Anion Phase-Transfer Catalysis Applied to the Direct Enantioselective Fluorinative Dearomatization of Phenols

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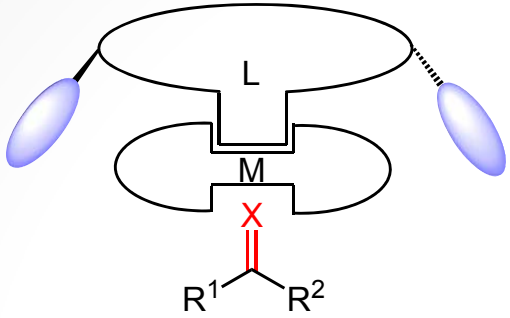
Checker : Ran-Ning Guo

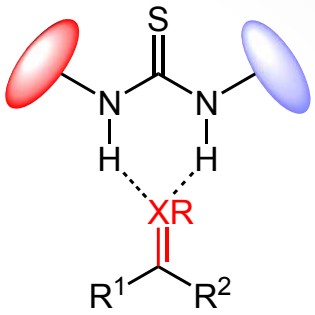
Date: 04/02/2013

Toste, F. D. *et al.*
J. Am. Chem. Soc. **2013**, *135*, 1268−1271.

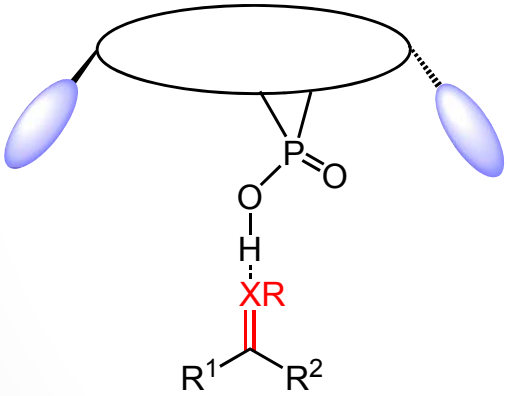
Representative Asymmetric Activation Modes



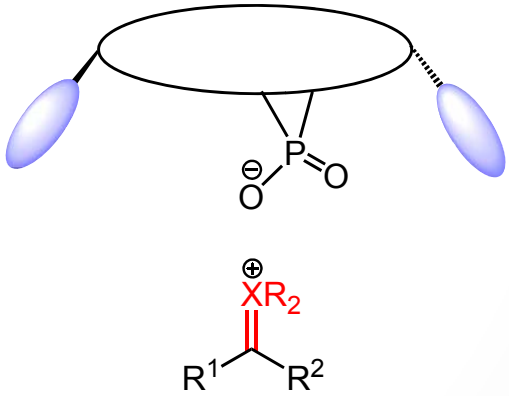
Coordinative interaction
Lewis acid catalysis



Double hydrogen-bonding interaction
Hydrogen-bonding catalysis



Single hydrogen-bonding interaction
Brønsted acid catalysis

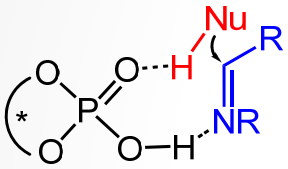


Electrostatic interaction only
Chiral anion catalysis

Toste, F. D. *et al*. *Nature Chem*. **2012**, *4*, 603-614.

Anion Phase-Transfer Catalysis

Chiral Phosphoric Acid Catalysis

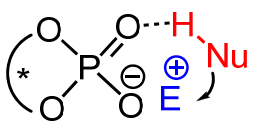


H-Bond

Electrophile latent until protonated

Limited to reactive nucleophiles

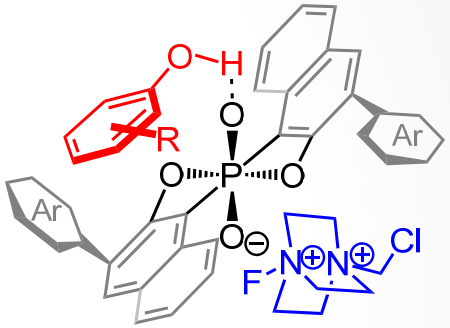
Chiral Anion Phase Transfer Catalysis



Ion Pair

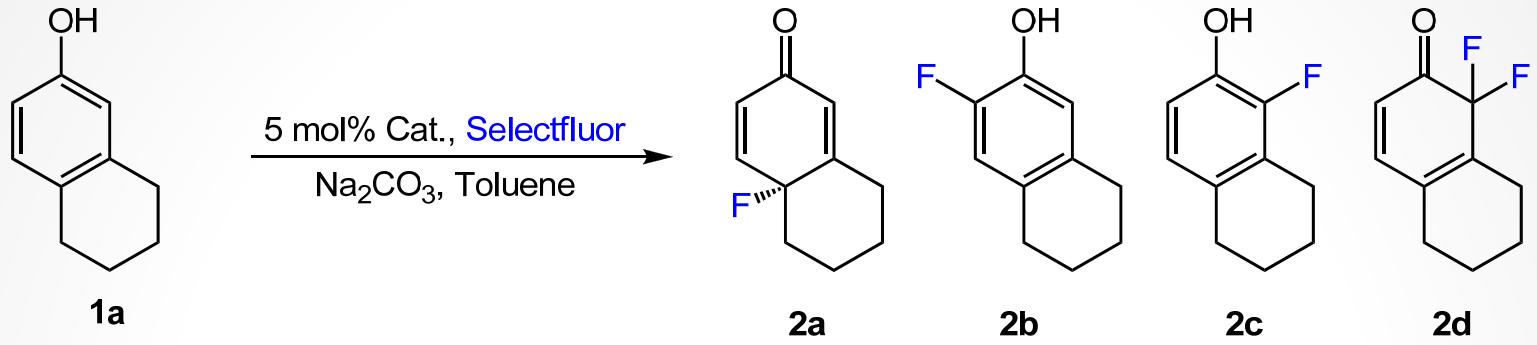
Electrophile latent until solubilized

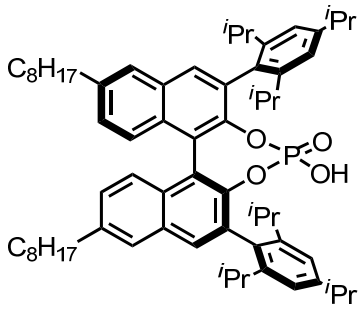
Nucleophile scope expanded?



