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REVIEW

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Asymmetric Fluorination Reactions Promoted by Chiral Hydrogen-Bonding-Based Organocatalysts

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Abstract. Fluorinated compounds can exhibit interesting biological properties. The importance of these species has made that the chemistry of fluorine has experienced a great development. On this review, the recent advances on asymmetric fluorination reactions promoted by chiral hydrogen-bonding-based organocatalysts are discussed. Hence, examples using phosphoric acid, carboxylic acid, (thio)urea and squaramide derivatives are illustrated. The growth of this field is amazing. We have only considered pivotal works in which direct fluorination takes place using a fluorinating agent, leaving aside the reactions where a fluorine atom is incorporated from the beginning as part of other reactants.
Herein, the scarce existing examples on this field of research have been compiled.

Keywords: fluorination; hydrogen-bond; organocatalysis; phosphoric acid; squaramide; thiourea.

1 Introduction

Over the last two decades, the chemistry of fluorine has drawn much attention in different fields of research, such as medicine, agricultural chemistry and materials science.[1] In this area, the results achieved in asymmetric catalysis deserve special mention for the construction of prominent fluorinated compounds. The importance of developing new asymmetric protocols lies in the interesting scaffolds produced through these fluorination reactions, mainly involved in the development of new agrochemical[2] and pharmaceutical targets (Figure 1).[3]

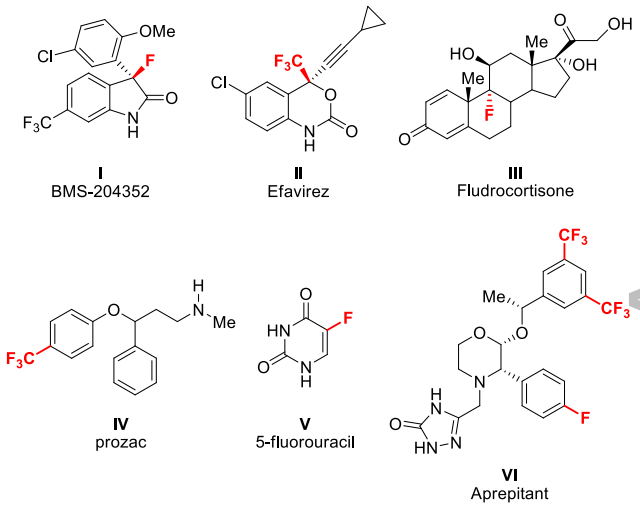

Figure 1. Small fluorinated bioactive compounds: **I**,[4] **II**,[5] **III**,[6] **IV**,[7] **V**[8] and **VI**.[9]

Interestingly, it has been found that the incorporation of a fluorine atom or a trifluoromethyl (CF_3) group into organic skeletons (aliphatic and

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aromatic) can alter their physical and chemical properties through steric and electronic effects, making an overall improvement to the final biological properties of the resulting compounds.[10] Focusing on asymmetric catalysis, many efforts have been devoted to the introduction of new C−F and C−CF_3 bonds, especially into alkyl chains.

Since the first asymmetric fluorination protocol reported by Togni and coworkers in 2000,[11] many other research groups have invested their energies in the progress of this field.[12,13] The interest arisen by this research area is reflected in the amazing amount of works compiled in many pivotal reviews. In the field of organocatalysis, a considerable number of works have been centered on the chemistry of aminocatalysis.[12,14] However, in this review we are discussing asymmetric organocatalytic protocols focused on hydrogen-bonding-based catalysts, such as (thio)ureas,[15] squaramides[16] chiral phosphoric acids[17] and chiral carboxylic acids[18] as the most representative chiral organocatalysts.[19] Although other reviews have covered many examples using some of these catalytic structures,[20] we are focusing our attention on those works in which direct fluorination takes place using a fluorinating agent, leaving aside the reactions where a fluorine atom is incorporated from the beginning as part of other reactants. With these statements in mind, we have been able to find a good number of essential examples in the literature catalyzed by these selected organocatalysts. Additionally, this kind of analysis has been overlooked in the literature so far to the best of our knowledge.

Although several strategies have been developed for the construction of chiral fluorinated organic structures using both nucleophilic[21] and electrophilic[22] sources, the catalysts revised in this work are mostly involved in electrophilic fluorination reactions with 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborates) (Selectfluor) or *N*-fluorobenzenesulfonimide (NFSI) (Figure 2). However, some other fluorinating sources will be also illustrated and commented on this revision.

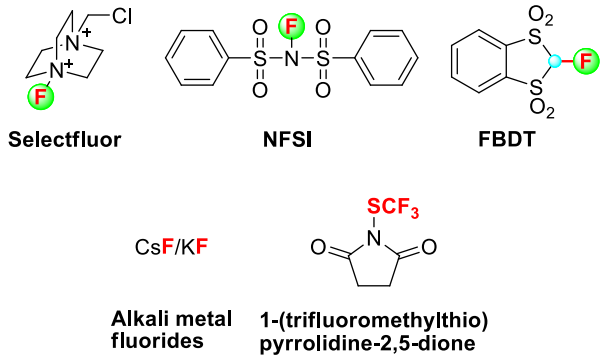

Figure 2. Commercially available fluorinating sources used in this review.

Fernando Auría-Luna was born in Zaragoza (Spain) in 1990. He obtained his B.Sc. in Chemistry in 2015 at the University of Zaragoza. Currently, he develops his Ph.D. in Organic Chemistry at the H-OCA group, under the supervision of Dr. Raquel P. Herrera and Dr. Eugenia Marqués-López at the ISQCH (CSIC)-University of Zaragoza. His research interest focuses on the asymmetric synthesis of new heterocyclic compounds that feature potential biological properties and the study of such activity.

Dr. Somayeh Mohammadi was born in Shiraz (Iran), in 1981. She received her B.Sc. (2004) and M.Sc. degrees (2007) at the University of Shiraz, Iran, and completed her Ph.D. (2008–2012) in organic chemistry under the supervision of Prof. Khalafi-Nezhad at the same university. In 2012, she spent 8 months working with Prof. Raquel P. Herrera and Prof. Eugenia Marqués-Lopez as a visiting predoctoral researcher at the ISQCH (CSIC)-University of Zaragoza, working on asymmetric organocatalysis. She is currently pursuing postdoctoral research at the Shiraz University of Medical Sciences, Iran, working on design and syntheses of new libraries of potential C-MET inhibitor compounds (anti-cancer) and BASE1 inhibitor compounds (anti-Alzheimer).

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Prof. Raquel P. Herrera was born in Alicante (Spain), in 1977. She received her B.Sc. (1999) and M.Sc. degrees (2000) at the University of Alicante, Spain, and completed her Ph.D. (1999–2003) under the supervision of Prof. Guijarro and Prof. Yus at the same university. Then, she took up a European postdoctoral contract with Prof. Ricci (Bologna, Italy) until March 2006, at which time she joined Prof. Lassaletta's and Fernández's group at the IIQ-CSIC (Seville, Spain). She was appointed as a permanent researcher (ARAID program) at the ISQCH-University of Zaragoza in January 2008, in 2012 she obtained a permanent position as Tenured Scientist of the Spanish Council of Research (CSIC) and in 2020 she has promoted to Scientific Researcher (CSIC) at the same Institute. In 2012 she was awarded with the Lilly Prize for the best young scientist less than 40 years, in Spain. Her research focuses on asymmetric organocatalysis and its biological applications. She is the head of the Asymmetric Organocatalysis research group.

2 Chiral anionic phase-transfer catalysts

2.1 Phosphoric acids as precatalysts

In this field, Toste's group pioneered the concept *chiral anion phase-transfer catalysis*,[23-25] using lipophilic chiral phosphate anion salts as phase-transfer catalysts. These precatalysts would transport insoluble electrophilic fluorinating agents, placed in a separate aqueous or solid phase, into organic solution in order to finally promote the reaction with different substrates. The original catalytic system was formed by a chiral phosphoric acid catalyst, such as **2a**, and Selectfluor **1** (Figure 3).[26]

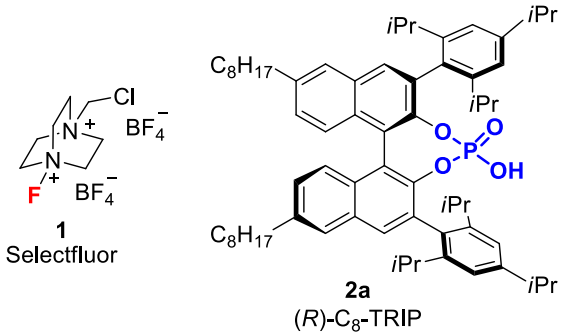

Figure 3. Chiral anionic phase-transfer catalytic system formed by Selectfluor **1** and chiral phosphoric acid derivative **2a**.

With the main objective of testing the catalytic potential of this system, the authors explored the efficiency of this chiral anion phase-transfer catalyst in the β-fluorination of dihydropyran substrates **3** (Scheme 1).[26] Therefore, after the optimization of the reaction conditions, including the Proton Sponge ([1,8-bis(dimethylamino)naphthalene] **4**) with the main aim of generating the anionic catalyst *in situ* as well as to neutralize the acid generated in the course of the reaction, spiroketals **5** were obtained with very high yields and enantioselectivities (Scheme 1).

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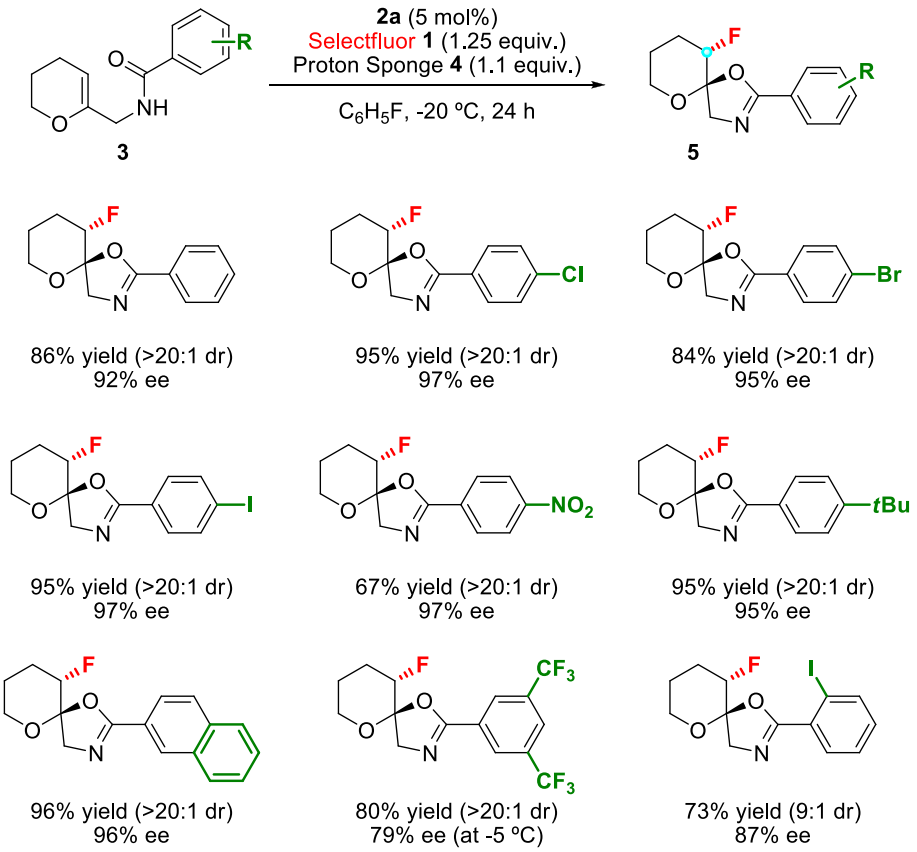
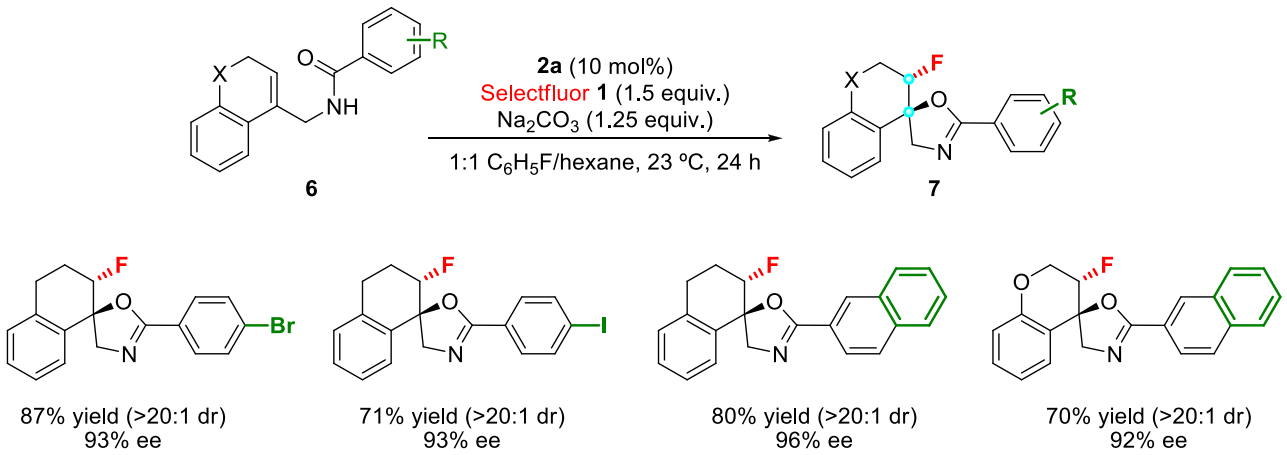


Scheme 1. Enantioselective fluorocyclization of dihydropyrans **3** giving rise to spiroketals **5**.

Then, the developed fluorocyclization approach was extended to other interesting and more challenging structures such as dihydronaphthalene and chromene substrates **6**, leading to the corresponding cyclic compounds **7** with very good results (Scheme 2). However, in this case a higher catalyst loading was required and the use of unactivated olefins led to only moderate yields and enantioselectivities.



Scheme 2. Enantioselective fluorocyclization of dihydronaphthalenes and chromene **6**.

Remarkably, a plausible reaction mechanism was proposed, as depicted in Scheme 3, based on additional experimental results and on the exploration of the scope of the process.

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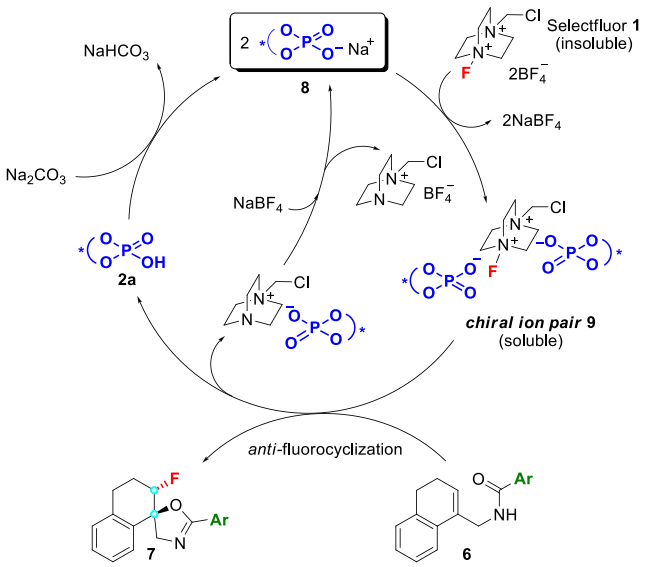
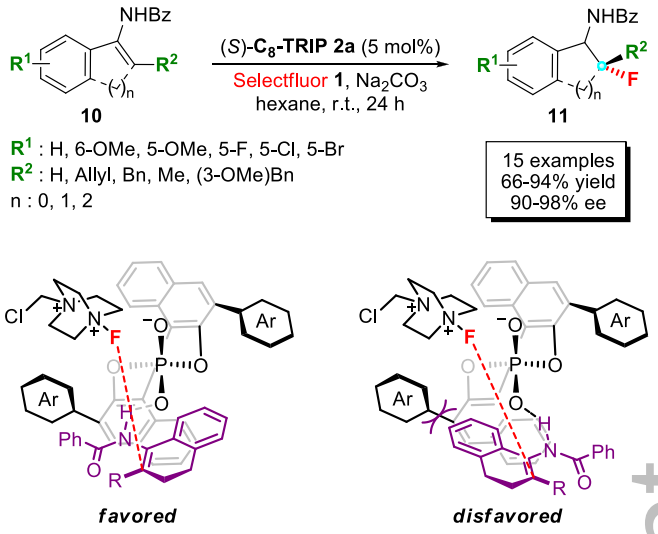


Scheme 3. Suggested catalytic cycle based on the experimental results.

In this cycle, two molecules of phosphoric acid **2a** would generate a chiral ion pair **9** with Selectfluor **1** by deprotonation and ion exchange, increasing the solubility of the active fluorinating agent. Then, the alkene **6** would simultaneously suffer a fluorocyclization process and the released molecule of phosphoric acid **2a** would be deprotonated by the base present in the reaction medium generating the species **8** once again. Two molecules of the anionic phosphate **8** would give rise to the chiral ion pair **9** restarting the catalytic cycle.

In close relation with this example, the authors also applied this idea to the fluorination of enamides **10** affording α-fluoroimines **11** using a similar catalytic system with very good results.[27] In this process, the authors went one step further to explain the enantioselectivities of the reaction. Therefore, founded on the well-known bifunctional role of phosphoric acid catalysts, they envisioned the plausible formation of an ion pair with the Selectfluor reagent **1** through one oxygen atom with concomitant activation of the enamide through hydrogen bonding with another oxygen atom. The steric hindrance of both possibilities would determine the preferred disposition of the tetralone in an "open" quadrant, with the amide group occupying a "closed" quadrant (favored TS, Scheme 4).



Scheme 4. Reasonable mechanistic attacks to explain the stereochemical course of the reaction.

