Late-stage C-H functionalization for drug development

2016/12/17

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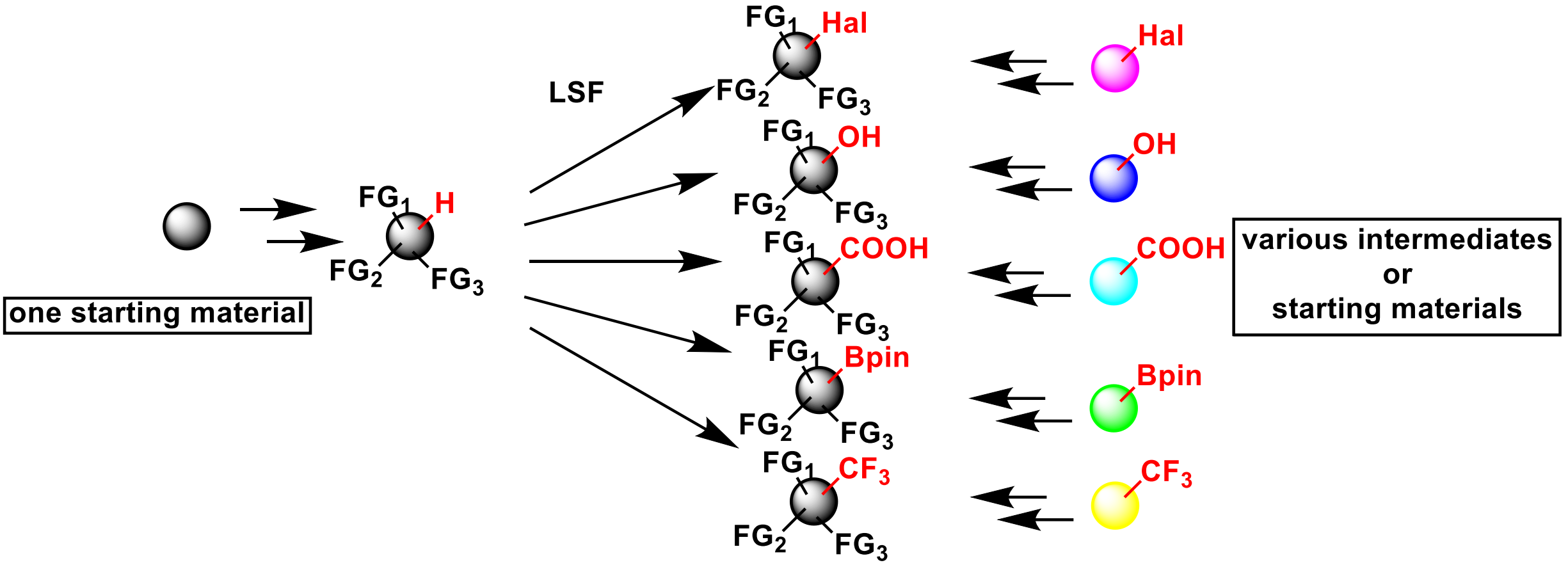
Today's topics

1. Introduction of late-stage C-H functionalization (LSF)
2. Strategies for obtaining regioselectivity in LSF
3. Application of LSF: Drug discovery
4. Summary

1. Introduction of late-stage C-H functionalization (LSF)

The concept of late-stage C-H functionalization (LSF)



Use of LSF

⇩

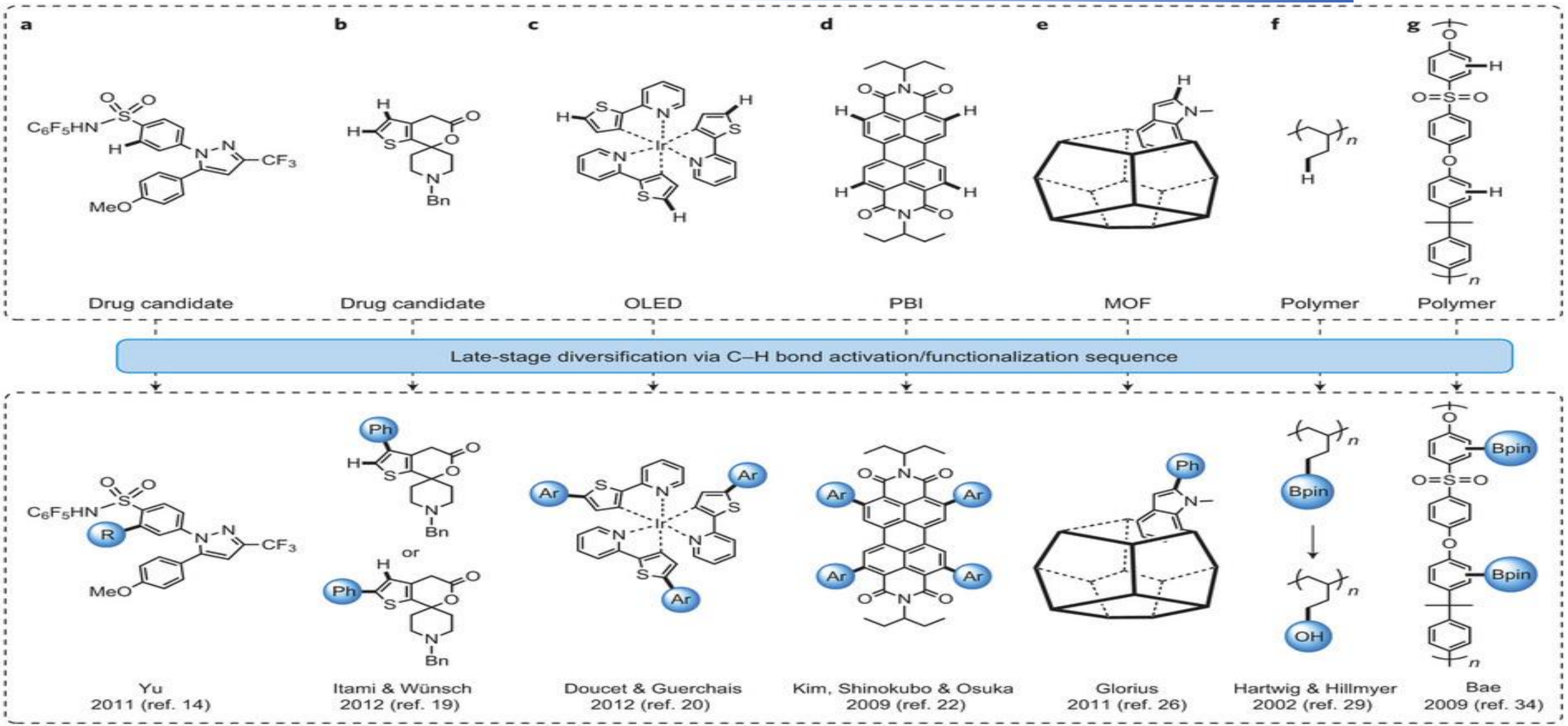
Direct and fast development of derivatives

Conventional method

⇩

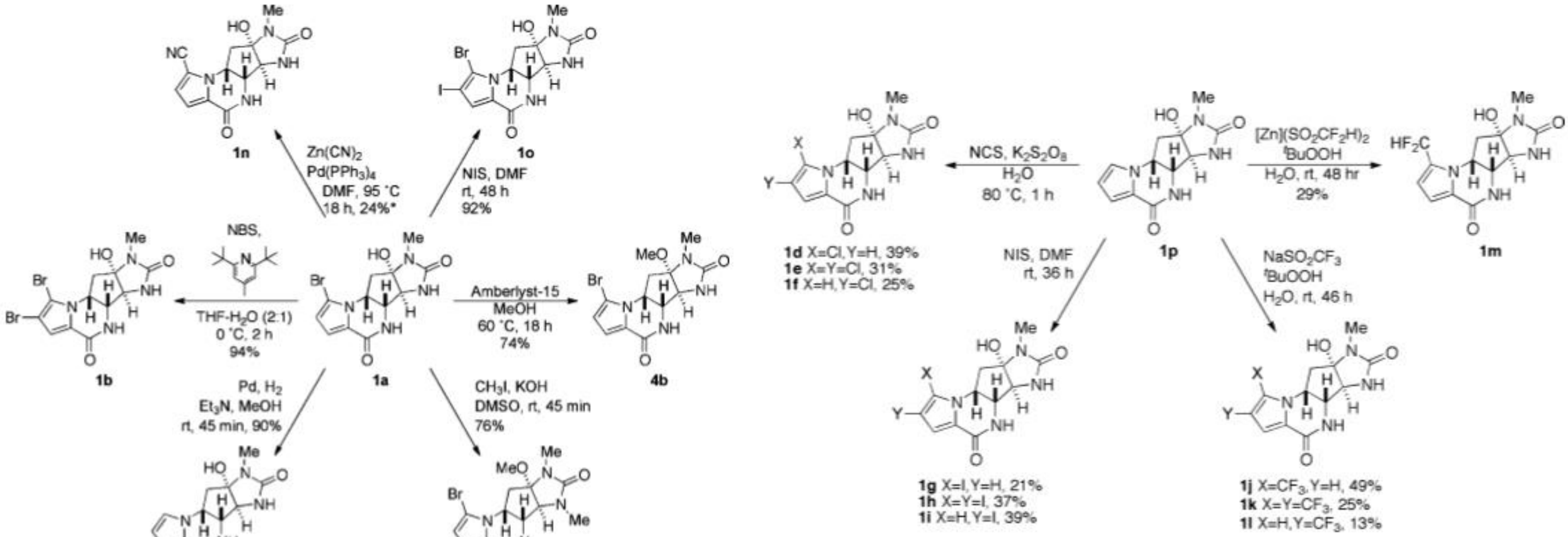
cumbersome protection/deprotection
lengthen the synthetic route

Application of LSF in various fields



Perspective: Wencel-Delord, J.; Glorius, F., *Nat. Chem.*, **2013**, *5*, 369.

LSF can modify natural products

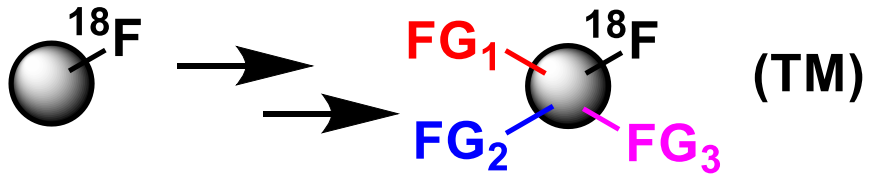


Stout E.P., Choi M. Y., Castro J. E. and Molinski T. F., *J. Med. Chem.*, **2014**, *57*, 5085.

LSF enables direct functionalization of natural complex products.

LSF enables the use of radioactive materials

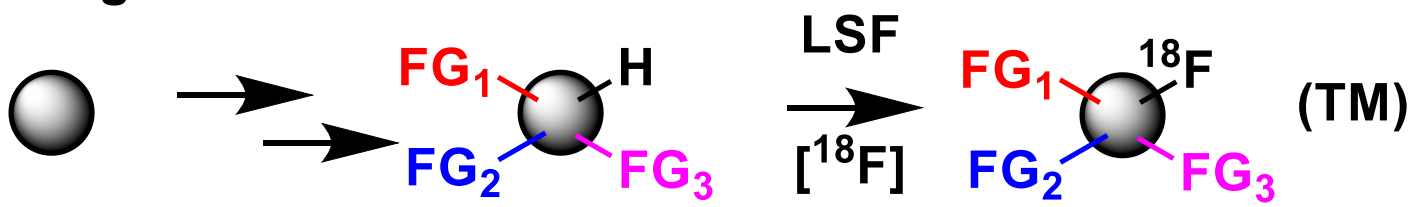
Conventional method



low radiochemical yields

^{18}F decays under long synthetic process. ($t_{1/2}$= 110 min)

