The Chiral Phosphate Anion Phase Transfer Catalysis and the Radical Trifluoromethylation

Reporter: Linrui Zhang

Supervisor: Prof. Yong Huang

Date: 2017-6-12

- **Part 1**

  Asymmetric Fluorination Using an Anionic Chiral Phase Transfer Catalyst by Toste

- **Part 2**

  The Chemistry of the Radical Trifluoromethylation

- **Part 1**

  Asymmetric Fluorination Using an Anionic Chiral Phase Transfer Catalyst by Toste

- Part2

  The Chemistry of the Radical Trifluoromethylation

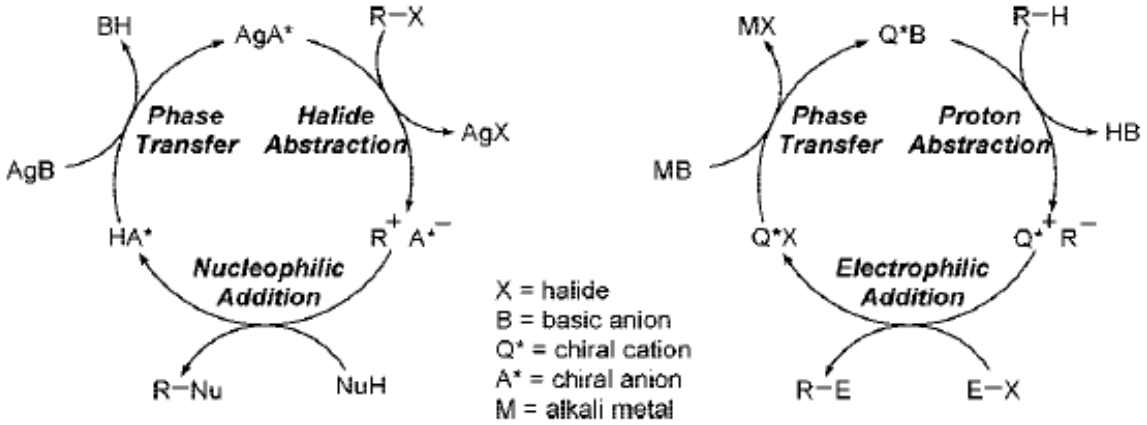
F. Dean Toste

Education and Positions

- 1989 -1993： B.Sc in Chemistry and Biochemistry University of Toronto
- 1993 -1995： M.Sc. in Organic Chemistry University of Toronto
- 1995 - 2000：Ph.D. in Organic Chemistry Stanford University
- 2001 - 2002： Post-Doctoral Fellow in California Institute of Technology
- 2002 – 2009： Assistant Professor in University of California, Berkeley
- 2009 – present：Professor in University of California, Berkeley

- **Fellowships and Awards**
- 2015: American Chemical Society, Creativity in Synthetic Organic Chemistry Award;
- 2014: Mitsui Catalysis Award; Miller Professorship, UC Berkeley;
- 2011: Society of Synthetic Organic Chemistry Japan, Mukaiyama Award; Tetrahedron Young Investigator Award ;
- 2010: Fellow of the Royal Society of Chemistry; Royal Society of Chemistry, Merck Award;
- 2009 : Solvias Ligand Prize;
- 2008 : Thieme-IUPAC Prize in Synthetic Organic Chemistry; American Chemical Society, Elias J. Corey Award;
- 2007: BASF Catalysis Award; Organometallic Chemistry Directed Towards Organic Synthesis (OMCOS) Award;
- 2006 : Novartis Young Investigator Award; Novartis Chemistry Lectureship; Roche Excellence in Chemistry Award;
- 2005 : AstraZeneca Excellence in Chemistry Award; Chevron Chair, UC Berkeley ;
- 2004 : GlaxoSmithKline Chemistry Scholar Award ; Eli Lilly Grantee Award; Dupont Young Investigator Award;
- 2003 :Amgen New Faculty Award; Boehringer-Ingelheim New Faculty Award;
- 2002 : Research Corporation, Research Innovation Award ; American Chemical Society, Nobel Laureate Signature Award;
- And so on ……

Chiral Anion Phase Transfer Catalysis

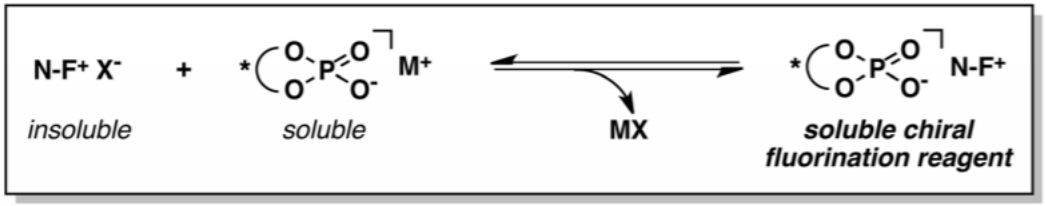


Proposed chiral anion phase transfer catalysis

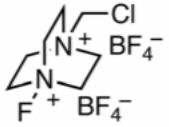
chiral cation PTC.

J. Am. Chem. Soc. **2008**, *130*, 14984–14986

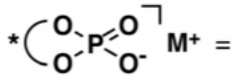
In 2011, the first asymmetric fluorination using an Chiral Anion Phase Transfer Catalyst



N-F+ X- =



1, Selectfluor



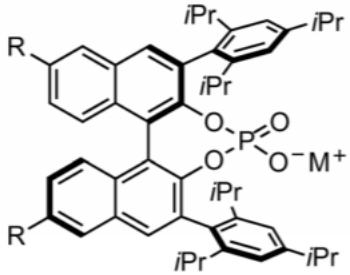
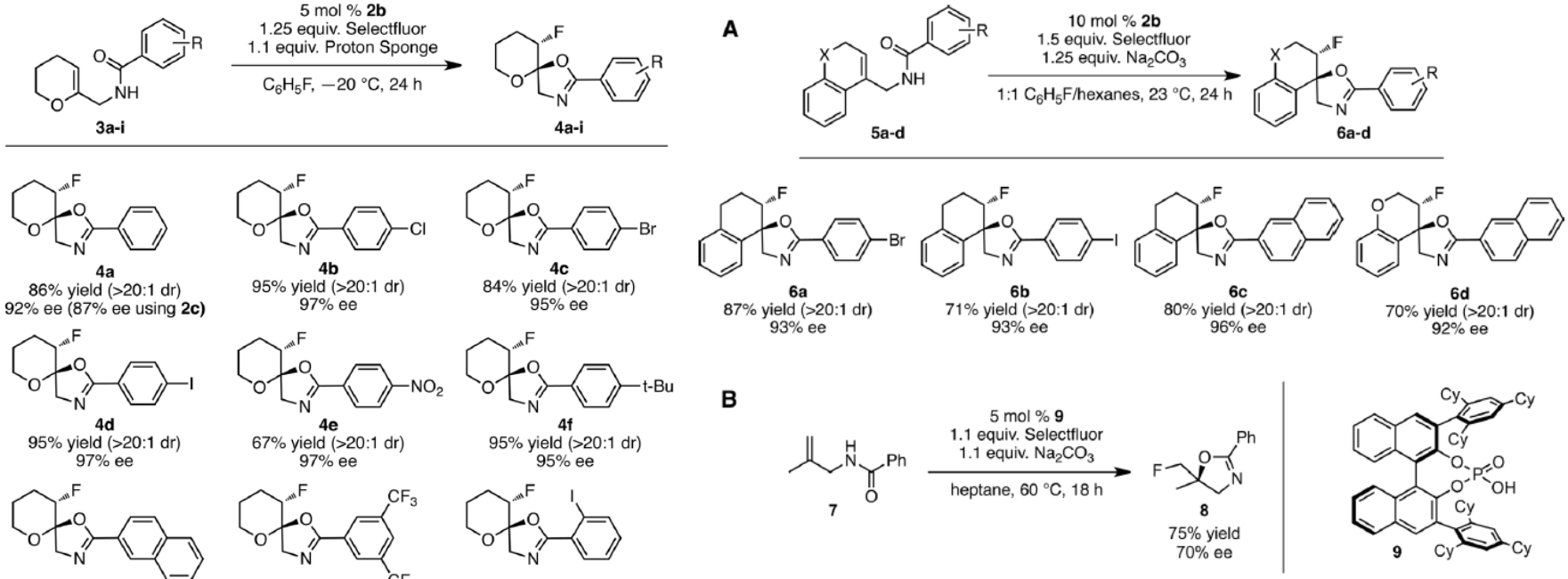


