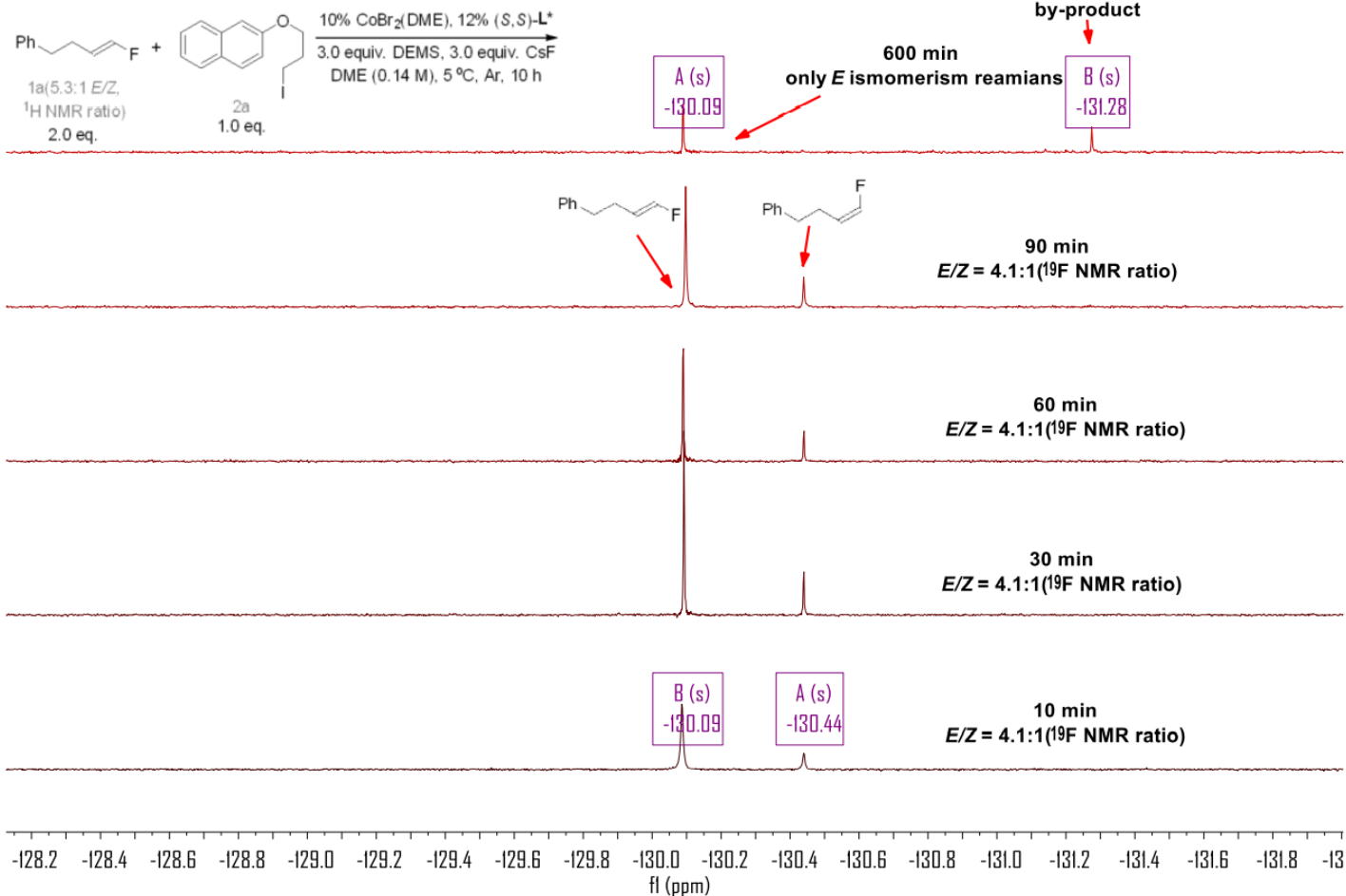
This work



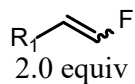
Cobalt-catalysed enantioselective hydroalkylation



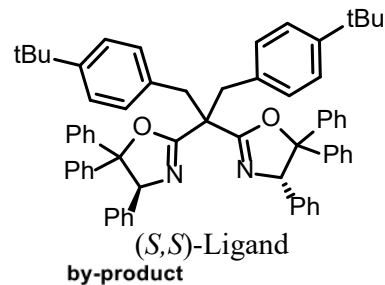
19F NMR spectra for 1a (1:5.3 Z/E)



