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Advances in Catalytic Enantioselective Fluorination, Mono-, Di-, and Trifluoromethylation, and Trifluoromethylthiolation Reactions

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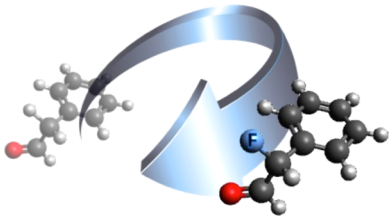

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1. INTRODUCTION

Despite being largely absent from natural products and biological processes, fluorine plays a conspicuous and increasingly important role within pharmaceuticals and agrochemicals, as well as in materials science.[1a−c] Indeed, as many as 35% of agrochemicals and 20% of pharmaceuticals on the market contain fluorine.[1d] Fluorine is the most electronegative element in the periodic table, and the introduction of one or more fluorine atoms into a molecule can result in greatly perturbed properties. Fluorine substituents can potentially impact a number of variables, such as the acidity or basicity of neighboring groups, dipole moment, and properties such as lipophilicity, metabolic stability, and bioavailability. The multitude of effects that can arise from the introduction of fluorine in small molecules in the context of medicinal chemistry has been extensively discussed elsewhere.[2]

For these reasons, methods to introduce fluorine into small organic molecules have been actively investigated for many years by specialists in the field of fluorine chemistry. However, particularly in the past decade, a combination of the increasing importance of fluorine-containing molecules and the successful development of bench stable, commercially available fluorine sources has brought the expansion of fluorine chemistry into the mainstream organic synthesis community. This has resulted in an acceleration in the development of new fluorination methods and consequently in methods for the asymmetric introduction of fluorine.[3] Catalytic asymmetric fluorination methods have inevitably lagged somewhat behind their nonasymmetric counterparts as understanding of the modes of reactivity of new fluorinating reagents must generally be developed and understood before they can be extended to enantioselective catalysis.[3b] Indeed, the last special issue of *Chemical Reviews* dedicated to fluorine chemistry, in 1996,

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contained no articles addressing asymmetric fluorine chemistry, and the editor of the issue noted that "although fluorine chemistry is much less abstruse now than when I entered the field a generation ago, it remains a specialized topic and most chemists are unfamiliar, or at least uncomfortable, with the synthesis and behavior of organofluorine compounds."[4] The field has undoubtedly undergone great change within the last two decades.

As with the incorporation of the fluorine atom, the introduction of the trifluoromethyl (CF_3) group into organic molecules can substantially alter their properties. As with fluorine, the prevalence of CF_3 groups in pharmaceuticals and agrochemicals coupled with the development of new trifluoromethylating reagents also has led to a recent surge in the development of asymmetric trifluoromethylation and perfluoroalkylation. Although the fluorine and trifluoromethyl moieties are often found on the aromatic rings of many pharmaceutical and agrochemicals rather than in aliphatic regions, this may be a result of the lack of efficient methods for the asymmetric introduction of C−F and C−CF_3 bonds into molecules; it could be the case that lack of chemical methods is restricting useful exploration of such molecules. However, there are still encouraging examples of drug candidates containing chiral fluorine and trifluoromethyl-bearing carbons (Figure 1).

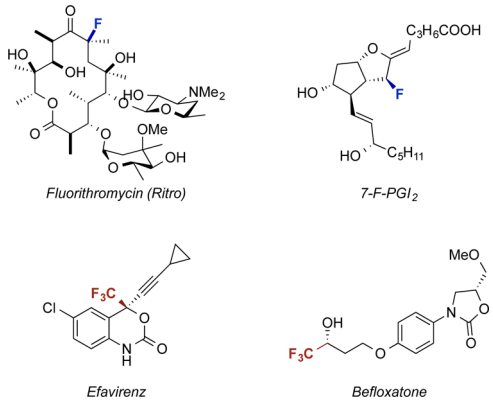


Figure 1. Molecules of medicinal interest bearing C−F and C−CF_3 stereocenters.

The asymmetric synthesis of fluorine-containing organic compounds using catalytic methods is of particular topical interest and is a vibrant area of chemical research. Since the beginning of the 21st century, much progress has been made in this field with significant advances being made since the preceding *Chemical Reviews* article in 2008 by Ma and Cahard.[3a] In this Review, we aim to comprehensively cover advances in catalytic enantioselective fluorination, trifluoromethylation, and perfluoralkylation reactions up to May 2014. Additionally, we will also include sections covering the introduction of mono- and difluoromethyl groups as well as trifluoromethylthiolation. In contrast to the 2008 review, due to the desire to focus on catalytic asymmetric processes, we will not include diastereoselective processes (with the arguable exception of tandem processes), noncatalytic reactions, or asymmetric functionalization of fluorine-containing compounds, unless these can explicitly lead to a mono- or difluoromethyl group.

2. CATALYTIC ENANTIOSELECTIVE FLUORINATION

2.1. Electrophilic Fluorination

Electrophilic fluorination reactions with highly oxidizing fluorinating reagents such as fluorine gas, hypofluorites, and fluoroxysulfates can be challenging to perform without special equipment and precautions, due to their high reactivity. This largely precluded the development of catalytic asymmetric methods until the development in the 1990s of bench-stable, easily handled electrophilic fluorinating reagents such as *N*-fluorobenzene-sulfonimide (NFSI), the family of *N*-fluoropyridinium salts, and 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo-[2.2.2]octane bis(tetrafluoroborates) (Selectfluor). It is the development of these "tamed" electrophilic reagents that allowed researchers to develop catalytic enantioselective fluorination of nucleophilic substrates (Figure 2).

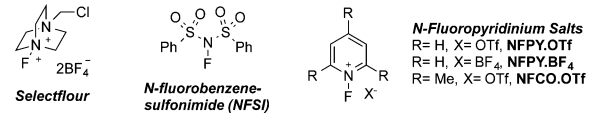
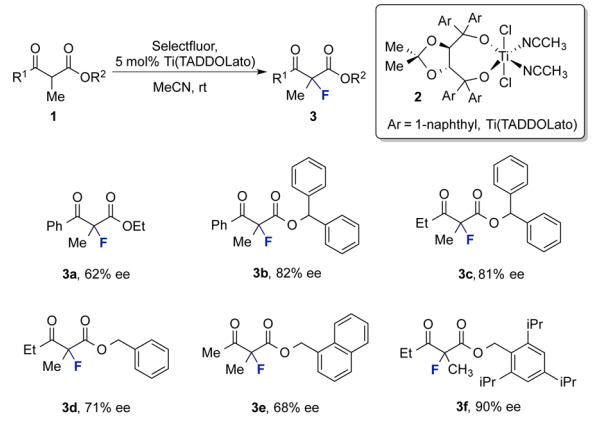


Figure 2. A selection of commonly used electrophilic fluorinating reagents.

2.1.1. Metal-Catalyzed Fluorination Involving Enolates. The earliest advances in catalytic asymmetric fluorination were made by exploiting transition metal enolates, capable of a bidentate mode of coordination to a metal. This approach provided activation of the substrate through enolate formation, together with the ability to impose a rigid chiral environment by virtue of chiral ligands bound to the transition metal.

2.1.1.1. Ti/TADDOL Catalysts. The first such reaction was developed by Hintermann and Togni in 2000.[5a] The authors reasoned that a catalytic amount of a Lewis acid would accelerate fluorination of β-ketoesters by catalyzing the enolization process. Fluorination of acyclic β-ketoesters **1** with Selectfluor and Ti(TADDOLato) catalyst **2** in MeCN at room temperature afforded the desired products **3** in high yield (>80%) and up to 90% ee (Scheme 1). The authors have recently advanced a steric model explaining the facial selectivity of the fluorination, which was arrived at by combining X-ray data with molecular modeling (Figure 3).[5b,c] While only a few examples in the original disclosure achieved the highest levels of enantioselectivity, this was an extremely influential study and set the stage for much work that followed.

Scheme 1



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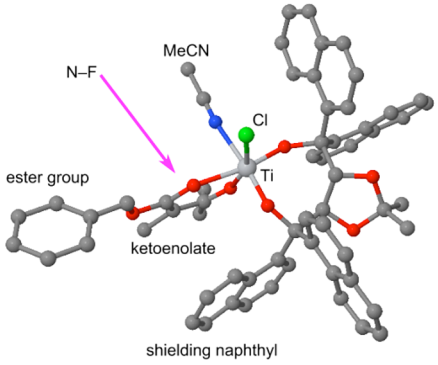
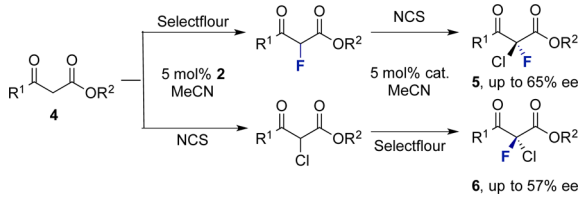


Figure 3. Proposed steric model explaining the facial selectivity in the titanium-TADDOLate-catalyzed fluorination. Reproduced with permission from ref 5b. Copyright 2011 Beilstein-Institut zur Foerderung der Chemischen Wissenschaften.

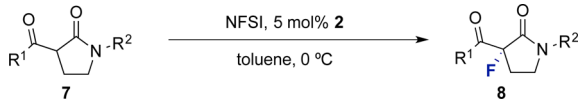
In 2003, Togni and co-workers applied the same catalytic system to the one-pot enantioselective heterodihalogenation of β-ketoesters with Selectfluor and NCS to afford α-chloro-α-fluoro-β-ketoesters (**5**, **6**) in moderate to good yield (Scheme 2).[6] The sequence of addition of the halogenating agents was found to determine the sense of asymmetric induction, although the enantioselectivities were moderate.

Scheme 2



In 2006, Togni and co-workers applied the Ti(TADDOLato) catalyst **2** to the asymmetric fluorination of α-acyl lactams **7** (Table 1).[7] They found that using NFSI as fluorinating reagent

Table 1. Asymmetric Fluorination of α-Acyl Lactams

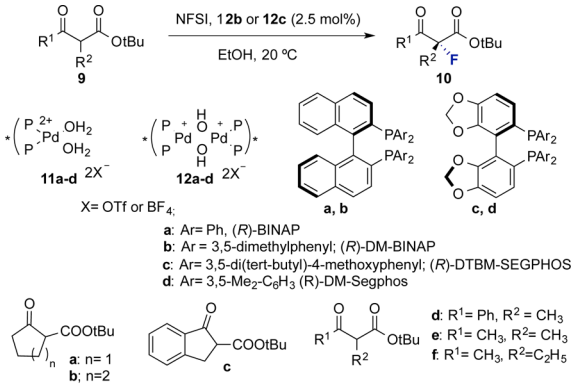


R^1	R^2	yield, %	ee, %
Me	CH_2Ph	75	26
Ph	CH_2Ph	78	15
Ph	Me	75	6
Me	Ph	75	87
Cy	Me	60	50
Me	Cy	nd	46
t-Bu	Me	40	20

gave superior enantioselectivity to Selectfluor; however, only one substrate (R^1 = Me, R^2 = Ph) afforded high enantioselectivity (75% yield, 87% ee).

2.1.1.2. Metal/BINAP Catalysts. In 2002, Sodeoka and co-workers reported the enantioselective fluorination of β-ketoesters catalyzed by a chiral palladium complex (Scheme 3).[8] The reaction was carried out with NFSI and 2.5 mol % of cationic palladium catalyst (**12b** and **12c**) to afford fluorinated β-ketoesters **10** (both cyclic and acyclic) in high enantioselectivity. In 2003, the same group reported the use of an ionic liquid immobilized palladium complex as catalyst for the same reaction. Similarly high enantioselectivity was achieved, and the immobilized catalyst could be reused up to 10 times with levels of efficiency comparable to those in conventional organic solvents.[9]

Scheme 3



ketoester	temp, °C	yield, %	ee, %
a	20	90	92
b	-10	91	94
c	-20	85	83
d	20	92	91
e	20	49	91
f	20	88	87

The proposed mechanism involves the β-ketoester coordinated in a bidentate manner to the cationic palladium catalyst. This coordination increases the acidity of the α-proton, allowing a nucleophilic metal enolate to be easily generated and to react with the NFSI (Figure 4). The enantioselectivity

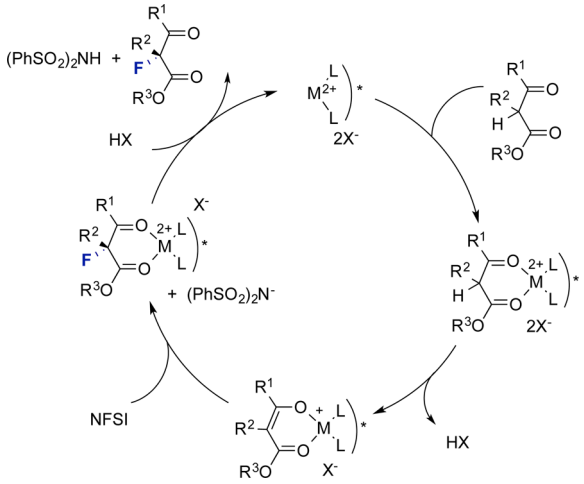


Figure 4. Proposed catalytic cycle for enantioselective Pd-catalyzed fluorination of β-ketoesters.

was rationalized by considering the structure of the square-planar chiral Pd enolate complex, which was proposed to arrange itself to minimize steric interactions between the ligand aryl groups and the ester *tert*-butyl group. This results in the *Si* face being shielded by the ester *tert*-butyl group, requiring the NFSI to approach from the less hindered *Re* face (Figure 5).[10]

In 2005, the same group reported the enantioselective fluorination of oxindoles using a similar approach (Table 2).[11]

dx.doi.org/10.1021/cr500277b | *Chem. Rev.* 2015, 115, 826–870

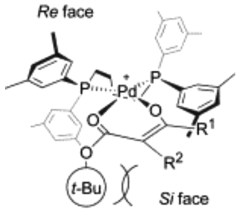
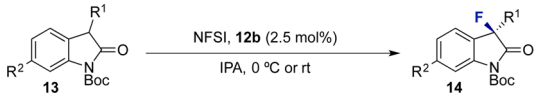
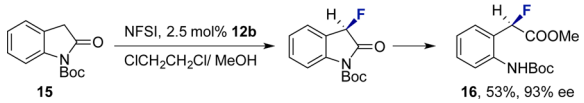


Figure 5. Proposed structure of the Pd–enolate complex to account for enantioselectivity. Reproduced with permission from ref 10. Copyright 2006 Elsevier.

Table 2. Enantioselective Fluorination of Oxindoles Using Palladium Catalysis



R^1	R^2	temp, °C	yield, %	ee, %
Ph	H	0	96	90
p-MeC_6H_4	H	rt	97	86
p-MeC_6H_4	H	0	92	88
p-FC_6H_4	H	rt	94	84
o-MeC_6H_4	CF_3	rt	80	75
Me	H	rt	86	95
Me	H	0	85	96
Et	H	rt	85	92
CH_2COCH_3	H	rt	85	86
Bn	H	rt	72	80
i-Bu	H	rt	85	75

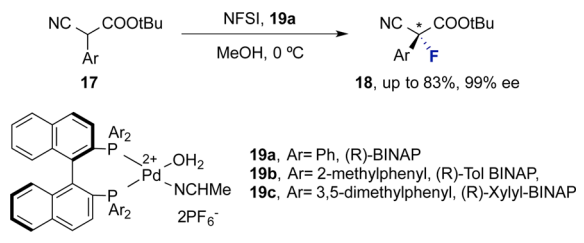


Treatment of 3-substituted oxindoles **13** with NFSI and 2.5 mol % palladium catalyst **12b** in 2-propanol gave the fluorinated products **14** in good yield with high to excellent enantioselectivities (75–96% ee). The method was applied to the synthesis of BMS 204352 (MaxiPost), a promising agent for the treatment of stroke. They also demonstrated the asymmetric fluorination of unsubstituted oxindoles; by changing the solvent to $ClCH_2CH_2Cl$/MeOH, **16** was obtained with high enantioselectivity.

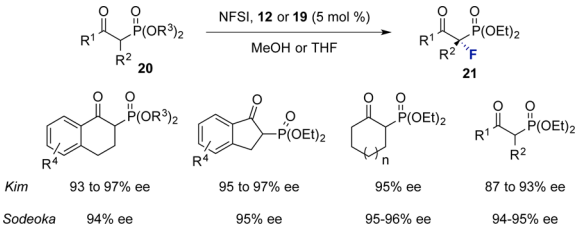
In 2005, Kim and co-workers reported the enantioselective fluorination of α-cyano esters, catalyzed by cationic palladium complex **19a** (Scheme 4).[12] Treatment of substrates **17** with NFSI as fluorine source under mild conditions afforded the α-cyano α-fluoro esters **18** in high yields with excellent enantiomeric excesses (85–99% ee).

Soon after, Kim[13a] and Sodoeka[10,14] reported the catalytic fluorination of β-ketophosphonates catalyzed by chiral palladium complexes, with high enantioselectivity for both cyclic and acyclic β-ketophosphonate substrates **20** (Scheme 5). Kim and co-workers later reported this reaction in ionic liquids, with the aim of simplified product isolation and catalyst recycling.[13b]

Scheme 4

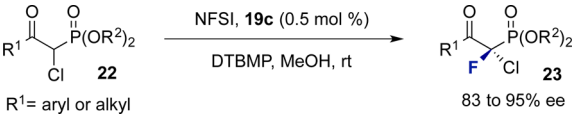


Scheme 5



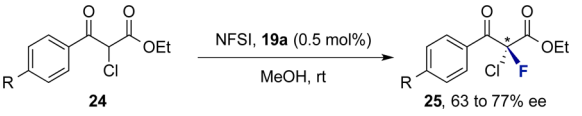
Kim and co-workers also developed enantioselective fluorination of α-chloro-β-keto phosphonates **22** catalyzed by chiral palladium complex **19c**, which gave the corresponding α-chloro-fluoro-β-keto phosphonates **23** with excellent enantioselectivity (up to 95% ee) (Scheme 6).[15]

Scheme 6



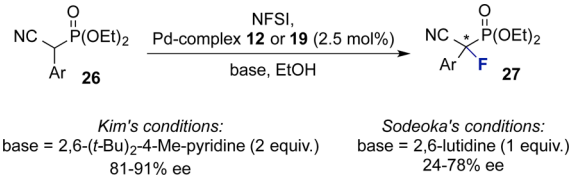
In 2007, Kim and co-workers reported employing the chiral Pd(II) complex **19a** in the catalytic enantioselective α-fluorination of α-chloro-β-ketoesters **24** with moderate enantioselectivity (Scheme 7).[16]

Scheme 7



In 2007, Kim[17] and Sodeoka[18] simultaneously reported the enantioselective fluorination of α-aryl-α-cyano-phosphonates **26** (Scheme 8). Because of the lower reactivity of this substrate

Scheme 8



class, an organic base was required to accelerate abstraction of the acidic proton. Kim selected 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) as base with 81–91% ee; Sodeoka selected 2,6-lutidine as base with 24–78% ee. In both cases, the aryl substituent was required; aliphatic substrates gave no reaction.

In 2007, Sodeoka and co-workers reported an efficient enantioselective fluorination of *tert*-butoxycarbonyl lactones and lactams **28** with excellent enantioselectivities (94–99% ee) (Scheme 9).[19] In the case of the less acidic lactam substrates,

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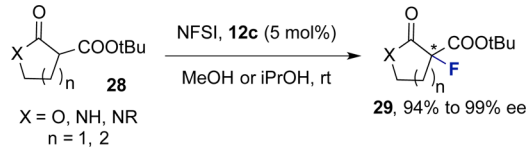
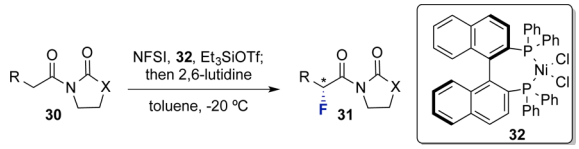
2,6-lutidine (0.5 equiv) was required to function as a non-nucleophilic, weak base.

Scheme 9



In an important advance demonstrating that this strategy could be applied to less acidic substrates, Sodeoka and co-workers in 2007 reported the $NiCl_2$–BINAP-catalyzed direct asymmetric fluorination of α-aryl acetic acid derivatives **30** (Table 3 and Figure 6).[20] Among the acid derivatives tested,

Table 3. Asymmetric Fluorination of α-Aryl Acetic Acid Derivatives Using Nickel Phosphine Complex 32



R	X	cat, mol %	yield, %	ee, %
Ph	S	5	99	88
p-FC_6H_4	S	5	90	83
p-$MeOC_6H_4$	S	5	92	81
m-$MeOC_6H_4$	S	10	95	82
o-$MeOC_6H_4$	S	10	87	78
2-naphthyl	S	10	99	83
1-naphthyl	S	5	94	87
Ph	O	10	95	87
n-propyl	S	10	15	11

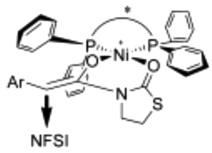
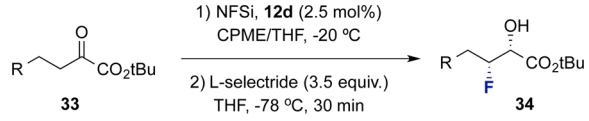


Figure 6. Proposed model to account for sense of asymmetric induction using catalyst **32**. Reproduced with permission from ref 20. Copyright 2007 John Wiley and Sons.

thiazolidin-2-one was optimal. In addition, 2,6-lutidine and triethylsilyl triflate were essential for efficient asymmetric fluorination. Triethylsilyl triflate was proposed to play an important role both in generating a dicationic nickel triflate complex and in rendering NSFI more reactive. 2,6-Lutidine was assumed to promote enolization of the substrate. Excellent yields and good enantioselectivities (up to 88% ee) were achieved with α-arylacetic acid derivatives; however, the alkyl derivative gave both poor reactivity and enantioselectivity.

In 2012, Sodeoka and co-workers reported the catalytic enantioselective monofluorination of α-ketoesters **33** using a chiral palladium μ-hydroxo complex **12d** (Table 4).[21] As the resulting monofluorinated α-ketoesters spontaneously converted into the hydrate during purification, in situ reduction with lithium tri-*sec*-butylborohydride (L-Selectride) was carried out to give products **34**. Aryl-substituted substrates all gave excellent enantioselectivities (up to 95% ee), and substrates

Table 4. Asymmetric Monofluorination of α-Ketoesters

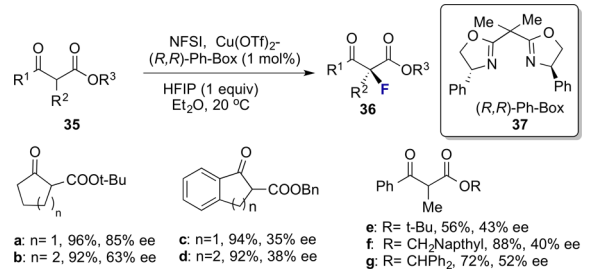


R	yield, %	ee, %	syn:anti
Ph	89	94	6.9:1
p-MeC_6H_4	83	91	4.6:1
p-$MeOC_6H_4$	75	94	4.7:1
p-FC_6H_4	68	95	6.5:1
p-ClC_6H_4	69	95	7.6:1
$PhCH_2$	65	83	4.2:1
$BnOCH_2$	66	83	1.4:1

with a longer alkyl chain and a benzyloxy-substituted compound gave the desired fluorinated product with reduced but acceptable enantioselectivity (83% ee). A stereochemical model related to that proposed earlier for β-ketoesters was invoked to rationalize the sense of enantioinduction.

2.1.1.3. Metal/Bis(oxazoline) Catalysts. In 2004, Ma and Cahard reported the catalytic enantioselective fluorination of both cyclic and acyclic β-ketoesters employing a chiral bis(oxazoline)–copper complex derived from **37** and Cu-$(OTf)_2$ (Scheme 10).[22] They found the use of HFIP

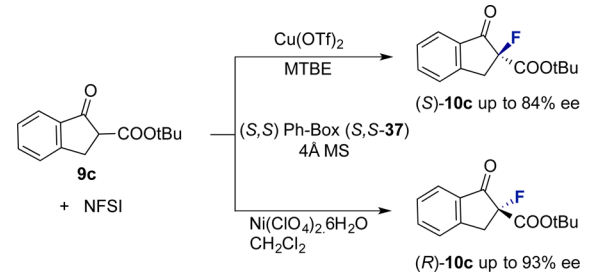
Scheme 10



(1,1,1,3,3,3-hexafluoroisopropanol) as additive was crucial for achieving high enantioselectivity, although only one substrate ultimately gave satisfactory enantiomeric excess (>80% ee).

In the same year, Shibata and co-workers reported fluorination of similar substrates using nickel and copper complexes of **37** (Scheme 11), with the use of MTBE as solvent

Scheme 11



leading to higher enantioselectivies.[23] An intriguing outcome of this report is that the (*S*,*S*)-bis(oxazoline)-Ph-Cu(II) complex provided the fluorination product **10c** with opposite configuration to that obtained by the use of (*S*,*S*)-bis(oxazoline)-Ph-Ni(II), both with high enantioselectivity. While use of different solvents with the different metal catalysts was required for

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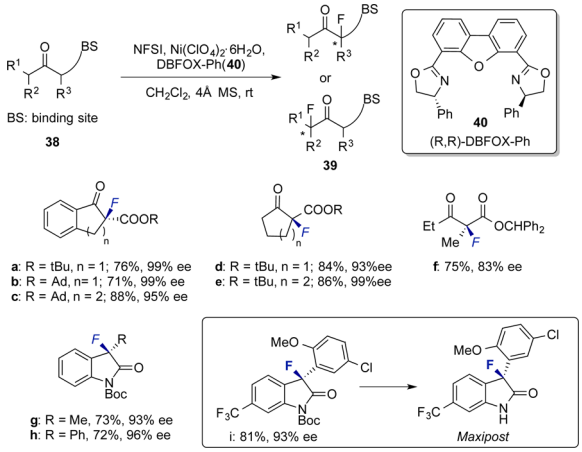
optimal enantioselectivity, control experiments using the same solvent for both demonstrated that the solvent choice was not responsible for the switch. The authors speculate that this could be a consequence of a change in metal center geometry and provide plausible transition states to support this hypothesis.

In 2005, Shibata and co-workers reported enantioselective chlorination and fluorination of carbonyl compounds capable of two-point binding (Scheme 12).[24] As the previously reported

Scheme 12

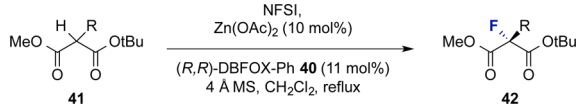


fluorination of β-ketoesters catalyzed by Cu(II) and Ni(II) complexes **37** still left room for improvement, they turned to the DBFOX-Ph ligand (**40**), which was highly effective in other reactions. A catalyst obtained from DBFOX-Ph and $Ni(ClO_4)_2 \cdot 6H_2O$ gave fluorinated compounds **39** with extremely high levels of enantioselectivity. The reaction scope was demonstrated on cyclic β-ketoesters (93−99% ee), acyclic β-ketoesters (83% ee), and 3-substituted oxindoles (93−96% ee). The methodology was showcased with a catalytic enantioselective preparation of Maxipost. They proposed an octahedral nickel complex as key intermediate, ligated by both substrate and ligand, and put forward a model to rationalize the absolute stereochemistry observed leading to compound **39a** (Figure 7).

In 2008, the same authors reported the enantioselective fluorination of malonates catalyzed by a DBFOX-Ph/$Zn(OAc)_2$ complex (Table 5).[25] In contrast to β-ketoesters, malonates **41** are relatively symmetrical, being differentiated by sterics only. They are also generally less acidic than β-ketoesters; however, reflux of the substrates with NFSI, $Zn(OAc)_2$, and DBFOX-Ph

Figure 7. Proposed model to account for fluorination leading to **39a**. Reproduced with permission from ref 24. Copyright 2005 John Wiley and Sons.

Table 5. Enantioselective Fluorination of Malonates

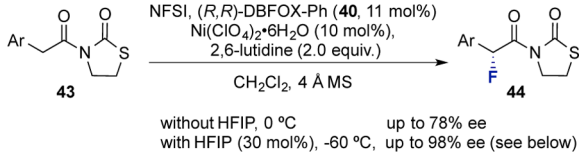


entry	R	yield, %	ee, %
a	CH_2Ph	90	98
b	Et	94	96
c	Me	90	99
d	Bu	93	99
e	Ph	95	99
f	OPh	85	98
g	SPh	81	90
h	NPht	91	93
i	NPht(4-Br)	93	97

in CH_2Cl_2 afforded the fluorinated malonates **42** with excellent levels of enantioselectivity. The scope of the reaction was broad, with a wide range of functional groups such as alkyl, aryl, oxygen, sulfur, and amino substitution being tolerated. $Ni(ClO_4)_2 \cdot 6H_2O$ could be used in place of $Zn(OAc)_2$, but generally the latter gave superior results.

In 2008, Shibata and co-workers reported the enantioselective fluorination of 3-(2-arylacetyl)-2-thiazolidinones **43** with NFSI employing DBFOX-Ph/metal complexes as catalysts (Table 6).[26a] The best results were obtained using DBFOX-Ph

Table 6. Enantioselective Fluorination of α-Aryl Acetic Acid Derivatives Using a Nickel−DBFOX Complex



entry	R	yield, %	ee, %
a	Ph	91	98
b	C_6H_4-*m*-OMe	93	96
c	C_6H_4-*p*-OMe	93	96
d	C_6H_4-*m*-Me	93	98
e	C_6H_4-*p*-Me	90	96
f	C_6H_4-*p*-CF_3	94	94
g	C_6H_4-*p*-F	90	94
h	C_6H_4-*p*-Br	96	93
i	1-naphthyl	87	92
j	2-naphthyl	94	95

(11 mol %), $Ni(ClO_4)_2 \cdot 6H_2O$ (10 mol %), and 2,6-lutidine (1.0 equiv) in CH_2Cl_2 at 0 °C. Later in 2009, they reported modified conditions in which HFIP (0.3 equiv) activated the DBFOX-Ph/Ni(II) catalyst system, permitting lower reaction temperatures.[26b] With the help of catalytic HFIP, the reaction proceeded smoothly at −60 °C to afford the desired fluorinated product in high yield with improved enantioselectivity.

As a further demonstration of the utility of this catalytic system, 3-butenoyl derivatives **45** were tested under these conditions, which gave the desired fluorinated products **46** in high yield and with good enantioselectivity (78−91% ee) (Scheme 13).

