Literature Report XI

Synergistic Transition Metal and Hydrogen Bonding Phase-Transfer Catalysis Enables Enantioconvergent Allylic Fluorination with KF

Reporter: Hao-Dong Chen
Checker: Yu Yang
Date: 2026-04-20

Wang, Z.; Dooley, C.; Chen, Z.; Poškaitė, G.; Paton, R. S.; Lloyd-Jones, G. C.;* Gouverneur, V.* *J. Am. Chem. Soc.* **2026**, *148,* 14213

CV of Prof. Véronique Gouverneur

Education & Experience:

- **1981-1985** MSc, Université Catholique de Louvain
- **1985-1991** Ph.D., Université Catholique de Louvain
- **1992-1994** Postdoctoral fellow, The Scripps Research Institute
- **1994-1998** Maître de Conférence, University Louis Pasteur in Strasbourg
- **1998-present** Independent Research, University of Oxford

Research:

- **18F-Radiochemistry for Positron Emission Tomography**
- **Method Development and Catalysis**

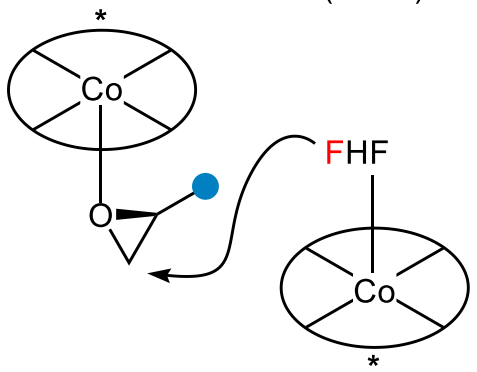
Contents

Introduction

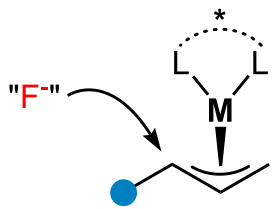
Asymmetric Fluorination

a. Asymmetric fluorination enabled by transition metal catalysis

(i) bi-functional chiral Co(salen)



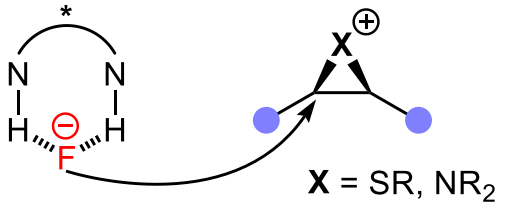
(ii) chiral metal-allyl complex



M = Pd, Ir, Rh

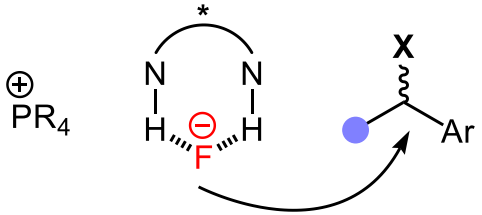
b. Asymmetric fluorination enabled by HBPTC