Fig. 1. Catalytic formation of a chiral fluorination reagent via chiral anion–mediated phase transfer in nonpolar solvents.

2a, R = C_8H_{17}, $M^+ = Na^+$
2b, R = C_8H_{17}, $M^+ = H^+$
2c, R = H, $M^+ = H^+$

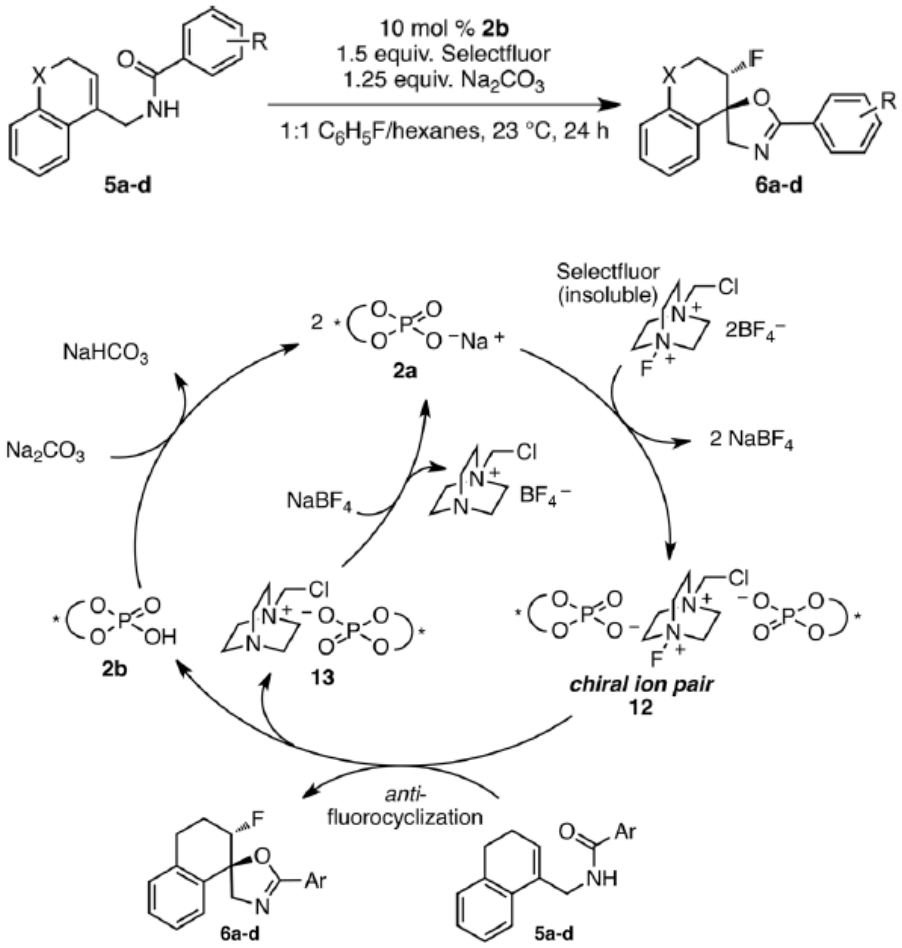
Science, **2011**, *334*, 1681-1684

Substrate scope



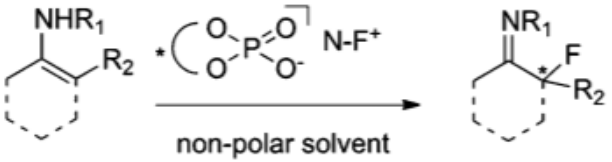
(A) Fluorocyclization of dihydronaphthalenes and chromenes.
(B) Successful extension to an unactivated alkene.

Mechanism



Science, **2011**, *334*, 1681-1684

In 2012, Asymmetric Fluorination of Enamides: Access to α-Fluoroimines



versatile and reactive precursor to β-fluoro amines and α-fluoroketones

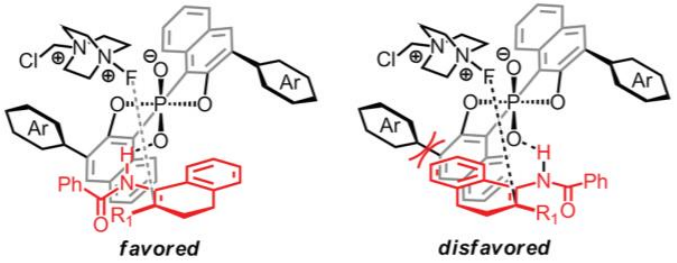
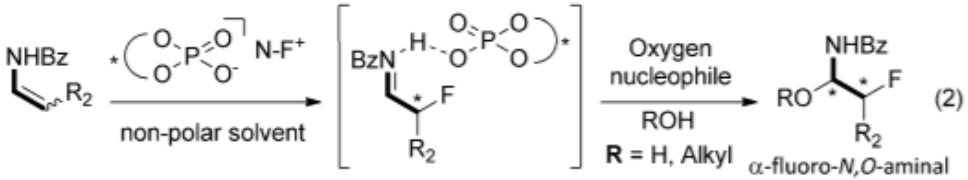
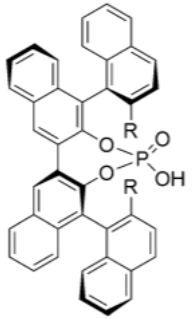


Figure 1. Mechanistic proposal for observed absolute stereochemistry.