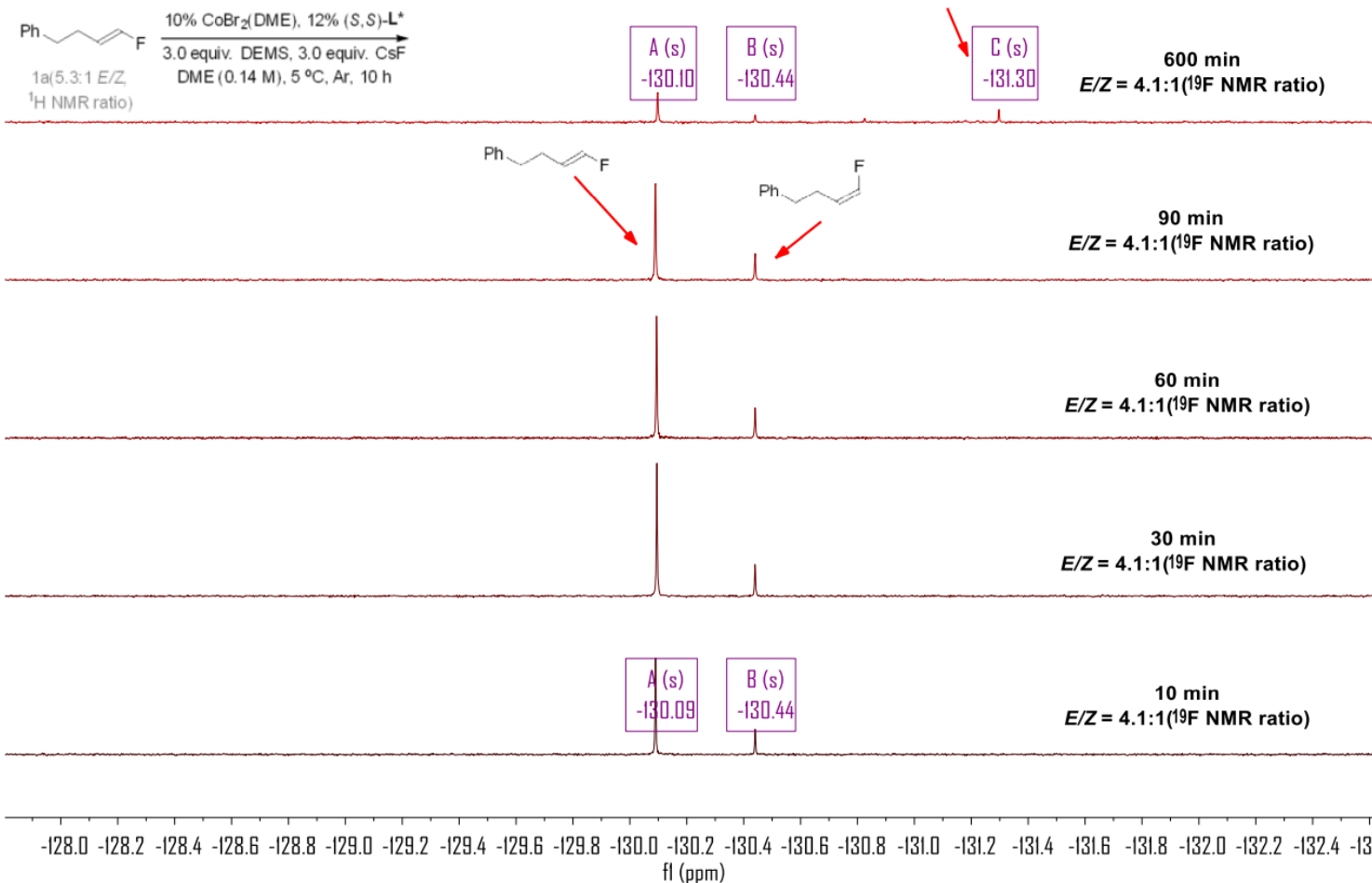
Cobalt-catalysed enantioselective hydroalkylation



10% CoBr₂(DME)
12% (S,S)-Ligand
3.0 equiv. DEMS
3.0 equiv. CsF
DME (0.14 M), Ar, 5°C



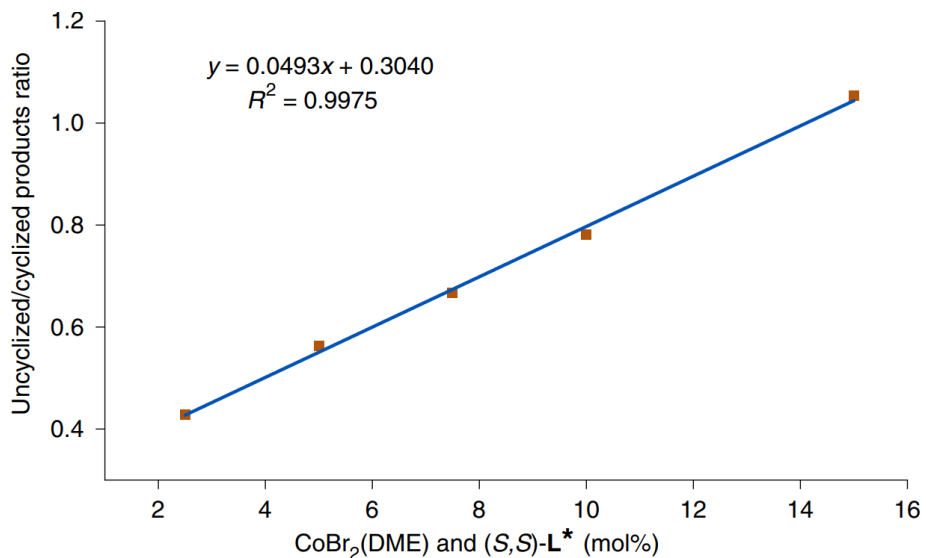
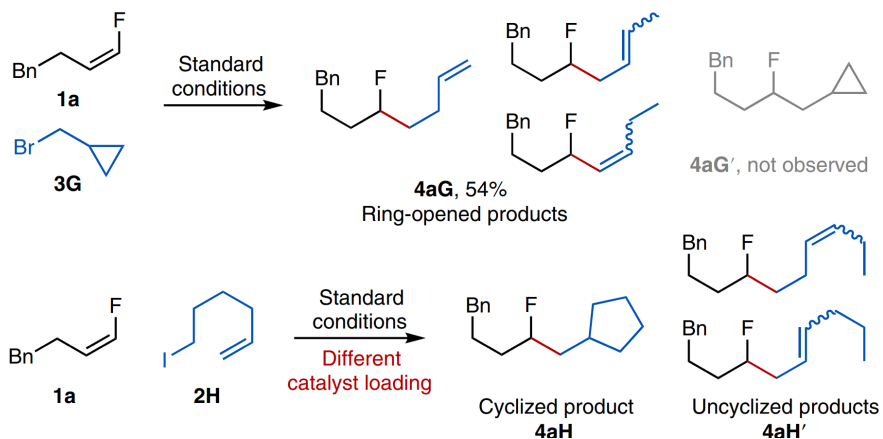
¹⁹F NMR spectra for 1a (1:5.3 Z/E), without 2a



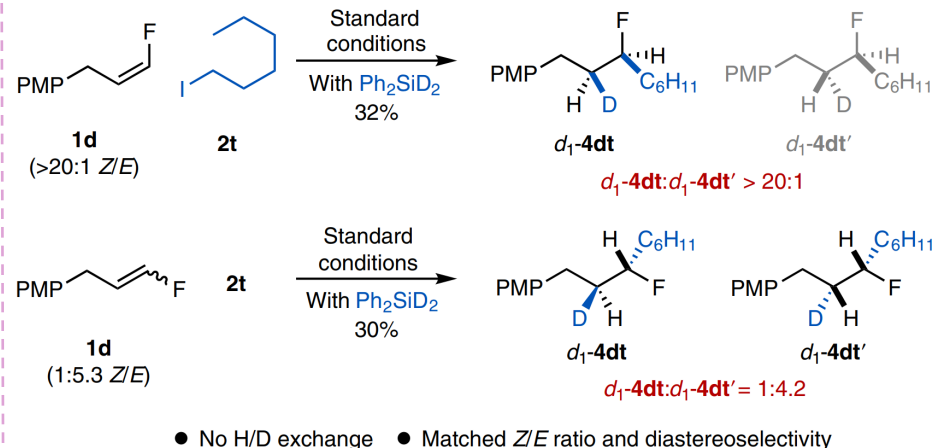
Cobalt-catalysed enantioselective hydroalkylation

