Literature Report IX

Enantioselective Aryl-Iodide-Catalyzed Wagner-Meerwein Rearrangements

Reporter : Yang Zhao

Checker : Bo Wu

Date : 2020-10-12

Haj, M. K.; Banik, S. M.; Jacobsen, E. N. *et al. Org. Lett.* **2019***, 21,* 4919
Sharma, H. A.; Mennie, K. M.; Jacobsen, E. N. *et al. J. Am. Chem. Soc*. **2020**, *142*, 16090

Contents

CV of Eric N. Jacobsen

Jacobsen, E. N.

Research:

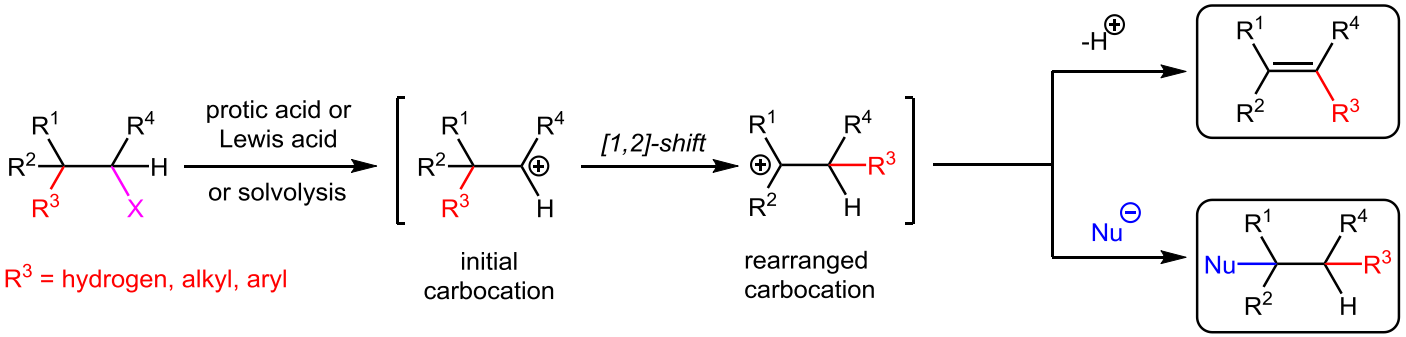
- Mechanistic and synthetic organic chemistry
- Development of new stereoselective catalytic reactions
- Enantioselective synthesis of natural products

Education:

- **1978–1982** B.S., New York University
- **1982–1986** Ph.D., University of California, Berkeley (Robert G. Bergman)
- **1986–1988** Postdoc., National Institutes of Health, MIT (K. Barry Sharpless)
- **1988–1991** Assistant Prof., University of Illinois at Urbana-Champaign
- **1991–1993** Associate Prof., University of Illinois at Urbana-Champaign
- **1993–Now** Professor, Harvard University

Introduction

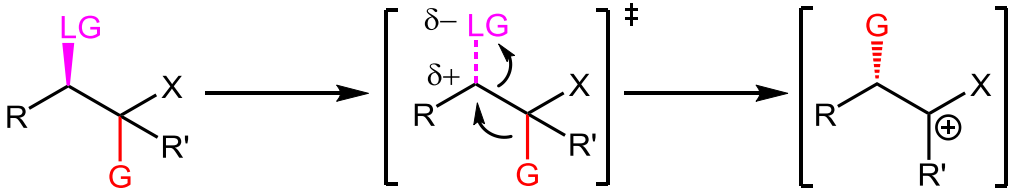
Wagner-Meerwein Rearrangement



- The generation of the initial carbocation: protonation of alkenes, alcohols, epoxides or cyclopropanes, solvolysis of secondary and tertiary alkyl halides, or sulfonates in a polar protic solvent, deamination of amines with nitrous acid, etc.
- Driving force: rearrange to a thermodynamically more stable structure.
- Order of migrating groups: CH_3O- > > Cl- > $H_2C{=}CH$- > 3 °C > 2 °C > 1 °C > CH_3- > H-