This arrangement would support that the variation in the enamide structure does not affect the catalyst-substrate binding and, consequently, the enantioselectivity of the process. The methodology tolerated well the substitution in the enamide functionality, including substrates with different electronic properties (without substitution in the α-position or even with α-haloenamides). Interestingly, only the corresponding 2-methylcyclohexanone-derived enamide was found as a limitation of the process.

Later on, Toste and co-workers reported an elegant approach of "dual" or "cooperative" catalysis,[28] using a combination of the chiral phosphoric acid catalyst **2a** (phase-transfer catalysis) and the amino acid ester **13** (enamine catalysis), focused on the asymmetric fluorination of α-branched cyclohexanones **12** (Scheme 5) leading to quaternary fluorine-containing stereocenters.[29] Among the catalysts explored, (*R*)-C_8-TRIP **2a** and an amino ester derivative **13** afforded the desired products **14** with high enantioselectivities. Moreover, the authors found that the level of moisture was affecting the final results of this approach. Therefore, $Na_2CO_3 \cdot H_2O$ with a small amount of water improved the ee from 32% to 88% with excellent repeatability.

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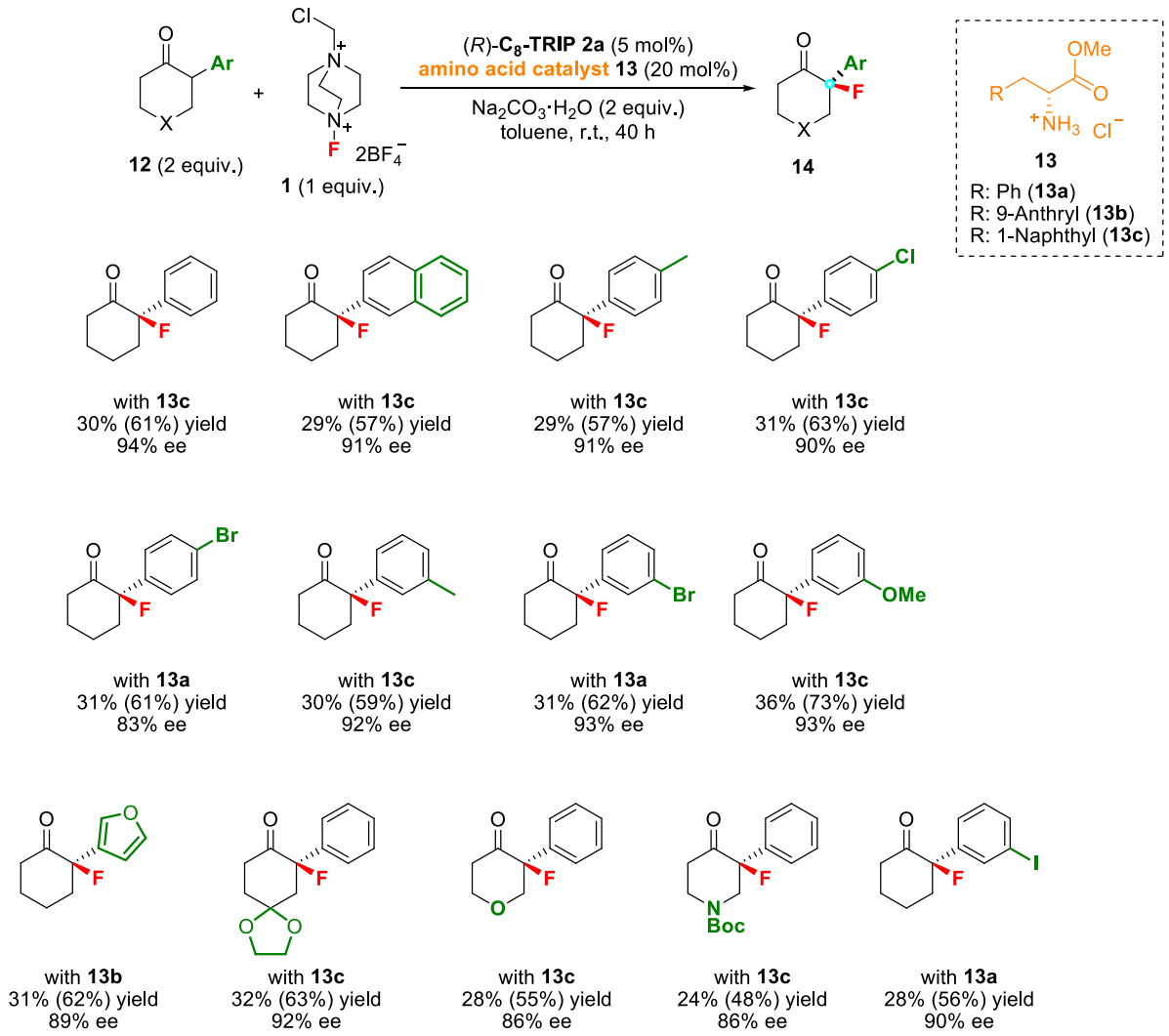

Scheme 5. Asymmetric α-fluorination of 2-substituted cyclohexanones **12**.

Hence, the efficiency of the developed methodology was demonstrated by the enantioselective fluorination reaction of different 2-arylcyclohexanones **12** (Scheme 5). Unfortunately, no fluorination was observed for 2-alkylcyclohexanones under the same reaction conditions, representing a limitation of this methodology. In all cases, excellent regio- and enantioselectivities were observed with no undesired fluorination products. Additionally, although the scope is limited to α-branched ketones and needs a precise study of the two chiral catalysts employed, this work represented a pioneering example of aminocatalysis using these substrates, which had been previously found unreactive against this activation mode.[30]

The proposed mechanism for this reaction is shown in Scheme 6. The reaction is expected to be initiated by activation of the ketone in an enamine activation cycle, using a protected amino acid **13** as organocatalyst. Then, the Selectfluor **1** would undergo the activation with the phosphoric acid **2a** giving rise to the anion phase-transfer catalyst. This active species generates a chiral quaternary fluorine derivative **14**. This was one of the first successful studies combining two chiral organocatalytic cycles.

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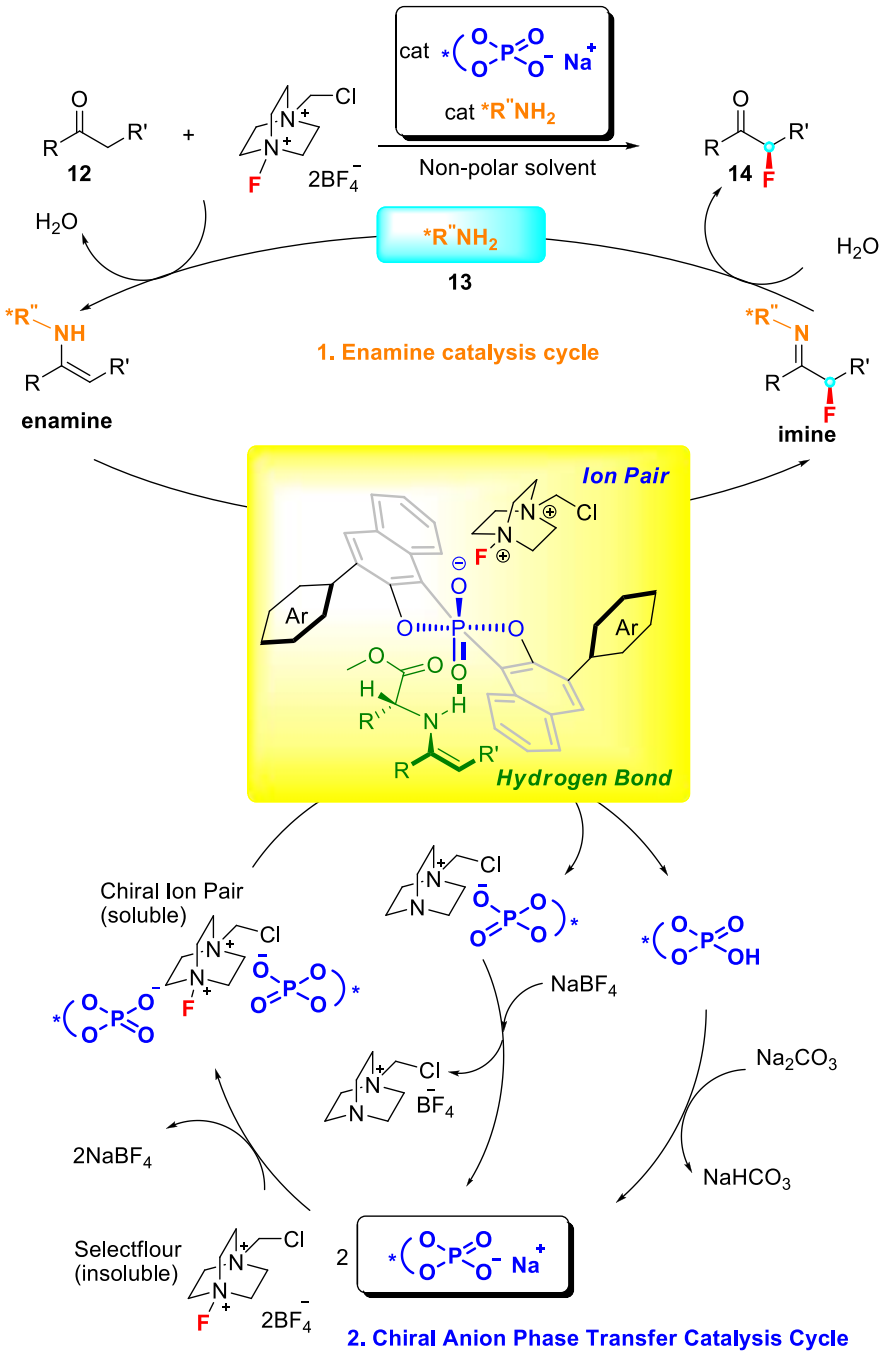

Scheme 6. Proposed catalytic cycle for the enantioselective α-fluorination of ketones **12**.

Another interesting study from the same research group was focused on the *in situ* directing group strategy for the fluorination of allylic alcohols **15** (Scheme 7).[31] The authors addressed this challenging task because the use of inactivated or weakly activated alkenes was a challenging aim,[32] since only π-activated olefins had been previously used.

Therefore, in continuation with their previous efforts concerning fluorination of double bonds[33] by a carboxamide or phenolic group at the allylic position of an alkene as a directing group, they investigated this new *in situ* directing group methodology using more fundamental and versatile substrates (Scheme 7). The authors combined their previous work[33] with a report by Falck´s group describing the use of boronic acids to promote a formal enantioselective conjugate addition of hydroxide,[34] as *in situ* directing group formed by condensation of boronic acid and alcohols **15** (Scheme 7).

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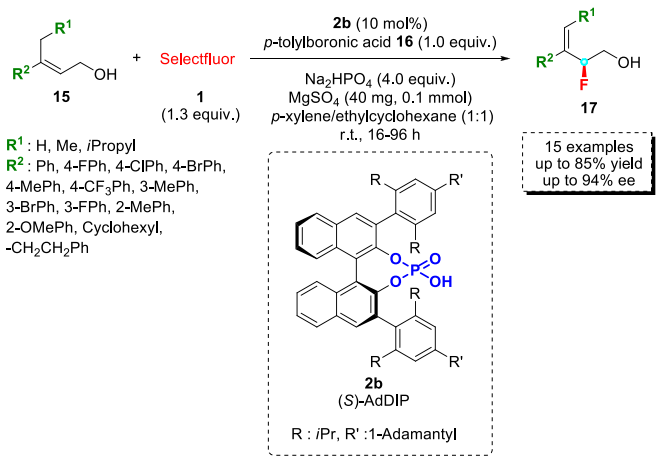
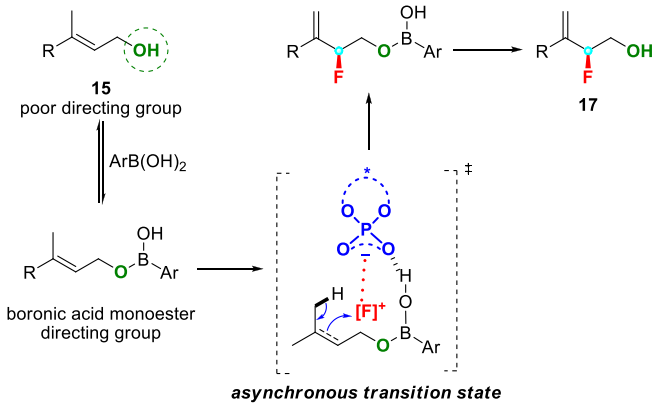


Scheme 7. Enantioselective fluorination of allylic alcohols **15** using phosphoric acid **2b**.

During the screening of the optimized reaction conditions, *p*-tolylboronic acid **16** was found to be particularly effective as the boronic acid source. Moreover, the elimination of water was necessary to shift the equilibrium in favor of the boronic ester formation. Indeed, among the different tested chiral phosphoric acids, phosphoric acid **2b** ((*S*)-AdDIP) was the best catalyst and Na_2HPO_4 was chosen as the best base to regenerate the chiral anion phase-transfer catalyst. Final fluorinated alcohols **17** were obtained in excellent yields and enantioselectivities from inactivated but synthetically versatile alcohols **15**. In fact, the process tolerated different substitutions of the alcohol **15**.

Moreover, based on more experimental information and kinetic isotope effect studies, a plausible concerted mechanism was suggested to explain the results obtained (Scheme 8).

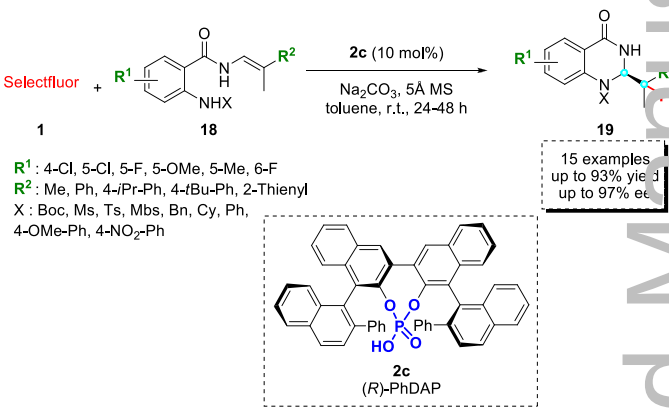


Scheme 8. Proposed concerted mechanism for the boronic acid-mediated enantioselective fluorination–elimination reaction of allylic alcohols **15**.

The authors proposed that both C–F bond formation and C–H bond cleavage occurred in a concerted enantio-determining transition state (TS, Scheme 8). Moreover, it was suggested that the cleavage of the C–H bond played an unusually important role in the asymmetric induction of this process.

More recently, Toste's group demonstrated that a double axially chiral anionic phase-transfer **2c** was able to promote the regioselective asymmetric fluorocyclization reaction of **18** under mild reaction conditions (Scheme 9).[35,36] This idea was founded on previous enamide fluorination methodologies developed by the same group.[27,37]

With this interesting idea in mind, a protocol for the asymmetric synthesis of two families of pharmaceutically privileged scaffolds **19**, dihydroquinazolone and benzooxazinone derivatives, was developed. Different substitutions of the enamide scaffold **18** reacted with Selecfluor **1** in the presence of Na_2CO_3 at room temperature, affording a broad scope of products with moderate to good yields and high enantioselectivities (Scheme 9). Furthermore, unsymmetrically substituted enamides were also employed and the expected products were obtained with excellent diastereoselectivities and moderate enantioselectivities (>20:1 dr, 57-87% ee).



Scheme 9. Enantioselective synthesis of fluoro–dihydroquinazolones and –benzooxazinones **19**.

In this field, this research group has put forth great effort into the development of other successful fluorination processes and many other pivotal examples have been reported.[38]

2.2 Carboxylic acids as precatalysts

Based on the previous work reported by Toste and co-workers, Hamashima's group described the first successful example of a highly enantioselective fluorolactonization process catalyzed by a bifunctional organocatalyst derived from carboxylic acid, as a novel family of phase-transfer catalysts (Scheme 10).[39,40] The bifunctional catalyst **21** was designed on the base of two important considerations: 1) to efficiently transfer the fluorinated agent **1** into the liquid phase, and 2) to undergo an associative interaction with the anionic substrate with the aim of inducing chirality. For this purpose, the catalyst **21**

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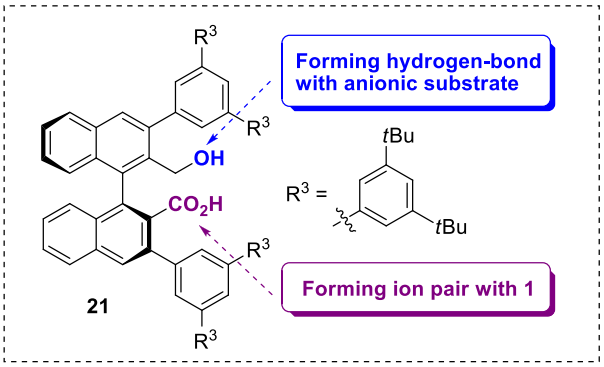
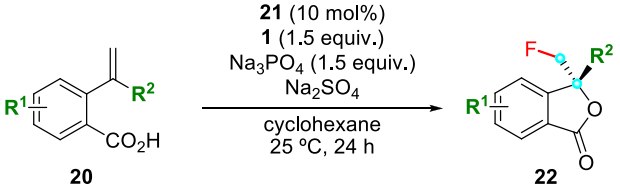
was built with a carboxylate group as an anionic moiety to form an ion pair with **1** and a OH group as hydrogen-bond donor to coordinate the anionic reagent.