➤ Preliminary mechanism studies

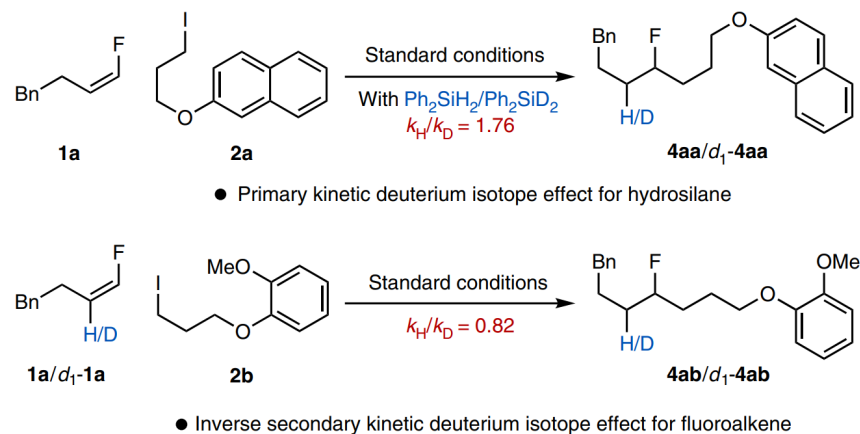
a. Radical clock experiments



b. Deuterium-labelling experiments

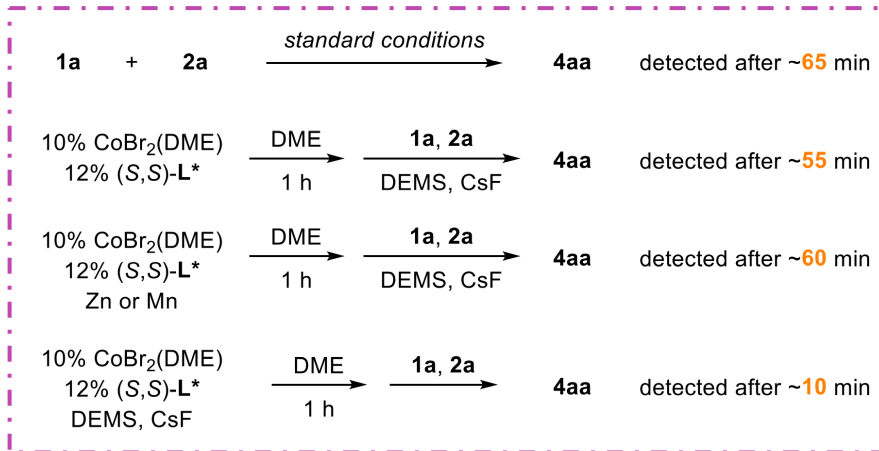
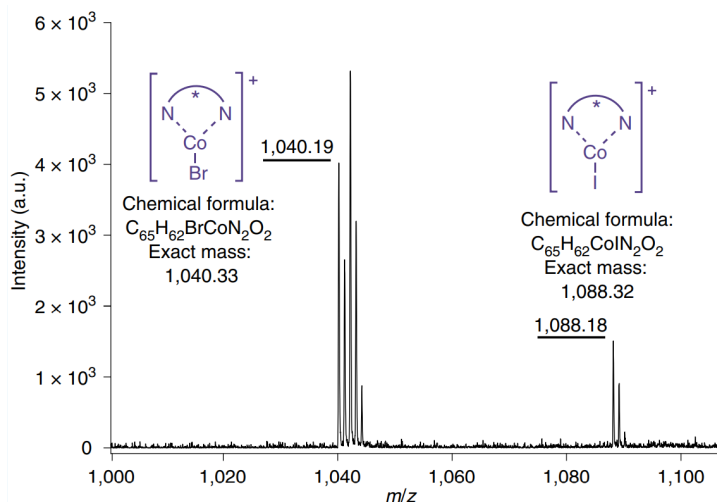
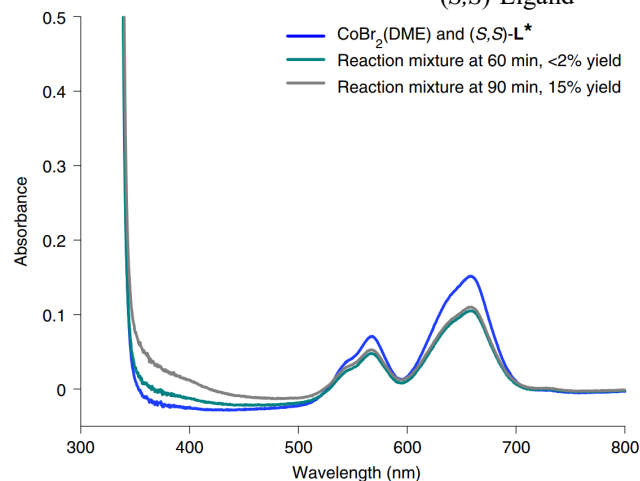
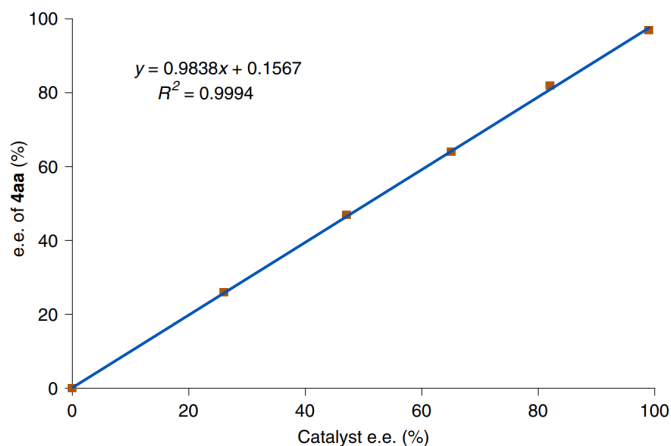
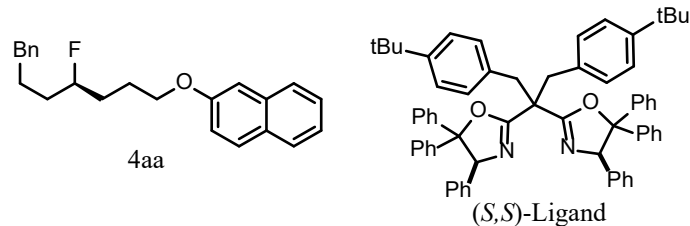
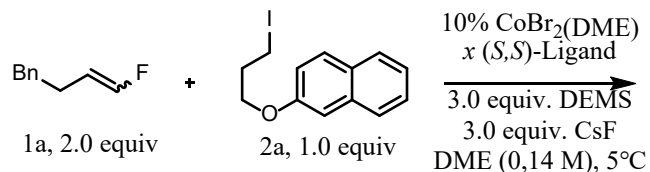