(i) ion-pairing with electrophile



X = SR, NR_2

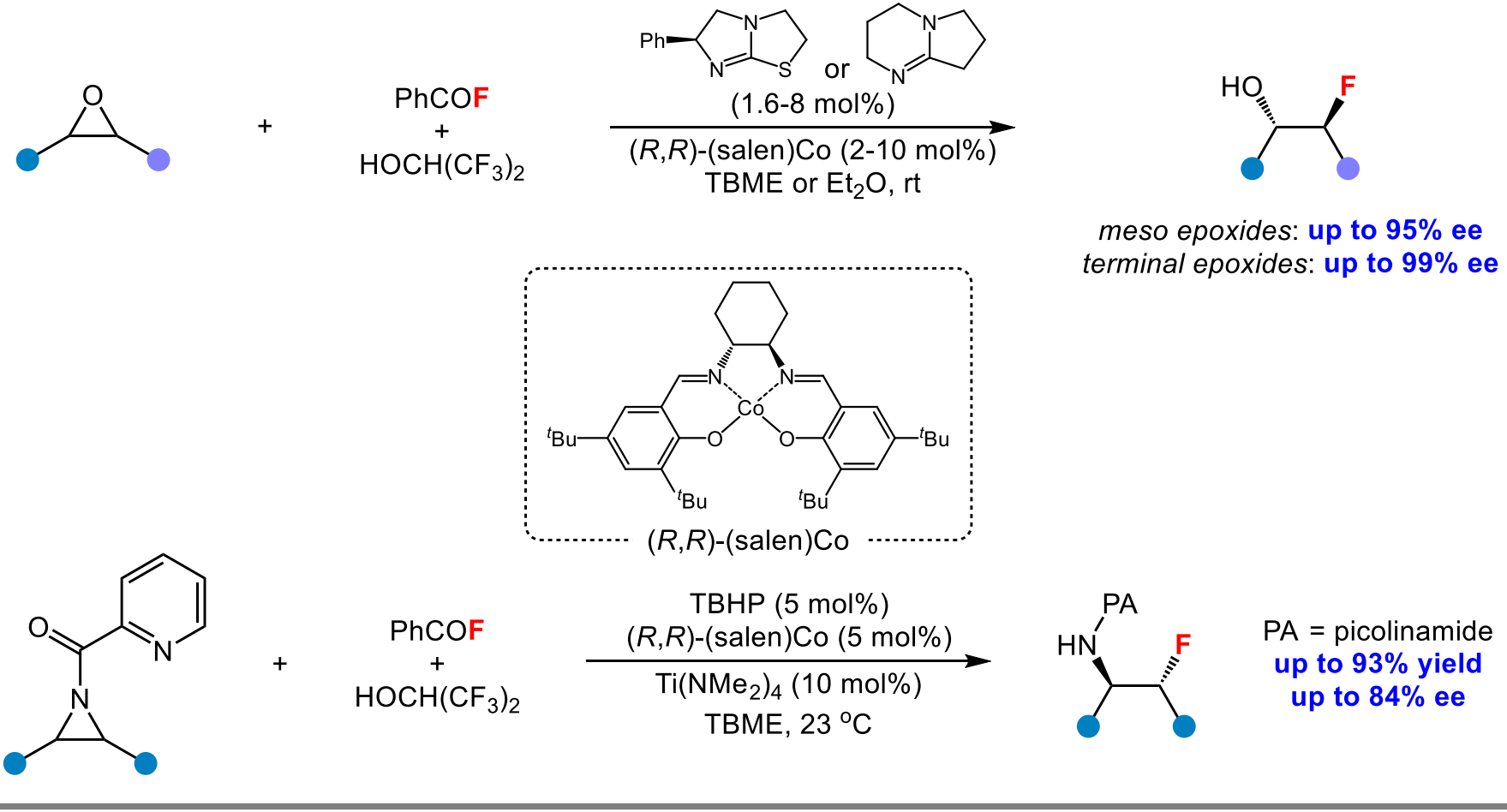
(ii) ion-pairing with onium co-catalyst



X = Br, I

Introduction

Asymmetric Fluorination Enabled by Transition Metal Catalysis

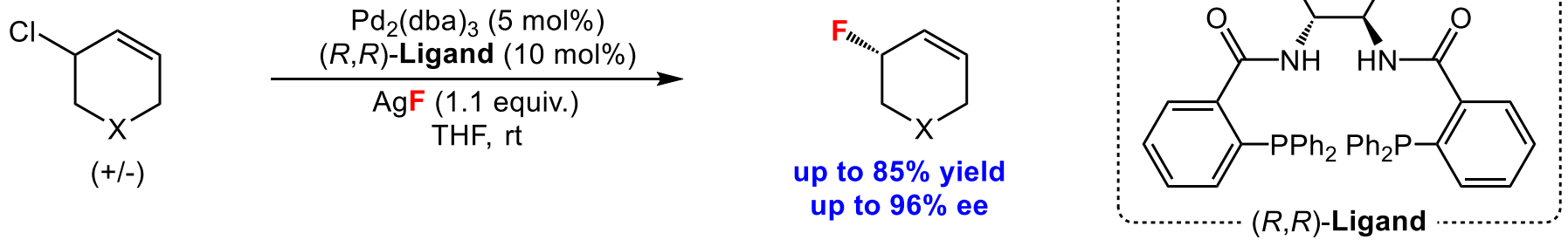


Kalow, J. A.; Doyle, A. G. *J. Am. Chem. Soc.* **2010**, *132*, 3268

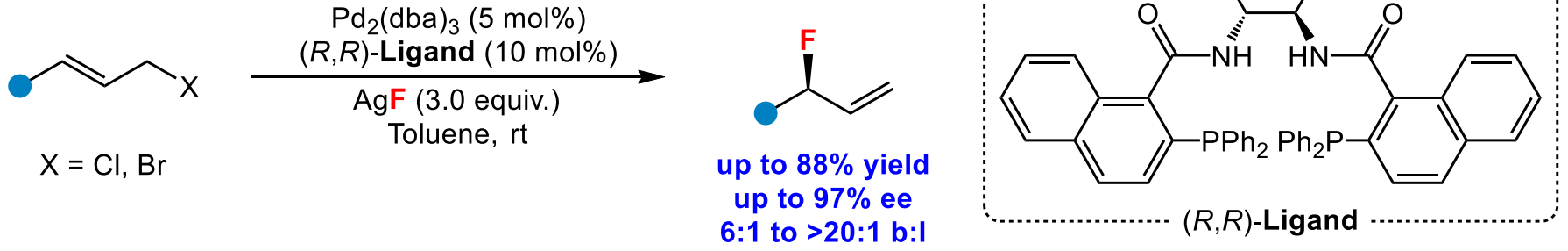
Kalow, J. A.; Doyle, A. G. *Tetrahedron* **2013**, *69*, 5702

Introduction

Asymmetric Fluorination Enabled by Transition Metal Catalysis



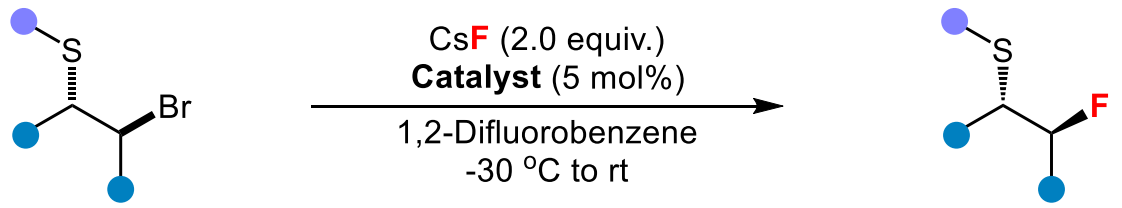
Katcher, M. H.; Doyle, A. G. *J. Am. Chem. Soc.* **2010**, *132*, 17402



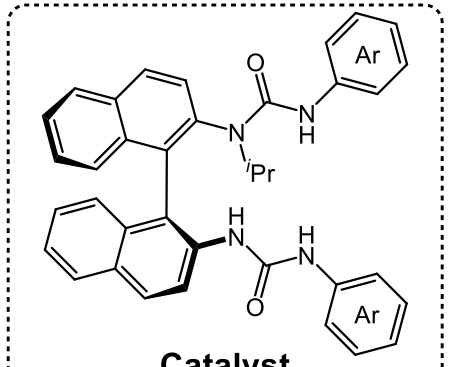
Katcher, M. H.; Sha, A.; Doyle, A. G. *J. Am. Chem. Soc.* **2011**, *133*, 15902

Introduction

Asymmetric Fluorination Enabled by HBPTC

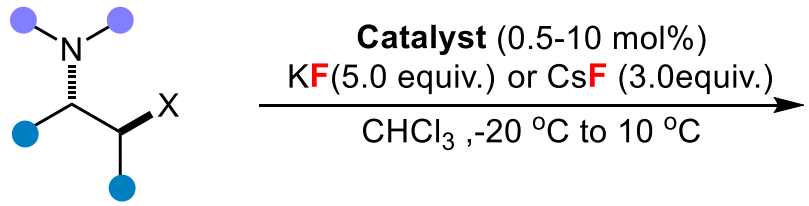


up to 98% yield
up up to 97:3 e.r.



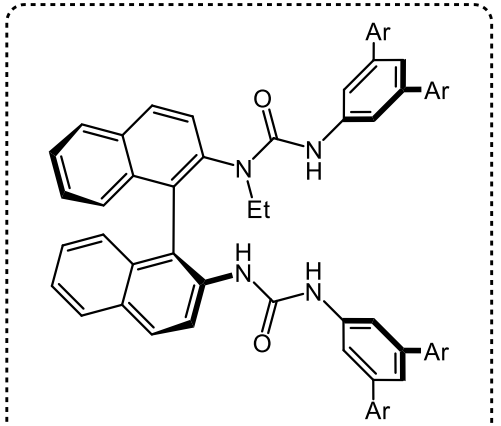
Catalyst
Ar = 3,5-$(CF_3)_2C_6H_3$

Pupo, G.; Ibba, F.; Ascough, D. M. H.; Gouverneur, V. *Science* **2018**, *360*, 638



X = Cl, Br

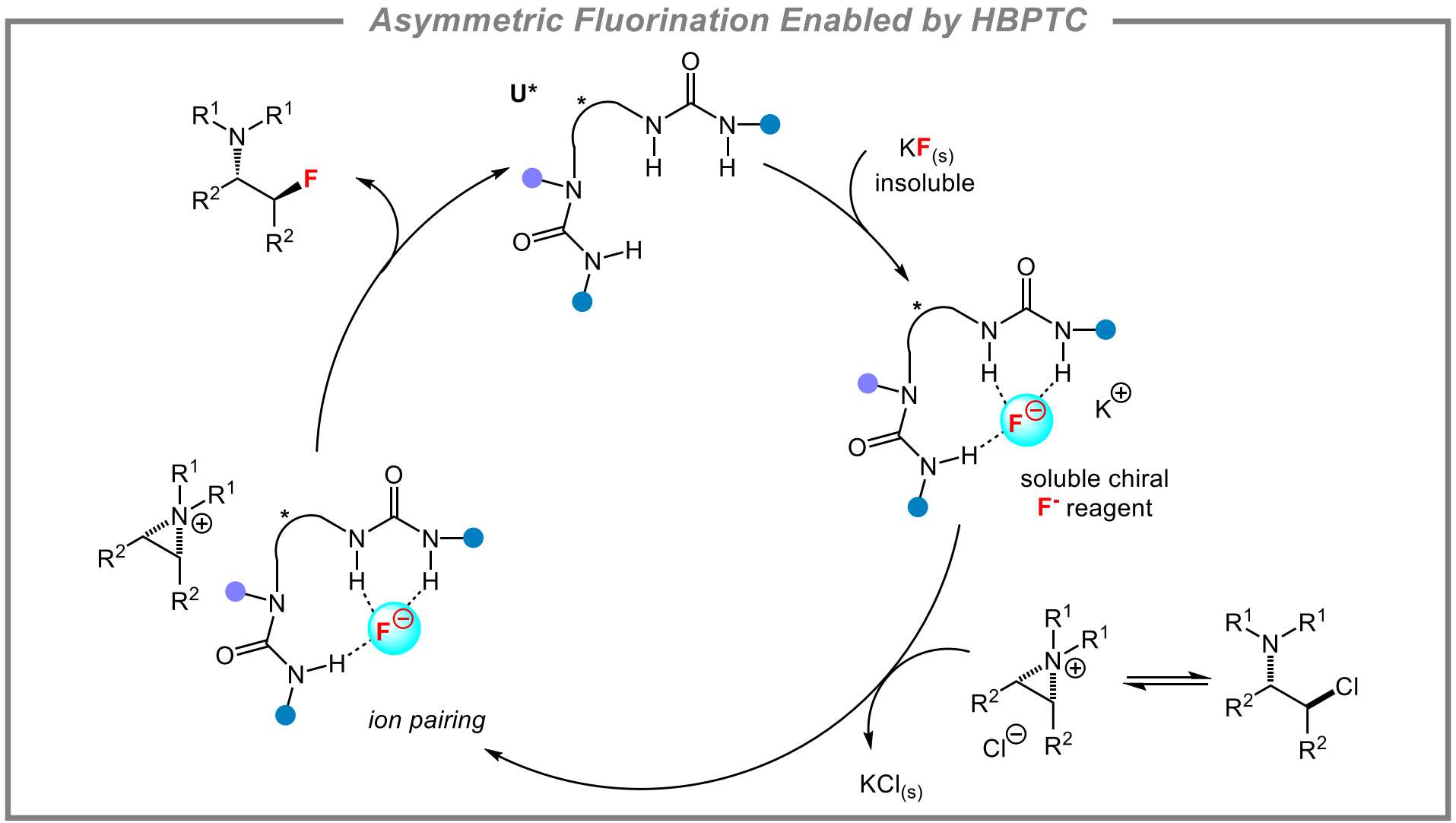
up to 92% yield
up to 96:4 e.r.



