Asymmetric Synthesis

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Synthesis of a Chiral Quaternary Carbon Center Bearing a Fluorine Atom: Enantio- and Diastereoselective Guanidine-Catalyzed Addition of Fluorocarbon Nucleophiles**

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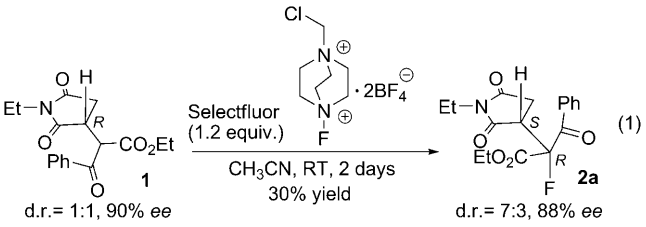
The C–F bond is highly polarized and its unique properties are often understood by considering its stereoelectronic interactions with neighboring bonds or lone pairs of electrons.[1] Whereas natural organofluoro compounds are rare, synthetic fluorinated compounds are useful in areas such as materials, agrochemicals, pharmaceuticals, and fine chemicals.[2] Strategic fluorination is commonly used in contemporary medicinal chemistry to improve metabolic stability, bioavailability, and protein–drug interactions.[3] The replacement of metabolically active hydrogen atoms with fluorine atoms increases the in vivo lifetime of drugs. As such, fluorine-containing compounds are ubiquitous in blockbuster drugs, for example, fluoxetine (antidepressant), atorvastatin (cholesterol-lowering), and ciprofloxacin (antibacterial). The specific incorporation of fluorine in a regio- and stereoselective manner has thus become the most pivotal consideration in the synthesis of fluorinated compounds. To date, both nucleophilic fluorination[4] and electrophilic fluorination[5] methods have been developed.

With the huge number of potential applications, asymmetric C–F bond formation has been become a subject of intense research and has emerged as an important goal in organic chemistry.[6] Hintermann and Togni reported the first example of an enantioselective catalytic electrophilic α-fluorination using a titanium/taddol complex (taddol = tetraaryl-1,3-dioxolane-4,5-dimethanol) and Selectfluor.[7] The emergence of other stable sources of electrophilic fluorinating agents such as *N*-fluorobenzenesulfonimide (NFSI) and the use of other metal complexes allowed the scope of asymmetric C–F bond formation to be dramatically expanded.[8] Organocatalytic approaches for asymmetric C–F bond transformation using proline and cinchona alkaloids and their derivatives as catalysts have recently been shown to be a viable alternative.[9] Catalytic enantioselective nucleophilic fluorination is not common; however, one example is the ring opening of epoxides with fluoride sources using salen/chromium complexes (salen = bis(salicylidene)ethylenediamine) as catalysts.[10] The use of a fluorocarbon nucleophile such as 1-fluorobis(phenylsulfonyl)methane (FBSM) as a synthetic equivalent of monofluoromethane was effectively exploited in a Mitsunobu reaction,[11] Michael reaction,[12a] Mannich reaction,[12b] and palladium-catalyzed allylation.[12c] The amination of 2-fluoro-*tert*-butyl benzoylacetate under phase-transfer conditions was found to proceed with moderate enantioselectivity.[13] Other novel approaches towards chiral quaternary carbon centers bearing a fluorine atom include the enantioselective decarboxylation of α-fluoro-β-ketoesters.[14] To the best of our knowledge, a highly enantioselective and diastereoselective reaction using a fluorocarbon nucleophile has not yet been reported.

We are keen to develop bicyclic guanidines as general Brønsted base catalysts, and we found that these bases work particularly well with conjugate addition type reactions providing adducts with high *ee* values.[15] We have previously shown that adduct **1** can be obtained by the guanidine-catalyzed addition of ethyl benzoylacetate and *N*-ethyl maleimide with an *ee* value of 90% and a d.r. of 1:1 [Eq. (1)].[15c] When **1** was used for the electrophilic fluorination reaction using 1.2 equivalents of Selectfluor, **2a** was



obtained with a d.r. of 7:3. The reaction proceeded slowly and required two days to achieve 30% conversion [Eq. (1); structure of major diastereoisomer is shown]. Conducting the experiment at low temperature should give a higher d.r. value, but this was not feasible because of the slow rate of the reaction.