c. Kinetic isotope effect experiments



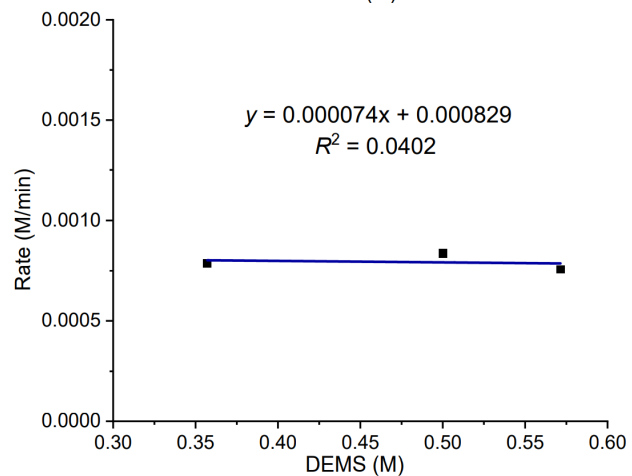
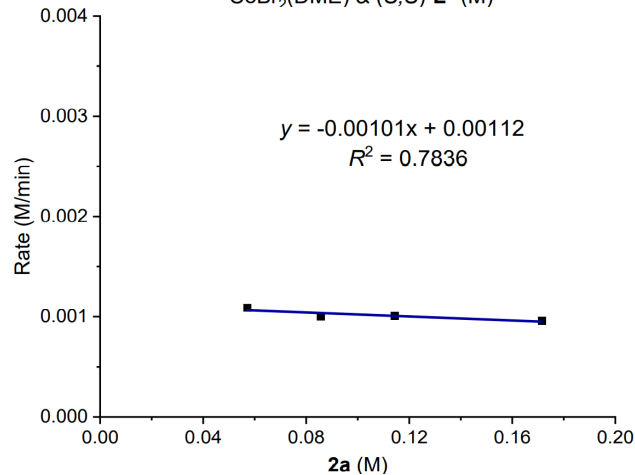
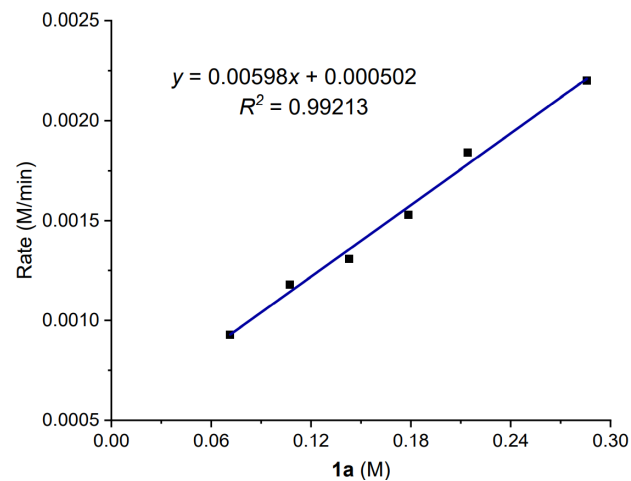
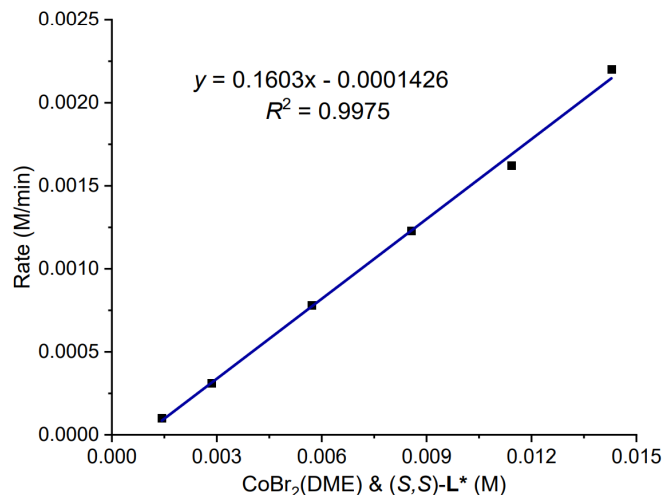
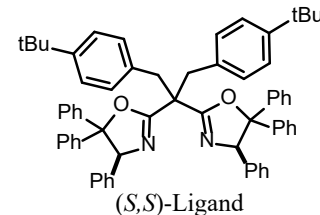
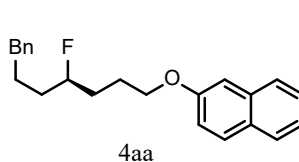
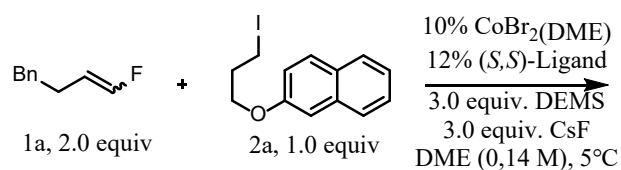
Cobalt-catalysed enantioselective hydroalkylation