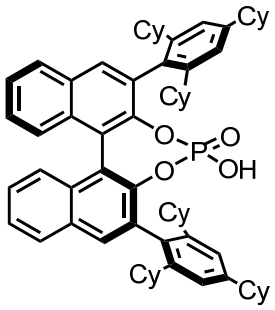
Interaction of non-symmetrical phenol with catalyst may allow face-selective fluorinative dearomatization

Initial Findings – *para*-Fluorination

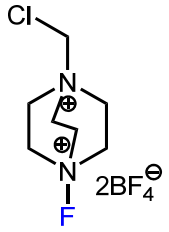




(*S*)-C_8-TRIP



(*S*)-TCYP

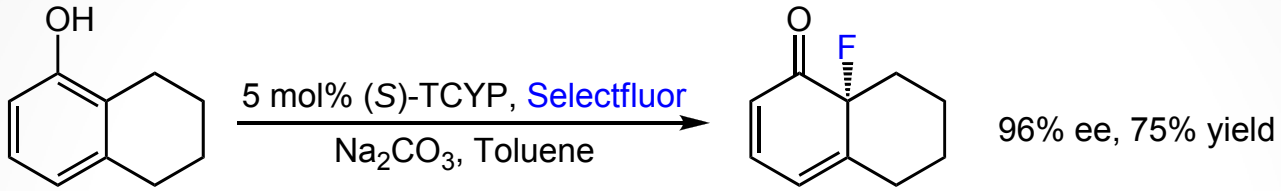


Selectfluor

Catalyst	Ratio **2a:2b:2c:2d**	Net *para*:*ortho*	Yield **2a** (% conv.)	ee **2a** (%)
(*S*)-C_8TRIP	1 : 0.28 : 0.51 : 0.15	1.1:1	41% (>95)	27
(*S*)-TCYP	1 : 0.19 : 0.51 : 0.32	1.0:1	41% (>95)	63
none	1 : 0.11 : 0.23 : 0.00	2.9:1	17% (23)	--

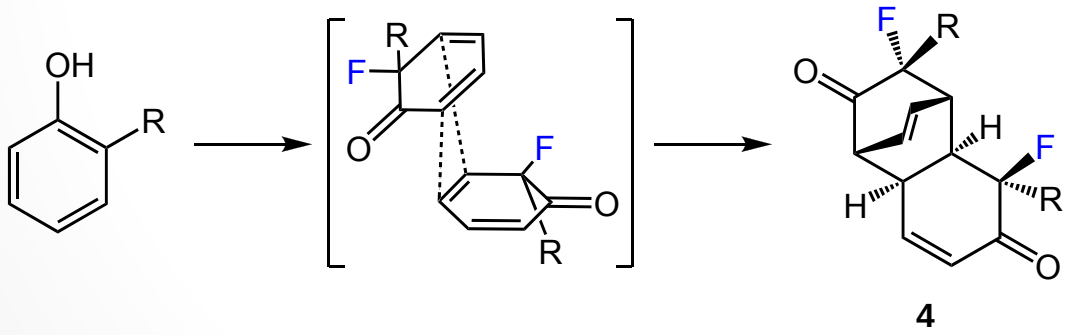
ortho-Fluorination

2,3-Disubstituted phenol



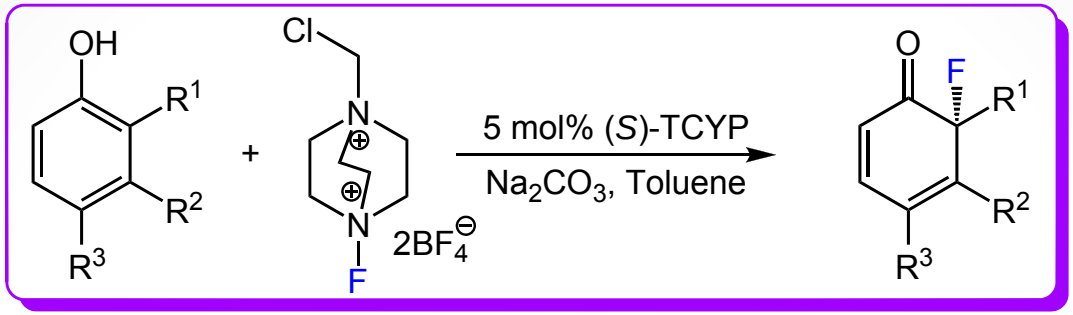
1b **3b**

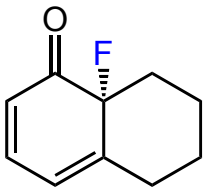
Absence of substitution at the 3-position