Catalyst
Ar = 3,5-$(CF_3)_2C_6H_3$

Pupo, G.; Vicini, A. C.; Ascough, D. M. H.; Gouverneur, V. *J. Am. Chem. Soc.* **2019**, *141*, 2878

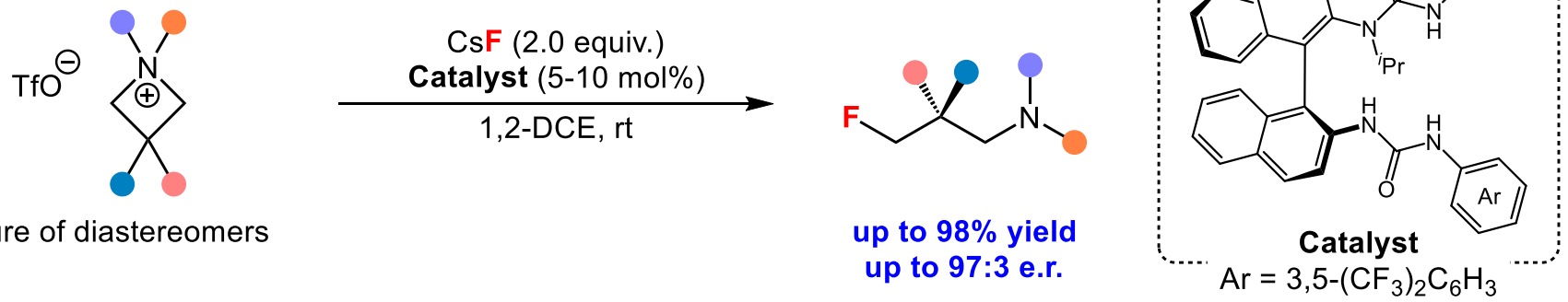
Introduction



Pupo, G.; Vicini, A. C.; Ascough, D. M. H.; Gouverneur, V. *J. Am. Chem. Soc.* **2019**, *141*, 2878

Introduction

Asymmetric Fluorination Enabled by HBPTC



Mixture of diastereomers

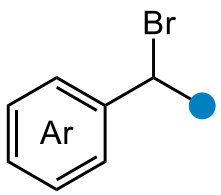
up to 98% yield
up to 97:3 e.r.

Catalyst
Ar = 3,5-$(CF_3)_2C_6H_3$

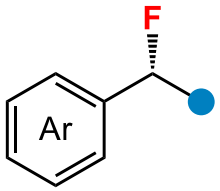
Roagna, G.; Ascough, D. M. H.; Pupo, G.; Gouverneur, V. *J. Am. Chem. Soc.* **2020**, *142*, 14045

Introduction

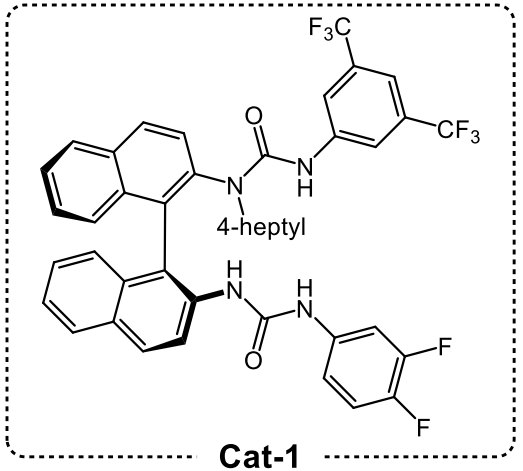
Asymmetric Fluorination Enabled by HBPTC



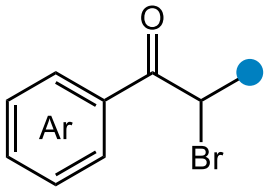
KF (2.5 equiv.)
Cat-1 (10 mol%)
$Ph_4P^+I^-$ (10 mol%)
p-Xylene, 25 °C



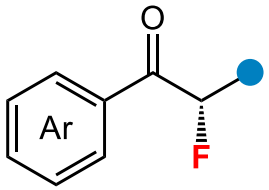
up to 95% yield
up to 97:3 e.r.



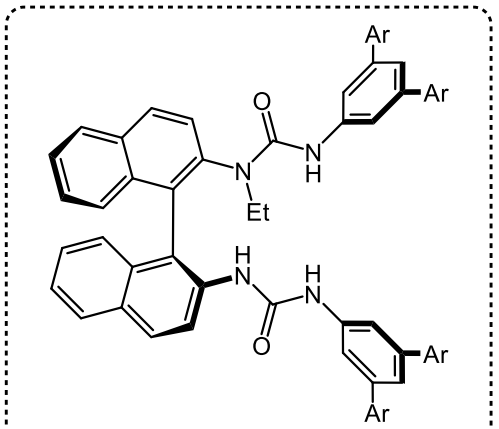
Cat-1



KF (5.0 equiv.)
Cat-2 (10 mol%)
$Et_4N^+I^-$ (10 mol%)
MeCN, 5 °C



up to 97% yield
up to 98:2 e.r.