➤ Preliminary mechanism studies



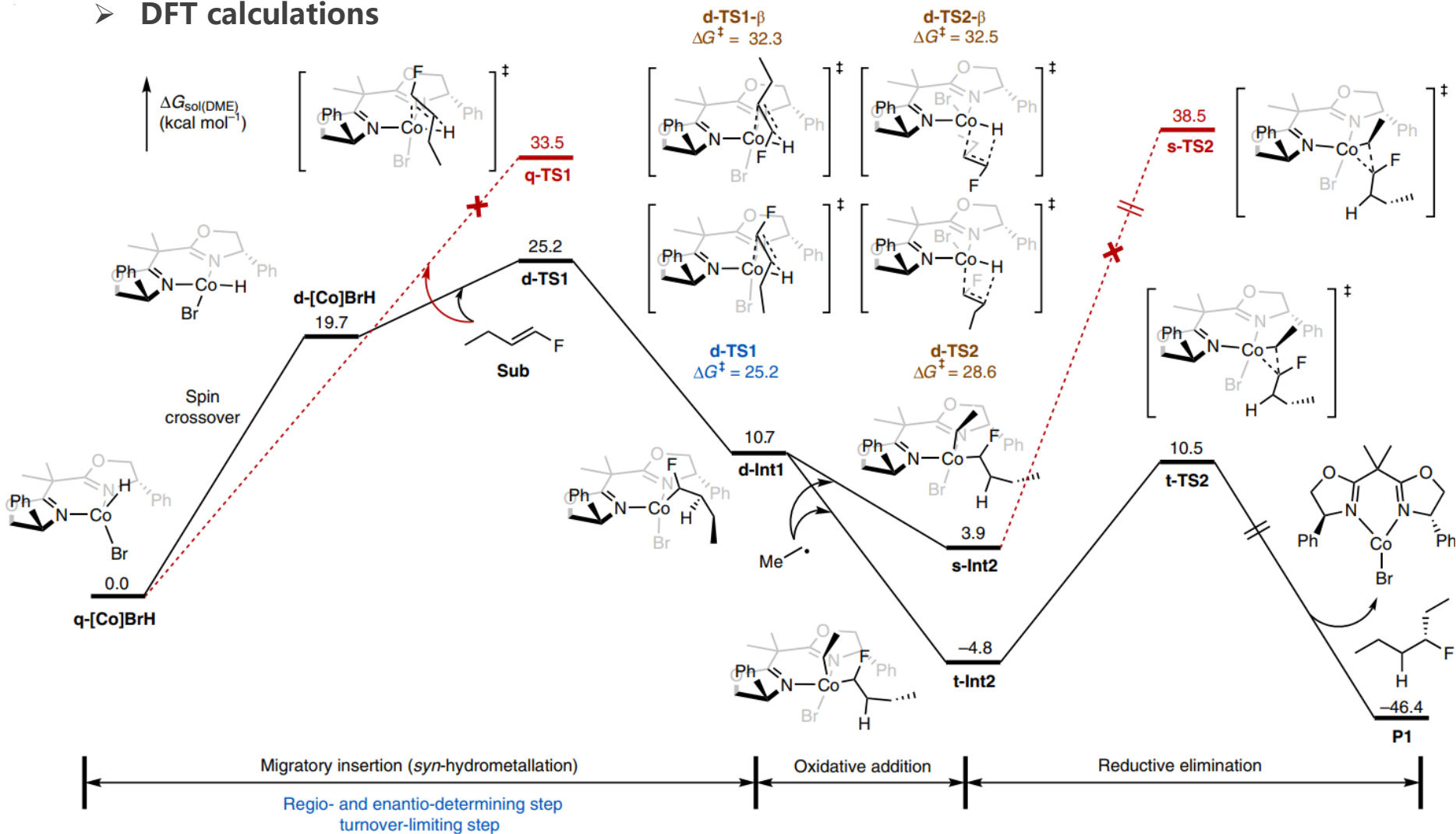
Cobalt-catalysed enantioselective hydroalkylation