Asymmetric Tandem Oxyfluorination of A Doubly Axially CPA Catalyst

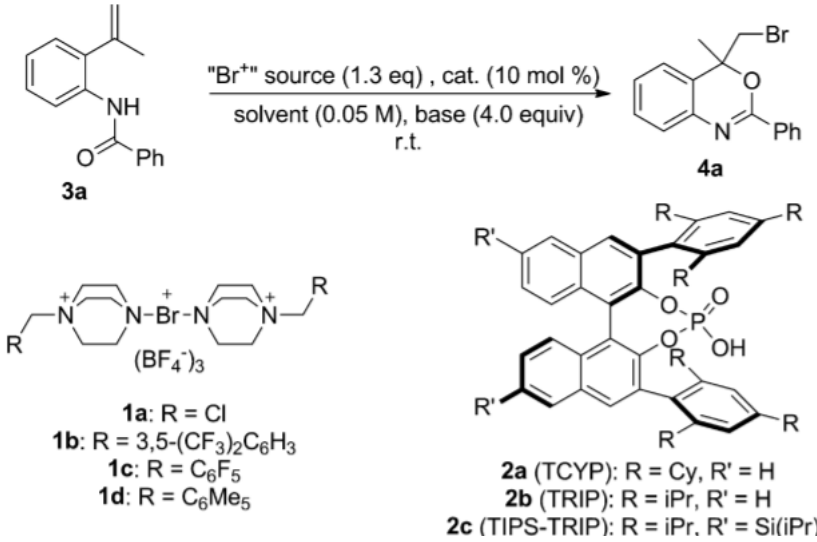


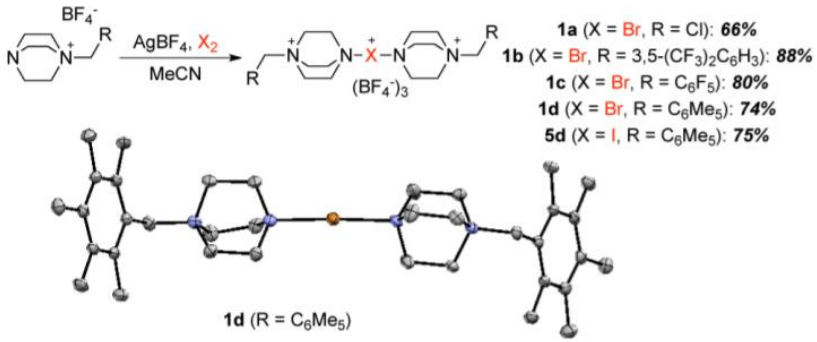


R = Ph, (*R*,*R*)-**PhDAP** (**2j**)

J. Am. Chem. Soc. **2012**, *134*, 8376−8379
Angew. Chem. Int. Ed. **2012**, *51*, 9684 –9688

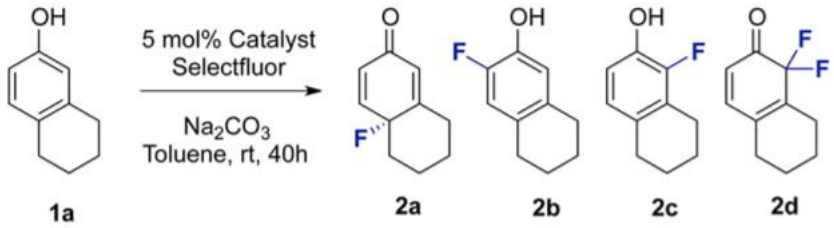
Enantioselective Halocyclization Using Reagents Tailored

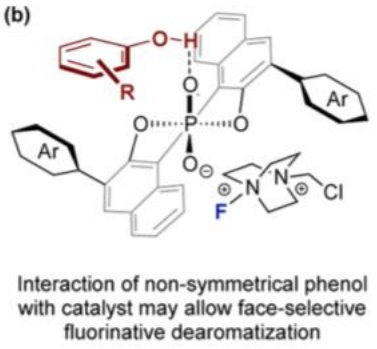




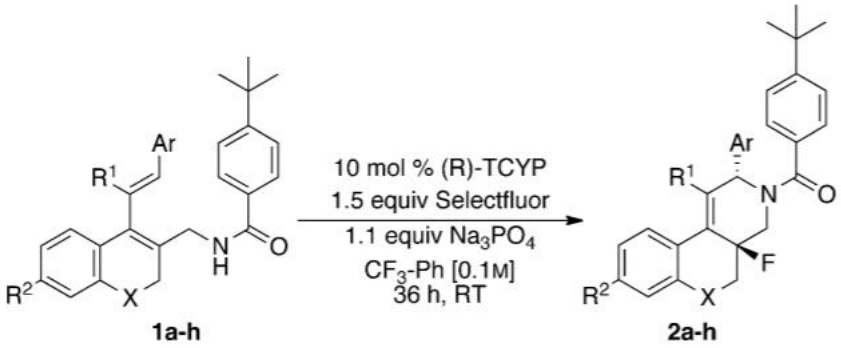
J. Am. Chem. Soc. **2012,** *134,* 12928−12931

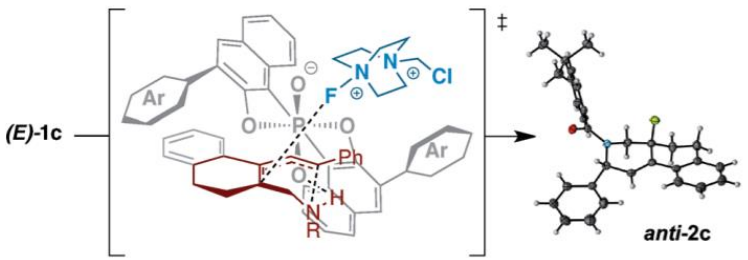
In 2013, applied to the Direct Enantioselective Fluorinative Dearomatization of Phenols





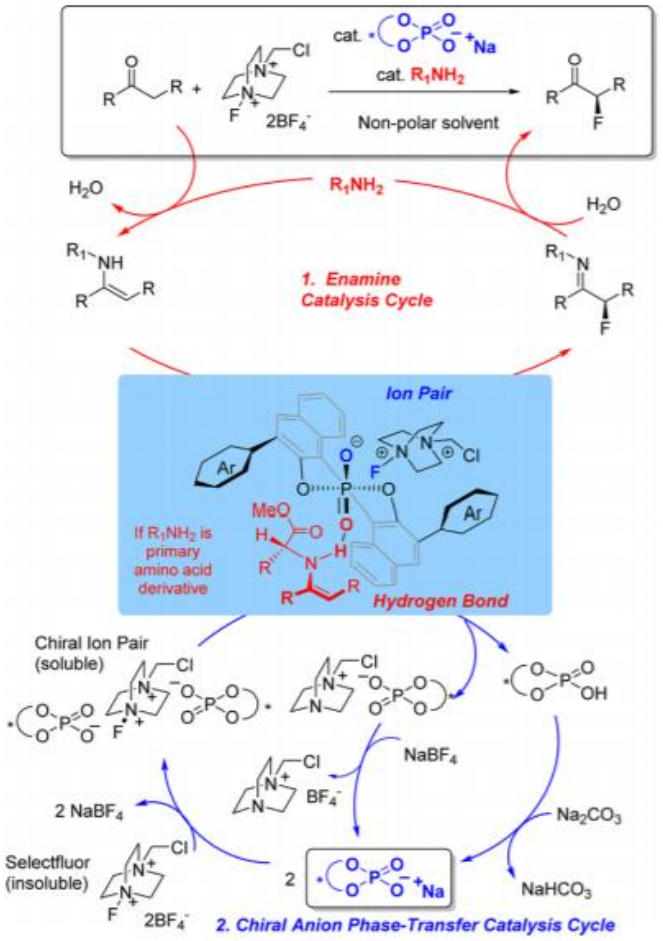
Enantioselective Fluoroamination: 1,4-Addition to Conjugated Dienes