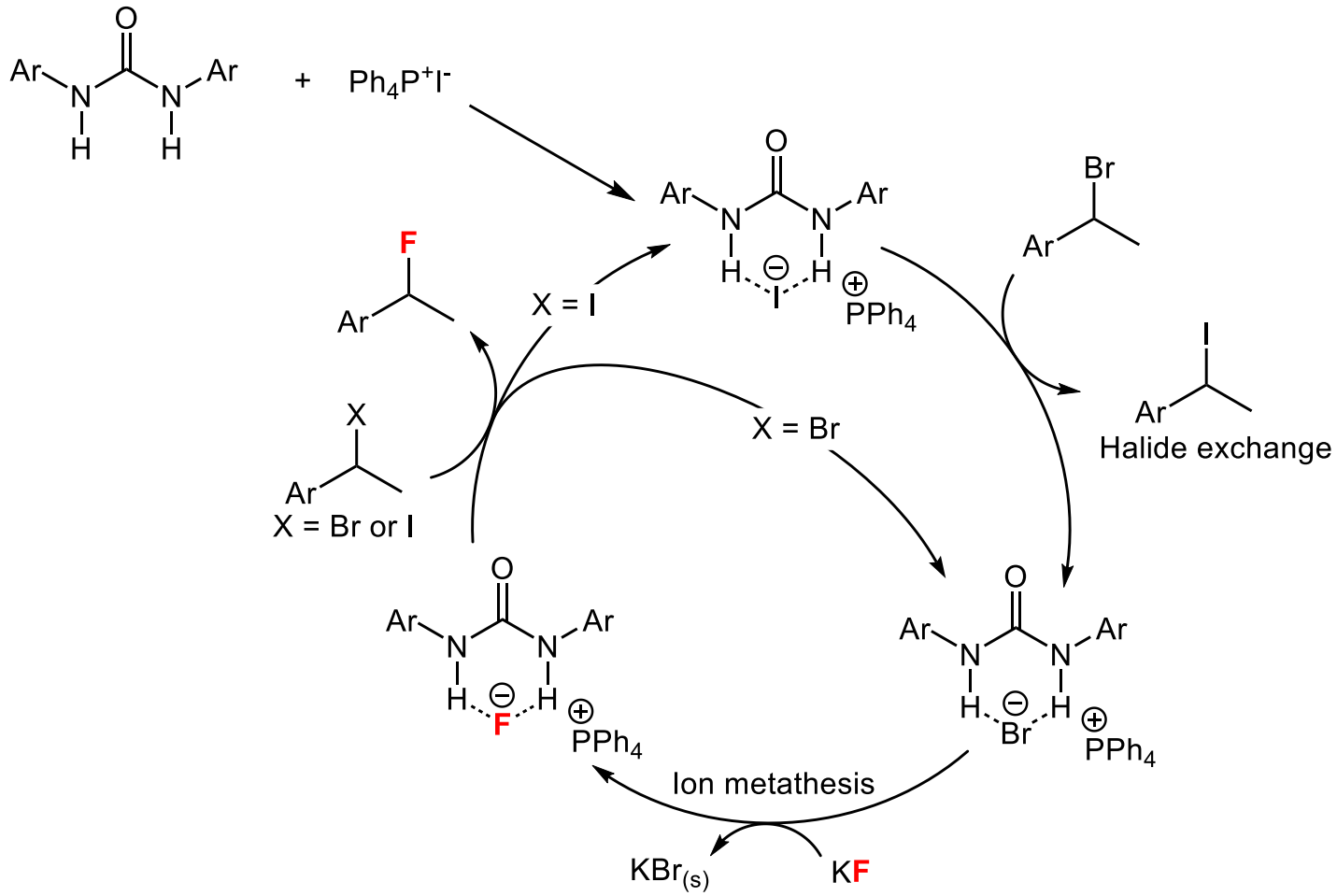


Cat-2
Ar = 3,5-$(CF_3)_2C_6H_3$

Dooley, C.; Ibba, F.; Lloyd-Jones, G. C.; Gouverneur, V. *Nat. Catal.* **2025**, *8*, 107

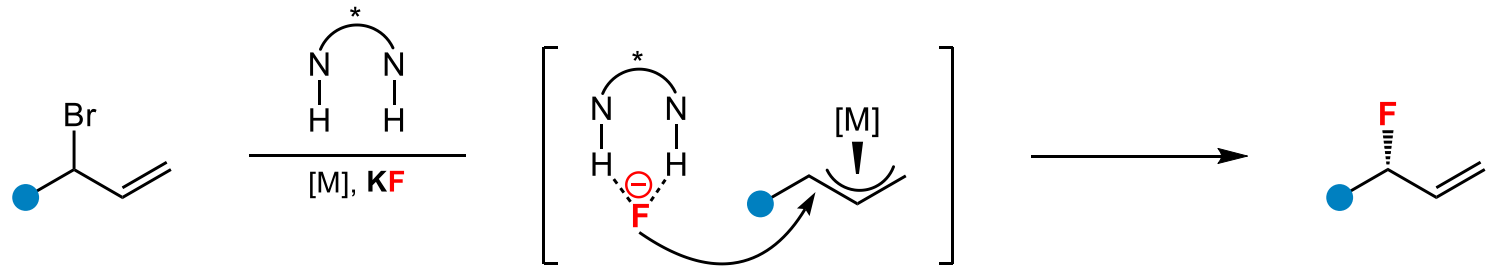
Introduction

Asymmetric Fluorination Enabled by HBPTC



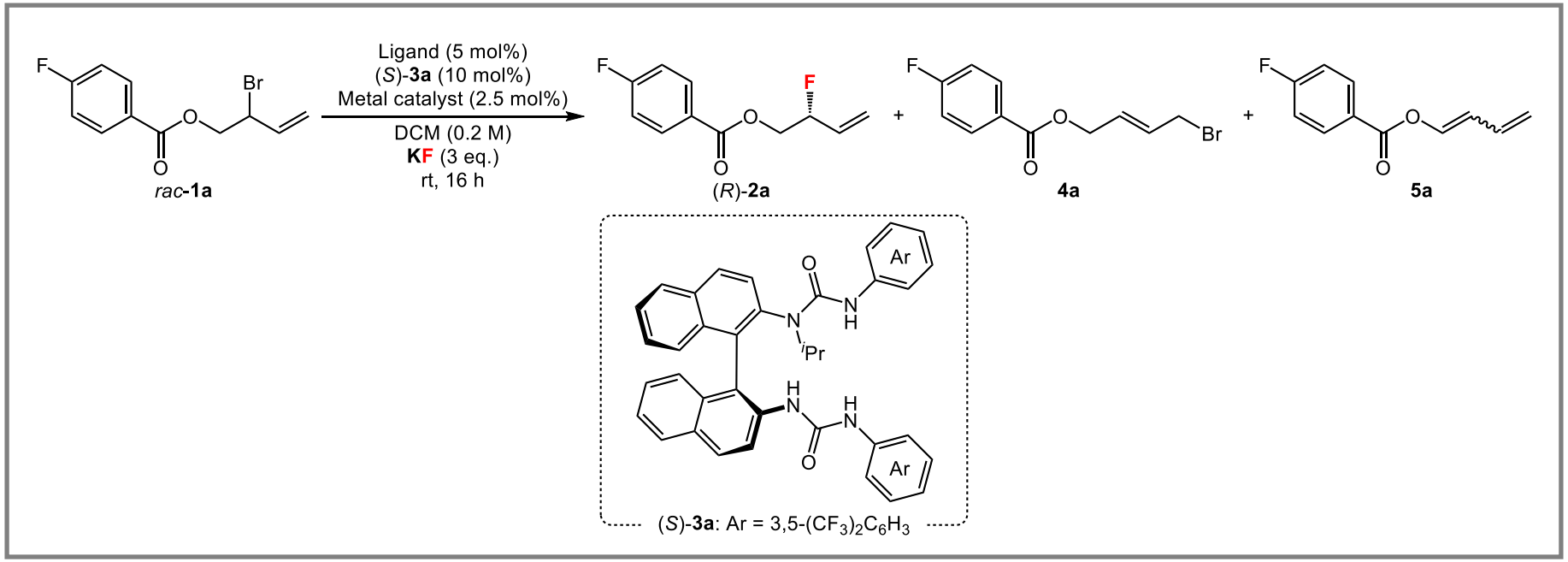
Dooley, C.; Ibba, F.; Lloyd-Jones, G. C.; Gouverneur, V. *Nat. Catal.* **2025**, *8*, 107

Project Synopsis



Challenges: ***1. Bis-urea catalysts could deactivate the transition metal.***
2. The compatibility is not well understood.

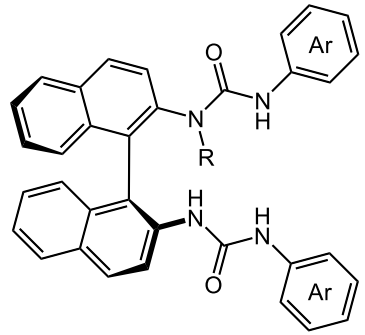
Optimization of the Reaction Conditions



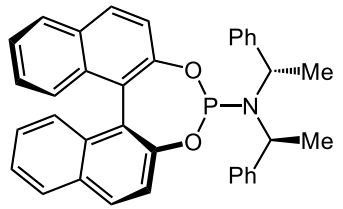
Entry	Metal catalyst	Ligand	2a Yield (%)[a]	4a (%)[a]	5a (%)[a]	2a e.r.[b]
1[c]	-	-	0	0	0	n.d.
2	$Pd_2(dba)_3$	PPh_3	0	0	0	n.d.
3	$[Ir(cod)Cl]_2$	-	34	6	6	56:44
4	$[Rh(cod)Cl]_2$	-	75	15	9	73:27

[a]Yield determined by 19F NMR using 4-fluoroanisole as an internal standard. [b]Enantiomeric ratio determined by HPLC analysis using a chiral stationary phase. [c]With PPh_4I (10 mol%) in *p*-xylene, 60 °C, 24 h