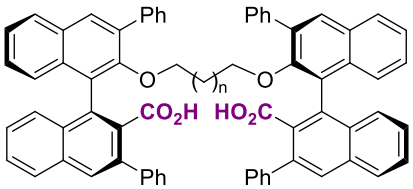
22a R^1 = H, R^2 = Ph: 99% yield, 88% ee
22b R^1 = 5-Me, R^2 = Ph: 65% yield, 94% ee
22c R^1 = 5-OMe, R^2 = Ph: 63% yield, 90% ee
22d R^1 = 3-F, R^2 = Ph: 99% yield, 88% ee
22e R^1 = 4-F, R^2 = Ph: 99% yield, 84% ee
22f R^1 = 5-Cl, R^2 = Ph: 85% yield, 91% ee
22g R^1 = 5-Br, R^2 = Ph: 77% yield, 90% ee
22h R^1 = H, R^2 = 4-MePh: 65% yield, 70% ee
22i R^1 = H, R^2 = 4-OMePh: 42% yield, 83% ee
22j R^1 = H, R^2 = 4-FPh: 85% yield, 86% ee
22k R^1 = H, R^2 = 3-FPh: 53% yield, 84% ee
22l R^1 = H, R^2 = 2-thienyl: 80% yield, 82% ee
22m R^1 = H, R^2 = Cyclopropyl: 78% yield, 44% ee
22n R^1 = H, R^2 = Cyclohexyl: 40% yield, 78% ee

Scheme 10. Scope of the enantioselective fluorolactonization reaction catalyzed by bifunctional catalyst **21**.

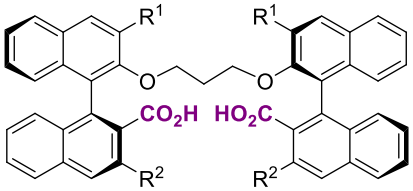
Fluorolactonization reaction using ene-carboxylic acids **20** worked smoothly giving rise to the corresponding fluorinated isobenzofuranones **22** in good yields (up to 99%) and with high to excellent enantioselectivities (up to 94%).

Additional experimental results using different structural analogues of catalyst **21** supported the necessity of both moieties (the carboxylate anion and the OH group) to provide the best chiral induction. The experimental results also agreed with the bifunctional role of the catalyst proposed by the authors, keeping in a concomitant coordination the substrate **20** as anion and the cationic fluorinating reagent in a chiral cavity.

Based on these initial results, the authors hypothesized that the cooperative action of two carboxylate anions situated with an appropriate distance in the precatalyst structure should provide higher reaction efficiency. For this purpose, the authors designed and synthesized a number of dicarboxylic acid precatalysts (Figure 4).[41,42]



24a: n = 1
24b: n = 2
24c: n = 3



24d: R^1 = H, R^2 = Ph
24e: R^1 = H, R^2 = H

Figure 4. Dicarboxylic acid derivatives **24**.

Then, the authors explored the efficiency of such structures in the unprecedented 6-*endo* fluorocyclization reaction of allylic amides described in Scheme 11 and Scheme 12.

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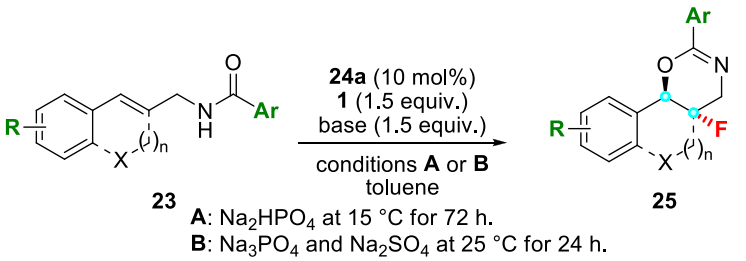
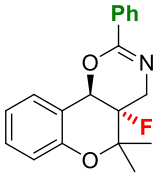
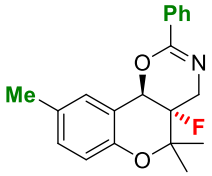


23 **25**

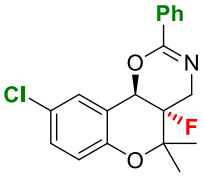
A: Na_2HPO_4 at 15 °C for 72 h.
B: Na_3PO_4 and Na_2SO_4 at 25 °C for 24 h.



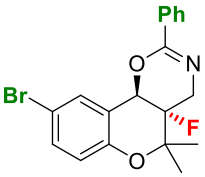
25a (**A**): 87% yield, 81% ee



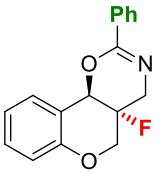
25b (**A**): 87% yield, 81% ee



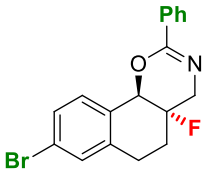
25c (**A**): 80% yield, 90% ee



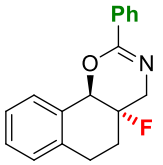
25d (**A**): 52% yield, 89% ee



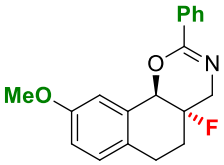
25e (**A**): 82% yield, 91% ee



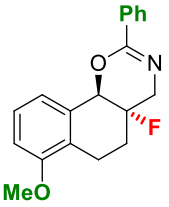
25f (**A**): 58% yield, 89% ee



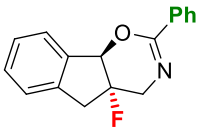
25g (**A**): 48% yield, 94% ee



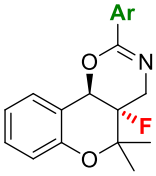
25h (**B**): 55% yield, 95% ee



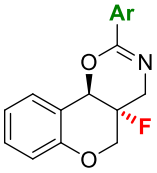
25i (**A**): 56% yield, 98% ee



25j (**A**): 63% yield, 93% ee



25k R = 4-$CO_2MeC_6H_4$ (**A**): 53% yield, 94% ee
25l R = 4-$MeOC_6H_4$ (**A**): 53% yield, 89% ee



25m R = 4-BrC_6H_4 (**A**): 64% yield, 93% ee
25n R = 4-$MeOC_6H_4$ (**A**): 55% yield, 81% ee

Scheme 11. Scope of 6-*endo* fluorocyclization reaction using cyclic allylic amides **23**.

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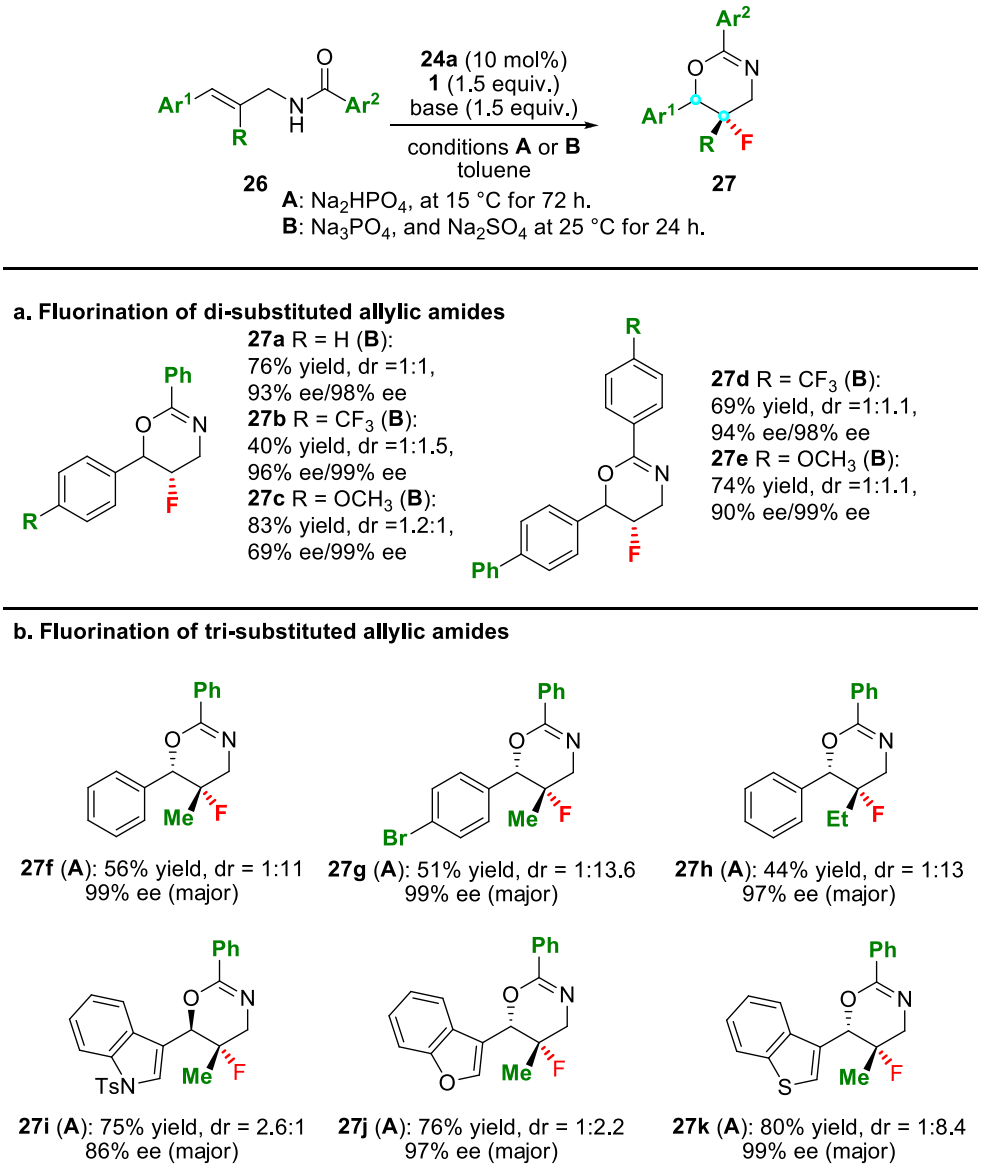

Scheme 12. Scope of 6-*endo* fluorocyclization reaction using acyclic allylic amides **26**.

Therefore, the authors were able to perform 6-*endo* fluorocyclization reactions with high enantioselectivities (up to 99%) and the new developed family of dianionic phase transfer catalysts could efficiently control the fluorine delivery step for this variety of substrates.

Using the same dicarboxylic acid precatalysts **24a** and more recently, Hamashima's group has developed two additional works. One of them is based on the development of an enantioselective 5-*exo*-fluorocyclization of ene-oxime compounds[43] and the most recent one is an asymmetric dearomative fluorination of 2-naphthols.[44] In all cases, the catalytic species is formed by a dicarboxylate dianion generated *in situ* by deprotonation of **24** and Selectfluor (**1**), allowing the transfer of **1** from the solid phase to the liquid phase giving rise to a chiral Selectfluor species as described in Figure 5.

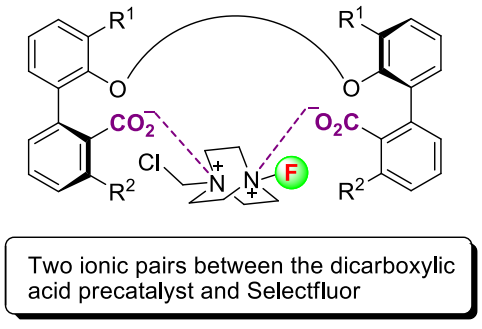

Figure 5. Proposed catalytic species formed by two ionic pairs.

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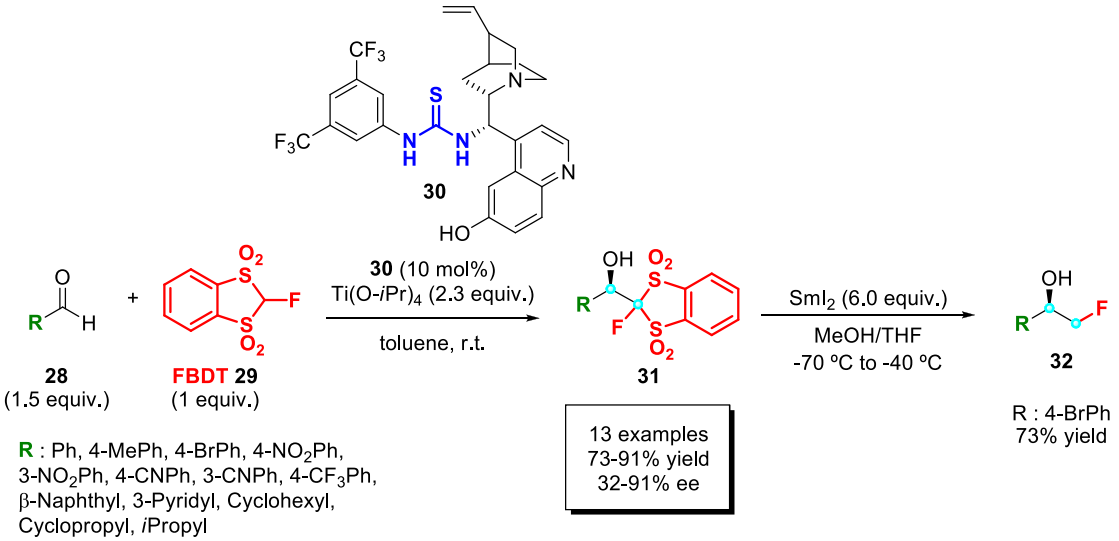
3 (Thio)urea derivatives as organocatalysts for asymmetric fluorination reactions

3.1 Chiral thiourea catalysts

In the field of thiourea organocatalysts,[45] Shibata and coworkers pioneered an organocatalytic procedure to fluoromethylate aldehydes.[46] Among the different strategies to achieve asymmetric fluorination, 2-fluoro-1,3-benzodithiole-1,1,3,3-tetraoxide (**29**, FBDT) was selected as the source of fluorine, based on their previous knowledge using this substance.[47] The authors envisioned that a tandem between a chiral thiourea **30** and a titanium complex as a Lewis acid could activate the aldehyde, affording the desired compounds **31** (Scheme 13).



Scheme 13. Organocatalytic asymmetric procedure developed by Shibata and coworkers.

On the first step of the reaction, the addition of FBDT **29** to the aldehydes **28** promoted by the cinchona-thiourea-Ti(O*i*Pr)$_4$ tandem would take place. The authors suggested that the extra hydrogen bond created by the –OH group in the quinoline moiety improves the selectivity of the process. This way, they obtained a scope of 13 compounds **31** using aromatic and aliphatic aldehydes **28** with moderate to good yields (73-91%) and enantioselectivities (32-91%). However, aliphatic aldehydes seemed to produce lower selectivities than their aromatic counterparts. Furthermore, to test their global hypothesis, the authors performed a C–S bond cleavage mediated by SmI_2 to obtain a final fluoromethylated alcohol **30** with a 73% yield. Finally, a derivatization process took place to obtain a single crystal and the measurement of the absolute configuration of the products afforded the enantiomer *R*. To the best of our knowledge, this is the pioneering and only example of a fluoromethylation reaction promoted by non-covalent organocatalysis.[48] Although the authors did not clarify completely the reaction mechanism, they successfully proved that hydrogen bonding is of utmost importance to enhance the selectivity of the process, obtaining the desired products **31** with good values of yield and trifluoromethylthiolation.

Focusing now on electrophilic monofluorination reactions, Hu and coworkers reported in 2012 the pioneering example of a cinchona-thiourea derivative capable of catalyzing the enantioselective fluorination of β-ketoesters (Scheme 14).[49]

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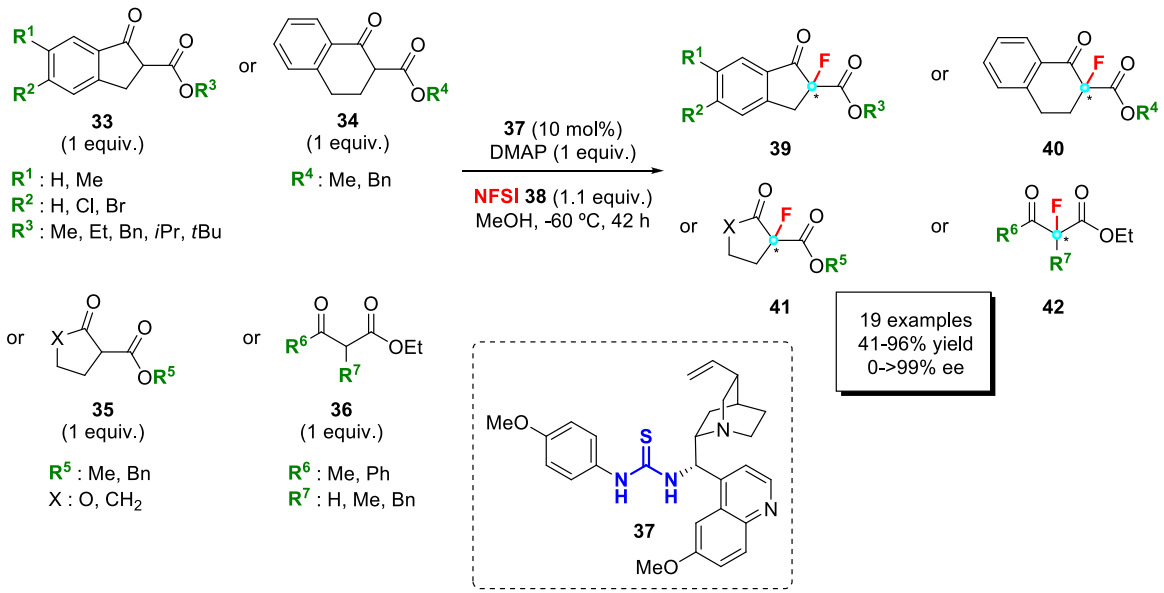

Scheme 14. Thiourea-catalyzed enantioselective fluorination of β-ketoesters **33**-**36**.

The reaction was conducted with indanone **33**, tetralone **34** and cyclopentanone **35** carboxylate derivatives and with acyclic β-ketoesters **36** as the model substrates. These compounds have been previously involved in other fluorination reactions with different catalytic systems.[50] *N*-Fluorodibenzenesulfonimide (**38**, NFSI) was used as a fluorine source and the process was promoted by the cinchona-thiourea derivative **37** using 4-dimethyl aminopyridine (DMAP) as an additive. The reaction proceeded smoothly in most cases. However, no or very low selectivity was observed when an extremely bulky substituent was placed on the ester and in the cases where a tetralone derivative **34** was used. On the other hand, acyclic substrates **36** had high variability in their results. Overall, the reaction produced a high number of examples with good diversity, moderate to excellent yields (41-96%), and no to excellent enantioselectivities (0->99%).