In 2007, Iwasa and co-workers reported the design and synthesis of a series of hybrid chiral oxazoline ligands **49**, incorporating an axially chiral binaphthyl unit. The Ni(II)

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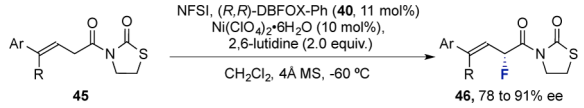
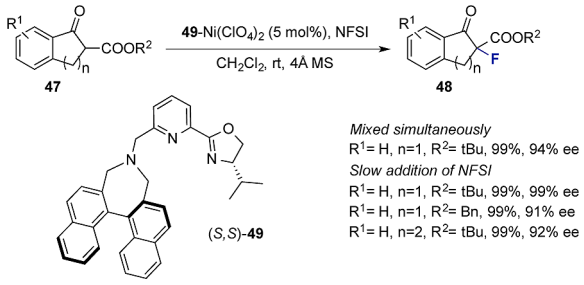
Scheme 13



complex of this tridentate ligand catalyzed the enantioselective fluorination of β-ketoesters with excellent yields and enantioselectivities (94% ee) (Scheme 14).[27a] Later, they

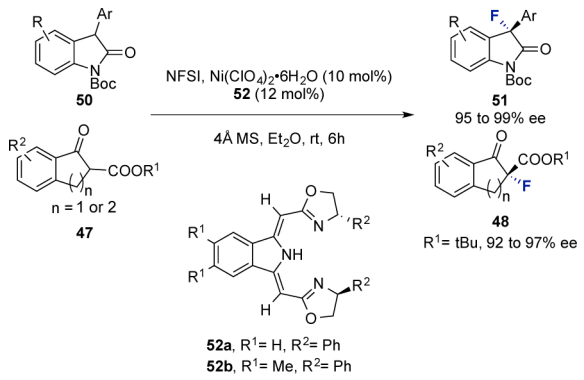
Scheme 14



found the enantiomeric excess of this reaction could be dramatically improved to 99% ee when a solution of NFSI was slowly added to the mixture of substrate and catalyst.[27b] A strong matched−mismatched effect was observed, arising from the two sources of chirality contained within the ligand backbone.

In 2011, Gade and co-workers described the synthesis of a new class of chiral tridentate *N*-donor pincer ligands, bis(oxazolinyl-methyldiene)isoindolines **52**. These ligands were subsequently applied in the Ni(II)-catalyzed enantioselective fluorination of oxindoles **50** and β-ketoesters **47** to afford the corresponding products with enantioselectivities of up to 99% ee (Scheme 15).[28]

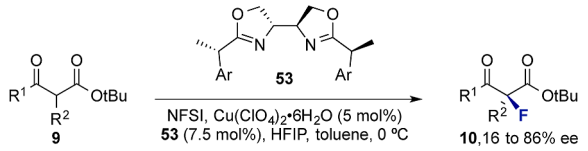
Scheme 15



In 2013, Kesavan and co-workers reported the enantioselective fluorination of aliphatic cyclic and acyclic β-ketoesters in excellent yield with moderate enantioselectivities using tartrate derived bidentate bisoxazoline−Cu(II) complex **53** (Scheme 16).[29] In this case, the bisoxazoline forms a five-membered chelate with the metal.

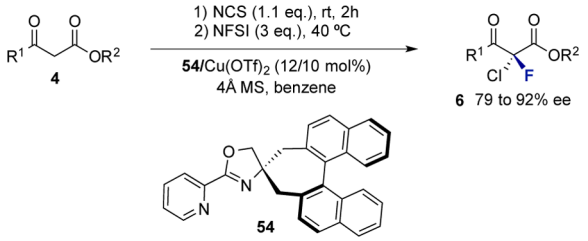
In 2011, Shibatomi and co-workers reported the asymmetric α-fluorination of α-chloro-β-ketoesters using $Cu(OTf)_2$ and chiral spiro-oxazoline ligand **54**, which was developed into a one-pot tandem chlorination−fluorination transformation, leading to products **6**.[30a] This could also be extended to

Scheme 16



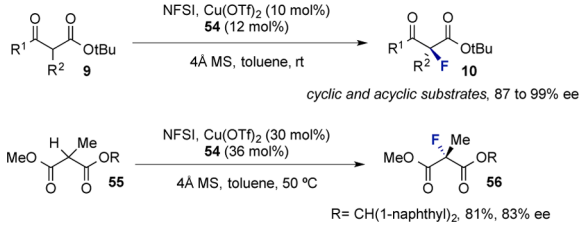
asymmetric *gem*-chlorofluorination of β-ketophosphonates. In both cases, high enantioselectivities could be achieved (Scheme 17).

Scheme 17



In 2013, the same authors reported the highly enantioselective fluorination of α-alkyl-β-ketoesters **9** using $Cu(OTf)_2$ and the same catalyst system (Scheme 18).[30b] The fluorination

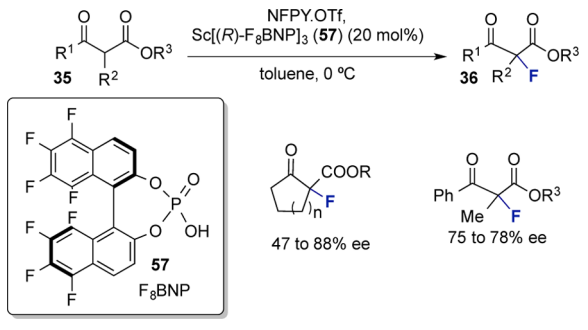
Scheme 18



proceeded in a highly enantioselective manner both when cyclic and acyclic substrates were applied. Fluorination of α-alkyl-malonate **55** was also performed to afford the corresponding product **56** in good enantioselectivity (83% ee).

2.1.1.4. Miscellaneous Catalysts. In 2006, Inanaga and co-workers reported the synthesis of a novel chiral rare earth perfluorinated binaphthyl phosphate, $Sc[(R)\text{-}F_8BNP]_3$ (**57**), and its application to the α-fluorination of cyclic and acyclic β-ketoesters with NFPY-OTf (Scheme 19).[31] This report is distinct as being a rare report of successful catalytic asymmetric fluorination using an *N*-fluoropyridinium salt as an electrophilic fluorine source.

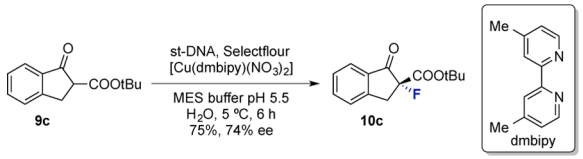
Scheme 19



dx.doi.org/10.1021/cr500277b | Chem. Rev. 2015, 115, 826−870

In 2007, Shibata and co-workers reported the enantioselective electrophilic fluorination of β-ketoesters using Selectfluor as fluorine source, and catalyzed by DNA and an achiral copper−bipyridine complex (Scheme 20).[32] DNA is thought to

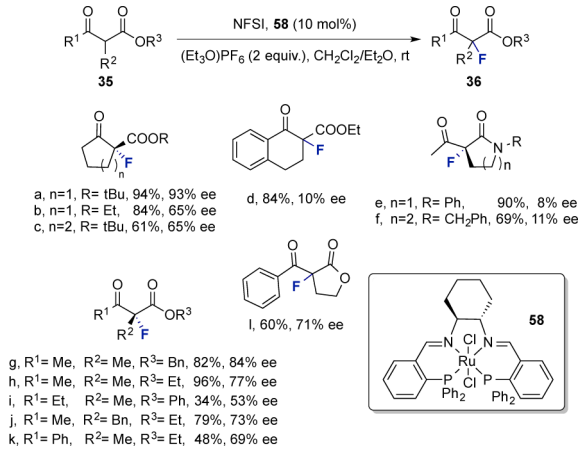
Scheme 20



act as a chiral scaffold, and the chirality transfer from DNA (in this case Salmon testis DNA, *st*-DNA) to the substrate appears to occur through intercalation or groove binding of the substrate−ligand−Cu(II) complex to DNA. The pH of the reaction needed to be carefully controlled, but impressive enantioselectivities were achieved for such a novel and innovative approach to asymmetric catalysis.

In 2007, Togni and co-workers reported the enantioselective electrophilic fluorination of 1,3-dicarbonyl compounds catalyzed by ruthenium(II) complex [RuCl(PNNP)] (**58**) upon activation with $(Et_3O)PF_6$ (2 equiv) (Scheme 21).[33] Oxygen donors, in particular Et_2O as cosolvent, increased the activity of the catalyst and, in some case, the enantioselectivity.

Scheme 21

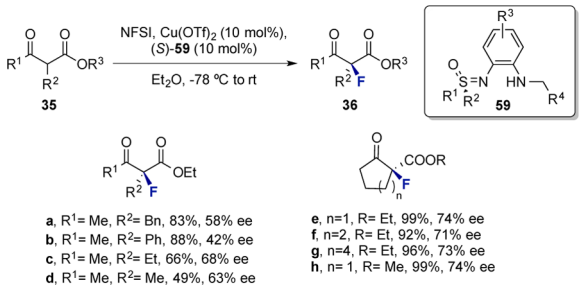


In 2009, Frings and Bolm reported the enantioselective fluorination of β-ketoesters catalyzed by $Cu(OTf)_2$ and amino sulfoximine ligands of the general structure **59** (Scheme 22).[34] Starting from both cyclic and acyclic substrates **35**, the corresponding products **36** were formed with moderate to good enantioselectivities.

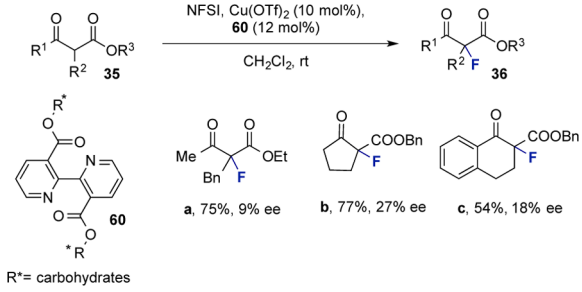
In 2009, Queneau, Billard, and co-workers reported the synthesis of a series of new carbohydrate-substituted bipyridines **60** and their application in the asymmetric fluorination of β-ketoesters (Scheme 23).[35] However, disappointingly low enantioselectivities were obtained with both cyclic and acyclic substrates.

In 2010, Kang and Kim reported the use of chiral nickel−diamine complexes such as **63** to catalyze the electrophilic fluorination of α-chloro-β-ketoesters **61**, which allowed access to chiral gem-chlorofluoro products **62** with high enantioselectivities (Scheme 24).[36]

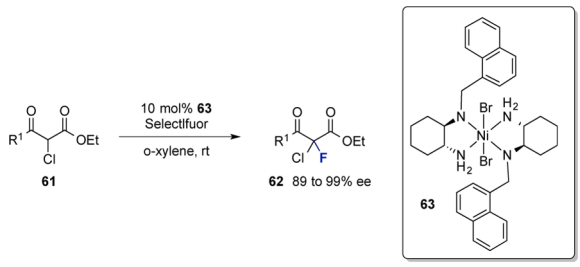
Scheme 22



Scheme 23

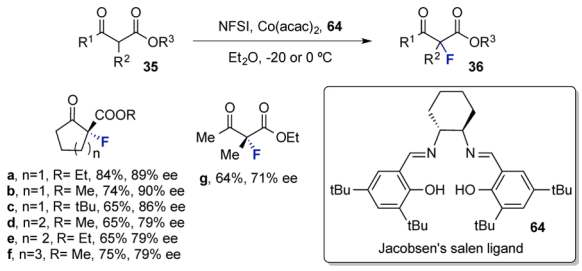


Scheme 24



In 2010, Itoh and co-workers reported the enantioselective α-fluorination of β-ketoesters catalyzed by $Co(acac)_2$ and Jacobsen's salen ligand (*R,R*)-(**64**) (Scheme 25).[37] Both cyclic and acyclic substrates **35** gave the corresponding products **36** in high yield with good enantioselectivities.

Scheme 25



In 2012, van Leeuwen and co-workers reported the synthesis of a series of new enantiopure wide-bite-angle diphosphanes **67** and their use in the palladium-catalyzed asymmetric fluorination of α-cyanoacetates **65** (Scheme 26).[38] However, the substrate scope was rather limited, with only one substrate (**65a**) giving greater than 90% ee.

In 2012, Feng and co-workers reported the enantioselective fluorination of 3-substitued oxindoles **68** catalyzed by Sc(III)/*N,N*′-dioxide complex **70** (Scheme 27).[39] Under mild reaction

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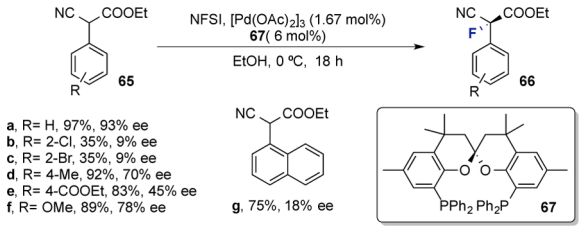
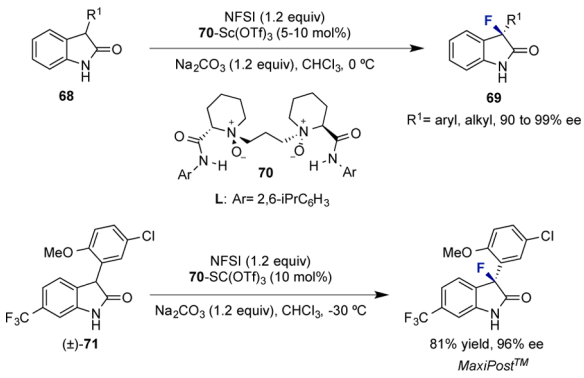
Scheme 26



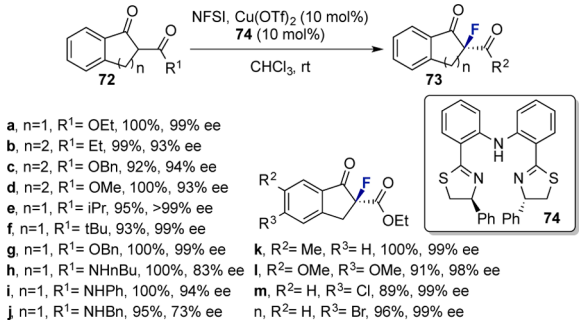
Scheme 27



conditions, a series of 3-aryl and 3-alkyl-3-fluoro-2-oxindoles **69** were obtained with high enantioselectivity. Employing this method, MaxiPost was synthesized with 96% ee.

In 2014, Peng and Du reported an efficient highly enantioselective fluorination of β-keto esters/amides catalyzed by diphenylamine-linked bis(thiazoline) **74**−Cu(OTf)$_2$ complex (Scheme 28).[40]

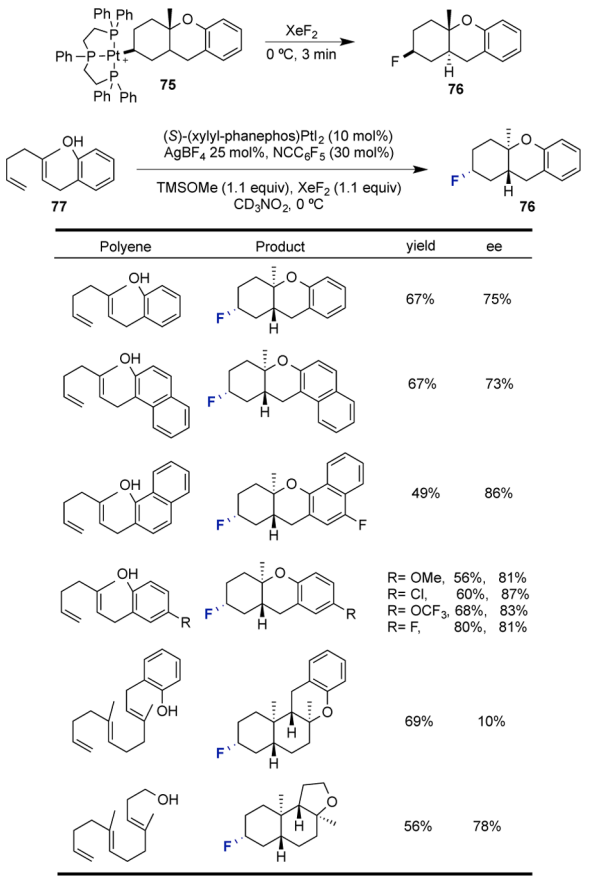
Scheme 28



Very recently in 2014, Xu, Che, and co-workers reported the enantioselective fluorination of β-keto esters and *N*-Boc oxindoles using iron(III)−salen complexes.[41]

2.1.2. Metal-Catalyzed Fluorination Not Involving Enolates. In 2013, Gagne and co-workers reported the enantioselective cyclization/fluorination of polyenes catalyzed by (Xylyl-phanephos)Pt^{2+} in combination with XeF_2, a rare example of metal-catalyzed asymmetric fluorination not proceeding through an enolate intermediate (Table 7).[42] The authors noted that electrophilic Pt(II) complexes are highly effective for initiating cation-olefin cascades and set out to investigate if the final Pt−C bond of a cascade could be converted to a C−F bond. Accordingly, the isolated complex [(triphos)Pt-alkyl][BF_4] (**75**) reacted rapidly with XeF_2 to yield the C−F containing product **76**. Under the optimized

Table 7. Platinum-Catalyzed Enantioselective Cyclization and C3-Fluorination of Polyenes



conditions, a variety of alcohol and phenol terminated dienes and trienes **77** were converted into corresponding C3-fluorinated bicyclic and tricyclic products **76** in moderate to good yield with good enantioselectivities (up to 87% ee). The proposed mechanism is as shown in Figure 8. NMR data

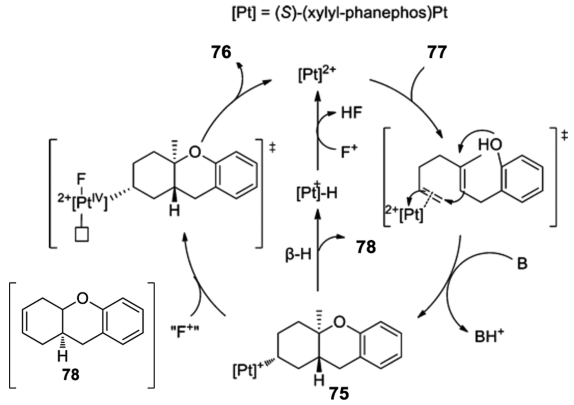


Figure 8. Proposed mechanism for the platinum-catalyzed cyclization/fluorination of polyenes, adapted from ref 42.

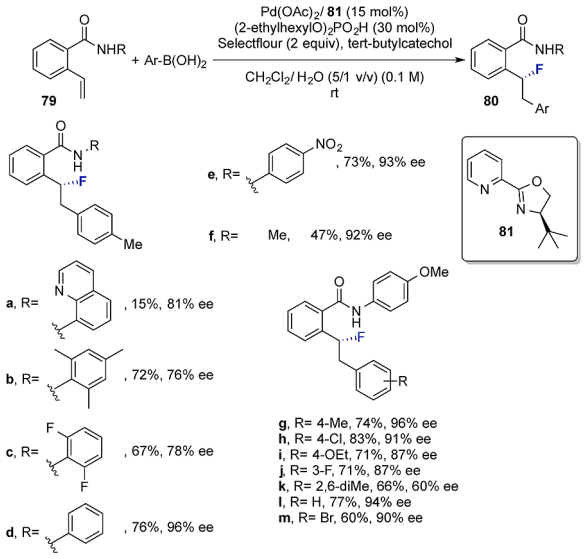
studies suggested that **75** is the catalyst resting state and either undergoes β-hydride elimination to give the nonfluorinated byproduct **78** or oxidation (with XeF_2) to give the dicationic Pt(IV) complex, which reductively eliminates to give **76**.

Recently, Toste and co-workers reported the palladium-catalyzed three-component coupling of Selectfluor, styrenes,

dx.doi.org/10.1021/cr500277b | *Chem. Rev.* 2015, 115, 826−870

and boronic acids, to provide chiral monofluorinated compounds in good yield and in high enantiomeric excess (Scheme 29).[43] They hypothesized that the aromatic amide

Scheme 29



could act as a directing group to control regioselectivity and to stabilize a high-valent Pd(IV) intermediate in conjunction with the bipyridine ligand. This would disfavor an oxidative Heck-type coupling reaction, with the intention of favoring C−F bond formation. A chiral ligand (pyridyl-oxazolidine ligand, **81**) was used for the asymmetric version of this reaction (81% ee); however, with the quinolone-based directing group, the yield was low (15%). Encouragingly, they found the simplified anilide derivatives **79** gave improved yield without significant negative effect on the enantioselectivity. Following these results, a range of boronic acids were tested on the 4-methoxyaniline substrate, and the desired products **80** were obtained in good yield with high enantioselectivities with the exception of the bulky 2,6-dimethylboronic acid (**79k**).

A proposed mechanism for the reaction is outlined in Figure 9. The catalytic cycle is initiated through formation of *N,N*-ligated palladium(II) intermediate. Transmetalation with the

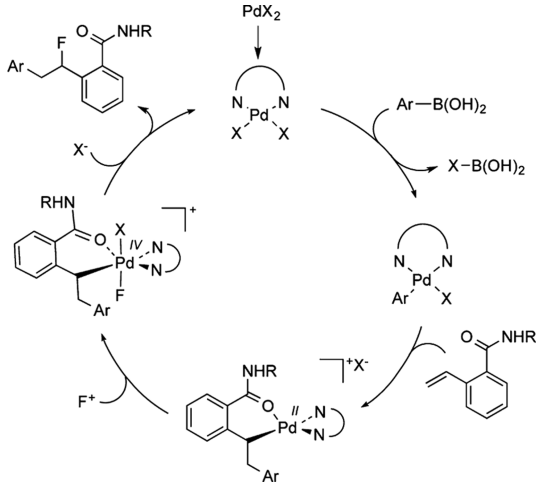


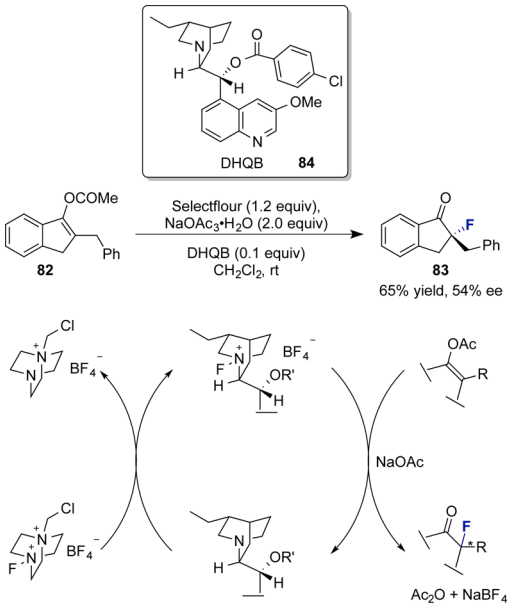
Figure 9. Proposed mechanism for the palladium-catalyzed three-component coupling of Selectfluor, a styrene, and a boronic acid.

boronic acid and thereafter coordination and insertion yield a *β*-arylated Pd(II) species. The coordination of the directing group and *N,N*-ligand may stabilize this intermediate and retard the competing *β*-hydride elimination process. Oxidation to the high-valent Pd(IV) intermediate is achieved using Selectfluor, and subsequent reductive elimination yields the desired monofluorinated product and the catalyst complex.

2.1.3. Organocatalytic Electrophilic Fluorination.

2.1.3.1. Tertiary Amine Catalysis. Chiral *N*-fluoro reagents have been investigated for some time in a stoichiometric sense, based on either camphorsultams[44] or other scaffolds, although the preparation of such reagents commonly involves multiple steps and the use of challenging fluorination methods.[45] A significant step forward was made in 2000 when Shibata and co-workers[46a] and Cahard and co-workers[46b] independently disclosed that combining cinchona alkaloids with Selectfluor results in *N*-fluoroammonium salts of the cinchona alkaloids, which are stable and isolable. These reagents were demonstrated as being remarkably effective for the enantioselective fluorination of preformed enolates equivalents, such as silyl enol ethers and metal enolates. While they are not catalytic reactions and thus will not be discussed in detail herein, these studies laid important groundwork for subsequent advances. Accordingly, in 2006, Shibata and co-workers reported transition to a catalytic method for the enantioselective fluorination of acyl enol ethers employing a cinchona alkaloid/Selectfluor combination (Scheme 30).[47] The authors

Scheme 30

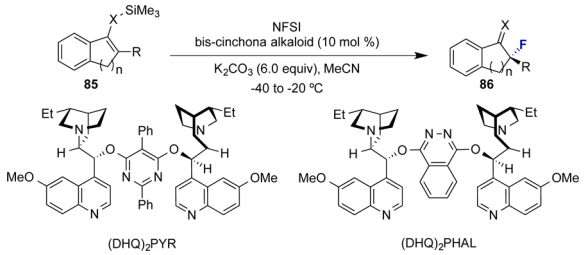


found acetyl enol ethers were not significantly reactive toward Selectfluor at room temperature, and this allowed formation of the reactive fluorinated cinchona alkaloid to occur. Addition of NaOAc as base was necessary for enolate activation. While the desired *α*-fluoroketones **83** were only afforded in moderate enantioselectivities (up to 54% ee), this proved that this approach is viable in a catalytic sense.

By 2008, Shibata and co-workers modified their approach to realize for the first time a highly enantioselective catalytic process (Table 8).[48] They employed NFSI as fluorinating reagent in combination with catalytic amounts of bis-cinchona alkaloids in the presence of excess base. Allyl silanes and silyl

dx.doi.org/10.1021/cr500277b | Chem. Rev. 2015, 115, 826−870

Table 8. Enantioselective Fluorination of Allyl Silanes and Silyl Enol Ethers Using Bis-cinchona Alkaloid Catalysts



X	R	*n*	catalyst	*T* (°C)	yield, %	ee, %
CH_2	$C_6H_5CH_2$	1	a	−40	75	94
CH_2	*p*-Me-$C_6H_4CH_2$	1	a	−20	75	95
CH_2	*p*-Cl-$C_6H_4CH_2$	1	a	−20	81	94
CH_2	*p*-Me-$C_6H_4CH_2$	1	a	−20	65	90
CH_2	*o*-Me-$C_6H_4CH_2$	1	a	−20	58	93
CH_2	2-naphthylmethyl	1	a	−20	69	91
CH_2	Me	1	a	−40	73	72
CH_2	H	1	a	−20	58	51
CH_2	$C_6H_5CH_2$	2	a	−20	74	81
CH_2	*p*-Me-$C_6H_4CH_2$	2	a	−20	71	81
O	$C_6H_5CH_2$	2	b	−40	82	82
O	*p*-Me-$C_6H_4CH_2$	2	b	−40	79	86
O	*p*-Cl-$C_6H_4CH_2$	2	b	−40	74	86
O	*p*-MeO-$C_6H_4CH_2$	2	b	−40	84	85
O	2-naphthylmethyl	2	b	−40	88	84
O	Et	2	b	−40	95	67

enol ethers **85** undergo efficient enantioselective fluorodesilylation to provide the corresponding fluorinated compounds **86** bearing an enantioenriched fluorine-substituted quaternary carbon center, although the requirement for a bulky substituent on the substrate is a limitation on the enantioselectivity of this method. NFSI was chosen as fluorinating reagent because of its low background reaction. The authors advance a mechanistic hypothesis in which excess base would form an *N*-fluoroammonium KCO_3^- salt intermediate, in which the KCO_3^- triggers fluorodesilylation of the substrate and would be followed by the enantioselective transfer of fluorine to the substrate. Additionally, they propose a transition state for the reaction, shown below, to account for the observed absolute stereochemistry (Figure 10).

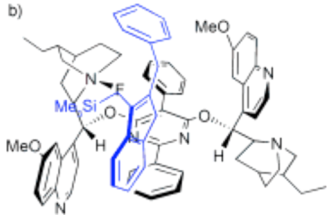
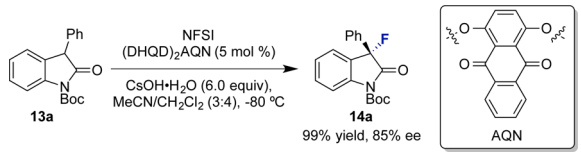


Figure 10. Proposed transition state for fluorination of silyl enol ether. Reproduced with permission from ref 48. Copyright 2008 John Wiley and Sons.

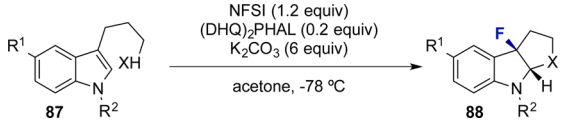
To demonstrate the further synthetic utility of this catalytic approach, they also investigated the catalytic enantioselective fluorination of oxindoles **13a** (Scheme 31). An ee value of 85% was able to be obtained when $CsOH·H_2O$ was used as a base at −80 °C, although this required use of the modified catalyst $(DHQD)_2AQN$.

Scheme 31



In 2011, Gouverneur and co-workers reported the enantioselective fluorocyclization of prochiral indoles **87** catalyzed by cinchona alkaloids (Table 9).[49] The best results

Table 9. Enantioselective Fluorocyclization of Prochiral Indoles Catalyzed by Cinchona Alkaloids

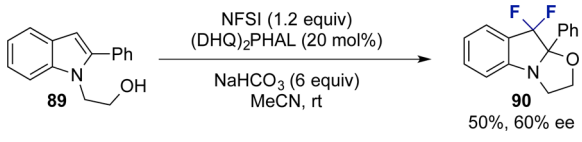


entry	R^1	R^2	XH	yield, %	ee, %
a	H	Me	OH	72	66
b	H	Et	OH	69	52
c	H	allyl	OH	76	60
d	OMe	Me	OH	65	74
e	OBn	Me	OH	78	74
f	OEt	Me	OH	78	72
g	Oallyl	Me	OH	65	78
h	Ph	Me	OH	61	62
i	Mes	Me	OH	55	84
j	H	Me	NHTs	59	64
k	OMe	Me	NHTs	51	70
l	Ph	Me	NHTs	70	70
m	Mes	Me	NHTs	80	84
n	H	Me	NHCOMe	95	80
o	Mes	Me	NHCOMe	65	92
p	H	Me	$NHCO_2Me$	76	74
q	H	Me	$NHCO_2BN$	47	77
r	H	Me	NHBoc	70	78

were afforded when using a catalytic amount of $(DHQ)_2PHAL$ at −78 °C in acetone with NFSI and an excess of K_2CO_3. The yields and enantiomeric excesses of the catalytic reaction were comparable to the corresponding stoichiometric reactions, which were also reported, although the relatively few results delivering the highest selectivities (>80%) demonstrate the challenging nature of the transformation. The process installs the fluorine substituent on a quaternary benzylic stereogenic carbon center and leads to new fluorinated analogues of natural products featuring the hexahydropyrrolo[2,3-*b*]indole or the tetrahydro-2*H*-furo-[2,3-*b*]indole skeleton **88**.