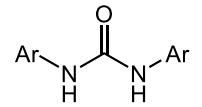
Optimization of the Reaction Conditions



(*S*)-**3a**: R = ^{i}Pr
Ar = 3,5-$(CF_3)_2C_6H_3$
(*S*)-**3d**: R = H
Ar = 3,5-$(CF_3)_2C_6H_3$
(*S*)-**3e**: R = ^{i}Pr
Ar = 3,5-$F_2C_6H_3$
(*S*)-**3f**: R = H
Ar = 4-$(SF_5)C_6H_4$
(*S*)-**3g**: R = H
Ar = Ph



L1

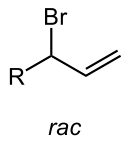


SU
Ar = 3,5-$(CF_3)_2C_6H_3$

Entry	Urea catalyst	Metal catalyst	Ligand	2a Yield (%)[a]	4a (%)[a]	5a (%)[a]	2a e.r.[b]
4	(*S*)-**3a**	$[Rh(cod)Cl]_2$	-	75	15	9	73:27
5	(*S*)-**3d**	$[Rh(cod)Cl]_2$	-	53	14	9	89:11
6	(*S*)-**3e**	$[Rh(cod)Cl]_2$	-	44	17	15	84:16
7	(*S*)-**3f**	$[Rh(cod)Cl]_2$	-	39	19	13	82:18
8	(*S*)-**3g**	$[Rh(cod)Cl]_2$	-	10	42	34	75:25
9	(*S*)-**3d**	$[Rh(cod)Cl]_2$	$P(OPh)_3$	61	16	6	88:12
10	(*S*)-**3d**	$[Rh(cod)Cl]_2$	**L1**	62	17	5	88:12
11	**SU**	$[Rh(cod)Cl]_2$	**L1**	15	26	10	50:50
12[c]	(*S*)-**3d**	$[Rh(cod)Cl]_2$	-	83	16	0	97:3

[a]Yield determined by 19F NMR using 4-fluoroanisole as an internal standard. [b]Enantiomeric ratio determined by HPLC analysis using a chiral stationary phase. [c]Reaction performed at -30 °C for 72 h.

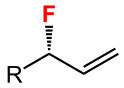
Substrate Scope

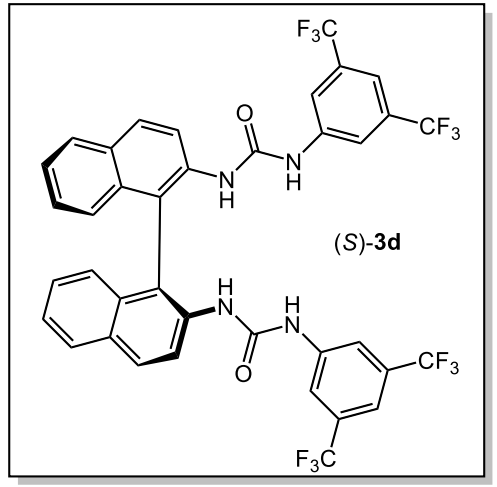


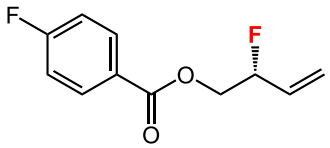
rac

(*S*)-**3d** (10 mol%)
$[Rh(cod)Cl]_2$ (2.5mol%)

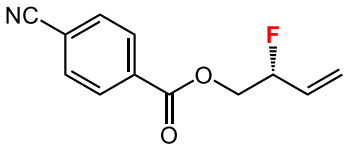
KF (3 equiv.), DCM (0.2 M)
-30 °C, 72 h



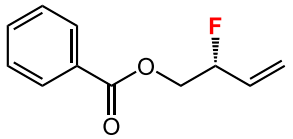




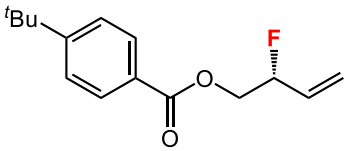
2a
74%, 97:3 e.r.



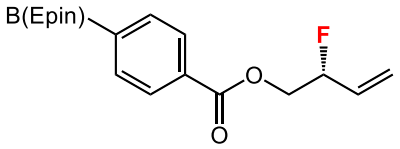
2b
74%, 95:5 e.r.



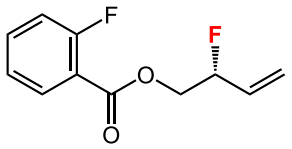
2c
51%, 96:4 e.r.



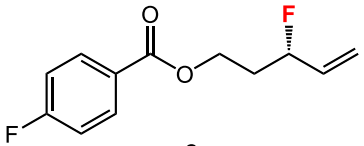
2d
36%, 95:5 e.r.



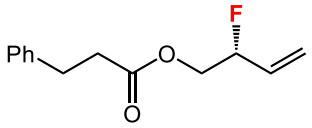
2e
36%, 95:5 e.r.



2f
78%, 95:5 e.r.

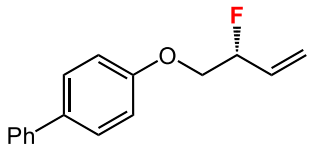


2g
85%, 83:17 e.r.

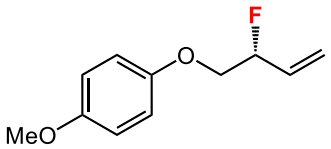


2h
75%, 97:3 e.r.

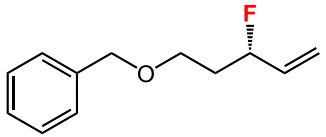
Substrate Scope



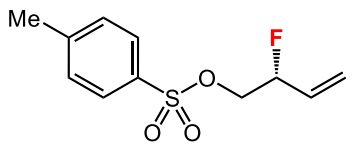
2i
52%, 99:1 e.r.



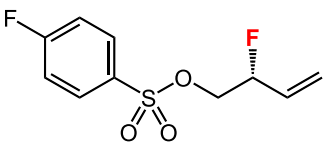
2j[a]
73%, 95:5 e.r.



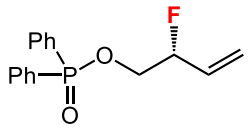
2k
51%, 89:11 e.r.



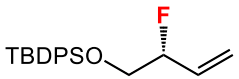
2l[a]
71%, 96:4 e.r.



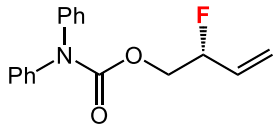
2m[a]
74%, 96:4 e.r.



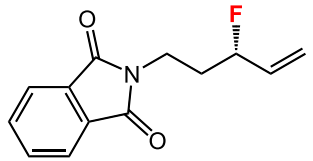
2n[b]
65%, 95:5 e.r.



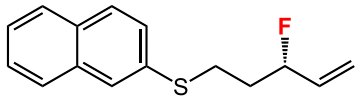
2o[b]
52%, 98:2 e.r.



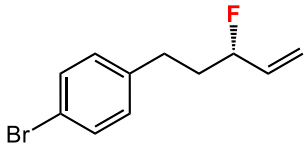
2p
32%, 96:4 e.r.



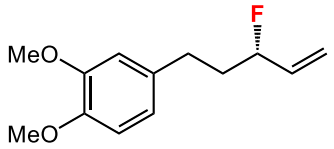
2q
79%, 90:10 e.r.



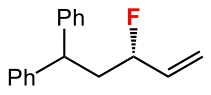
2r
34%, 67.5:32.5 e.r.



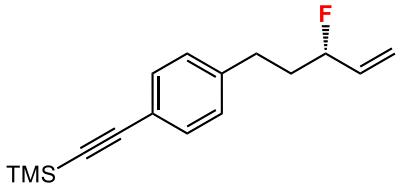
2s
81%, 87:13 e.r.



2t
83%, 84:16 e.r.



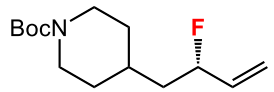
2u
58%, 83:17 e.r.



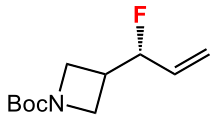
2v
50%, 87:13 e.r.

[a]Reaction performed at r.t. for 24 h. [b]Reaction performed at 0 °C for 72 h.