On the base of all experimental results, the authors also reported a mechanistic proposal depicted in Scheme 15.

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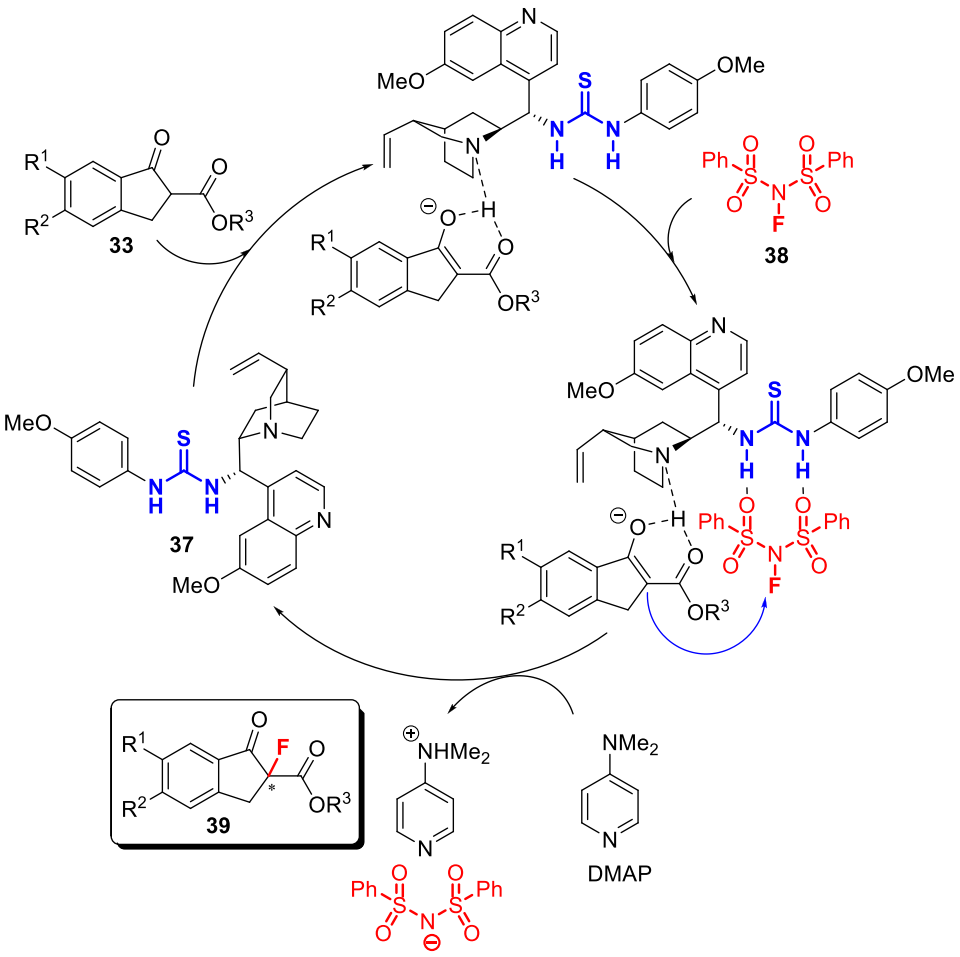
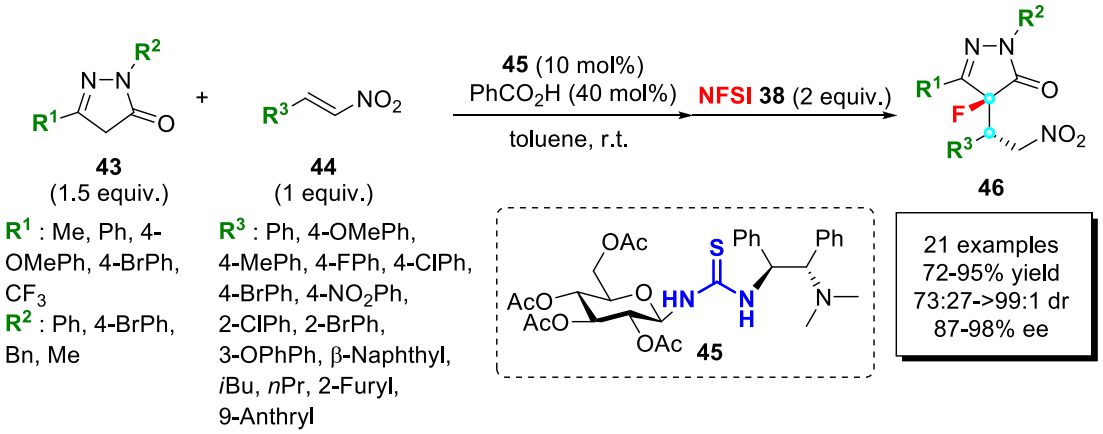


Scheme 15. Reaction mechanism proposed for the enantioselective fluorination of β-ketoesters **33-36** catalyzed by thiourea **37**.[51]

As is shown, first the basic center of the thiourea **37** would activate the β-ketoester **33**. Then, NFSI **38** would be activated in the acidic site of the thiourea, making the reaction to take place. Then, the basic additive would take the leftover proton to stabilize the dibenzenesulfonimidate, closing the cycle. The authors did not provide further insight into the absolute configuration of the products.

Ma and coworkers developed, in two related works in 2012 and 2013, a one-pot sequential 1,4-addition/dearomative-fluorination transformation.[52] This methodology proceeded with the addition of pyrazolone **43** or isoxazolone **47** derivatives to nitroalquenes **44** followed by the fluorination with NFSI **38**. On the first methodology, the authors used the thiourea derivative **45** to catalyze the full process based on previous works concerning thiourea-saccharide catalysts of the same group (Scheme 16).[53]



Scheme 16. One-pot synthesis of the fluorinated pyrazolone derivatives **43**, promoted by the thiourea **45**.

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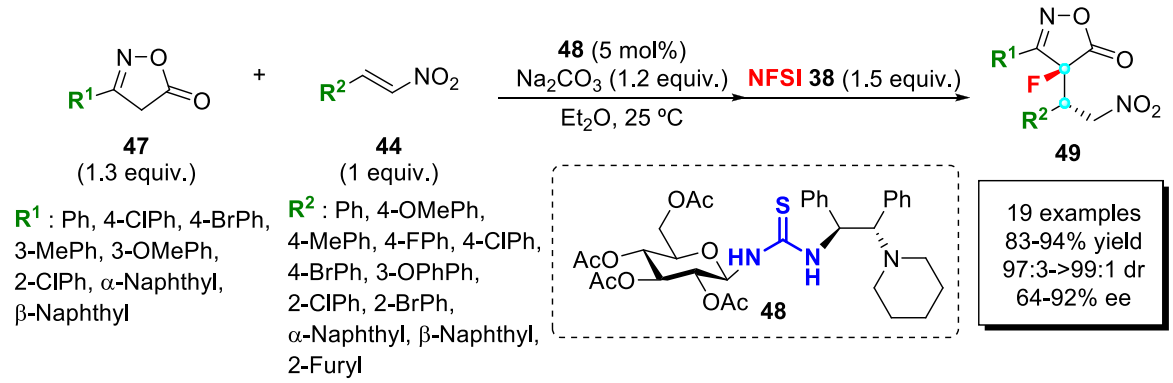
On the first step of the process, the *trans*-β-nitrostyrene derivative **44** would be activated by the thiourea **45** and the 1,4-addition of the pyrazolone derivative **43** would take place. Then, the fluorination with NFSI **38** would be carried out. Moreover, a weak Brønsted acid improved the results, though a 40% loading was needed. The protocol provided a broad scope of products **46**, including aliphatic examples, achieving good to excellent yields (72-95%), moderate to excellent diastereoselectivities (73:27->99:1) and good to excellent enantioselectivities of the major isomer (87-98%).

In the second work, the developed procedure is very similar to the first one. In this case, the chiral thiourea **48** catalyzed the addition of the isoxazolone derivative **47** (Scheme 17).



Scheme 17. One-pot synthesis of the fluorinated isoxazolone derivatives **49** promoted by the thiourea **48**.

The main differences with the previous work were a better overall atom economy, lower catalyst loading (5 - 10 mol%), different solvent (Et_2O - toluene) and the absence of aliphatic examples. Interestingly, the results were improved by the addition of a weak Brønsted base (Na_2CO_3) instead of an acid ($PhCO_2H$). With this setup, this approach provided a similar number of products with better overall yields (83-94%) and diastereomeric ratio (97:3->99:1), but slightly worse enantioselectivities (64-92%).

Due to the similarity of the reactions, only the key steps of the mechanism proposals are depicted in Figure 6.

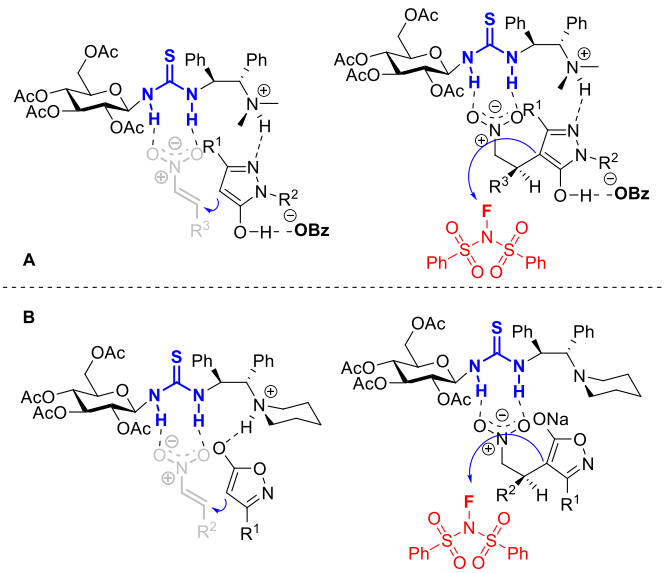


Figure 6. 1,4-Addition and fluorination steps of the processes developed by Ma and coworkers.[54] **A** = pyrazolone derivatives **46**. **B** = isoxazolone derivatives **49**.

Section **A** explains the important role played by the Brønsted acid additive. First, it would protonate the basic moiety of the catalyst to establish a hydrogen bond with the pyrazolone **43**. Then, the counterion would force a tautomerization from the keto to the enolic form of the pyrazolone derivative **43** for the addition to be carried out. The same tautomerization occurs to facilitate the fluorination step. As depicted in section **B**, despite the additive not taking part in the first step, it was essential in the fluorination step to deprotonate the isoxazolone **47** and to promote the attack to the fluorine source.

These two works are an interesting example of the cooperative behavior between a non-covalent organocatalyst and its potential additives, being basic or acid. In spite of the complexity of the system involved, the developed procedures led to the desired products with very good results.

The last thiourea catalyzed fluorination process was reported by Yi, Zhang and coworkers in 2013.[55] They developed a one-pot fluorination and asymmetric Michael addition promoted by recyclable fluorinated organocatalyst **50**. In this work, the authors explored the thiourea catalyst **50** bearing a perfluorinated alkylic chain to make it recoverable (Scheme 18).

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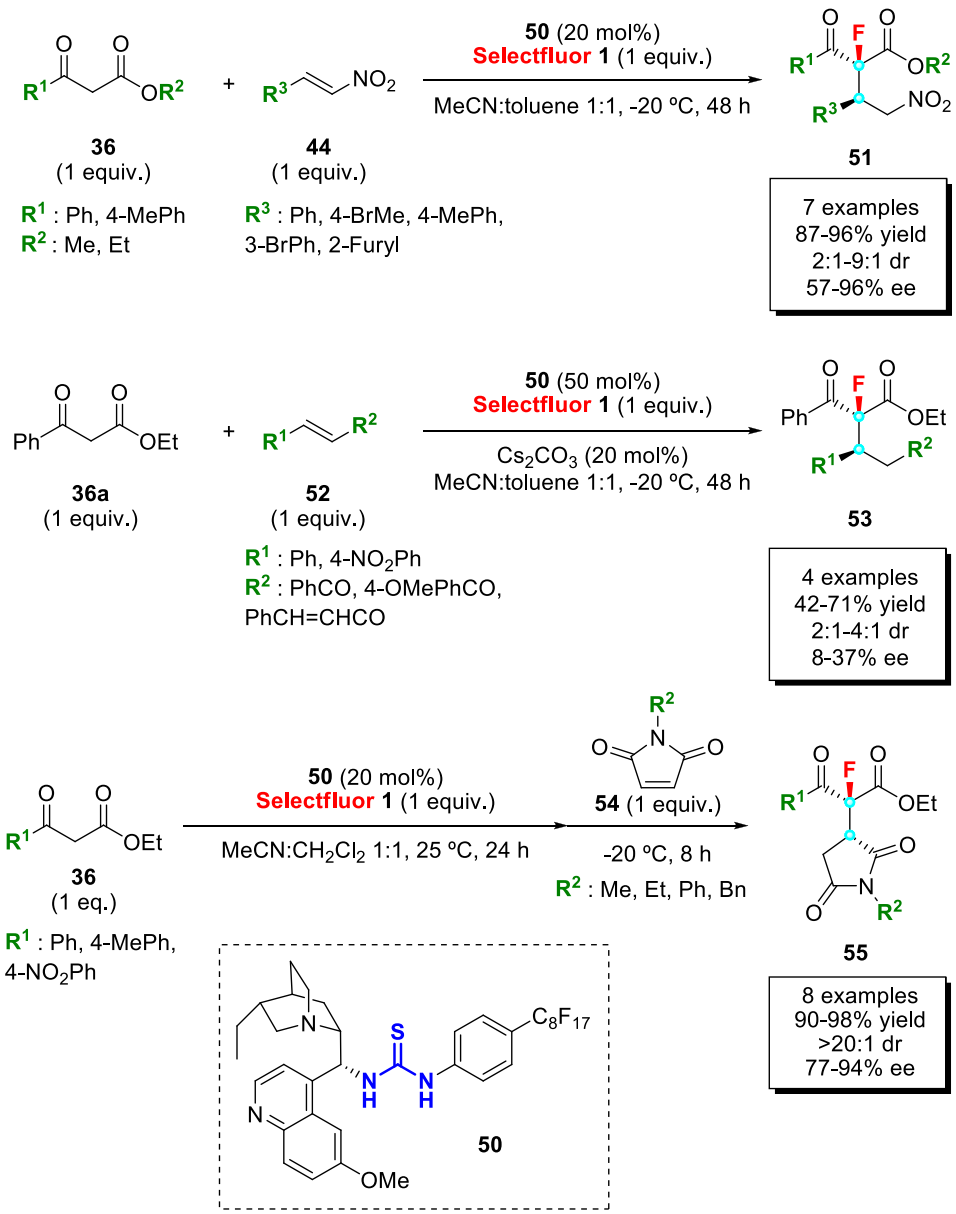

Scheme 18. Enantioselective one-pot asymmetric Michael addition and fluorination of β-ketoesters **36**.

As the fluorinating agent, the authors chose Selectfluor **1**. They used a series of β-ketoesters **36** and explored their Michael addition to nitroalkenes **44**, chalcone **52** and maleimide **54** derivatives and further fluorination of the resulting intermediates. The reaction with nitroalkenes **44** proceeded with good to excellent yields (87-96%), moderate to good diastereoselectivities (2:1-9:1) and moderate to excellent enantiomeric excesses (57-96%) to obtain seven different products **51**. However, when a chalcone derivative **52** was used as a Michael acceptor the results were a bit worse (4 examples, 42-71% yield, 2:1-4:1 dr, 8-37% ee), even using higher catalyst loadings (20-50 mol%) and adding Cs_2CO_3 as an additive. In contrast, the fluorination of the β-ketoesters **36** followed by their addition to the maleimide derivatives **54** produced 8 different examples with excellent yields (90-98%), diastereoselectivities (>20:1) and good to excellent enantioselectivities of the major isomer (77-94%).

Moreover, as expected, the recovery of the catalyst **50** by fluorous solid-phase extraction (F-SPE)[56] was successful. Additionally, the use of the recovered catalyst in a further process yielded the same results as before. This fact means that no appreciable poisoning of the catalyst took place, at least, in 2 cycles of reaction.

3.2 Chiral urea catalysts

Generally, urea derivatives are not explored as extensively as their thiourea counterparts.[57] This fact could be explained by the generally superior performance of thioureas because of their higher acidity[58] and lesser self-aggregation.[59] Still, there is a similar number of examples of ureas and thioureas

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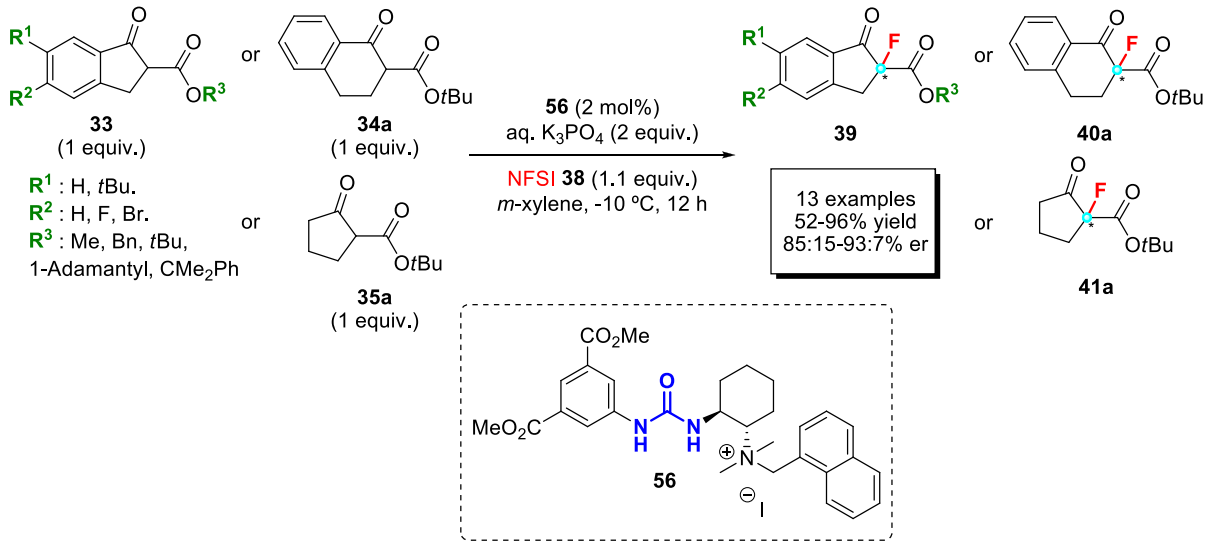
catalyzing direct asymmetric fluorination reactions in the literature.