➤ Preliminary mechanism studies



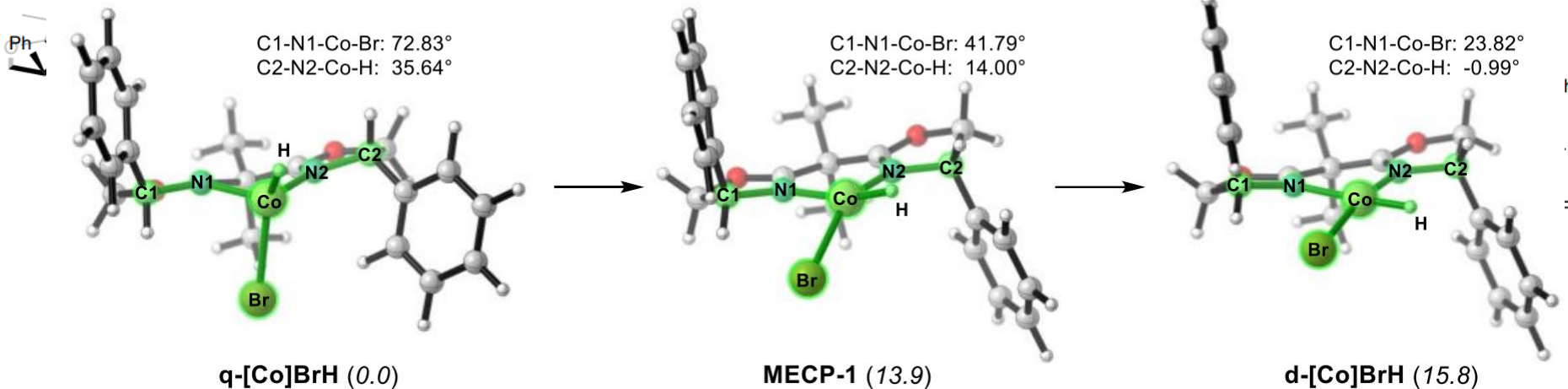
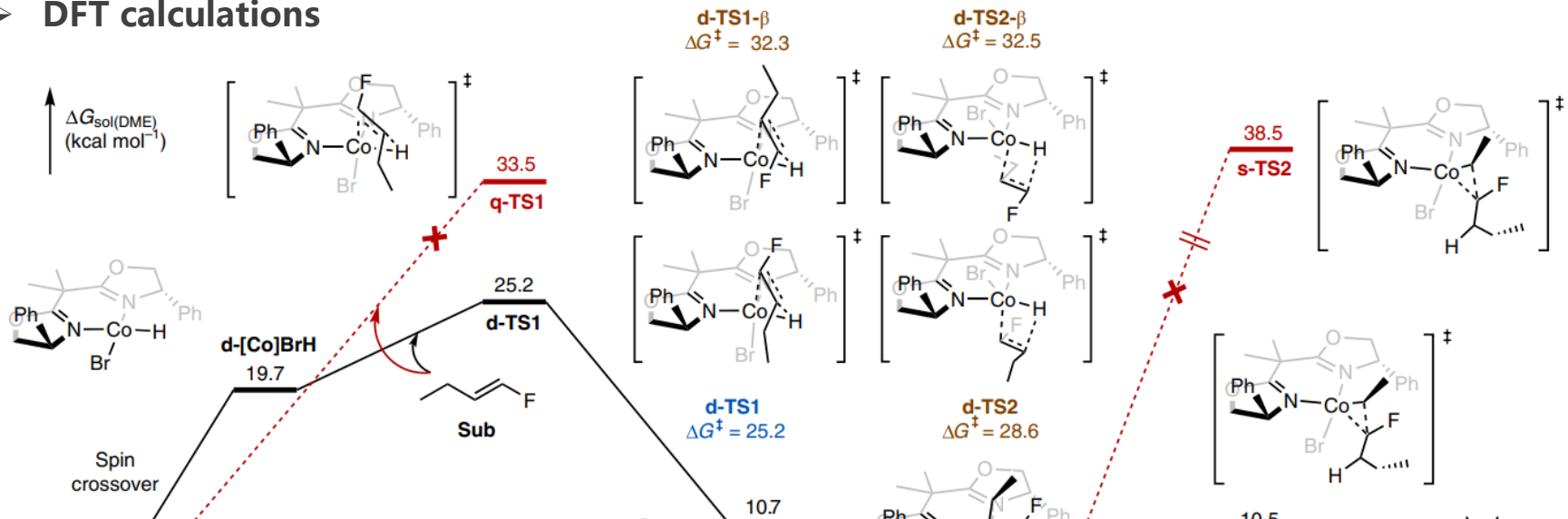
Cobalt-catalysed enantioselective hydroalkylation

➤ DFT calculations



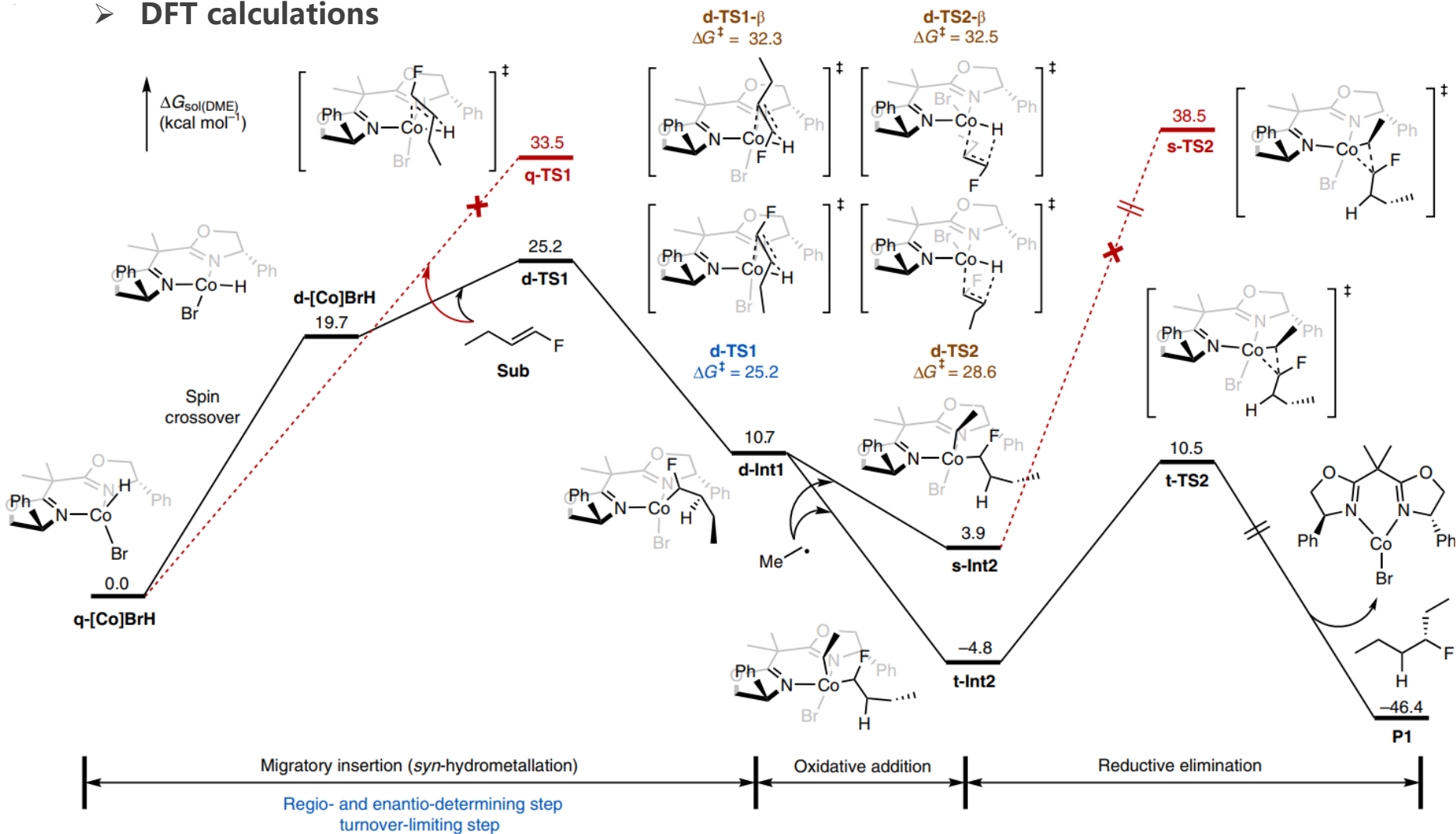
Cobalt-catalysed enantioselective hydroalkylation