Prochiral indole **89** was also subjected to the optimized fluorocyclization conditions, which afforded the difluorinated tricyclic tetrahydrooxazolo[3,2-*a*] indole **90** in 50% yield, 60% ee (Scheme 32).

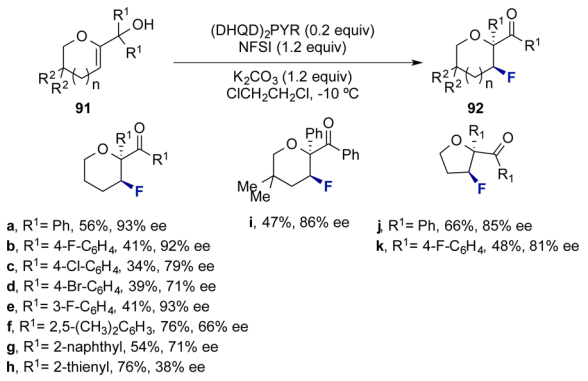
Scheme 32



dx.doi.org/10.1021/cr500277b | *Chem. Rev.* 2015, 115, 826−870

In 2012, Tu and co-workers reported the asymmetric fluorination/semipinacol rearrangement of 2-oxa allylic alcohols **91** to afford the corresponding chiral β-fluoroketones **92**, catalyzed by cinchona-alkaloid derivatives (Scheme 33).[50]

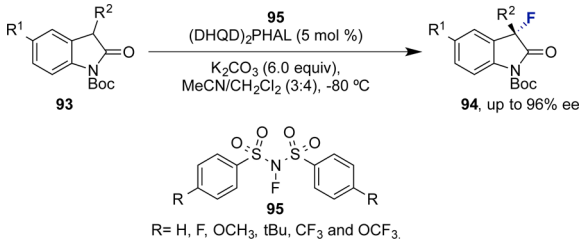
Scheme 33



Moderate to good enantioselectivities of the β-fluoroketones **92** were afforded using an NFSI (1.2 equiv)/$(DHQD)_2PYR$ (0.2 equiv) combination with K_2CO_3 as base at −10 °C. Comparable enantioselectivities of the antipodes were afforded when $(DHQ)_2PYR$ was used as catalyst.

In 2013, He and co-workers reported using structurally modified *N*-fluorobenzenesulfonimides (NFSI) in the enantioselective fluorination of oxindoles **93** in the presence of a bis-cinchona alkaloid, $(DHQD)_2PHAL$, as the catalyst (Scheme 34).[51a,b] They investigated a range of NSFI analogues **95** and

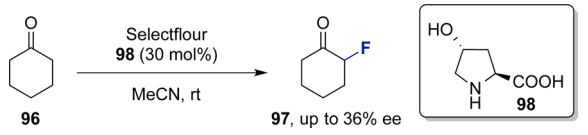
Scheme 34



found that the analogue bearing *tert*-butyl groups at the *para*-position of the phenyl rings led to an enhanced enantioselectivity in most cases, although with relatively slow reaction rate and low yield.

2.1.3.2. Enamine Catalysis. The rapid advances in enantioselective enamine catalysis seen in the early 2000s were quickly extended to fluorination. In 2005, several groups almost concurrently reported the enantioselective fluorination of aldehydes catalyzed by chiral secondary amines, proceeding via enamine intermediates. Enders and Hüttl reported the organocatalytic direct α-fluorination of aldehydes and ketones employing Selectfluor and proline-related secondary amine **98** as catalyst (Scheme 35).[52] However, only low enantioselectivity

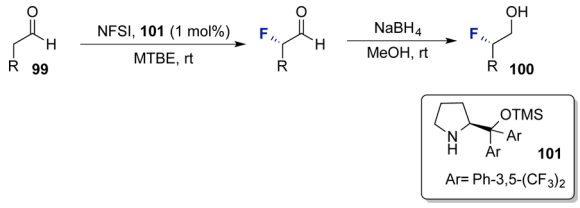
Scheme 35



(36% ee) was afforded when the best conditions were applied to cyclohexanone (**96**), and enantioselectivities for the aldehyde substrates were not reported.

Jørgensen and co-workers reported the application of silylated prolinol derivative **101** to tackle the enantioselective α-fluorination of aldehydes. They used NFSI as fluorine source in MTBE, with high enantioselectivities (91−97% ee) (Table 10).[53] Because of their instability, the α-fluorinated aldehydes were reduced in situ to afford the β-fluorinated alcohols **100** for subsequent analysis.

Table 10. Scope of Reaction for Enantioselective α-Fluorination of Aldehydes Using Catalyst 101



entry	R	yield, %	ee, %
a	Pr	95	96
b	Bu	>90	91
c	Hex	55	96
d	$BnO(CH_2)_3$	64	91
e	Bn	74	93
f	Cy	69	96
g	*t*Bu	>90	97
h	1-Ad	75	96

The authors proposed a catalytic cycle for this reaction (Figure 11), and rationalize the stereochemical outcome by

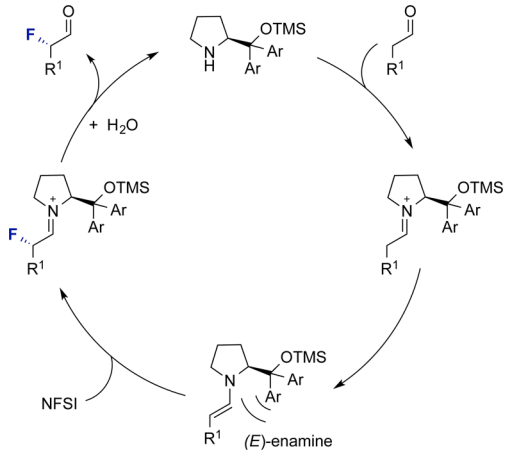


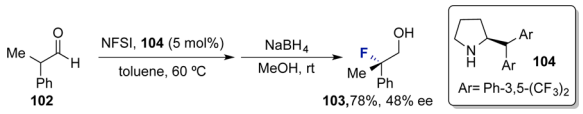
Figure 11. Proposed catalytic cycle for enantioselective α-fluorination of aldehydes.

invoking formation of the more stable *E*-configured enamine, with the 3,5-di(trifluoromethyl)phenyl groups blocking the *Re* face. As a consequence, the electrophilic fluorination occurs from the *Si* face, with excellent stereocontrol.

They also demonstrated preliminary results on the extension of the reaction scope to the formation of quaternary stereocenters (Scheme 36). The sterically encumbered substrate **102** required less bulky catalyst **104** and a higher temperature, allowing product formation with a moderate but encouraging 48% ee.

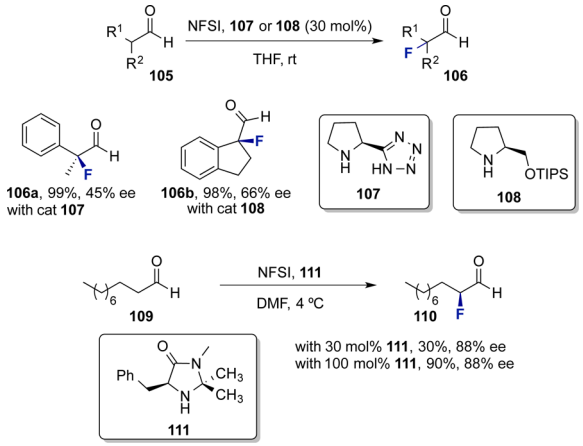
dx.doi.org/10.1021/cr500277b | *Chem. Rev.* 2015, 115, 826−870

Scheme 36



At a similar time, Barbas and co-workers focused on the enantioselective fluorination of α-branched aldehydes **105** using chiral secondary amine catalysts (Scheme 37).[54] After a

Scheme 37

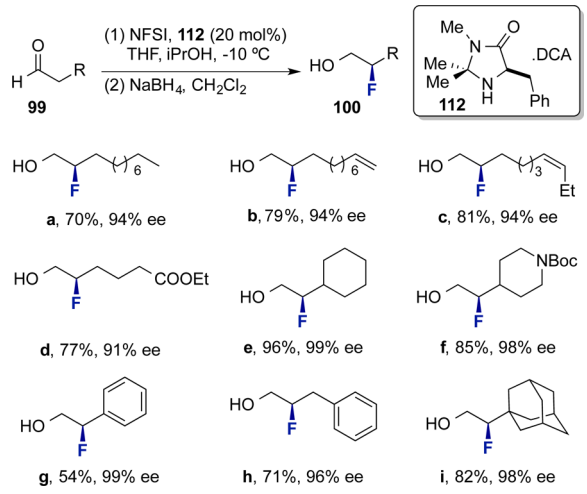


catalyst screen in THF at room temperature, moderate enantioselectivities of the fluorinated products were obtained (45% ee for **106a**; 66% ee for **106b**). The authors found that better results were obtained when applying these conditions to nonbranched aldehydes. While formation of the α,α-difluoro product was initially a problem, a screen of the solvents revealed that DMF could inhibit formation of this byproduct, and the desired product was formed with 88% ee when imidazolidinone catalyst **111** (30 mol %) was employed, although the yield was low (30%). Unfortunately, use of a stoichiometric amount of the catalyst was required to achieve good yield.

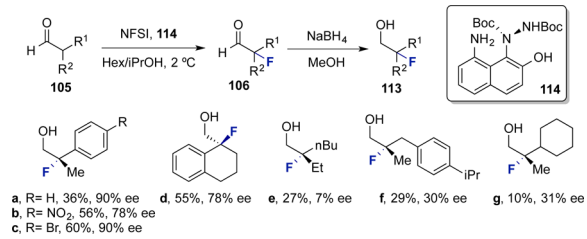
MacMillan and co-workers reported the use of imidazolidinone dichloroacetate **112** for the fluorination of linear aldehydes **99** with NFSI to achieve excellent enantioselectivity (up to 99% ee) (Scheme 38).[55] The authors found that addition of 10% *i*-PrOH as cosolvent generally improved enantiocontrol and efficiency, although the origin of this effect is not clear. A wide range of functional groups, including olefins, esters, amine, carbamates, aryl rings, and sterically demanding substituents, could be readily tolerated on the aldehyde substrates, although α-branched aldehydes were not discussed. They also evaluated the effect of the catalyst loading on reaction efficiency and found that loadings as low as 2.5 mol % could be used without loss of enantiocontrol.

In 2006, Jørgensen and co-workers reported using chiral 8-amino-2-naphthol derivative **114**, the product of an asymmetric Friedel–Craft amination, as an organocatalyst in the asymmetric α-fluorination of α-branched aldehydes.[56] This catalyst delivered the products **113** in up to 90% ee (Scheme 39). In general, good enantioselectivities were achieved when R^1 was an aromatic substituent, although the yields were low to moderate due to suspected instability of the products upon column chromatography. In the case of substrates bearing two aliphatic substituents, the enantioselectivities of the reaction

Scheme 38



Scheme 39



dropped significantly, highlighting the challenging nature of these substrates. The authors advanced a mechanistic hypothesis for asymmetric induction, inspired by an X-ray structure of an acylated analogue of the catalyst, which suggested that the catalyst naphthol substituents may sit at right angles to the naphthol core and a hydrogen bond may be present between the BOC group and enamine NH (Figure 12).

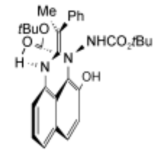
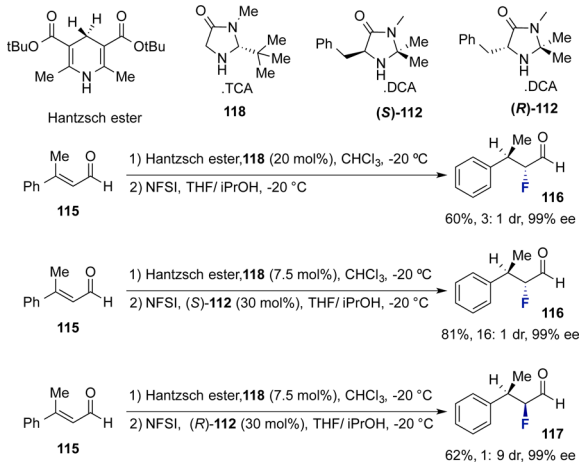


Figure 12. Proposed structure of enamine intermediate showing one face blocked and an intramolecular hydrogen bond. Reproduced with permission from ref 56. Copyright 2006 John Wiley and Sons.

In 2005, MacMillan and co-workers reported a combination of transfer hydrogenation using Hantzsch ester and electrophilic fluorination using NFSI on enal substrates, which would allow the formal asymmetric addition of HF across trisubstituted olefin systems using a cascade-catalysis approach (Scheme 40).[57] The authors assumed that the iminium and enamine steps might be discretely controlled by separate catalysts, although a single catalyst could also enable both activation cycles. Using imidazolidinone catalyst **118** (20 mol %), the product **116** was obtained in 60% yield with 99% ee, albeit with 3:1 anti:syn diastereoselectivity. Implementation of catalyst combination A (**118** 7.5 mol % and (*S*)-**112** 30 mol %) allowed the formal addition of HF to the trisubstituted enal with 16:1 anti:syn selectivity (99% ee). Remarkably, the *syn* HF addition product **117** could be accessed with 9:1 selectivity and

dx.doi.org/10.1021/cr500277b | *Chem. Rev.* 2015, 115, 826–870

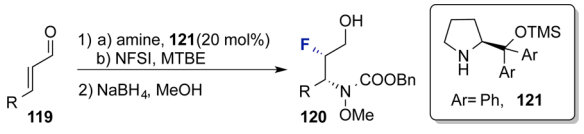
Scheme 40



in 99% ee by simply changing the enantiomeric series of **112** employed in this catalyst combination (**118** 7.5 mol % and (*R*)-**112** 30 mol %).

In 2010, Brenner-Moyer and co-workers reported organocatalyzed enantioselective aminofluorination of enals to afford chiral α-fluoro-β-amino aldehydes using the Jørgensen−Hayashi diarylprolinol catalyst **121** (Table 11).[58] The consistently

Table 11. Scope of Reaction for Enantioselective Aminofluorination of Enals



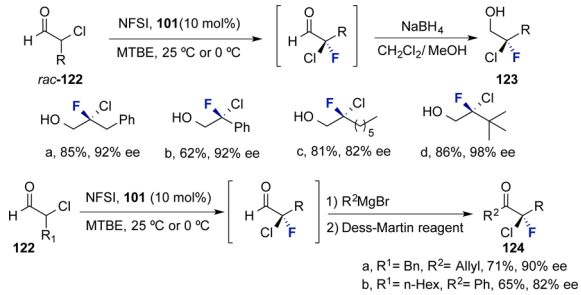
entry	R	yield, %	dr (syn:anti)	ee, %
a	Et−	73	95:5	99
b	*n*-Pr−	64	94:6	99
c	*n*-Bu−	66	95:5	99
d	$PhCH_2CH_2$−	51	95:5	98
e	$(CH_3)_2CHCH_2$−	41	90:10	99
f	*i*-Pr−	24	98:2	80
g	CH_2=$CH(CH_2)_3$−	61	93:7	99
h	$PhCH_2OCH_2$−	57	87:13	99
i	N=$C(CH_2)_5$−	41	91:9	99

high diastereo- and enantioselectivities are a testament to the power of the enamine/iminium modes of catalysis. The presence of other olefins, ether protecting groups, and remote reactive functional groups, such as cyano groups, was well tolerated.

In 2008, Yamamoto and Shibatomi reported enantioselective fluorination of α-chloro-aldehydes **122** to afford α,α-chlorofluoro aldehydes in high enantioselectivity catalyzed by the catalyst (**101**) developed by Jørgensen et al. (Scheme 41).[59] In situ reduction of the aldehydes with $NaBH_4$ afforded β,β-chlorofluoro alcohols **123** in high enantioselectivity. The products could be further elaborated to the corresponding α,α-chlorofluoro ketones **124**. Subsequent mechanistic studies suggest that the reaction mechanism involves a kinetic resolution of the starting α-chloro-aldehyde.[60]

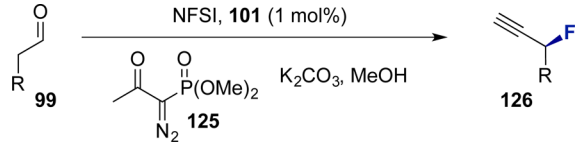
In 2009, Jørgensen and co-workers reported an extension to their earlier published work: a simple, direct one-pot organocatalytic approach to the formation of optically active

Scheme 41



propargylic fluorides **126** (Table 12).[61] This consists of organocatalytic α-fluorination of aldehydes followed by

Table 12. One-Pot Organocatalytic Approach to Enantioenriched Propargylic Fluorides

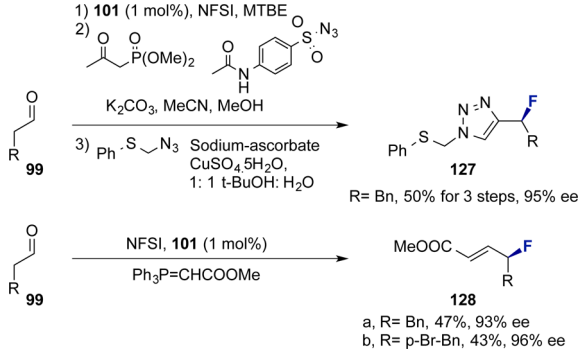


entry	R	yield, %	ee, %
a	−Bn	56	95
b	$-(CH_2)_7CH_3$	67	93
c	$-(CH_2)_{13}CH_3$	65	99
d	$-(CH_2)_7CH$=CH_2	55	92
e	*p*-OMe-$C_6H_4CH_2$−	65	91
f	*p*-Br-$C_6H_4CH_2$−	69	92
g	*o*-Me-$C_6H_4CH_2$−	58	99
h	*o*-Br-$C_6H_4CH_2$−	47	94
i	$-(CH_2)_3COOMe$	45	93

homologation with the Ohira−Bestman reagent **125**, providing optically active propargylic fluorides **126** with enantioselectivities of up to 99% ee.

The authors also extended this approach further to the direct synthesis of click adducts **127** from aldehydes in three steps in one pot in 50% yield with 95% ee (Scheme 42). The Wittig

Scheme 42

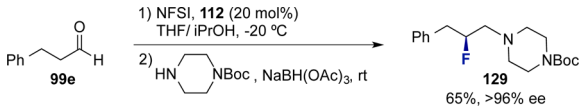


reaction is also fully compatible with the organocatalytic asymmetric reaction. The one-pot reaction, organocatalytic formation of α-fluoro aldehydes in combination with the commercially available methyl (triphenylphosphoranylidene) acetate, furnished the corresponding allylic fluorides **128** in moderate yield and high enantioselectivities.

dx.doi.org/10.1021/cr500277b | *Chem. Rev.* 2015, 115, 826−870

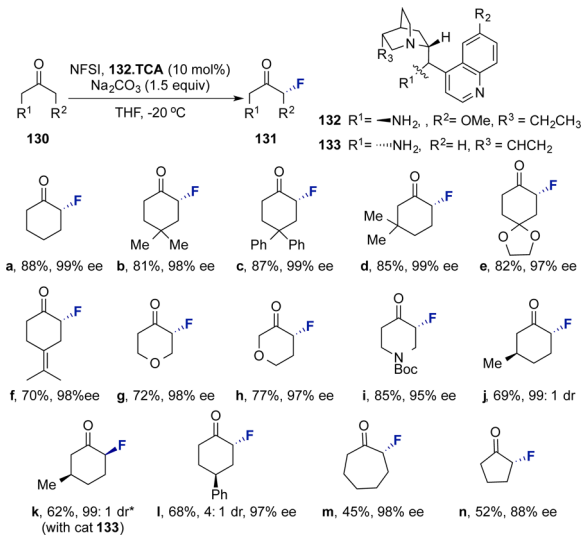
In 2009, Lindsley and co-workers reported the one-pot catalytic enantioselective synthesis of chiral β-fluoramines **129** via organocatalysis, again proving the versatility of the α-fluorination methodology (Scheme 43).[62] This was accomplished using NFSI with imidazolidinone catalyst **112** (20 mol %), at −20 °C in 10% *i*-PrOH/THF, followed by direct addition of Boc-piperazine and $NaBH(OAc)_3$. The desired β-fluoroamine **129** was isolated in 65% yield and with >96% ee.

Scheme 43



In 2011, MacMillan and co-workers reported the first highly enantioselective α-fluorination of cyclic ketones, catalyzed by a cinchona alkaloid-derived primary amine (Scheme 44).[63a] This catalyst was identified after a high-throughput evaluation of a library of chiral amine catalysts. Use of the dihydroquinidine catalyst **132** with trichloroacetic acid (TCA) as cocatalyst at −20 °C provided the α-fluoro cyclic ketones **131** in good yield with excellent enantioselectivities (up to 99% ee). The scope of this reaction was well examined; geminal disubstituted cyclohexanones and a wide array of heterocycles were well tolerated. The five-membered and seven-membered cyclic ketones also worked well (88% and 98% ee), albeit with moderate yield. They also successfully applied this methodology to the diastereoselective fluorination of cyclic ketones bearing pre-existing stereocenters. For example, in fluorination of (*R*)-3-methyl cycylohexanone (**130j**), the diastereoselectivity of the fluorinated product could be completely controlled by the choice of catalyst.

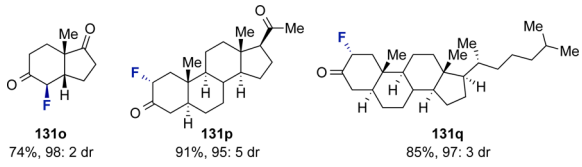
Scheme 44



They also employed the fluorination conditions to more complex substrates, including the hydrogenated Hajos−Parrish ketone **131o**, *allo*-pregnanedione **131p**, and cholestanone **131q** (Scheme 45).

Very recently, Lam and Houk reported a detailed computational study of MacMillan's ketone fluorination, to determine the origin of enantioselectivity.[63b] They proposed that fluorination of the quinuclidine portion of the catalyst by NFSI is fast and that the enantiodetermining step is intramolecular transfer of fluorine to the enamine, the latter being formed from condensation of the catalyst primary amine and the ketone substrate. They concluded that there are two key determining factors in the enantiocontrol: first the preferred chair conformation of the seven-membered ring in the transition state and second the steric bulk of the C9-quinoline of the catalyst giving it a strong equatorial preference (Figure 13).

Scheme 45



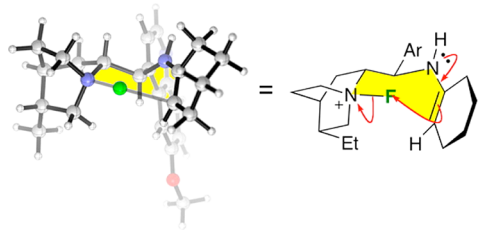
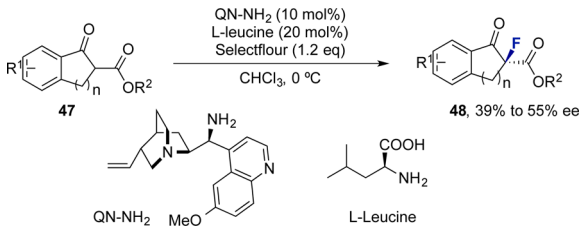


Figure 13. Two views of calculated lowest energy transition structure for fluorination of cyclohexanone using amine catalyst **132**. Reproduced with permission from ref 63b. Copyright 2014 American Chemical Society.

Recently, Xu and co-workers reported the enantioselective fluorination of β-ketoesters catalyzed by a combination of chiral primary amine catalysts (Scheme 46).[64] The desired fluorinated product **48** was afforded in moderate enantioselectivities (39−55% ee) only when QN-NH_2 and L-leucine were used together catalysts, and the exact function of each catalyst is unclear.

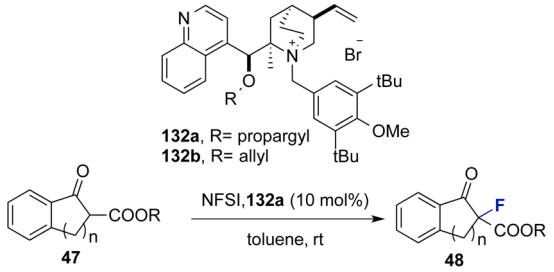
Scheme 46



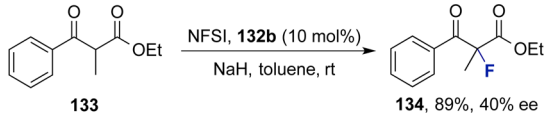
2.1.3.3. Phase-Transfer Catalysis. 2.1.3.3.1. Cationic Phase-Transfer Catalysis. In 2002, Kim and Park reported the first catalytic enantioselective fluorination of β-ketoesters employing phase-transfer catalysis using chiral quaternary ammonium salts (Table 13).[65] They found that a bulky group at the bridgehead nitrogen of cinchona alkaloids was crucial for high stereoselectivity, as in catalysts **132**. Several cyclic β-ketoesters were submitted to fluorination using NFSI and **132a** (10 mol %) as catalyst, affording the desired fluorinated products **48** in high yield with moderate enantioselectivities (48−69% ee). The authors found that for different substrates, tailoring of the base was required to obtain the best results. Fluorination of an acylic substrate **133** required

dx.doi.org/10.1021/cr500277b | *Chem. Rev.* 2015, 115, 826−870

Table 13. Enantioselective Fluorination of β-Ketoesters by Phase-Transfer Catalysis



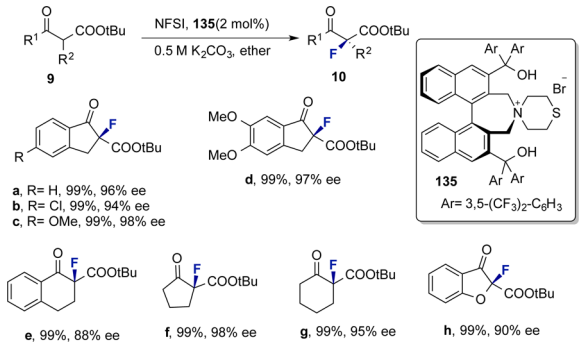
entry	*n*	R	base	yield, %	ee, %
a	1	Me	K_2CO_3	92	69
b	1	Et	Cs_2CO_3	91	63
c	2	Me	Cs_2CO_3	88	48
d	2	Et	CsOH	78	52



NaH as base, and afforded the α-fluoro product **134** in only 40% ee.

In 2010, Maruoka and co-workers reported the highly enantioselective fluorination of β-ketoesters catalyzed by chiral bifunctional phase-transfer catalysts (Scheme 47).[66] Fluorination of various cyclic β-ketoesters **9** gave the desired α-fluorinated products with excellent enantioselectivities (up to 99% ee) under the catalysis of thiomorpholine-derived catalyst **135**. The authors found the presence of hydroxyl groups in **135** is crucially important to obtain high enantioselectivity. They proposed that in the transition state, the *Z*-enolate would be stabilized by both the ionic interaction of the ammonium enolate and the hydrogen bonding between the enolate oxygen and one hydroxyl group of the catalyst (Figure 14). This would lead to approach of the NFSI from the upper face of the enolate, as depicted. Unfortunately, these conditions were unsuitable for the fluorination of acyclic substrates.

Scheme 47



In 2013, Lu and co-workers reported the enantioselective fluorination of indanone-derived β-ketoesters **47** catalyzed by adamantoyl-derivatized cinchona alkaloid phase-transfer catalyst **136**, affording the α-fluorinated products **48** in high enantioselectivities (84−94% ee) (Scheme 48).[67]

Ma, Cahard, and co-workers have recently explored the use of *P*-spiro phosphonium salts for the fluorination of 3-substituted benzofuran-2-(3*H*)-ones **137**, but only moderate enantioselectivities have been obtained thus far (Scheme 49).[68]

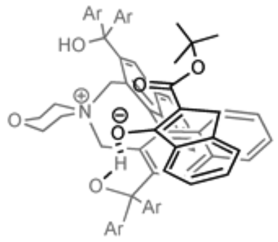
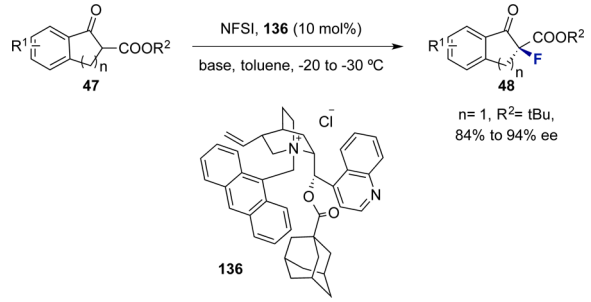
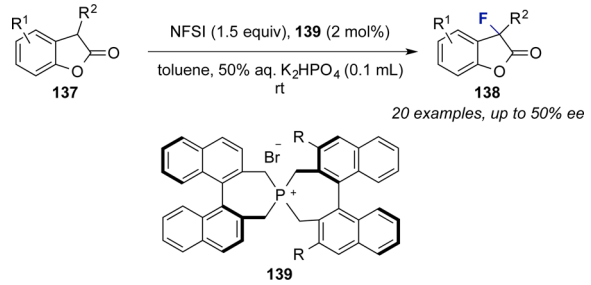


Figure 14. Proposed transition state structure. Reproduced with permission from ref 66. Copyright 2010 The Royal Society of Chemistry.

Scheme 48



Scheme 49



2.1.3.3.2. Anionic Phase-Transfer Catalysis. The use of chiral cationic salts as phase-transfer catalysts for anionic reagents is well precedented; however, an analogous charge-inverted strategy in which the salt of chiral anion brings an insoluble cationic promoter into solution has been rather less explored.[69] In 2011, Toste and co-workers reported an advance in this field, asymmetric fluorocyclization using an anionic chiral phase-transfer catalyst.[70] Selectfluor is normally insoluble in nonpolar media, but the authors hypothesized that lipophilic, bulky chiral phosphate anions such as the conjugate base of acid **140** may exchange with the tetrafluoroborate anions associated with Selectfluor to bring the reagent into solution. The resulting chiral ion pair could then mediate an asymmetric fluorination of substrate in solution. Given the insolubility of Selectfluor, little background fluorination of the substrate would be anticipated (Figure 15).