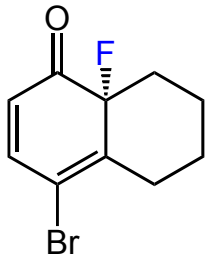
4

Scope of Fluorinative Phenols Dearomatization

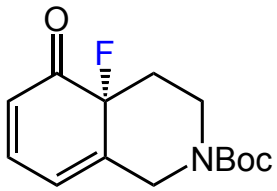




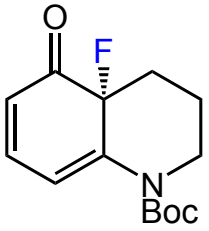
96% ee, 75% yield



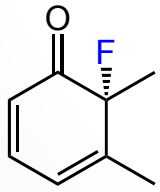
87% ee, 54% yield



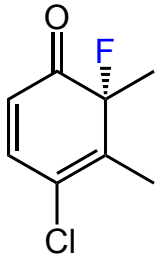
96% ee, 57% yield



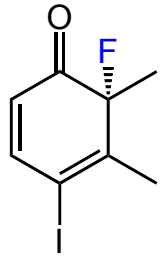
87% ee, 28% yield



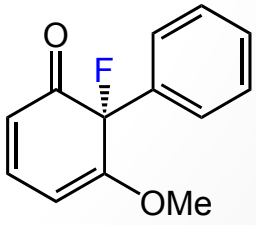
88% ee, 71% yield



90% ee, 74% yield

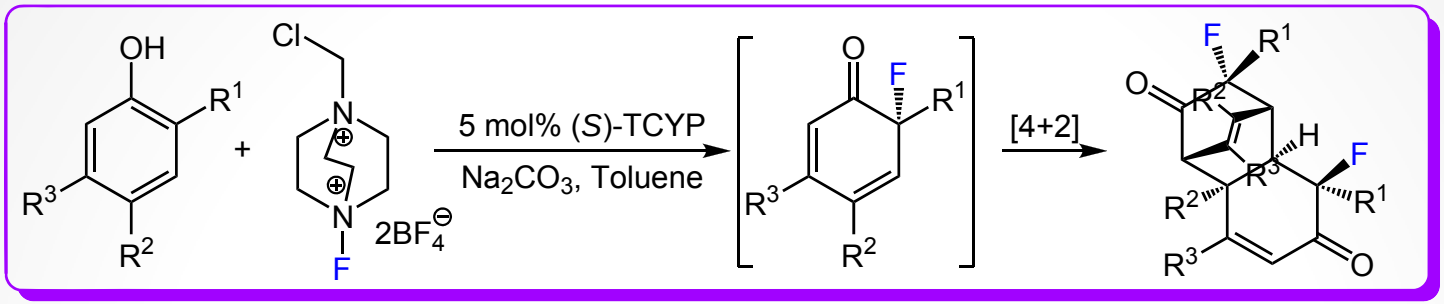


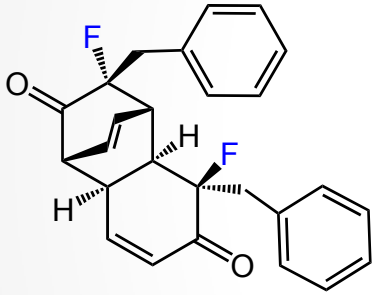
90% ee, 42% yield



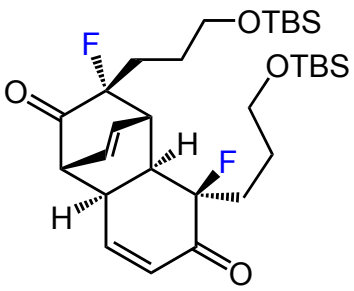
91% ee, 70% yield

Dimerization of Phenols Lacking 3-Substitution

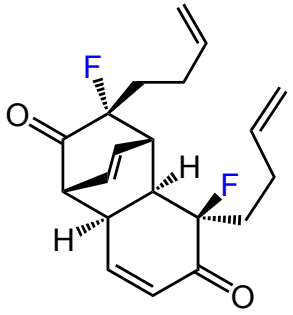




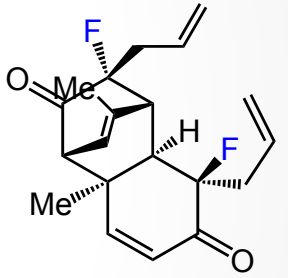
97% ee, 81% yield



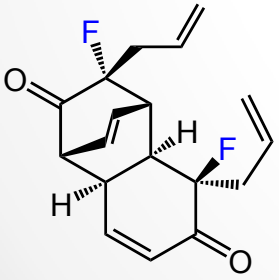
91% ee, 77% yield



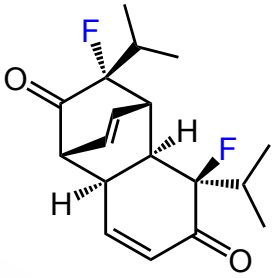
90% ee, 65% yield



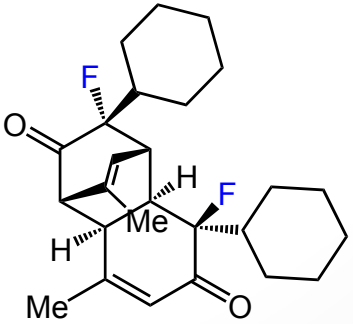
92% ee, 51% yield



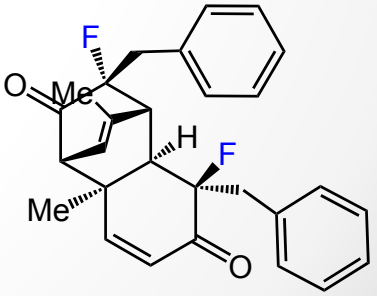
87% ee, 71% yield



91% ee, 96% yield