➤ DFT calculations



Cobalt-catalysed enantioselective hydroalkylation

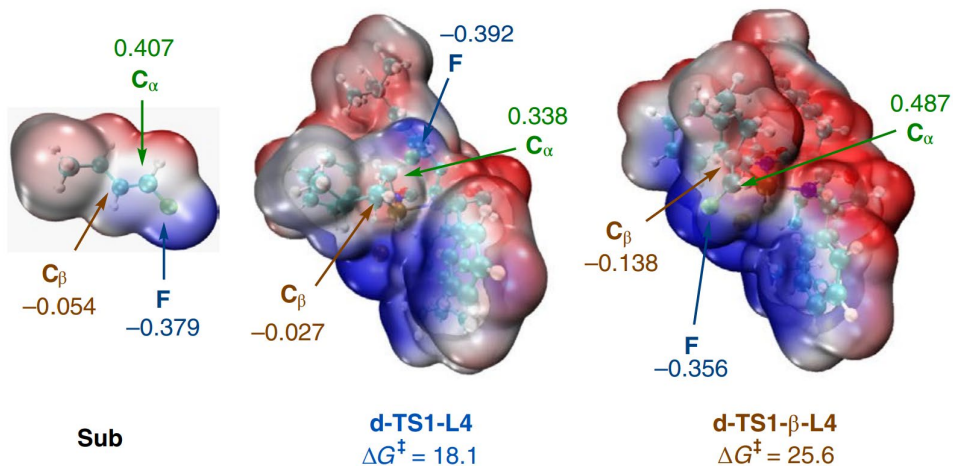
DFT calculations



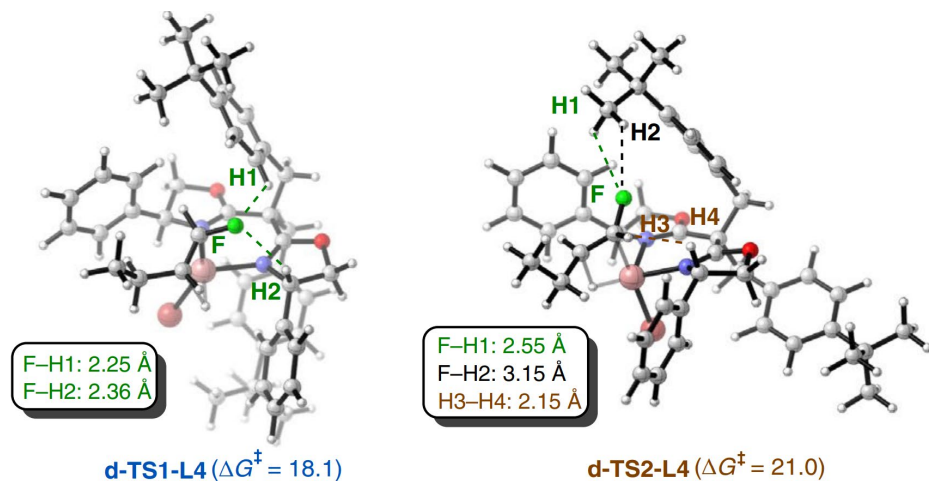
Cobalt-catalysed enantioselective hydroalkylation

Proposed mechanism

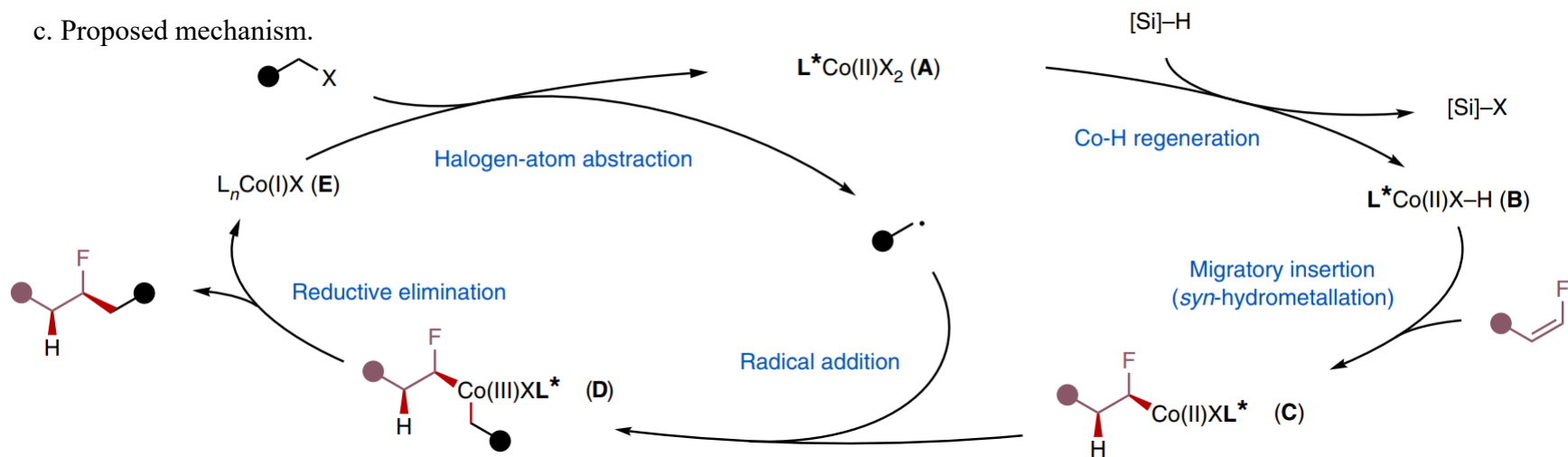
a. Electronic effect analysis of the regio-determining step.