Employing optimized conditions (5 mol % **140a**, 1.25 equiv of Selectfluor, and 1.1 equiv of proton sponge in C_6H_5F at −20 °C) on electron-rich enol ether substrates **141** gave the desired fluorocyclization product **142** in high yield with excellent enantio- and diastereoselectivities (Scheme 50). Consistent with their hypothesis, the hydrophobic alkyl chains attached to

dx.doi.org/10.1021/cr500277b | *Chem. Rev.* 2015, 115, 826−870

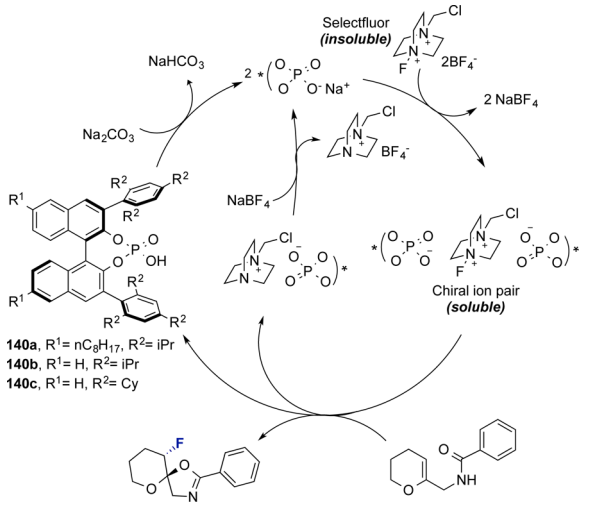
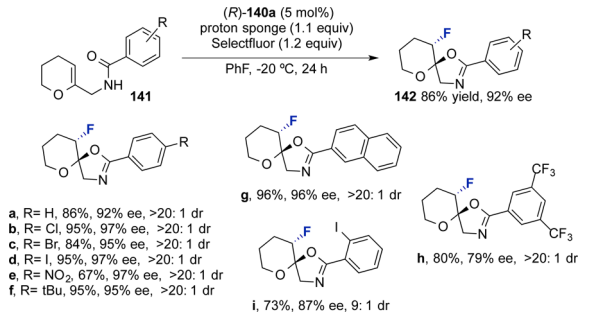


Figure 15. Proposed catalytic cycle for chiral anion phase-transfer catalysis, leading to fluorocyclization.

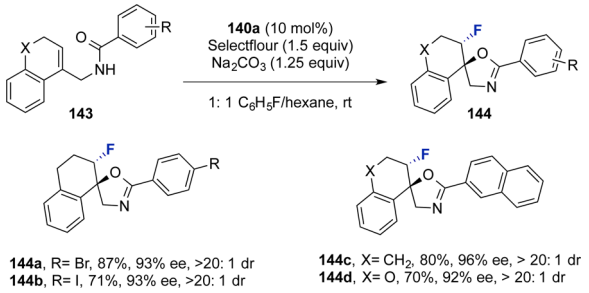
Scheme 50



the backbone of the catalyst proved beneficial for the phase-transfer aspect, improving enantioselectivity from 87% with **140b** to 92% with **140a**.

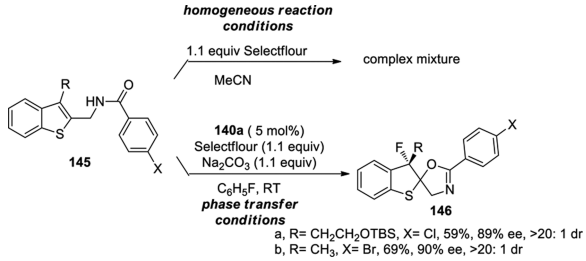
They also extended the methodology to less electron-rich alkenes **143** (Scheme 51). Accordingly, fluorocyclization of dihydronaphthalene (**143a−c**) and chromene (**143d**) substrates also gave excellent enantio- and diastereoselectivities at room temperature.

Scheme 51



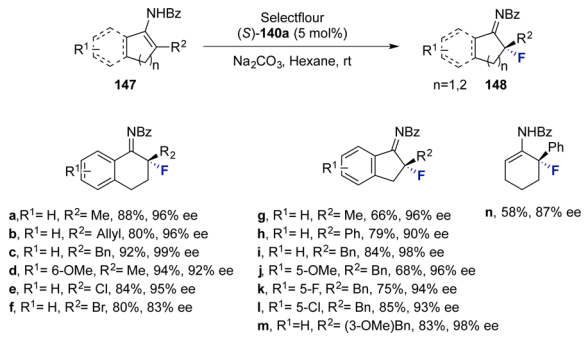
An unanticipated benefit of the phase-transfer protocol was an improved tolerance toward sensitive functionality. For example, when treated with Selectfluor under homogeneous conditions, benzothiophene substrates **145** were converted to a complex mixture of products. However, when the chiral anion phase-transfer reaction conditions were applied, fluorocyclization products **146** were isolated in good yield and high optical purity (Scheme 52).

Scheme 52



In 2012, Toste and co-workers reported the asymmetric fluorination of enamides to access α-fluoroimines using the same chiral anion phase-transfer catalysis strategy (Scheme 53).[71] Applying conditions similar to those previously

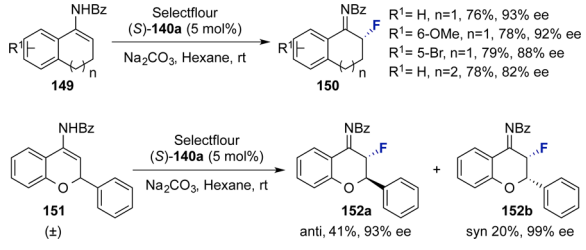
Scheme 53



employed (Selectfluor, chiral phosphoric acid **140a**, Na_2CO_3 in hexane), enamides or ene-carbamates gave the desired α-fluoroimine products, which were stable and isolable. However, only the *N*-benzoylenamide substrates **147** gave very high enantioselectivities. A number of cyclic indanone and tetralone-derived enamides provided enantioenriched α-(fluoro)-benzoylimines **148** bearing a variety of diversely substituted quaternary fluorinated stereocenters. Under the phase-transfer fluorination conditions, chloro- and bromo-substituted enamides also gave the novel β,β-chloro,fluoro and bromo,fluoro compounds with high enantioselectivities. A beneficial effect in enantioselectivity was observed for some substrates when the reaction was run in the presence of 5 equiv of 3-hexanol, although the exact role of this additive is unclear.

Unsubstituted tetralone-derived enamides **149** also delivered stable imine products that did not racemize (Scheme 54). Fluorination of a racemic flavanone-derived enamide **151**, which has a pre-existing stereocenter, resulted in approximately

Scheme 54



dx.doi.org/10.1021/cr500277b | Chem. Rev. 2015, 115, 826−870

equal ratio of separable *anti* and *syn* diastereomers (**152a**, **152b**), both with excellent enantioselectivities, illustrating the high selectivity of the catalytic system, regardless of the presence of an existing adjacent stereocenter.

On the basis of the experimentally observed absolute stereochemistry, they advanced a tentative model for interactions with the catalyst (Figure 16). The phosphate

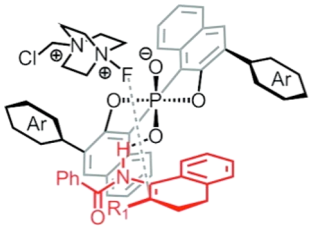


Figure 16. Proposed model for selectivity in fluorination of enamides using chiral anion phase-transfer catalysis. Reproduced with permission from ref 71. Copyright 2012 American Chemical Society.

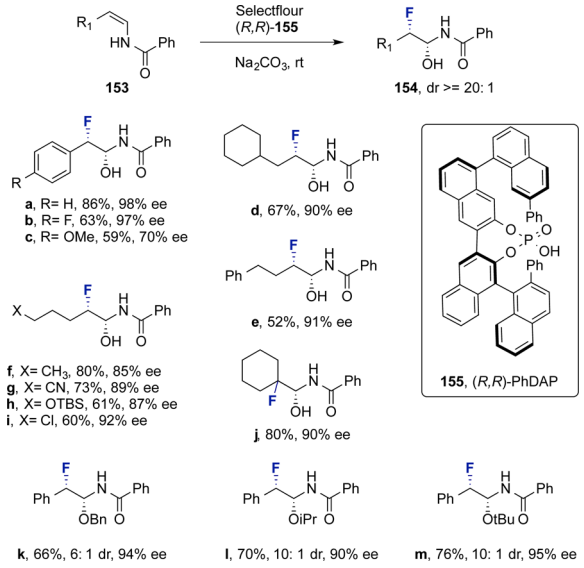
anion is thought to form an ion pair with the Selectfluor reagent on the phosphate oxygen, while the phosphoryl oxygen activates the enamide through hydrogen bonding. The absolute stereochemistry can be rationalized by placing the aromatic ring of the tetralone in the "open" quadrant of the catalyst.

Subsequently, Toste and co-workers developed an enantioselective tandem oxyfluorination of enamides using a doubly axially chiral phosphoric acid.[72] They proposed that the fluorination of aldehyde-derived enamides **153** would generate, in the first instance, a protonated α-fluoro-*N*-acyliminium ion. This intermediate should exhibit hydrogen-bonding interactions with the chiral phosphate anion, allowing catalyst-controlled addition of an external oxygen nucleophile, constituting an oxyfluorination of enamides. Optimization of the reaction revealed that only the *Z*-enamides gave high diastereo- and enantioselectivities when the novel doubly axially chiral catalyst **155** was used. They anticipated this catalyst would generate a more rigid and constrained pocket for the substrate, leading to higher selectivity. Both aromatic and aliphatic substituted enamides **153** were effective in the tandem hydroxyfluorination process (Scheme 55). In accord with the hypothesis that catalyst control is operative in the hydration step, product **154j** was produced in high enantioselectivity, in which only the *N*,*O*-aminal carbon is chiral. When the reaction was run in the presence of alcohols, alcohol addition was observed rather than hydration, the latter being thought to arise from moisture in the Selectfluor (**154k**–**m**).

They also explored substrates that would generate a chiral quaternary fluorine stereocenter (Scheme 56). Fluorination of (*E*)-**156** gave poor diastereoselectivity but extremely high enantioselectivity for the *anti*-**157** and low enantioselectivity for *syn*-**158**, which was believed to be a result of double stereodifferentiation. However, this effect was not as pronounced for (*Z*)-**159**.

In 2013, Toste and co-workers reported the catalytic asymmetric 1,4-aminofluorination of conjugated dienes using chiral anion phase-transfer catalysis (Table 14).[73] The 6-*endo*-*trig* fluorination of diene substrate **160** would produce an allylic fluoride, an important chemical motif. Optimization revealed catalyst **140c** to be superior. Although far from the reactive center, substitution on the benzamide arene exerted a strong influence on the selectivity, with *tert*-butyl substitution at the *para* position giving the best results.

Scheme 55



Scheme 56

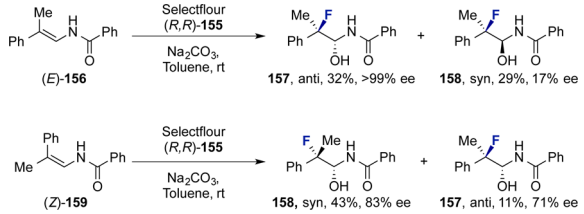
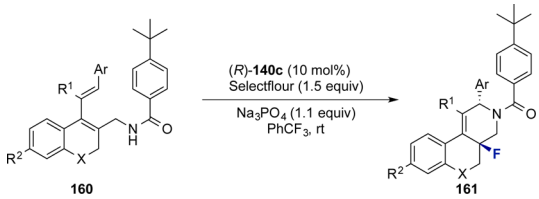


Table 14. Asymmetric 1,4-Aminofluorination of Conjugated Dienes Using Chiral Anion Phase-Transfer Catalysis

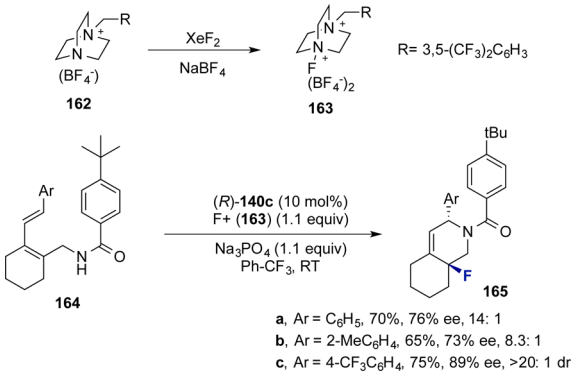


entry	Ar	R^1	R^2	X	yield, %	ee, %	dr
a	2-MeC_6H_4	H	H	CH_2	91	96	>20:1
b	3-MeC_6H_4	H	H	CH_2	92	92	5.9:1
c	C_6H_5	H	H	CH_2	90	92	6.9:1
d	C_6H_5	H	OMe	CH_2	90	93	6.9:1
e	C_6H_5	H	H	O	85	91	5.5:1
f	4-$CF_3C_6H_4$	H	H	CH_2	94	95	10:1
g	4-MeOC_6H_4	H	H	CH_2	89	93	7.5:1
h	C_6H_5	*n*Bu	H	CH_2	85	94	>20:1

The fluorocyclization of less-reactive dienes **164** was also examined (Scheme 57). When subjected to the optimized reaction conditions using Selectfluor as the fluorine source, dienes **164** (not tetralone-derived, as before) reacted sluggishly, affording only racemic product. The authors hypothesized that the reactivity of the fluorinating reagent may be increased by attaching an electron-deficient aryl group in place of the chlorine atom of Selectfluor. Different derivatives were accessed simply by treating tetrafluoroborate salts **162** with XeF_2. The more electron-deficient reagent **163** produced the cyclized product **165c** with the highest levels of enantioselectivity (89% ee).

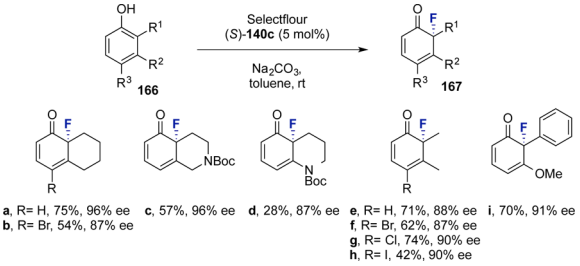
dx.doi.org/10.1021/cr500277b | *Chem. Rev.* 2015, 115, 826–870

Scheme 57



In 2013, Phipps and Toste applied this chiral anion phase-transfer catalysis strategy to the asymmetric fluorinative dearomatization of phenols.[74] They hypothesized that hydrogen bonding of the phenolic hydroxyl group with the phosphoryl oxygen of the catalyst might enable discrimination between the enantiotopic faces of the phenol in a subsequent fluorination reaction. Accordingly, they found that fluorination of 2,3-di- and 2,3,4-trisubstituted phenols under optimized conditions using 5 mol % (*S*)-**140c** afforded *ortho*-fluorinated dearomatized products with high enantioselectivities (Scheme 58).

Scheme 58

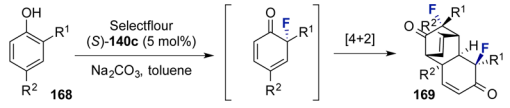


They also investigated substrates without substitution at the 3-position (Table 15). The isolated products **169** were found to be dimers resulting from [4 + 2] cycloaddition of the chiral 2,4-cyclohexadienones produced after the initial fluorination. They demonstrated the further transformation of the dimeric products in the form of retro-[4 + 2]/[4 + 2] reactions with *N*-phenylmaleimide and cyclopentadiene dimer to provide rapid access to a diverse fluorinated scaffolds (**170**, **171**) with no loss of enantioenrichment.

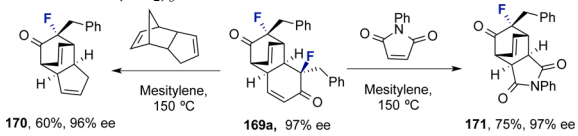
A number of *para*-fluorinated products were also demonstrated to be obtainable with good enantioselectivities by incorporating the geminal 8,8′ disubstitution to increase the steric bulk. Throughout the study, the authors noted that steric bulk on one side of the phenol was required to achieve high selectivities. In the case of the *para*-fluorination process, yields were moderate due to competitive S_EAr arene fluorination at the *ortho* position (Scheme 59).

In 2013, Toste and co-workers reported the enantioselective fluorination of alkenes using chiral anion phase-transfer catalysis and employing remote directing groups (Scheme 60).[75a] On the basis of their previous success with amides as pendant nucleophiles, they posited that allylic amides may be used as remote directing groups to direct alkene fluorination to provide access to allylic fluoride products after elimination.

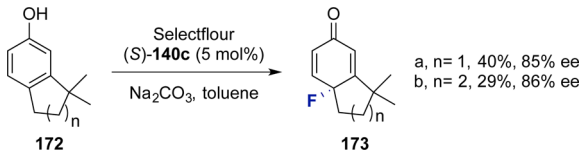
Table 15. Asymmetric Fluorinative Dearomatization of Phenols − Scope of Phenols Lacking 3-Substitution and Further Transformation of the Products



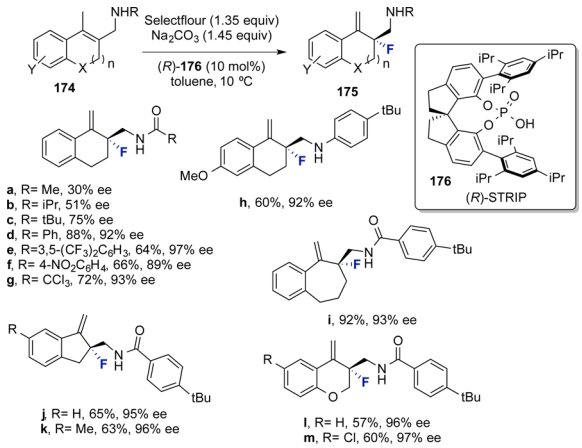
entry	R^1	R^2	yield, %	ee, %
a	Bn	H	81	97
b	Ph	H	55	90
c	homoallyl	H	65	90
d	allyl	H	71	87
e	*i*Pr	H	96	91
f	allyl	Me	51	92
g	Bn	Me	67	90
h	$(CH_2)_3$OTBS	H	77	91



Scheme 59



Scheme 60



Optimization revealed the catalyst STRIP (**176**) gave superior enantioselectivity and chemoselectivity to TRIP (**140b**), which may be caused by its tighter binding pocket. An *N*-methylated analogue of **174** was unreactive under the same conditions, supporting their hypothesis that a substrate hydrogen-bond donor is required to direct the fluorination. Investigation of the scope of compatible amide directing groups revealed the best enantioselectivities were observed with larger groups on the amide (**174a−e**). The scope of this reaction was explored; substrates with different ring sizes, benzamide substitution patterns, substitution on the bicyclic core, and heterocyclic substrates were well tolerated.

In addition to amides, 2-hydroxyphenyl was found to be an effective directing group to enable enantioselective fluorination of a number of tethered alkenes under similar conditions

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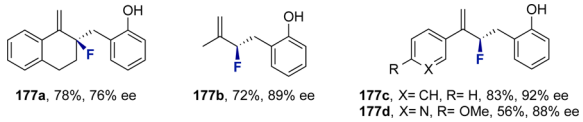
(Scheme 61). As compared to related allyl substrates that were previously observed to undergo fluorinative dearomatization

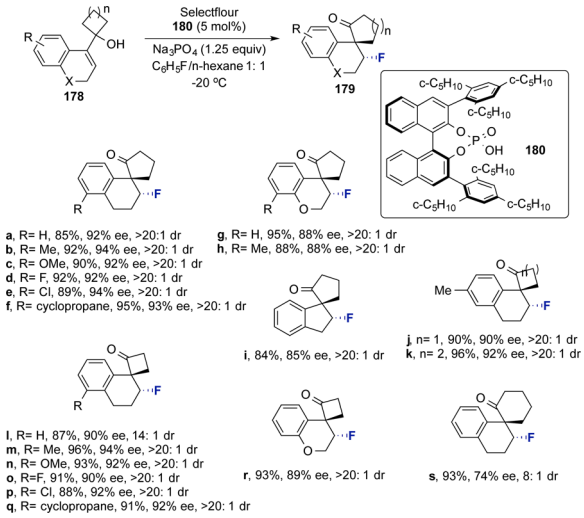
Scheme 61



under similar conditions (Table 15), increased substitution on the alkene switches the chemoselectivity with fluorination at the alkene being seen exclusively, rather than fluorination at the phenol. Both β-phenolic tertiary and quaternary fluorides **177a−d** with alkyl, aryl, or heteroaryl substituents were obtained with good to excellent enantioselectivities. This concept was extended to allylic alcohols using a boronic acid as an in situ directing group.[75b]

In 2013, Alexakis and co-workers reported the enantioselective fluorination-induced Wagner−Meerwein rearrangement of strained allylic alcohols using chiral anion phase-transfer catalysis (Scheme 62).[76] Fluorination of substrates **178** with

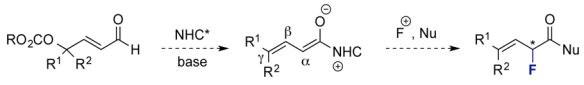
Scheme 62



Selectfluor, Na_3PO_4 in C_6H_5F/hexane (1:1) at −20 °C with catalyst **180** afforded the ring expanded products **179** with good diastereo- and enantioselectivities. Interestingly, both the enantioselectivity and the diastereoselectivity of the present transformation were controlled by the catalyst. Thus, racemic reaction (using an achiral phosphoric acid) gave low diastereoselectivities. The substrate scope encompasses both allylic cyclobutanols and allylic cyclopropanols based on the tetralone scaffold, as well as the chromanone scaffold. However, allylic alcohol substrates lacking the aromatic ring gave good yields but only moderate stereoselectivities under the optimized conditions.

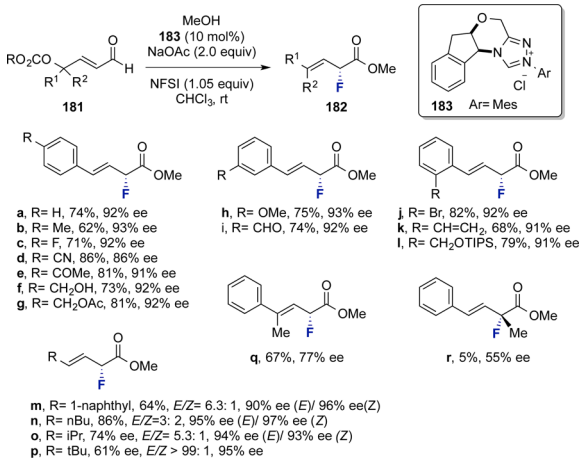
2.1.3.4. Miscellaneous Catalysts. In 2012, Sun and co-workers reported the enantioselective synthesis of β,γ-unsaturated α-fluoroesters catalyzed by *N*-heterocyclic carbenes (NHCs).[77] NHCs are well-known for their unique capability to reverse the normal polarity of aldehydes. The authors hypothesized that an enal bearing a leaving group in γ-position would provide access to a chiral NHC-bound dienolate that may subsequently react with an electrophilic fluorinating reagent and a nucleophile to afford an enantioenriched fluorinated product (Scheme 63).

Scheme 63



Fluorination of γ-methyl-carbonate-substituted α,β-unsaturated enals **181** with NFSI using **183** as catalyst afforded the desired fluorinated products **182** in good yield with high enantioselectivities (Scheme 64). A variety of functional groups

Scheme 64



on the substrates were well tolerated, including ethers, halides, cyanides, alkenes, aryl aldehydes, ketones, free alcohols esters, and silyl-protected alcohols. The presence of a quaternary carbon atom in γ-position (**181q**) did not significantly affect the reaction efficiency, and a trisubstituted alkene could be obtained as a single *E* isomer. In contrast, a substituent at the α-position (**181r**) significantly retarded the reaction (<10% conversion) and led to moderate enantioselectivity. Alkenes with alkyl substituents at the γ position also participated smoothly in this reaction, albeit with low *E*/*Z* ratio. The *E*/*Z* ratio could be improved by employing bulkier alkyl groups, such as *i*Pr and *t*Bu.

The authors also proposed a possible transition state to account for the control of enantioselectivity (Figure 17). In the proposed favored dienolate, the chiral backbone of the NHC blocks the *Si* face, leading to the observed enantiomer. DFT calculations revealed that the less favored rotamer, in which the *Re* face is blocked, is about 5.3 kca $lmol^{-1}$ higher in energy than

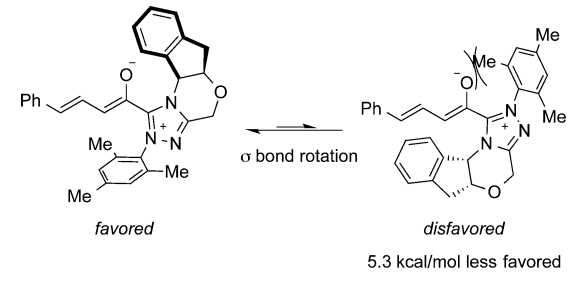


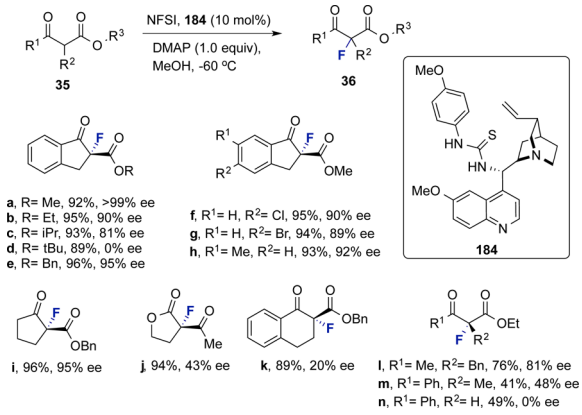
Figure 17. Summary of DFT calculations leading to hypothesis to account for absolute stereochemistry.

dx.doi.org/10.1021/cr500277b | *Chem. Rev.* 2015, 115, 826−870

the favored one due to an unfavorable interaction between the enolate oxygen atom and a catalyst methyl group when the system is fully conjugated.

In 2012, Niu and co-workers reported the thiourea-catalyzed enantioselective fluorination of β-ketoesters (Scheme 65).[78]

Scheme 65



They found that chiral bifunctional thiourea catalyst **184** could efficiently catalyze the fluorination of β-ketoesters **35** with NFSI with the assistance of DMAP in MeOH at −60 °C to afford the desired fluorinated product in high yield with good to excellent enantioselectivities. The alkoxy group of the indanonecarboxylate derivatives had a great influence on enantioselectivity, with Me and Bn being optimal. The tetralone derivatives and acyclic β-ketoesters gave low enantioselectivities in some cases.

The authors also proposed a mechanism proceeding via a dual-activation process wherein the NFSI hydrogen bonds to the catalyst thiourea group and the 1,3-dicarbonyl compound interacts with the basic nitrogen of the catalyst (Figure 18).

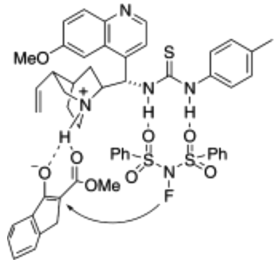
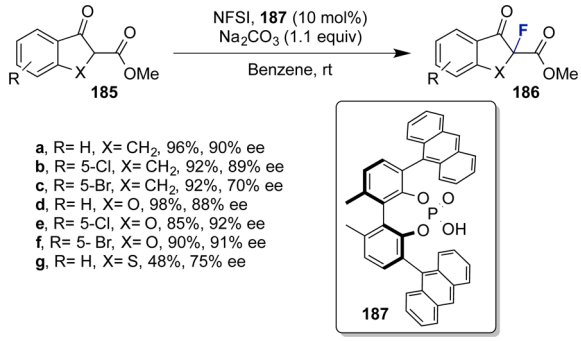


Figure 18. Proposed intermediate in dual-activation process. Reproduced with permission from ref 78. Copyright 2012 John Wiley and Sons.

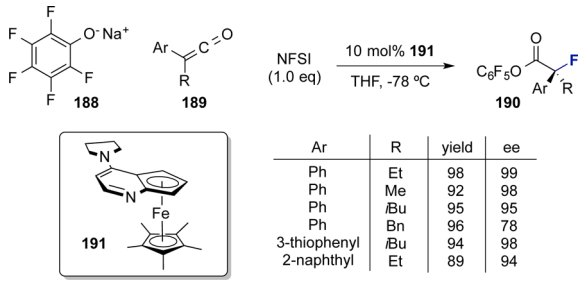
In 2014, Akiyama and co-workers reported enantioselective fluorination of β-ketoesters catalyzed by a chiral sodium phosphate derived from acid **187** (Scheme 66).[79] The authors supposed that simultaneous formation of the sodium enolate and sodium phosphate under basic conditions is the key to achieving excellent selectivity. Indanone derivatives **185a−c** as well as benzofuranone derivatives **185d−f** were employed in this reaction to afford the fluorinated products in good yields with good to excellent enantioselectivities.

Very recently, Fu and co-workers reported the asymmetric synthesis of tertiary alkyl fluorides via a nucleophile-catalyzed α-fluorination of ketenes (Scheme 67).[80] In this process, the planar-chiral nucleophilic catalyst **191** reacts with the ketene

Scheme 66



Scheme 67



Ar	R	yield	ee
Ph	Et	98	99
Ph	Me	92	98
Ph	*i*Bu	95	95
Ph	Bn	96	78
3-thiophenyl	*i*Bu	94	98
2-naphthyl	Et	89	94

189 to form a catalyst-derived chiral enolate. This intermediate undergoes electrophilic fluorination, and the resulting cationic intermediate is attacked by a phenoxide additive (**188**), which releases the nucleophilic catalyst and forms the product **190**. The phenoxide additive needed to be carefully chosen to ensure turnover, and mechanistic studies ruled out an alternative pathway whereby the catalyst itself is directly fluorinated (Figure 19). Using this approach, a range of valuable tertiary α-fluoroesters could be accessed from aryl alkyl ketenes, with very high levels of enantioselectivity.