Method using LSF

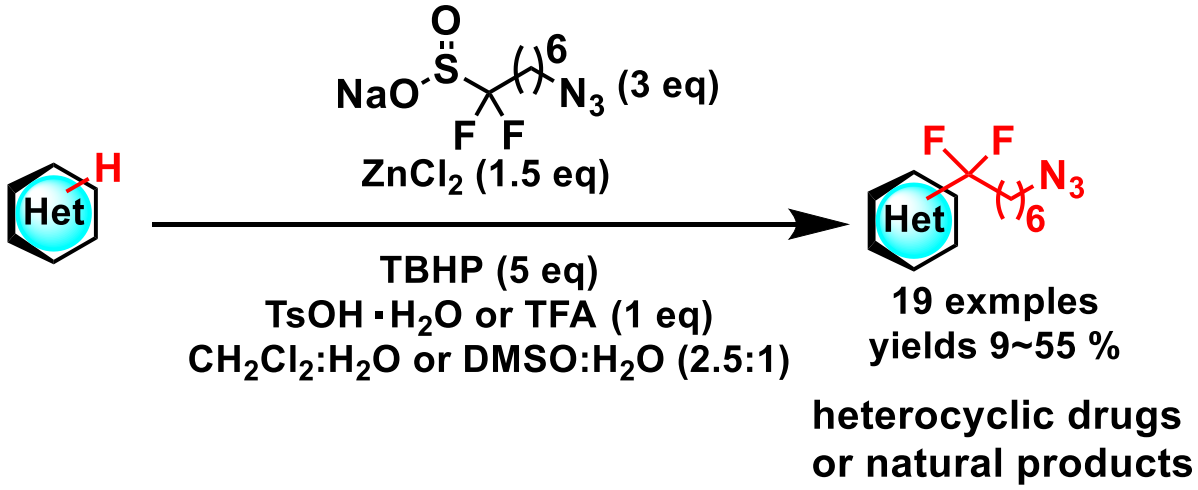


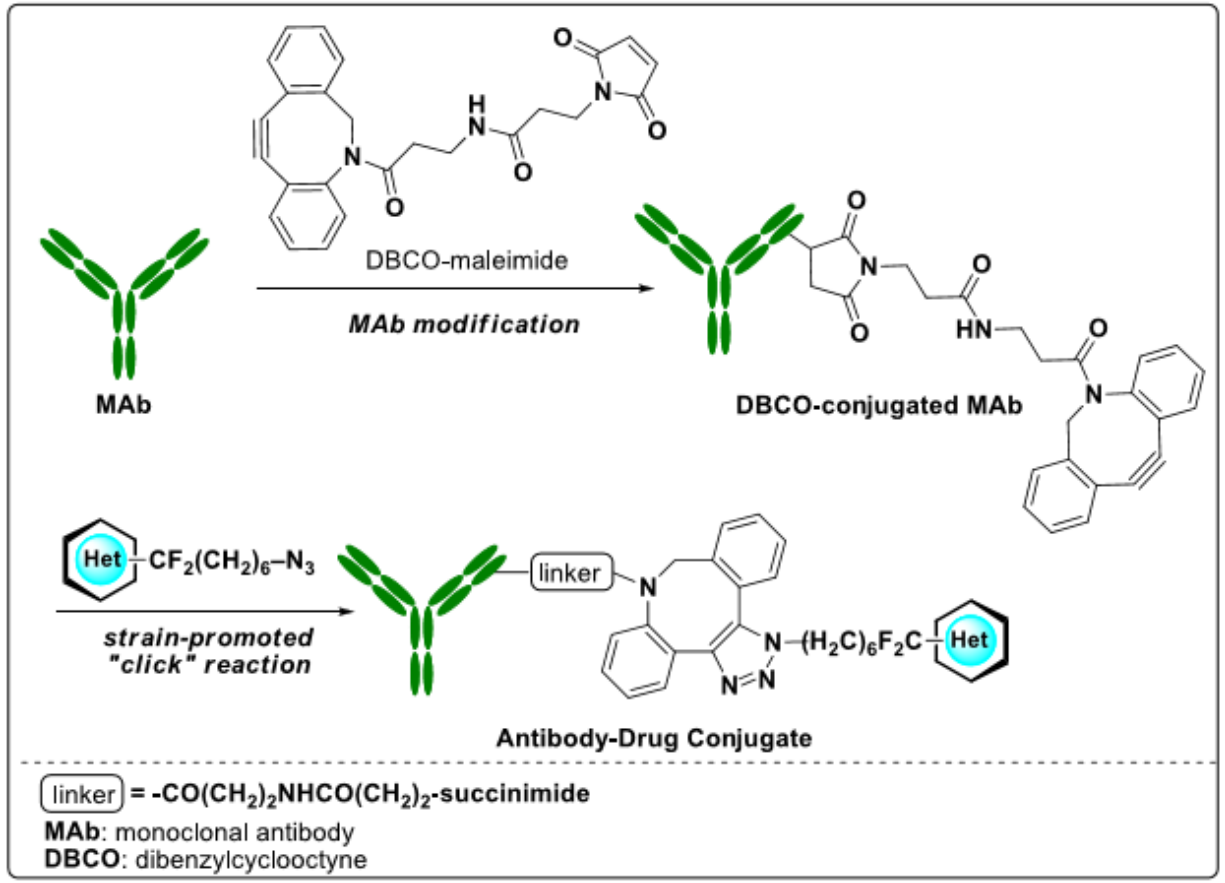
high radiochemical yields

⇩

LSF can contribute to making materials containing radioactive isotopes.

Application of LSF for ADC





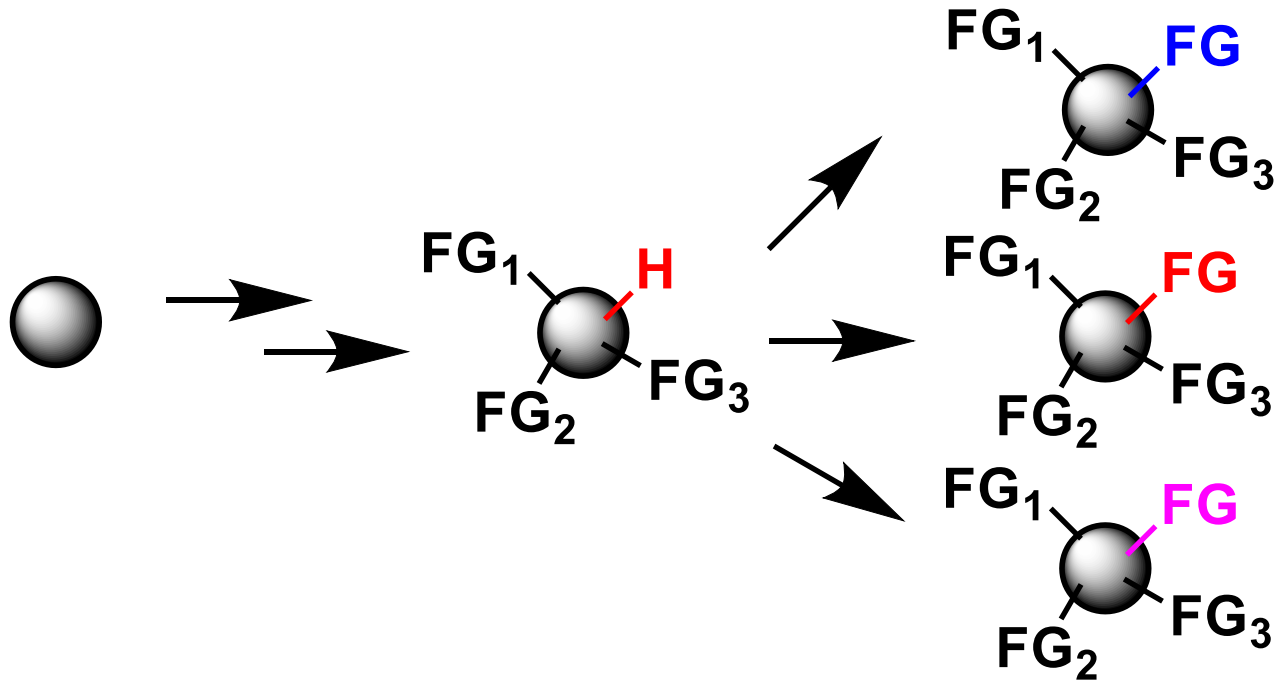
Q. Zhou, J. Gui, C.-M. Pan, E. Albone, X. Cheng, E. M. Suh, L. Grasso, Y. Ishihara and P. S. Baran, *J. Am. Chem. Soc.*, **2013**, *135*, 12994.

LSF can contribute to the synthesis of antibody-drug conjugates.

Summary of section 1

Late-stage C-H functionalization

= Conversion of C-H bonds to various functional groups at the end of synthetic process



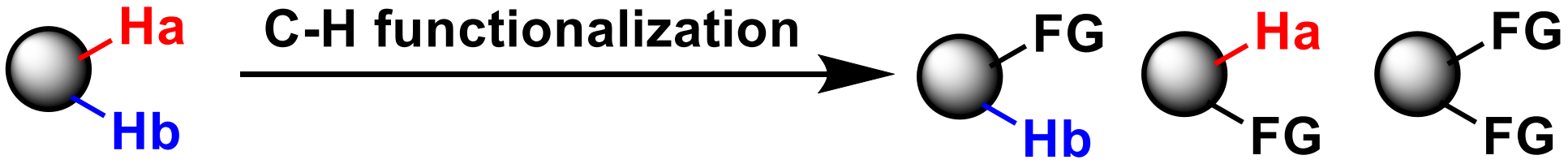
LSF has potential applications in various fields.

Modification of complex products such as natural products and functional molecules.

2. Strategies for obtaining regioselectivity in LSF

The difficulties of LSF

conventional conditions (non-suitable for LSF)

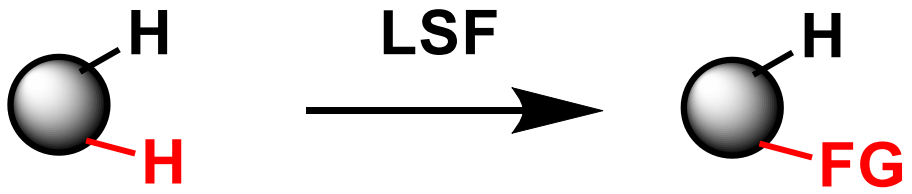


unseparatable compex mixture

→ **low yields, variable functions, low-quality products,...**

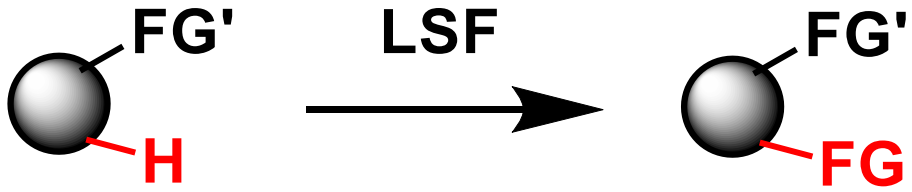
Many C-H bonds

⇨ Regioselectivity



Many reactive functional groups

⇨ Functional group tolerance, chemoselectivity



Strategies for obtaining regioselectivity in LSF

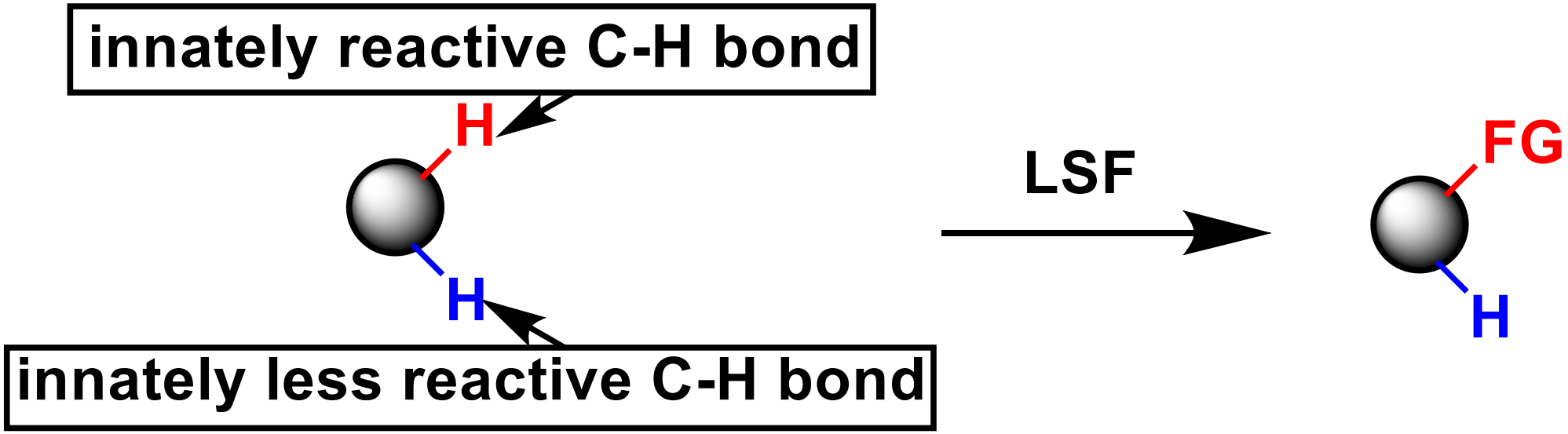
1. Functionalize innately reactive C-H bonds

2. Use of bulky reagents sensitive to steric factor

3. Use of directing groups (DG)

4. Use of other convertible functional groups which can be introduced regioselectively

Strategy①-1: LSF by innate C-H functionalizations

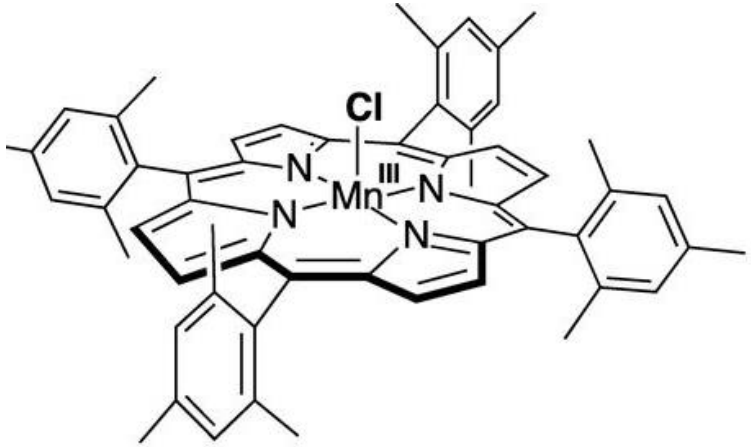


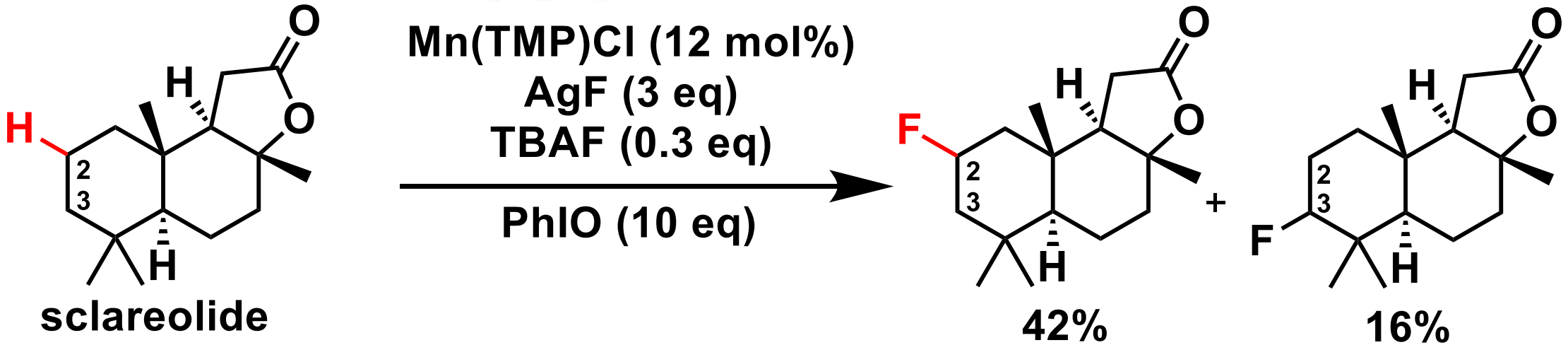
Innate reactivity depends on the structures of substrates.
For example, electron density and acidity

Merit
No extra conversion is required.