Firstly, in 2014, Waser and coworkers developed the pioneering example in this field, performing the fluorination of indanone **33**, tetralone **34a** and cyclopentanone **35a** carboxylate derivatives, using NFSI **38** as the source of fluorine (Scheme 19).[60]



Scheme 19. Enantioselective fluorination of β-ketoester **33-35** catalyzed by chiral urea **56**.

The authors successfully used the urea derivative **56** to obtain a broad scope of products with moderate to excellent yields (52-96%) and good to very good enantioselectivities (85:15-93:7). However, the use of the tetralone **34a** and cyclopentanone **35a** derivatives afforded slightly lower values (73% yield 87:13 er and 66% yield 89:11 er respectively). It should be highlighted that the process included aqueous K_3PO_4 as an additive. Furthermore, the authors proposed a plausible mechanism for the reaction, depicted in Figure 7.

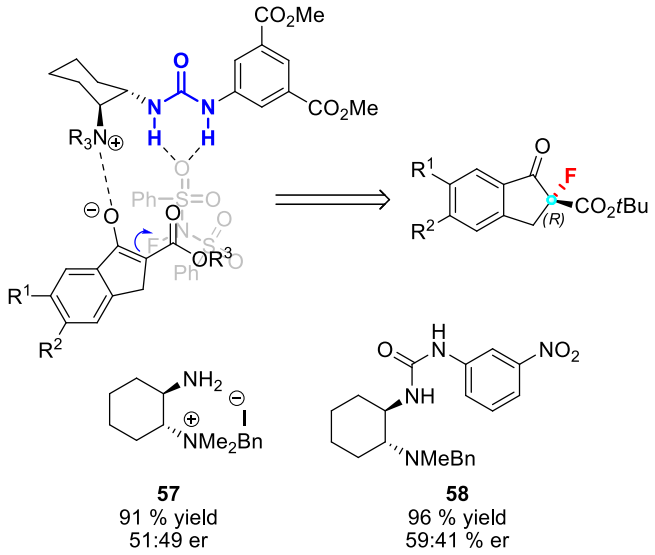


Figure 7. Transition state proposed to explain the absolute configuration observed.

Following the proposed mechanism, the amine of the catalyst would drive the attack to the NFSI **38** fixed in the acidic site of the urea by the *Re* face, affording the absolute *R* configuration observed in all final products. In addition to that, the proposal showed the importance of the catalyst-enolate electrostatic interaction and this statement was supported with two supplementary experiments with a catalyst without the urea moiety **57** and without the charged amine **58**, giving rise to poorer selectivities (51:49 and 59:41 er respectively).

Based on the previous report,[60] Shi and coworkers developed in 2016 a new protocol in which they were able to support a similar catalyst **59** on polyethylene glycol (PEG). This approach makes it easy to recover the catalyst by precipitation in diethyl eter,[61] still being able to operate in homogeneous conditions. This catalyst was also used to carry out the enantioselective fluorination of β-ketoesters **33-36** (Scheme 20).[62]

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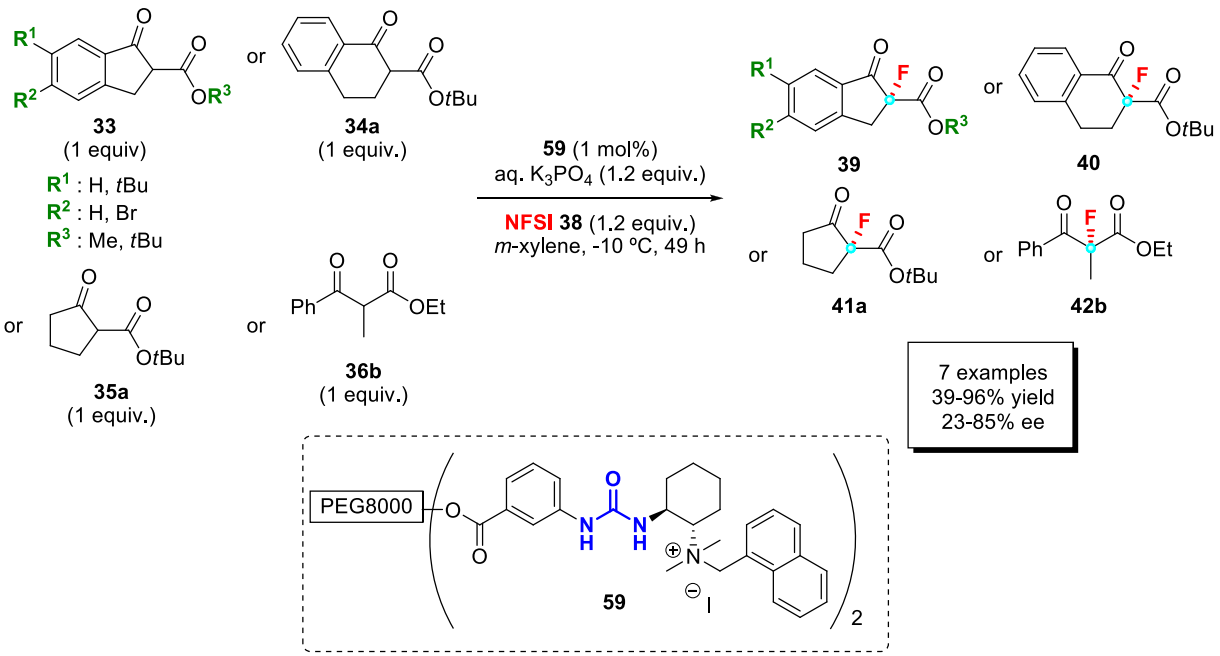
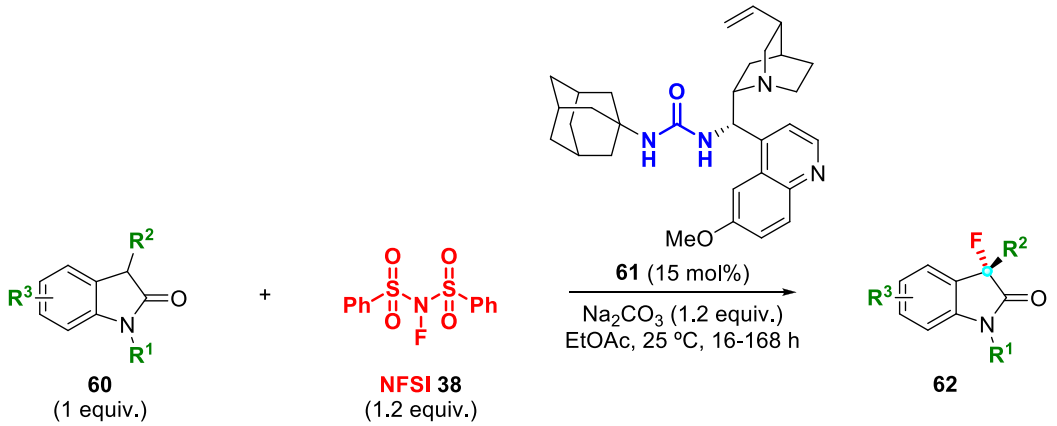


Scheme 20. Enantioselective fluorination of β-ketoesters **33-36** catalyzed by the supported urea catalyst **59**.

Under these conditions, the authors were able to perform the reaction using NFSI **38** as the fluorine source with indanone **33**, tetralone **34a** and cyclopentanone **35a** carboxylate derivatives and the β-ketoester **36b**. Furthermore, they were able to halve the catalyst loading used before to achieve moderate to excellent yields (39-96%) and moderate to good selectivities (23-85%). However, using the β-ketoester **36b** produced a lower yield (39%) and enantiomeric excess (23%). Additionally, the authors proposed that the absolute configuration of the products would be *R* by comparison with previously reported optical rotation values and retention times.[63]

In 2018, Jiang, Yeung and coworkers developed a method to perform the enantioselective fluorination of 3-substituted oxindole derivatives (Scheme 21).[64]



R1 : H, Me, Et, Ph, Allyl, Proparyl, $CH_2CHC(CH_3)_2$, $CH_2C(CH_3)CH_2$.
R2 : Me, Ph, Allyl, CH_2CN, $(CH_2)_2NHBoc$, $(CH_2)_2NHTs$, $(CH_2)_2OH$, $(CH_2)_3OH$, CH_2 COOMe, $CH_2CONHMe$, (*S*)-$CH_2CH(COOMe)(NHBoc)$, (*R*)-$CH_2CH(COOMe)(NHBoc)$.
R3 : H, 4-Me, 5-Me, 6-Me, 7-Me, 6-F, 5-Cl, 5-Br, 6-Br, 5-OMe.

Scheme 21. Enantioselective fluorination of oxindole derivatives **60**.

The reaction proceeded smoothly using urea **61** as the catalyst and NFSI **38** as the fluorine source in the presence of Na_2CO_3. Differently substituted oxindole derivatives **60** underwent the catalysis, obtaining 30 examples with moderate to excellent yields (51-99%) and selectivities (82:18-97:3). Both *N*-protected and unprotected oxindole derivatives (which had been less explored in the past)[65] could be used in this process with no drawbacks. However, unprotected oxindole derivatives needed overall longer reaction

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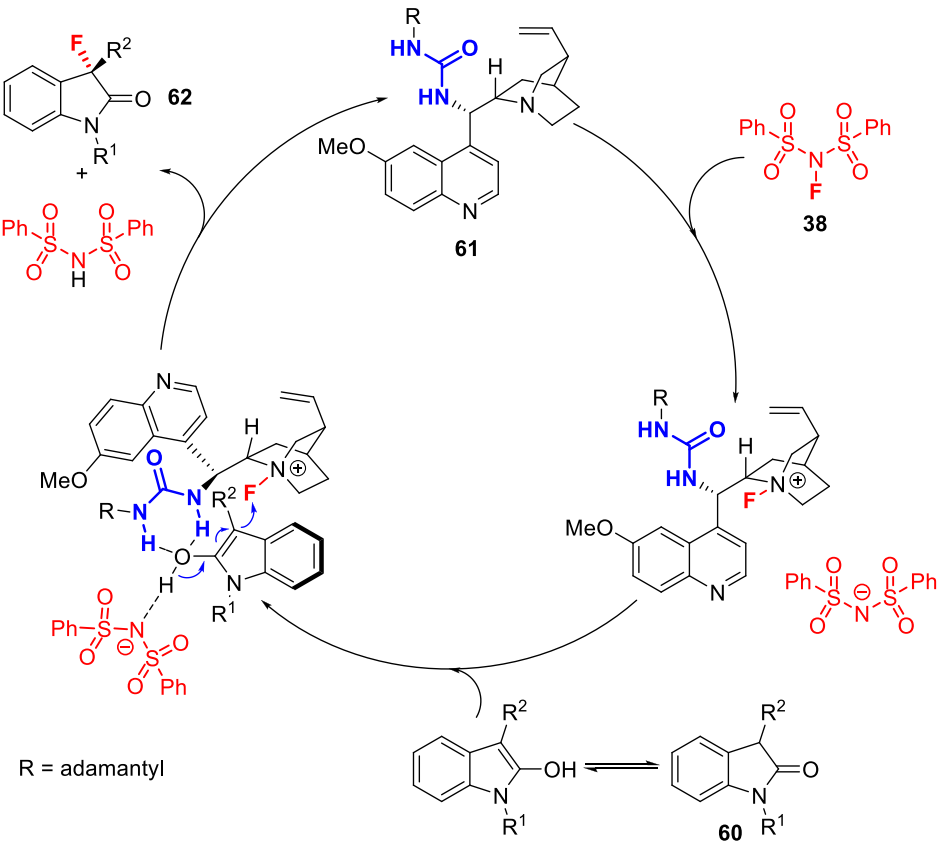
times and 3-aryl substituted ones yielded to the worst results in terms of enantioselectivity (82:18).

Furthermore, the authors proposed the following reaction mechanism (Scheme 22).

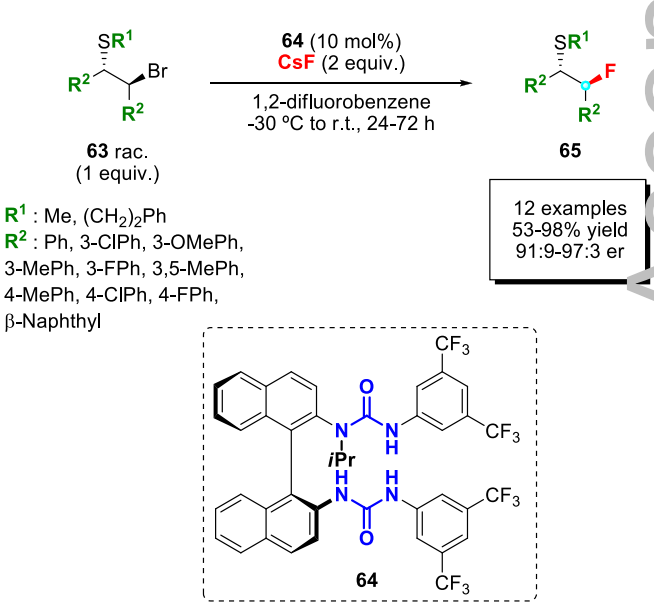


Scheme 22. Reaction mechanism proposed for the enantioselective fluorination of oxindole derivatives **60** catalyzed by urea **61**.

In the first step, catalyst **61** would subtract the fluorine atom from the NFSI molecule. Then, the oxindole derivative would coordinate with the urea moiety, and the remaining benzenesulfonimidate would launch the nucleophilic attack to produce the enantioselective fluorination. It is worth noting that urea **61** lacks a traditional electron-withdrawing group such as 3,5-bis(trifluoromethyl)phenyl; instead, the authors speculated that having an adamantly group would provide an optimal steric environment for the process to take place. In addition to that, using single-crystal X-ray diffraction, the authors were able to assign the absolute configuration of the products, being it *S*.

Lastly, Gouverneur and coworkers reported, in three consecutive works in 2018, 2019 and 2020, a new prospect using solid fluoride salts as the nucleophilic fluorine source. Since electrophilic fluorination reagents are predominant in this field as shown in this review, these are the only examples of nucleophilic fluorination using this kind of catalysts, given that the use of such reactants is highly problematic. Moreover, the authors envisioned that a urea derivative should be able to coordinate the F^- ion, taking it into an organic solution from the solid source. To prove the previous hypothesis, they investigated the use of a urea-fluoride complex to achieve a nucleophilic substitution reaction with alkyl bromides.[66]

In the first reported work, β-bromosulfides **63**, as reactants, and solid CsF, as the fluorine source, were employed and the process is depicted in Scheme 23.[67]



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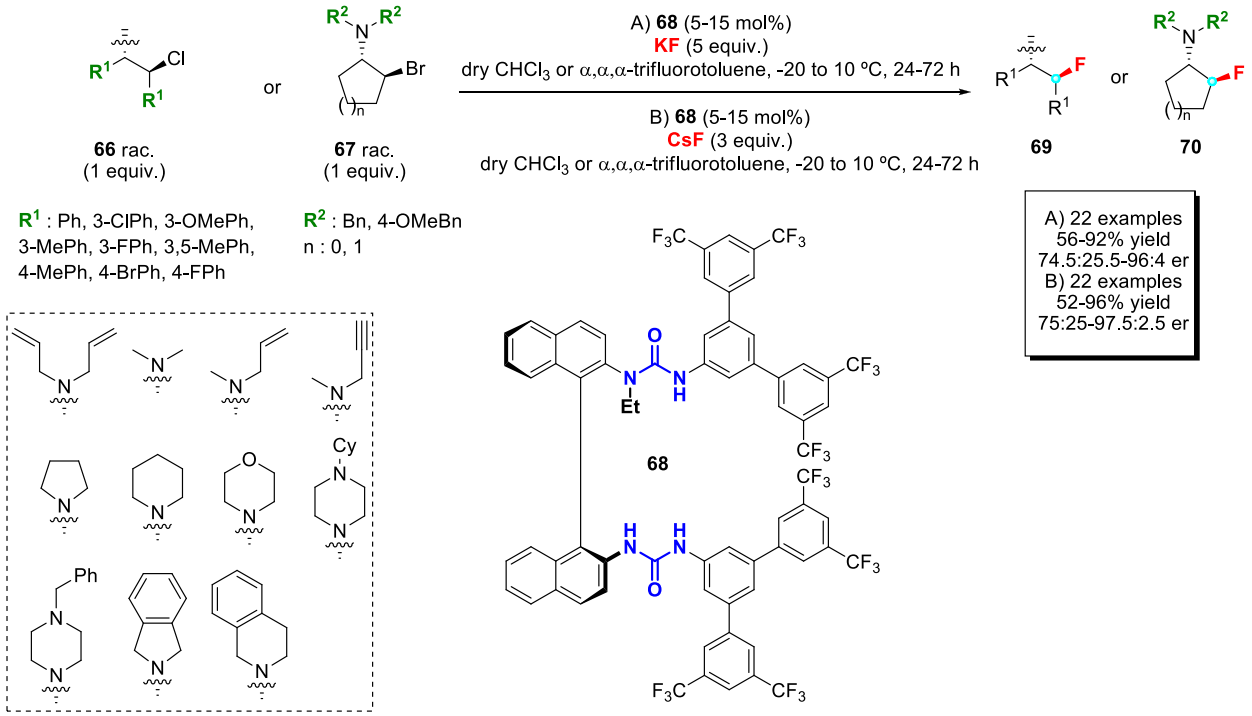
Scheme 23. Enantioselective nucleophilic fluorination of β-bromosulfides **63**.