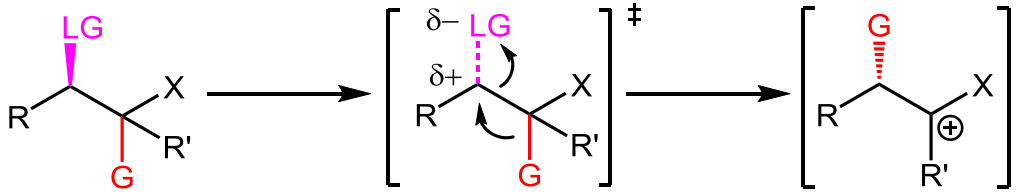
Introduction

Stereospecific cationic rearrangements

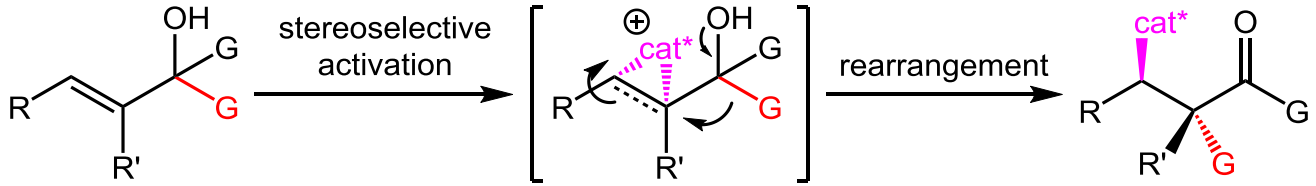


Introduction

Stereospecific cationic rearrangements

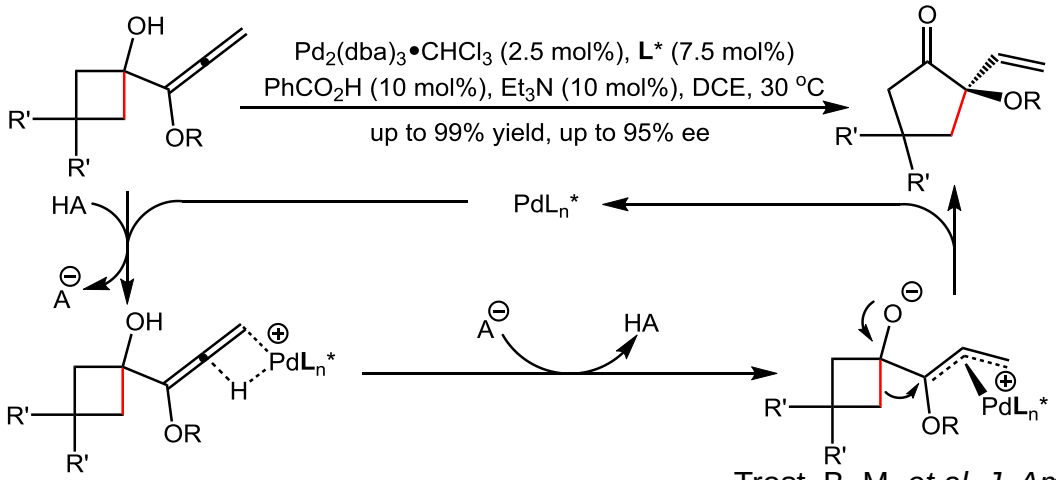


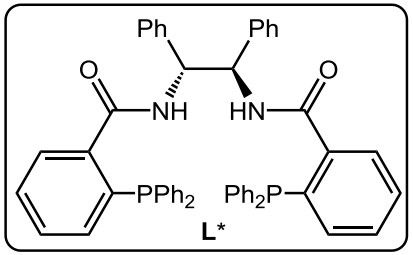
Catalytic semipinacol reactions



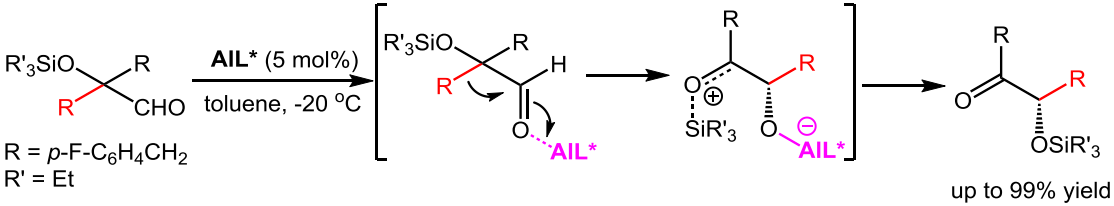
Introduction

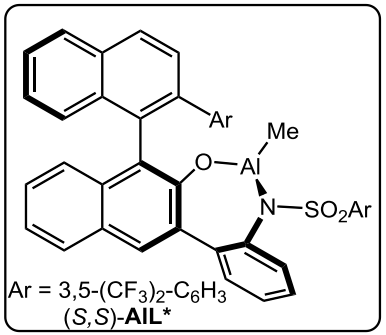
Catalytic semipinacol reactions (Transition-metal)





Trost, B. M. *et al. J. Am. Chem. Soc.* **2006**, *128*, 6044

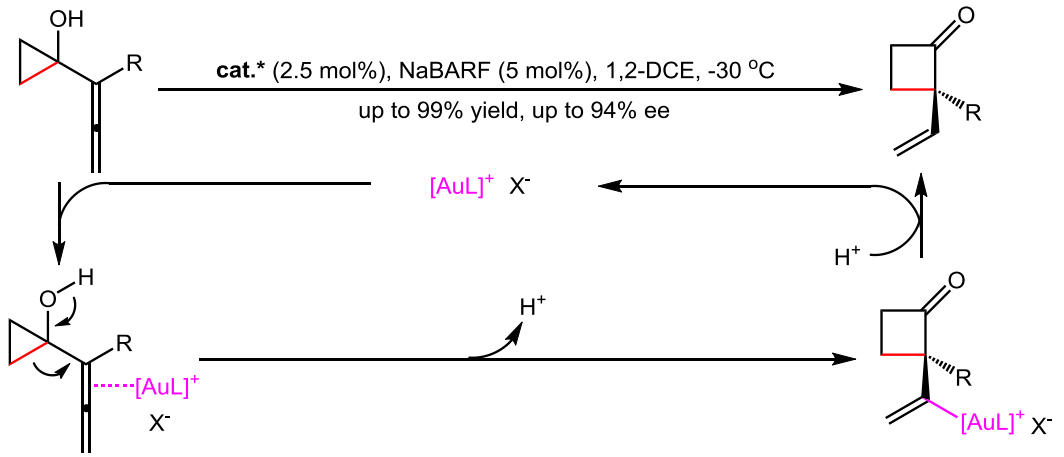


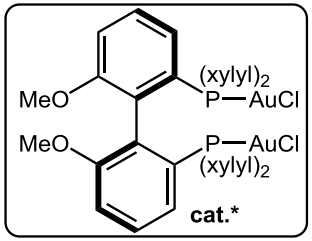


Maruoka, K. *et al. J. Am. Chem. Soc.* **2007**, *129*, 2410

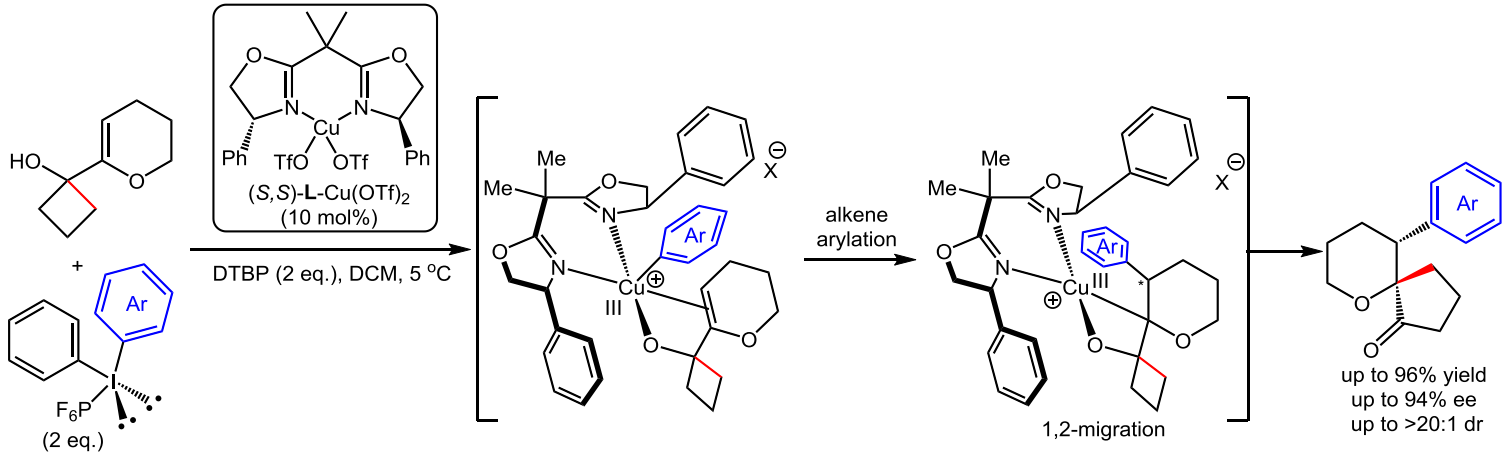
Introduction

Catalytic semipinacol reactions (Transition-metal)





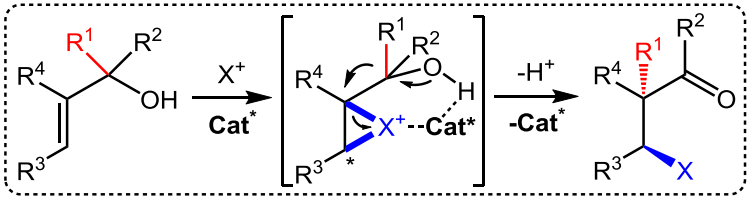
Toste, F. D. *et al. J. Am. Chem. Soc.* **2009**, *131*, 9178

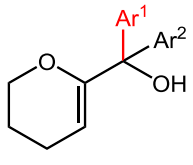


Gaunt, M. J. *et al. J. Am. Chem. Soc.* **2017**, *139*, 9160

Introduction

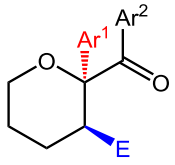
Catalytic semipinacol reactions (Organocatalytic halogenation)