Problem
Regioselectivity mainly depends on substrates.

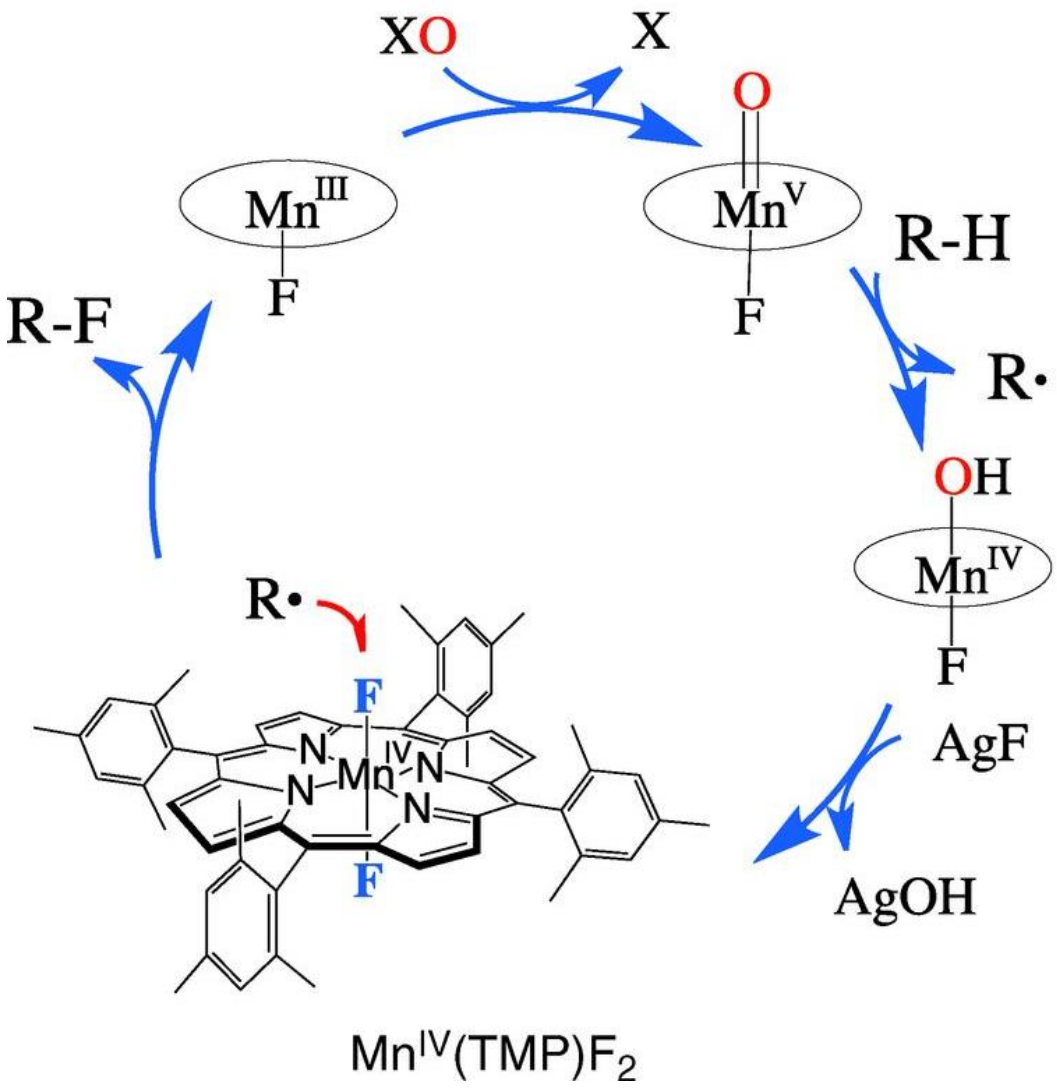
Strategy①-2: LSF by innate C-H functionalizations



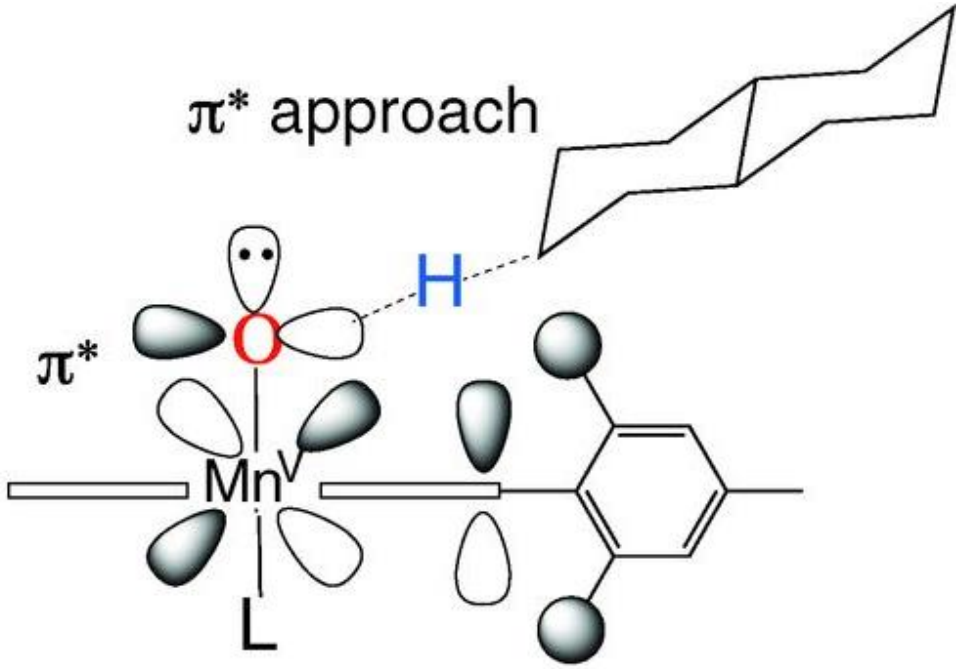


Liu, W.; Huang, X.; Cheng, M.-J.; Nielsen, R. J.; Goddard, W. A., III; Groves, J. T., *Science* **2012**, *337,* 1322.

Strategy①-3: LSF by innate C-H functionalizations

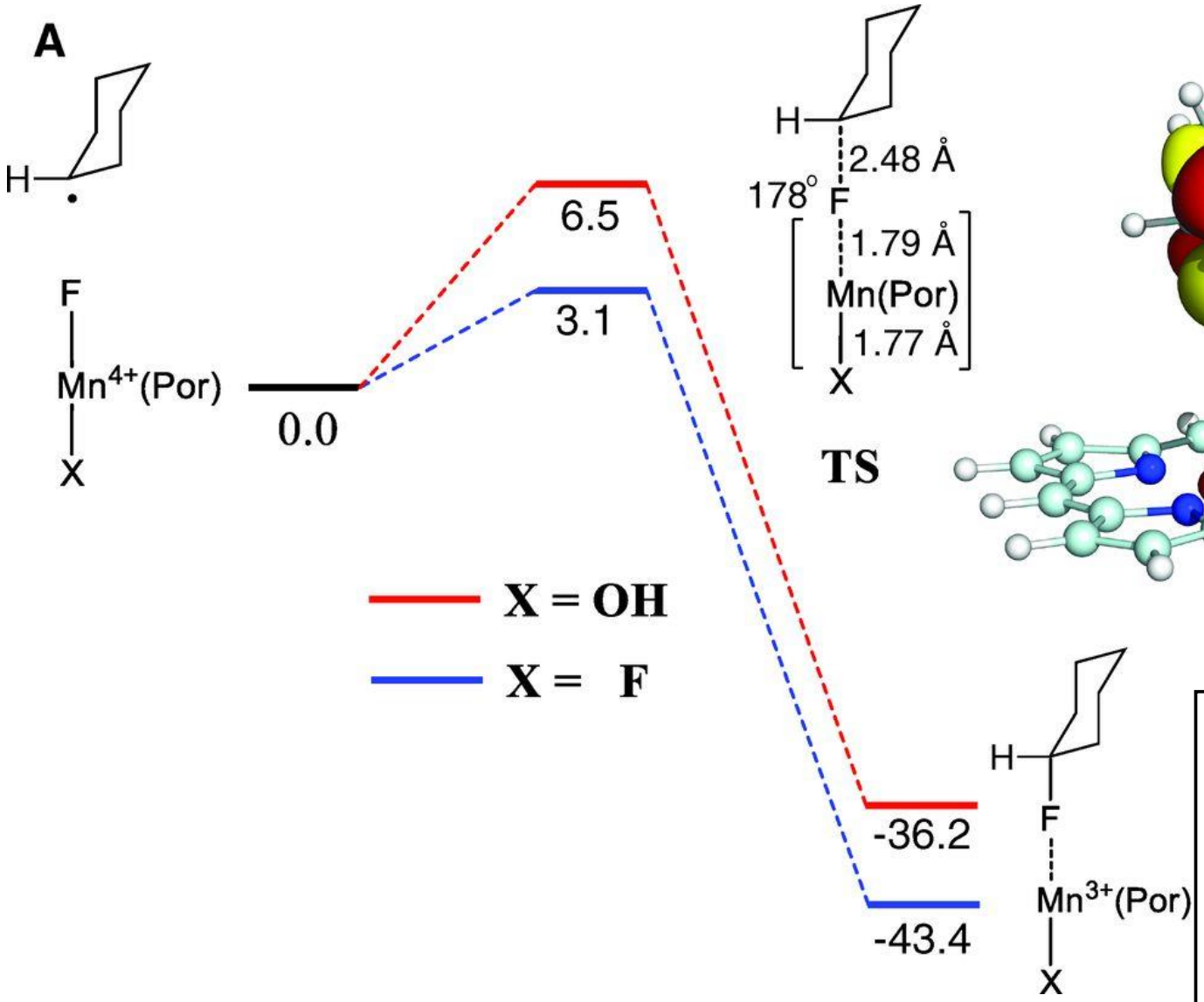


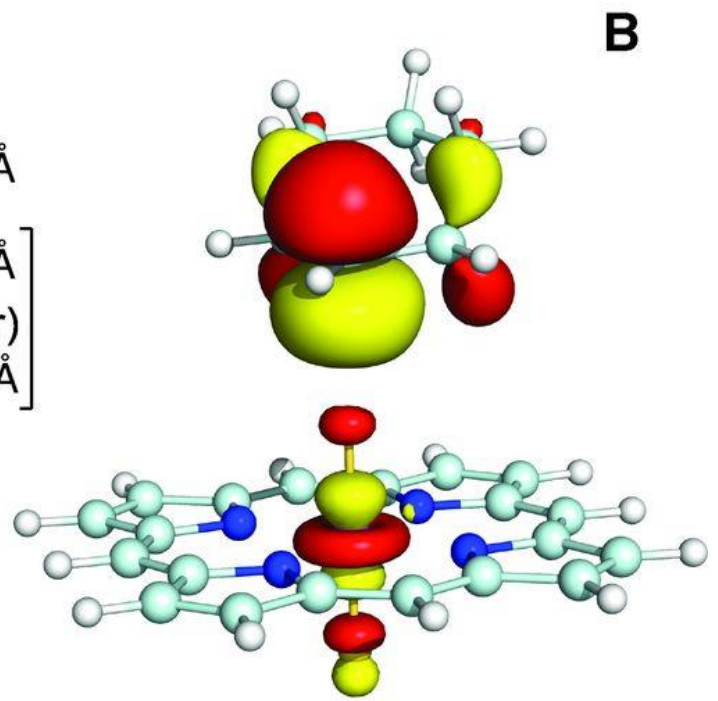
$Mn^{IV}(TMP)F_2$



Proposed catalytic cycle

Strategy①-4: LSF by innate C-H functionalizations



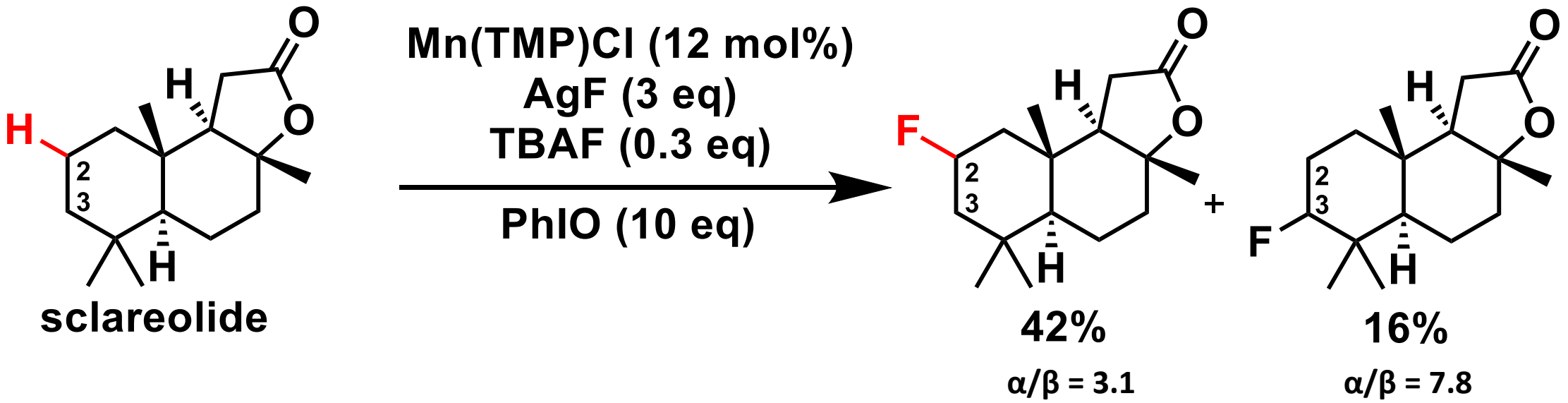


Method for DFT computations

For the geometry optimizations and zero-point vibrational energy
Mn: B3LYP/LACVP**
other atoms: B3LYP/6-31G**