The reaction proceeded smoothly in 1,2-difluorobenzene to afford a broad scope of products **65** with moderate to excellent yields (53-98%) and good to excellent selectivities (91:9-97:3).

In the second crucial work, β-haloamines **66** and **67** were selected as reactants (Scheme 24).[68]



Scheme 24. Enantioselective nucleophilic fluorination of β-haloamines **66** and **67**.

In this work, the procedure was adapted using a different catalyst **68**, $CHCl_3$ or α,α,α-trifluorotoluene as solvents and either solid KF or CsF as fluorine sources in two twin methodologies. With these two catalytic systems, the authors were capable of obtaining a huge number of compounds with similar results, with moderate to excellent yields (A = 56-92%; B = 52-96%) and selectivities (A = 74.5:25.5-96:4; B = 75:25-97.5:2.5).

In addition to that, the authors explained why β-bromosulfides **63** and β-haloamines **66** and **67** were selected as substrates to explore the reaction. These works were inspired by the ring opening reactions of aziridinium and episulfonium salts previously developed by Jacobsen and Toste.[69] These studies came along with a mechanistic proposal supported by theoretical calculations (Scheme 25).

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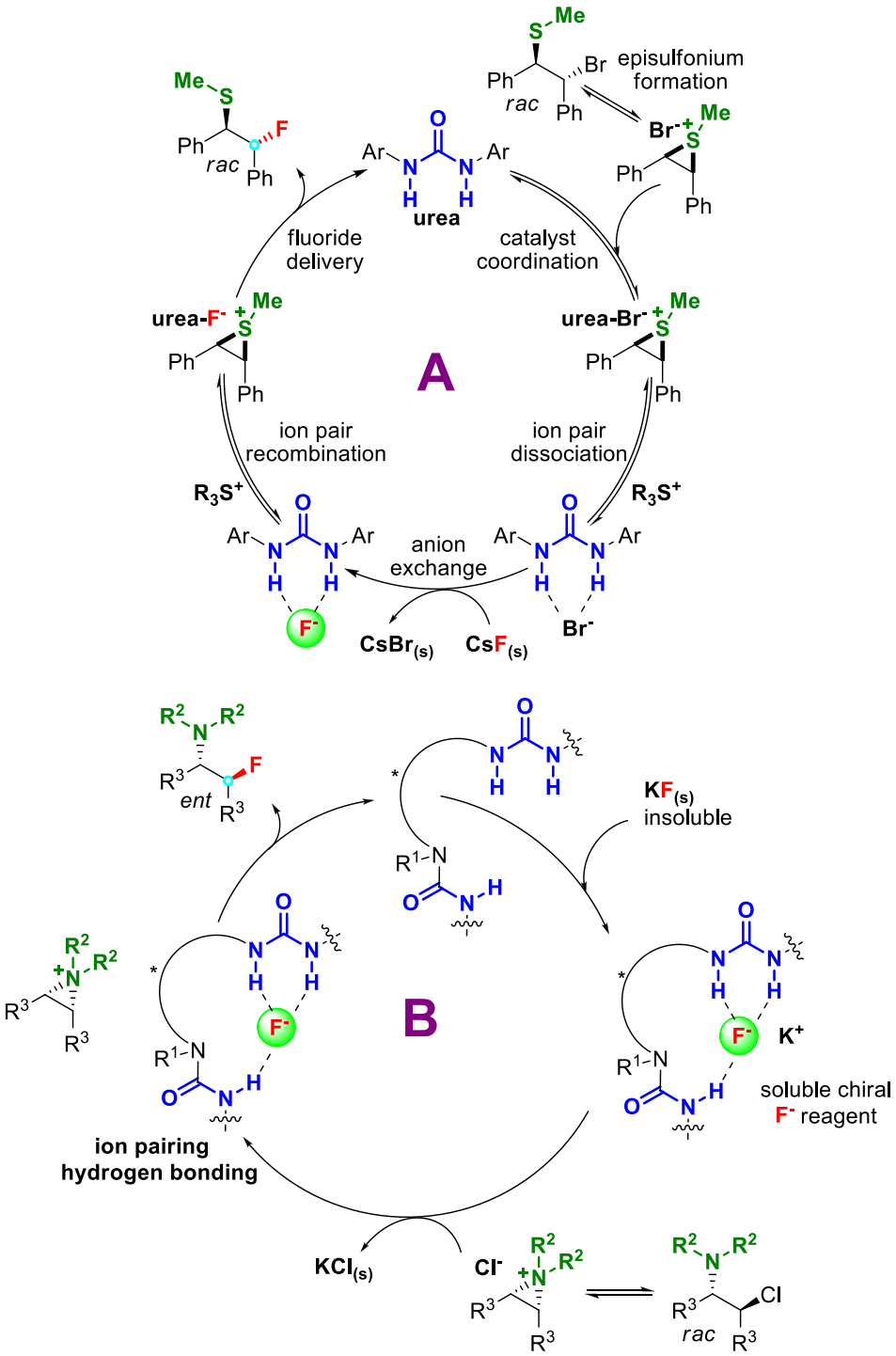

Scheme 25. Mechanistic proposal to explain the nucleophilic fluorination reactions. First work (mechanism **A**) and second one (mechanism **B**).

In these proposals, the first one (**A**) being a racemic approach, the key step was the ability of the β-bromosulfides **63** and β-haloamines **66** and **67** to form episulfonium and aziridinium ions, respectively, to receive a further nucleophilic additions. The urea catalysts **64** or **68** would subtract an F^- ion from the solid phase forming a complex and entering the organic phase. After that, the β-bromosulfides **63** or β-haloamines **66** and **67** would enter the cycle and undergo the diastereoselective nucleophilic addition to yield the desired products. Furthermore, the authors gave an *S*,*S* absolute configuration for the products based on single-crystal X-ray diffraction.

Lastly, in their most recent methodology, the authors explored the desymmetrization of achiral azetidinium salts, inspired by a previous work of Sun and coworkers.[70] This approach could produce γ-fluoroamines, an important target in medicinal chemistry.[71] The scope of this interesting reaction is summarized in Scheme 26.[72]

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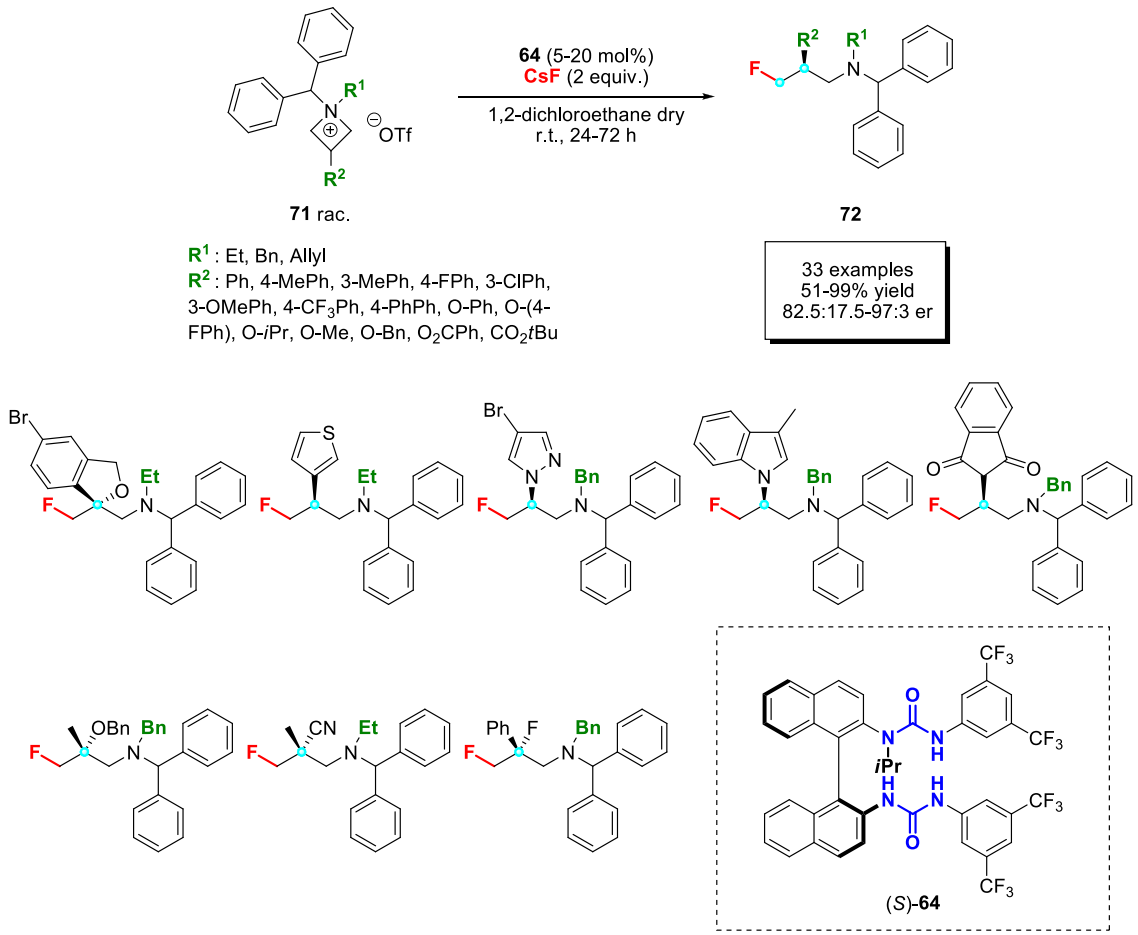


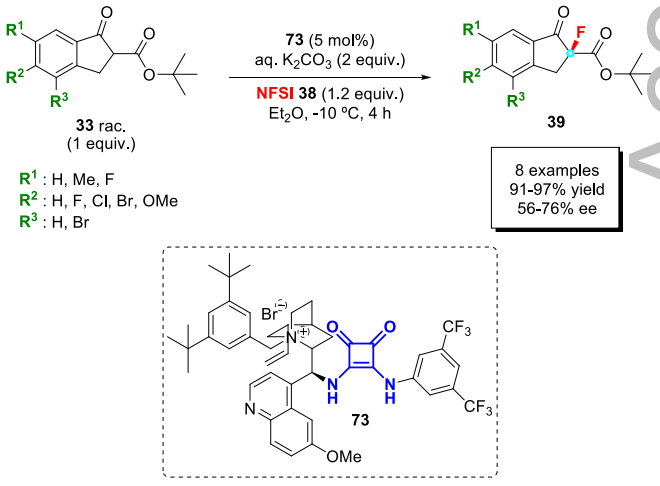
Scheme 26. Desymmetrization of azetidinium salts **71**.

The reaction was driven by urea **64**, using CsF as the fluorine source to produce the aperture of the racemic azetidinium salts **71**. In a first exploration of the ideal substituents, the authors found that the benzhydryl group was decisive to obtain good results. Therefore, modifying other groups, the authors were able to obtain 33 examples with moderate to excellent yields (51-99%) and good to excellent selectivities (82.5:17.5-97:3 er). Nevertheless, alkylated compounds at position 3 and those with heteroaromatic substituents were slightly less successful. To conclude, using single-crystal X-ray diffraction, the authors were able to assign the absolute configuration *S* to the products.

4 Chiral Squaramides as Organocatalysts for Asymmetric Fluorination Reactions

Squaramides have gained great relevance in non-covalent organocatalysis, generally outperforming urea, thiourea and guanidine derivatives. They are capable of establishing stronger hydrogen bonds, with better angles to activate carbonyl groups and a lesser tendency to form aggregates than their predecessors.[16] Due to these properties, squaramide derivatives have been also explored as suitable catalysts in direct asymmetric fluorination reactions.[73]

In 2015, the first example of this kind of procedure was reported by Lin, Duan and coworkers. Inspired by previous procedures in which urea and thiourea derivatives were used (as described in section 3), they envisioned that the squaramide catalyst **73** could carry out the asymmetric fluorination reaction of β-ketoesters **33** giving rise to better results (Scheme 27).[74]



Scheme 27. Asymmetric fluorination of β-ketoesters **33** catalyzed by phase transfer squaramide **73**.

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The reaction selected to test their hypothesis was the asymmetric fluorination of indanone carboxylate derivatives **33** using NFSI **38** as the source of fluorine. The reaction was performed in Et_2O using aqueous K_2CO_3 as an additive to form the corresponding enolate from the selected β-ketoester **33**. This approach allowed them to obtain some different examples with excellent yields (91-97%) and moderate to good selectivities (56-76%). It is noteworthy that the authors suggested a plausible mechanism, explaining the absolute configuration of the products obtained with this catalytic system (Figure 8).

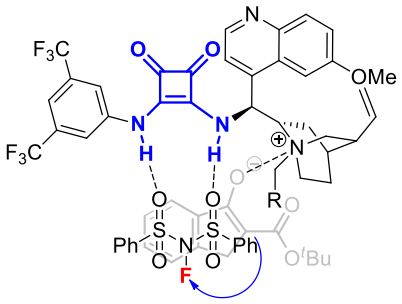
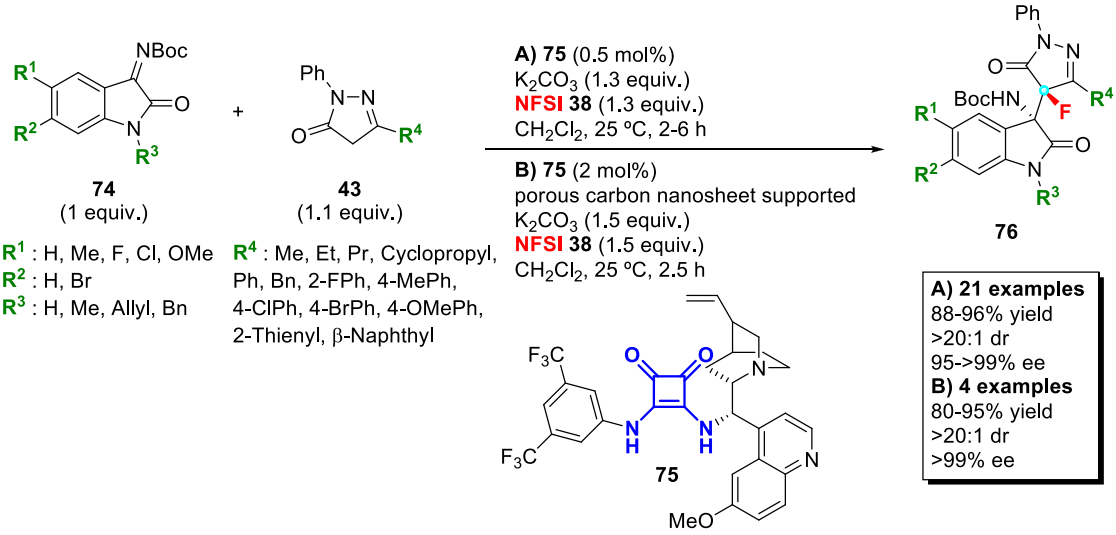


Figure 8. Proposed enantioselective attack of β-ketoesters **33** catalyzed by phase transfer squaramide **73**.[75]

In this proposal, the basic additive would form an enolate from the β-ketoester **33**, enabling its electrostatic union with the quaternary amine on the catalyst. Hence, an attack from the *Si* face of the enolate would be driven by the catalyst to the electrophilic F donor substrate (NFSI, **38**) fixed in the acid moiety, giving rise to the corresponding products **39** with an (*S*) configuration.

In 2015, Wang and coworkers reported another example based on the use of squaramide derivatives **75** (Scheme 28, A).[76] In 2018, the same group developed another work in which the authors supported such catalysts on carbon nanosheets (Scheme 28, B).[77]



Scheme 28. Enantioselective fluorination of isatin and pyrazolone derivatives **74** and **43**.

The selected reactants for this work were isatin **74** and pyrazolone **43** derivatives, using NFSI **38** as the fluorine source. The authors developed a one-pot protocol in which firstly the enantioselective addition of the pyrazolone **43** would take place, creating an adequate environment for the fluorination to be carried out. It is noteworthy that this system needed K_2CO_3 as an additive to work. Furthermore, the catalyst loading (0.5 mol %) is one of the lowest used in non-covalent organocatalysis.[78] With this methodology, the authors could obtain a broad scope of products with very good to excellent yields (88-96 %), high diastereoselectivities (>20:1) and excellent enantiomeric excesses for the major isomer (95->99 %). In addition to that, the authors gave an absolute configuration for the products of (3*S*,4′*R*) based on single-crystal X-ray diffraction.

Afterwards, the same group developed a procedure to attach the previous catalyst **75** to porous carbon nanosheets (PCN).[79] This material is known for its macropores, cavities with the potential to transport different substances or to be used as catalytic microreactors. Hence, after the immobilization procedure, the same reaction was performed, achieving similar results to the ones before with the only drawbacks being higher catalyst loading, a narrower scope of products and a slightly worse atom economy. However, this setup made the catalyst recoverable and the authors were able to make a continuous flow system to perform the reaction. The system had a productivity of 0.7 mmol h^{-1} g^{-1} obtaining the product with an excellent yield (91%) and very good selectivity (88%) with no appreciable loss of catalytic activity for 6 hours.