The use of 2-substituted benzoylacetates,[16a] such as α-fluoro-β-ketoester **4a**,[16b] as the fluorocarbon nucleophile is an alternative approach for making the C–F bond in **2a**. The strong inductive effect of the C–F bond in α-fluoro-β-ketoester **4a** should increase the acidity of the α-carbon atom. We have shown previously that a more acidic donor will

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result in an increase in the rate of reaction of the guanidine-catalyzed reactions.[15c] The increase in the acidity was verified by comparing the pK_a values of ethyl benzoylacetate (9.85) and α-fluoro-β-ketoester **4a** (8.20).[17]

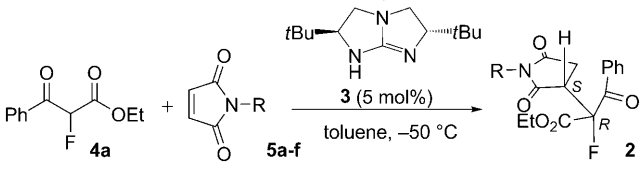
In the presence of 5 mol% of catalyst **3**, α-fluoro-β-ketoester **4a** and various *N*-alkyl maleimides (Table 1, **5a–f**) underwent conjugate additions to afford adducts with excellent *ee* values (93–97%). Excellent diastereoselectivities (d.r. > 99:1) were also observed.[18] Under the same reaction conditions, the reaction was additionally explored using several substituted aryl α-fluoro-β-ketoesters **4b–l** (Table 2). High enantioselectivities (up to > 99% *ee*) and diastereoselectivities (> 99:1 d.r.) were observed for different substitution patterns on the aromatic ring. Both electron-withdrawing and electron-donating substrates, as well as the heteroaromatic substrate **4l** (Table 2, entry 11) gave excellent results.

Linear Michael acceptors such as *trans*-4-oxo-4-arylbutenamides **6a** and **6b** [Eq. (2)] were also found to be suitable for this reaction. 4-Oxo-4-arylbutenamides were previously shown to participate in Michael reactions of arylboronic acids catalyzed by rhodium complexes.[19a] Aza-Michael reactions with 4-oxo-4-arylbutenamides were also reported to show high regioselectivities.[19b] Initial investigations using aryl α-fluoro-β-ketoesters **4i** and **4k**, showed low reactivity towards the arylbutenamides. Optimization studies revealed that with 10 equivalents of triethylamine as an additive[15e] and an increase in the catalyst loading to 20 mol%, adducts were obtained in excellent enantioselectivities (up to 96%), diastereoselectivities (99:1), and regioselectivities.[20]

To shed light on the mechanism of the guanidine-catalyzed addition, density functional theory (DFT) calculations at the B3LYP/6-31G* level were performed.[21] The catalytic reaction is initiated by a proton transfer from the α-fluoro-β-ketoester to the guanidine catalyst **3** to form a hydrogen-bonded complex between the guanidinium cation and the ketoester anion. This ion-pair complex is characterized by two hydrogen bonds between the guanidinium NH protons and the oxygen atoms of the carbonyl groups in the α-fluoro-β-ketoester.[22a] The complex has a large binding energy of $-49\ kJ\,mol^{-1}$ with respect to the two neutral substrates. It is important to note that the corresponding neutral guanidine/enol complex is significantly less stable (by $14\ kJ\,mol^{-1}$) than the ion-pair complex.