For single-point energy calculations
Mn: B3LYP/LANL2TZ(f)
other atoms: B3LYP/6-311++G**

Strategy①-5: LSF by innate C-H functionalizations



Carbon radical was involved

→ Innately reactive C-H bonds were electron rich C-H bonds

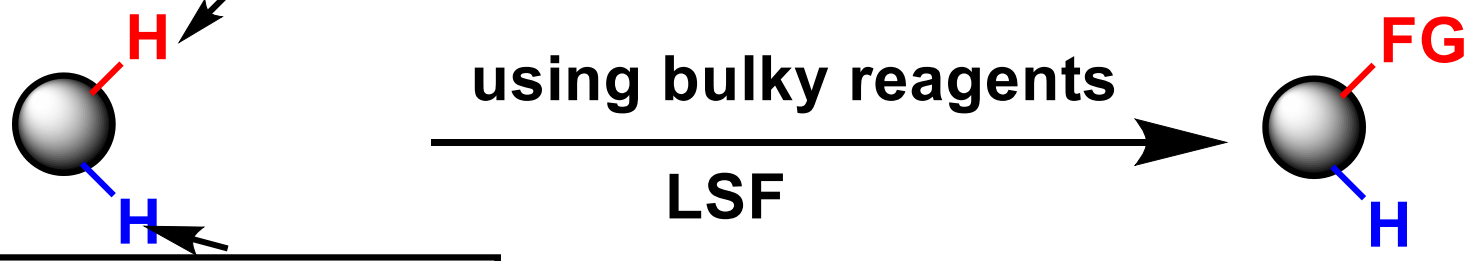
For example

(A) distant from electron withdrawing groups

(B) tertiary or secondary C-H bonds

Strategy②-1: LSF by bulky reagents

Sterically less hindered C-H bond



Sterically hindered C-H bond

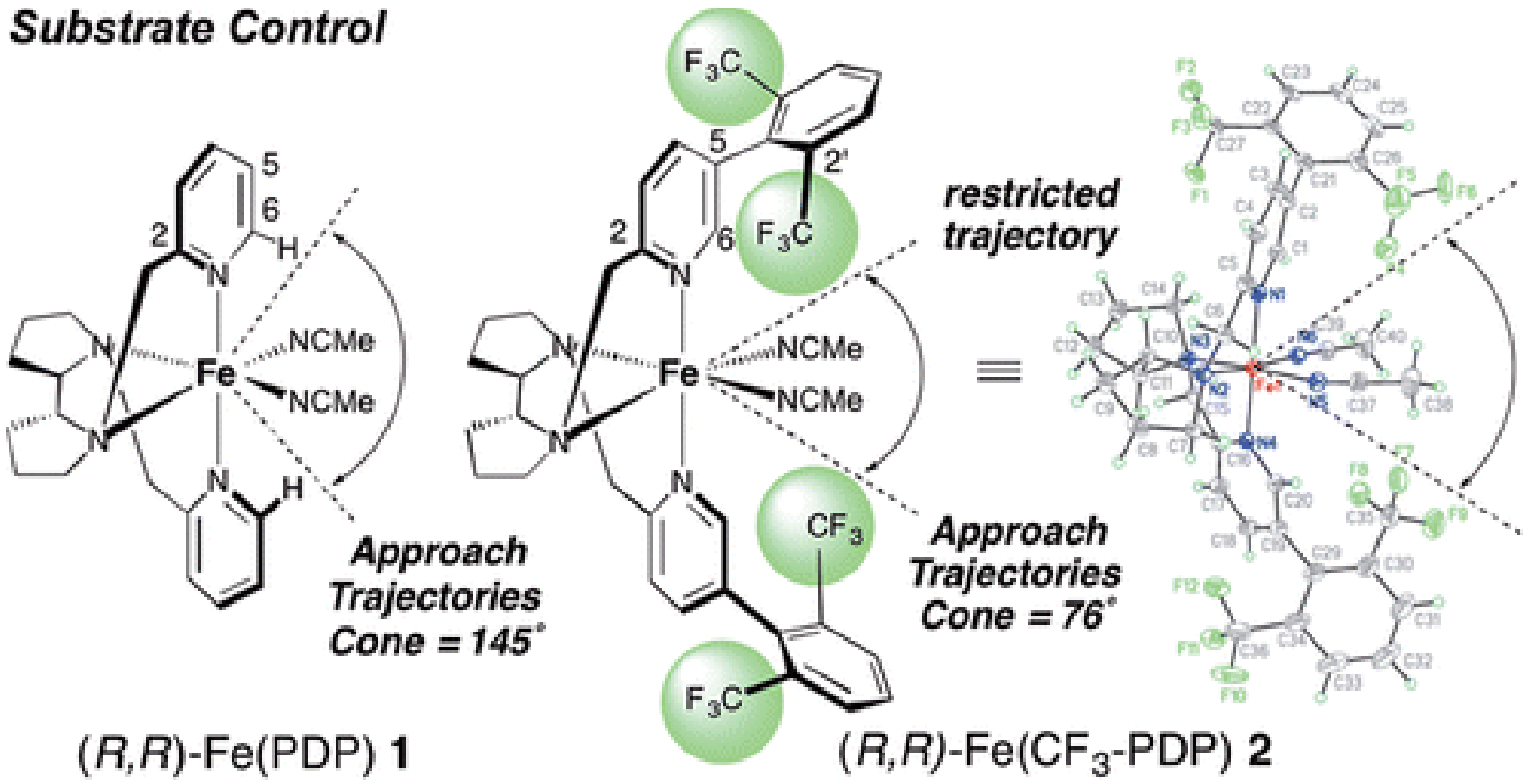
Use of bulky reagents

→ Sterically accesible C-H bonds are likely to be functionalized.

Merit
It is possible to functionalize innately less reatctive C-H bonds.

Problem
It is necessary to strengthen the activity of the reagent because the active site is hindered.

Strategy②-2: LSF by bulky reagents

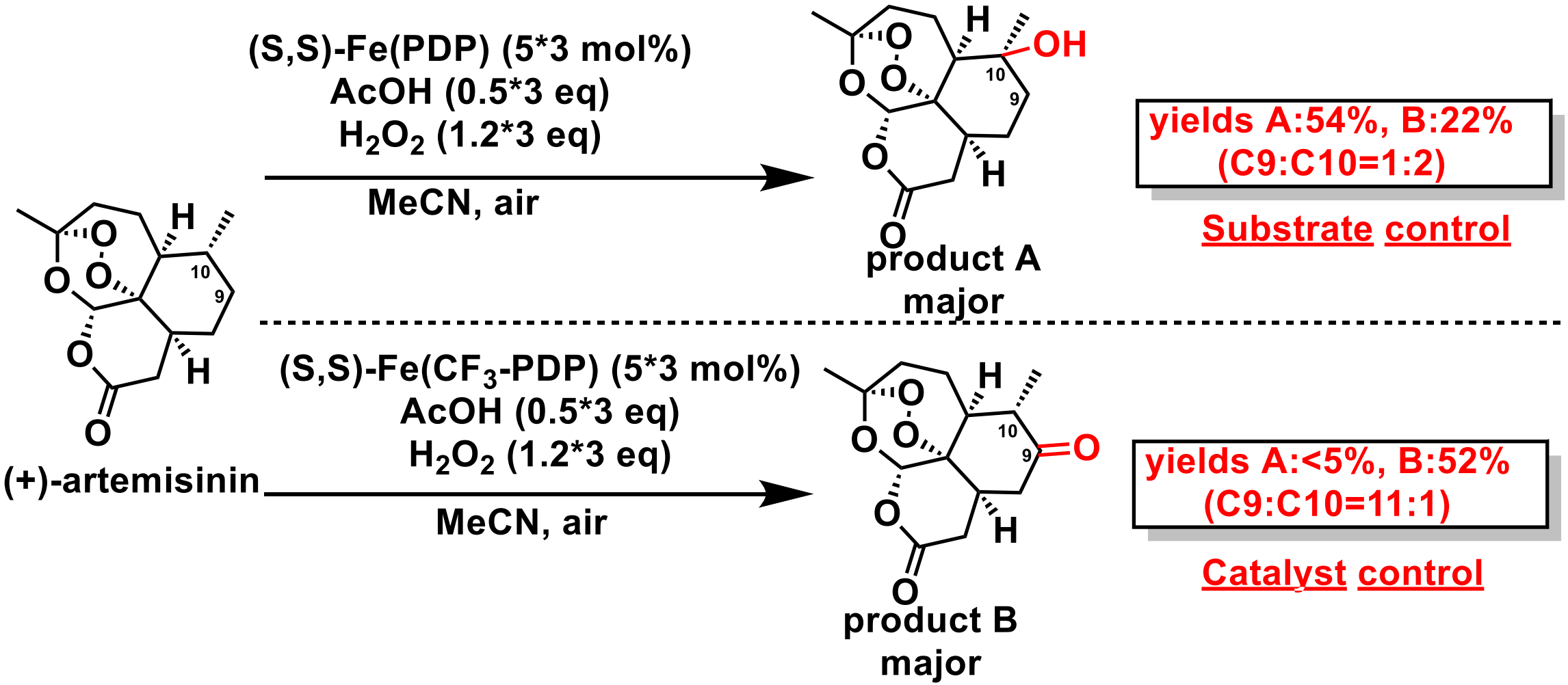


Gormisky, P. E.; White, M. C., *J. Am. Chem. Soc.*, **2013**, *135*, 14052

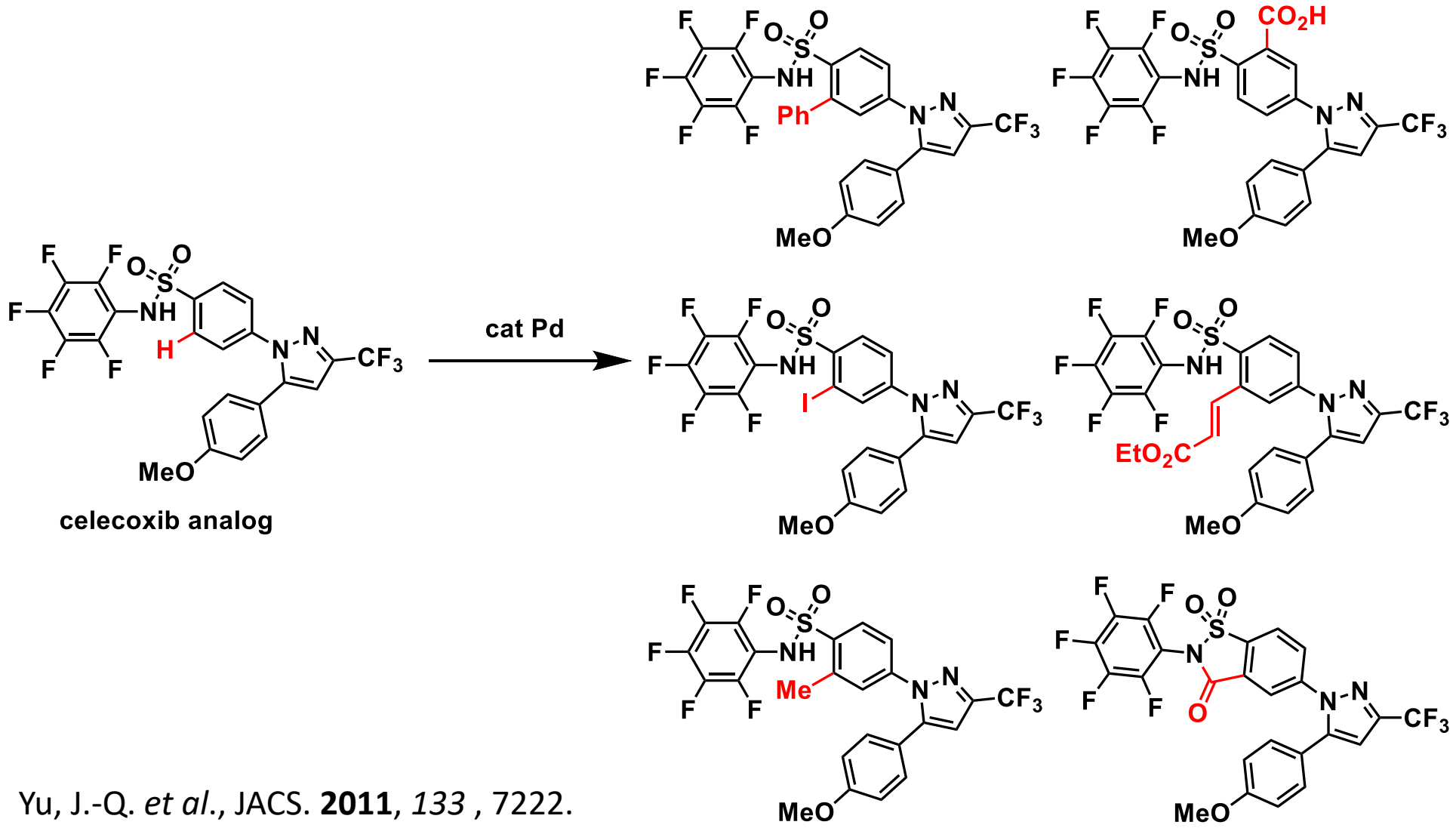
Approach trajectories cone became narrow.