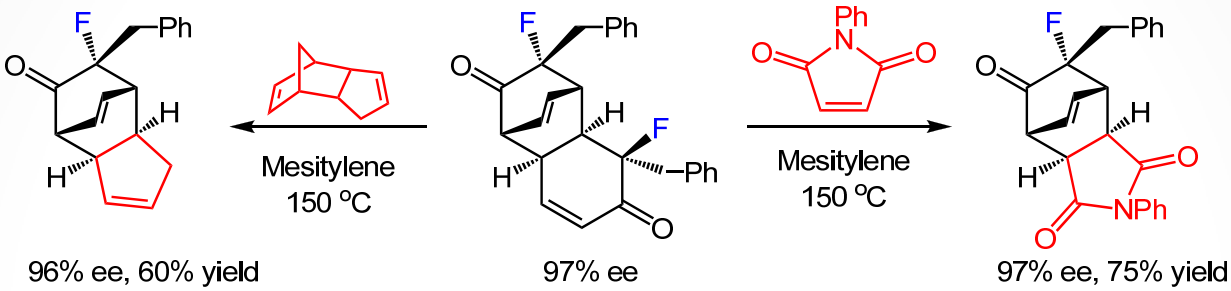
79% ee, 75% yield



90% ee, 67% yield

Further Application

Retro-[4+2]/[4+2] derivatization of products

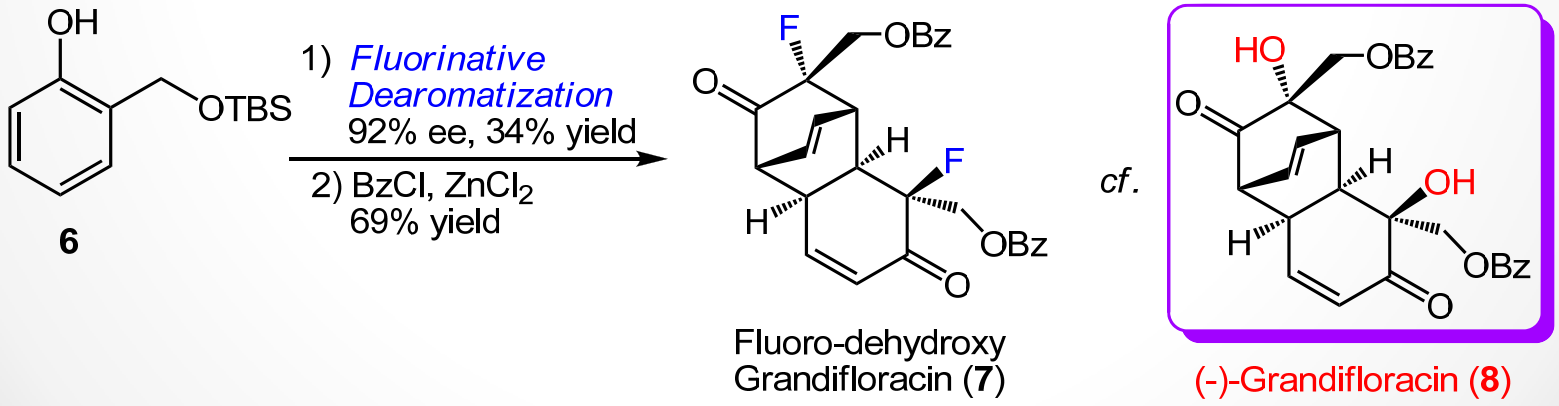


96% ee, 60% yield

97% ee

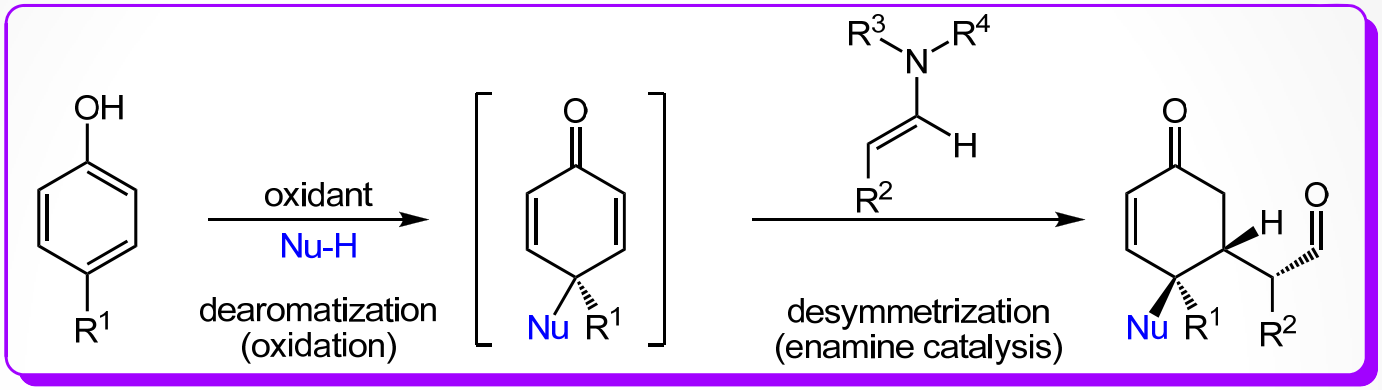
97% ee, 75% yield

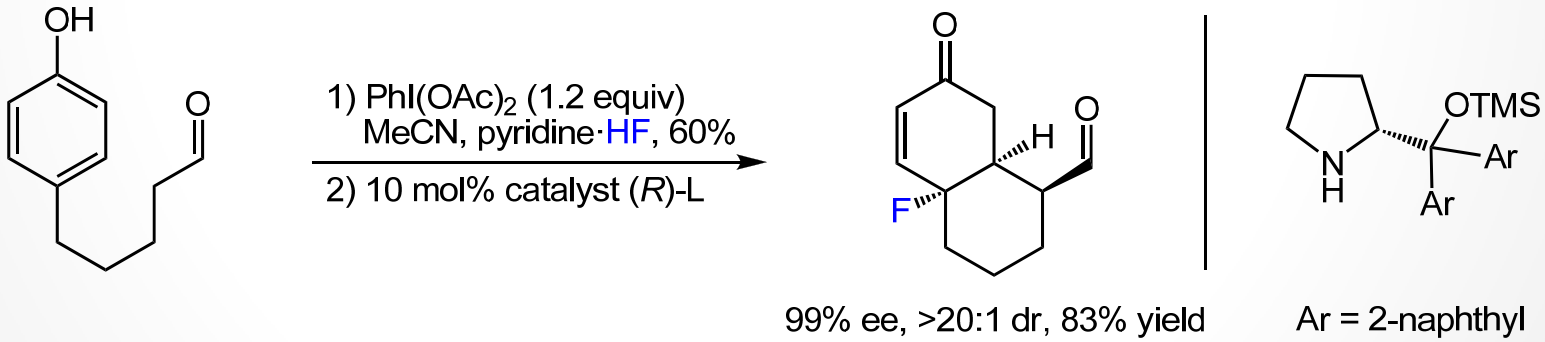
Asymmetric synthesis of Grandifloracin analogue **7**



Fluorinative Dearomatization of Phenols

Catalytic dearomatization strategy



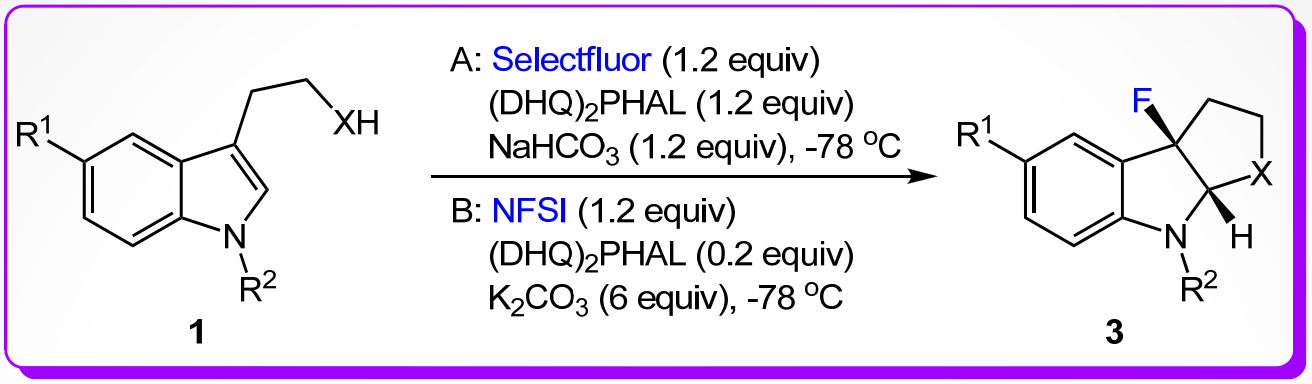


99% ee, >20:1 dr, 83% yield

Ar = 2-naphthyl

Gaunt, M. J. *et al*. *J. Am. Chem. Soc*. **2008**, *130*, 404-405.

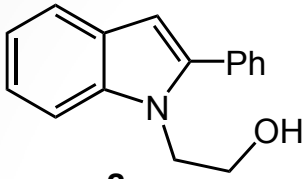
Fluorinative Dearomatization of Indole



Entry	Cond.	R^1	R^2	XH	Yield (%)	ee (%)
1	A	H	Me	OH	56	74
2	A	H	H	OH	33	40
3	A	OMe	Me	OH	90	86
4	A	OBn	Me	OH	69	84
5	A	H	Me	NHTs	54	76
6	B	H	Me	NHTs	59	64
7	A	OMe	Me	NHTs	55	78
8	B	Mes	Me	NHCOMe	65	92
9	A	H	Me	$NHCO_2Bn$	40	78
10	A	H	Me	NHBoc	67	86
11	B	H	Me	NHBoc	70	78

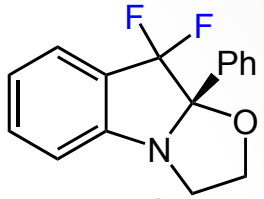
Gouverneur, V. *et al*. *Angew. Chem. Int. Ed*. **2011**, *50*, 8105–8109.