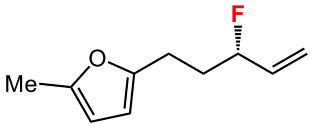
Substrate Scope



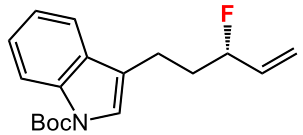
2w
45%, 86:14 e.r.



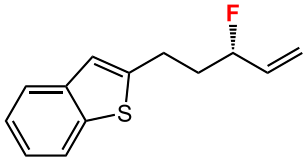
2x[a]
38%, 71.5:28.5 e.r.



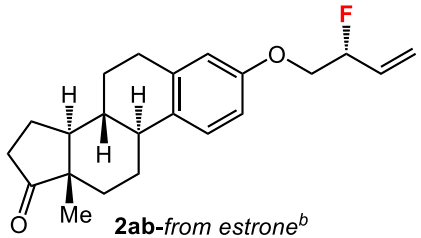
2y
52%, 73:27 e.r.



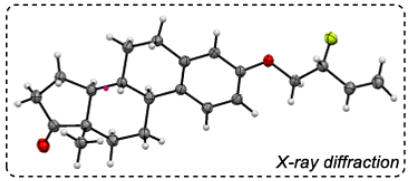
2z
47%, 87:13 e.r.



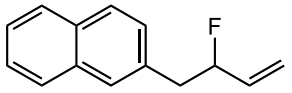
2aa
59%, 80:20 e.r.



2ab-*from estrone*[b]
80%, 96:4 d.r.



Limitations

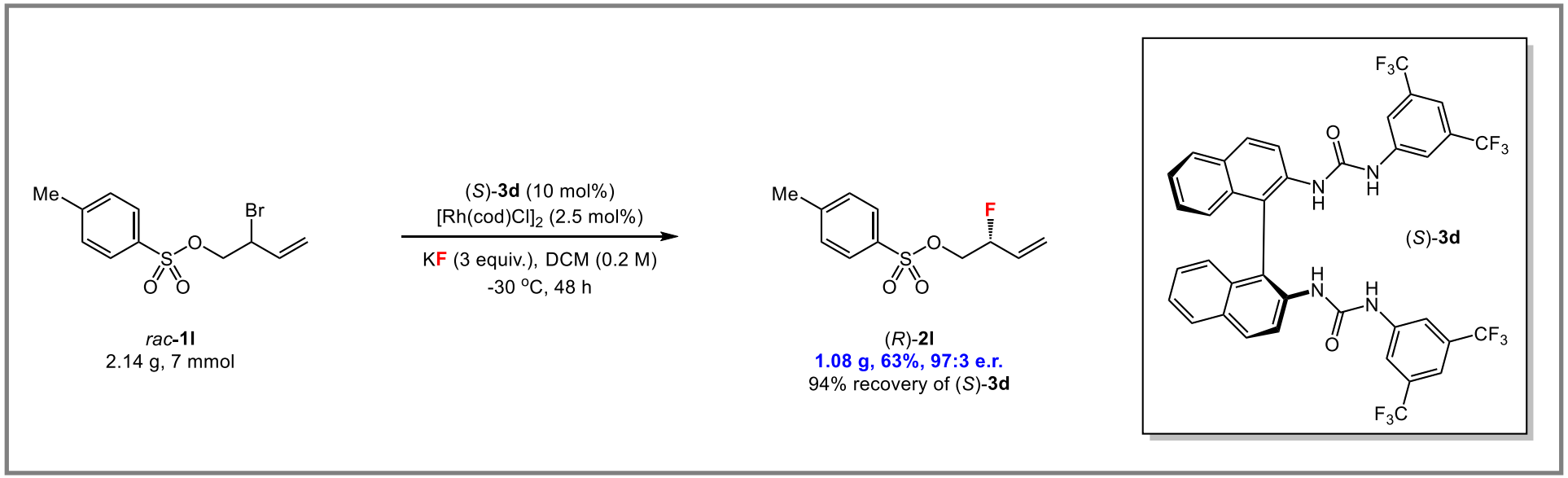


2ac
7%

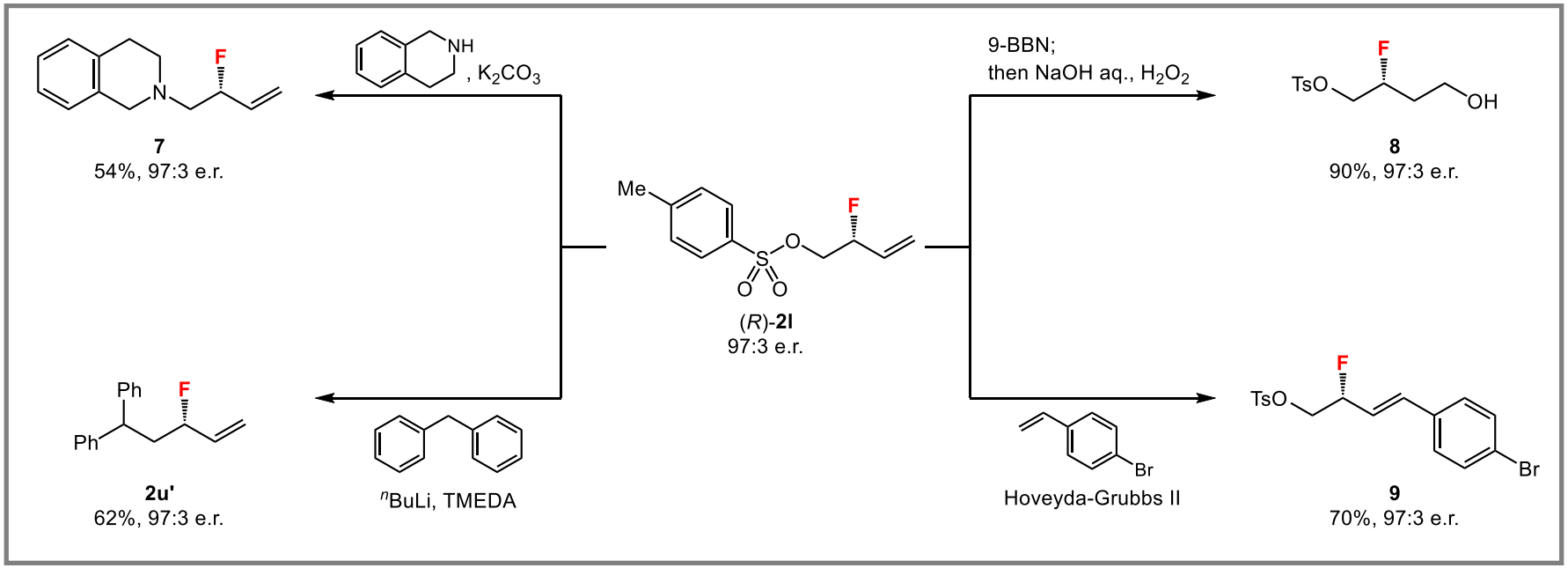
2ad
0%

[a]Reaction performed at r.t. for 24 h. [b]Reaction performed at 0 °C for 72 h.