The maleimide would then approach the guanidinium/ketoester ion-pair complex to form a pretransition-state complex; two possible structures, face-on and side-on, of this complex are conceivable.[22a] In the side-on complex, the guanidinium catalyst forms hydrogen bonds with both reactants, whereas the guanidinium catalyst forms hydrogen bonds only with the β-ketoester substrate in the face-on complex.[22a] Likewise, face-on and side-on approaches are possible for the C–C bond-forming transition state (TS). The side-on TS is strongly preferred over the face-on TS mainly because of the stronger hydrogen bond associated with the maleimide carbonyl group. Hence, the guanidine catalyst in

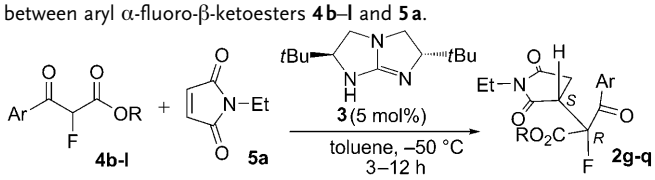
Table 1: Highly enantioselective and diastereoselective reactions between α-fluoro-β-ketoester **4a** and *N*-alkyl maleimides **5a–f**.



Entry	5	R	*t* [h]	2	Yield [%][a]	d.r.[b]	*ee* [%][c]
1	**5a**	Et	2	**2a**	99	> 99:1	96
2	**5b**	Me	6	**2b**	99	> 99:1	95
3	**5c**	cyclohexyl	6	**2c**	99	> 99:1	96
4	**5d**	Bn	3	**2d**	91	> 99:1	93
5	**5e**	*n*-hexyl	3	**2e**	87	> 99:1	95
6	**5f**	*t*-butyl	12	**2f**	99	> 99:1	97

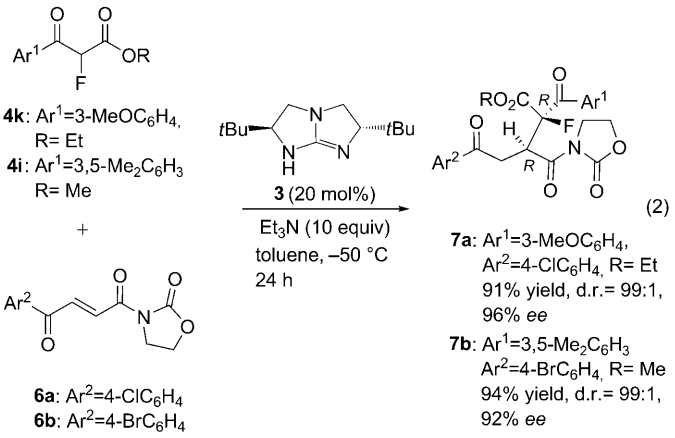
[a] Yield of isolated product. [b] Determined by ^{1}H NMR analysis. [c] Determined by HPLC methods.

Table 2: Highly enantioselective and diastereoselective reactions between aryl α-fluoro-β-ketoesters **4b–l** and **5a**.



Entry	4	Ar	R	2	Yield [%][a]	d.r.[b]	*ee* [%][c]
1	**4b**	4-$NO_2C_6H_4$	Et	**2g**	80	98:2	83
2	**4c**	4-$CF_3C_6H_4$	Et	**2h**	83	> 99:1	96
3	**4d**	4-ClC_6H_4	Et	**2i**	98	> 99:1	95
4	**4e**	4-BrC_6H_4	Me	**2j**	85	> 99:1	95[97][d]
5	**4f**	4-(4-BrC_6H_4)-C_6H_4	Me	**2k**	99	> 99:1	93[> 99][e]
6	**4g**	4-$MeOC_6H_4$	Et	**2l**	87	> 99:1	96
7	**4h**	4-$BnOC_6H_4$	Et	**2m**	99	> 99:1	97
8	**4i**	3,5-$Me_2C_6H_3$	Me	**2n**	99	> 99:1	96
9	**4j**	2-naphthyl	Me	**2o**	99	> 99:1	96[> 99][e]
10	**4k**	3-$MeOC_6H_4$	Et	**2p**	99	> 99:1	96
11	**4l**	2-thiophenyl	Et	**2q**	99	> 99:1	93

[a] Yield of isolated product. [b] Determined by ^{1}H NMR analysis. [c] Determined by HPLC methods. [d] –60 °C, 24 h, 99% yield, d.r. > 99:1, 1.0 mmol scale. [e] *ee* values improved after a single recrystallization.