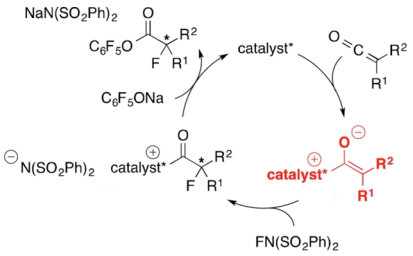


Figure 19. Proposed mechanism for α-fluorination of ketenes. Reproduced with permission from ref 80. Copyright 2014 American Chemical Society.

2.1.4. Fluorination Using Multiple Catalysts. In 2008, Lectka and co-workers reported a catalytic, highly enantioselective α-fluorination of acid chlorides.[81] This reaction exploits a "dual activation" strategy in which a chiral Lewis base catalyst (a cinchona alkaloid derivative) is combined with a transition metal-based Lewis acid cocatalyst (Pd or Ni were particularly effective) to catalytically generate metal-coordinated, chiral ketene enolates. These are fluorinated by NFSI at the α position, followed by attack of the liberated dibenzenesulfonimide anion that can be subsequently quenched with different nucleophiles to afford fluorinated carboxylic acids, amides, esters, and even peptides (Scheme 68).

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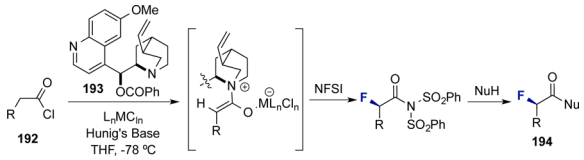
Scheme 68



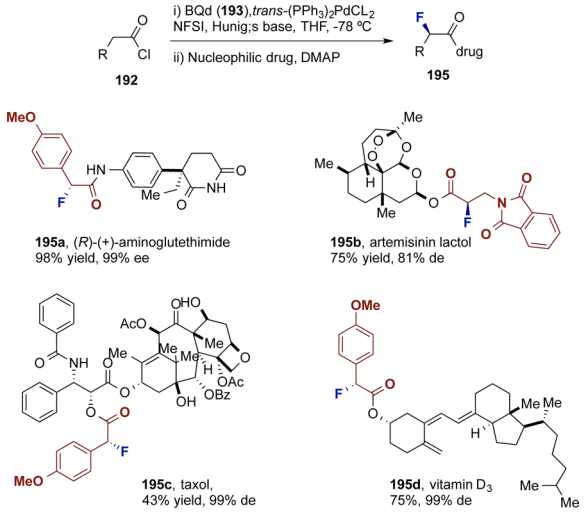
Treatment of acid chlorides **192** with NFSI, Hünig's base, 10 mol % BQd catalyst (**193**), and *trans*-$(Ph_3P)_2PdCl_2$ or $(dppp)NiCl_2$, followed by quenching with nucleophiles after 6−15 h afforded the desired α-fluorinated acid derivatives **194** in good yield with excellent enantioselectivities. Acid chlorides containing aromatic as well as heterocyclic substituents proved to be compatible substrates (Table 16).

In 2010, the same group reported the quenching of the above reaction with nucleophilic natural products to produce biologically relevant α-fluorinated carbonyl derivatives (Scheme 69).[82] They found that the solubility of the nucleophile used to quench the reaction proved critical. Glutathione, morphine, and 6-aminopenicillanic displayed marginal solubility, leading to drastically decreased yields. Some site selectivity was also observed; for example, when *p*-methoxylphenylacetyl chloride was fluorinated and quenched with taxol, the sole product (**195c**) resulted from acylation at the hydroxyl shown.

Although the fluorination of aryl and heteroaryl acetyl chlorides (**192**, R = aromatic) using the above approach proved to be very successful, the related aliphatic substrates (**196**) worked poorly, delivering low yields of fluorinated products. Following initial mechanistic studies, Lectka and co-workers speculated that addition of a second Lewis acid may coordinate NFSI selectively, thereby increasing its electrophilicity and reactivity (Scheme 70).[83] After optimization, the authors found that addition of 10 mol % $LiClO_4$ combined with the slow addition of Hünig's base over 12 h could increase the yield of the aliphatic substituted products **197** while still delivering excellent enantioselectivities (>99% ee).

After a subsequent in-depth mechanistic analysis, which took into account the presence of three catalysts, Lewis acid activation of the fluorinating agent by a lithium cation was deduced to be crucial to the efficient reaction (Figure 20).

Scheme 69



Scheme 70

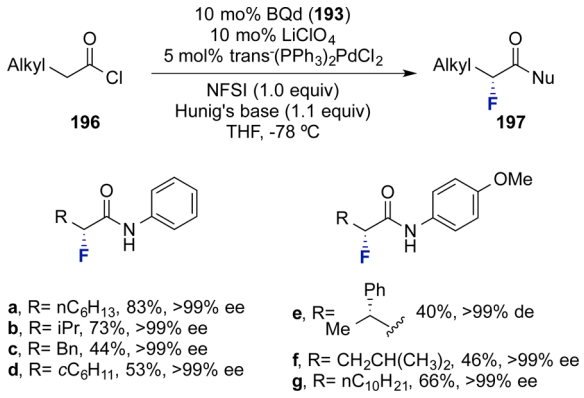
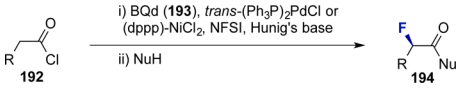


Table 16. Substrate Scope of the Fluorination of Acid Chlorides Using a Dual Catalyst System



entry	R	catalyst [M]	NuH	yield, %	ee/de, %
1	*p*-MeOPh	Ni	MeOH	83	99
2	*p*-MeOPh	Pd	L-NH_2-Ph-OEt	68	>99
3	*p*-MeOPh	Pd	PhSH	67	98
4	*p*-MeOPh	Ni	N-Boc-L-prolinol	90	>99
5	Ph	Ni	MeOH	61	99
6	Ph	Ni	H_2O	60	99
7	1-Np	Ni	MeOH	68	98
8	1-Np	Ni	N-Coc-L-Cys-OMe	80	>99
9	2-Np	Pd	MeOH	63	>99
10	2-thiophene	Pd	MeOH	69	99
11	2-(*N*-benzoylindolyl)	Pd	MeOH	58	94
12	2-(3-Ph-(ethylcinnamate)	Ni	MeOH	71	99
13	phthalimido-CH_2	Pd	MeOH	72	>99
14	phthalimido-CH_2	Pd	$NH(CH_2)_5$	79	>99
15	indo	Pd	MeOH	84	95
16	phthalimido-CH_2	Pd	(+)-emetine	91	>99

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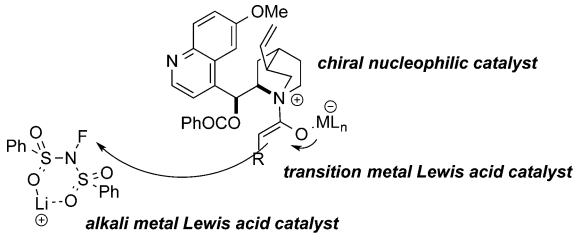


Figure 20. Summary of the key mechanistic aspects involved in enabling the enantioselective fluorination of alkyl-substituted acid chlorides.

In 2014, Toste and co-workers reported the asymmetric fluorination of α-branched cyclohexanones enabled by a combination of chiral anion phase-transfer catalysis and enamine catalysis using protected amino acids.[84] While simple ketones did not undergo fluorination under conditions that had previously been successful on other substrate classes, they supposed that inclusion of a catalytic amount of a primary amine may form an enamine that should be reactive to electrophilic fluorination and also act as a hydrogen-bond donor for interaction with the chiral phosphate catalyst (Figure 21, cycle 1). Independently, the lipophilic chiral phosphate would undergo anion exchange with the achiral tetrafluoroborate counteranions of insoluble Selectfluor to catalytically generate a soluble, chiral electrophilic fluorinating reagent (cycle 2).

The authors found that the addition of achiral primary amine catalysts did increase the yield of fluorinated product, but without any significant enantioselective induction (Table 17). Because glycine methyl ester gave reasonable yield, chiral amino acid methyl esters were subsequently evaluated. While L-phenylalanine methyl ester gave −40% ee, the two chiral catalysts were evidently mismatched in this case, as switching to D-phenylalanine methyl ester gave the desired fluorinated product in 88% ee. This was able to be increased to 94% ee by the use of a 1-naphthyl version of D-phenylalanine as increased steric bulk on the amine acid side chain was found to play a key role. In the absence of either catalyst, both yield and ee were found to be <10%, demonstrating the crucial nature of both chiral catalysts to an effective transformation.

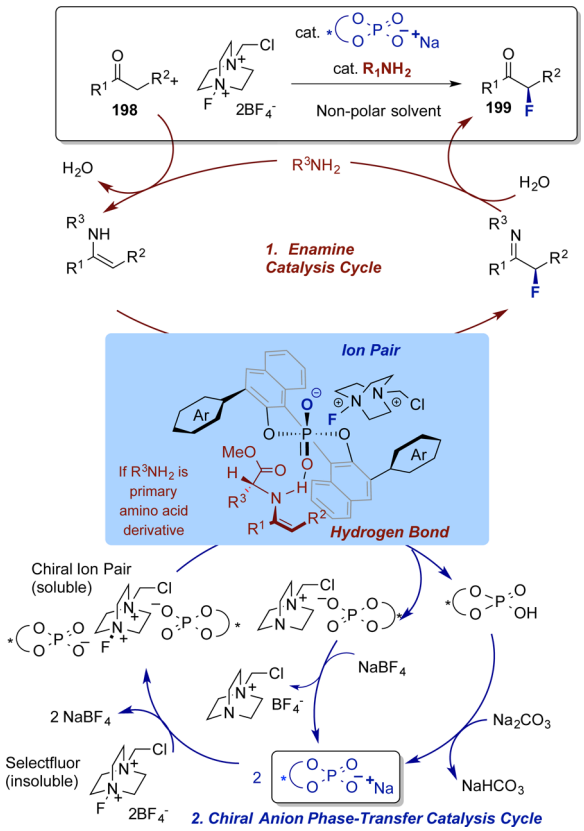
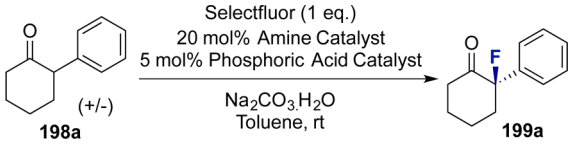


Figure 21. Proposed combination of two catalytic cycles for the enantioselective fluorination of ketones. Reproduced with permission from ref 84. Copyright 2014 American Chemical Society.

Table 17. Optimization of the Fluorination of 2-Phenylcyclohexanone Using Two Chiral Catalysts



Amine Catalyst	Phosphoric Acid Catalyst	NMR Yield, %	ee, %
None	(*R*)-**140a**	5	-2
Benzylamine	(*R*)-**140a**	29	-3
Butylamine	(*R*)-**140a**	24	-2
MeO_2C $NH_3^+Cl^-$	(*R*)-**140a**	50	+10
Ph, MeO_2C $NH_3^+Cl^-$	(*R*)-**140a**	70	-40
Ph, MeO_2C $NH_3^+Cl^-$	(*R*)-**140a**	74	+88
Ph, MeO_2C $NH_3^+Cl^-$	None	10	+10
MeO_2C $NH_3^+Cl^-$	(*R*)-**140a**	62	+94

The scope and limitations of this transformation were explored (Scheme 71). A range of *para*- and *meta*-substituted aryl groups are well tolerated in the α-position of the cyclohexanone, as well as heteroatom-substituted cyclohexanones (**198l**, **m**). They also demonstrated that several 2-alkenyl and 2-alkynyl cyclohexanones (**198o**−**r**) are also viable substrates in their fluorination, delivering good to high enantioselectivities (77−86% ee). Complete regioselectivity was observed for fluorination at the α-position and no undesired fluorination of either the alkene or the alkyne was observed, although 2-alkyl-substituted cyclohexanones were not reactive toward fluorination.

2.1.5. One-Pot and Tandem Processes. A tandem process can be broadly thought of as one in which the substrate undergoes multiple distinct reactions in a single synthetic operation. If such a process involves the fluorine stereocenter being formed after an initial step, the stereoselectivity of the fluorination step could be either controlled by

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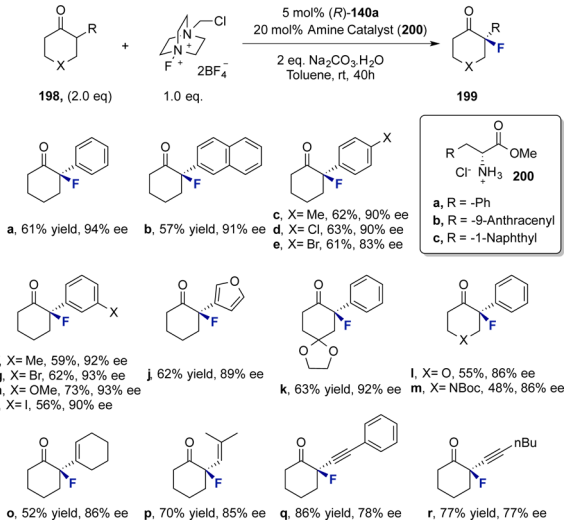
Scheme 71

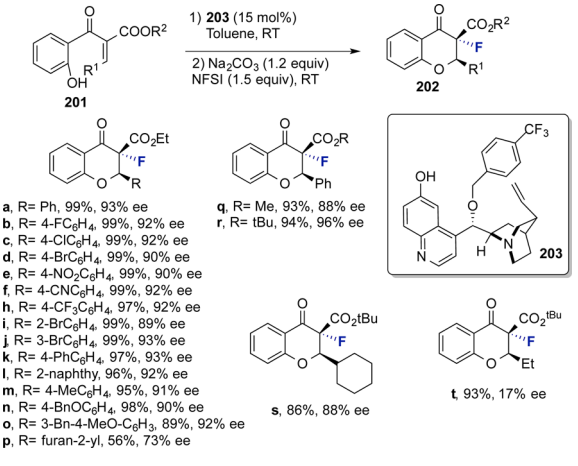


the first stereocenter or be under catalyst control. While this Review is not intended to cover strictly diastereoselective fluorination reactions, tandem processes will be given an overview in this section due to the potential ambiguities of determining whether or not the fluorination step is under catalyst control.

In 2009, Zhao and co-workers reported an organocatalyzed intramolecular oxa-Michael addition/electrophilic fluorination tandem reaction for the synthesis of a series of chiral fluorinated flavanones.[85] They envisioned that by using a bifunctional catalyst, an organocatalytic, asymmetric, intramolecular oxa-Michael addition of **201** would produce enantioenriched enolate, which could be subjected to electrophilic fluorination to provide chiral, fluorinated flavanone derivatives **202**. After careful optimization, it was found that catalyst **203** efficiently catalyzed the oxa-Michael addition of the substrate in toluene, after which NFSI and Na_2CO_3 were added into the mixture to afford the desired fluorinated flavanone product **202** in high enantioselectivities (Scheme 72). The authors found that the rate of fluorination varied with the catalyst used and proposed that the catalyst may be involved in the fluorination step.

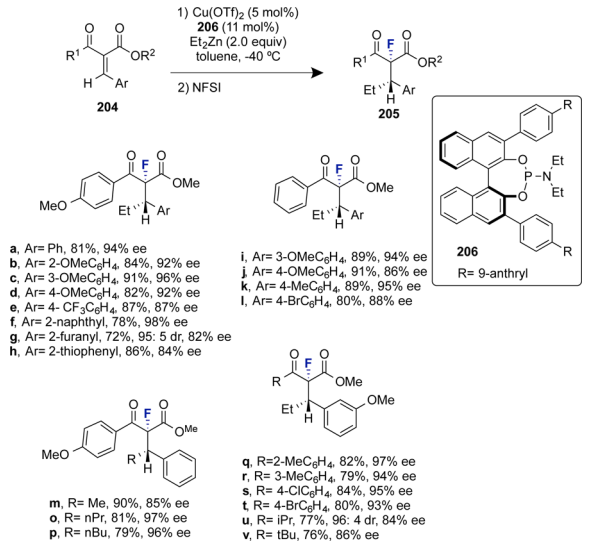
In 2011, Ma and co-workers reported the diastereo- and enantioselective tandem 1,4-addition/fluorination catalyzed by

Scheme 72



chiral monodentate phosphoramidite ligands **206** and copper (Scheme 73).[86] In this reaction, conjugate addition of

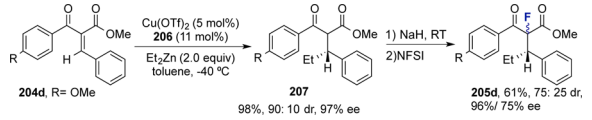
Scheme 73



organometallic reagents to alkylidene *β*-ketoesters **204** was followed by fluorination with NFSI to afford the fluorinated products **205**. In screening of the ligands, the authors developed a superior catalyst **206** bearing bulky substituents at the 3- and 3′-positions of the binaphthol unit, with the aim of narrowing the space around the *P*-ligated metal center as well as relaying the axial chirality to the reaction site. The scope of this reaction was broad, with aryl substituents on both the ketone and the alkylidene moieties. Alkyl-substituted substrates (**204u**, **v**) also provide the tandem products in good yield and enantioselectivities, and various dialkylzinc reagents also participated to give the corresponding products (**205m**−**p**).

The authors also demonstrated that if the reaction was conducted in a stepwise manner, the diastereoselectivity of the product was significantly reduced, suggesting that the one-pot operation is important to achieve stereoselectivity (Scheme 74).

Scheme 74



In 2012, Ma and co-workers reported an organocatalytic, asymmetric, one-pot sequential 1,4-addition/dearomative-fluorination transformation using pyrazolones (**208a**, X = NR) as the aromatic partners, thus leading to optically active fluorine-containing products with two adjacent stereogenic centers (Scheme 75).[87] This transformation is catalyzed by a chiral tertiary-amine-thiourea compound **211a** in combination with benzoic acid. Other nucleophilic donors were also tested for the sequential reaction, and similarly high levels of reactivity and stereocontrol were observed.

The Michael-addition product **212** could be isolated in almost quantitative yield with excellent levels of enantioselectivity by omission of the fluorination step (Scheme 76). Subjecting this intermediate to triethylamine and NFSI afforded dearomatization-fluorination product **213** in high yield

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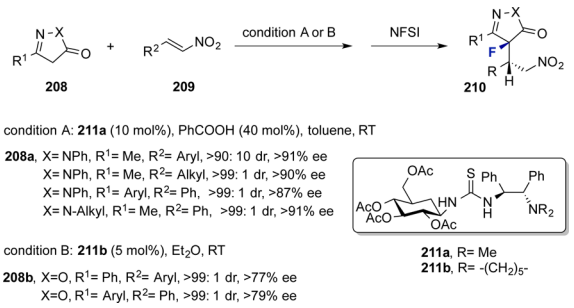
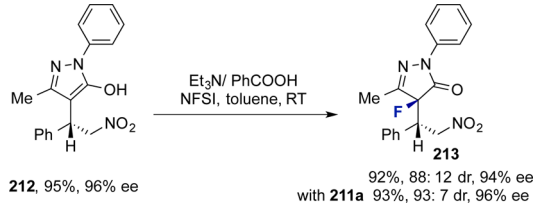
Scheme 75



Scheme 76



although with slightly lower diastereoselectivity. The authors suggested that the thiourea catalyst also plays some role in stereocontrol for the fluorination step.

A possible mechanism for this transformation was proposed by the authors. In the first cycle, the nitroalkene binds with the thiourea of the catalyst through hydrogen bonding while the pyrazolone in its enol form hydrogen bonds with the ammonium center of the chiral catalyst, providing enantiocontrol in the 1,4 addition. The product then reassociates with the catalyst, again through multiple hydrogen-bond interactions for the subsequent fluorination step (Figure 22).

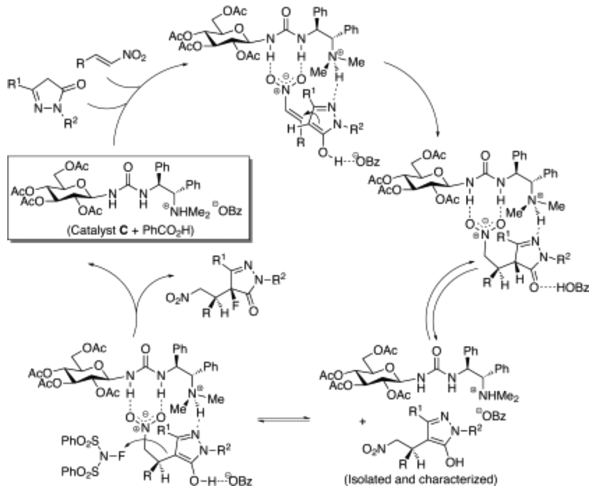


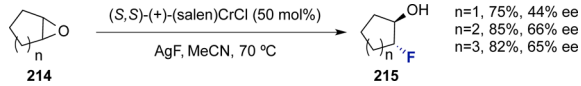
Figure 22. Proposed mechanism for the tandem 1,4-addition/fluorination. Reproduced with permission from ref 87. Copyright 2012 John Wiley and Sons.

Ma and co-workers also reported a variation of this reaction using isoxazol-5(4*H*)-ones (**208b**, X= O) as substrates (Scheme 75).[88] In this reaction, 1.2 equiv of Na_2CO_3 as an additive was found to be essential for the high yield of the fluorination step. A variety of different substitutions on the aryl ring of the nitroalkenes were tolerated, although alkyl substituents were unsuitable. The authors observed that the catalyst made some contribution to the control of diastereoselectivity in the fluorination step.

2.2. Nucleophilic Fluorination

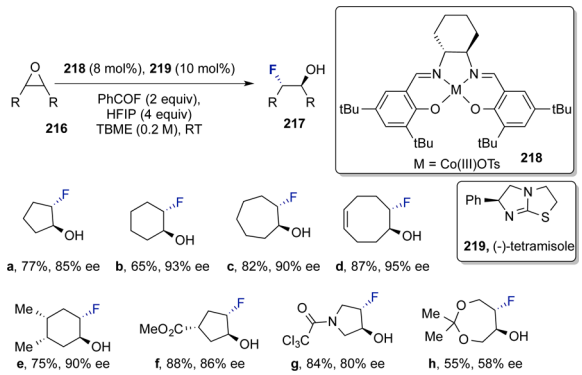
Nucleophilic sources of fluorine have only been harnessed in the context of asymmetric catalysis much more recently when compared to their electrophilic counterparts. This could be partially attributed to difficulties in dealing with the high basicity of fluoride, relative to its often fairly low nucleophilicity. In an important early report in 2000, Bruns and Haufe described the moderately enantioselective ring opening of *meso*-epoxides using a stoichiometric amount of Jacobsen's (*S,S*)-(+)-salen)chromium chloride complex and KHF_2/18-crown-6 as fluoride source.[89a] One year later, they reported opening of *meso*-epoxides **214** with AgF mediated by similar chiral complexes with moderate enantioselectivities (Scheme 77).[89b,c]

Scheme 77



In 2010, Kalow and Doyle achieved a catalytic version of the same reaction (Scheme 78).[90] Their strategy involved amine-

Scheme 78



catalyzed slow generation of HF from benzoyl fluoride and an alcohol, which was hypothesized to permit the mild conditions and efficient catalysis. They envisaged that the use of a chiral amine as catalyst may provide a route into enantioselective catalysis. However, neither achiral nor chiral bases [e.g., (−)-tetramisole (**219**)] induced measurable reactivity for epoxide opening at room temperature until a Lewis acid was added as a cocatalyst. A combination of (−)-tetramisole (**219**) and Co(salen) catalyst (*R,R*)-**218** gave excellent enantioselectivities. A pronounced matched/mismatched effect for the combination of the two catalysts was observed in this dual-catalysis approach. Various *meso*-epoxides were well tolerated in these reactions, including five-, six-, seven-, and eight-membered cyclic epoxides with alkene, ester, and protected amine functionalities, affording fluorohydrins **217** in 85−95% ee.

Kinetic resolution of terminal epoxides **220** was also investigated under these conditions (Scheme 79). Regioselective opening at the terminal position afforded the corresponding fluorohydrins **221** with up to 99% ee. The tolerance of a silyl protecting group in one substrate (**220c**) under these

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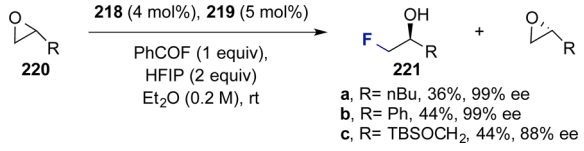
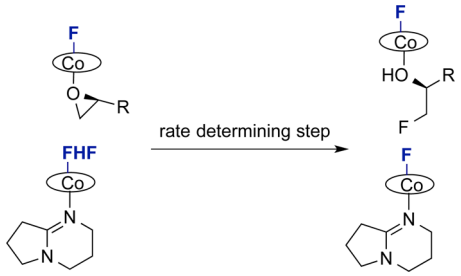
Scheme 79



conditions demonstrated the relative mildness of the catalytically generated fluoride.

In 2011, the same authors described elegant and detailed mechanistic studies of their Co(salen) and amine cocatalyzed reaction.[91] Substituent effects in the opening of *para*-substituted styrene oxides established that ring opening is the rate-limiting step. The authors deduced that this step proceeds via a bimetallic mechanism, based on a combination of nonlinear effects studies with monomeric catalysts and further experiments using linked, dimeric catalysts and that the active nucleophilic fluorine source is a metal bifluoride (Scheme 80).

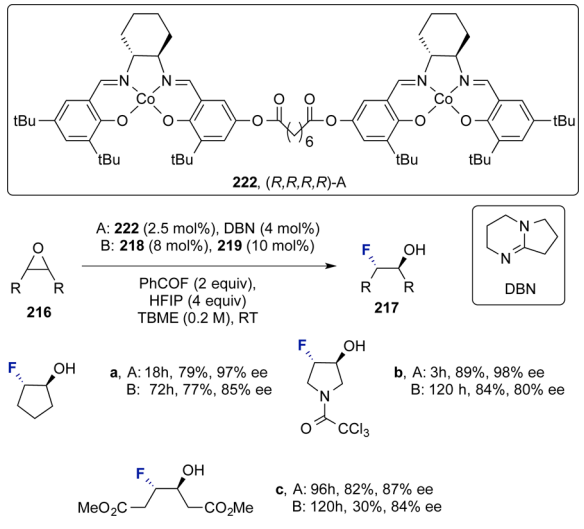
Scheme 80



With these insights, they improved the reaction protocol by developing linked Co(salen) catalyst **222**, which afforded significantly elevated rates, expanded substrate scope, and high enantioselectivity for the desymmetrization of *meso*-epoxides **216** in conjunction with cocatalyst DBN (conditions A, Scheme 81). Notably, an acyclic meso epoxide (**216c**), which underwent slow ring opening previously (conditions B), provided product **217c** in good yield and enantioselectivity.

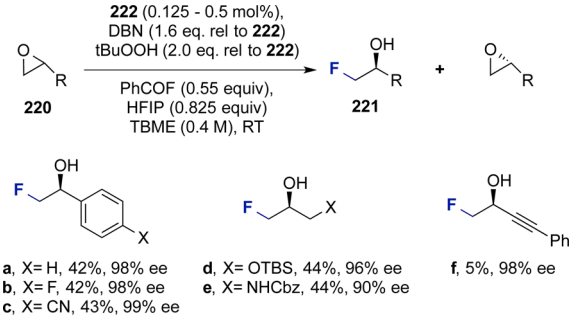
Using the dimeric catalyst, rate enhancement was also observed for resolution of terminal epoxides, allowing reactions

Scheme 81



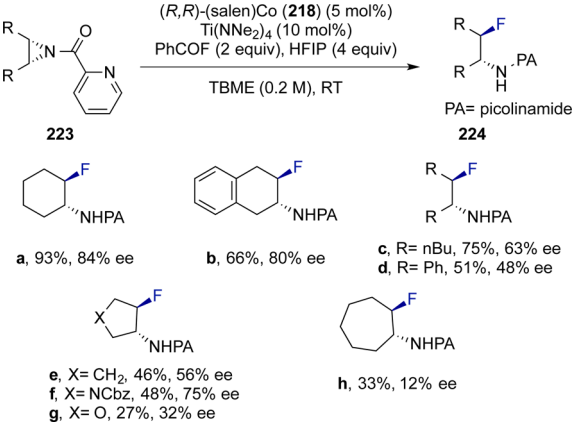
to be carried out in shorter times with impressively low catalyst loadings (Scheme 82).

Scheme 82



In 2013, Kalow and Doyle reported the enantioselective ring opening of aziridines.[92] While Co(salen) complexes proved effective Lewis acids for activation of epoxides, they were unsuitable for protected aziridines, so the authors employed a distinct Lewis acid to achieve this. Ultimately, a combination of two Lewis acids, the chiral Co(salen) (**218**) and an achiral Ti(IV) cocatalyst, provided optimal reactivity and enantioselectivity to deliver the *trans*-β-fluoroamine product **224**. The use of a chelating protecting group was crucial to reactivity, with picolinamide being optimal. Acyclic and cyclic meso *N*-picolinamide aziridines **223** underwent fluoride ring opening in up to 84% ee (Scheme 83).

Scheme 83



Mechanistic studies supported the proposal that the chiral (salen)Co catalyst delivers the fluoride nucleophile while the Ti(IV) cocatalyst activates the aziridine (Figure 23). Unlike the previous work, dimeric Co(salen) catalysts provided no rate acceleration, consistent with the proposed mechanistic scenario.

Doyle and co-workers have very recently applied this methodology in a stoichiometric sense to ^{18}F radiolabeling for PET imaging.[93] In this procedure, the Co(salen)F reagent is readily accessed by anion metathesis from the corresponding tosylate with [^{18}F]fluoride. This can then be reacted with a range of epoxides directly to obtain the "hot" enantioenriched fluorohydrins.