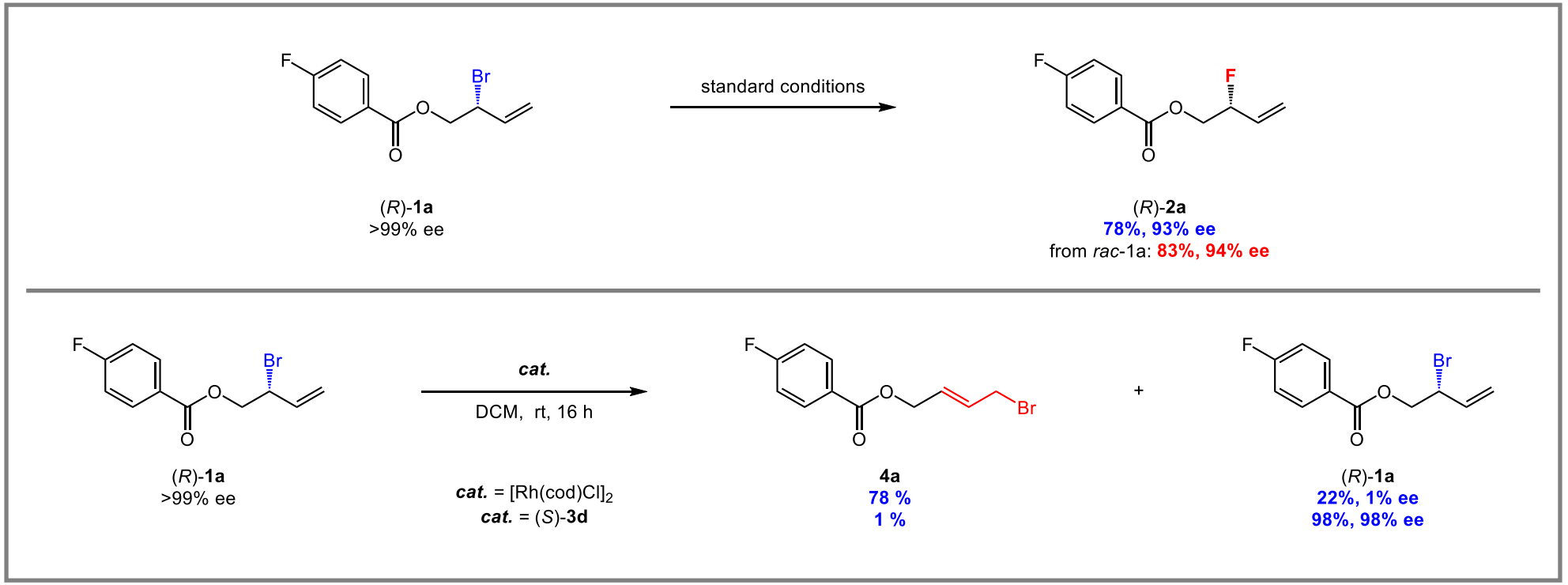
Gram-scale Synthesis



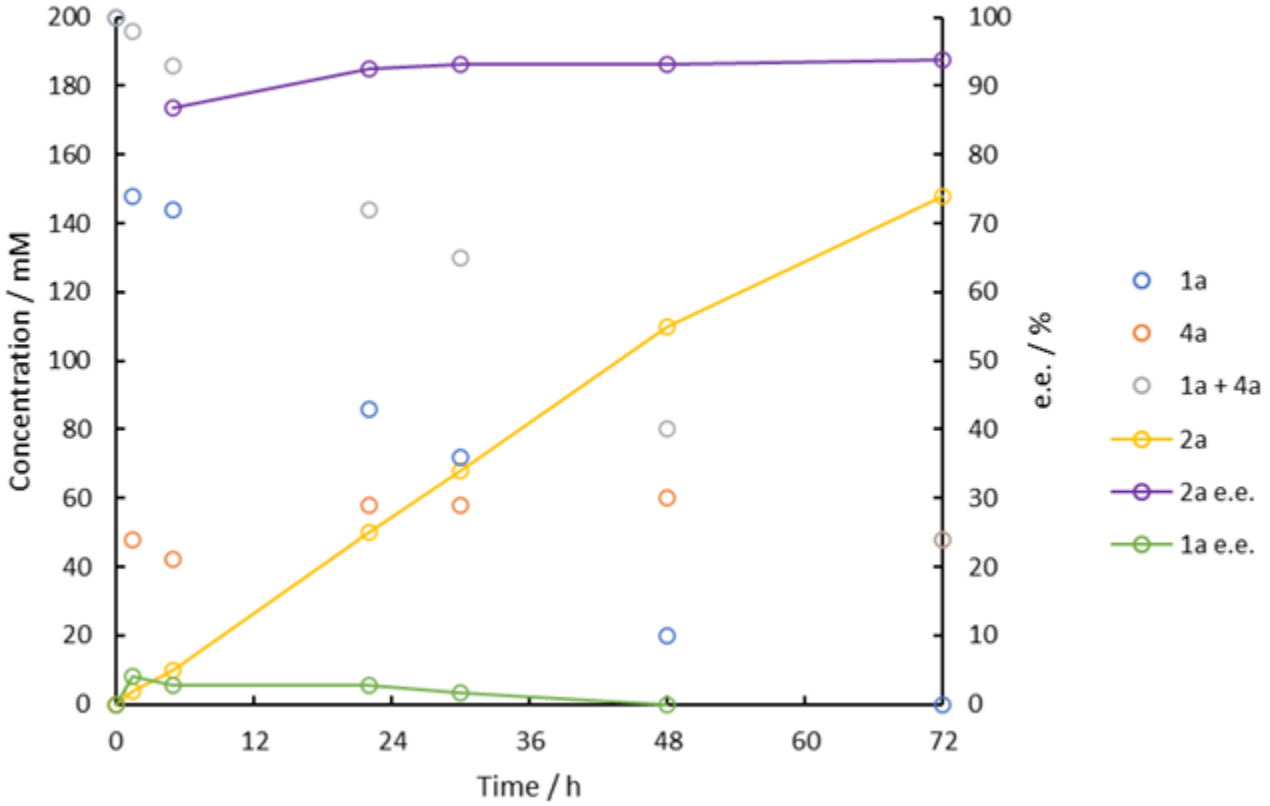
Further Product Derivatization



Control Experiments

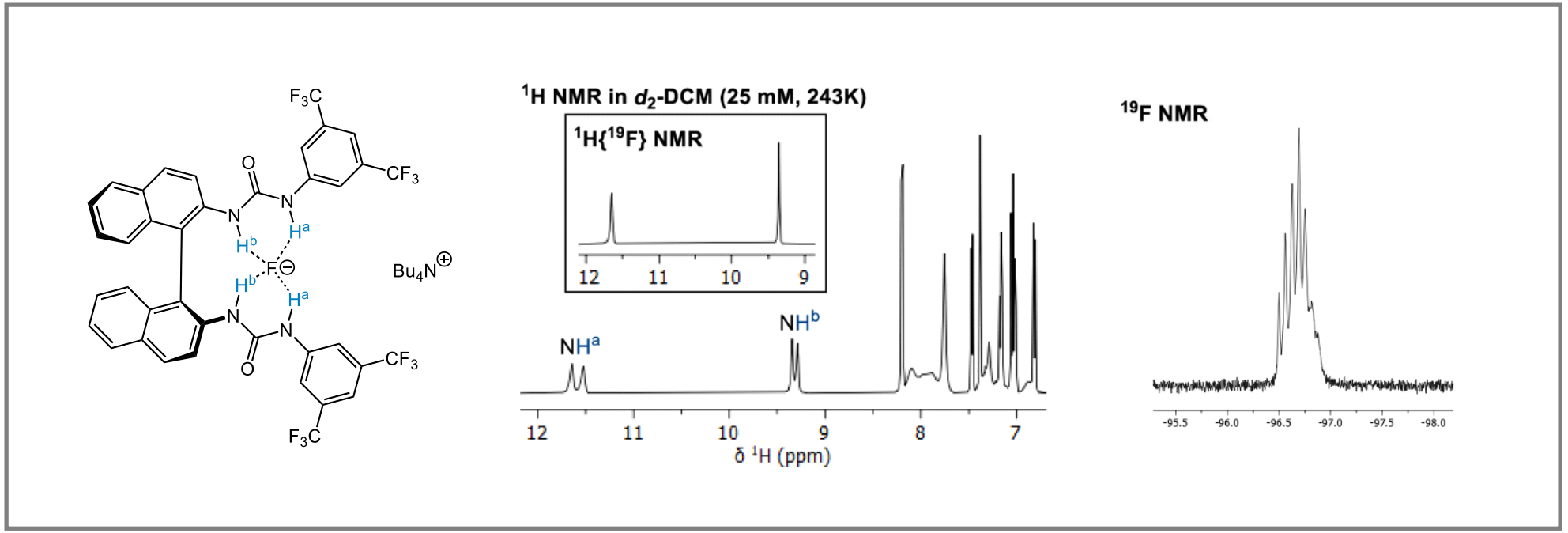


Control Experiments

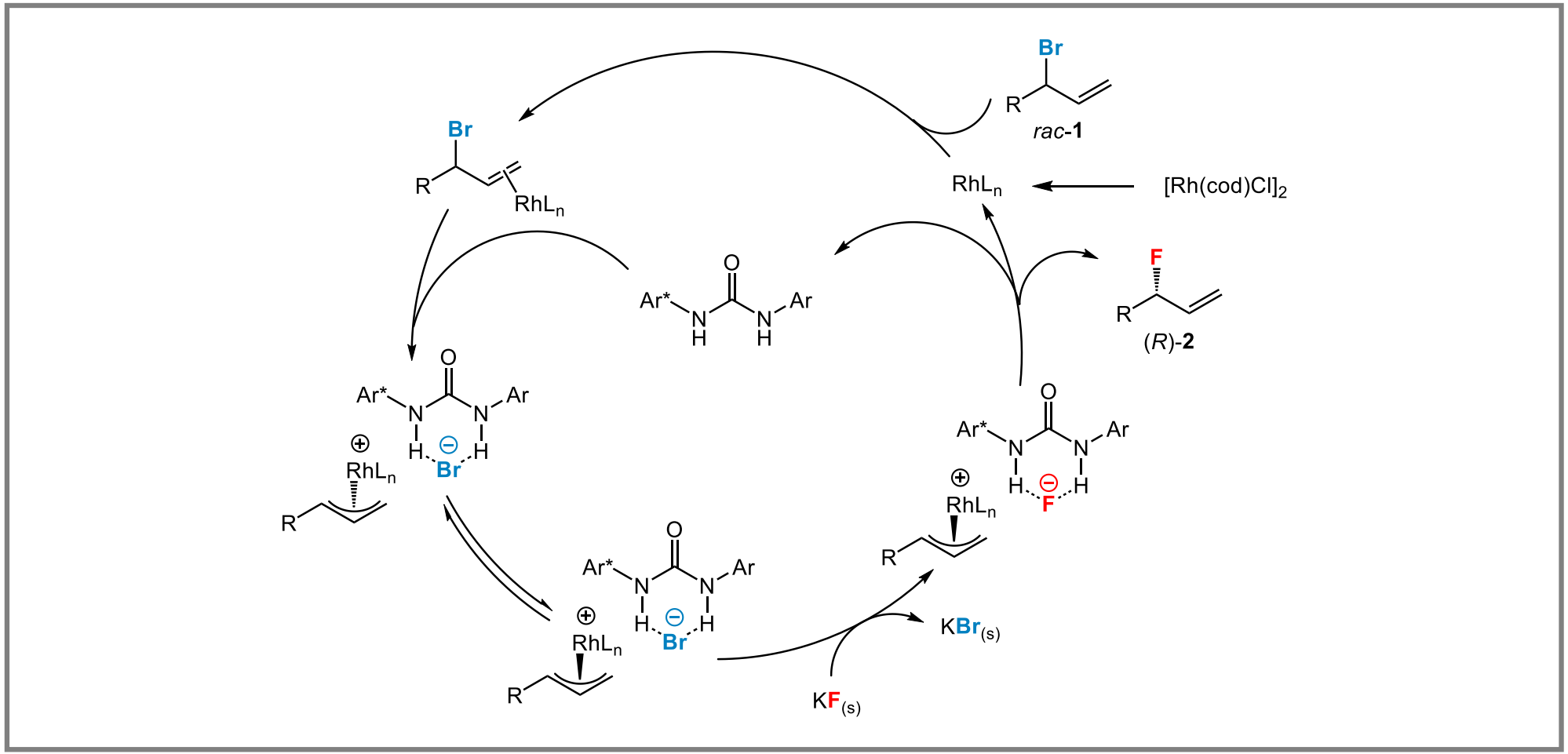


Plot of the yield and enantiomeric excess of **1a**, **2a** and **4a** over time

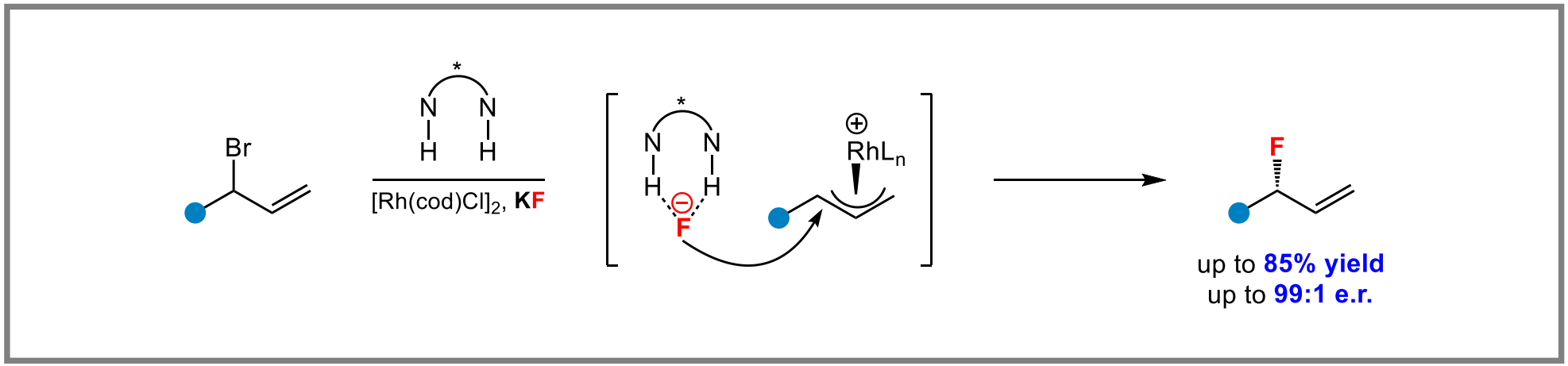
Control Experiments



Proposed Mechanistic Pathway



Summary



- ***HBD catalyst for solubilisation of KF***
- ***Complete regioselectivity***
- ***No exogenous ligand***
- ***Gram-scale synthesis***

Writing Strategy

The First Paragraph

The Importance of Chiral Fluorinated Molecules

↓

Prior Art

↓

The Challenges of Asymmetric Fluorinations

- Chiral fluorinated molecules are in demand in modern medicinal chemistry because molecular three-dimensionality is becoming increasingly important in lead optimization, and fluorine substitution controls parameters such as metabolic stability and lipophilicity.
- For synthesis, most studies on catalytic enantioselective carbon−fluorine bond construction make use of an electrophilic fluorine reagent.
- Asymmetric catalytic nucleophilic fluorinations have developed more slowly because the high basicity of the fluoride ion could out-compete its nucleophilicity, and the small size of fluoride makes it particularly challenging for stereodifferentiation of prochiral electro-philes.

Writing Strategy

The Last Paragraph