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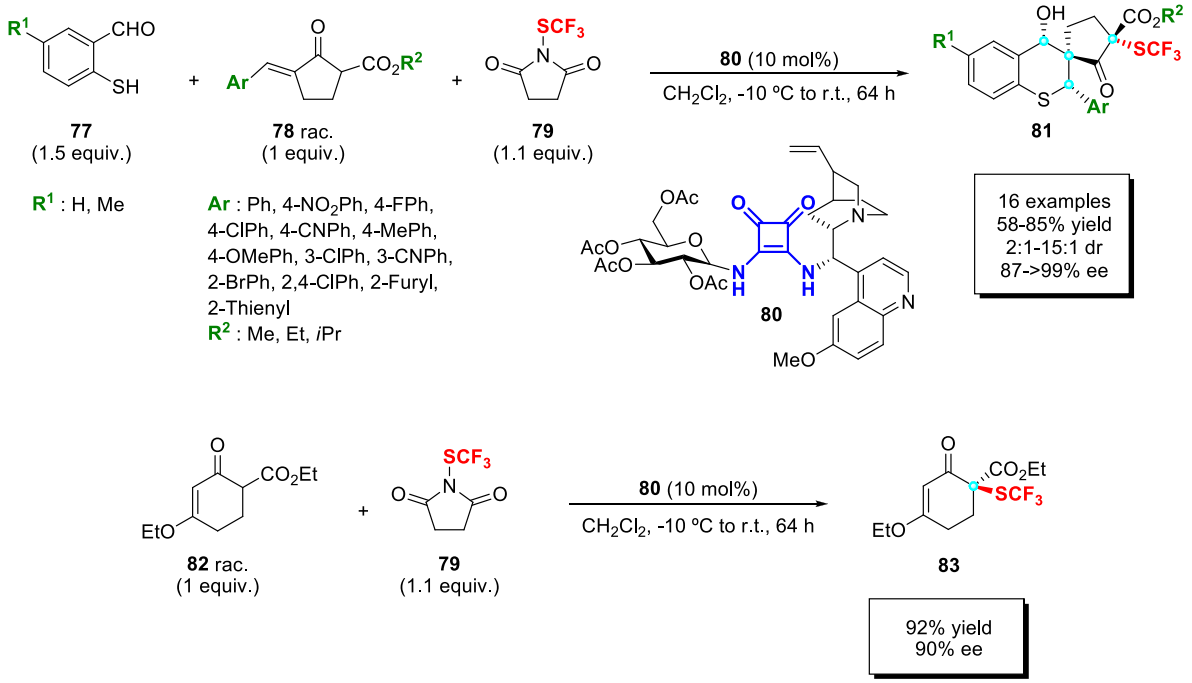
The last example was reported by Du and coworkers in 2017. This work is the only asymmetric organocatalytic example, using (thio)urea or squaramide derivatives, of a trifluoromethylthiolation reaction separated from the predominant monofluorination reactions (Scheme 29).[80]



Scheme 29. First trifluoromethylthiolation reaction organocatalyzed by squaramide **80**.

In the first procedure, the authors investigated the reaction between the benzylidenecyclopentanone carboxylate derivative **78** and the mercaptobenzaldehyde derivative **77**. After the first step, they explored different trifluoromethylthiolating reagents,[81] finally selecting 1-(trifluoromethylthio)pyrrolidine-2,5-dione **79** as the best option. With this setup, the authors were able to obtain 16 different products with moderate to very good yields (58-85%) and diastereoselectivities (2:1-15:1) and very good to excellent enantiomeric excesses (87->99%). Electron-withdrawing groups in the benzylidene position (Ar) seemed to produce lower yields, while the opposite happens with electron-donating groups.

In the second protocol, the authors made use of the cyclohexenone carboxylate derivative **79** to expand the scope of the methodology, obtaining excellent yields (92%) and enantioselectivities (90%).

5 Summary and Outlook

This review covers all existent examples involving chiral phosphoric and carboxylic acids, (thio)urea and squaramide derivatives in fluorination reactions, where hydrogen bond interactions are the main activation tool. The use of organocatalysts in fluorination reactions is still growing, but in this work the different catalysts and approaches reported in this scarcely developed subarea of research are shown and discussed.

Most of the examples involve electrophilic fluorination reactions using 1-chloromethyl-4-fluoro 1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborates) (Selectfluor) or *N* fluorobenzenesulfonimide (NFSI) as the source of fluorine for the production of interesting fluorinated compounds. There is still plenty of room for new organocatalysts or improvements to the known ones and new fluorinated reagents to be discovered.

This review is also a small tribute to the efforts and the crucial contributions made by all authors. We hope that this work encourages researchers working with hydrogen-bonding-based catalysts to expand the chemistry of fluorine in the next future. This will be vital for the progress of this field of high interest in the pharmaceutical industry.

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References

[1] C. N. Neumann, T. Ritter, *Angew. Chem. Int. Ed.* **2015**, *54*, 3216–3221.

This article is protected by copyright. All rights reserved.

Accepted Manuscript

[2] a) P. Jeschke, *ChemBioChem* **2004**, *5*, 570−589; b) T. Fujiwara, D. O'Hagan, *J. Fluor. Chem.* **2014**, *167*, 16−29.

[3] a) K. L. Kirk, *J. Fluor. Chem.* **2006**, *127*, 1013−1029; b) D. O'Hagan, *J. Fluor. Chem.* **2010**, *131*, 1071−1081; c) J. Wang, M. Sánchez-Roselló, J. L. Aceña, C. del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok, H. Liu, *Chem. Rev.* **2014**, *114*, 2432−2506.

[4] a) H.-J. Böhm, D. Banner, S. Bendels, M. Kansy, B. Kuhn, K. Müller, U. Obst-Sander, M. Stahl, *ChemBioChem* **2004**, *5*, 637–643; b) C. Isanbor, D. O'Hagan, *J. Fluor. Chem.* **2006**, *127*, 303–319; c) J.-P. Bégué, D. Bonnet-Delpon, *J. Fluor. Chem.* **2006**, *127*, 992−1012; d) K. Müller, C. Faeh, F. Diederich, *Science* **2007**, *317*, 1881−1886; e) W. K. Hagmann, *J. Med. Chem.* **2008**, *51*, 4359−4369; f) S. Purser, P. R. Moore, S. Swallow, V. Gouverneur, *Chem. Soc. Rev.* **2008**, *37*, 320–330; g) K. L. Kirk, *Org. Process Res. Dev.* **2008**, *12*, 305–321; h) L. Hunter, *Beilstein J. Org. Chem.* **2010**, *6*, No. 38; i) X.-L. Qiu, X.-H. Xu, F.-L. Qing, *Tetrahedron* **2010**, *66*, 789–843.

[5] P. Hewawasam, V. K. Gribkoff, Y. Pendri, S. I. Dworetzky, N. A. Meanwell, E. Martinez, C. G. Boissard, D. J. Post-Munson, J. T. Trojnacki, K. Yeleswaram, L. M. Pajor, J. Knipe, Q. Gao, R. Perrone, J. E. Starrett Jr., *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1023–1026.

[6] J. C. Adkins, S. Noble, *Drugs* **1998**, *56*, 1055–1064.

[7] J. Fried, E. F. Sabo, *J. Am. Chem. Soc.* **1954**, *76*, 1455–1456.

[8] D. T. Wong, F. P. Bymaster, E. A. Engleman, *Life Sci.* **1995**, *57*, 411–441.

[9] C. Heidelberger, N. K. Chaudhuri, P. Danneberg, D. Mooren, L. Griesbach, R. Duschinsky, R. J. Schnitzer, *Nature* **1957**, *179*, 663–666.

[10] a) P. J. Pye, K. Rossen, S. A. Weissman. A. Maliakal, R. A. Reamer, R. Ball, N. N. Tsou, R. P. Volante, P. J. Reider, *Chem. Eur. J*. **2002**, *8*, 1372–1376; b) M. M. Zhao, J. M. McNamara, G.-J. Ho, K. M. Emerson, Z. J. Song, D. M. Tschaen, K. M. J. Brands, U.-H. Dolling, E. J. J. Grabowski, P. J. Reider, *J. Org. Chem.* **2002**, *67*, 6743–6747.

[11] For the scarce examples of oxidation of alcohols in iminium catalysis, see: a) A. Quintard, A. Alexakis, C. Mazet, *Angew. Chem. Int. Ed.* **2011**, *50*, 2354–2358; b) M. Rueping, H. Sundén, E. Sugiono, *Chem. Eur. J.* **2012**, *18*, 3649–3653; c) M. Rueping, H. Sundén, L. Hubener, E. Sugiono, *Chem. Commun*. **2012**, *48*, 2201–2203; d) C. W. Suh, D. Y. Kim, *Org. Lett.* **2014**, *16*, 5374–5377; e) N. K. Rana, H. Joshi, R. K. Jha, V. K. Singh, *Chem. Eur. J.* **2017**, *23*, 2040–2043.

[12] For selected reviews covering organocatalyzed examples, see: a) D. O'Hagan, *Chem. Soc. Rev.* **2008**, *37*, 308–319; b) Z. Ye, G. Zhao, *Chimia* **2011**, *65*, 902–908; c) Y. Zhao, Y. Pan, S.-B. Derek Sim, C.-H. Tan, *Org. Biomol. Chem.* **2012**, *10*, 479–485; d) J.-H. Lin, J.-C. Xiao, *Tetrahedron Lett.* **2014**, *55*, 6147–6155; e) X. Yang, T. Wu, R. J. Phipps, F. D. Toste, *Chem. Rev.* **2015**, *115*, 826−870; f) P. A. Champagne, J. Desroches, J.-D. Hamel, M. Vandamme, J.-F. Paquin, *Chem. Rev.* **2015**, *115*, 9073−9174.

[13] For selected reviews covering metal-catalyzed examples, see: a) S. Lectard, Y. Hamashima, M. Sodeoka, *Adv. Synth. Catal.* **2010**, *352*, 2708–2732; b) R. Szpera, D. F. J. Moseley, L. B. Smith, A. J. Sterling, V. Gouverneur, *Angew. Chem. Int. Ed.* **2019**, *58*, 14824–14848.

[14] G. Valero, X. Companyó, R, Rios, *Chem. Eur. J.* **2011**, *17*, 2018–2037.

[15] For some selected reviews about (thio)ureas, see: a) P. R. Schreiner, *Chem. Soc. Rev.* **2003**, *32*, 289–296; b) Y. Takemoto, *Org. Biomol. Chem.* **2005**, *3*, 4299–4306; c) J. A. J. Breuzard, M. L. Christ-Tommasino, M. Lemaire, *Top Organomet. Chem.* **2005**, *15*, 231–270; d) M. S. Taylor, E. N. Jacobsen, *Angew. Chem. Int. Ed.* **2006**, *45*, 1520–1543; *Angew. Chem.* **2006**, *118*, 1550–1573; e) A. G. Doyle, E. N. Jacobsen, *Chem. Rev.* **2007**, *107*, 5713–5743; f) Z. Zhang, P. R. Schreiner, *Chem. Soc. Rev.* **2009**, *38*, 1187–1198; g) M. Kotke, P. R. Schreiner in *Hydrogen Bonding in Organic Synthesis* (Ed.: P. M. Pihko), Wiley-VCH, Weinheim, **2009**, pp. 141–351; h) E. Marqués-López, R. P. Herrera, *An. Quim.* **2009**, *105*, 5–12; i) Y. Takemoto, *Chem. Pharm. Bull.* **2010**, *58*, 593–601; j) Y. Sohtome, K. Nagasawa, *Synlett* **2010**, 1–22; k) E. Marqués-López, R. P. Herrera in *New Strategies in Chemical Synthesis and Catalysis* (Ed.: B. Pignataro), Wiley-VCH, Weinheim, **2012**, pp 175–199; l) G. Jakab, P. R. Schreiner in *Comprehensive Enantioselective Organocatalysis* (Ed.: P. I. Dalko), Wiley-VCH, Weinheim, **2013**, pp. 315–341, and references therein cited; m) Y. Xi, X. Shi, *Chem. Commun.* **2013**, *49*, 8583–8585; n) S. Narayanaperumal, D. G. Rivera, R. C. Silva, M. W. Paixão, *ChemCatChem* **2013**, *5*, 2756–2773; o) Z. Zhang, Z. Bao, H. Xing, *Org. Biomol. Chem.* **2014**, *12*, 3151–3162; p) E. Marqués-López, R. P. Herrera *in Targets in Heterocyclic Systems – Chemistry and Properties, O. A. Attanasi. Società Chimica Italiana, Vol. 18.* Chapter 8, **2014**, pp. 236–261; q) M. Zabka, R. Sebesta, *Molecules* **2015**, *20*, 15500–15524; r) G. Koutoulogenis, N. Kaplaneris, C. G. Kokotos, *Beilstein J. Org. Chem.* **2016**, *12,* 462–495.

[16] For some selected reviews about squaramides, see: a) R. I. Storer, C. Aciro, L. H. Jones, *Chem. Soc. Rev.* **2011**, *40*, 2330–2346; b) J. Alemán, A. Parra, H. Jiang, K. A. Jørgensen, *Chem. Eur. J.* **2011**, *17*, 6890–6899; c) M. Tsakos, C. G. Kokotos, *Tetrahedron* **2013**, *69*, 10199–10222; d) F. R. Wurm, H. A. Klok, *Chem. Soc. Rev.* **2013**, *42*, 8220–8236; e) J. V. Alegre-Requena, *Synlett* **2014**, *25*, 298–299; f) P. Chauhan, S. Mahajan, U. Kaya, D. Hack, D. Enders, *Adv. Synth. Catal.* **2015**, *357*, 253–281; g) A. Rouf, C. Tanyeli, *Curr. Org. Chem.* **2016**, *20*, 2996–3013; h) X. Han, H.-B. Zhou, C. Dong, *Chem. Rec.* **2016**, *16*, 897–906; i) C. Xiong-Jie, L. Zhi, C. Wen-Hua, *Mini. Rev. Org. Chem.* **2018**, *15*, 148–156; j) L. A. Marchetti, L. K. Kumawat, N. Mao, J.

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C. Stephens, R. B. P. Elmes, *Chem.* **2019**, *5*, 1398–1485.

[17] For some selected reviews about phosphoric acid organocatalysts, see: a) S. J. Connon, *Angew. Chem. Int. Ed.* **2006**, *45*, 3909–3912; b) T. Akiyama, *Chem. Rev.* **2007**, *107*, 5744–5758; c) M. Terada, *Chem. Commun.* **2008**, 4097–4112; d) S.-L. You, Q. Cai, M. Zeng, M. *Chem. Soc. Rev.* **2009**, *38*, 2190–2201; e) D. Kampen, C. M. Reisinger, B. List, *Top. Curr. Chem.* **2010**, *291*, 385–456; f) M. Terada, *Bull. Chem. Soc. Jpn.* **2010**, *83*, 101–119; g) A. Zamfir, S. Schenker, M. Freund, S. B. Tsogoeva, *Org. Biomol. Chem.* **2010**, *8*, 5262–5276; h) M. Terada, *Synthesis* **2010**, 1929–1982; i) M. Rueping, A. Kuenkel, I. Atodiresei, *Chem. Soc. Rev.* **2011**, *40*, 4539–4549; j) S. Schenker, A. Zamfir, M. Freund, S. B. Tsogoeva, *Eur. J. Org. Chem.* **2011**, 2209–2222; k) M. Terada, *Curr. Org. Chem.* **2011**, *15*, 2227–2256; l) A. Parra, S. Reboredo, A. M. M. Castro, J. Alemán, *Org. Biomol. Chem*. **2012**, *10*, 5001–5020; m) D. Parmar, E. Sugiono, S. Raja, M. Rueping, *Chem. Rev.* **2014**, *114*, 9047−9153.

[18] C. Min, D. Seidel, *Chem. Soc. Rev.* **2017**, *46*, 5889−5902.

[19] For the use of chiral guanidines in a fluorination protocol, see: L. Zou, X. Bao, H. Zhang, Y. Song, J. Qu, B. Wang, *Aust. J. Chem.* **2014**, *67*, 1115–1118.

[20] X.-H. He, Y.-L. Ji, C. Peng, B. Han, *Adv. Synth. Catal.* **2019**, *361*, 1923–1957.

[21] a) X. Liu, C. Xu, M. Wang, Q. Liu, *Chem. Rev.* **2015**, *115*, 683−730; b) C. Alonso, E. M. de Marigorta, G. Rubiales, F. Palacios, *Chem. Rev.* **2015**, *115*, 1847−1935.

[22] N. Shibata, *Bull. Chem. Soc. Jpn*. **2016**, *89*, 1307–1320.

[23] C. Carter, S. Fletcher, A. Nelson, *Tetrahedron Asymmetry* **2003**, *14*, 1995–2004.

[24] For selected reviews concerning chiral anions in catalysis, see: a) R. J. Phipps, G. L. Hamilton, F. D. Toste, *Nat. Chem.* **2012**, *4*, 603–614; b) U. Hennecke, *Angew. Chem. Int. Ed.* **2012**, *51*, 4532–4534; c) M. Mahlau, B. List, *Angew. Chem. Int. Ed.* **2013**, ***52***, 518−533; d) K. Brak, E. N. Jacobsen, *Angew. Chem. Int. Ed.* **2013**, *52*, 534−561; d) Y. A. Serguchev, M. V. Ponomarenko, N. V. Ignat'ev, *J. Fluor. Chem.* **2016**, *185*, 1–16.

[25] Other interesting examples in this field that also deserve to be mentioned are: a) K. Mori, A. Miyake, T. Akiyama, *Chem. Lett.* **2014**, *43*, 137–139; b) X.-W. Liang, C. Liu, W. Zhang, S.-L. You, *Chem. Commun.* **2017**, *53*, 5531–5534; c) X.-W. Liang, Y. Cai, S.-L. You, *Chin. J. Chem.* **2018**, *36*, 925−928.

[26] V. Rauniyar, A. D. Lackner, G. L. Hamilton, F. D. Toste, *Science* **2011**, *334*, 1681−1684.

[27] R. J. Phipps, K. Hiramatsu, F. D. Toste, *J. Am. Chem. Soc.* **2012**, *134*, 8376−8379.

[28] a) A. E. Allen, D. W. C. MacMillan, *Chem. Sci.* **2012**, *3*, 633–658; b) C. S. Schindler, E. N. Jacobsen, *Science* **2013**, *340*, 1052−1053.

[29] X. Yang, R. J. Phipps, F. D. Toste, *J. Am. Chem. Soc.* **2014**, *136*, 5225−5228.