➔ Fe(CF_3-PDP) is more bulky than Fe(PDP).

Strategy②-3: LSF by bulky reagents



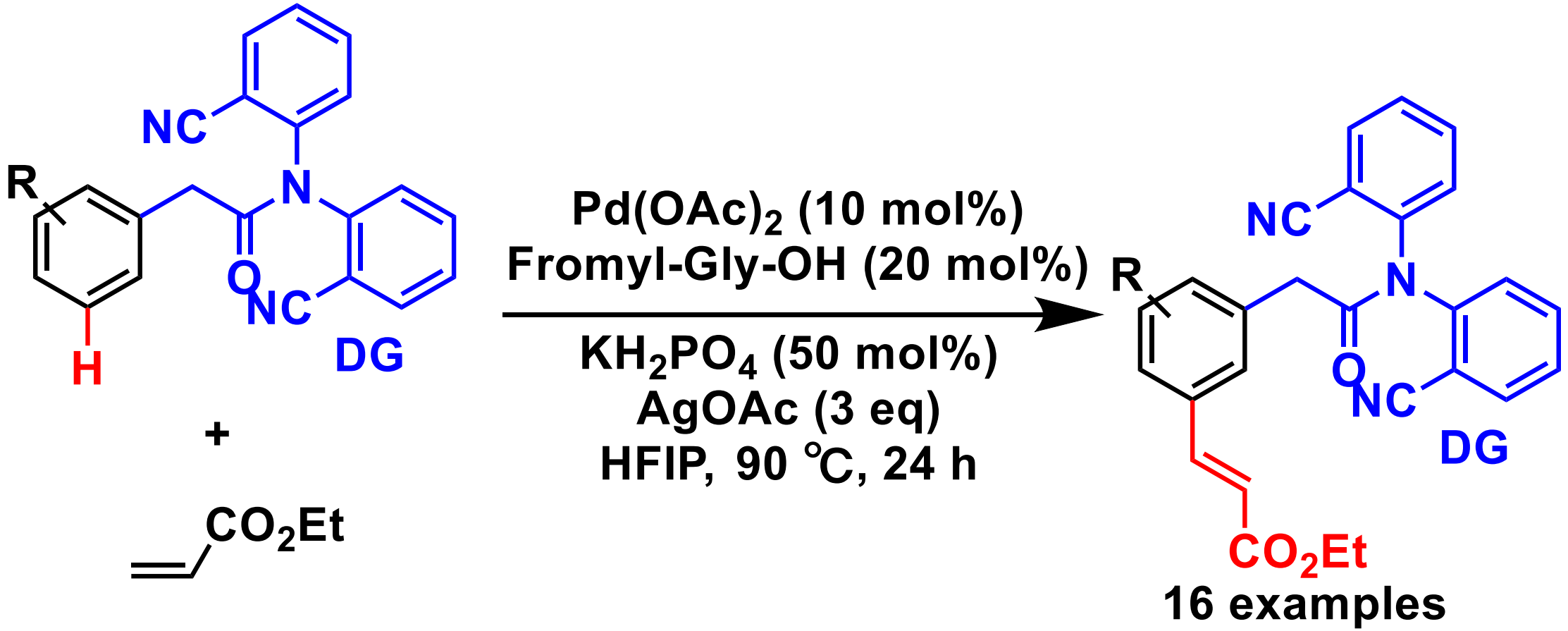
Strategy③-1: Guided by directing groups (DG)



Yu, J.-Q. *et al.*, JACS. **2011**, *133* , 7222.

Use of DG → Regioselectivity was obtained.

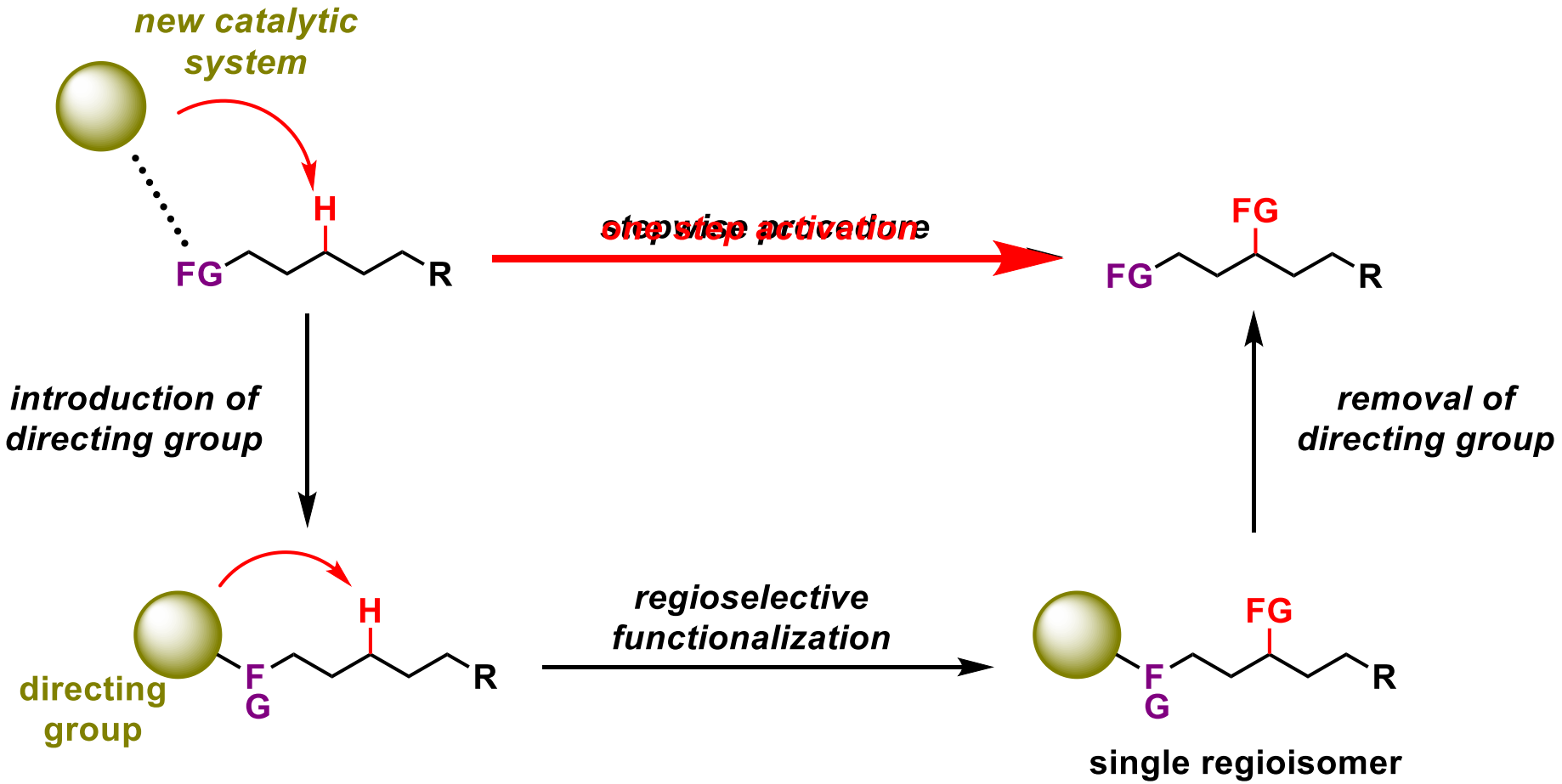
Strategy③-2: Guided by directing groups (DG)



Deng, Y.; Yu, J.-Q., *Angew. Chem. Int. Ed.*, **2015**, *54*,888.

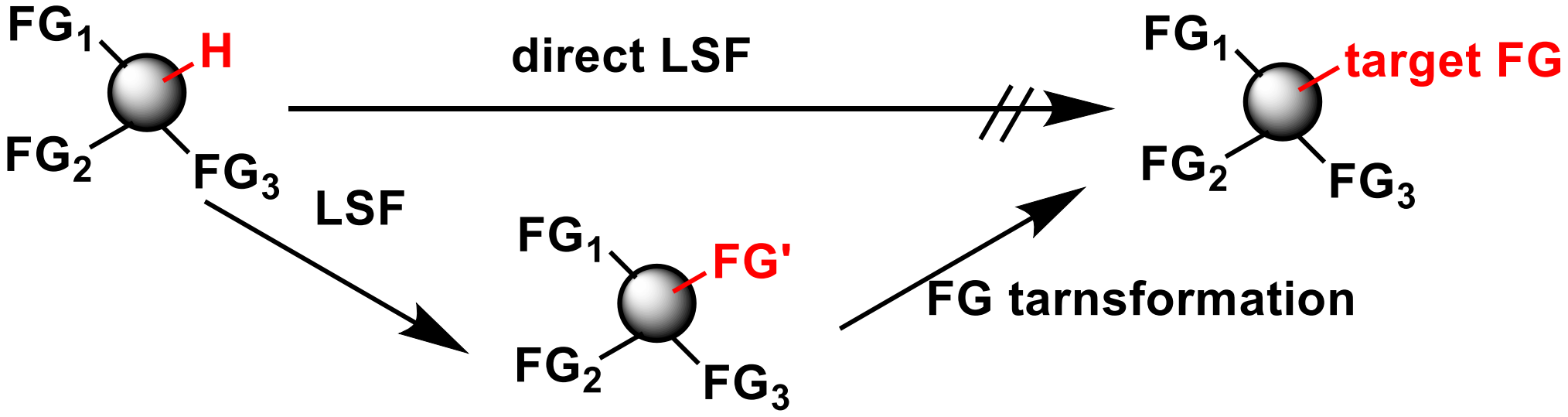
Other locations (for example, meta and para) selective reaction is limited.

Strategy③-3: Guided by directing groups (DG)



✓ 1. Stepwise procedure
✓ Usage of ubiquitous FG as DG is desirable.
✓ 2. Usage of stoichiometric amount of DG

Strategy④-1: Use of other FG regioselectivity

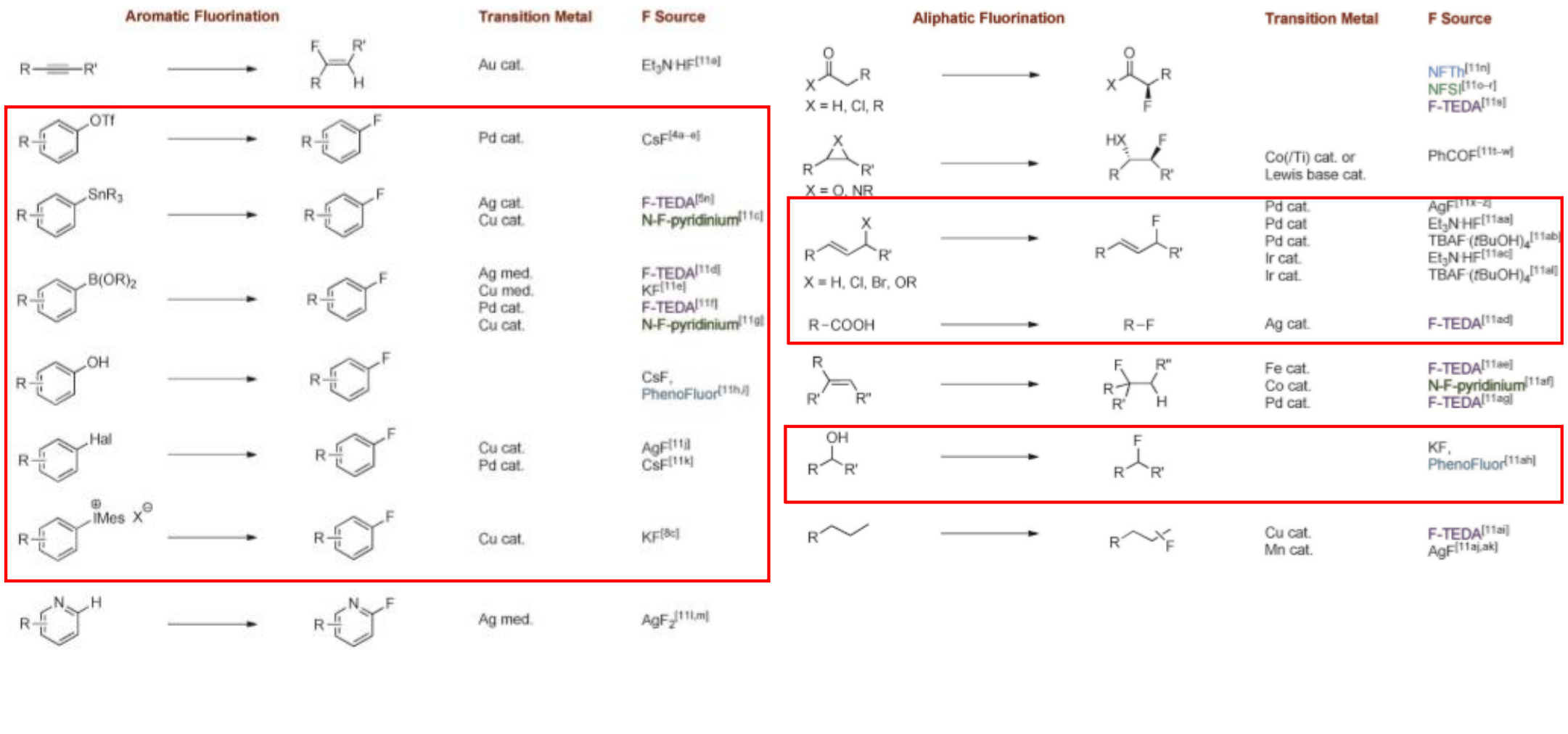


FG' = B, Si, halogen, Sn, ----

Merit
It is not necessary to transform regioselectively from other FGs to target FG.
Strategies of the introduction of target FGs increase.