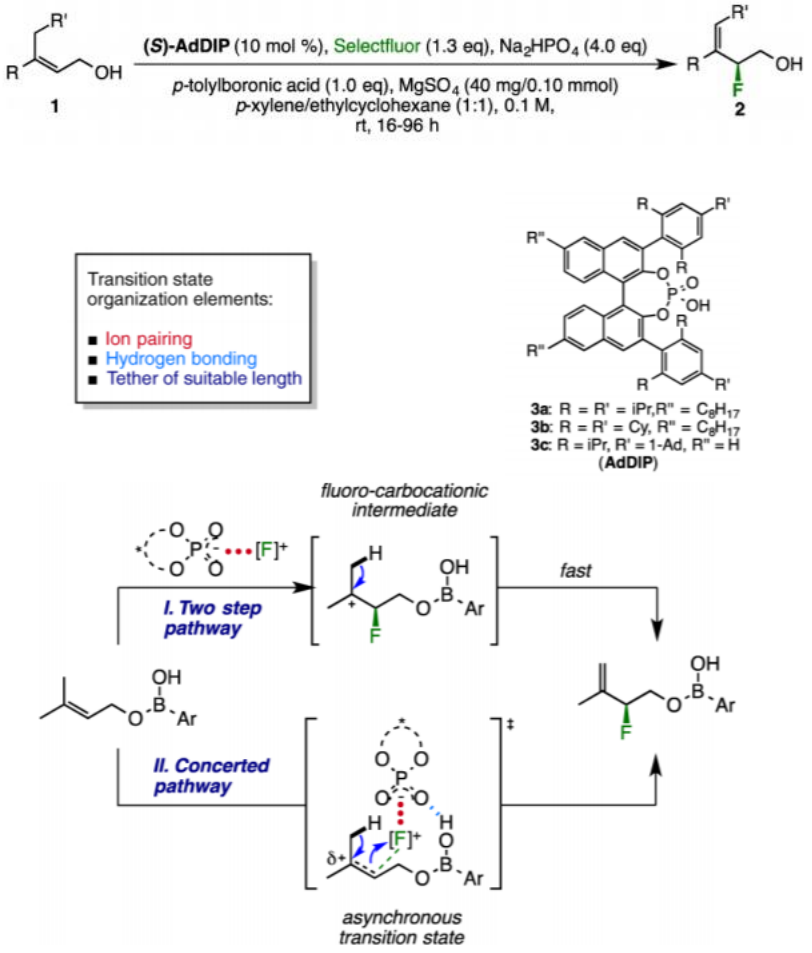
J. Am. Chem. Soc. **2013**, *135*, 1268−1271
Angew. Chem. Int. Ed. **2013**, *52*, 7724 –7727

In 2014, a Combination of Chiral Anion Phase-Transfer Catalysis and Enamine Catalysis using Protected Amino Acids



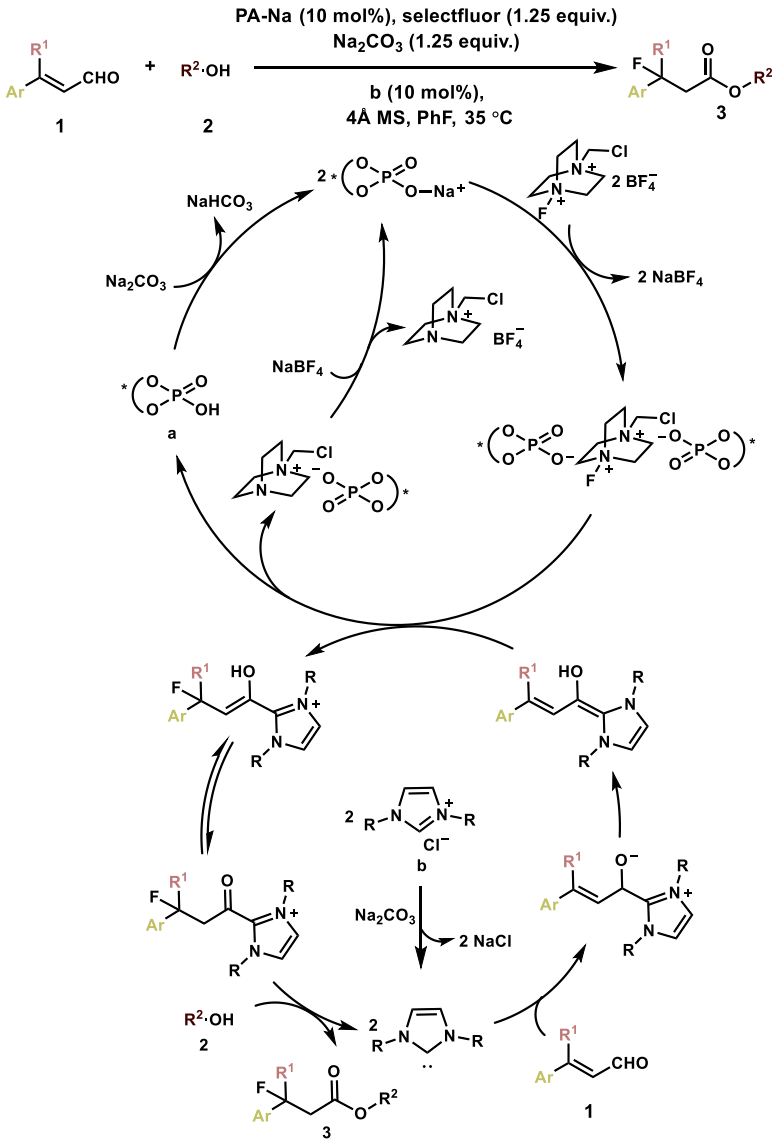
J. Am. Chem. Soc. **2014**, *136*, 5225−5228

Directing Group Strategy for Chiral Anion Phase-Transfer Fluorination of Allylic Alcohols



J. Am. Chem. Soc. **2014**, *136*, 12864−12867

Proposed catalytic cycle of asymmetric β-fluorination using CPA Phase Transfer catalysis and achiral NHCs