Fluorinative Dearomatization of Indole



2

Conditions A or B



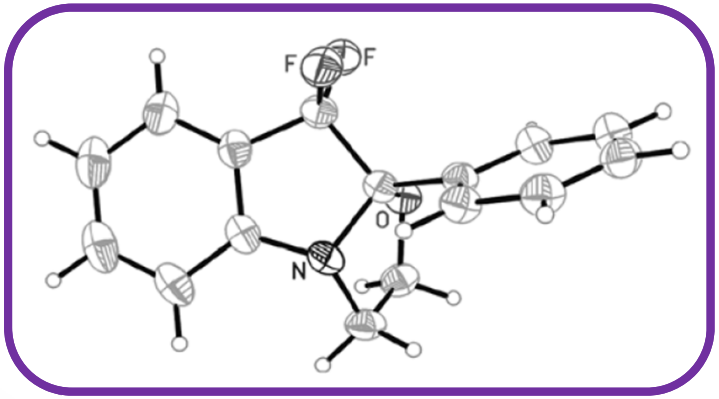
4

A: Selectfluor (1.2 equiv)
$(DHQ)_2PHAL$ (1.2 equiv)
$NaHCO_3$ (1.2 equiv), rt

50% yield
68% ee

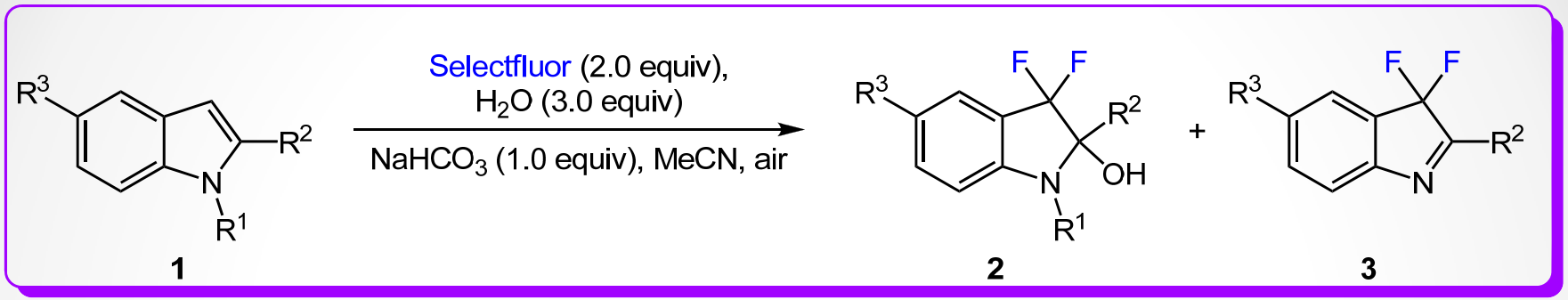
B: NFSI (1.2 equiv)
$(DHQ)_2PHAL$ (0.2 equiv)
K_2CO_3 (6 equiv), rt

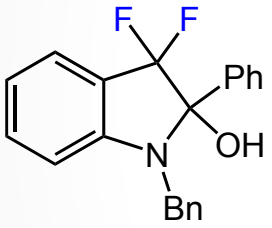
50% yield
60% ee



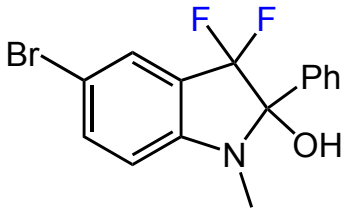
Crystal structure of **4**

Fluorinative Dearomatization of Indole

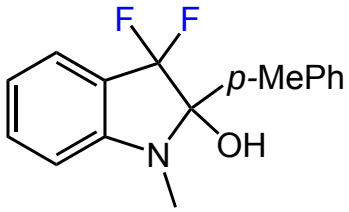




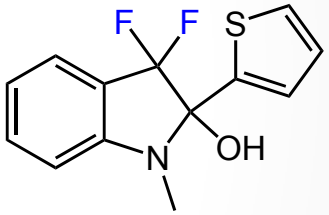
80% yield



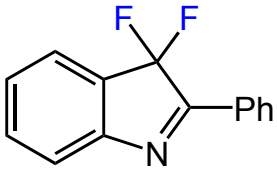
70% yield



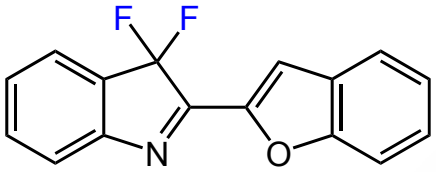
87% yield



87% yield



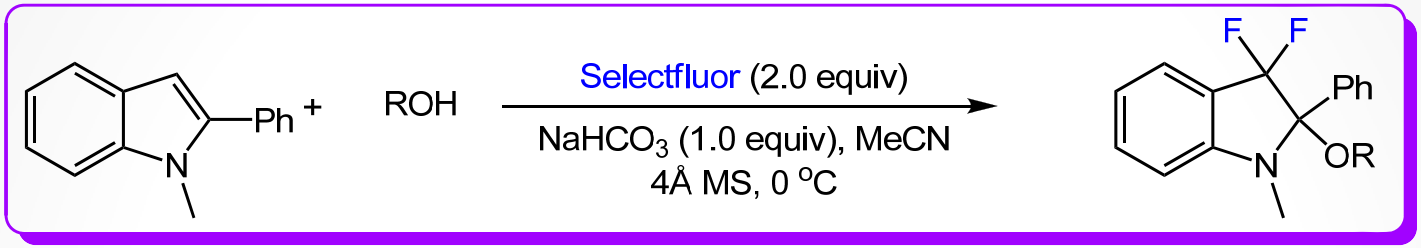
73% yield

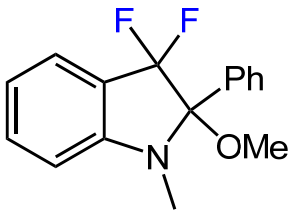


74% yield

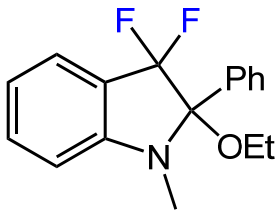
Jiao, N. *et al*. *Org. Lett*. **2011**. *13*, 4498–4501.