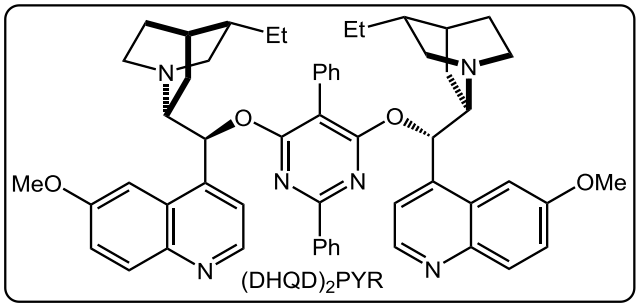


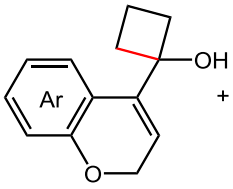
$E^+ = Br^+$ or Cl^+

$(DHQD)_2PYR$ (0.1 eq.)
$CH_3CONHBr$ (1.1 eq.) or DCDMH (1.1 eq.)
NBLP (0.1eq.), toluene, -20 °C



single diastereomer
up to 95% yield
up to 99% ee





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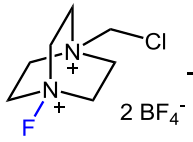
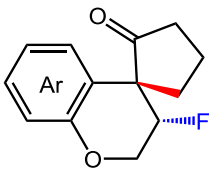
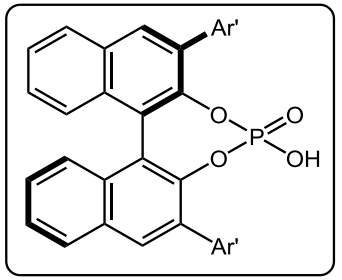


2 BF_4^-

cat. (5 mol%), Na_3PO_4 (1.25 eq.)
C_6H_5F/*n*-hexane 1:1, -20 °C



up to 97% yield
up to 95% ee
up to >20:1 dr



Tu, Y.-Q. *et al. J. Am. Chem. Soc.* **2011**, *133*, 8818
Alexakis, A. *et al. Angew. Chem. Int. Ed.* **2013**, *52*, 9266

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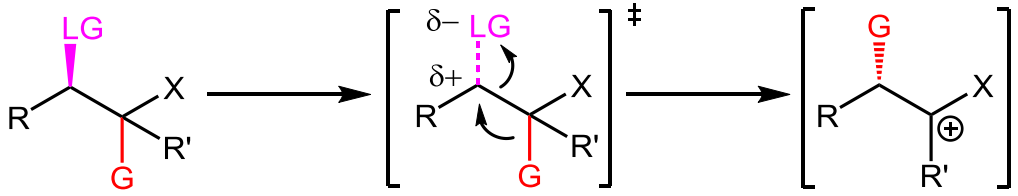
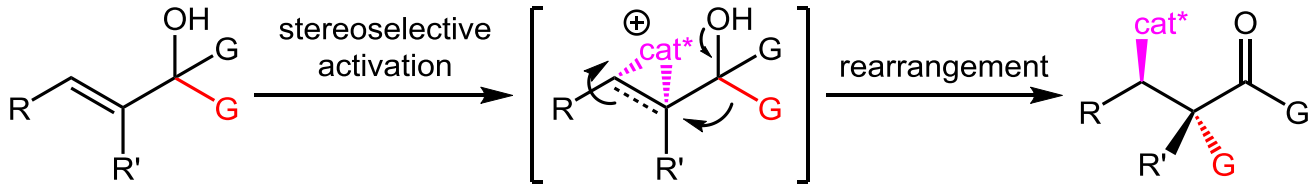
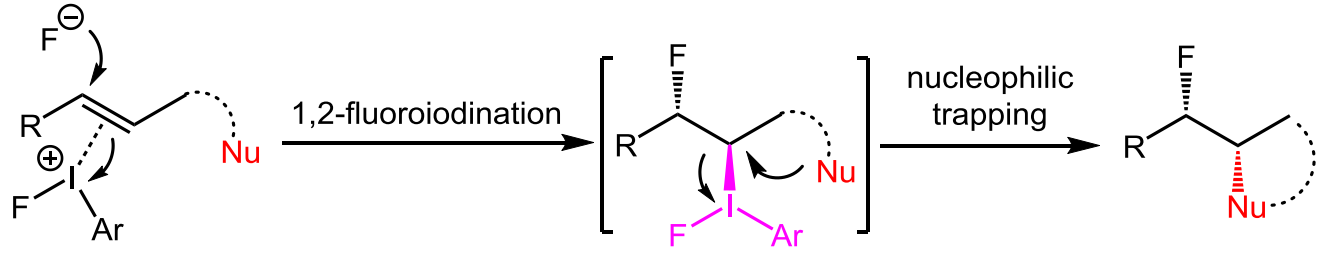
Stereospecific cationic rearrangements



Catalytic semipinacol reactions



ArI-catalyzed difunctionalization



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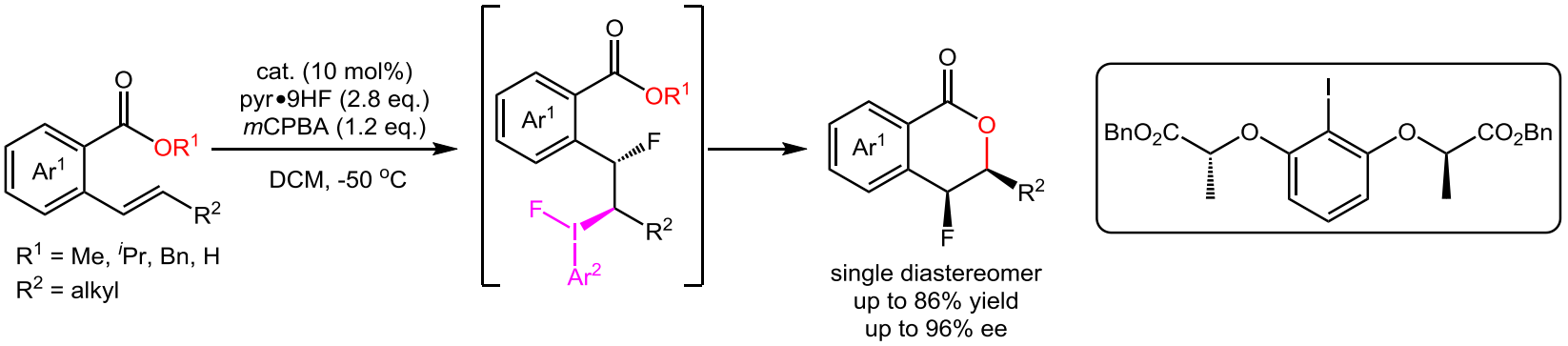
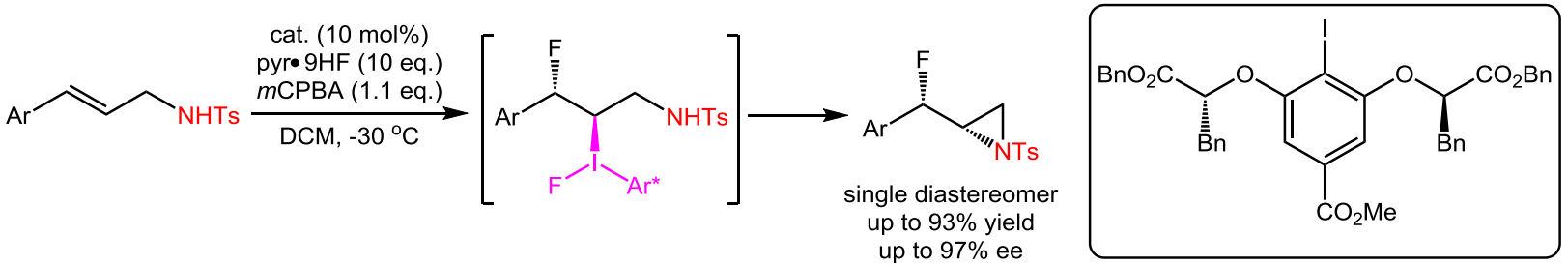
ArI-catalyzed difunctionalization