In 2010, Katcher and Doyle reported a palladium–bisphosphine complex-catalyzed enantioselective fluorination of allylic chlorides with AgF (Scheme 84).[94] They hypothesized that efficient and mild allylic C–F bond formation proceeded

dx.doi.org/10.1021/cr500277b | Chem. Rev. 2015, 115, 826–870

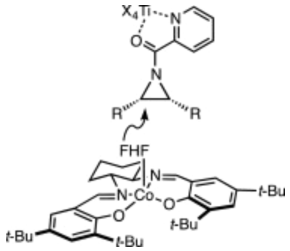
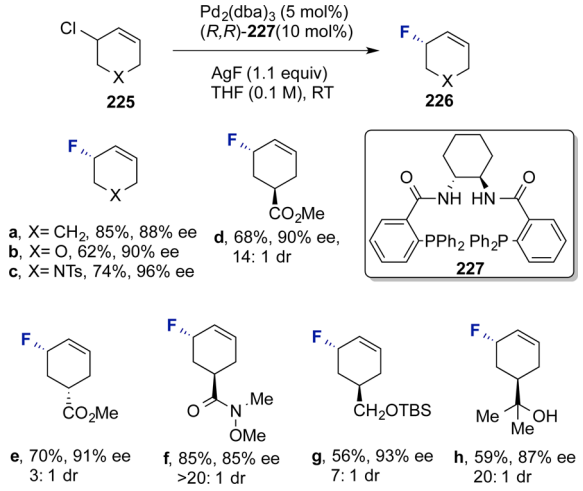


Figure 23. Proposed mechanistic scenario for ring opening of aziridines. Reproduced with permission from ref 92. Copyright 2013 Elsevier.

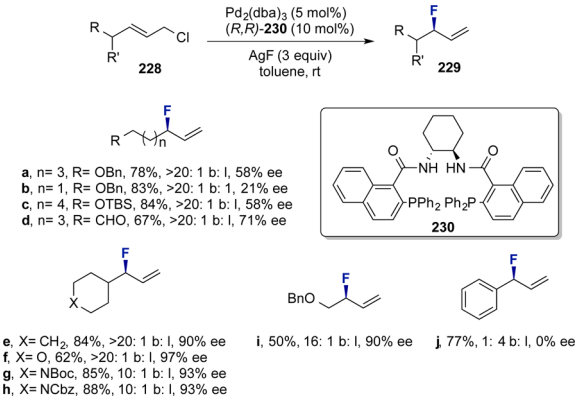
Scheme 84



by the nucleophilic attack of fluoride on an electrophilic Pd(II)-allyl intermediate of the type that is well-established for Pd-catalyzed allylic alkylation. Investigations of nucleophilic attack on a stoichiometric Pd(II)−allyl complex showed that more basic alkali metal fluoride sources mostly resulted in elimination; only AgF produced a good yield of the desired substitution. Substrates possessing traditional leaving groups for Pd-catalyzed allylic alkylation were unreactive with the Pd(0) catalyst and AgF; however, the authors discovered that allylic chlorides gave good yields and high enantioselectivities of the desired products. They proposed that precipitation of AgCl provides a strong driving force for C−F bond formation. The commercially available Trost ligand **227** imparted high levels of enantioinduction in the production of the allylic fluoride products **226** (85−96% ee). The scope of the reaction includes six-membered cyclic allylic chlorides with various functional groups.

In 2011, Doyle and co-workers successfully extended their methodology to encompass the regio- and enantioselective fluorination of acyclic allylic halides (Scheme 85).[95] Interestingly, with triphenylphosphine as ligand their reaction exhibited good selectivity for the branched allyl fluoride, rather than the linear. They found that bidentate phosphines with larger bite angles gave higher regioselectivity, with the commercial Trost naphthyl ligand **230** giving >20:1 selectivity for the branched product. They hypothesized that one reason for this preference could be that the small size of fluorine favors attack at the more hindered terminus of the Pd π-allyl complex. They also suggest the possibility of hydrogen bonding of the fluoride with the ligand, effectively directing the nucleophile to give the branched product. Support for this latter hypothesis is provided by the

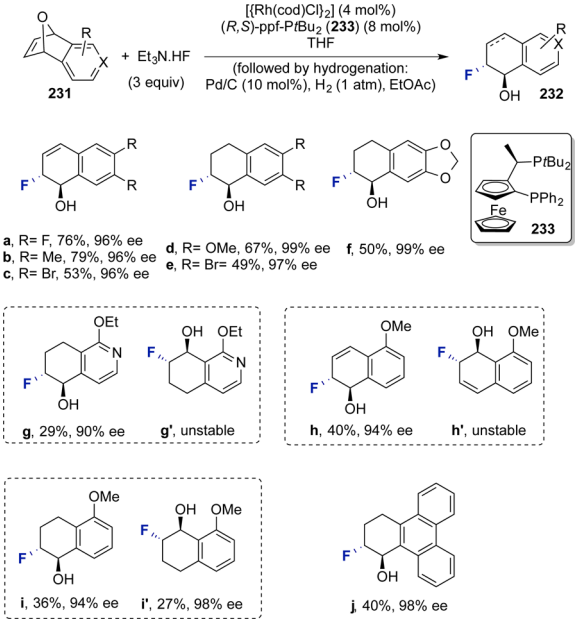
Scheme 85



superior regioselectivity in nonpolar solvents. Despite the high regioselectivity, moderate to low enantioselectivities were attained with linear substrates **228a−d**. The authors found that substrates possessing allylic substitution performed well, **228e−i** bearing α-branching or heteroatom substituents undergo fluorination with 90−97% ee. However, fluorination of cinnamyl chloride (**228j**) as substrate gave the minor branched isomer with 0% ee, revealing the current limitations of the method.

In 2012, Lautens and co-workers reported the rhodium-catalyzed asymmetric ring opening of oxabicyclic alkenes (Scheme 86).[96] Triethylamine trihydrofluoride ($Et_3N{\cdot}3HF$)

Scheme 86



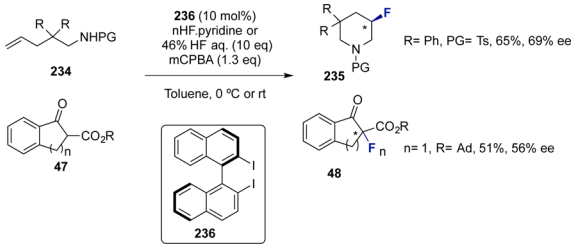
was the optimal source of fluoride; sources such as TBAF, KF, or Doyle's conditions resulted in no product formation. Use of $[Rh(cod)Cl]_2$ and chiral Josiphos ligand (*R*,*S*)-ppf-P*t*Bu$_2$ (**233**) afforded the ring-opened products with high enantioselectivity. The reaction is suggested to follow a pathway proceeding by S_N2' nucleophilic displacement, giving the 1,2-*trans* product. Various substituents on the aryl ring were well tolerated. However, with electron-donating groups on the aryl ring (**231d**, **f**), the ring-opened products would decompose to 1-naphthol by elimination of HF on silica gel, a problem that was

dx.doi.org/10.1021/cr500277b | *Chem. Rev.* 2015, 115, 826−870

solved by mild hydrogenation after aqueous workup, affording the stable alkyl fluorohydrin products. For unsymmetrical oxabicyclic alkenes (**231g**, **h**), both regioisomers were formed with high enantioselectivities, although some isomers proved to be unstable (**233g′**, **h′**).

Recently, Shibata and co-workers reported a catalytic fluorination system consisting of catalytic iodoarene together with HF and *m*CPBA.[97] This system was applicable to two classes of substrates including the fluorination of *β*-dicarbonyl compounds **47** and the intramolecular aminofluorination of *ω*-amino-alkenes **234** (Scheme 87). Mechanistically, the catalyst/

Scheme 87



reagent combination was proposed to generate $ArIF_2$ in situ. In the case of substrates **47**, enolate attack onto the active reagent is followed by displacement by fluoride to give **48**. In the case of aminoalkenes **234**, oxidation of the nitrogen by $ArIF_2$ is thought to lead to aziridinium intermediates, which are subsequently opened by attack of fluoride to give piperidines **235**. Preliminary trials of catalytic asymmetric variants were also conducted, and promising enantioselectivities for the desired products were obtained when (*R*)-binaphthyldiiodide (**236**) was used as catalyst.

3. CATALYTIC ENANTIOSELECTIVE TRIFLUOROMETHYLATION AND PERFLUOROALKYLATION

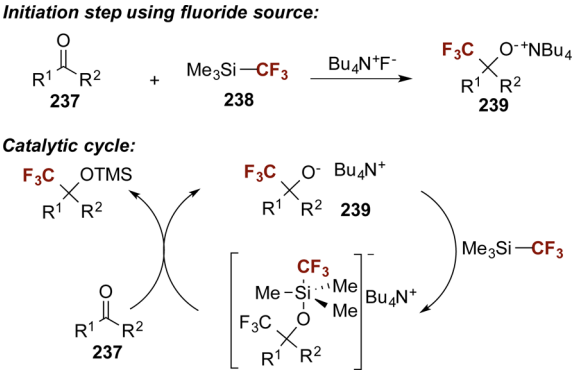
Among perfluoroalkyl groups, the trifluoromethyl group is the most widespread, appearing in numerous pharmaceuticals and agrochemical compounds and being often employed in materials science. The increased lipophilicity and often superior metabolic stability as compared to methyl analogues often accounts for an improved activity profile in a medicinal chemistry context.[2f] Hence, the development of approaches for the straightforward introduction of trifluoromethyl groups into small molecules has received much recent attention, including methods for their asymmetric introduction.[3a] Methods for their incorporation can be broadly classed as nucleophilic, electrophilic, or free radical processes. However, when compared to nonfluorinated alkyl halides, the reactivity of perfluoroalkyl halides diverges somewhat, due to the strong negative inductive effect of the perfluoroalkyl portion. As result of this strong stabilization of negative charge, perfluoroalkyl iodides in some instances can be used as electrophilic iodination reagents, resulting in the relatively stable perfluoroalkyl anion. In other cases, their behavior can be analogous with that of electrophilic reactivity, although closer analysis often reveals that the mechanism involves a series of single electron transfer steps with radical intermediates.[1c] Perhaps due to this element of mechanistic unpredictability, it is only relatively recently that advances in catalytic asymmetric electrophilic trifluoromethylation have been made.[3c,l,n]

3.1. Asymmetric Nucleophilic Trifluoromethylation

3.1.1. Overview of Nucleophilic Trifluoromethylation. Asymmetric nucleophilic trifluoromethylation of carbonyl compounds is an effective and direct strategy to obtain optically active trifluoromethylated alcohols.[98] These fluorine-containing chiral structures have been involved in the design and modification of molecules such as Befloxatone,[99] Efavirenz,[100] and ferroelectric liquid crystals,[101b,c] among other applications.

Me_3SiCF_3 (**238**) (commonly known as the Ruppert–Prakash reagent) is the most commonly employed synthetic equivalent of the trifluoromethyl anion.[102] The first example of nucleophilic trifluoromethylation of carbonyl compounds using this reagent was reported in 1989 by Prakash (Scheme 88).[103]

Scheme 88

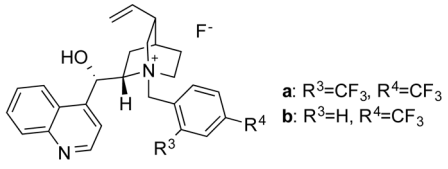


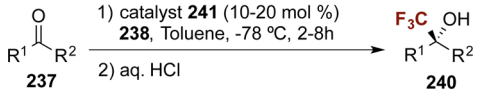
Commonly, nucleophilic activators such as tetrabutyl ammonium fluoride (TBAF) are used in a catalytic manner to activate the Ruppert–Prakash reagent, initially generating alkoxide **239**. The generally accepted mechanism for this transformation is depicted in Scheme 88. The fluoride anion acts as an initiator and reacts at the silicon of **238** to form Me_3SiF and tertbutylammonium alkoxide intermediate **239**. Following this initiation step, the catalytic cycle can commence as **239** reacts with an equivalent of Me_3SiCF_3 to form a pentavalent silicate that delivers a trifluoromethyl anion equivalent to an equivalent of ketone. In this step, alkoxide **239** is regenerated to restart the catalytic cycle.

3.1.2. Asymmetric Trifluoromethylation Using Chiral Ammonium Fluorides. Given the anionic nature of the species proposed to attack the prochiral carbonyl compound in the generally accepted mechanism for trifluoromethylation using the Ruppert–Prakash reagent, an early approach to induce asymmetry aimed to take advantage of a chiral cation strategy. Iseki, Kobayashi, and co-worker reported the first example of such an approach catalyzed by chiral quaternary ammonium fluorides in 1994.[104] The chiral catalysts **241** derived from cinchona alkaloids were able to convert the carbonyl compounds to corresponding trifluoromethylated alcohols in high yield with moderate but encouraging enantioselectivity (Table 18). It has been described that Prakash showed in unpublished results in 1993 that 9-anthraldehyde was converted to the corresponding trifluoromethylated alcohol with 95% ee.[3a] This employed a similar strategy but by using *N*-benzylquinidinium fluoride **241c**; however, further details such as the amount of chiral fluoride employed and the yield of **242** are not readily available, making comparison difficult (Scheme 89).

dx.doi.org/10.1021/cr500277b | *Chem. Rev.* 2015, 115, 826–870

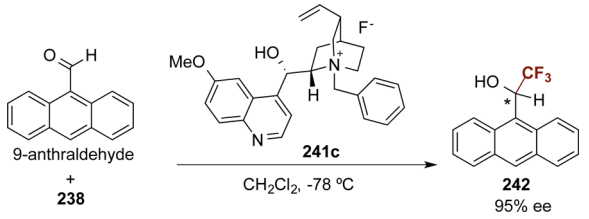
Table 18. Asymmetric Trifluoromethylation of Aldehydes and Ketones Using Chiral Ammonium Fluoride Catalysts 241





entry	R^1	R^2	cat. (mol %)	yield (%)	ee
1	Ph	H	**241a** (20)	>99	46 (*R*)
2	nC_7H_{15}	H	**241b** (20)	>99	15
3	9-anthraldehyde		**241b** (10)	98	45 (*R*)
4	Ph	Me	**241b** (20)	91	48
5	Ph	*i*Pr	**241b** (20)	87	51

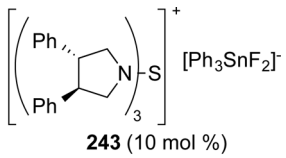
Scheme 89



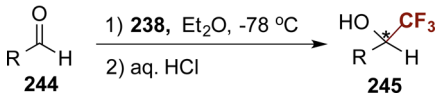
In related work not involving ammonium fluorides, Kuroki and Iseki designed and synthesized novel chiral triaminosulfonium salts **243** in an attempt to improve their previous results. Unfortunately, the observed enantioselectivities and substrate scope were not significantly improved, and only the case of benzaldehyde gave improvement, with 52% ee (Table 19).[105]

Caron and co-workers at Pfizer successfully optimized the trifluoromethylation of a particular aryl ketone of interest to them, to give up to 92% ee after a thorough screening of conditions and chiral ammonium fluorides (Scheme 90).[106] Ammonium fluoride **241d** was found to be very effective for the

Table 19. Asymmetric Trifluoromethylation of Aldehydes Using Chiral Triaminosulfonium Catalysts 243

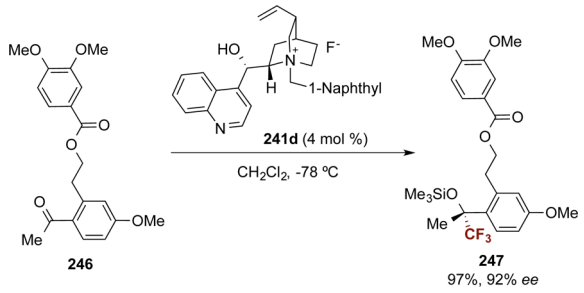


243 (10 mol %)



entry	RCHO	yield (%)	ee (%)
a	R = Ph	96	52 (*S*)
b	R = 4-$MeOC_6H_4$	97	37
c	R = 4-$CF_3C_6H_4$	90	24
d	R = 4-ClC_6H_4	93	30
e	R = (*E*)-PhCH=CH	99	18
f	R = C_6H_{11}	88	10

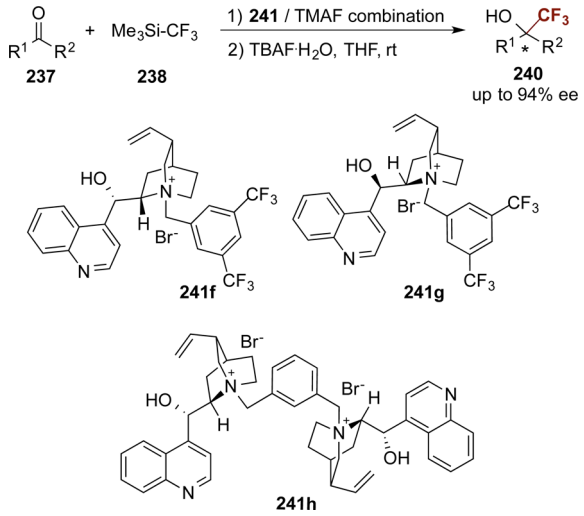
Scheme 90



trifluoromethylation of the target substrate; however, the catalyst did not prove to be generally applicable. While demonstrating what is possible, their report suggests that enantioselective induction using this approach may be rather substrate dependent, and extensive catalyst screening may be required to tackle new substrates.

3.1.3. Trifluoromethylation Catalyzed by Chiral Ammonium Bromides Combined with a Fluoride Source. In the methodology described in the previous section, the practicalities associated with handling the highly hygroscopic chiral ammonium fluorides somewhat limited their application. Shibata and Toru sought to address this deficiency, and in 2007 developed the highly enantioselective trifluoromethylation of aryl ketones with Me_3SiCF_3 catalyzed by a combination of the less hygroscopic ammonium bromide of cinchona alkaloids and tetramethylammonium fluoride (TMAF) (Scheme 91).[107] Their approach is especially

Scheme 91

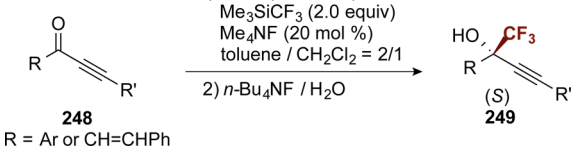


impressive because of unprecedented high enantioselectivities of up to 94% ee for acyclic and cyclic aryl ketones. However, aryl aldehydes and aliphatic ketones gave much poorer results. They proposed that the obtained high enantioselectivity may result from π-stacking interactions between the aromatic ring in the substrates and those present in the catalysts.

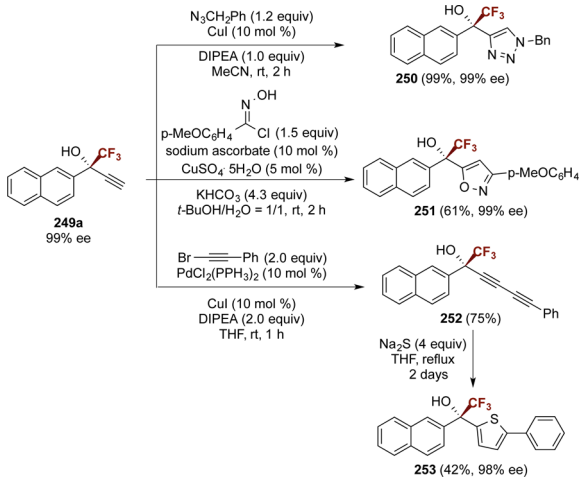
In 2010, Shibata and co-workers extended the scope of this transformation to encompass propargyl ketones, delivering trifluoromethyl-propargyl alcohols with up to 96% ee (Scheme 92).[108] The products were transformed into aryl heteroaryl trifluoromethyl carbinols without any loss of enantiomeric purity of **249a** (Scheme 93).

dx.doi.org/10.1021/cr500277b | *Chem. Rev.* 2015, 115, 826−870

Scheme 92

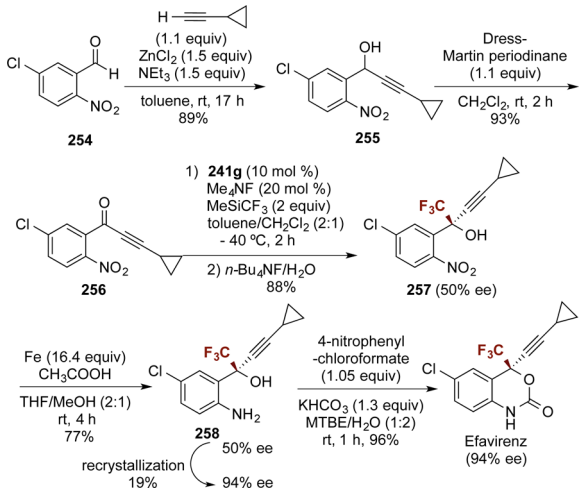


Scheme 93



The same authors also demonstrated the asymmetric synthesis of Efavirenz in five steps from a commercially available precursor through the enantioselective trifluoromethylation of an alkynyl ketone (Scheme 94).[109] Subsequent catalyst modifications have allowed for improvement in selectivity in the key step.[110]

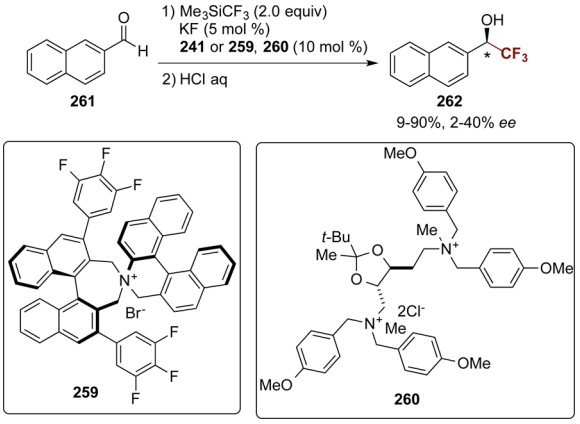
Scheme 94



The authors then turned their attention to expanding the substrate of the transformation to aryl aldehydes, which failed under the previous conditions. However, the reaction of 2-naphthaldehyde (**261**) with Me_3SiCF_3 gave poor results despite extensive optimization attempts using various chiral ammonium bromides combined with TMAF or KF (Scheme 95).[111]

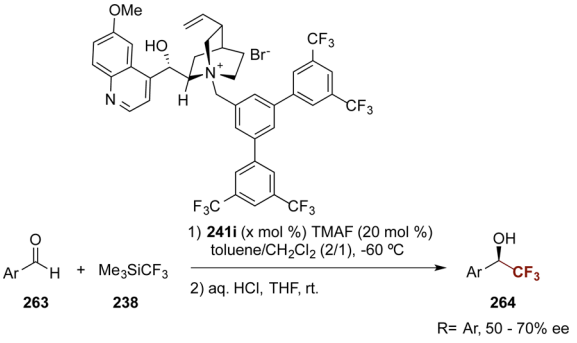
In 2013, the same authors obtained some improvement for these aryl aldehyde substrates by incorporating sterically bulky groups into the catalyst (Scheme 96).[112] After screening of a

Scheme 95



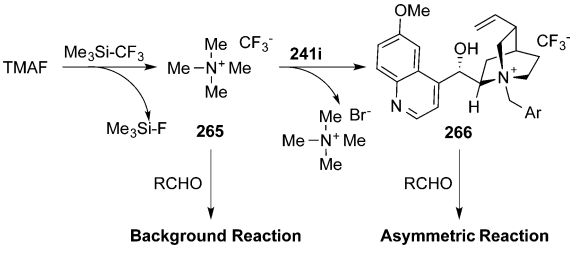
range of catalysts, **241i** gave enantiomeric excesses of 50−70% for a range of aldehydes.

Scheme 96



The authors detailed a mechanistic proposal that involved TMAF first reacting with Me_3SiCF_3 to provide trifluoromethyl tetramethylammonium **265** and releasing stable Me_3SiF (Scheme 97). The ammonium **265** reacts with **241i** to generate

Scheme 97



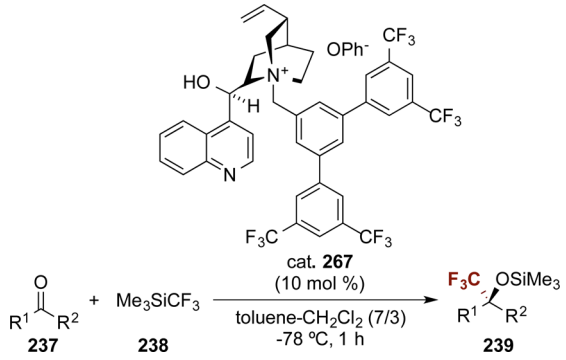
chiral trifluoromethylammonium **266** and tetramethylammonium bromide (TMAB). This chiral salt **266** then performs the trifluoromethylation of aldehyde **263** in an asymmetric manner. However, achiral ammonium **265** is also reactive to aldehyde **263** furnishing racemic products, perhaps explaining why very high enantioselectivities are still elusive using this approach.

3.1.4. Trifluoromethylation Catalyzed by Chiral Ammonium Phenoxides. In 2007, Mukaiyama reported the asymmetric trifluoromethylation of ketones with $TMSCF_3$ catalyzed by cinchonidine-derived quaternary ammonium phenoxides, which proceeded smoothly to afford the trifluoromethylated compounds in high yields with moderate

dx.doi.org/10.1021/cr500277b | Chem. Rev. 2015, 115, 826−870

to high enantioselectivities (Table 20).[113] Further studies found that α-ketoesters were also converted to the corresponding

Table 20. Asymmetric Trifluoromethylation of Ketones Catalyzed by Quaternary Ammonium Phenoxides

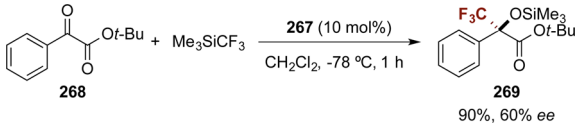


237 238 239

entry	R^1	R^2	yield (%)	ee (%)
1	2-$(NO_2)C_6H_4$	Me	93	71
2	4-$(NO_2)C_6H_4$	Me	97	73
3	3-$(CN)C_6H_4$	Me	96	71
4	3-BrC_6H_4	Me	97	61
5	3-$(MeO)C_6H_4$	Me	90	59
6	1-naphthyl	Me	91	51
7	2-naphthyl	Me	95	77
8	3-pyridyl	Me	90	46
9	4-pyridyl	Me	93	60
10	3-$(NO_2)C_6H_4$	Et	99	64

trifluoromethylated adducts smoothly under similar conditions, potentially offering a route to Mosher's acid derivatives (Scheme 98).[114]

Scheme 98

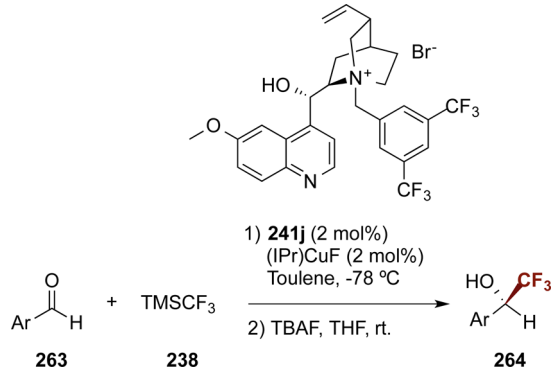


268 269

90%, 60% *ee*

3.1.5. Chiral Ammonium Bromide and (IPr)CuF-Catalyzed Trifluoromethylation. A general enantioselective trifluoromethylation of aldehydes was developed by Chen and co-workers in 2012 using (IPr)CuF and quinidine-derived quaternary ammonium salt as the two cooperative catalysts to activate the Ruppert–Prakash reagent. A wide range of aromatic aldehydes participate, giving up to 92% yield and 81% ee at only 2 mol % of catalyst loading (Table 21).[115] To gain insight into the operation of the two catalysts, control experiments were carried out (Table 22). Neither (IPr)CuF nor quaternary ammonium salt **241j** alone produced any product, and both yields and ee values decreased to zero by changing the anion of the copper salt from F^- to *t*-BuO^- or Cl^-. Use of the fluoride salt of the chiral ammonium catalyst (**241c**) without the copper catalyst still gave good yield but with somewhat reduced ee (57%). This is in contrast to use of the ammonium bromide salt that gave no conversion without the copper fluoride. By use of (IPr)CuCl rather than (IPr)CuF with the latter ammonium salt, the enantioselectivity increased to 67% ee. The authors propose that (IPr)CuF is of key importance for high catalytic performance, and the enhanced activity and enantioselectivity result from the rapid generation

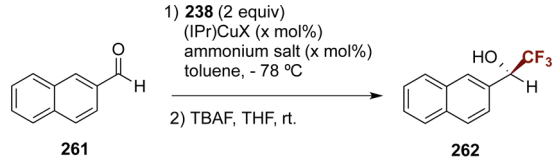
Table 21. Asymmetric Trifluoromethylation of Aldehydes Using (IPr)CuF and Quinidine-Derived Quaternary Ammonium Salts



263 238 264

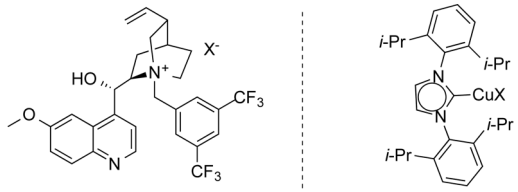
Ar	yield (ee)
2-naphthyl	90%, 75%
1-naphthyl	88%, 60%
Ph	80%, 60%
4-BrC_6H_4	81%, 57%
3-BrC_6H_4	82%, 51%
4-MeC_6H_4	88%, 68%
4-PhC_6H_4	90%, 66%
3-$MeOC_6H_4$	89%, 74%
3,4-$O(CH_2)C_6H_3$	92%, 81%
3,4-$O(CH_2)_2C_6H_3$	92%, 79%
4-$EtSC_6H_4$	85%, 74%

Table 22. Control Experiments



261 262

entry	ammonium salt (mol %)	(IPr)CuX (mol %)	yield (%)	ee (%)
1	**241j** (2)		NR	
2		(IPr)CuF (2)	trace	nd
3	**241j** (2)	(IPr)CuF (2)	90	75
4	**241j** (2)	(IPr)CuO*t*-Bu (2)	57	45
5	**241j** (2)	(IPr)CuCl (2)	NR	
6	**241c** (5)		87	57
7	**241c** (5)	(IPr)CuCl (5)	84	67



X = F, **241c**
= Br, **241j**

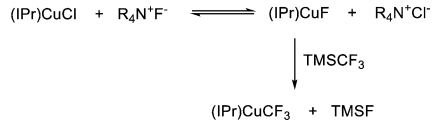
(IPr)CuX

of active [(IPr)$CuCF_3$] upon reaction with $TMSCF_3$ (Scheme 99).[116]

3.1.6. Trifluoromethylation Catalyzed by Chiral Ammonium Bromide and Sodium Phenoxide. In 2007, Feng and co-workers developed a new dual catalyst system comprising a disodium binaphtholate salt prepared in situ and a chiral quaternary ammonium salt. This allowed enantioselective trifluoromethylation of aromatic aldehydes in up to 71% ee

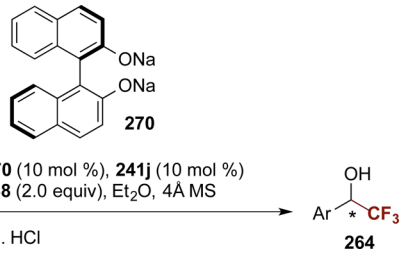
dx.doi.org/10.1021/cr500277b | *Chem. Rev.* 2015, 115, 826–870

Scheme 99



(Table 23).[117] The authors observed that the monosodium binaphtholate salt was not an effective catalyst and speculated

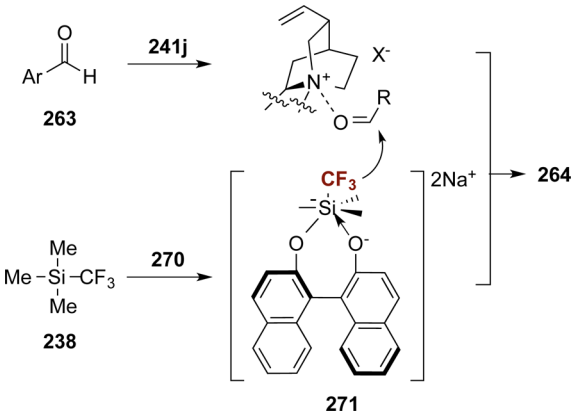
Table 23. Asymmetric Trifluoromethylation Using a Dual Catalyst Approach Comprising a Disodium Binaphtholate Salt and a Chiral Quaternary Ammonium Salt



entry	aldehyde	yield (%)	ee (%)
1	2-naphthaldehyde	85	71
2	benzaldehyde	72	56
3	4-methylbenzaldehyde	87	60
4	3-methylbenzaldehyde	88	58
5	4-chlorobenzaldehyde	72	50
6	3-chlorobenzaldehyde	95	56
7	4-phenylbenzaldehyde	73	56
8	4-methoxybenzaldehyde	87	41
9	piperonal	95	46
10	4-fluorobenzaldehyde	86	57
11	3-thiophenecarboxaldehyde	68	45

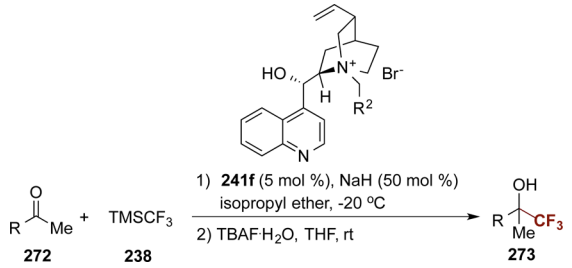
that the role of disodium binaphtholate might be as a Lewis base to activate the $TMSCF_3$ and form the hexavalent intermediate **271** (Scheme 100).