Problem
Synthetic steps increase because of stepwise synthesis.

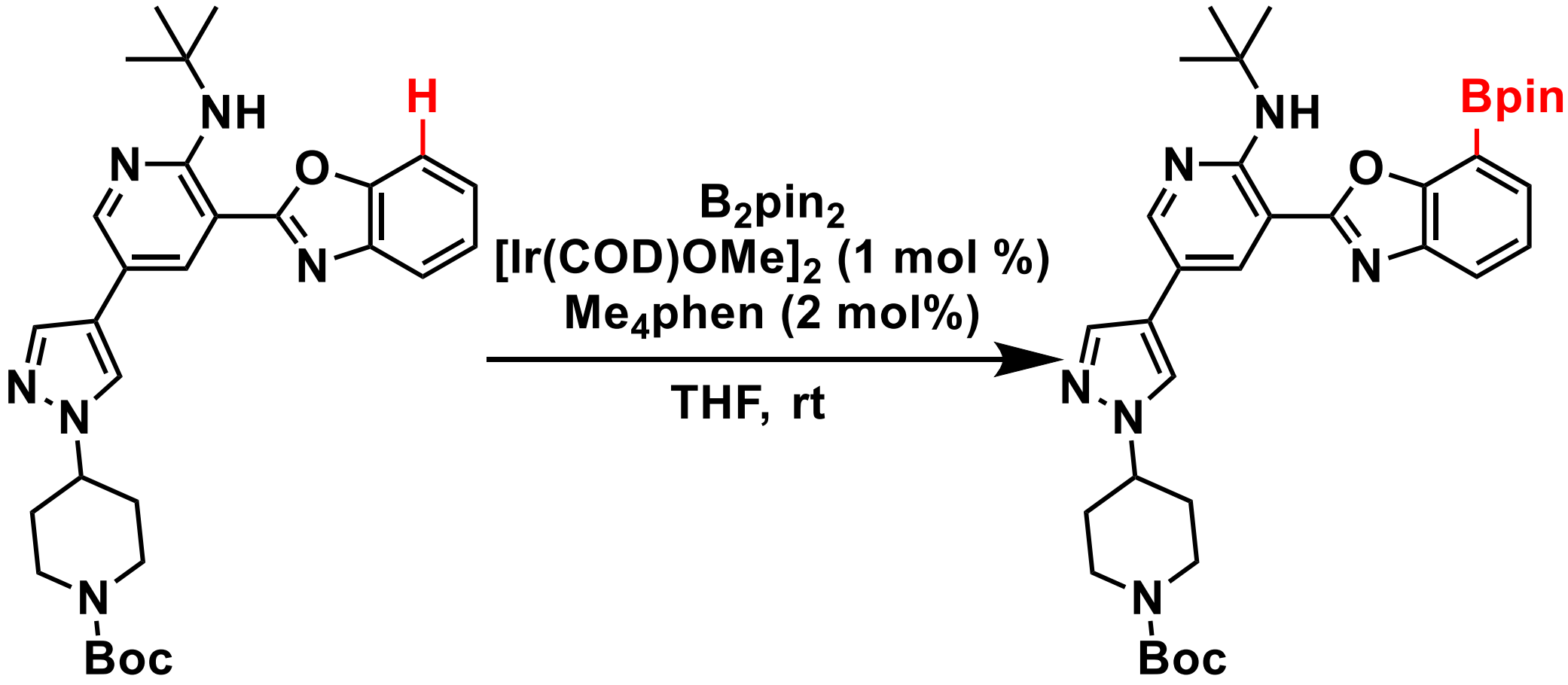
Strategy④-2: Use of other FG regioselectivity



C. Neumann, T. Ritter, *Angew. Chem. Int. Ed.*, **2015**, *54*, 3216

To introduce F at the late stages, other FGs are often used.

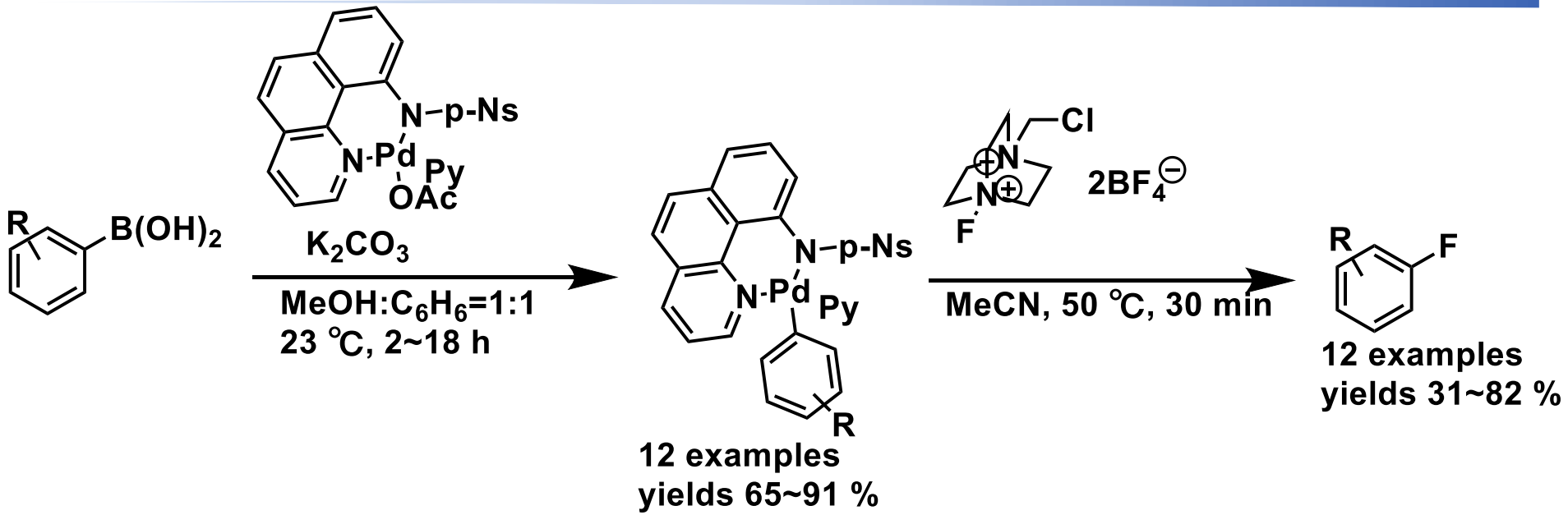
Strategy④-3: C-H → C-Bpin → C-F



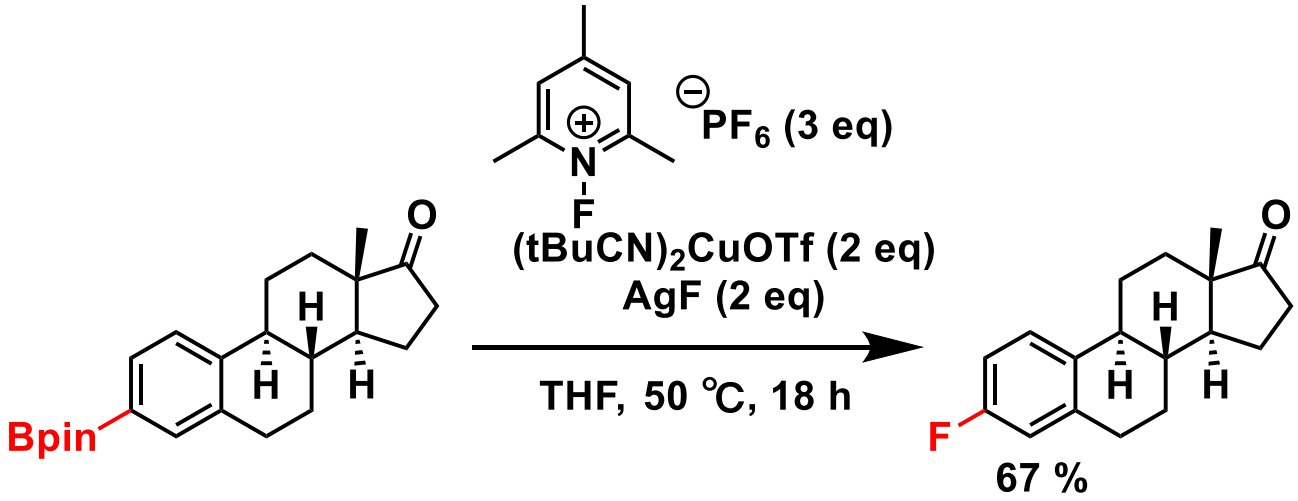
Larsen, M. A.; Hartwig, J. F., *J. Am. Chem. Soc.*, **2014**, *136*, 4287.

Some regioselective borylation reactions can use in LSF.

Strategy④-4: C-H → C-Bpin → C-F



T. Furuya; H. M. Kaiser; T. Ritter, *Angew. Chem. Int. Ed.*, **2008**, *47*, 5993.



P. S. Fier, J. Luo, J. F. Hartwig, *J. Am. Chem. Soc.*, **2013,** *135,* 2552

Summary of section 2

1, Functionalize innately reactive C-H bonds
2, Use of bulky reagents

Merit: Functionalization is mainly one step.
Demerit: Regioselectivity highly depends on substrates and reagents.

3, Use of directing groups(DG)
4, Use of other functional groups

Merit: Regioselectivity can be reliably obtained.
Demerit: Synthesis efficacy decreases because of stepwise process.

3. Application of LSF: Drug discovery

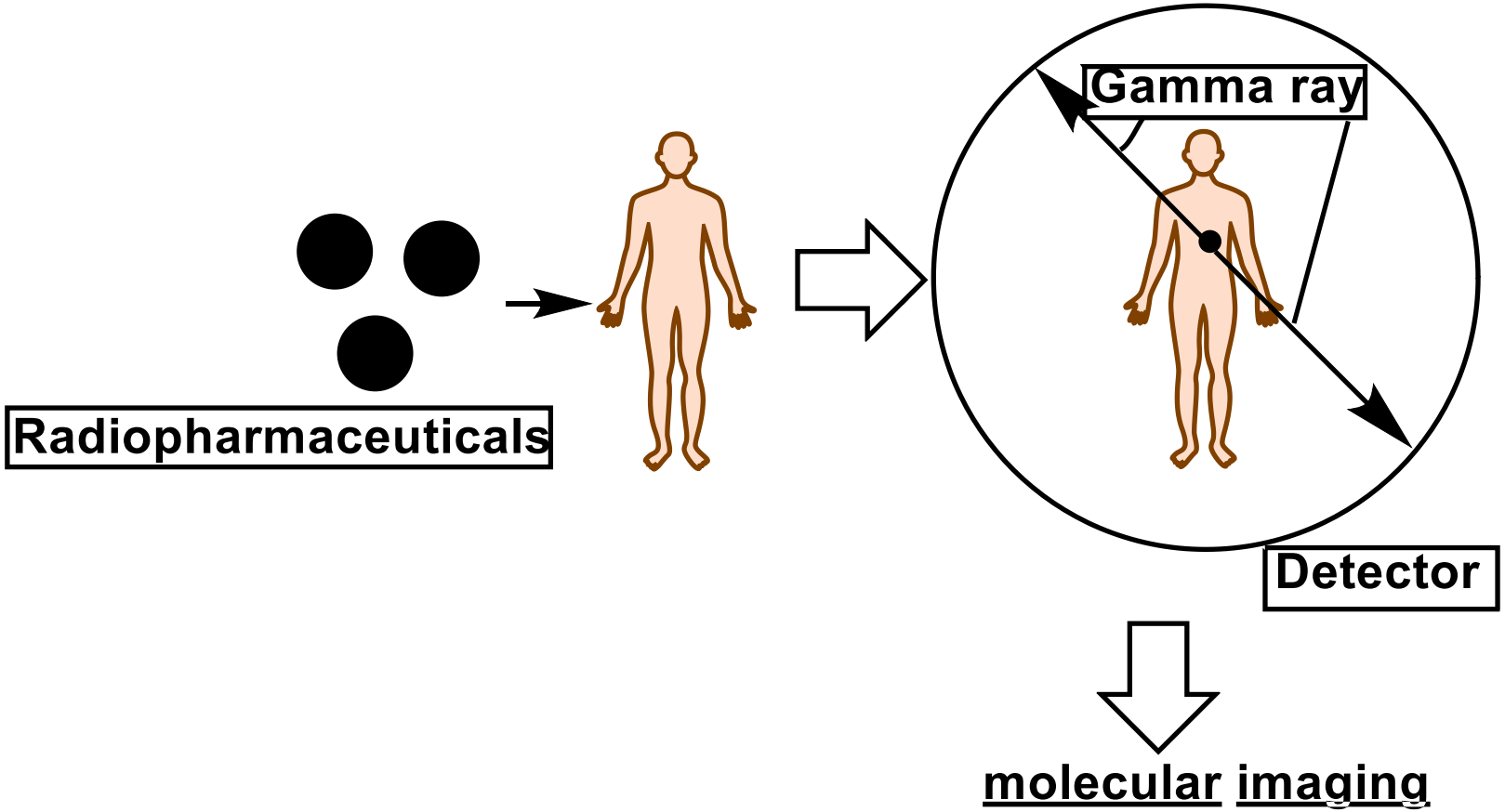
Application of LSF to drug discovery

1. Development of positron emmision tomography (PET) tracer

2. Lead optimization
   structure-activity relationship (SAR) and structure-property relationship (SPR)

LSF is used in the development of PET tracer (1)