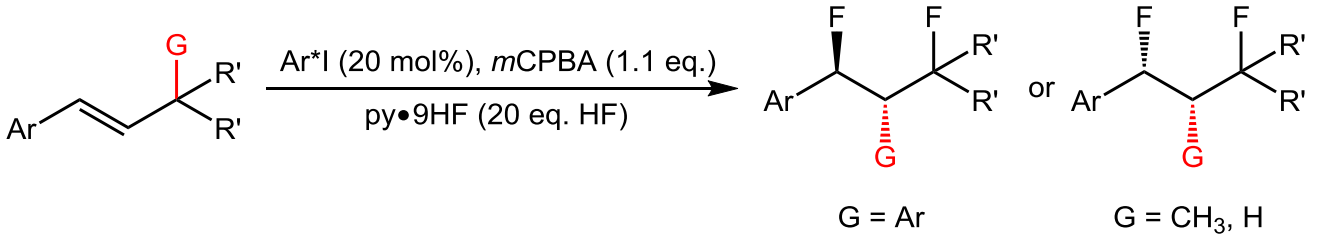
Jacobsen, E. N. *et al. J. Am. Chem. Soc.* **2016**, *138*, 13858



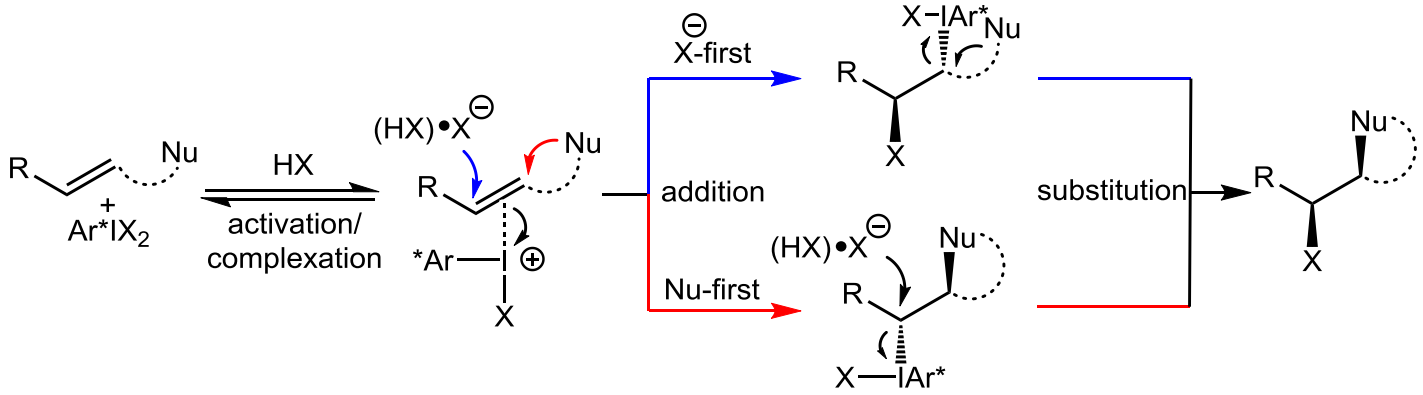
Jacobsen, E. N. *et al. J. Am. Chem. Soc.* **2018**, *140*, 4797

Wagner-Meerwein Rearrangements

This work: enantioselective catalytic Wagner-Meerwein rearrangements



General mechanistic considerationsin I(III)-promoted oxidative difunctionalizations of alkenes



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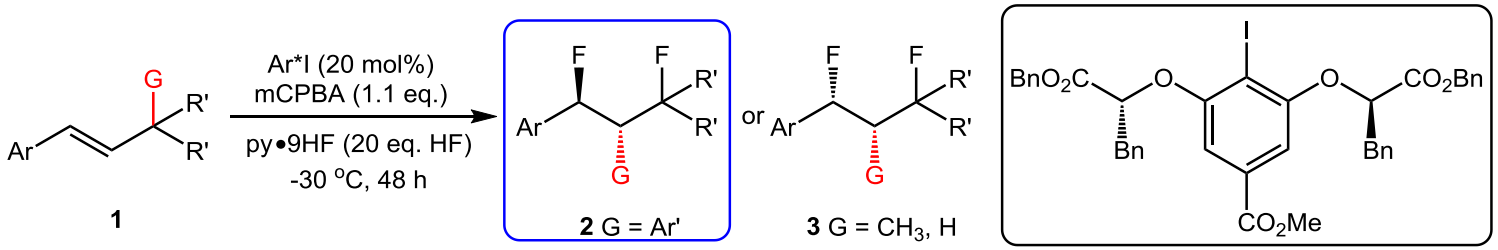
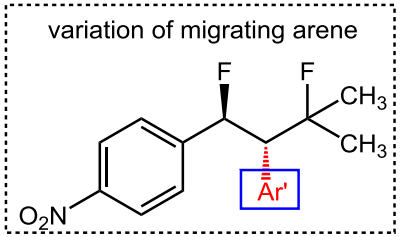
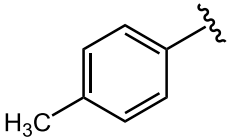
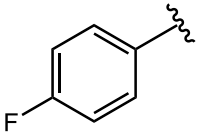
Wagner-Meerwein Rearrangements