(2)

this catalytic reaction is best described as a bifunctional catalyst.[22b]

On the basis of the fact that there are two potential centers for forming C–C bonds in maleimide and various modes of approach between the two reactants, there are four plausible side-on transition states. The relative energies of the most stable transition states leading to the formation of (*S*,*R*)-, (*S*,*S*)-, (*R*,*S*)-, and (*R*,*R*)-products are 0, 10, 18, and 20 kJ mol^{-1}, respectively. The calculated preference for the (*S*,*R*)-stereoisomer is in excellent agreement with the observed high enantioselectivty and diastereoselectivity. The optimized geometries of the four transition states are shown in Figure 1. Interestingly, only one of the two carbonyl

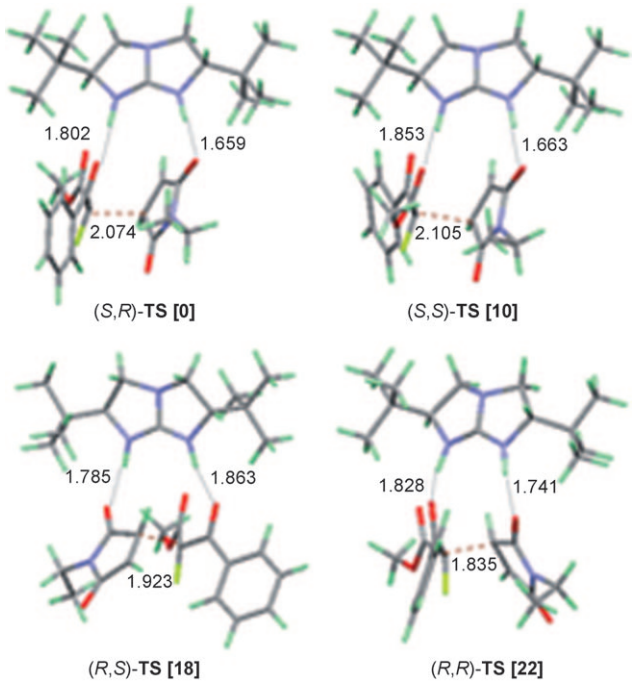


Figure 1. Optimized (B3LYP/6-31G*) geometries of the four transition states leading to the (*S*,*R*)-, (*S*,*S*)-, (*R*,*S*)-, and (*R*,*R*)-products. Calculated relative energies are given in square brackets in kJ mol^{-1} and the bond lengths are given in Å.

oxygens of the β-ketoester forms a hydrogen bond with a guanidinium NH proton in all cases. The calculated relative energies of various transition states can be rationalized in terms of the relative strength of the hydrogen-bond interactions. The calculated intrinsic barriers are relatively small, for example, 30 kJ mol^{-1} for the (*S*,*R*)-induced TS. The pre-TS complex,[22a] having an interaction energy of −24 kJ mol^{-1}, brings the reactants and catalyst in close proximity. As a result, the energy required for structural and electronic reorganization to form the transition state is significantly smaller. The calculated activation barrier for the (*S*,*R*)-induced TS is fairly small (30 kJ mol^{-1}), which is consistent with the low-temperature requirement of this catalytic conjugate addition reaction.

Fluorohydrins are important precursors in the synthesis of monofluorinated analogues of natural products.[23] Our first attempt at reducing the ketone moiety in the fluorinated adduct **2f** with $NaBH_4$ (THF, −78 °C), resulted in a diastereomeric ratio of 1:1. Subsequently, we tried several other reducing agents and found that $TiCl_4/BH_3{\cdot}Me_2S$[24] resulted in perfect diastereoselectivity; only one diastereoisomer **8a**, with three contiguous chiral centers, was obtained [Eq. (3)]. The relative and absolute configuration of **8b** was confirmed by single-crystal X-ray analysis.[25] The antiperiplanar orientation of $\sigma_{C\text{-}H}$ with $\sigma^*_{C\text{-}F}$ was clearly demonstrated in the crystal structure of **8b**. Both the chelation-controlled addition[24] (Figure 2, **A**) and Felkin–Anh[26] (Figure 2, **B**) models predicted the correct diastereoisomer.