Scheme 100



Later, the same authors combined cinchonine-derived quaternary ammonium salt **241f** with NaH to establish an effective and fluoride-free system for the catalytic asymmetric trifluoromethylation of methyl ketones in moderate to good ee (up to 82%) and yield (up to 98%) (Table 24).[118] Control experiments showed that when the hydroxyl in **241f** was methylated, the reaction still proceeded efficiently, affording the

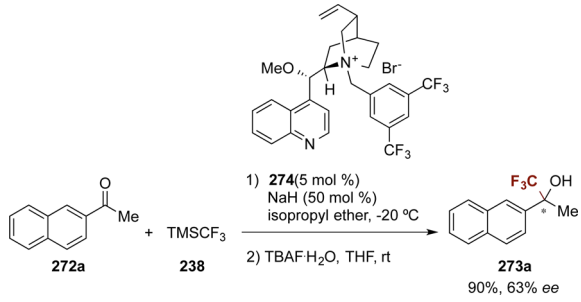
Table 24. Asymmetric Trifluoromethylation Using Chiral Quaternary Ammonium Salt 241f with NaH



entry	R	time (h)	yield (%)	ee (%)
1	2-naphthyl	6	96	81 (*R*)
2	1-naphthyl	6	98	82
3	2-FC_6H_4	19	47	68
4	3-ClC_6H_4	19	96	68
5	4-ClC_6H_4	19	83	61
6	4-BrC_6H_4	48	43	60
7	3-$NO_2C_6H_4$	48	30	68 (*R*)
8	4-$NO_2C_6H_4$	24	64	50
9	3-$MeOC_6H_4$	96	38	58
10	4-MeC_6H_4	3	70	67
11	(*E*)PhCH=CH	22	31	59

product in 63% ee and 90% yield; however, in the absence of NaH, **274** could not catalyze the reaction. On the basis of these observations, the authors speculated that the hydride ion might serve as the Lewis base to activate $TMSCF_3$ (Scheme 101).

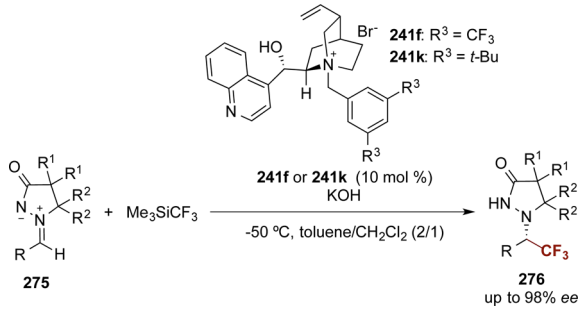
Scheme 101



3.1.7. Asymmetric Trifluoromethylation Using Phase-Transfer Catalysis. The catalytic asymmetric addition of nucleophilic trifluoromethyl to imines would constitute a concise approach to trifluoromethyl amines. Despite the extensive studies on addition to carbonyl compounds, this was not reported until 2009 when Shibata and co-workers reported the enantioselective trifluoromethylation of azomethine imines **275** with Me_3SiCF_3 (Scheme 102).[119] The authors found that conventional imines, such as *N*-tosylimines, were poor in terms of both reactivity and selectivity. They attributed the poor conversion to the poor nucleophilicity of the sulfonamide intermediates that are generated upon CF_3^- addition, recalling that this species must be sufficiently nucleophilic to attack Me_3SiCF_3 in the autocatalytic process previously described (Scheme 88). On this basis, the authors selected azomethine imines **275** as likely being superior, because the resulting anion following addition is delocalized onto the carbonyl oxygen. They also envisaged that the more sterically demanding and rigid nature may increase stereoselectivity of addition. By employing bromide salts of cinchona

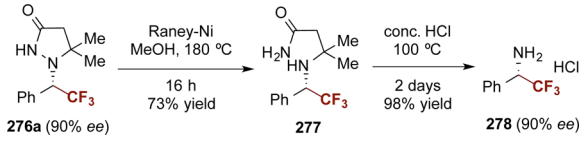
dx.doi.org/10.1021/cr500277b | *Chem. Rev.* 2015, 115, 826−870

Scheme 102



alkaloids and KOH as catalysts, trifluoromethylated amines **276** were obtained with very high enantiomeric excess. Additionally, it was demonstrated that the trifluoromethylated adduct **276a** can be readily transformed to amine **278** (Scheme 103).

Scheme 103



The authors proposed a transition state model for the reaction in which the catalyst hydroxyl group hydrogen bonds with the carbonyl oxygen, the sterically demanding portion of the imine is located in the less sterically congested space, and interactions between the aromatic rings stabilize the transition state (Figure 24).

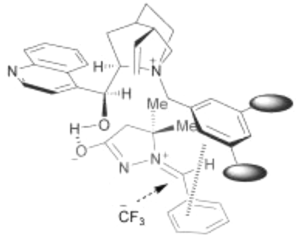


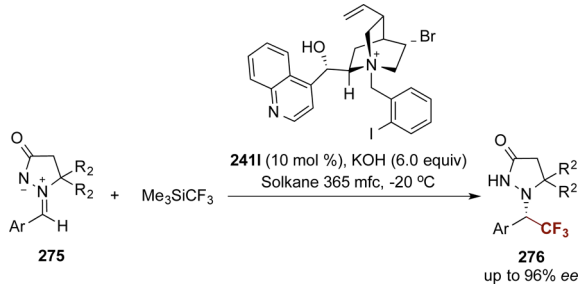
Figure 24. Proposed transition state model to account for observed enantioselectivity. Reproduced with permission from ref 119. Copyright 2009 John Wiley and Sons.

Later, the same authors demonstrated that this transformation is viable in the environmental benign solvent-Solkane365mfc with simple cinchona alkaloid ammonium salt **241l**. Improved chemical yields and enantioselectivities could be obtained (Scheme 104).[120]

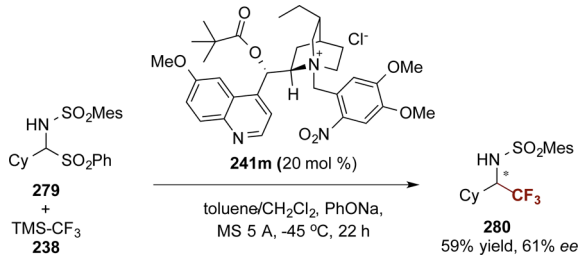
In 2012, Bernardi and co-workers disclosed a racemic protocol for trifluoromethylation of imines employing phase-transfer catalysis using a stoichiometric amount of an insoluble metal phenoxide as promoter. This modification was found to overcome the aforementioned difficulties of standard imines inhibiting the autocatalytic cycle. They disclosed a single example of an enantioselective variant using imine equivalent **279** and cinchona alkaloid derivative **241m** as catalyst, that proceeded with moderate yield and enantiomeric excess (Scheme 105).[121]

Shibata and co-workers disclosed a novel and interesting approach using a cation-binding C_2-symmetric chiral crown

Scheme 104

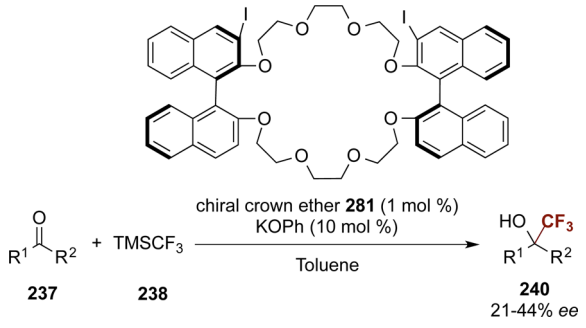


Scheme 105



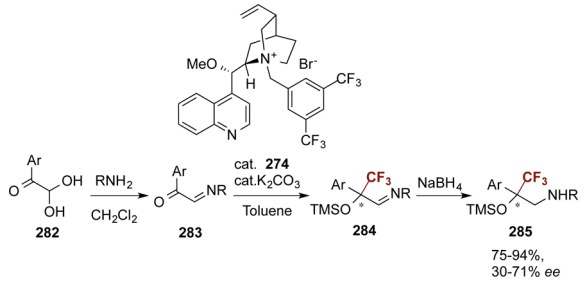
ether **281** for the enantioselective trifluoromethylation of aldehydes and ketones, effectively creating a chiral cation (Scheme 106).[122] Unfortunately, the enantioselectivities induced in the desired trifluoromethylated adducts were low to moderate.

Scheme 106



In 2013, Obijalska and co-workers disclosed enantioselective addition of $TMSCF_3$ to α-imino ketones **283** derived from aryl glyoxals **282** using a chiral ammonium bromide catalyst and catalytic K_2CO_3, to form *O*-silyated β-imino alcohols **284**. These products were reduced to determine the ee values, which ranged from 30% to 71% (Scheme 107).[123]

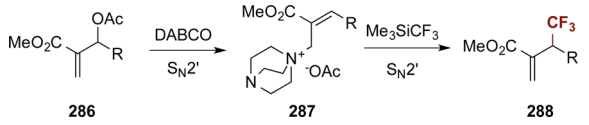
Scheme 107



dx.doi.org/10.1021/cr500277b | Chem. Rev. 2015, 115, 826−870

3.1.8. Allylic Trifluoromethylation of Morita–Baylis–Hillman Adducts. In 2010, Shibata and co-workers published a highly enantioselective allylic trifluoromethylation of Morita–Baylis–Hillman adducts **286** using the Ruppert–Prakash reagent and commercially available bis-cinchona alkaloid catalyst, $(DHQD)_2PHAL$.[124] This process takes advantage of the framework of the MBH adducts, which contain an allylic leaving group to enable an S_N2' displacement if the alcohol is suitably derivatized (R^1 = Ac or Boc). The authors found initially that if a suitably nucleophilic amine, such as DABCO, was employed, the cationic intermediate generated (**287**) was liable to a second S_N2' reaction from $TMSCF_3$, the latter reagent presumably activated by acetate (Scheme 108).

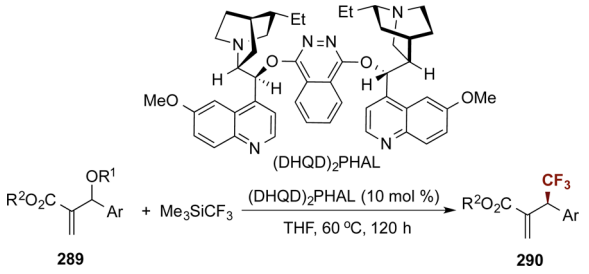
Scheme 108



286 **287** **288**

Once the reaction was optimized in a racemic sense, they then employed the chiral tertiary amine catalyst $(DHQD)_2PHAL$ in place of DABCO and were able to realize excellent enantioselectivities when R^1 = Boc, in what they describe as a successive S_N2'/S_N2' process (Table 25).

Table 25. Enantioselective Allylic Trifluoromethylation of Morita–Baylis–Hillman Adducts



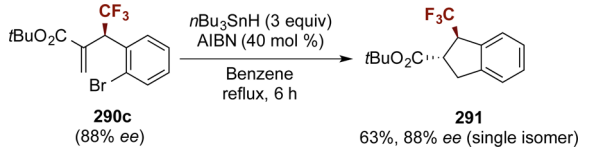
289 **290**

entry	R^1	R^2	Ar	yield (%)	ee (%)
a	Ac	*t*Bu	C_6H_5	trace	nd
b	Boc	*t*Bu	C_6H_5	39	92
c	Boc	*t*Bu	2-BrC_6H_4	37	88
d	Boc	*t*Bu	4-BrC_6H_4	60	90
e	Boc	Me	C_6H_5	52	94

The authors showed that the *β*-trifluoromethyl esters **290** obtained can be efficiently converted into potentially interesting carbocyclic and heterocyclic compounds without loss of enantiomeric purity (Scheme 109).

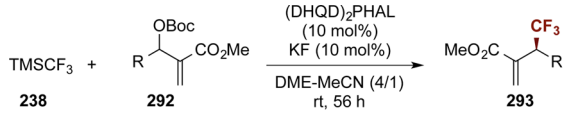
Very shortly after this report, Jiang and co-workers described an almost identical transformation (Scheme 110).[125] They found that they were able to perform the reaction at room temperature using a mixed solvent system and demonstrated a broader scope of aryl and heteroaryl substitution on the starting material, although in some cases enantioselectivity was moderate.

Scheme 109



290c (88% *ee*) **291** 63%, 88% *ee* (single isomer)

Scheme 110

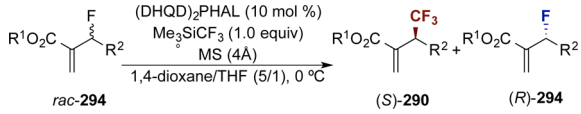


238 **292** **293**

ee up to 95%
yield up to 86%

Building on their previous insights, Shibata and co-workers recently disclosed a remarkable transformation involving the kinetic resolution of allyl fluorides **294** by enantioselective allylic trifluoromethylation, relying on enantioselective, silicon-assisted C–F bond cleavage.[126] When the transformation is halted at 50% conversion, enantioenriched starting material **294** and enantioenriched trifluoromethylated compound **290** could both be isolated with extremely high enantiomeric excesses, using $(DHQD)_2PHAL$ as catalyst (Table 26). Similarly, excellent results could also be obtained for pentafluorethylation and pentafluorophenylation.

Table 26. Kinetic Resolution of Racemic Allyl Fluorides by Enantioselective C–F Bond Cleavage/Allylic Trifluoromethylation

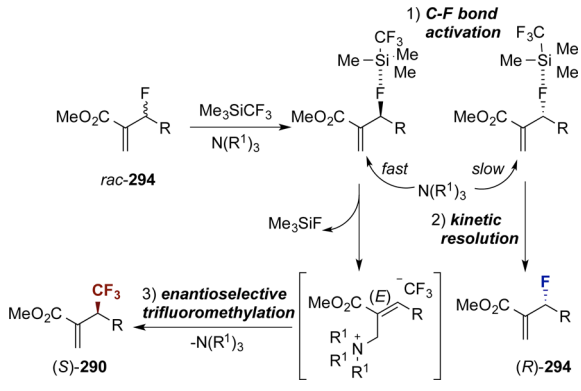


rac-**294** (*S*)-**290** (*R*)-**294**

entry	R^1	R^2	conv. (%)	(*S*)-**290** ee (yield) (%)	recovered **294** ee (yield) (%)
1	Me	Ph	54	95 (51)	97 (41)
2	Me	4-MeC_6H_4	53	95 (48)	96 (40)
3	Me	3-$MeOC_6H_4$	55	94 (50)	97 (40)
4	*t*Bu	Ph	50	94 (48)	93 (42)

The proposed mechanism commences with activation of the C–F bond by coordination to the silicon atom of $TMSCF_3$. This is followed by the kinetic resolution step whereby the chiral catalyst selectively participates in S_N2' reaction with only one enantiomer of the activated starting material. Finally, the resulting cationic intermediate is attacked by CF_3^- in an enantioselective trifluoromethylation (Scheme 111). This mechanistic picture is supported by the observation that the ee of **290** is consistently high throughout the course of the

Scheme 111

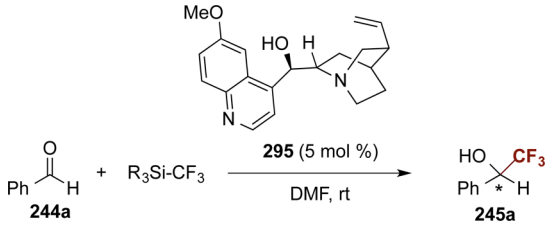


dx.doi.org/10.1021/cr500277b | *Chem. Rev.* 2015, 115, 826–870

reaction, while that of **294** increases steadily from 0 to ~95% as the reaction progresses.

3.1.9. Miscellaneous. In 1997, Kobayashi and co-workers investigated the use of nonquaternized cinchona alkaloids as catalysts for the trifluoromethylation of aldehydes. However, only modest yields and low enantioselectivities were observed (Table 27).[127]

Table 27. Investigation of Nonquaternized Cinchona Alkaloids To Catalyze Trifluoromethylation of Aldehydes

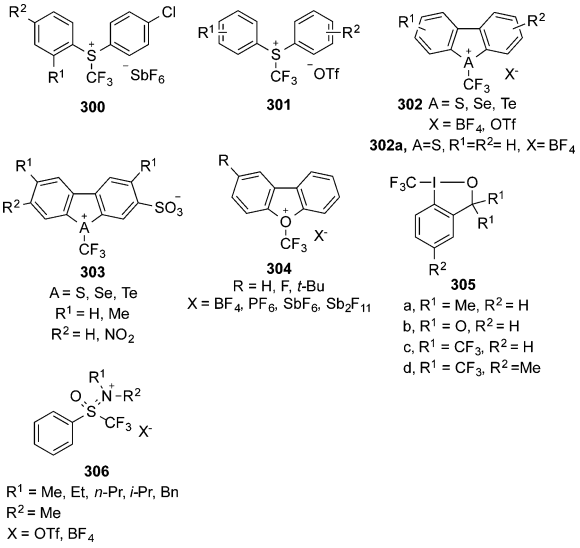


entry	silane	yield (%)	ee (%)
1	Me_3Si-CF_3 **238**	49	9
2	$PhMe_2Si-CF_3$ **296**	39	6
3	$Ph_2MeSi-CF_3$ **297**	35	12
4	Et_3Si-CF_3 **298**	24	21
5	$i\text{-}Pr_3Si-CF_3$ **299**	trace	

3.2. Electrophilic Trifluoromethylation

In contrast to their nucleophilic counterparts, enantioselective electrophilic trifluoromethylation reactions remain far less developed. A number of electrophilic reagents have been developed for generation of what can be regarded as a "synthetic equivalent" of a trifluoromethyl cation, the development of which has been reviewed elsewhere (Scheme 112).[3s,128] It should be considered that apparent electrophilic

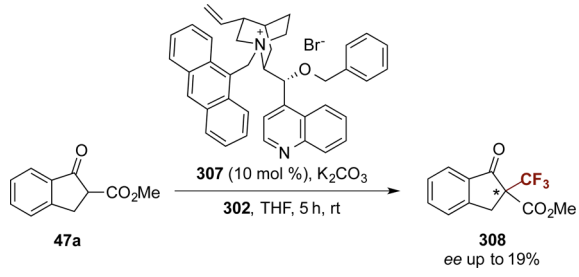
Scheme 112



reactivity may well proceed via electron-transfer induced radical mechanisms, as perfluoroalkyl radicals tend to be of an electrophilic nature.[1c] This behavior is particularly likely with readily oxidizable substrates such as enols and enamines.

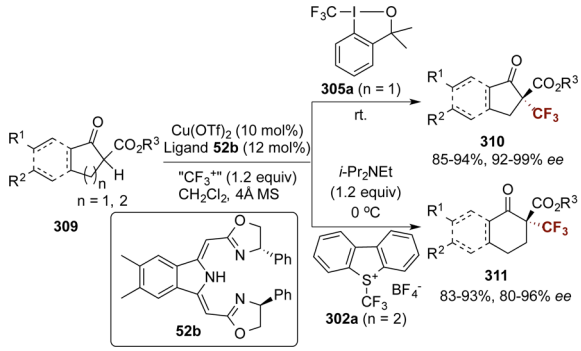
Among the first reported investigations of a catalytic enantioselective electrophilic trifluoromethylation reaction was that of Ma and Cahard in 2007. They examined the use of chiral ammonium salts acting as phase-transfer catalysts for trifluoromethylation of β-ketoester **47a**, although the highest enantiomeric excess recorded was only 19% (Scheme 113).[129]

Scheme 113



Enantioselective trifluoromethylation of this substrate class was not improved until Gade's disclosure in 2012 of the trifluoromethylation of similar β-ketoesters **309** using commercial electrophilic trifluoromethylating agents **305a** and **302a** and employing chiral "boxmi" pincer ligands **52b** in conjunction with copper catalysts (Scheme 114).[130] Both

Scheme 114

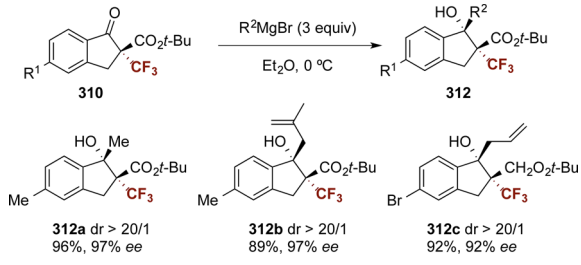


five- and six-membered ring β-ketoesters were converted to the corresponding products **310** and **311** in high yields with up to 99% ee. To highlight the utility of the enantioselective trifluoromethylation developed in this work, the authors demonstrated highly diastereoselective transformations of the trifluoromethylated products (Scheme 115).

In a distinct approach utilizing both enamine organocatalysis and transition metal catalysis, Allen and MacMillan in 2010 reported the highly asymmetric α-trifluoromethylation of aldehydes using Togni's reagent **305a** (Scheme 116).[131]

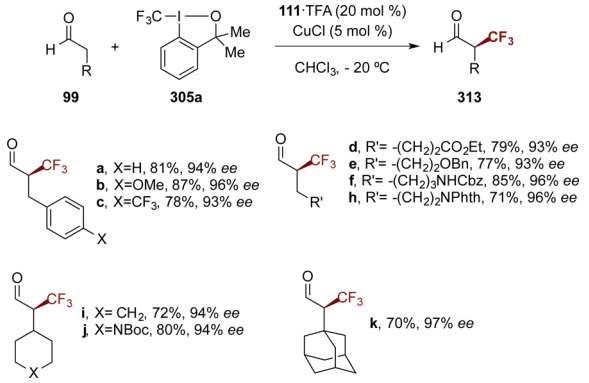
They envisioned that **305a** should undergo Lewis acid promoted bond cleavage to generate the highly electrophilic

Scheme 115



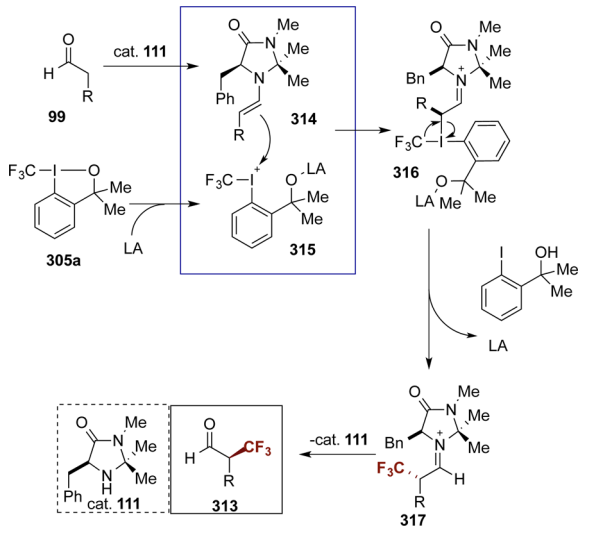
dx.doi.org/10.1021/cr500277b | Chem. Rev. 2015, 115, 826–870

Scheme 116



iodonium salt **315**. Condensation of the amine catalyst with an aldehyde would generate a chiral enamine that will participate in an enantioselective C−I bond formation via a closed-shell pathway. The resulting λ^3-iodane species **316** was envisaged to undergo reductive elimination with stereoretentive alkyl transfer, thus forming the new C−CF_3 bond, although a single electron transfer mechanism cannot be completely ruled out for this latter sequence. Hydrolysis would then release the amine catalyst and the desired enantioenriched α-trifluoromethyl aldehyde product **313** (Scheme 117). A range of Lewis acidic

Scheme 117



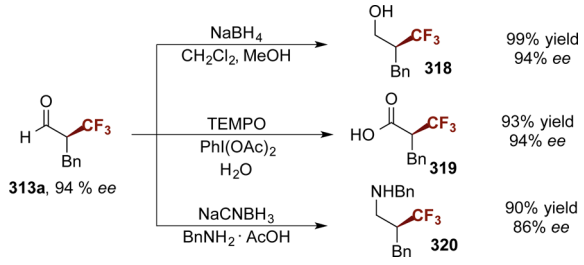
metals provided conversion and enantioenrichment, but CuCl proved to be the most effective and a range of substituted aldehydes were demonstrated to be effective.

The authors demonstrated that the α-trifluoromethylated aldehydes **313** were easily converted to a variety of valuable synthons containing the trifluoromethyl group (Scheme 118).

3.3. Radical Trifluoromethylation

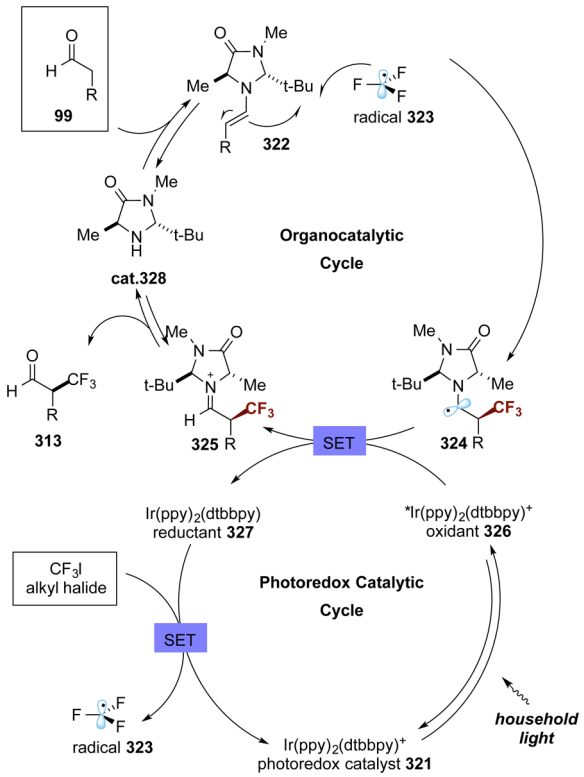
Trifluoromethyl radicals can be purposely generated by a number of methods and under the right conditions can be long-lived enough to be exploited in useful reactivity. In contrast with alkyl radicals that are generally nucleophilic, trifluoromethyl radicals have electrophilic character.[1c] Nevertheless, it is only recently that the first progress has been made to harness these species in the context of catalytic asymmetric synthesis. In 2009, Macmillan and co-workers described a conceptually novel

Scheme 118



approach to the asymmetric α-trifluoromethylation of aldehydes via the merger of enamine catalysis and photoredox catalysis (Scheme 119).[132] In their proposed cataytic cycle,

Scheme 119

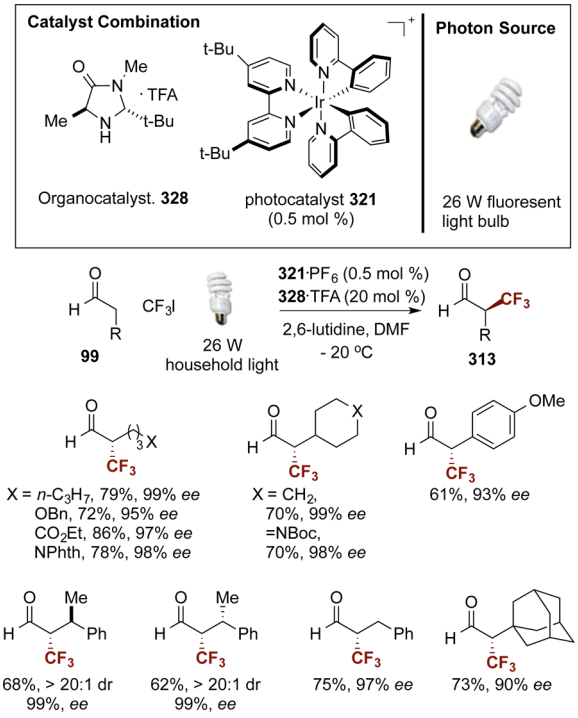


photoredox catalyst $Ir(ppy)_2(dtbbpy)^+$ **321** accepts a photon from a visible spectrum light source to populate the excited-state complex **326** that would then accept a single electron from a sacrificial equivalent of enamine to form a strong reductant $Ir(ppy)_2(dtbbpy)$ (**327**). At this stage, **327** engages in single electron transfer with trifluoromethyl iodide, resulting in an electrophilic trifluoromethyl radical **323**, at the same time regenerating the photoredox catalyst **321**. In concert with this trifluoromethyl radical formation pathway, the separate organocatalytic cycle would be initiated by condensation of amine catalyst **328** with aldehyde substrate **99** to form the reactive enamine **322**. These two cycles would intersect in the trifluoromethylation step via addition of the trifluoromethyl radical **323** to the nucleophilic enamine to form the α-amino radical **324**. A second electron transfer event with the excited-state photocatalyst **326** would close the photoredox cycle and deliver the iminium ion **325**, prior to hydrolysis.

dx.doi.org/10.1021/cr500277b | Chem. Rev. 2015, 115, 826−870

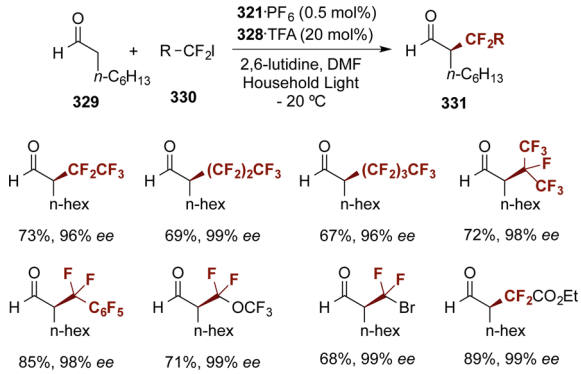
They demonstrated the effectiveness of this approach to trifluoromethylation of a range of aldehydes, using a 26 W household light bulb as the visible light source (Scheme 120). The authors noted that at room temperature the products racemized rapidly, but this was prevented by running the reactions at −20 °C.