Image of PET inspection



^{11}C, ^{13}N, ^{15}O and ^{18}F are used for PET

LSF is used in the development of PET tracer (2)

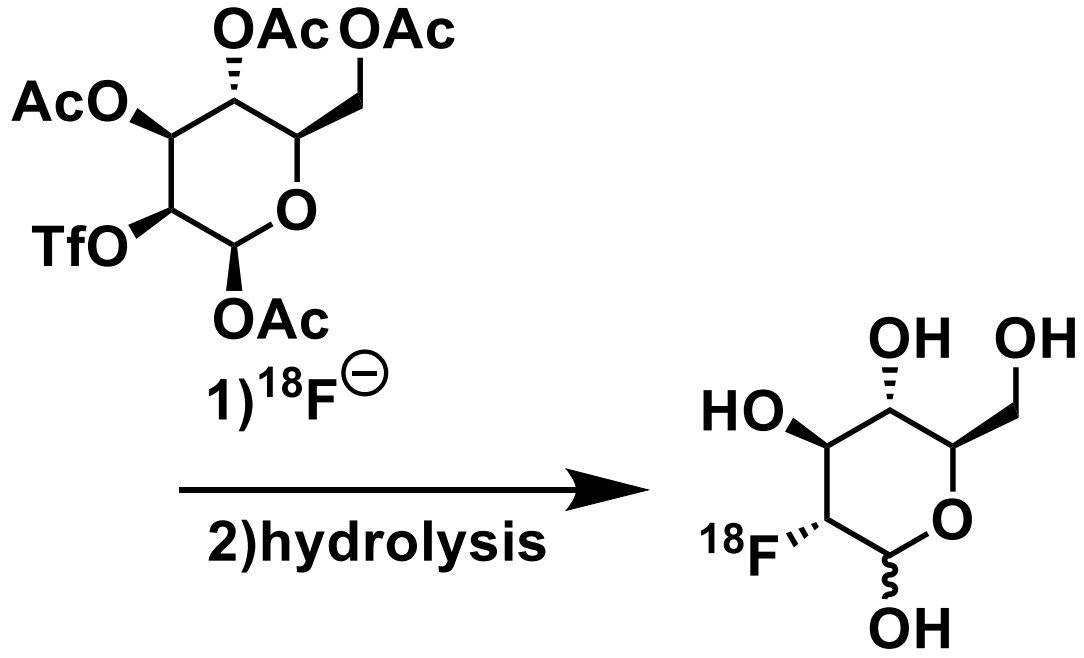
Generation of ^{18}F source

^{20}Ne —(Deuteron irradiation; using cyclotron)→ $^{18}F_2$

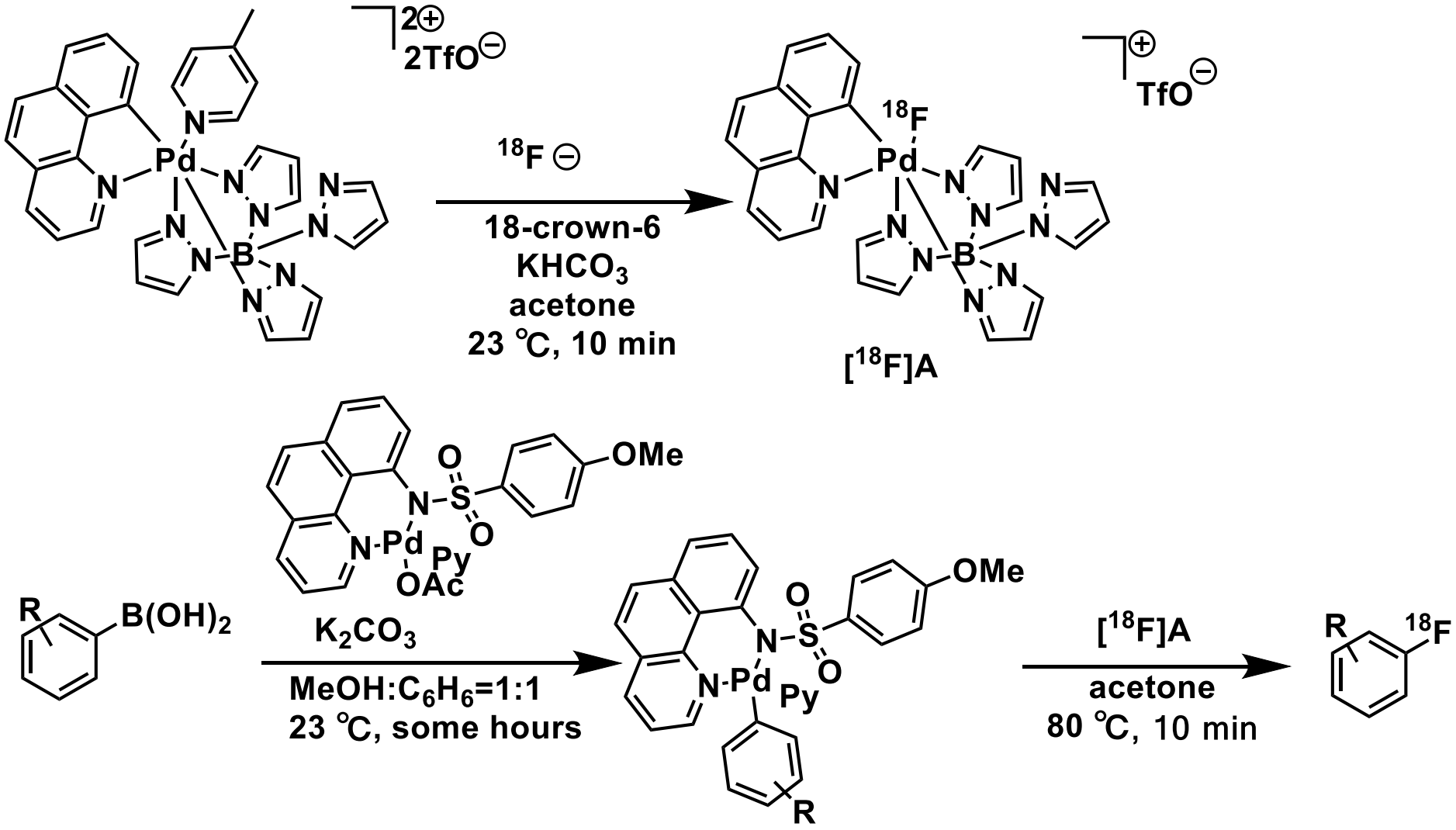
$H_2{}^{18}O$ —(Proton irradiation; using cyclotron)→ $^{18}F^{\ominus}$

$^{18}F_2$ and $^{18}F^{\ominus}$ can be obtained.

Synthesis of ^{18}F-FDG

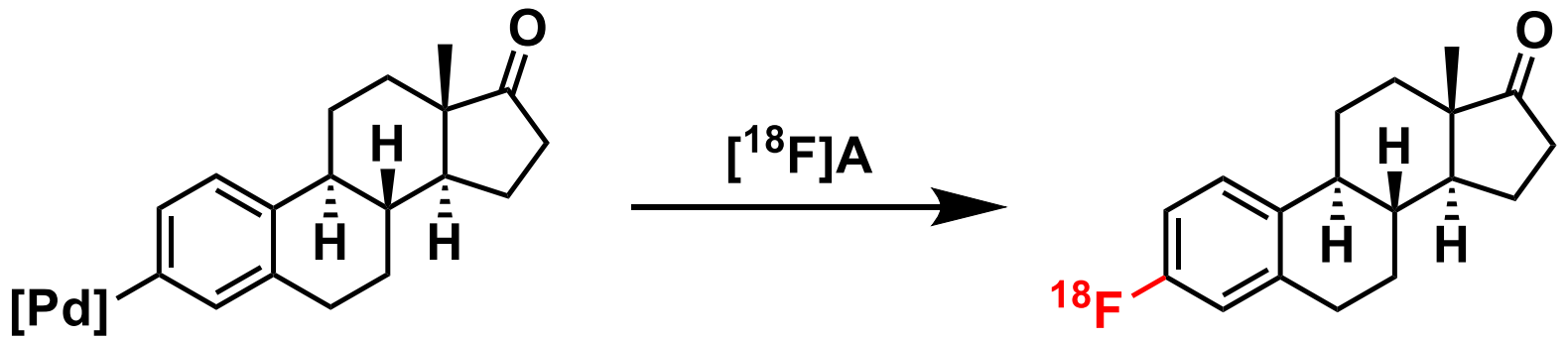


LSF is used in the development of PET tracer (3)



E. Lee, A. S. Kamlet, D. C. Powers, C. N. Neumann, G. B. Boursalian, T. Furuya, D. C. Choi, J. M. Hooker, T. Ritter, *Science*, **2011**, *334*, 639

LSF is used in the development of PET tracer (4)



radiochemical yields(2steps): 33 % ± 7 %
2steps: Generation of [^{18}F]A + this step

Challenges still remain.

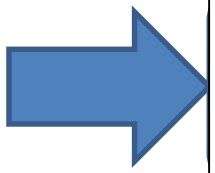
New PET tracers may be developed using LSF.
Information obtained from PET is used for drug development.

- **the selection of potential drug candidates at an earlier stage of development**
- **an understanding of a drugs mechanism of action**
- **aid in guiding dose selection**

P. W. Miller, N. J. Long, R. Vilar and A. D. Gee, *Angew. Chem., Int. Ed.*, **2008,** *47*, 8998

LSF is used in the lead optimization (1)

For the success of lead optimization



The construction of structure-activity relationship (SAR) and structure-property relationship (SPR) are essential

<u>LSF contributes to rapid development of derivatives, SAR and SPR.</u>

LSF is used in the lead optimization (2)

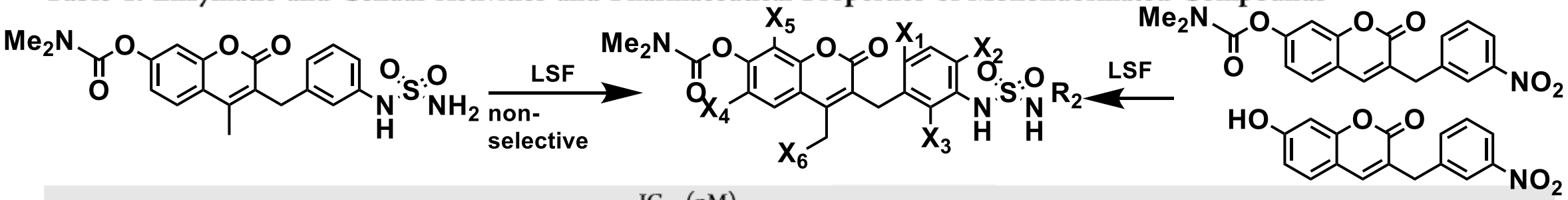


Table 1. Enzymatic and Celluar Activities and Pharmaceutical Properties of Monofluorinated Compounds

								IC$_{50}$ (nM)						
compd	X_1	X_2	X_3	X_4	X_5	X_6	R_2	HCT116	MEK1	C-Raf	solubility (μg/mL)	CL human (μL/min/mg)	PAMPA (10^{-6} cm/s)	AUC $_{po}$[a] (μM·h)
1a	H	H	H	H	H	H	H	95	230	530	32	6	6	104[c]
1b	F	H	H	H	H	H	H	950	940	830	9	6	5	176
1c	H	F	H	H	H	H	H	610	44	1100	37	6	6	ND
1d	H	H	F	H	H	H	H	18	53	13	273	6	6	40[b,c]
1e	H	H	H	F	H	H	H	87	110	180	114	6	5	61[b]
1f	H	H	H	H	F	H	H	140	240	120	ND	ND	ND	ND
1g	H	H	H	H	H	F	H	200	60	220	14	7	4	84
8a	H	H	H	H	H	H	Me	24	110	300	32	20	6	78[c]
8b	F	H	H	H	H	H	Me	550	2900	2400	51	22	5	75
8d	H	H	F	H	H	H	Me	9	38	8	81	13	5	70[c]
8e	H	H	H	F	H	H	Me	22	64	ND	55	13	5	99
8g	H	H	H	H	H	F	Me	30	66	120	72	22	4	86

[a]Compounds were evaluated in 24 h exposure studies in mice at 100 mg/kg and formulated as solutions of 5% DMSO, 5% Cremophor EL, 15% PEG400, 15% HPCD, and 60% water. [b]At 50 mg/kg. [c]Sodium salt was used.