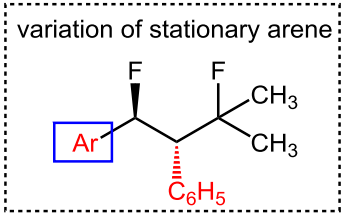


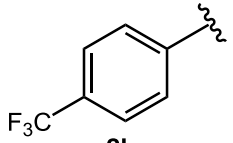


2a
90% yield, 90% ee
>20:1 dr

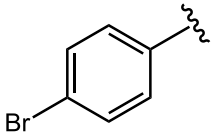


2b
87% yield, 93% ee
>20:1 dr

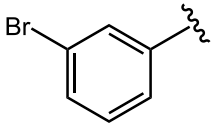




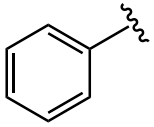
2h
82% yield, 90% ee
5:1 dr



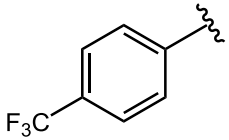
2c
85% yield[a], 88% ee
10:1 dr



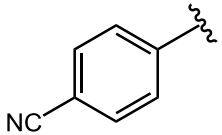
2d
84% yield[a], 90% ee
4:1 dr



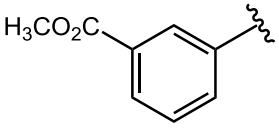
2e
85% yield, 92% ee
>20:1 dr



2f
83% yield[a], 94% ee
2:1 dr



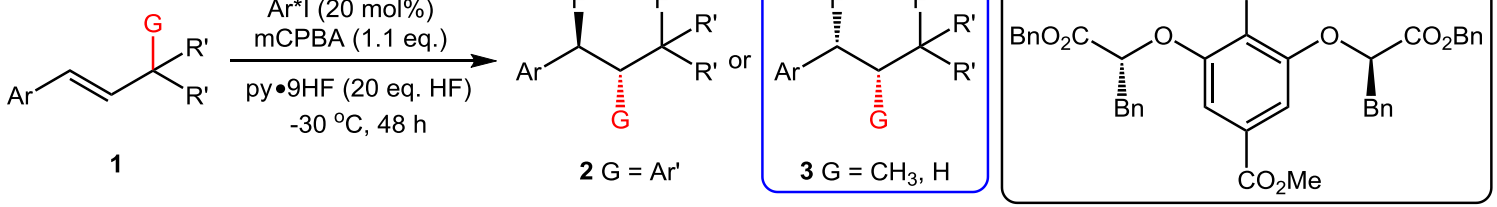
2g
78% yield, 91% ee
14:1 dr

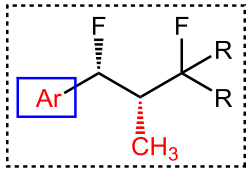


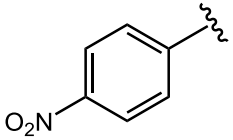
2i
81% yield, 88% ee
2:1 dr

Substrate scope for the enantioselective, catalytic Wagner-Meerwein rearrangements. Reactions were carried out using 0.52 mmol scale of styrenyl substrate **1**, catalyst (20 mol %), *m*CPBA (0.57 mmol), and pyr·9HF (10.4 mmol HF) in DCM (3.0 mL). [a]100 equiv HF were employed.