[30] J. Y. Kang, R. G. Carter, *Org. Lett.* **2012**, *14*, 3178–3181.

[31] W. Zi, Y.-M. Wang, F. D. Toste, *J. Am. Chem. Soc.* **2014**, *136*, 12864–12867.

[32] a) D. Parmar, M. S. Maji, M. Rueping, *Chem. Eur. J.* **2014**, *20*, 83–86; b) N. A. Cochrane, H. Nguyen, M. R. Gagne, *J. Am. Chem. Soc.* **2013**, *135*, 628–631; c) F. Romanov-Michailidis, L. Guénée, A. Alexakis, *Angew. Chem. Int. Ed.* **2013**, *52*, 9266–9270.

[33] J. Wu, Y.-M. Wang, A. Drljevic, V. Rauniyar, R. J. Phipps, F. D. Toste, *Proc. Natl. Acad. Sci. U.S.A.* **2013**, *110*, 13729–13733.

[34] D. R. Li, A. Murugan, J. R. Falck, *J. Am. Chem. Soc.* **2008**, *130*, 46–48.

[35] K. Hiramatsu, T. Honjo, V. Rauniyar, F. D. Toste, *ACS Catal.* **2016**, *6*, 151–154.

[36] For previous use of this family of phosphoric acid catalysts in asymmetric amination of imines, see: a) G. B. Rowland, H. Zhang, E. B. Rowland, S. Chennamadhavuni, Y. Wang, J. C. Antilla, *J. Am. Chem. Soc.* **2005**, *127*, 15696−15697; b) Y. Liang, E. B. Rowland, G. B. Rowland, J. A. Perman, J. C. Antilla, *Chem. Commun.* **2007**, 4477−4479.

[37] T. Honjo, R. J. Phipps, V. Rauniyar, F. D. Toste *Angew. Chem. Int. Ed.* **2012**, *51*, 9684−9688.

[38] For additional fluorinating examples from the same group, see: a) R. J. Phipps, F. D. Toste, *J. Am. Chem. Soc.* **2013**, *135*, 1268–1271; b) H. P. Shunatona, N. Früh, Y.-M. Wang, V. Rauniyar, F. D. Toste, *Angew. Chem. Int. Ed.* **2013**, *52*, 7724–7727; c) A. J. Neel, A. Milo, M. S. Sigman, F. D. Toste, *J. Am. Chem. Soc.* **2016**, *138*, 3863−3875; d) J. A. S. Coelho, A. Matsumoto, M. Orlandi, M. J. Hilton, M. S. Sigman, F. D. Toste, *Chem. Sci.* **2018**, *9*, 7153–7158.

[39] For a previous racemic version of this reaction, see: D. Parmar, M. S. Maji, M. Rueping, *Chem. Eur. J.* **2014**, *20*, 83–86.

[40] H. Egami, J. Asada, K. Sato, D. Hashizume, Y. Kawato, Y. Hamashima, *J. Am. Chem. Soc.* **2015**, *137* 10132−10135.

[41] H. Egami, K. Sato, J. Asada, Y. Kawato, Y. Hamashima, *Tetrahedron* **2015**, *71*, 6384−6388.

[42] a) H. Egami, T. Niwa, H. Sato, R. Hotta, D. Rouno, Y. Kawato, Y. Hamashima, *J. Am. Chem. Soc.* **2018**, *140*, 2785−2788; b) T. Niwa, K. Ujiie, H. Sato, H. Egami, Y. Hamashima, *Chem. Pharm. Bull.* **2018**, *66*, 920–922.

[43] T. Rouno, T. Niwa, K. Nishibashi, N. Yamamoto, H. Egami, Y. Hamashima, *Molecules* **2019**, *24*, 3464.

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[44] H. Egami, T. Rouno, T. Niwa, K. Masuda, K. Yamashita, Y. Hamashima, *Angew. Chem. Int. Ed*. **2020**, *59*, 14101−14105.

[45] For other examples using (thio)urea catalysts but starting from already fluorinated reagents, see: a) X. Han, J. Luo, Y. Lu, *Chem. Commun*. **2009**, 2044–2046; b) X. Han, J. Kwiatkowski, F. Xue, K.-W. Huang, Y. Lu, *Angew. Chem. Int. Ed.* **2009**, *48*, 7604–7607; c) Y.-K. Kang, S.-J. Yoon, D.-Y. Kim, *Bull. Korean Chem. Soc*. **2011**, *32*, 1195–1200; d) H.-F. Zhang, Z.-Q. Ye, G. Zhao, *Chin. Chem. Lett*. **2014**, *25*, 535−540.

[46] H. Ma, K. Matsuzaki, Y.-D. Yang, E. Tokunaga, D. Nakane, T. Ozawa, H. Masuda, N. Shibata, *Chem. Commun.* **2013**, *49*, 11206−11208.

[47] For a previous racemic version of the procedure depicted, see: a) T. Furukawa, Y. Goto, J. Kawazoe, E. Tokunaga, S. Nakamura, Y. Yang, H. Du, A. Kakehi, M. Shiro, N. Shibata, *Angew. Chem. Int. Ed*. **2010**, *49*, 1642−1647. For selected examples: b) S.Mizuta, N. Shibata, Y. Goto, T. Furukawa, S. Nakamura, T. Toru, *J. Am. Chem. Soc.* **2007**, *129*, 6394−6395; c) T. Furukawa, W. Zhang, T. Nishimine, E. Tokunaga, T. Matsumoto, M. Shiro, N. Shibata, *Angew. Chem. Int. Ed*. **2011**, *50*, 9684−9688; d) T. Furukawa, N. Shibata, S. Mizuta, S. Nakamura, T. Toru, M. Shiro, *Angew. Chem. Int. Ed.* **2008**, *47*, 8051−8054; e) M. Ogasawara, H. Murakami, T. Furukawa, T. Takahashi, N. Shibata, *Chem. Commun.* **2009**, 7366−7368; f) K. Matsuzaki, T. Furukawa, E. Tokunaga, T. Matsumoto, M. Shiro, N. Shibata, *Org. Lett*. **2013**, *15*, 3282−3285.

[48] M. Reichel, K. Karaghiosoff, *Angew. Chem. Int. Ed.* **2020**, *59*, 12268–12281.

[49] J. Xu, Y. Hu, D. Huang, K.-H. Wang, C. Xu, T. Niu, *Adv. Synth. Catal*. **2012**, *354*, 515–526.

[50] a) N. Shibata, T. Ishimaru, S. Nakamura, T. Toru, *J. Fluor. Chem*. **2007**, *128*, 469–483; b) K. Shibatomi, Y. Tsuzuki, S.-I. Nakata, Y. Sumikawa, S. Iwasa, *Synlett* **2007**, 551–554; c) N. Shibata, J. Kohno, K. Takai, T. Ishimaru, S. Nakamura, T. Toru, S. Kanemasa, *Angew. Chem*. **2005**, *117*, 4276–4279; *Angew. Chem. Int. Ed*. **2005**, *44*, 4204–4207; d) T. Ishimaru, N. Shibata, T. Horikawa, N. Yasuda, S. Nakamura, T. Toru, M. Shiro, *Angew. Chem*. **2008**, *120*, 4225–4229; *Angew. Chem. Int. Ed*. **2008**, *47*, 4157–4161; e) M. Marigo, N. Kumaragurubaran, K. A. Jørgensen, *Chem. Eur. J*. **2004**, *10*, 2133–2137; f) N. Shibata, H. Yasui, S. Nakamura, T. Toru, *Synlett* **2007**, 1153–1157.

[51] The authors draw a confusing structure of their catalyst in their mechanism proposal. A redrawing has been performed in Scheme 15 for the sake of clarity.

[52] a) F. Li, L. Sun, Y. Teng, P. Yu, J. C.-G. Zhao, J.-A. Ma, *Chem. Eur. J.* **2012**, *18*, 14255–14260; b) W.-T. Meng, Y. Zheng, J. Nie, H.-Y. Xiong, J.-A. Ma, *J. Org. Chem.* **2013**, *78*, 559–567.

[53] a) K. Liu, H.-F. Cui, J. Nie, K.-Y. Dong, X.-J. Li, J.-A. Ma, *Org. Lett*. **2007**, *9*, 923–925; b) X.-J. Li, K. Liu, H. Ma, J. Nie, J.-A. Ma, *Synlett* **2008**, 3242–3246; c) H. Ma, K. Liu, F.-G. Zhang, C.-L. Zhu, J. Nie, J.-A. Ma, *J. Org. Chem.* **2010**, *75*, 1402–1409.

[54] The authors draw a wrong catalyst in the first mechanism (Ref 52a), a correction has been done in Figure 6 to show the correct structure.

[55] W.-B. Yi, Z. Zhang, X. Huang, A. Tanner, C. Cai, W. Zhang, *RSC Adv*. **2013**, *3*, 18267–18270.

[56] W. Zhang, D. P. Curran, *Tetrahedron* **2006**, *62*, 11837–11865.

[57] P. M. Pihko (Ed.) *Hydrogen Bonding in Organic Synthesis*. Wiley-VCH: Weinheim, Germany, **2009**.

[58] F. G. Bordwell, D. J. Algrim, J. A. Harrelson, Jr. *J. Am. Chem. Soc.* **1988**, *110*, 5903–5904.

[59] a) A. Masunov, J. J. Dannenberg, *J. Phys. Chem. A* **1999**, *103*, 178–184; b) A. Masunov, J. J. Dannenberg, *J. Phys. Chem. B* **2000**, *104*, 806–810.

[60] J. Novacek, N. Waser, *Eur. J. Org. Chem*. **2014**, 802–809.

[61] M. Benaglia, T. Danelli, F. Fabris, D. Sperandio, G. Pozzi, *Org. Lett*. **2002**, *4*, 4229–4239.

[62] B. Zhang, L. Shi, R. Guo, S. Liu, *ARKIVOC* **2016**, *(iv)*, 363–370.

[63] a) D. Y. Kim, E. J. Park, *Org. Lett*. **2002**, *4*, 545–547; b) X. Wang, Q. Lan, S. Shirakawa, K. Maruoka, *Chem. Commun.* **2010**, *46*, 321–323; c) E.-M. Tanzer, W. B. Schweizer, M.-O. Ebert, R. Gilmour, *Chem. Eur. J*. **2012**, *18*, 2006–2013; d) J. Luo, W. Wu, L.-W. Xu, Y. Meng, Y. Lu, *Tetrahedron Lett*. **2013**, *54*, 2623–2626.

[64] X. Jiang, H. Wang, H. He, W. Wang, Y. Wang, Z. Ke, Y.-Y. Yeung, *Adv. Synth. Catal.* **2018**, *360*, 4710–4714.

[65] J. Li, Y. Cai, W. Chen, X. Liu, L. Lin, X. Feng, *J. Org. Chem.* **2012**, *77*, 9148–9155.

[66] L. Pfeifer, K. M. Engle, G. W. Pidgeon, H. A. Sparkes, A. L. Thompson, J. M. Brown, V. Gouverneur, *J. Am. Chem. Soc.* **2016**, *138*, 13314–13325.

[67] G. Pupo, F. Ibba, D. M. H. Ascough, A. C. Vicini, P Ricci, K. E Christensen, L. Pfeifer, J. R. Morphy, J. M. Brown, R. S. Paton, V. Gouverneur, *Science* **2018**, *360*, 638–642.

[68] G. Pupo, A. C. Vicini, D. M. H. Ascough, F. Ibba, K. E. Christensen, A. L. Thompson, J. M. Brown, R. S. Paton, V. Gouverneur, *J. Am. Chem. Soc*. **2019**, *141*, 2878–2883.

[69] a) G. L. Hamilton, T. Kanai, F. D. Toste, *J. Am. Chem. Soc*. **2008**, *130*, 14984–14986; b) S. Lin, E. N. Jacobsen, *Nat. Chem.* **2012**, *4*, 817–824.

[70] D. Qian, M. Chen, A. C. Bissember, J. Sun, *Angew. Chem. Int. Ed.* **2018**, *57*, 3763–3766.

[71] a) M. Rowley, D. J. Hallett, S. Goodacre, C. Moyes, J. Crawforth, T. J. Sparey, S. Patel, S. Thomas, L. Hitzel, D. O´Connor, N. Szeto, J. L. Castro, P. H. Hutson, A. M. MacLeod, *J. Med. Chem.* **2001**, *44*, 1603–1614; b) Z.-Q. Yang, J. C. Barrow, W. D. Shipe, K.-A. S.

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Schlegel, Y. Shu, F. V. Yang, C. W. Lindsley, K. E. Rittle, M. G. Bock, G. D. Hartman, V. N. Uebele, C. E. Nuss, S. V. Fox, R. L. Kraus, S. M. Doran, T. M. Connolly, C. Tang, J. E. Ballard, Y. Kuo, E. D. Adarayan, T. Prueksaritanont, M. M. Zrada, M. J. Marino, V. K. Graufelds, A. G. DiLella, I. J. Reynolds, H. M. Vargas, P. B. Bunting, R. F. Woltmann, M. M. Magee, K. S. Koblan, J. J. Renger, *J. Med. Chem.* **2008**, *51*, 6471–6477; c) W. D. Shipe, J. C. Barrow, Z.-Q. Yang, C. W. Lindsley, F. V. Yang, K.-A. S. Schlegel, Y. Shu, K. E. Rittle, M. G. Bock, G. D. Hartman, C. Tang, J. E. Ballard, Y. Kuo, E. D. Adarayan, T. Prueksaritanont, M. M. Zrada, V. N. Uebele, C. E. Nuss, T. M. Connolly, S. M. Doran, S. V. Fox, R. L. Kraus, M. J. Marino, V. K. Graufelds, H. M. Vargas, P. B. Bunting, M. Hasbun-Manning, R. M. Evans, K. S. Koblan, J. J. Renger, *J. Med. Chem.* **2008**, *51*, 3692–3695.

[72] G. Roagna, D. M. H. Ascough, F. Ibba, A. C. Vicini, A. Fontana, K. E. Christensen, A. Peschiulli, D. Oehlrich, A. Misale, A. A. Trabanco, R. S. Paton, G. Pupo, V. Gouverneur, *J. Am. Chem. Soc.* **2020**, *142*, 14045−14051.

[73] For other examples using squaramide catalysts but starting from already fluorinated reagents, see: a) J. Peng, B.-L. Zhao, D.-M. Du, *Adv. Synth. Catal.* **2015**, *357*, 3639–3647; b) Y. Zhu, X. Li, Q. Chen, J. Su, F. Jia, S. Qiu, M. Ma, Q. Sun, W. Yan, K. Wang, R. Wang, *Org. Lett*. **2015**, *17*, 3826–3829; c) M. Blümel, P. Chauhan, C. Vermeeren, A. Dreier, C. Lehmann, D. Enders, *Synthesis* **2015**, *47*, 3618–3628; d) Y. Kim, Y. J. Kim, H. I. Jeong, D. Y. Kim, *J. Fluor. Chem.* **2017**, *201*, 43–48; e) B.-Y. Li, D.-M. Du, *Adv. Synth. Catal*. **2018**, *360*, 3164–3170; f) R. Ding, C. Wolf, *Org. Lett*. **2018**, *20*, 892–895; g) Q.-D. Zhang, B.-L. Zhao, B.-Y. Li, D.-M. Du, *Org. Biomol. Chem*. **2019**, *17*, 7182–7191; h) E. Matador, M. de G. Retamosa, A. Jiménez-Sánchez, D. Monge, R. Fernández, J. M. Lassaletta, *Eur. J. Org. Chem*. **2019**, 130–138.

[74] B. Wang, Y. He, X. Fu, Z. Wei, Y. Lin, H. Duan, *Synlett* **2015**, *26*, 2588–2592.

[75] The authors do not accurately depict and explain the absolute configuration of the catalyst either in the main body or in the supplementary information of their work. Therefore, some arrangements have been done in Figure 6 and Scheme 21 in order to show a coherent structure.

[76] X. Z. Bao, B. M. Wang, L. C. Cui, G. D. Zhu, Y. L. He, J. P. Qu, Y. M. Song, *Org. Lett*. **2015**, *17*, 5168–5171.

[77] L. Zhao, X. Bao, Q. Hu, B. Wang, A.-H. Lu, *ChemCatChem* **2018**, *10*, 1248–1255.

[78] a) J. V. Alegre-Requena, E. Marqués-López, R. P. Herrera, *Adv. Synth. Catal.* **2016**, *358*, 1801–1809; b) J. V. Alegre-Requena, E. Marqués-López, R. P. Herrera, *ACS Catal.* **2017**, *7*, 6430–6439; c) J. V. Alegre-Requena, E. Marqués-López, R. P. Herrera, *Chem. Eur. J.* **2017**, *23*, 15336–15347.

[79] G. P. Hao, Z. Y. Jin, Q. Sun, X. Q. Zhang, J. T. Zhang, A.-H. Lu, *Energy Environ. Sci*. **2013**, *6*, 3740–3747.

[80] B.-L. Zhao, D.-M. Du, *Org. Lett.* **2017**, *19*, 1036–1039.

[81] a) M. Li, J. Guo, X.-S. Xue, J.-P. Cheng, *Org. Lett*. **2016**, *18*, 264–267.

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REVIEW

Asymmetric Fluorination Reactions Promoted by Chiral Hydrogen-Bonding-Based Organocatalysts

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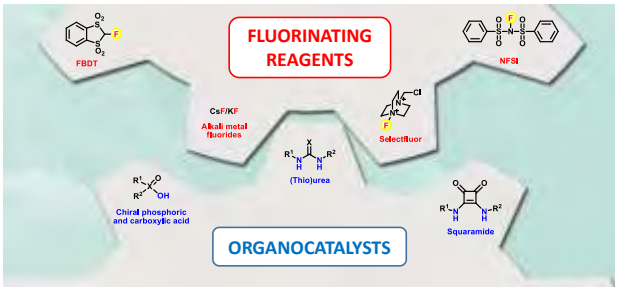

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