Fluorinative Dearomatization of Indole

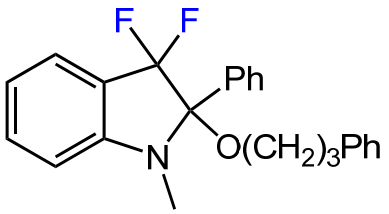




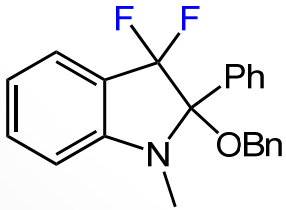
81%



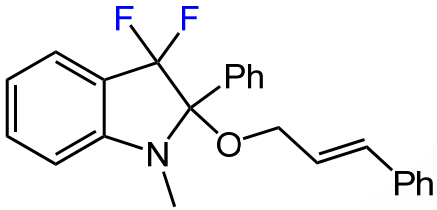
76%



66%

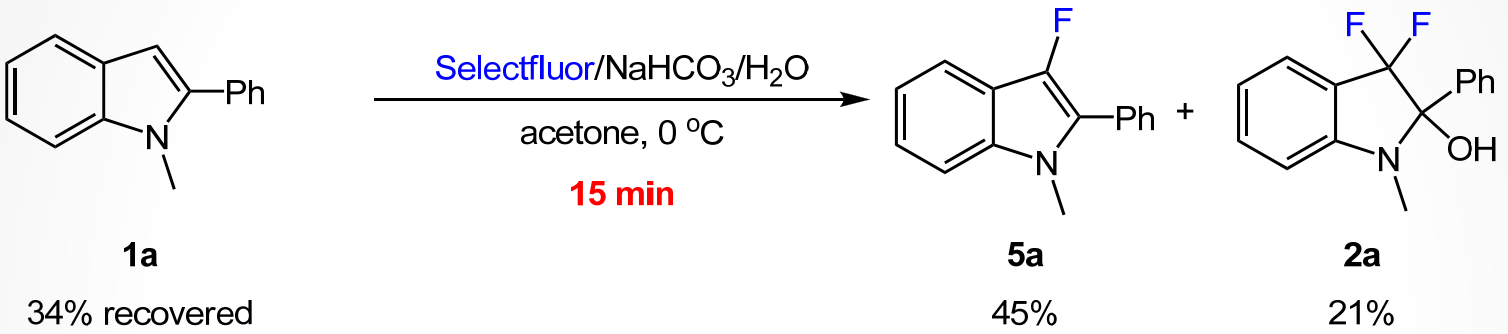


54%



62%

Fluorinative Dearomatization of Indole



1a

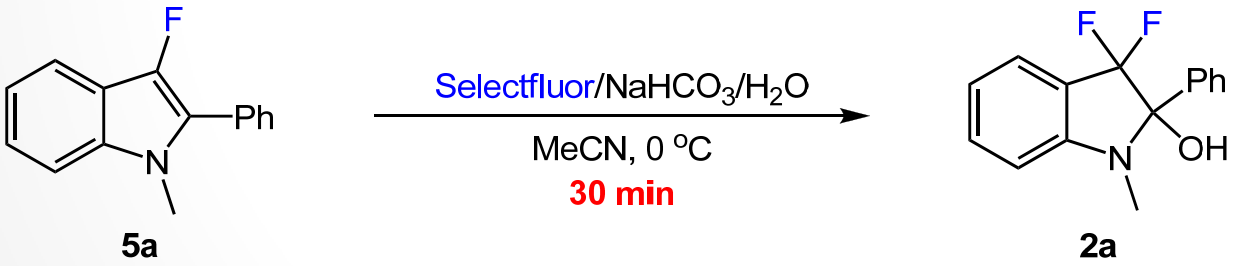
34% recovered