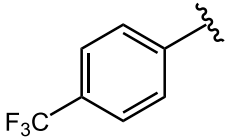
Wagner-Meerwein Rearrangements



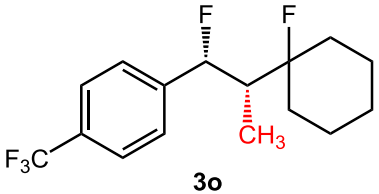




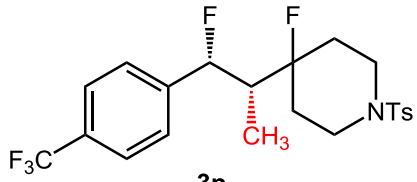
3j
85% yield, 88% ee
>20:1 dr



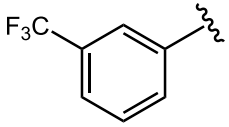
3k
87% yield, 97% ee
>20:1 dr



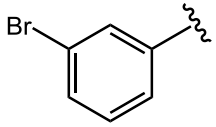
3o
81% yield, 99% ee
>20:1 dr



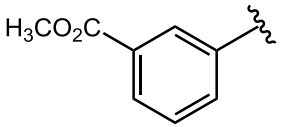
3p
70% yield, 98% ee
>20:1 dr



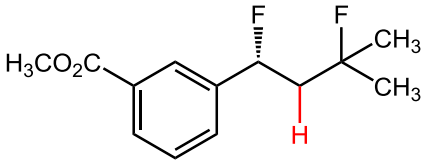
3l
88% yield, 99% ee
>20:1 dr



3m
64% yield, 99% ee
>20:1 dr

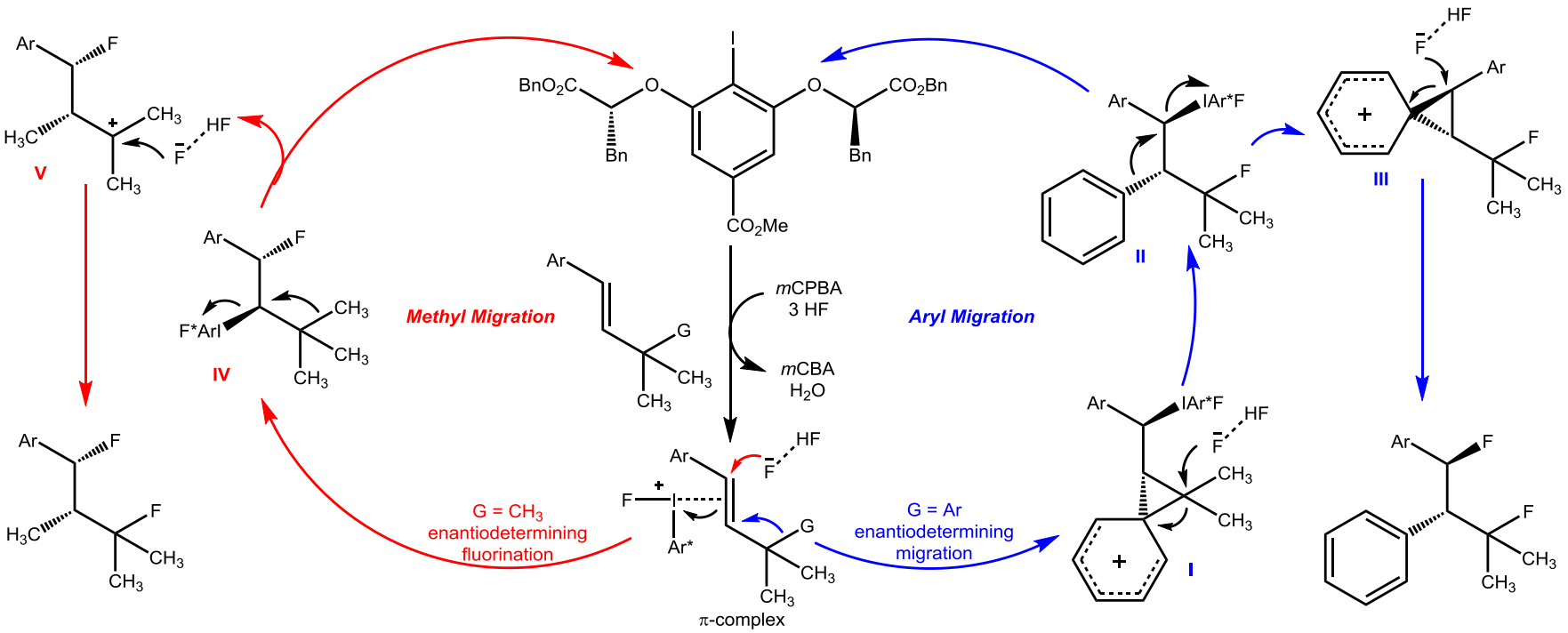


3n
86% yield, 99% ee
>20:1 dr



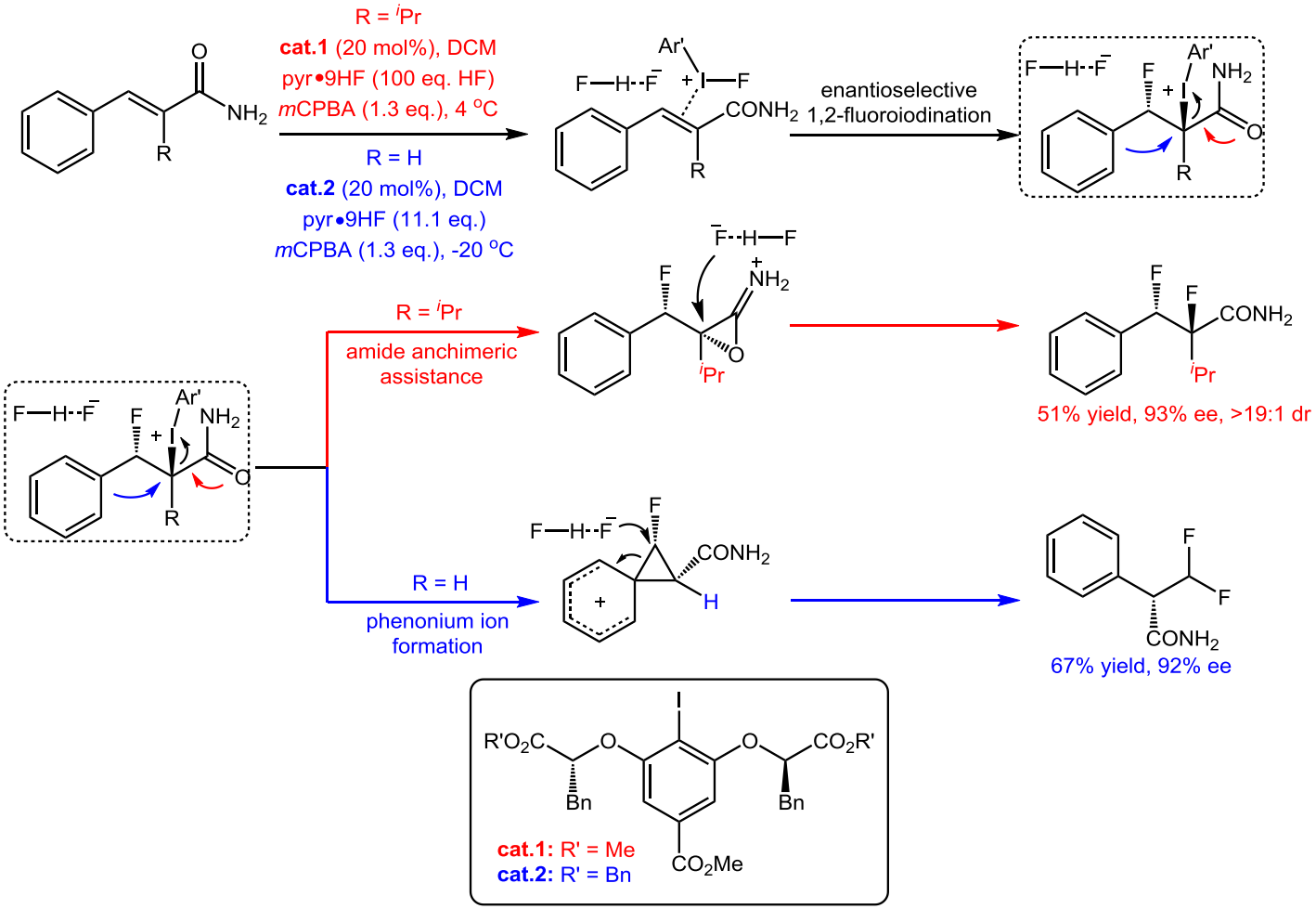
3q
70% yield, 83% ee

Wagner-Meerwein Rearrangements



1,2-Difluorination of Cinnamamides

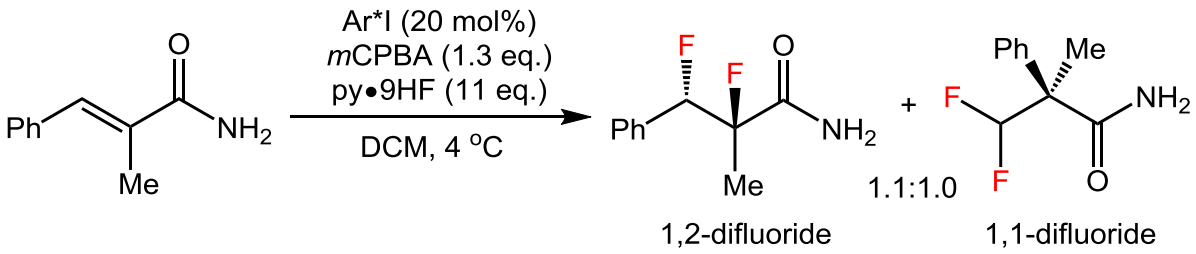
ArI-catalyzed difunctionalization (1,2- vs. 1,1-difluorination)



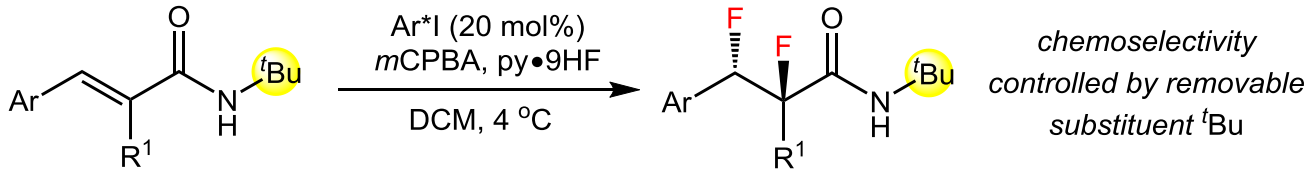
Jacobsen, E. N. *et al. J. Am. Chem. Soc.* **2016**, *138*, 5000
Jacobsen, E. N. *et al. Science* **2016**, *353*, 51

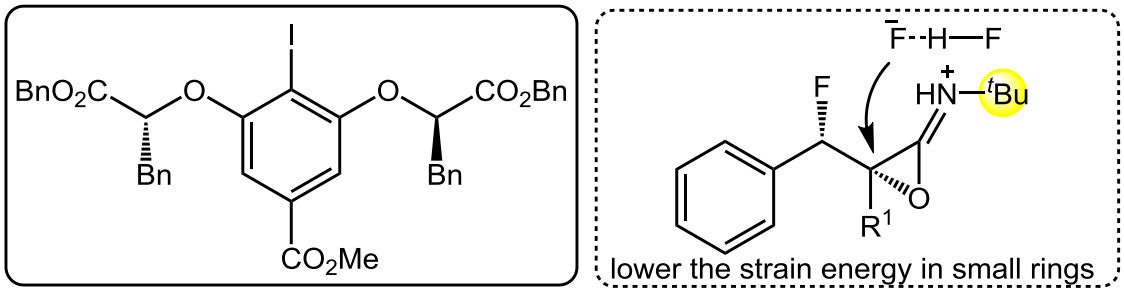
1,2-Difluorination of Cinnamamides

Competition between 1,2- and 1,1-difluorination



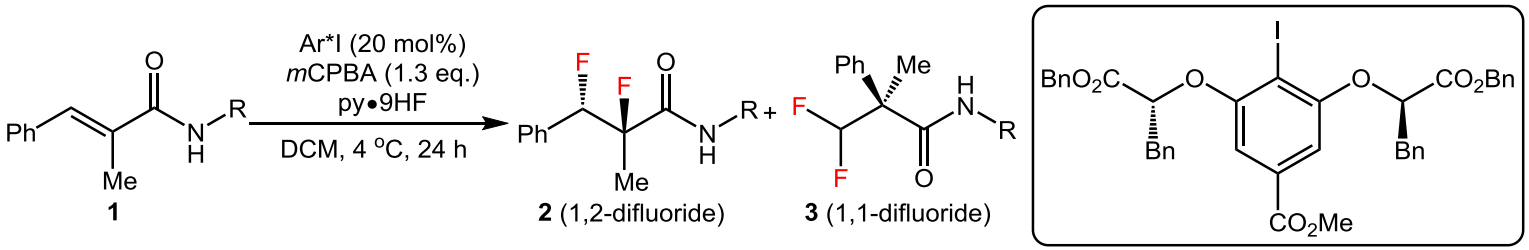
This work: Chemo-, diastereo-, and enantioselective 1,2-difluorination