- Part 1

  Asymmetric Fluorination Using an Anionic Chiral Phase Transfer Catalyst by Toste

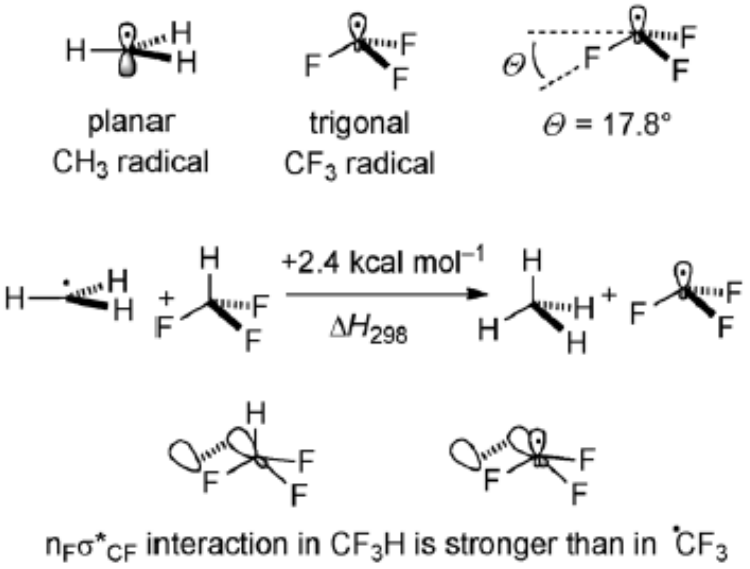
- **Part 2**

  The Chemistry of the Radical Trifluoromethylation

Part 2: The Chemistry of the Radical Trifluoromethylation

- 1. Structure and reactivity
- 2. Radical trifluoromethylation reagent

1. Structure and Reactivity



- pyramidal
- less stable
- stereoelectronic effects
- electrophilic radical

J. Am. Chem. Soc. **1976**, *98*, 230 –232.
Wiley, Chichester, **2012**, *pp*. 449 – 475.

2. Radical trifluoromethylation reagent

2.1 CF_3I

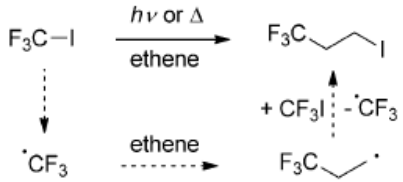
2.2 CF_3SO_2Cl

2.3 Togni reagent

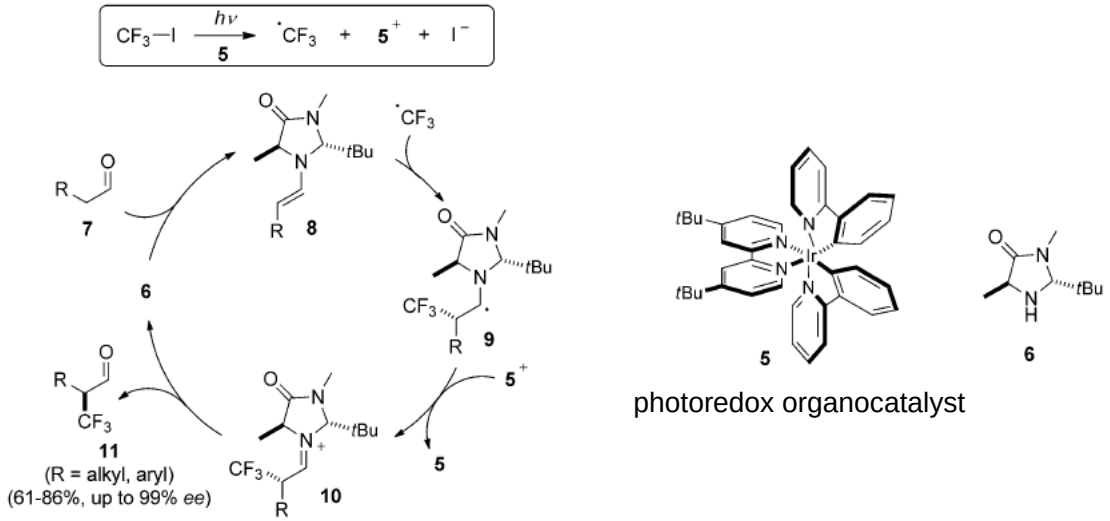
2.4 Shreeve–Umemoto reagent

2.1 CF_3I

An atom transfer/radical addition (ATRA)



A mild enantioselective trifluoromethylation

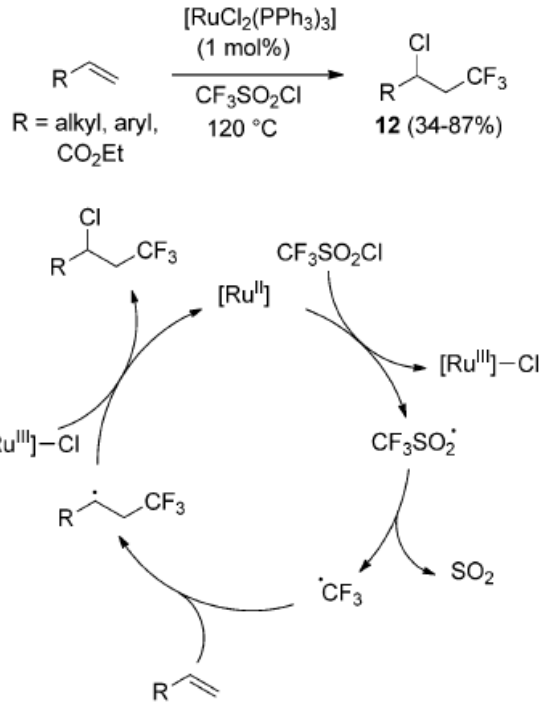


photoredox organocatalyst

J. Am. Chem. Soc. **1949,** 2856 – 2861.
J. Am. Chem. Soc. **2009,** *131*, 10875 – 10877.

2.2 CF_3SO_2Cl

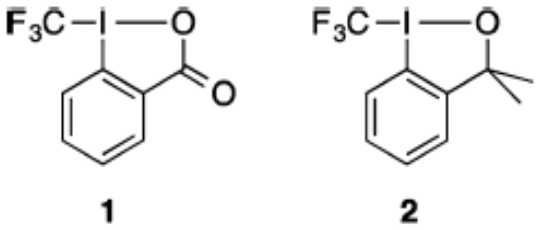
In 1991, Sawada used CF_3SO_2Cl as a valuable source for CF_3 radicals.



ATRA of various alkenes
Not restricted to electron-rich alkenes.
Even as acrylates