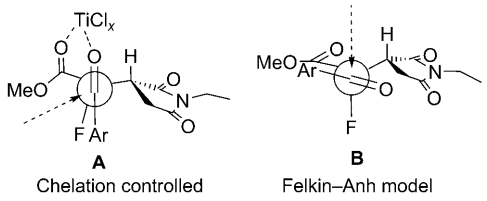
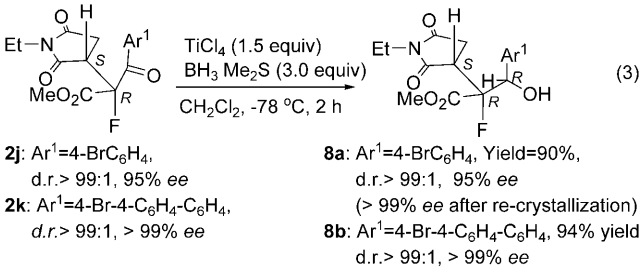


Figure 2. Models for highly diastereoselective reduction of **2j**,**k**.

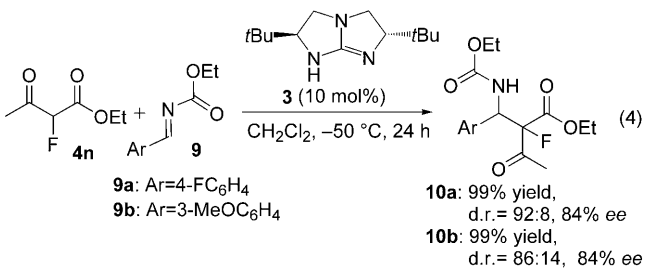


2j: Ar^1=4-BrC_6H_4, d.r.> 99:1, 95% *ee*
2k: Ar^1=4-Br-4-C_6H_4-C_6H_4, *d.r.*> 99:1, > 99% *ee*

8a: Ar^1=4-BrC_6H_4, Yield=90%, d.r.> 99:1, 95% *ee* (> 99% *ee* after re-crystallization)
8b: Ar^1=4-Br-4-C_6H_4-C_6H_4, 94% yield d.r.> 99:1, > 99% *ee*

The interest in β-amino acids and β-peptides arises from the desire to understand protein folding as well as its potential as mimics of naturally occurring peptides.[27] Current methodologies did not describe a simple, direct approach to prepare α-fluoro-β-amino acids, particularly the concomitant construction of a quaternary C–F bond. Mannich reactions between β-ketoesters and imines can be catalyzed with organocatalysts, most commonly, the bifunctional cinchona alkaloids and chiral Brønsted acids.[28] α-Fluoro-β-ketoesters were shown to form well-defined transition states with bicyclic guanidine that led to highly diastereoselective and enantioselective reactions. We extended this concept to Mannich reactions and our preliminary results show that α-fluoro-β-ketoester **4n** added to imines **10a** and **10b** each with a high level of diastereoselectivity and enantioselectivity. Optimization of the reaction and investigations to determine the absolute configuration of β-amino esters **10a** and **10b** is ongoing.

In conclusion, we have developed a highly enantioselective and diastereoselective guanidine-catalyzed conjugate addition of fluorocarbon nucleophiles. Several compounds having chiral quaternary carbon centers bearing a fluorine atom and contiguous chiral centers were obtained. The mechanism for the catalysis and the origin of stereoselectivity were investigated by DFT methods. Our calculations strongly



support the observed remarkable stereoselectivity. The bifunctional mode of the guanidine catalyst was clearly demonstrated in the transition states.

Experimental Section

Representative procedure for the synthesis of **2a**: 2-Fluoroethyl benzoyl acetate **4a** (25.2 mg, 0.12 mmol, 1.2 equiv) and *N*-ethyl maleimide **5a** (12.5 mg, 0.1 mmol, 1.0 equiv) were dissolved in toluene (795 μL). The reaction was stirred at −50 °C for 30 minutes, and then a precooled solution of catalyst **3** (0.005 mmol, 0.05 equiv, 1.12 mg in 5 μL toluene) was added. The reaction mixture was stirred at −50 °C and monitored by TLC. After 2 h, the reaction was completed. Flash chromatography afforded product **2a** (33.1 mg, 99 % yield) as a colorless oil.

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