Jacobsen, E. N. *et al. Org. Lett.* **2019**, *21*, 4919

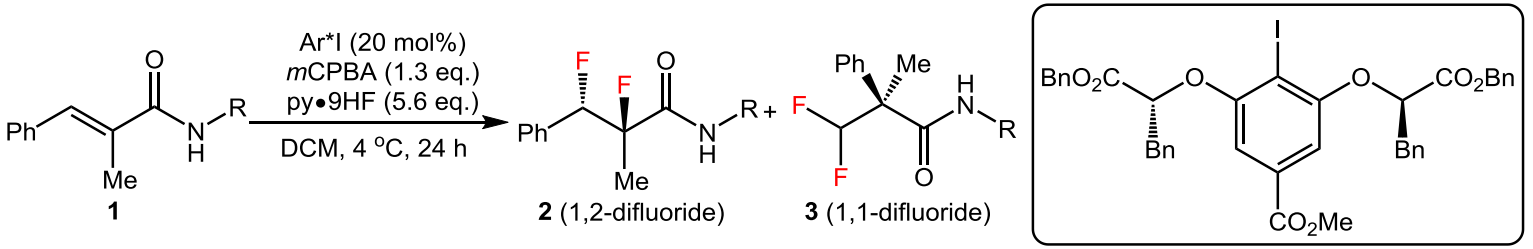
1,2-Difluorination of Cinnamamides

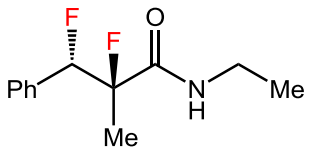


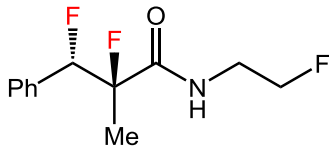
entry	substrate	R	pyr•9HF (eq.)	**2**:**3**	**2** yield (%)	**2** ee (%)
1[a]	**1a**	H	11	1.1:1.0	17	91
2[a]	**1b**	Me	11	1.1:1.0	38	95
3	**1b**	Me	5.6	3.3:1.0	51	94
4	**1c**	Et	5.6	4.3:1.0	61	95
5	**1d**	*i*-Pr	5.6	4.8:1.0	56	95
6	**1e**	*n*-Bu	5.6	6.9:1.0	63	94
7	**1f**	*t*-Bu	5.6	39:1.0	81	96
8[b]	**1f**	*t*-Bu	11	5.9:1.0	65	96

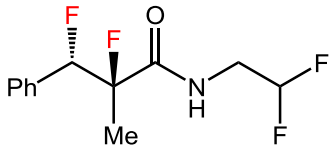
[a] Unless noted otherwise, reactions were conducted on a 1.00 mmol scale and isolated yields of **2** are listed. Reported ratios of 1,2-difluoride to 1,1-difluoride were determined by ^{19}F NMR analysis of crude product mixtures. [b] Reaction conducted on 0.10 mmol scale, with yields of 1,2-difluoride determined by ^{1}H NMR against an internal standard.

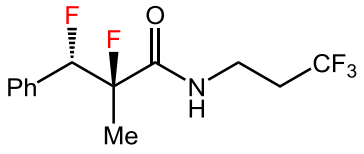
1,2-Difluorination of Cinnamamides



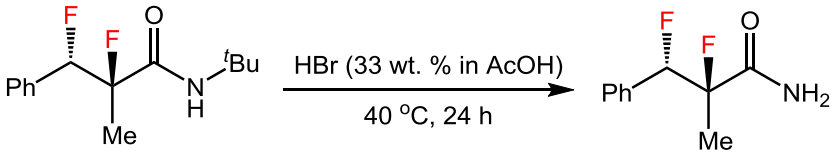

4.3:1.0 **2g:3g**


3.4:1.0 **2h:3h**


2.1:1.0 **2i:3i**


1.1:1.0 **2j:3j**

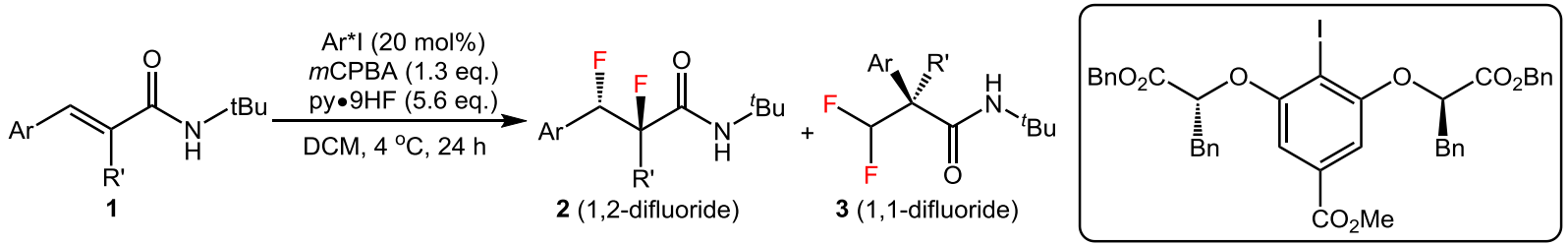
Reactions were conducted on a 1.00 mmol scale. Reported ratios of 1,2-difluoride to 1,1-difluoride were determined by ^{19}F NMR analysis of the crude mixture.

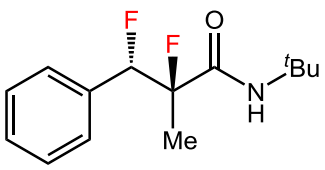


2f 96% ee

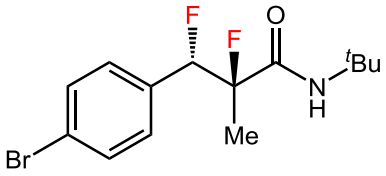
2a 89% yield, 96% ee

1,2-Difluorination of Cinnamamides

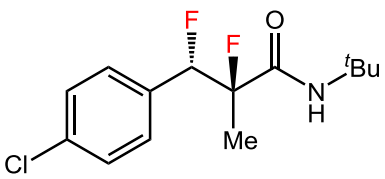




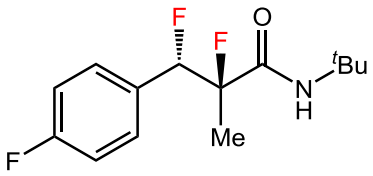
39:1.0 **2f:3f**
81% yield, 96% ee



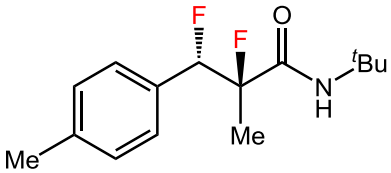
>100:1.0 **2k:3k**
84% yield, 98% ee



86:1.0 **2l:3l**
84% yield, 97% ee

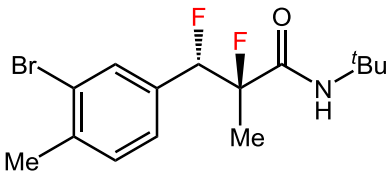


16:1.0 **2m:3m**
72% yield, 98% ee

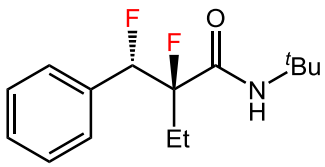


2.2:1.0 **2n:3n**
40% yield, 98% ee[a]