J. Chem. Soc. Perkin Trans. 1 **1991**, 627 – 633.

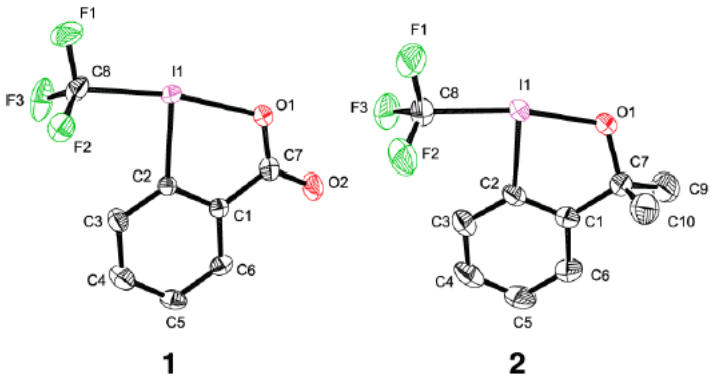
2.3 Togni reagent



1

2

- easily prepared
- effective
- versatile

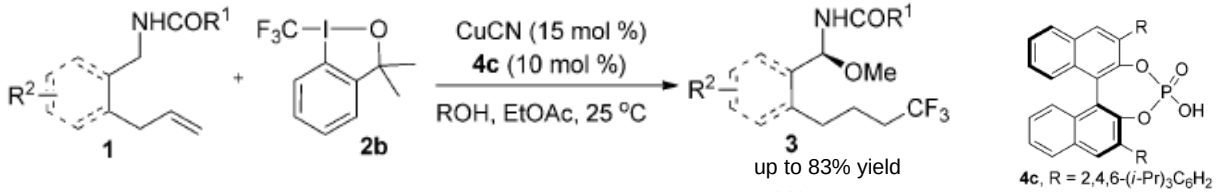


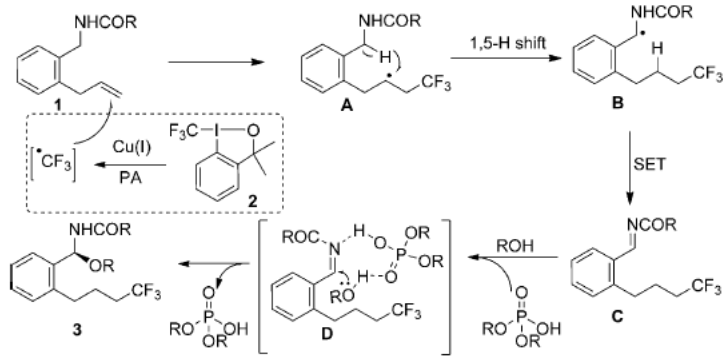
1 2

- 3c-4e
- through-lone-pair-coupling

2.3 Togni reagent

2.3.1 Cu(I)/CPA-catalyzed trifluoromethylation reactions of unactivated alkenes



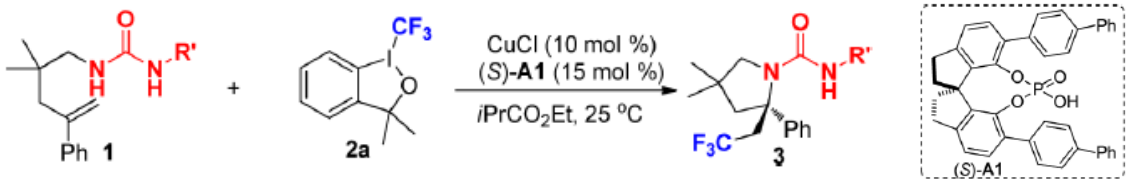


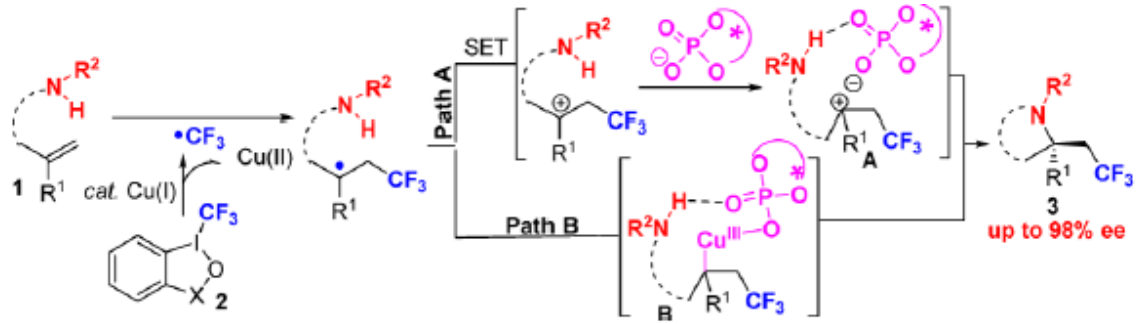
Proposed mechanism for the current reaction system.

Angew. Chem. Int. Ed. **2014**, *53*, 11890 –11894

2.3 Togni reagent

2.3.2 Cu(I)/CPA-catalyzed trifluoromethylation reactions of alkenes

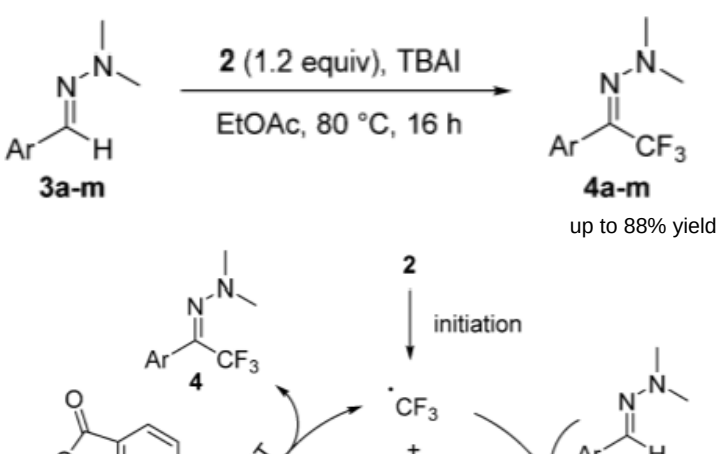


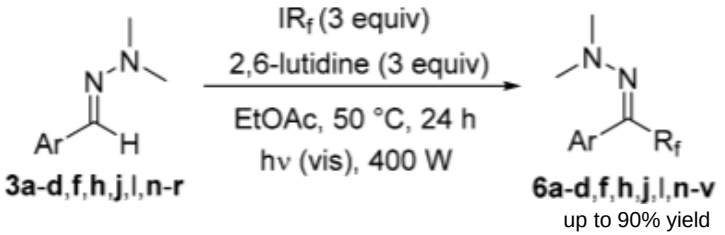


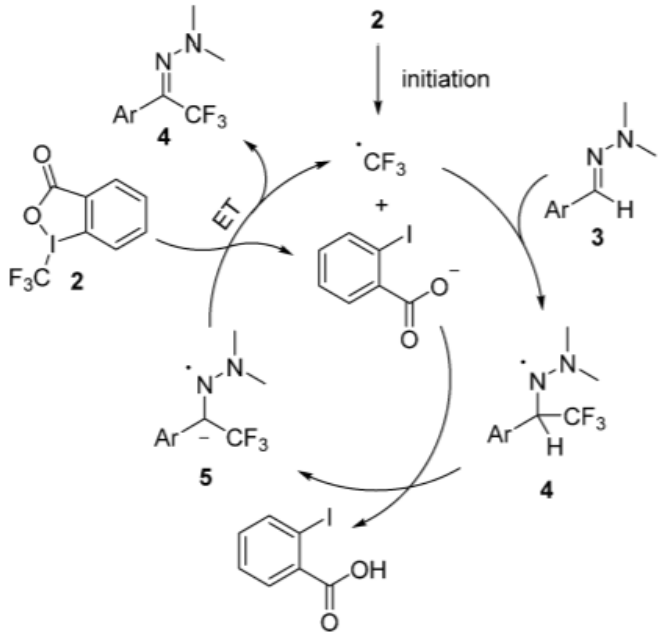
J. Am. Chem. Soc. **2016,** *138*, 9357−9360