Summary of This Work

↓

Elucidate the Highlights

↓

Outlook of this Work

- In summary, we have developed a novel synergistic catalytic manifold that enables the highly enantioselective allylic fluorination of racemic allyl bromides with KF.
- The rhodium(I) catalyst provides a rapidly racemizing electrophilic π-allyl intermediate, allowing for enantioconvergence. Catalyst (*S*)-**3d** solubilizes fluoride in a well-characterized, 4-fold hydrogen bonding complex, which tunes fluoride reactivity and contributes to the high level of regio- and enantiocontrol.
- We anticipate that this strategy of synergistic catalysis can be extended to more classes of substrates intractable to HBPTC or transition-metal catalysis alone.

Representative Examples

- Building on these precedents, enantioselective fluorination under synergistic HBPTC and metal catalysis would represent a new catalytic manifold by featuring a chiral hydrogen-bonded nucleophilic fluoride ion-paired with a cationic metal-substrate complex. (building on these precedents, 以这些先例为基础)
- The final optimized conditions afforded **2a** in 83% NMR yield and 97:3 e.r., and completely circumvented elimination (**5a**). (circumvent, v. 规避；绕过；绕行；设法回避；绕道旅行)
- We anticipate that this strategy of synergistic catalysis can be extended to more classes of substrates intractable to HBPTC or transition-metal catalysis alone. (anticipate, v. 预料，预见，预计)

Acknowledgement

Thanks for your attention!