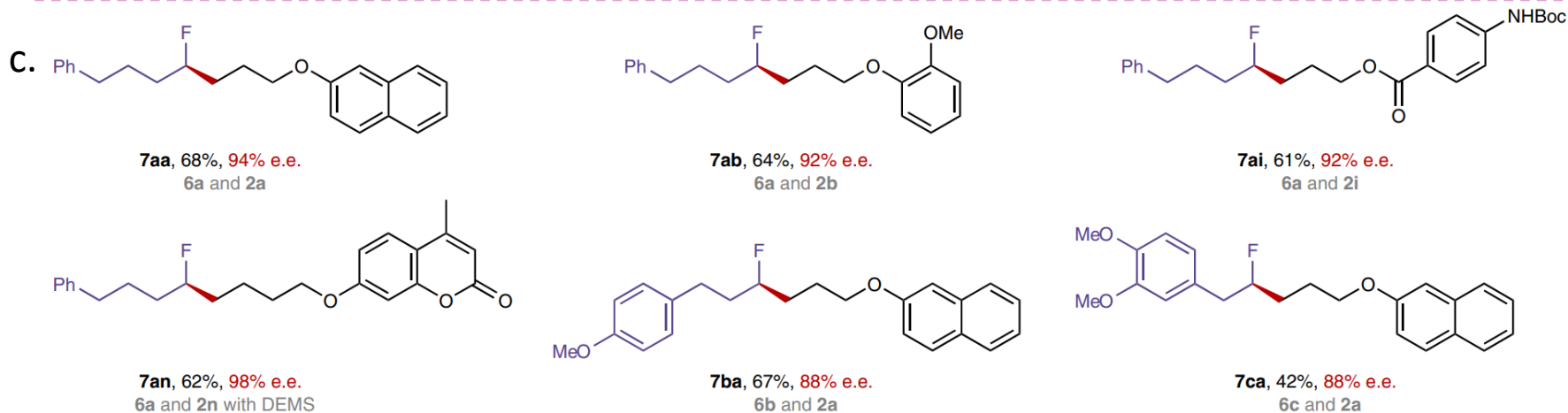
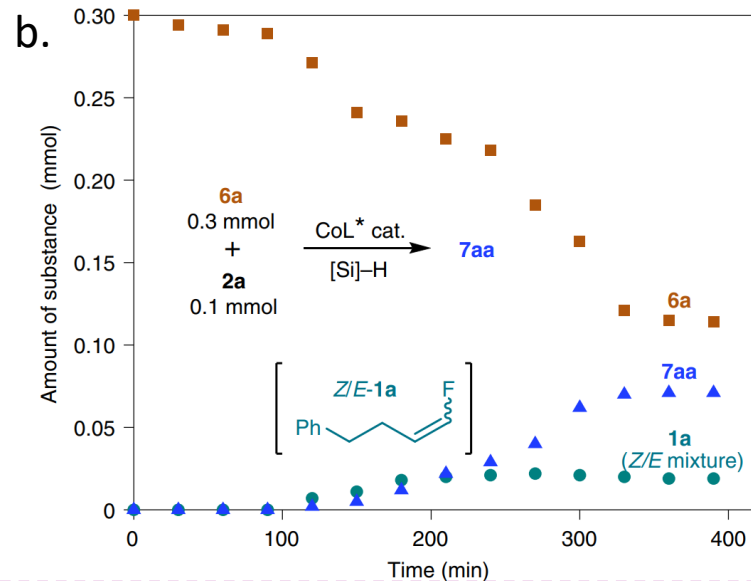
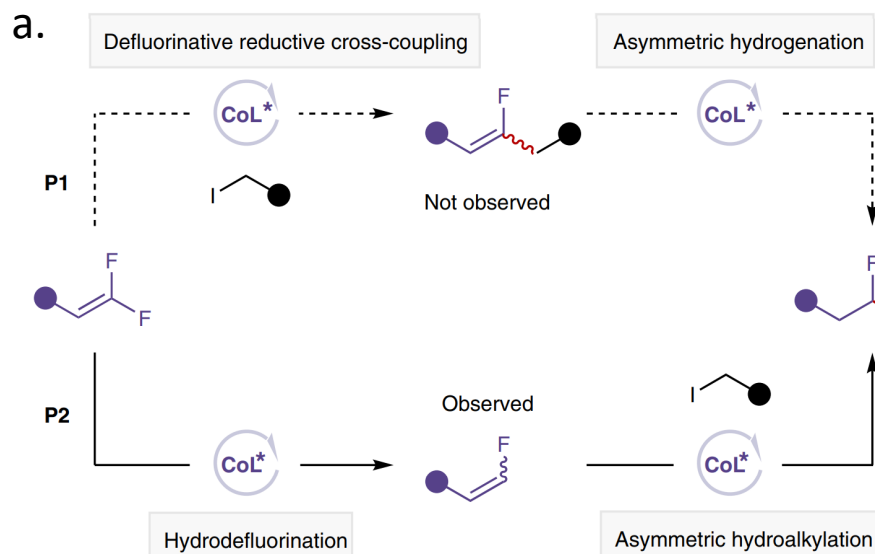
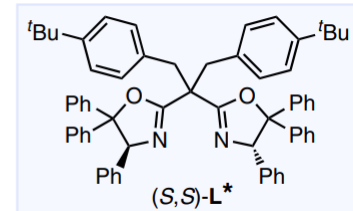
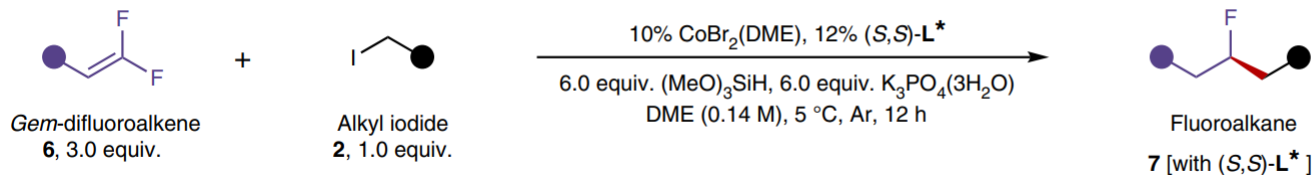
b. Optimized structures of d-TS1-L4 and d-TS2-L4.



c. Proposed mechanism.



Cobalt-catalysed enantioselective hydroalkylation



Summary

- ❑ The reaction products were chiral Fluoroalkanes.
- ❑ This reaction exhibits a catalyst-controlled enantioselectivity, making traditional directing or auxiliary groups unnecessary.
- ❑ Preliminary mechanistic studies indicate that hydrometalation was the turnover-limiting step and stereo-determining step.

Thank you!