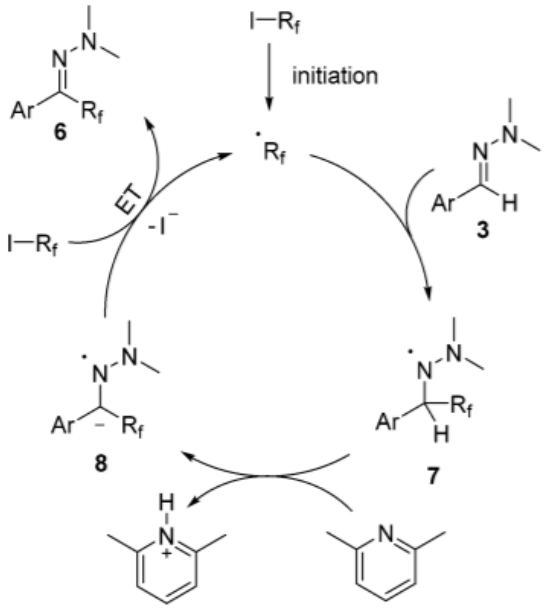
2.3 Togni reagent

2.3.3 Trifluoromethylation/ Perfluoroalkylation of Aryl-N,N-dimethyl Hydrazones



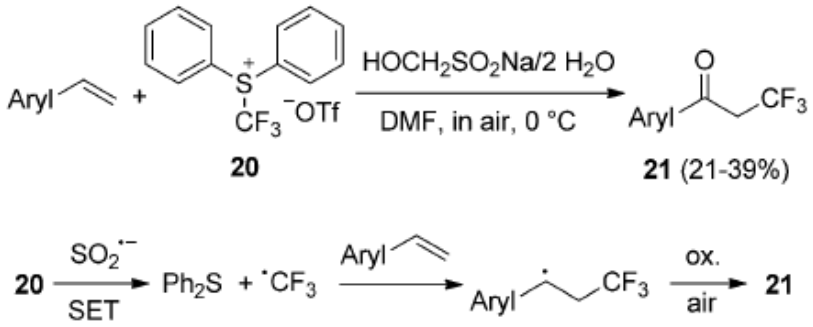






J. Org. Chem. **2017**, *ASAP.* DOI: 10.1021/acs.joc.7b00934

2.4 Shreeve–Umemoto reagent



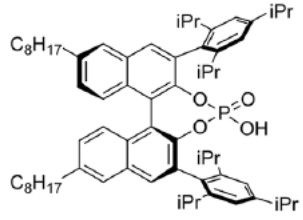
Chem. Commun. **2011**, *47*, 6632 – 6634

Summary

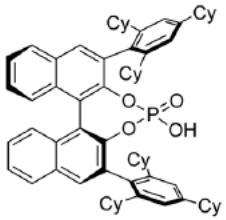
- Highlight the PTC concept for asymmetric fluorination.
- Propose a catalytic cycle of asymmetric β-fluorination using CPA Phase-Transfer catalysis and achiral NHCs.
- Research the radical trifluoromethylation .
- Selective learning Togni reagent and their applications.
- Significant advances have been made in the asymmetric fluorination, mechanistic studies and further synthetic applications of this filed should be under investigation.

Thank you for your attention!

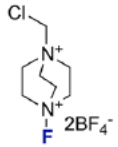
(a) Catalysts/reagents employed



(*S*)-C_8-TRIP

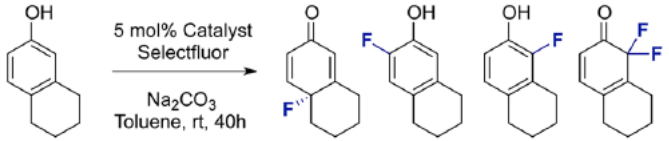


(S)-TCYP



Selectfluor

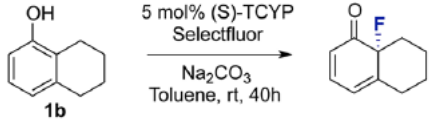
(b) Initial findings - *Para*-fluorination



1a **2a** **2b** **2c** **2d**

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%[c] (23)	--

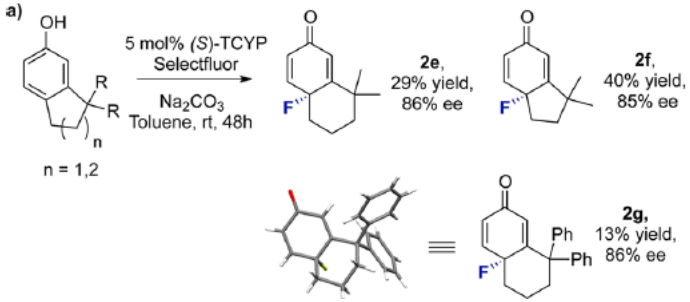
(c) *Ortho*-fluorination



1b

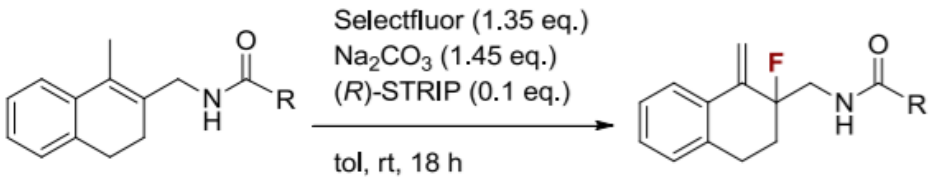
3a, 75% yield, 96% ee

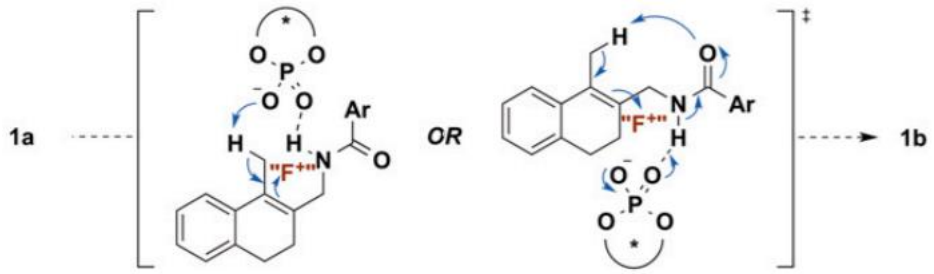
a)



To obtain some insights into the reaction mechanism, radical trapping experiments were conducted with 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO) and 1,4-benzoquinone (BQ) (Scheme S5, eq 1). The reaction was found to be remarkably inhibited by these reagents, and together with the previous studies of radical trifluoromethylation of alkenes with Togni's reagent by Cu(I) catalysts,[2,3] this suggests that the CF_3 radical is likely involved as the reactive species under the current reaction conditions.[17] To further understand the role of the phosphoric acid, treatment of **1a** with **2a** under otherwise identical conditions in the presence of either CuCl alone or (*S*)-**A1** alone (see Scheme S5, eq 2 and Table S1, entry 19) gave the corresponding product **3A** in only low yield (the detailed kinetic behavior is shown in Figure S2), thus revealing that both the Cu(I) salt and the phosphoric acid are necessary for the reaction and that the activation of Togni's reagent could be facilitated by the phosphoric acid in this dual-catalytic system.[11b,18] Furthermore, no desired product was observed under the standard conditions with methyl-protected urea derivative **6** as the substrate (Scheme 4a and Scheme S5, eq 3), clearly indicating that the urea with two acidic N–H at the appropriate positions plays a crucial role in asymmetric induction.

A Combination of Directing groups and Chiral Anion Phase-transfer Catalysis for Enantioselective Fluorination of Alkenes