5a

45%

2a

21%

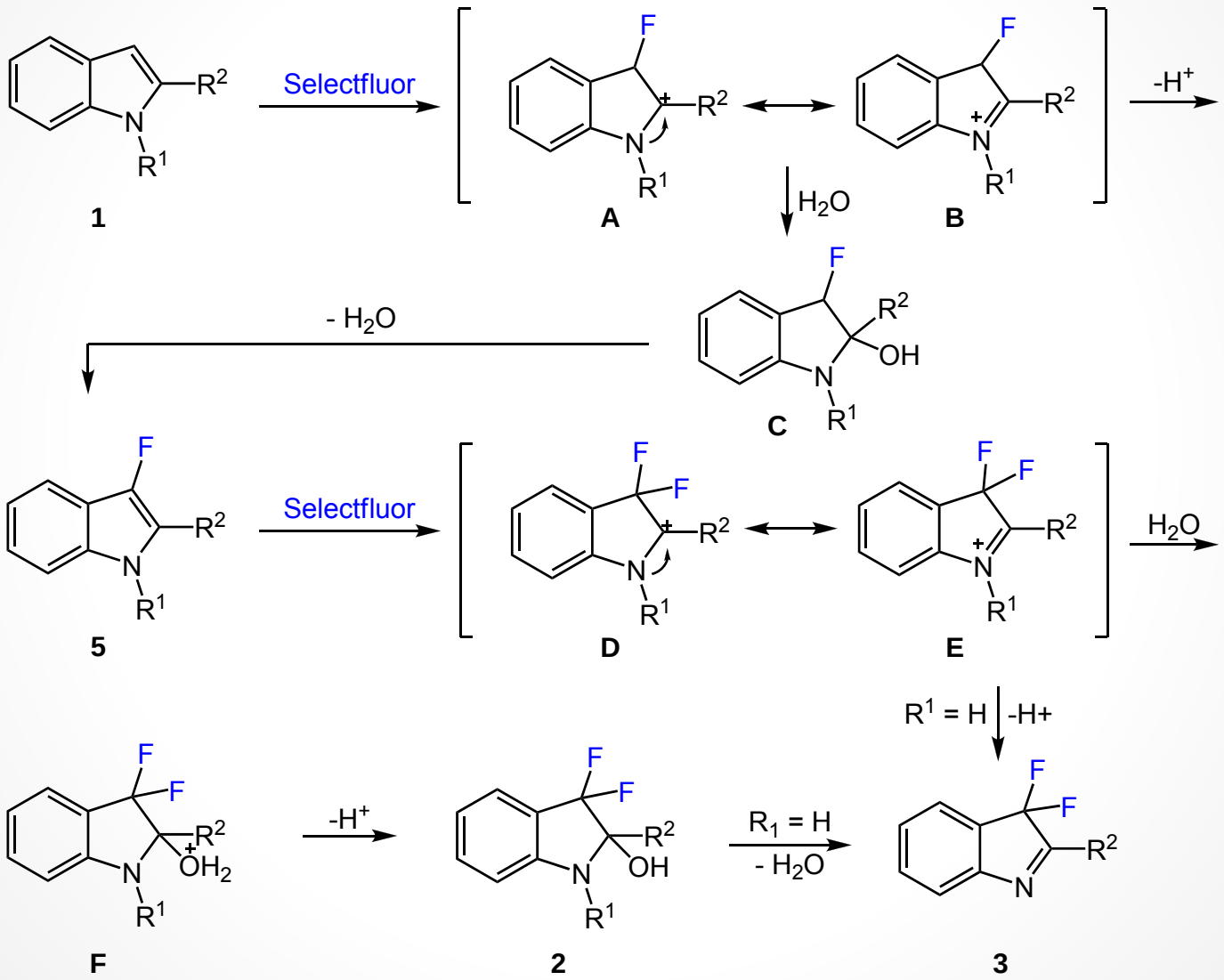


5a

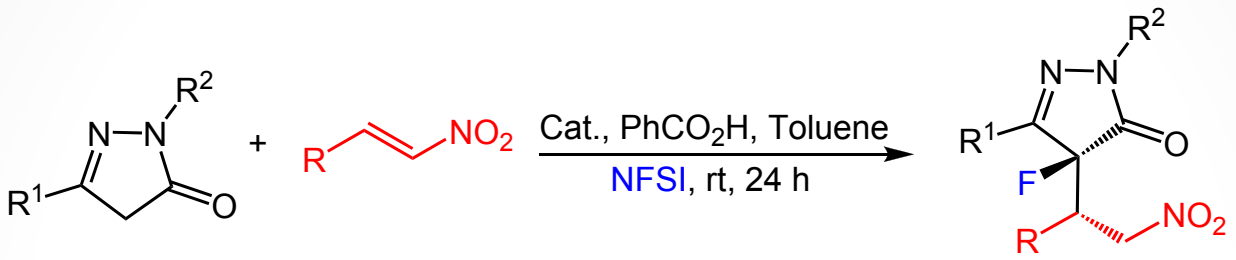
2a

80%

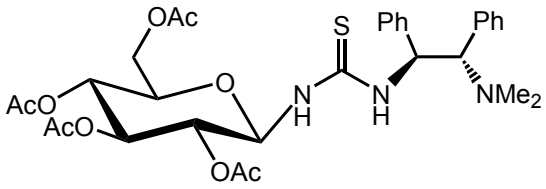
Fluorinative Dearomatization of Indole



Fluorinative Dearomatization of Pyrazol Derivatives



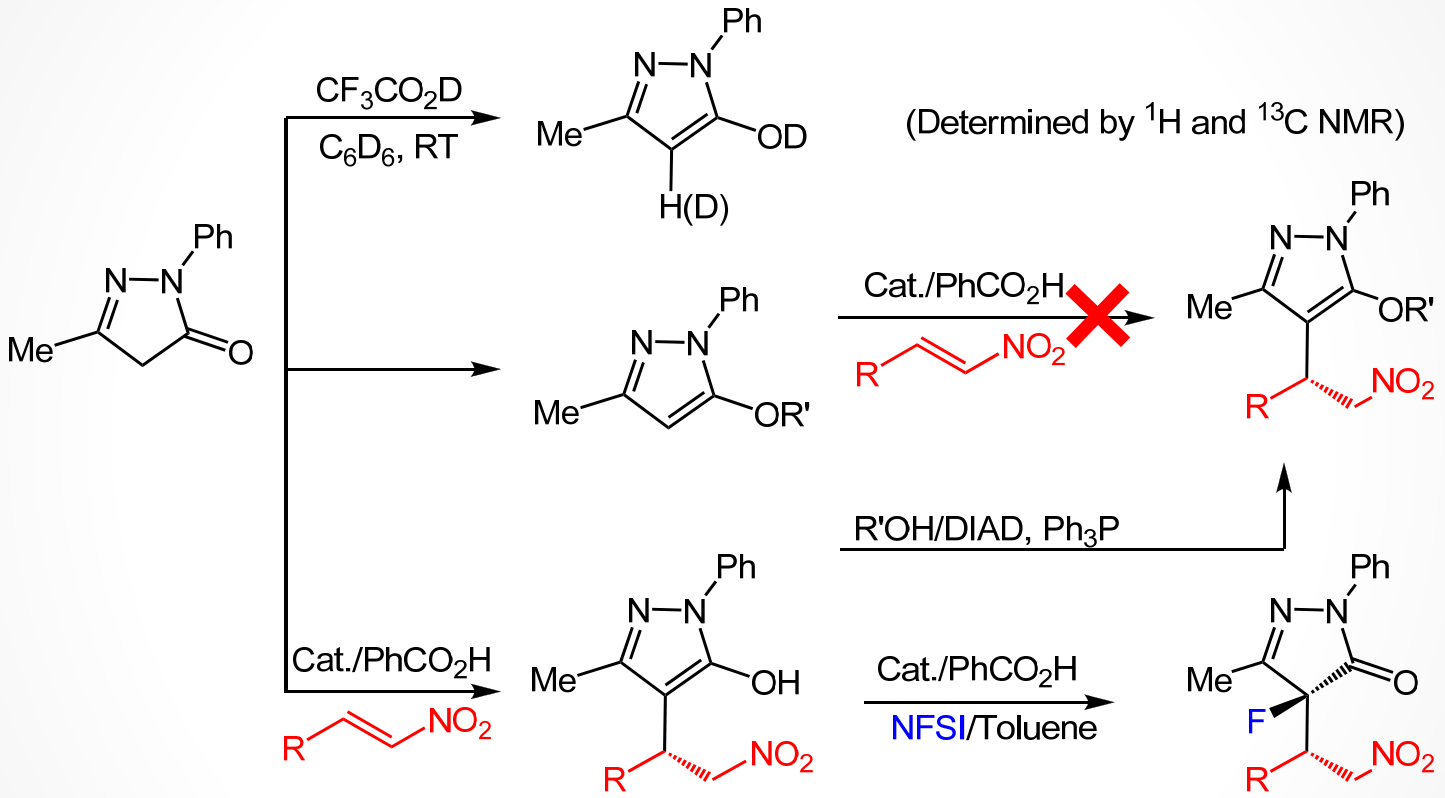
21 examples, ee 87% to 98%, dr 9:1 to 99:1