Scheme 120



They nicely demonstrated that their strategy could also be extended to perfluoroalkylation of aldehydes using the same conditions (Scheme 121).

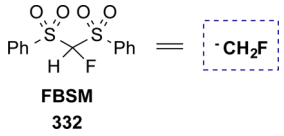
Scheme 121



4. CATALYTIC ENANTIOSELECTIVE MONOFLUOROMETHYLATION

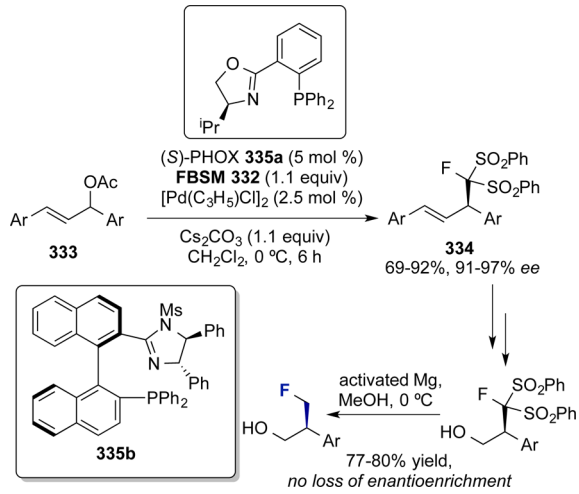
Recognizing that despite the increasing methods for the introduction of the fluorine atom and perfluoroalkyl groups, there was little attention given to reactions resulting in monofluoromethylation, Shibata, Toru, and co-workers introduced 1-fluorobis(phenylsulfonyl)methane (FBSM) as a fluoromethide equivalent (Scheme 122).[133a,134] This reagent

Scheme 122



was found to participate in Tsuji−Trost allylic substitution reactions on substrates **333** to afford the enantioenriched fluoromethylated products **334** (Scheme 123) using PHOX

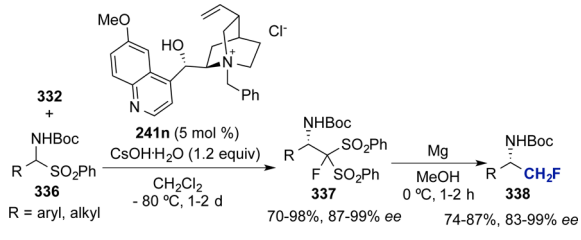
Scheme 123



ligand **335a**. A similar process has also been reported using the chiral imidazoline-phosphine ligand **335b**.[133b] Importantly, it was demonstrated after further transformation of the aldehyde the two sulfone groups could be reductively cleaved using activated magnesium to leave a monofluoromethyl group.

The versatility of this reagent was demonstrated by the same authors in the catalytic enantioselective Mannich-type monofluoromethylation of imines.[135] The prochiral imine substrates were generated in situ in the presence of a chiral phase-transfer catalyst and CsOH·H_2O as base. With regard to the scope of the reaction, both alkyl and aryl imines gave high enantioselectivities, and for all substrates the reductive desulfonylation using magnesium was demonstrated to occur without loss of enantioenrichment (Scheme 124).

Scheme 124



The same authors also reported the catalytic, asymmetric conjugate addition of FBSM to α,β-unsaturated ketones **339** (Scheme 125).[136] The ammonium salts of cinchona alkaloids possessing sterically demanding substituents catalyzed the conjugate addition reaction efficiently to give Michael adducts **340** in high yield with excellent enantioselectivity.

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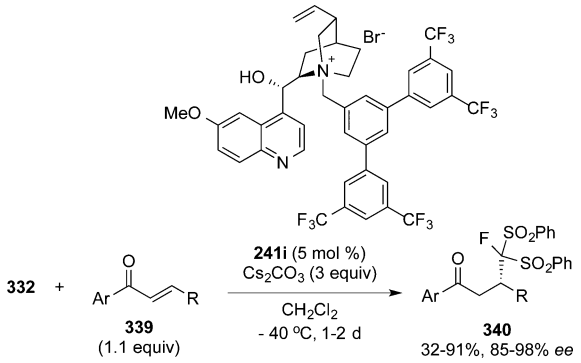
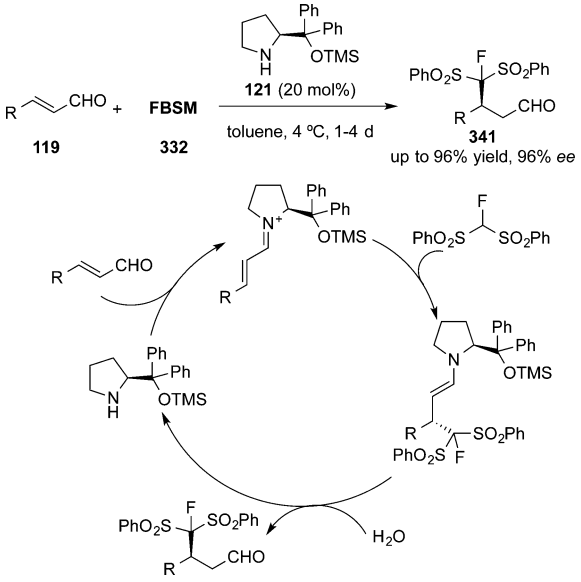
Scheme 125



In 2009, several groups demonstrated that FBSM is effective as a nucleophile for asymmetric conjugate addition to α,β-unsaturated aldehydes, using established amine catalyst **121** and a catalytic cycle proceeding via iminium activation (Scheme 126).[137−139]

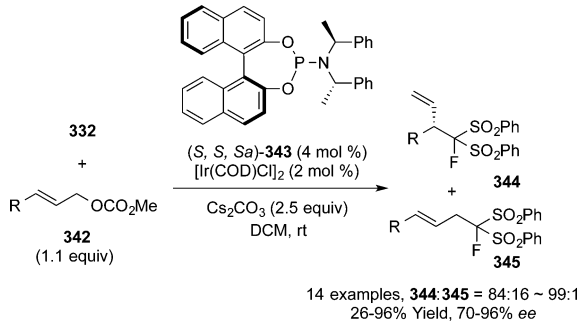
Scheme 126



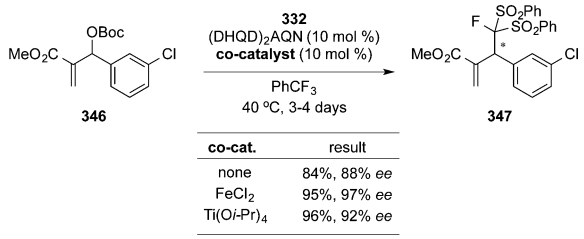
Building on Shibata and Toru's earlier work, Zhao, You, and co-workers in 2009 demonstrated that $[Ir(COD)Cl]_2$ in combination with phosphoramidite ligand **343** is an efficient catalytic system to allow allylic alkylation of **FBSM** with 1,3-unsymmetrical allylic substrates, leading to chiral products bearing a terminal alkene with good to excellent regioselectivity (Scheme 127).[140]

In 2011, Shibata and co-workers disclosed another application of FBSM, the enantioselective allylic monofluoromethylation of Morita−Baylis−Hillman carbonates using cooperative catalysis (biscinchona alkaloid and $FeCl_2$). This provided chiral α-methylene β-monofluoromethyl esters with high ee's of up to 97% (Scheme 128).[141] The transformation is envisaged to proceed by S_N2' attack of the quinuclidine nitrogen atom of the cinchona alkaloid catalyst to afford a cationic intermediate, which is then attacked by the FBSM anion in another S_N2' reaction to give the product (see section 3.1.8 for further discussion of this approach). The authors proposed a transition state model to account for the observed

Scheme 127



Scheme 128



absoute stereochemistry and suggested that the conformation shown may be stabilized by $\pi-\pi$ interations in the U-shaped cleft of the $(DHQD)_2AQN$ (Figure 25). As the *Si* face would

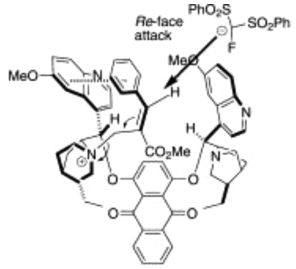


Figure 25. Proposed transition-state model for addition of FBSM to catalyst-bound intermediate. Reproduced with permission from ref 141. Copyright 2011 John Wiley and Sons.

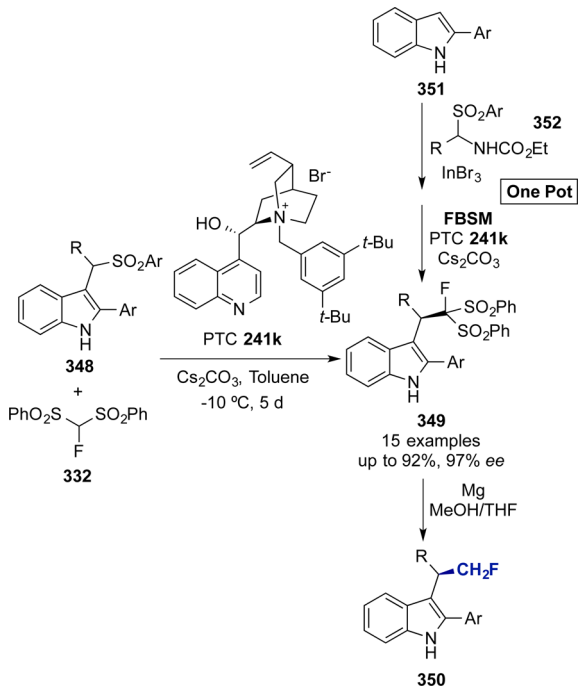
be blocked by the left half of the catalyst (as depicted), FBSM would attack from the *Re* face. Supporting this scenario is the observation that low enantioselectivities were observed in nonaromatic substrates. The addition of a metal cocatalyst provided a modest rather than a dramatic increase in efficiency, and the authors speculated that this could be due to bidentate chelation to FBSM increasing its reactivity.

Recently, enantioselective addition of **FBSM** to vinylogous imines generated in situ from 2-aryl-3-(1-arylsulfonylmethyl)-indoles **348** was achieved by the same authors using a phase-transfer catalysis strategy (Scheme 129).[142] Reductive desulfonylation gave the monofluoromethyl adduct **350**. A one-pot reaction starting from simple indoles **351** was also viable, the first step in the procedure being indium-promoted Friedel−Crafts alkylation with α-amido sulfones **352**.

In 2010, Shibata and co-workers introduced a variant of FBSM, 2-fluoro-1,3-benzodithiole-1,1,3,3-tetraoxide (**FBDT**) **353**, as a further fluoromethide equivalent.[143] They developed this reagent due to the inability of FBSM to undergo nucleophilic addition to aldehydes. The authors hypothesized that this is due to the instability of the resulting addition

dx.doi.org/10.1021/cr500277b | Chem. Rev. 2015, 115, 826−870

Scheme 129

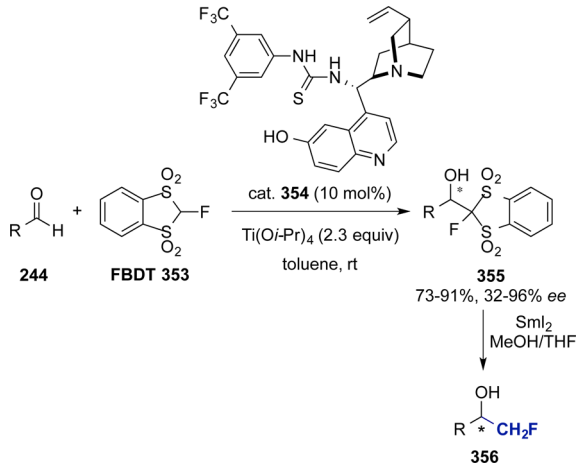


product due to steric hindrance of the two phenylsulfonyl groups; hence, the reverse reaction is overwhelmingly favored. FBDT was developed as a less sterically demanding reagent to address this problem. The authors initially demonstrated that this was successful in a racemic sense. In 2013, they reported a catalytic enantioselective variant using a bifunctional cinchona alkaloid-derived thiourea catalyst and stoichiometric titanium complex. While some excellent selectivities were obtained, this was rather dependent on the precise structure of the substrate. The authors showed that samarium diiodide is effective in unmasking the monofluoromethyl motif without loss of enantioenrichment (Scheme 130).[144]

5. CATALYTIC ENANTIOSELECTIVE DIFLUOROMETHYLATION

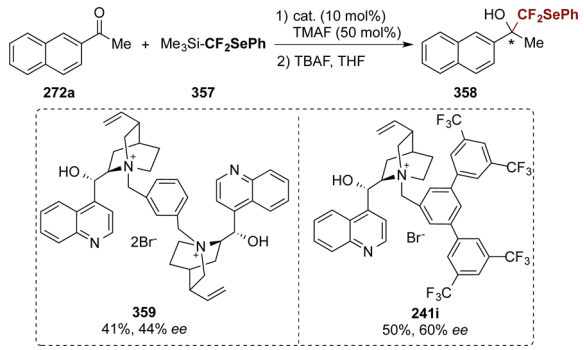
Shibata and co-workers extended their protocol previously employed for enantioselective trifluoromethylation to reagents

Scheme 130



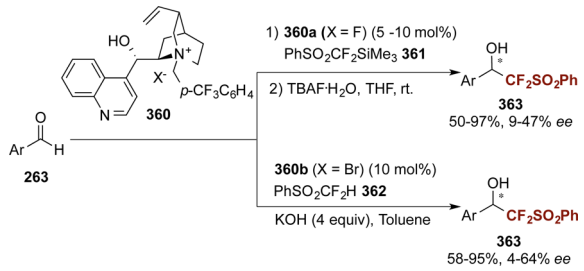
acting as nucleophilic difluoromethyl equivalents. Using $Me_3SiCF_2SePh_3$ as nucleophile, enantioselective difluoromethylation of 2-naphthylmethyl ketone (**272a**) was investigated (Scheme 131). The corresponding difluoromethylated compound **358** was obtained in 41% yield with 44% ee. Some improvements in the enantioselectivity were made by employing the more sterically hindered cinchona alkaloid **241i**, although the result was still moderate.[145]

Scheme 131



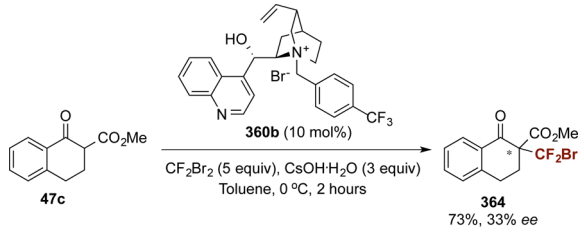
In 2008, Hu and co-workers described the catalytic enantioselective difluoroalkylation of aromatic aldehydes with $Me_3SiCF_2SO_2Ph$ (**361**) and $PhSO_2CF_2H$ (**362**) employing a chiral quaternary ammonium salt as catalyst and KOH as base (Scheme 132).[146] They found that the enantioselectivity was substrate-dependent; for 2-chloro benzaldehyde, ee of up to 64% was obtained.

Scheme 132



Shibata and co-workers also attempted catalytic electrophilic or radical enantioselective difluorobromination of β-ketoesters, using CBr_2F_2 and **360b** as catalyst, with excess CsOH as base. The α-bromodifluoromethyl tetralone carboxylate **364** was obtained in 73% yield with 37% ee (Scheme 133).[145]

Scheme 133



dx.doi.org/10.1021/cr500277b | Chem. Rev. 2015, 115, 826−870

6. CATALYTIC ENANTIOSELECTIVE TRIFLUOROMETHYLTHIOLATION

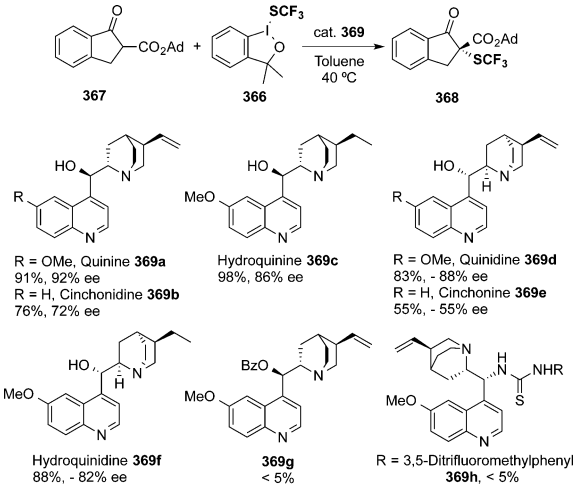
The trifluoromethanesulfenyl group (SCF_3) is of special interest due to its extremely high lipophilicity, with a Hansch parameter of 1.44 as compared to 0.88 for CF_3.[147] This could be particularly beneficial in tuning compound pharmacokinetic properties. While this group has been utilized for some time, it is only very recently that methods for its direct introduction have come into the mainstream.[148] With the development of new reagents such as **365**[149] and **366**,[150] new possibilities have been realized for catalytic asymmetric introduction of the SCF_3 group (Scheme 134).

Scheme 134

365 366

Very recently, Lu, Shen, and co-workers reported the preparation of trifluoromethylthiolated hypervalent iodine reagent **366**. They went on to demonstrate that this could be employed for the asymmetric trifluoromethylsulfenylation of β-ketoesters in the presence of cinchona alkaloid-based phase-transfer catalysts.[151] They found that several of the catalysts in this family were effective and that the hydroxyl group of the cinchona alkaloids was important for the high reactivity of the transformation (Scheme 135).

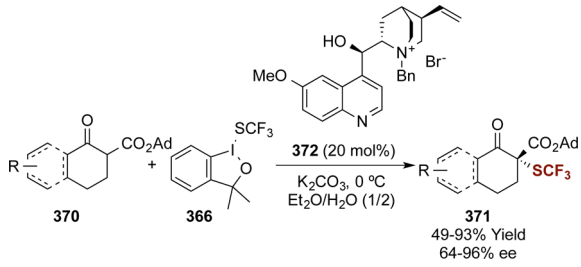
Scheme 135



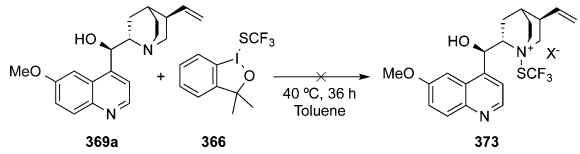
While these conditions were suitable for indanone-derived substrates, tetralone- or benzosuberone-derived β-ketoesters required phase-transfer catalysts in combination with a base to be used to get conversion, and under these conditions the enantioselectivities were generally not as high (Scheme 136).

The authors considered two plausible pathways. In the first, the catalyst **369a** reacts with **366** to give a quaternary ammonium ion **373** that is attacked by the β-ketoester. However, they could not observe formation of this putative species in a stoichiometric reaction (Scheme 137). In the second, quinine deprotonates the β-ketoester and forms a hydrogen-bonded intermediate that is activated to attack **366**.

Scheme 136

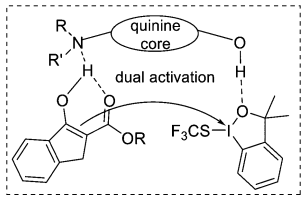


Scheme 137



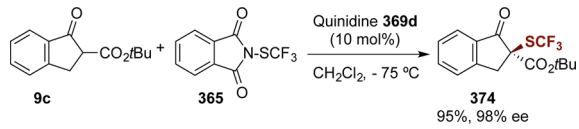
The authors favor the latter and propose that the hydroxyl group of the catalyst activates **366**; thus, the catalyst acts as a bifunctional catalyst to generate a highly organized transition state that is sensitive to the exact steric nature of the substrate (Scheme 138). They go on to present an argument to explain the difference in reactivity between the tetralone and indanone systems.

Scheme 138



In a back-to-back publication with Shen's report, Rueping and co-workers reported trifluoromethylsulfenylation of similar substrates using the electrophilic SCF_3 source **365** in combination with cinchona alkaloid catalysts (Scheme 139).[152] The majority of their scope was comprised of indanones, although a tetralone-derived substrate also gave high enantioselectivity but with only moderate yield.

Scheme 139



The same authors subsequently found that 3-aryl oxindoles **50** also underwent enantioselective trifluoromethylthiolation using $(DHQD)_2Pyr$ as organocatalyst (Scheme 140).[153]

Transition metals catalysis has also very recently been utilized for enantioselective SCF_3-transfer reactions. In 2014, Gade and co-workers reported the highly enantioselective Cu-catalyzed trifluoromethylthiolation of β-ketoesters by using **366** as SCF_3-transfer reagent (Scheme 141).[154] They deployed their copper "boxmi" pincer complexes, which they had previously shown to be effective for trifluoromethylation of β-ketoesters, to great effect.[130]

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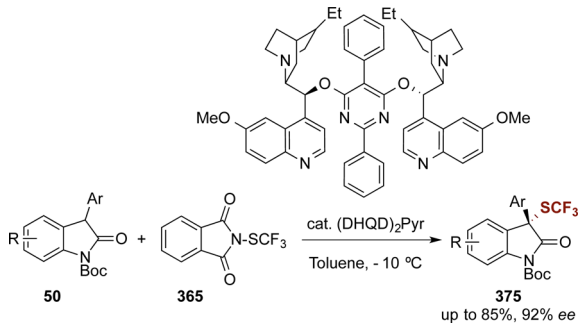
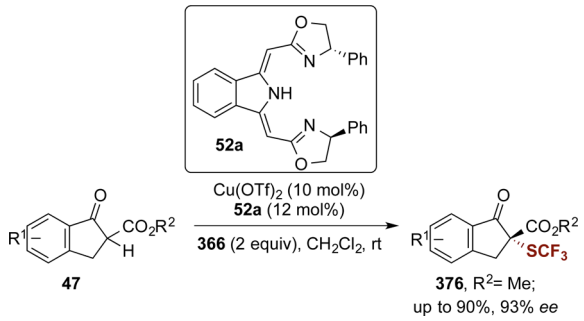
Scheme 140

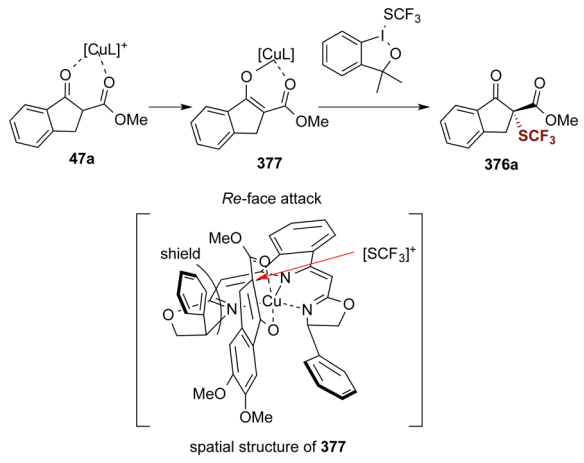


Scheme 141



They propose that the copper(II) catalyst acts as a Lewis acid, to stabilize and orientate the ester-enolate form of the substrate, giving rise to the observed high enantioselectivity according to the model shown (Scheme 142). They propose

Scheme 142



that in the complexed intermediate, the *Si* face of the substrate is blocked by the phenyl group of the oxazolinyl unit and the trifluoromethylthiolation reagent **366** therefore preferentially approaches from the *Re* face of the substrate, consistent with the absolute configuration of product **376a**.[155]

7. SUMMARY AND OUTLOOK

There has been remarkable progress in the past decade toward catalytic asymmetric methods for the introduction of fluorine and a range of fluorine-containing groups into small molecules. No doubt this has been spurred by the demand particularly in the pharmaceutical and agrochemicals sectors, but these advances have necessarily gone hand-in-hand with the development of stable and easily handled reagents. Some of the earlier material included in this comprehensive review has been also covered by previous reviews, but even in the five years since 2009 there have been a remarkable number of advances, which have in some cases arisen as a result of the introduction of new reactivity concepts, for example, photoredox catalysis and chiral anion phase-transfer catalysis. The rapid growth and development of this field makes it a particularly stimulating area of study with new advances being made almost on a daily basis. Yet despite this, there are still limitations; efforts need to be made to expand the substrate classes that can be addressed, so that new methods truly cover new ground. To this end, new fundamental approaches to asymmetric catalysis must be sought as it is in this way that the variety of substrates can be significantly expanded into new and previously unimaginable areas. One certainty is that the introduction of fluorine and fluorine-containing groups is now high on the list of ways to test any new asymmetric method, which makes this an exciting arena in which to witness the latest developments in the field of enantioselective catalysis.

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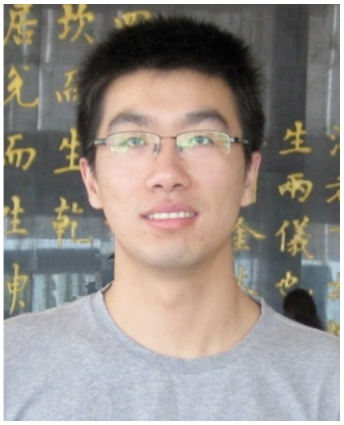
Author Contributions

‡X.Y. and T.W. contributed equally to this work.

Notes

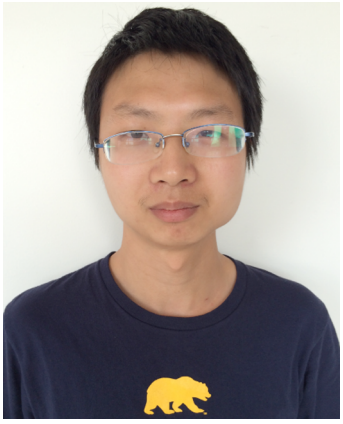
The authors declare no competing financial interest.

Biographies

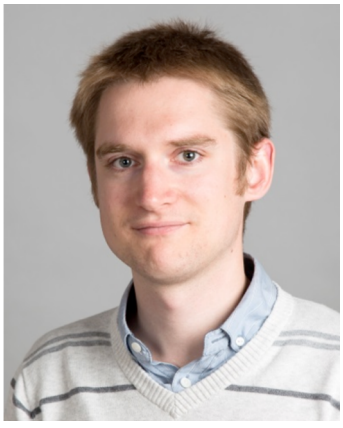


Xiaoyu Yang obtained his B.Sc. from Nanjing University in 2007. He then moved to Shanghai Institute of Organic Chemistry to pursue a Ph.D. degree in Prof. Biao Yu's lab. His Ph.D. work was focused on the total synthesis of complex natural glycoconjugates, landomycins and jadomycins. In 2013, he joined the Toste group as a postdoctoral fellow, and his research is focused on the development of asymmetric fluorination reactions using chiral anion phase-transfer catalysis.

dx.doi.org/10.1021/cr500277b | *Chem. Rev.* 2015, 115, 826–870



Tao Wu obtained his B.Sc. from Beijing Normal University, where he conducted organometallic chemistry research on nickel-catalyzed C–O activation under the supervision of Prof. Zhangjie Shi (Peking University). He then worked with Prof. Guosheng Liu at SIOC to pursue a Ph.D. degree starting in 2007. His graduate work mainly focused on palladium-catalyzed difunctionalization of alkenes. In 2013, he joined the Toste group as a postdoctoral researcher and is conducting research in the area of asymmetric catalysis using chiral anions.



Robert J. Phipps obtained his undergraduate degree from Imperial College, London, in 2006 before moving to the University of Cambridge where he completed his Ph.D. studies with Prof. Matthew Gaunt in 2010 on the development of copper-catalyzed arylation. He spent two years working with Prof. F. Dean Toste at UC Berkeley on asymmetric fluorination as a Marie Curie Postdoctoral Fellow. In 2013, he returned to Cambridge where he will commence independent research from 2014 as a Royal Society University Research Fellow.

F. Dean Toste obtained his B.Sc. in Chemistry and Biochemistry (1993) and M.Sc. in Organic Chemistry (1995) from the University of Toronto. He then moved to Stanford University where he completed his Ph.D. in 2000 under the guidance Professor Barry Trost. After a postdoctoral appointment with Professor Robert Grubbs at the California Institute of Technology, he took a position as an Assistant Professor of Chemistry at the University of California, Berkeley, in 2002. In 2006, he was promoted to Associate Professor, and Professor of Chemistry in 2009. Professor Toste's honors include an Alfred P. Sloan Research Fellowship (2005), the Cope Scholar (2006), E. J. Corey Award (2008), and Creativity in Organic Synthesis (2015) Awards from the American Chemical Society, BASF (2007) and Mitsui (2014) Catalysis Awards, the Organometallic Chemistry Directed Towards Organic Synthesis (OMCOS) Award (2007) and Thieme-IUPAC Prize in Synthetic Organic Chemistry (2008) from IUPAC, the Merck Award (2010) from the Royal Society of Chemistry, and the Mukaiyama Award (2011) from the Society of Synthetic Organic Chemistry Japan.

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