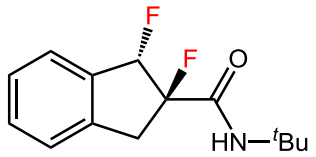
6.5:1.0 **2n:3n**
60% yield, 97% ee[b]



79:1.0 **2o:3o**
83% yield, 98% ee



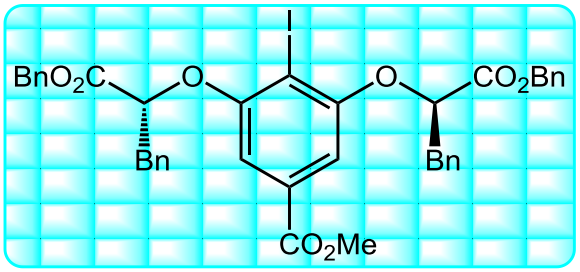
>100:1.0 **2p:3p**
58% yield, 95% ee



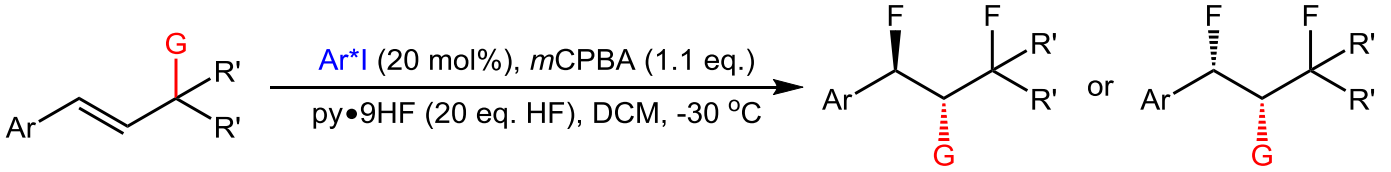
2q 43% yield, 77% ee

Scope of the enantioselective 1,2-difluorination of *N-tert*-butyl cinnamamides. Reactions were conducted on 1.00 mmol scale with 5.6 equiv of HF-pyridine. Ratios of 1,2-difluoride to 1,1-difluoride were determined by ^{19}F NMR analysis of crude product mixtures. Isolated yields of diastereomerically pure 1,2-difluoride are reported unless otherwise noted. [a] Reaction conducted with 2.8 equiv of HF-pyridine. [b] Reaction conducted on 0.20 mmol scale with 2.8 equiv of HF-pyridine and added pyridine (pyr/HF = 1:4.5). The reported yield was determined by ^{1}H NMR using nitrobenzene as an internal standard.

Summary



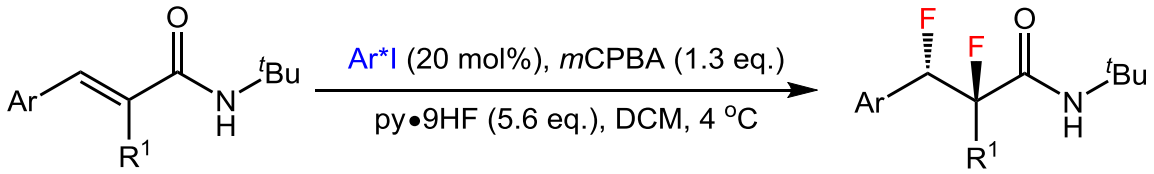
Enantioselective Wagner-Meerwein Rearrangements



G = Ar
up to 90% yield
up to 92% ee
up to >20:1 dr

G = CH_3, H
up to 88% yield
up to 99% ee
up to >20:1 dr

Enantioselective 1,2-Difluorination of Cinnamamides



up to 84% yield, up to 98% ee
1,2-difluoride:1,1-difluoride up to >100:1

Jacobsen, E. N. *et al. Org. Lett.* **2019**, *21*, 4919
Jacobsen, E. N. *et al. J. Am. Chem. Soc*. **2020**, *142*, 16090

The Structure of First Paragraph

控制碳正离子重排反应选择性困难

↓

实现立体化学控制的成功策略

↓

本文报道内容

The First Paragraph

Carbocations are highly reactive intermediates that can undergo skeletal rearrangements through the migration of strong σ bonds, thereby enabling access to valuable carbon frameworks. The energetic barriers to σ-bond migrations in free carbocations are generally low, so control over selectivity in such rearrangement pathways is intrinsically challenging. Successful strategies identified to date for stereochemical control have relied on engagement of electrophiles bearing excellent leaving groups as carbocation surrogates that undergo stereospecific substitutions. For example, catalytic, enantioselective semipinacol rearrangements have been developed in which transient electrophiles generated stereoselectively by coordination of chiral transition metal complexes or halonium ion equivalents to π-systems undergo stereospecific migration of a C−C or C−H bond from an adjacent carbinol. The weakly electrophilic nature of the π-adducts generally limits the scope of these reactions to those generating oxocarbenium and iminium ions.

The First Paragraph

In considering approaches to enantioselective catalytic asymmetric Wagner-Meerwein rearrangements, i.e., 1,2-migrations involving nonheteroatom-stabilized carbocations, we were drawn to the possibility of leveraging the configurational stability and extraordinarily high electrophilicity of chiral alkyl iodane intermediates generated via hypervalent iodine catalysis. Here, we report the successful application of this approach to enantioselective catalytic rearrangements of β-substituted styrene derivatives through the 1,2-migration of aryl, methyl, or hydride groups. These reactions provide a novel approach to chiral 1,3-difluorinated molecules possessing unique conformational properties driven by the minimization of unfavorable 1,3-dipolar interactions.

The Structure of Last Paragraph

The Last Paragraph

The C2-symmetric aryl iodide was shown to catalyze Wagner-Meerwein rearrangements involving aryl, alkyl, and hydride migrations to afford a variety of 1,3-difluorinated products in good yields and high enantio- and diastereoselectivities. These reactions provide new and compelling illustrations of the remarkably high electrophilicity and versatile reactivity of the intermediate alkene-iodonium π-complexes and alkyl iodanes. The most remarkable conclusion from these studies, however, is that the mechanism of catalysis and identity of the enantiodetermining event are dependent on the identity of the migrating group. In reactions involving alkyl-group migration, intermolecular fluoride attack is product- and enantiodetermining, whereas aryl rearrangement pathways proceed via enantiodetermining intramolecular 1,2-migration. It is noteworthy that both pathways are operative under the same conditions for closely related substrates, and both are promoted by the same chiral aryl iodide catalyst with high enantioselectivity, thereby providing a compelling illustration of generality across reaction mechanisms in asymmetric catalysis.

Representative Examples

Due to their known preference for adopting gauche conformations, vicinal difluorides represent a particularly interesting subset of organofluorine compounds. (由于…， …是…中有趣的一类化合物)

There has been remarkable progress over the past decade in the develop-ment of enantioselective alkene difunctionalization reactions using hyperv-alent iodine reagents and catalysts. (过去十年关于…已经取得显著进展)

The direct, enantioselective 1,2-difluorination of alkenes represents a most appealing approach to this class of compounds, but no general methods have yet been identified for accomplishing such a transformation. (但尚未确定用于…)