H. Iikura et al., *ACS Med. Chem. Lett.*, **2013**, *4*, 1059.

LSF is used in the lead optimization (3)

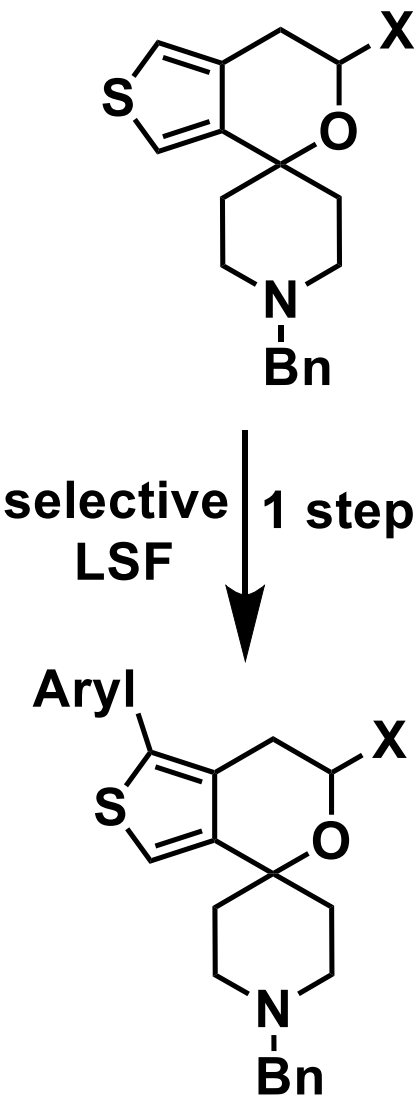
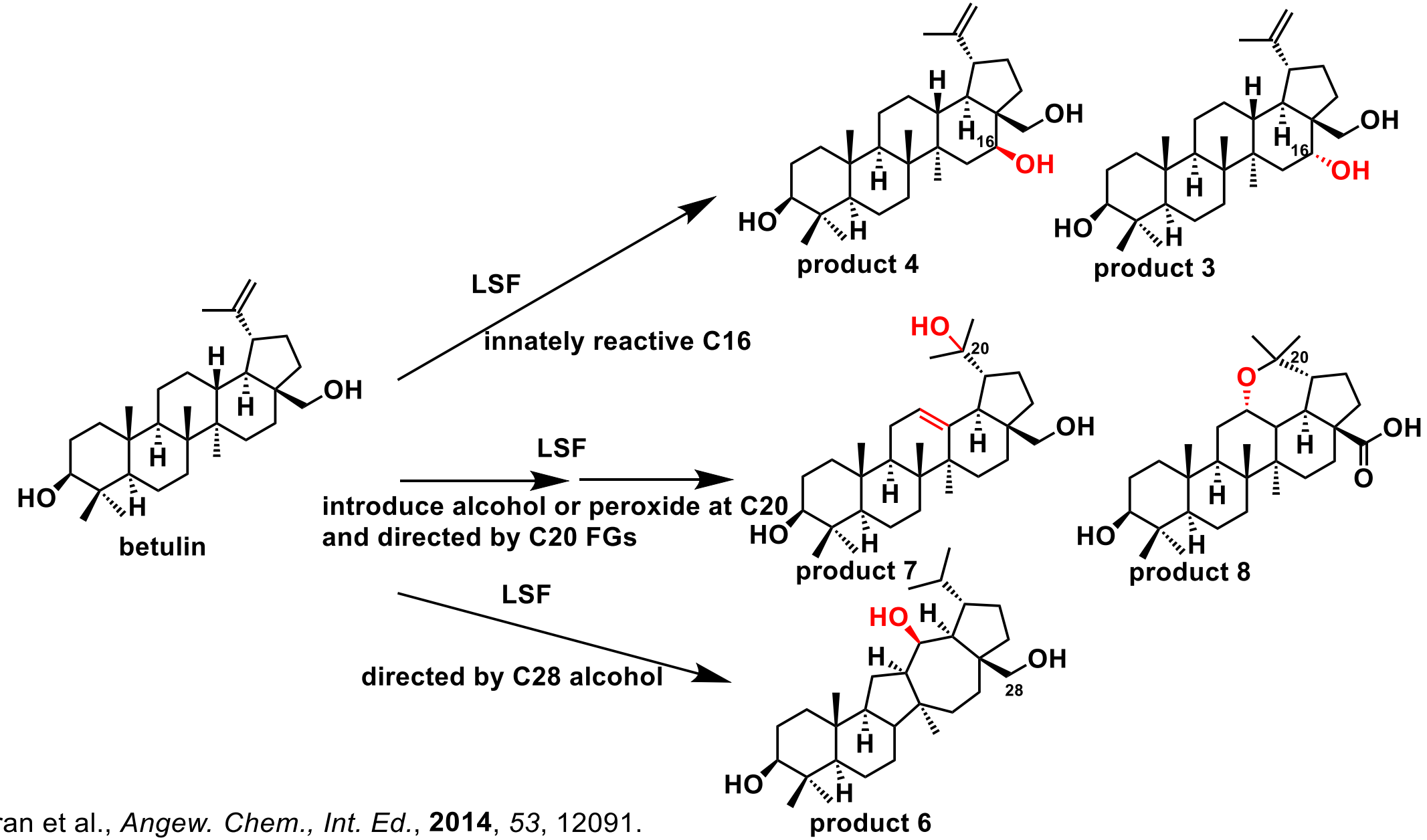


Table 3 σ_1 and σ_2 receptor affinities of the synthesized spirocyclic thiophenes and reference compounds

Compd.	X	Aryl	$K_i \pm$ SEM [nM] ($n = 3$) σ_1	σ_2	Selectivity σ_1/σ_2
1a	OCH_3	CH_3	21 ± 2.3	> 1 µM	> 47
1b	OCH_3	C_6H_5	1.5 ± 0.08	> 1 µM	> 660
2	OCH_3	H	0.32 ± 0.10	> 1 µM	> 3125
3a	H	C_6H_5	4.5 ± 2.9	> 1 µM	> 222
3b	H	*p*-$MeOC_6H_4$	1.5 ± 0.54	926	617
3c	H	*p*-MeC_6H_4	3.6 ± 0.40	1.6 µM	444
3d	H	*p*-$NO_2C_6H_4$	1.7 ± 0.79	> 1 µM	> 588
3e	H	*p*-CNC_6H_4	3.4 ± 0.90	> 1 µM	> 294
3f	H	1-naphthyl	4.0 ± 1.9	51	13
4a	OCH_3	C_6H_5	1.0 ± 0.40	>1 µM	> 1000
4b	OCH_3	*p*-$MeOC_6H_4$	2.2 ± 0.13	751	341
4c	OCH_3	*p*-MeC_6H_4	2.0 ± 0.81	> 1 µM	> 500
4d	OCH_3	*p*-$NO_2C_6H_4$	1.0 ± 0.16	> 1 µM	> 1000
4e	OCH_3	*p*-AcC_6H_4	1.6 ± 0.86	> 1 µM	> 625
4f	OCH_3	*p*-CNC_6H_4	0.25 ± 0.14	923	3692
4g	OCH_3	*p*-$CF_3C_6H_4$	5.7 ± 2.3	>1 µM	> 175
4h	OCH_3	1-naphthyl	5.0 ± 0.50	2.1 µM	420
4i	OCH_3	3-pyridyl	2.2 ± 0.42	> 1 µM	> 450
4j	OCH_3	*p*-biphenyl	30 ± 18	> 1 µM	> 33
5	H	H	0.35 ± 0.06	230	657
6	OCH_3	H	0.22 ± 0.06	806	3664
13	OH	H	3.2 ± 0.41	266	83
14	$HC^3{=}C^4H$	H	1.9 ± 0.66	84.6 ± 25.4	45
haloperidol			3.9 ± 1.5	78 ± 2.0	20
di-*o*-tolylguanidine			61 ± 8	42 ± 15	0.7

K. Itami, B. Wünsch et al., *Org. Biomol. Chem.*, **2011**, *9*, 8016.

LSF is used in the lead optimization (4)



P. S. Baran et al., *Angew. Chem., Int. Ed.*, **2014**, *53*, 12091.

LSF is used in the lead optimization (5)

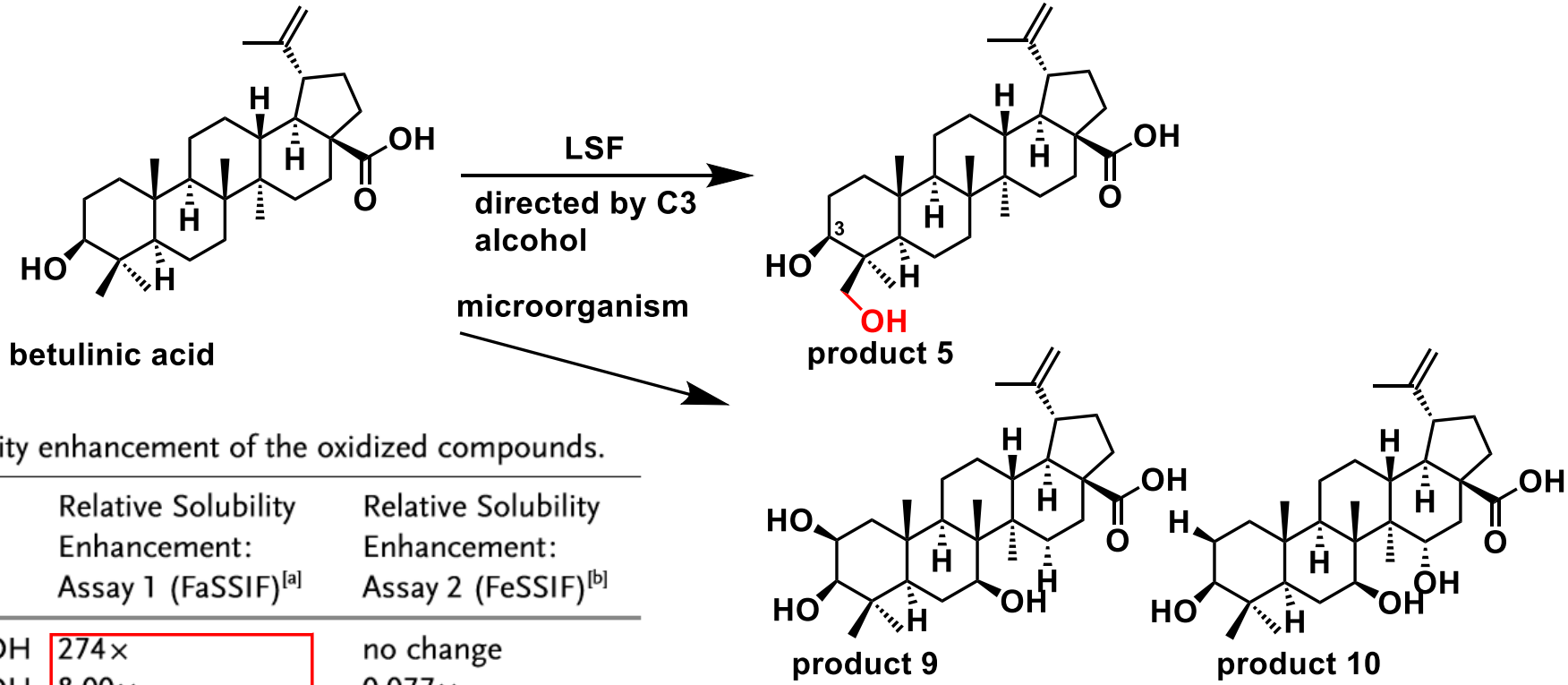


Table 1: Relative solubility enhancement of the oxidized compounds.

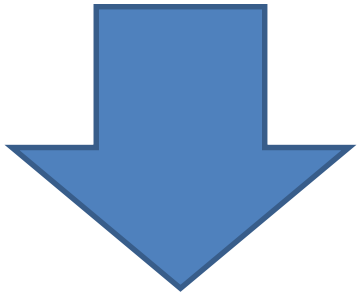
Entry	Substrate	R^1	Relative Solubility Enhancement: Assay 1 (FaSSIF)[a]	Relative Solubility Enhancement: Assay 2 (FeSSIF)[b]
1	**3**	CH_2OH	274×	no change
2	**4**	CH_2OH	8.00×	0.077×
3	**7**	CH_2OH	121×	0.357×
4	**6**	CH_2OH	no change	0.077×
5	**5**	CO_2H	0.056×[c]	0.115×[c]
6	**8**	CO_2H	0.112×[c]	17.4×[c]
7	**9**	CO_2H	0.019×[c]	3.38×[c]
8	**10**	CO_2H	0.002×[c]	0.462×[c]

[a] Solubility ratio substrate/**1** in the fasted state simulated intestinal fluid. [b] Solubility ratio substrate/**1** in the fed state simulated intestinal fluid. [c] Solubility ratio substrate/**2**. R^1 refers to the position shown in the structure of Figure 5 (C17).

Summary of section 3

1. Rapid synthesis of derivatives
   → SAR and SPR

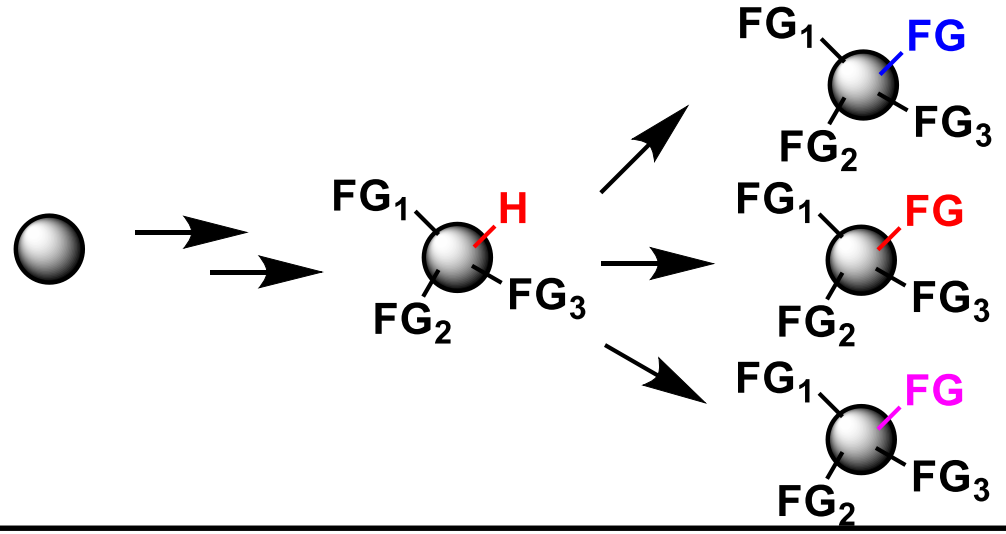
2. Synthesis of molecules which cannot obtained by conventional method
   → PET tracer



LSF contributes to drug development.

4. Summary

Summary of today's literature seminar



LSF contributes to various fields including drug discovery.

LSF has several challenges including regioselectivity.

The reactions used in LSF are limited and have limited substrate scopes.

It is necessary to develop new excellent reactions which can be used in LSF.
They contribute not only to chemistry but also to various fields.