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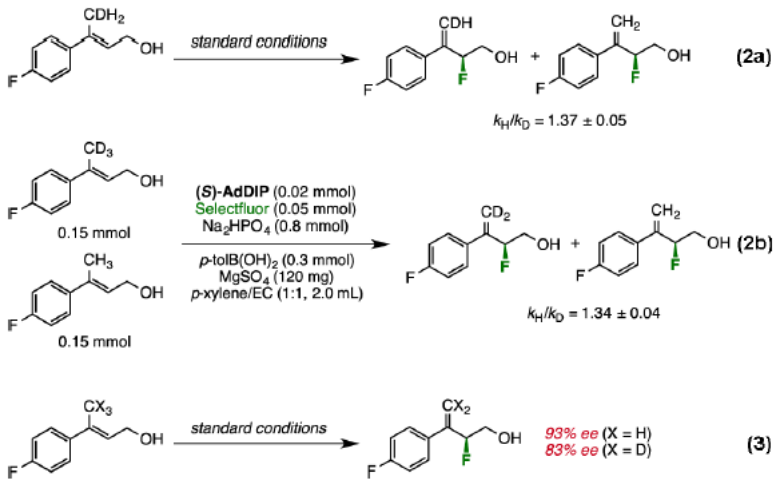
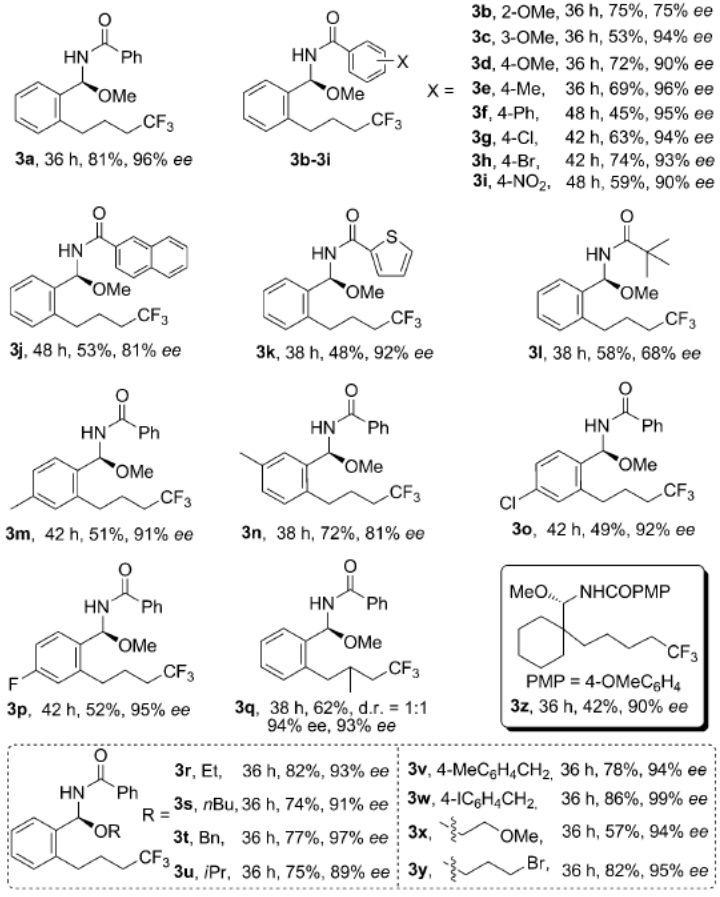
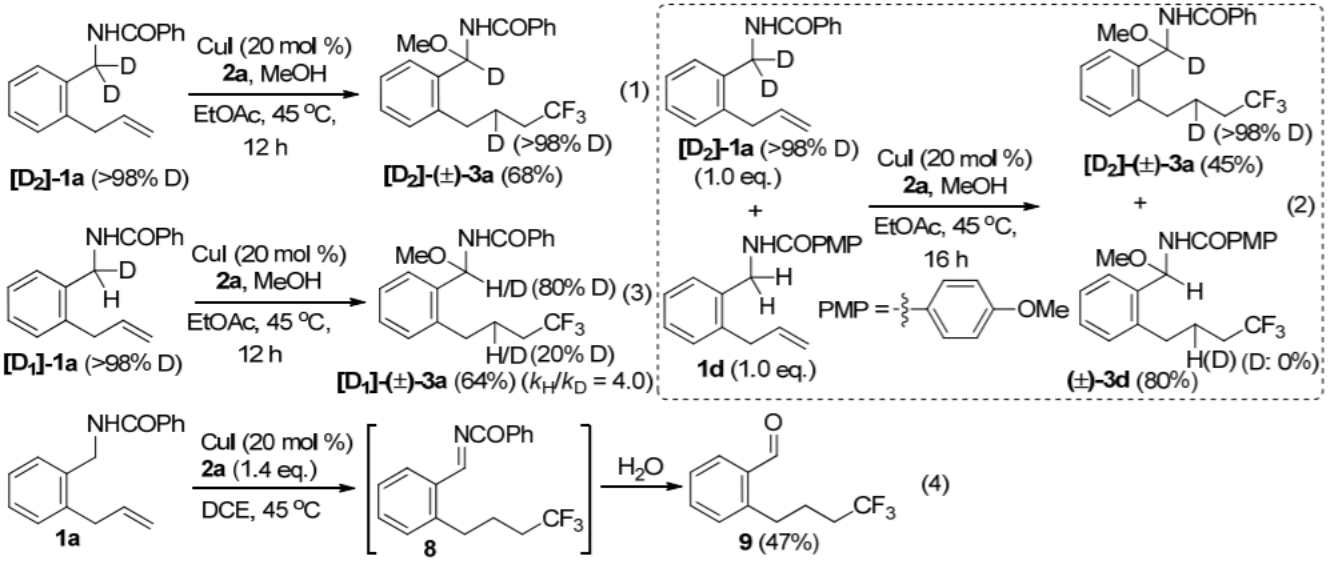


Selectfluor π-complex (pathway II).[17] In support of this interpretation, subjecting trideuterated substrate **1b**-d_3 to standard reaction conditions resulted in significantly diminished enantioselectivity (83% vs 93% ee) compared to unlabeled **1b** (eq 3), implicating the cleavage of the C–H bond in the enantiodetermining step. In a broader context, while chiral acids have previously been utilized in reactions in which protonation is the enantiodetermining step,[18] these results suggest that in chiral anion catalysis, the microscopic reverse of this process (i.e., enantiodetermining deprotonation) may occur.

2.3.1



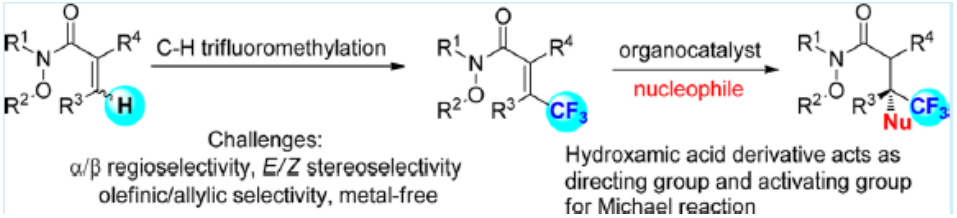
This finding can be attributed to the fact that 2-iodobenzoic acid, generated by the reaction system, prevents enantioselective reaction catalyzed by CPAs.



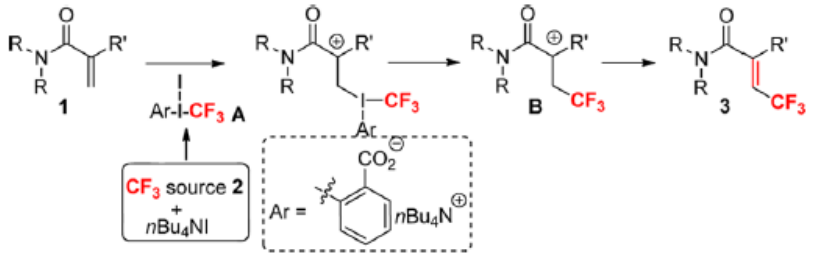
Notably, for the reaction in the presence of TEMPO, the TEMPO-CF3 adduct was formed in 95% (racemic) and 88% (chiral) yield (see Scheme S1). The results reveal that the CF3 radical is likely involved as the reactive species under the current reaction conditions.[7]

2.3 Togni reagent

2.3.1 electrophilic species from the reaction of nBu_4NI with Togni's reagent 2



Proposed Mechanism



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