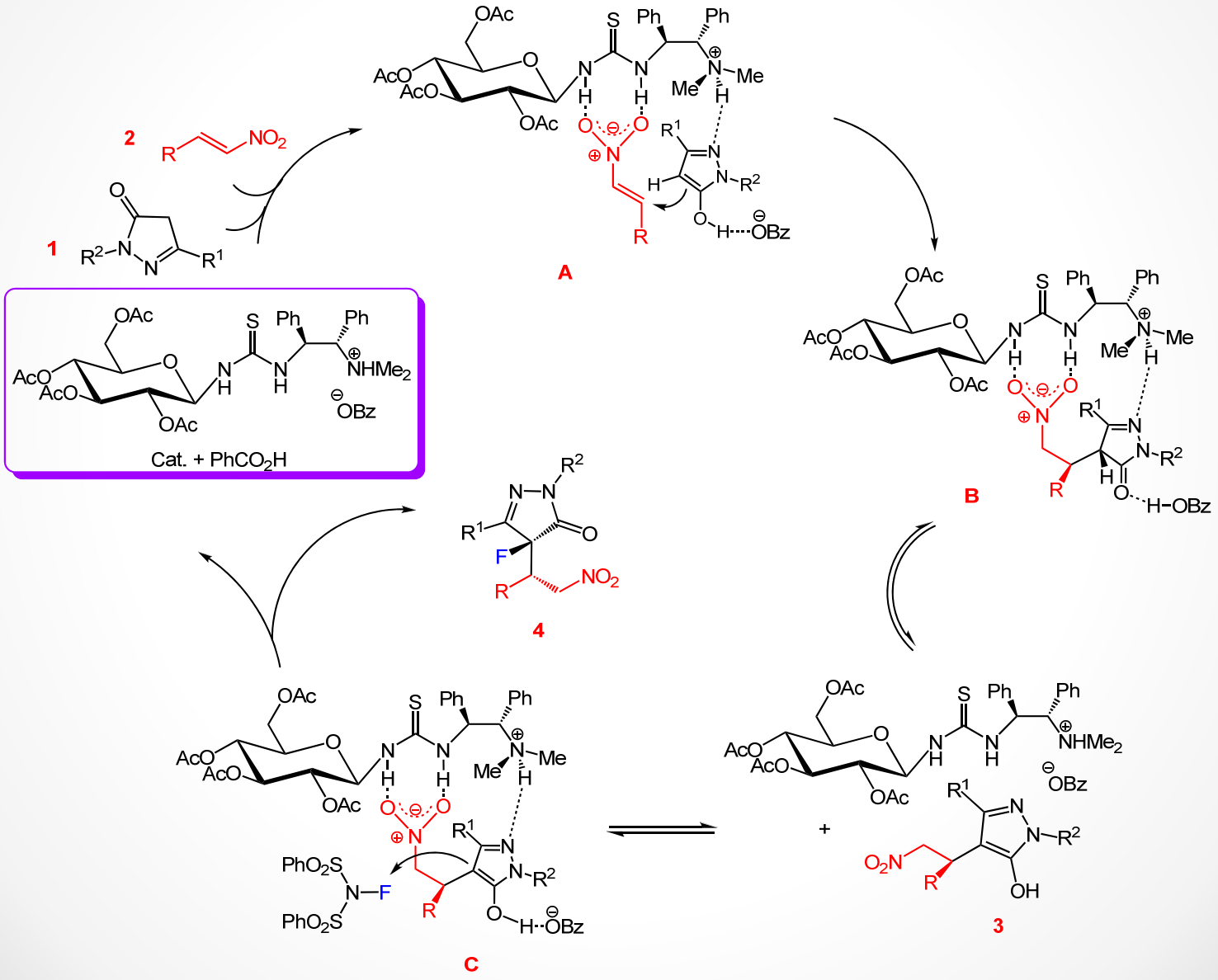
Cat. (D, *S*, *S*)

Ma, J.-A. *et al*. *Chem. Eur. J*. **2012**, *18*, 14255 –14260.

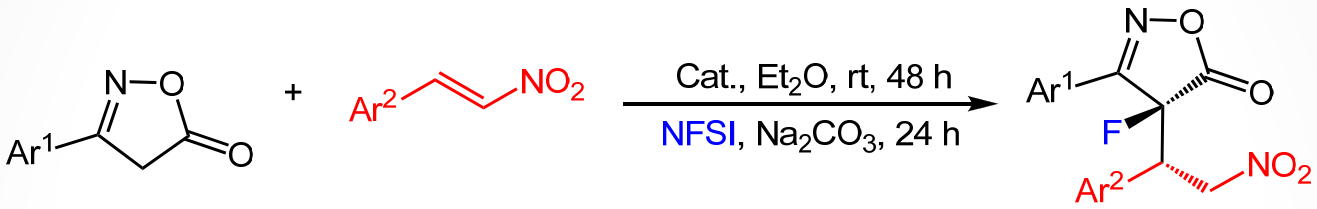
Fluorinative Dearomatization of Pyrazol Derivatives

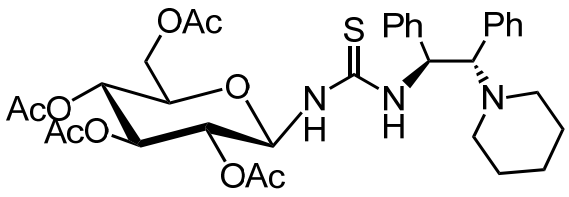


Fluorinative Dearomatization of Pyrazol Derivatives



Fluorinative Dearomatization of Isoxazol derivatives





Cat. (D, *S*, *S*)

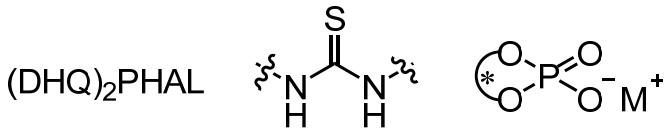
Ma, J.-A. *et al*. *J. Org. Chem*. **2013**, *78*, 559−567.

Summary

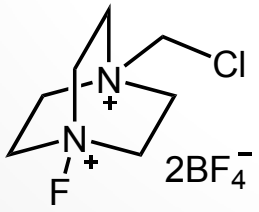
1. Scope of aromatic compounds:

Phenol; Indole; **Pyrazol**; **Isoxazol**

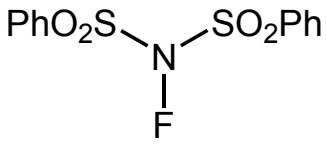
2. Catalysts:



3. Fluorination reagents:



Selectfluor



NFSI

The rapid and controlled generation of complex, readily functionalizable three-dimensional structures from simple planar starting materials is a highly attractive goal, as it allows fast access to diverse molecular architectures. Dearomatization of arenes is a powerful approach that has been proposed as a key component in putative biosynthetic pathways for a range of bioactive natural products, inspiring a range of elegant syntheses. A highly desirable factor in such constructions is the induction of asymmetry into the product, which has generally been achieved by three distinct chemical approaches: diastereoselective dearomatization of a substrate bearing an existing stereocenter; dearomatization followed by enantioselective desymmetrization of the prochiral intermediate; and finally, direct asymmetric dearomatization, which requires discrimination between the enantiotopic faces of the arene during the dearomatizing event. The last category represents a significant challenge, and to date, several elegant albeit noncatalytic metal- and hypervalent iodine-mediated approaches have been reported. To the best of our knowledge, only a handful of direct catalytic asymmetric arene dearomatization protocols exist (all but one being intramolecular), although the benefits are evident. Herein we report an intermolecular dearomatization that incorporates a quaternary fluorine stereocenter into the product, which is desirable because of the current interest in the effect of fluorine incorporation into pharmaceuticals but has been restricted by the limited number of general approaches to the asymmetric construction of such stereocenters.

In summary, we have demonstrated the broad generality of our chiral anion phase-transfer catalysis strategy by applying it to the asymmetric fluorinative dearomatization of phenols. Notably, it represents a rare application of chiral phosphoric acid catalysts to simple phenol nucleophiles by virtue of our chiral-anion PTC approach to activation of Selectfluor. The small but densely functionalized products incorporating an enantioenriched quaternary F-containing stereocenter represent valuable building blocks of potential interest in synthetic and medicinal chemistry. Their close relationship to well-studied *o*-quinols provides numerous avenues for elaboration as well as exciting opportunities for bioisosteric replacement of −OH with −F in the numerous natural products thought to be derived from *o*-quinols.